Prodrugs of a Subnanomolar Inhibitor of Dehydroquinate Synthase

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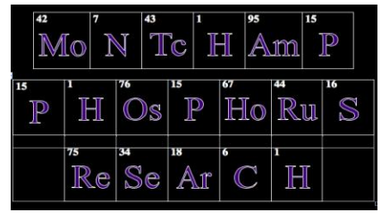
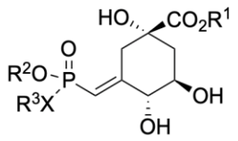


Introduction:

The World Health Organization has identified antimicrobial resistance as one of the top 10 global health threats, highlighting the urgent need for new antimicrobials with novel mechanisms of action. One promising strategy is to target the aromatic amino acid biosynthesis pathway, which is essential in bacteria and plants but absent in mammals. As a result, targeting this pathway is expected to minimize toxicity in humans.

Previously, Dr. Montchamp synthesized several potent inhibitors of the enzyme 3-dehydroquinate synthase (DHQS), the second enzyme in the shikimate pathway responsible for aromatic amino acid biosynthesis.[1] DHQS catalyzes the conversion of 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP, K_m = 4 μM) to 3-dehydroquinate (DHQ). Among these inhibitors, compound **1**, a vinylphosphonate compound, was selected as the lead compound for this study (K_i = 0.29 nM). However, compound **1** is highly hydrophilic, limiting its ability to efficiently cross cell membranes. To address this limitation, prodrug strategies were explored.[2] Prodrugs can mask charged functional groups, improving membrane permeability and enabling biological activity in vivo. Therefore, compound **1** serves as a precursor for the development of prodrug derivatives.

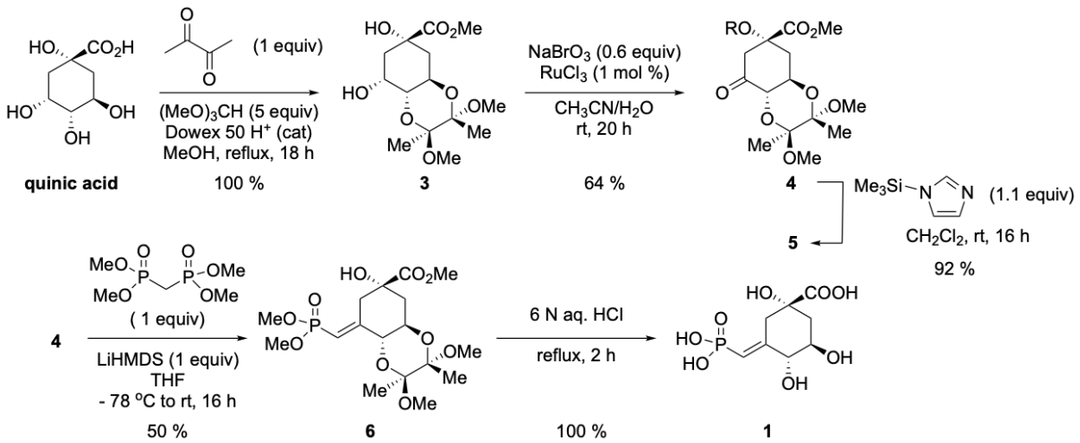
In this project, the lead inhibitor was re-synthesized,[3] and multiple approaches for preparing prodrug derivatives were investigated. Additionally, the synthesis of prodrugs for related compounds was explored.



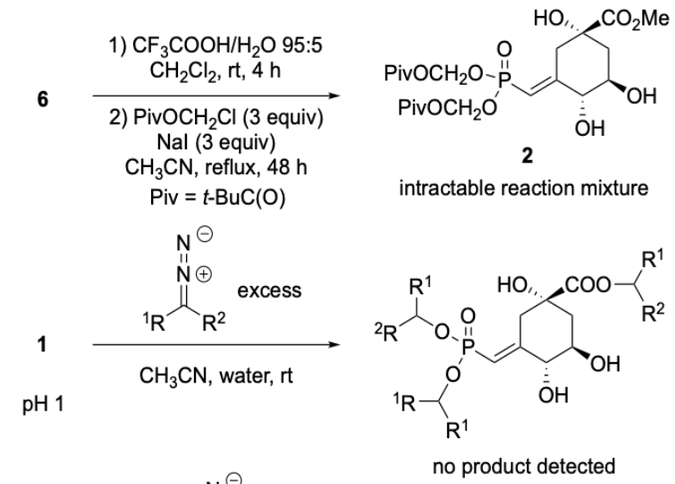
1 $R^1 = R^2 = R^3$ = H, X = O
2 R^1 = Me, $R^2 = R^3$ = POM, X = O
R^1 = Me, $R^2 = R^3$ = SATE, X = O
R^1 = H, $R^2 = R^3$ = SATE, X =O
$R^1 = R^2 = R^3$ = POM, X = O
R^1 = Me, R^2 = Ph, R^3 = $MeOCOCH_2$, X = N
R^1 = H, R^2 = 1-naphthyl, R^3 = $MeOCOCH_2$, X = N

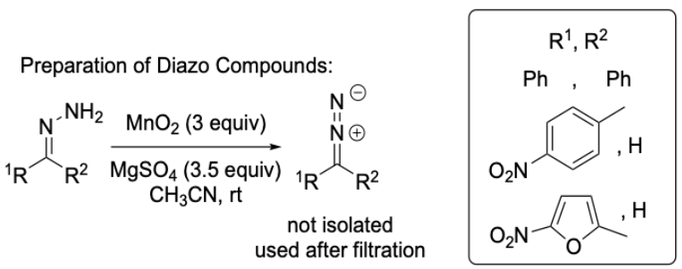
POM = $CH_2OC(O)t$-Bu
SATE = $CH_2CH_2SC(O)t$-Bu

Synthesis of Compound 1:



Attempted Synthesis of Prodrugs:



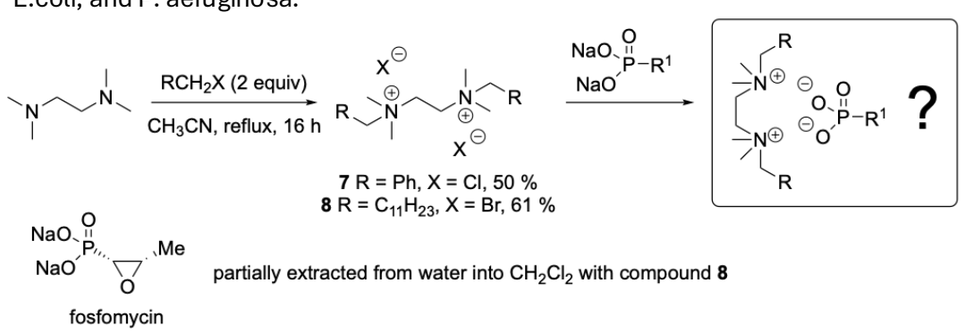


Conclusion:

The planned synthesis of prodrugs of compound **1** has been unsuccessful thus far. Attempts at preparing compound **2** using different reaction conditions are currently underway. Regardless, it is possible that this pathway is not a good target for antibacterial activity due to the possibility of amino acid salvage. The strategy to combine two antibacterial compounds as a double salt will be examined further.

Future Direction:

An alternative prodrug strategy for compound **1** was considered, in which a dication is paired with a dianionic phosphonate. Preliminary studies using the antibiotic fosfomycin disodium showed promising results. Compound **8** is reported to have an MIC below 4μg/mL on S. aureus, E. fecalis, E.coli, and P. aeruginosa.[4]



Acknowledgements:

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References:

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2. Wiemer, A. J.; Wiemer, D. F. Top. Curr. Chem. 2015, 360, 115-160.
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4. Black, J. W.; Jennings, M. C.; Azarewicz, J.; Paniak, T. J.; Grenier, M. C.; Wuest, W. M.; Minbiole, K. P. C. Bioorg. Med. Chem. Lett. 2014, 24, 99-102.