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Brief Article

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Alpha-Heteroatom Derivatized Analogues of 3-(Acetylhydroxyamino)propyl Phosphonic Acid (FR900098) as Antimalarials

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Supporting Information

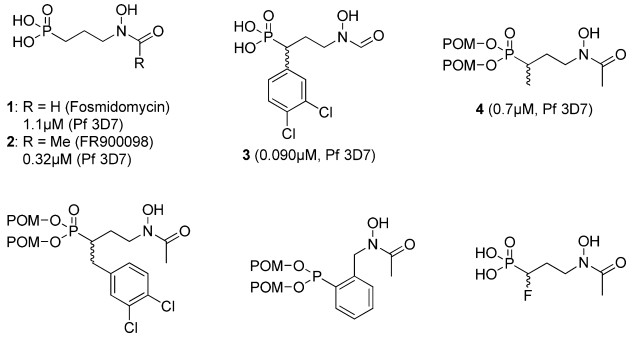
ABSTRACT: To explore the hitherto successful derivatization of the α-carbon of fosmidomycin, a series of new α-substituted analogues was prepared. This was done by introduction of a heteroatom (N or O) in α-position to the phosphonate and using the resultant OH and NH_2 groups as a handle for appending a variety of substituents by means of several functional groups such as ether, amide, urea, and 1,4-triazole. The synthesized molecules, as a racemic mixture, were assayed for their EcDXR inhibitory potency. Both the α-azido-analogue and the α-hydroxylated analogue proved most promising, and docking experiments were performed. Although several compounds showed high potency when assayed against *Plasmodium falciparum* K1 in human erythrocytes, a clear correlation between the enzyme inhibition constants and *P. falciparum* inhibition concentrations could not be found.

INTRODUCTION

With over 200 million clinical cases and more than half a million fatalities per year, malaria is still one of the major infectious diseases. As resistance against almost all currently used antimalarial drugs is emerging or already established, there is a high need for new therapies, preferably affecting hitherto unexploited targets. Moreover, these drugs should be well-tolerated because malaria is often a disease of small children and pregnant women.[1] Over the past decade, the non-mevalonate route for isoprenoid biosynthesis has become an attractive target for the development of antimalarials. Of highest interest so far is the second step, the conversion of 1-deoxy-D-xylulose-5-phosphate (DOXP) into 2-C-methyl-D-erythritol-4-phosphate (MEP), catalyzed by DOXP-reductoisomerase (DXR).[2] Well-known leads for the development of DXR inhibitors are fosmidomycin (**1**) and its acetyl congener FR900098[3] (**2**) (Chart 1). Fosmidomycin has been clinically tested as an antimalarial combination partner for clindamycin and artesunate and found to be very safe and nontoxic.[4,5] Unfortunately, repeated high doses of fosmidomycin are required to achieve acceptable cure rates.

Significant efforts have been made to improve fosmidomycin's activity.[6] The available SAR indicates that both the free phosphonic acid group (which may be masked as a prodrug) and an intact retrohydroxamic or hydroxamic acid functionality are essential for DXR inhibition. Instead, the 3-carbon spacer in **1** lends itself for derivatization. Particularly, the introduction of substituents on the α-carbon of the phosphonate has afforded promising inhibitors, with aryl substituents as in **3** being best explored.[7,8]

Chart 1. Structures of α-Substituted Fosmidomycin Analogues with Their IC_{50} Values Against *P. falciparum*



After α-phenyl-fosmidomycin analogues were shown to exhibit stronger antiplasmodial activity than fosmidomycin, many SAR studies[9−11] and crystallographic[12,13] studies were dedicated to α-aryl modifications, not only to combat *Plasmodium falciparum* but also in the search for DXR inhibitors directed against *Mycobacterium tuberculosis*. Until now, fosmidomycin analogues with other α-substituents are rather scarce.

The Geffken group introduced α-alkyl, α-hydroxymethyl, and α,α-bismethyl substituents onto prodrug forms of **1** and **2** but noticed that, with the exception of a simple α-methyl group as in **4**, none of these substitutions were well tolerated by the

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DXR enzyme.[8] Kurz and co-workers described the synthesis of arylmethyl substituted prodrugs of **1**[14] in which a methylene linker is inserted between the α-carbon and various aryl substituents, resulting in analogues such as **5** with reasonable to good DXR inhibitory activities. Incorporation of a phenyl ring in the 3-carbon spacer (as in **6**),[15] led to loss of potency. Recently, we reported a series of α-halogenated analogues of **2**, which gave comparable to slightly better growth inhibition of *P. falciparum* K1 in human erythrocytes.[16] Accordingly, compared to **2**, α-fluorinated **2** (**7**) slightly increased the mean survival time of *Plasmodium berghei* infected mice.

RESULTS AND DISCUSSION

In this study, we describe the synthesis and evaluation of a series of analogues of **2**, characterized by various O- or N-based substituents in α position (Figure 1).

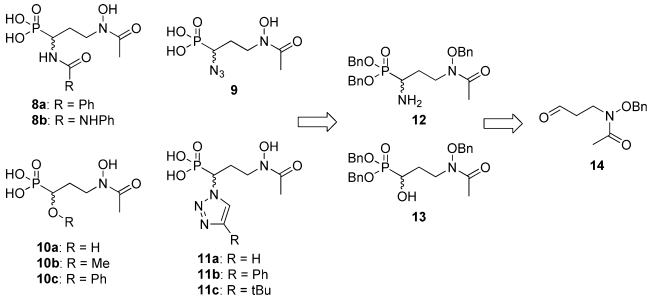
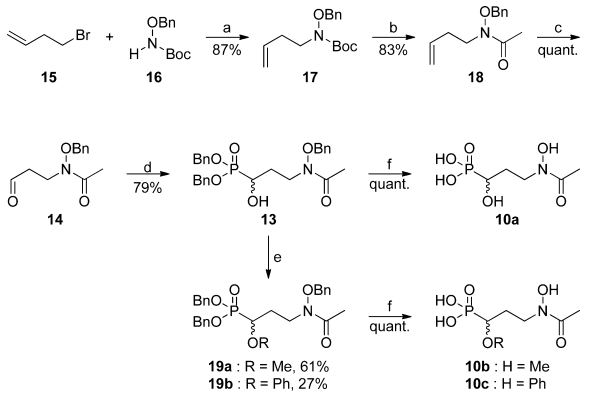


Figure 1. Target analogues and retrosynthetic strategy.

Aldehyde **14**, already equipped with a protected retrohydroxamate moiety, served as a starting point for the synthesis of α O-based analogues via a Pudovik reaction. Its synthesis started with the alkylation of *N*-Boc-*O*-benzylhydroxylamine (**16**) with bromobutene (**15**) in DMF,[17] followed by a one-pot deprotection−acetylation[18] to afford terminal alkene **18**. Oxidative cleavage of the double bond with periodate and osmate quantitatively afforded the desired aldehyde **14**. For the synthesis of benzyl protected α-hydroxylated **2**:**13** (Scheme 1), we chose a base-assisted Pudovik reaction with dibenzyl phosphite at low temperature for it resulted in a cleaner reaction mixture and higher yields than when using "classical" Pudovik conditions. Using benzyl protection for both the phosphonate and the retrohydroxamate allowed a gentle one-step final deprotection. **13** was converted into its methyl ether **19a** by a Williamson reaction with iodomethane and silver oxide. Attempted synthesis of α-phenyl ether **19b** under standard Mitsunobu conditions in THF failed. Therefore, we switched to more forcing conditions as described by Lepore et al.,[19] which allowed us to synthesize **19b**, albeit the complex reaction mixture called for fractionating by flash chromatography followed by purification by preparative HPLC.

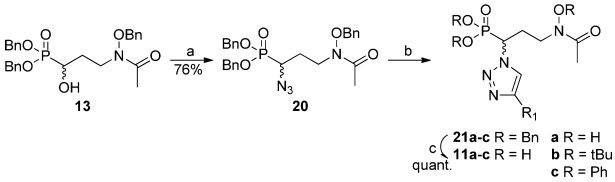
Starting from intermediate **13**, α-azidophosphonate **20** was synthesized by means of a Mitsunobu reaction with hydrazoic acid as the pronucleophile (***Caution*: HN_3 is volatile, highly toxic, and explosive!**) (Scheme 2). Using "classical" Mitsunobu conditions (2 equiv of both triphenyl phosphine and diethylazodicarboxylate (DEAD), excess hydrazoic acid, submolar concentrations in toluene), we were able to synthesize the desired α-azide in what appeared to be pure form according to TLC or HPLC. However, persistent ethyl signals were observed in the ^{1}H NMR spectrum of the product. Originally assigned to ethyl acetate trapped in the oily product, it later turned out that these signals arose from the α-ethylcarbonate formed by attack of alcohol **13** on one of the carbonyl groups of DEAD. The formation of this unwanted product, which coelutes with α-azidophosphonate **20** both on TLC and RP-HPLC, was avoided by switching to the more sterically hindered diisopropylazodicarboxylate (DIAD) and mixing the reactants in a different order (precomplexing triphenylphosphine and DIAD, followed by adding the hydrazoic acid solution and finally the α-hydroxyphosphonate). The obtained α-azidophosphonate **20** subsequently served in the synthesis of α-1,4-triazole-substituted analogues by copper-catalyzed azide−alkyne cycloaddition (CuAAC) with two acetylene derivatives. To the best of our knowledge, no precedents on the CuAAC of α-azidophosphonates are known and only thermal, non-regiospecific, phosphonomethylazide−alkyne cycloadditions have been performed before.[20] Attempted CuAAC using copper(II)sulfate and ascorbic acid with phenyl- or *t*-butylacetylene at room temperature or with conventional heating failed, but upon switching to microwave heating clean products were obtained in good yields. The unsubstituted triazole **21a** was synthesized using the protocol of Hansen et al.,[21] i.e., heating azide **20** in vinyl acetate under microwave irradiation for several hours.

Scheme 1. Synthesis of Key Intermediate 13 and α-O-Based Analogues[a]



[a]Reagents and conditions: (a) NaH, DMF, rt; (b) (i) acetyl chloride, MeOH, NaI, MeCN, 1h, rt, (ii) Et_3N, DMAP; (c) $NaIO_4$, $K_2OsO_4{\cdot}2H_2O$, H_2O, THF; (d) $HPO(OBn)_2$, LiHMDS, THF, −78 °C; (e) for **19a**, MeI, Ag_2O, DMF, rt; for **19b**, PhOH, PPh_3, DIAD, THF, ultrasound; (f) Pd/C, ammonium formate, MeOH, reflux, 20 min.

Scheme 2. Synthesis of α-(1,2,3-Triazolyl) Analogues[a]



[a]Reagents and conditions: (a) PPh_3, DIAD, HN_3, toluene, rt; (b) for **21a**, vinyl acetate, μW (69%); for **21b**, 3,3-dimethylbut-1-yne, $CuSO_4$, Na-ascorbate, DMF, μW (97%); for **21c**, phenylacetylene, $CuSO_4$, Na-ascorbate, DMF, μW (95%); (c) for **11a,c**, Pd/C, NH_4OOCH, MeOH, reflux; for **11b**, Pd/C, H_2, MeOH.

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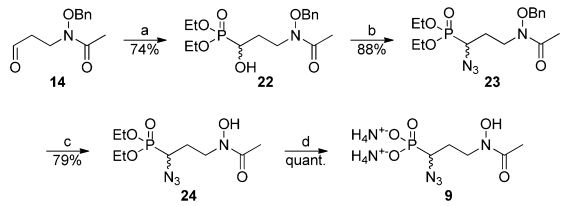
We considered α-azido-**2** also of interest as a potential DXR inhibitor, but for obvious reasons deprotection by reductive debenzylation of precursor **20** was not an option. Hence, we chose to synthesize an α-azido precursor with orthogonal protective groups, i.e., a benzyl ether for the retrohydroxamate and ethyl esters for the phosphonate (Scheme 3). A Pudovik

Scheme 3. Synthesis of α-Azido-2 (9)[a]

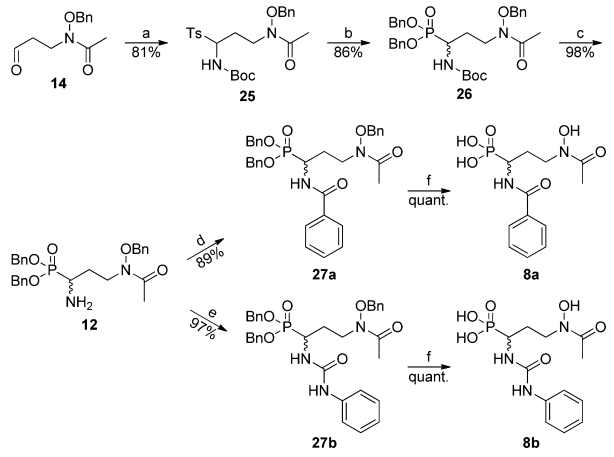


[a]Reagents and conditions: (a) $HPO(OEt)_2$, LiHMDS, THF, −78 °C; (b) PPh_3, DIAD, HN_3, toluene, rt; (c) BCl_3, CH_2Cl_2, −75 °C; (d) (i) TMSBr, BSTFA, MeCN, (ii) aq NH_4OH, MeCN.

reaction with diethyl phosphite afforded diethyl α-hydroxyphosphonate **22**, which was converted to the α-azide **23** as before. The retrohydroxamate moiety of **23** was first debenzylated with boron trichloride, followed by purification of **24** on deactivated silica gel prior to removal of the phosphonate esters by trimethylsilyl bromide in acetonitrile and basic workup, yielding α-azido-**2** (**9**) as a bisammonium salt.

The synthesis of the α-N-based analogues (Scheme 4) started from the benzyl protected α-Boc-amino-**2** (**26**),

Scheme 4. Synthesis of α-*N*-Based Analogues[a]



[a]Reagents and conditions: (a) Na-*p*-toluenesulfinate, *t*-butylcarbamate, HCOOH, THF, MeCN, H_2O, rt, overnight; (b) $HPO(OBn)_2$, NaH, THF, rt; (c) TFA, CH_2Cl_2, 0 °C; (d) BzCl, DMAP, Et_3N, CH_2Cl_2; (e) phenylisocyanate, DMAP, Et_3N, CH_2Cl_2; (f) Pd/C, H_2, MeOH/H_2O/*t*-BuOH.

prepared in two steps as described by Klepacz et al.[22] First, aldehyde **14** was subjected to a three-component reaction with *t*-butylcarbamate and sodium *p*-toluenesulfinate and the resulting sulfone **25** was displaced with dibenzyl phosphite. The Boc-protecting group of **26** and was removed, and amine **12** was used without further purification. Although numerous alternatives for the synthesis of α-aminophosphonates are known, such as a Kabachnik−Fields reaction with HMDS or ammonium carbonate (which only gave marginal results in our hands) or the evident Staudinger reduction of azide **20** (which would be less economic), this method benefits from high yields and easy purification. Conversion of amine **12** into benzamide **27a** and phenylurea **27b** was carried out under standard conditions.

The use of only benzyl protecting groups allowed mild final deprotection upon hydrogenation on palladium on carbon. However, we noticed the importance of avoiding the use of standard metal hydrogenation needles, as metal ions were found to poison the reaction. Therefore, hydrogen gas was bubbled into the reaction mixture through a glass capillary, resulting in clean formation of **8a**, **8b**, and **11b**. During deprotection of analogues **21a,c**, acid-mediated breakdown of the retrohydroxamic acid moiety was observed. This problem was solved by using catalytic transfer hydrogenation with ammonium formate as the hydrogen donor, whereby ammonium neutralized the formed phosphonates. Excess ammonium formate was removed by lyophilization, yielding **11a,c** as monoammonium salts.

The final compounds were tested for their inhibition of *Escherichia coli* DXR activity in a spectrophotometric assay by monitoring the reduction of NADPH in $NADP^+$. Inhibition constants for all analogues as well as reference **2** are shown in Table 1.

Table 1. K_i Values on *E. coli* DXR (or % Inhibition at 100 nM) and in Vitro Growth Inhibition of the *P. falciparum* Strain K1

compd	IC_{50} (nM) *E. coli* DXR	IC_{50} (μM) Pf-K1
2	15.11	0.42
8a	(1.42%)	49.02
8b	(1.30%)	>64
9	74.6	1.98
10a	52.2	1.82
10b	(4.14%)	4.00
10c	n.i.	13.02
11a	(3.32%)	8.96
11b	207.3	7.76
11c	1129	2.75

Remarkably, potent DXR inhibition is conferred to analogues with small substituents (azido and hydroxy) in α-position. In light of the appreciable DXR affinity obtained with α phenylpyridyl substituents,[13] we were surprised to see that none of the α-triazoles showed appreciable inhibitory activity. Possibly the triazole ring is too electron rich to form strong π-stacking with Trp211 described in this study.

Docking of both enantiomers of **9** into PfDXR suggests an interaction between the azide group and Trp296 (Figure 1, Supporting Information (SI)). The vicinity of an azido group and an indole has been found in 15 structures in the Cambridge Structure Database, suggesting they may form favorable interactions. A similar experiment for both enantiomers of **10a** resulted in poses that place the OH group in H-Bond distance to Glu233 for the *R*-enantiomer and Ser306 for the *S*-enantiomer (Figures 2 and 3, SI).

Several compounds show high potency in the low micromolar range when assayed against *P. falciparum* K1 in human erythrocytes. Strikingly, there's no clear correlation between the enzyme inhibition constants and *P. falciparum* inhibition concentrations. Besides other possible factors such as off-target effect, the considerable degree of species DXR inhibitory

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specificity, recently demonstrated by the Kurz group,[13] may account for this phenomenon.

EXPERIMENTAL SECTION

General Methods and Materials. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded in $CDCl_3$, CD_3OD, acetone-d_6, DMSO-d_6, or D_2O on a Varian Mercury 300 spectrometer. Chemical shifts are given in parts per million (ppm) (δ relative to TMS for ^{1}H and ^{13}C and to external D_3PO_4 for ^{31}P). All solvents and chemicals were used as purchased unless otherwise stated. Purity of the final compounds was assessed by RP-LC-DAD-MS, using a Phenomenex Luna C-18 2.5 μm particle (100 mm × 2.00 mm) column in a Waters Alliance 2695 XE HPLC system with quaternary pump, coupled to a DAD detector and a Waters LCT Premier XE orthogonal time-of-flight spectrometer with API-ES source with a H_2O/CH_3CN gradient with 0.05% HCOOH. All the compounds showed purity above 95%.

Dibenzyl 3-(*N*-(Benzyloxy)acetamido)-1-hydroxy-propyl-phosphonate (13). Dibenzyl phosphite (4330 mg, 16.5 mmol) was dissolved in THF (20 mL), the solution was cooled to −78 °C, and LiHMDS (15 mL of a 1 M solution in THF) was added slowly. After 15 min, a solution of aldehyde **14** (3320 mg, 15 mmol) in 30 mL of dry THF was added via syringe and the ice bath was removed. After another 15 min of stirring, the reaction mixture had warmed up to room temperature, at which point it was quenched by the addition of saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The resulting crude mixture was purified by dry column vacuum chromatography with a gradient of ethyl acetate in toluene containing 0.1% formic acid to yield 5.22g (72%) of **13** as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85−2.03 (m, 1 H), 2.05 (s, 3 H), 2.07−2.25 (m, 1 H), 3.56−3.72 (m, 1 H), 3.83−3.96 (m, 1 H), 4.05 (br s, 1 H), 4.57 (br s, 1 H), 4.71−4.85 (m, 2 H), 4.98−5.14 (m, 4 H), 7.11−7.42 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.32, 29.21, 42.09, 65.02 (d, $^{1}J_{C-P}$ = 167.0 Hz), 68.01 (d, $^{2}J_{C-P}$ = 5.8 Hz), 68.10 (d, $^{2}J_{C-P}$ = 5.8 Hz), 76.43, 127.92, 128.31, 128.50, 128.70, 128.99, 129.19, 134.12, 136.22 (d, $^{3}J_{C-P}$ = 2.2 Hz), 136.3 (d, $^{3}J_{C-P}$ = 2.2 Hz), 173.12. HRMS (ESI): calcd for $C_{26}H_{30}NO_6P + H^+$, 484.1884; found $[(M + H)^+]$, 484.1852.

3-(*N*-Hydroxyacetamido)-1-hydroxypropyl-phosphonic Acid, Ammonium Salt (10a). A mixture of **13** (261 mg, 0.54 mmol), ammonium formate (520 mg, 8.10 mmol) and 10% Pd/C in MeOH (10 mL) was heated at reflux for 20 min, followed by filtration over a glass microfiber pad. The filter was rinsed with methanol and water, and the filtrate was concentrated in vacuo. The resulting residue was lyophilized from a mixture of water and *t*-BuOH to give the product as an extremely hygroscopic resinous solid in quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 1.67−1.98 (m, 1 H), 2.13 (s, 4 H), 3.46−3.80 (m, 2 H), 3.80−4.12 (m, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 20.64, 30.98, 46.70 (d, J = 14.9 Hz), 67.99 (d, J = 157.8 Hz). ^{31}P NMR (121 MHz, CD_3OD) δ 19.86. HRMS (ESI): calcd for $C_5H_{12}NO_6P - H^+$, 212.0329; found $[(M - H)^+]$, 212.0351.

3-(*N*-Hydroxyacetamido)-1-azidopropylphosphonic Acid, Bisammonium Salt (9). 24 (165 mg, 0.561 mmol) was coevaporated with toluene (3 × 10 mL), taken up in acetonitrile (5 mL), and BSTFA (600 μL, 2.24 mmol) added. After 15 min of stirring at rt, an ice bath was installed and TMSBr (2.5 mL, 19 mmol) was added. The ice bath was removed after 10 min, and the reaction was stirred further at room temperature until, after 2.5 h, ^{31}P NMR confirmed that the starting phosphonate was completely deprotected (shift from δ = 23−3 ppm). All volatiles were removed in vacuo, followed by coevaporation with toluene (3 × 10 mL). The resulting oil was taken up in acetonitrile, concentrated ammonia was added, and the mixture was stirred at room temperature for 30 min and evaporated to give the crude material as a brown oil. This was dissolved in methanol, decolorized over activated carbon, and lyophilized from water to give the product as a hygroscopic resin in quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 1.63−1.87 (m, 1 H), 2.03−2.35 (m, 4 H), 3.18−3.37 (m, 1 H), 3.45−3.69 (m, 1 H), 3.88−4.11 (m, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 20.57, 28.60, 46.73 (d, J = 13.0 Hz), 59.09 (d, J = 143.5 Hz), 173.94. ^{31}P NMR (121 MHz, CD_3OD) δ 16.45. HRMS (ESI): calcd for $C_5H_{11}N_4O_5P - H^+$, 237.0394; found $[(M - H)^+]$, 237.0423.

3-(*N*-Hydroxyacetamido)-1-(benzamido)propyl-phosphonic Acid (8a). To a solution of **27a** (309 mg, 0.53 mmol) in a mixture of MeOH−H_2O−*t*-BuOH (10 mL) was added 10% Pd/C. Hydrogen gas was bubbled through via a glass capillary at atmospheric pressure for 3.5 h, after which the reaction mixture was filtered and concentrated in vacuo. The residue was taken up in *t*-BuOH, frozen, and lyophilized to give the product as a white foam in quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 1.72−2.11 (m, 3 H), 2.42 (ddd, J = 14.2, 6.6, 3.2 Hz, 1 H), 3.52−3.79 (m, 1 H), 3.90 (d, J = 4.7 Hz, 1 H), 4.34 (t, J = 12.6 Hz, 1 H), 7.23−7.51 (m, 5 H), 7.61 (d, J = 7.0 Hz, 1 H). ^{13}C NMR (75 MHz, CD_3OD) δ 21.53, 26.55, 30.04, 44.60 (d, J = 155.91 Hz), 129.90, 128.12, 130.33, 134.59, 172.20. ^{31}P NMR (121 MHz, CD_3OD) δ 22.53. HRMS (ESI): calcd for $C_{12}H_{17}N_2O_6P - H^+$, 315.0751; found $[(M - H)^+]$, 315.0767.

ASSOCIATED CONTENT

Supporting Information

Docking data for analogues **9** and **10a**, additional experimental data, and ^{1}H NMR and ^{31}P spectra for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

CuAAC, copper catalyzed azide−alkyne cycloaddition; DEAD, diethyl azodicarboxylate; DIAD, di-isopropyl azodicarboxylate; DOXP, 1-deoxy-D-xylulose-5-phosphate; DXR, 1-deoxy-D-xylulose-5-phosphate reductoisomerase; EcDXR, *Escherichia coli* 1-deoxy-D-xylulose-5-phosphate reductoisomerase; HMDS, bis-(trimethylsilyl)amine; MEP, 2-*C*-methyl-D-erythritol-3-phosphate; SAR, structure−activity relationship; TMSBr, bromotrimethylsilane; TLC, thin layer chromatography

REFERENCES

(1) *World Malaria Report 2011*; World Health Organization: Geneva, Dec 2011.

(2) Wiesner, J.; Jomaa, H. Isoprenoid biosynthesis of the apicoplast as drug target. *Curr. Drug Targets* **2007**, *8*, 3−13.

(3) Hemmi, K.; Takeno, H.; Hashimoto, M.; Kamiya, T. Studies on Phosphonic Acid Antibiotics. 4. Synthesis and Antibacterial Activity of Analogs of 3-(*N*-Acetyl-*N*-hydroxyamino)-propylphosphonic Acid (FR-900098). *Chem. Pharm. Bull.* **1982**, *30*, 111−118.

(4) Borrmann, S.; Adegnika, A.; Matsiegui, P.; Issifou, S.; Schindler, A.; Mawili-Mboumba, D.; Baranek, T.; Wiesner, J.; Jomaa, H.; Kremsner, P. Fosmidomycin−clindamycin for *Plasmodium falciparum* infections in African children. *J. Infect. Dis.* **2004**, *189*, 901−908.

(5) Borrmann, S.; Issifou, S.; Esser, G.; Adegnika, A.; Ramharter, M.; Matsiegui, P.; Oyakhirome, S.; Mawili-Mboumba, D.; Missinou, M.; Kun, J.; Jomaa, H.; Kremsner, P. Fosmidomycin−clindamycin for the

treatment of *Plasmodium falciparum* malaria. *J. Infect. Dis.* **2004**, *190*, 1534−1540.
(6) Jackson, E. R.; Dowd, C. S. Inhibition of 1-Deoxy-D-Xylulose-5-Phosphate Reductoisomerase (Dxr): A Review of the Synthesis and Biological Evaluation of Recent Inhibitors. *Curr. Top. Med. Chem.* **2012**, *12*, 706−728.
(7) Haemers, T.; Wiesner, J.; Van Poecke, S.; Goeman, J.; Henschker, D.; Beck, E.; Jomaa, H.; Van Calenbergh, S. Synthesis of alpha-substituted fosmidomycin analogues as highly potent *Plasmodium falciparum* growth inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1888−1891.
(8) Kurz, T.; Schluter, K.; Kaula, U.; Bergmann, B.; Walter, R.; Geffken, D. Synthesis and antimalarial activity of chain substituted pivaloyloxymethyl ester analogues of Fosmidomycin and FR900098. *Bioorg. Med. Chem.* **2006**, *14*, 5121−5135.
(9) Deng, L. S.; Sundriyal, S.; Rubio, V.; Shi, Z. Z.; Song, Y. C. Coordination Chemistry Based Approach to Lipophilic Inhibitors of 1-Deoxy-D-xylulose-5-phosphate Reductoisomerase. *J. Med. Chem.* **2009**, *52*, 6539−6542.
(10) Deng, L. S.; Diao, J. S.; Chen, P. H.; Pujari, V.; Yao, Y.; Cheng, G.; Crick, D. C.; Prasad, B. V. V; Song, Y. C. Inhibition of 1-Deoxy-D-Xylulose-5-Phosphate Reductoisomerase by Lipophilic Phosphonates: SAR, QSAR, and Crystallographic Studies. *J. Med. Chem.* **2011**, *54*, 4721−4734.
(11) Deng, L. S.; Endo, K.; Kato, M.; Cheng, G.; Yajima, S.; Song, Y. C. Structures of 1-Deoxy-D-Xylulose-5-Phosphate Reductoisomerase/Lipophilic Phosphonate Complexes. *ACS Med. Chem. Lett.* **2011**, *2*, 165−170.
(12) Andaloussi, M.; Henriksson, L. M.; Wieckowska, A.; Lindh, M.; Bjorkelid, C.; Larsson, A. M.; Suresh, S.; Iyer, H.; Srinivasa, B. R.; Bergfors, T.; Unge, T.; Mowbray, S. L.; Larhed, M.; Jones, T. A.; Karlen, A. Design, Synthesis, and X-ray Crystallographic Studies of alpha-Aryl Substituted Fosmidomycin Analogues as Inhibitors of *Mycobacterium tuberculosis* 1-Deoxy-D-xylulose 5-Phosphate Reductoisomerase. *J. Med. Chem.* **2011**, *54*, 4964−4976.
(13) Behrendt, C. T.; Kunfermann, A.; Illarionova, V.; Matheeussen, A.; Pein, M. K.; Grawert, T.; Kaiser, J.; Bacher, A.; Eisenreich, W.; Illarionov, B.; Fischer, M.; Maes, L.; Groll, M.; Kurz, T. Reverse fosmidomycin derivatives against the antimalarial drug target IspC (Dxr). *J. Med. Chem.* **2011**, *54*, 6796−802.
(14) Schluter, K.; Walter, R. D.; Bergmann, B.; Kurz, T. Arylmethyl substituted derivatives of Fosmidomycin: synthesis and antimalarial activity. *Eur. J. Med. Chem.* **2006**, *41*, 1385−97.
(15) Kurz, T.; Schluter, K.; Pein, M.; Behrendt, C.; Bergmann, B.; Walter, R. D. Conformationally restrained aromatic analogues of fosmidomycin and FR900098. *Arch. Pharm.* **2007**, *340*, 339−44.
(16) Verbrugghen, T.; Cos, P.; Maes, L.; Van Calenbergh, S. Synthesis and Evaluation of α-Halogenated Analogues of 3-(Acetylhydroxyamino)propyl Phosphonic Acid (FR900098) as Antimalarials. *J. Med. Chem.* **2010**, *53*, 2342−2346.
(17) Sulsky, R.; Demers, J. P. Alkylation of *N*-Benzyloxyureas and Carbamates. *Tetrahedron Lett.* **1989**, *30*, 31−34.
(18) Nazih, A.; Heissler, D. One-pot conversion of *t*-butyl carbamates to amides with acyl halide−methanol mixtures. *Synthesis* **2002**, 203−206.
(19) Lepore, S. D.; He, Y. Use of sonication for the coupling of sterically hindered substrates in the phenolic Mitsunobu reaction. *J. Org. Chem.* **2003**, *68*, 8261−8263.
(20) Palacios, F.; Deretana, A. M. O.; Pagalday, J. Synthesis of Diethyl 1,2,3-Triazolealkylphosphonates through 1,3-Dipolar Cycloaddition of Azides with Acetylenes. *Heterocycles* **1994**, *38*, 95−102.
(21) Hansen, S. G.; Jensen, H. H. Microwave Irradiation as an Effective Means of Synthesizing Unsubstituted N-Linked 1,2,3-Triazoles from Vinyl Acetate and Azides. *Synlett* **2009**, 3275−3278.
(22) Klepacz, A.; Zwierzak, A. An expeditious one-pot synthesis of diethyl *N*-Boc-1-aminoalkylphosphonates. *Tetrahedron Lett.* **2002**, *43*, 1079−1080.