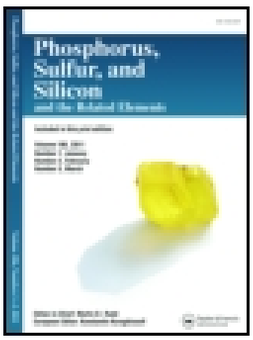

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SHORT COMMUNICATION

Synthesis of ortho-formylphenylphosphonic acids as covalent probes of active site lysines

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ABSTRACT

During the course of an investigation of targeted inhibition of DNA polymerase beta (pol β) lyase activity using small molecules, we observed the formation of an aldimine between (2-formyl)phenylphosphonic acid (2FPP) and butylamine under basic aqueous conditions; complete deprotonation of the phosphonate group was required to stabilize the imine product. Results of computational docking studies suggested that the reaction of Lys-72 on the lyase active site with an aldehyde group could be facilitated by a proximal phosphonate, not only because of the phosphonate's ability to mimic phosphate interacting with the DNA binding site, but also because of its ability to shield the imine against hydrolysis. Novel pol β lyase inhibitors were thus prepared using a 2FPP analogue with an amine linker; P-C bond formation in synthesis of this intermediate was possible with an unprotected aldehyde using palladium-catalyzed, microwave-assisted Michaelis–Arbuzov chemistry. These compounds, and structurally related derivatives lacking the aldehyde or phosphonate, were evaluated in an assay for pol β to assess their potential for inhibition.

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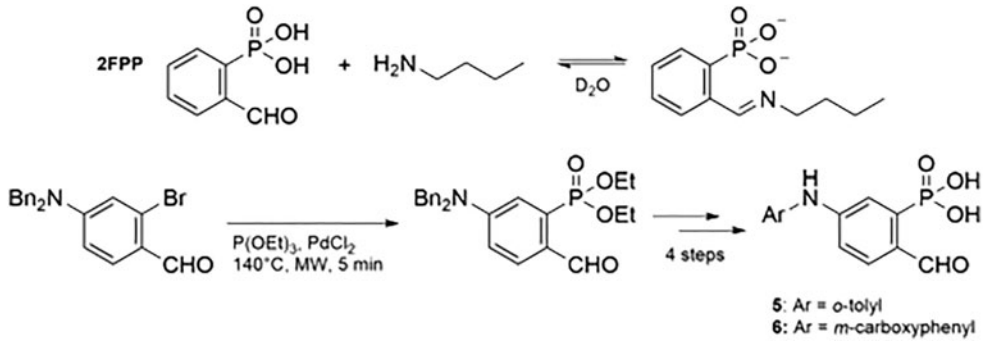
KEYWORDS
DNA polymerase; lyase; phosphonate; inhibitor

GRAPHICAL ABSTRACT



Results and discussion

Based on preliminary computational covalent docking studies, we hypothesized that incorporating an aldehyde *ortho* to a phosphonate on a diphenylamine scaffold might mimic deoxyribose-5-phosphate and could provide enhanced inhibition of DNA polymerase β (pol β) lyase activity through the formation of a covalent bond with Lys-72 on the active site. To confirm the formation of such imines, we performed NMR studies of the reaction between butylamine and 2-formylphenylphosphonic acid (2FPP). Here, we describe the first reported synthesis of 2FPP (Scheme 1); the key step is a palladium-catalyzed, microwave-assisted Michaelis–Arbuzov-like reaction[1–2] which afforded 2FPP diethyl ester (**1**) in good yield even in the presence of an unprotected aldehyde. Dealkylation with bromotrimethylsilane (BTMS) yielded 2FPP; all compounds were characterized spectroscopically. NMR studies showed that in aqueous media, an alkaline pH drives formation of a stable aldimine between 2FPP and butylamine (68% conversion by ^{31}P NMR in D_2O, pD 10.9); the imine concentration is decreased by dilution or acidification with $NaHSO_4$. The phosphonate *ortho* to the aldehyde of 2FPP is expected to be fully deprotonated above pH 8, suggesting that its negative charge may play a role in shielding the imine against hydrolysis.

2FPP-based pol β inhibitors **5** and **6** were synthesized via the amino derivative **4** (Scheme 2) from aryl bromide **3**. Results of preliminary assays for pol β lyase inhibition show

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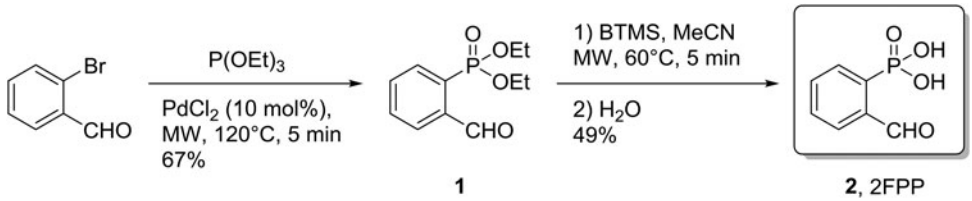
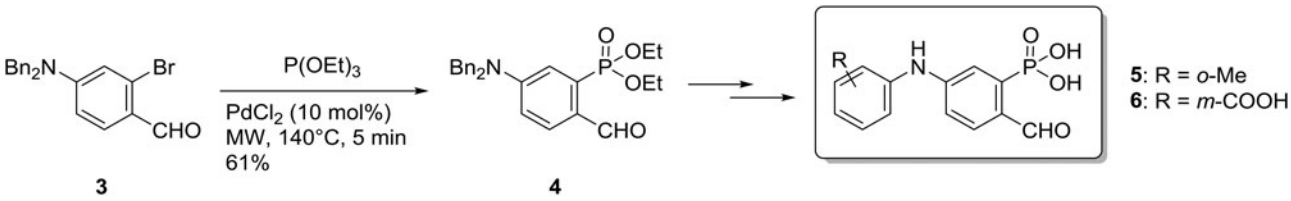


Scheme 1. Microwave-assisted synthesis of 2FPP.



Scheme 2. Synthesis of novel pol β inhibitors.

that these "rationally designed" compounds are significantly more potent than pamoic acid, a known pol β inhibitor.[3] However, further investigation will be required to determine the underlying mechanism in terms of a covalent vs. non-covalent interaction with the enzyme.

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