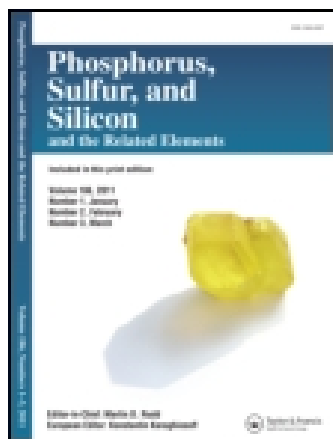


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### Synthesis and Biochemical Studies of Phosphorus-Based "Tetrahedral Mimics" as Inhibitors of ATP-Dependent Ligases

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# Synthesis and Biochemical Studies of Phosphorus-Based "Tetrahedral Mimics" as Inhibitors of ATP-Dependent Ligases

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The synthesis of several phosphapeptides and the biochemical evaluation of these compounds as inhibitors of glutathionylspermidine synthetase and folylpolyglutamate synthetase is described.

**Keywords:** ATP-dependent ligase; glutathionylspermidine; folylpolyglutamates; tetrahedral mimics; trypanothione

## RESULTS AND DISCUSSION

We have completed the synthesis of several phosphapeptides (1-3) as mimics of the putative tetrahedral intermediate involved in the reaction catalyzed by glutathionylspermidine (Gsp) synthetase (Figure 1). In the process, we have developed new synthetic methods for obtaining precursor phosphoamino acids and also three classes of phosphapeptides. Syntheses of these compounds involved the assembly of molecules containing a challenging array of functional groups with diverse, often conflicting chemical properties.<sup>1-3</sup> Schemes describing the successful synthetic routes are provided on the following pages (Figures 2-4).

In collaboration with Prof. Christopher Walsh's group at Harvard, we have evaluated the biochemical properties of these compounds as inhibitors of Gsp synthetase in comparison with the kinetic properties of similarly modified analogs of one of the

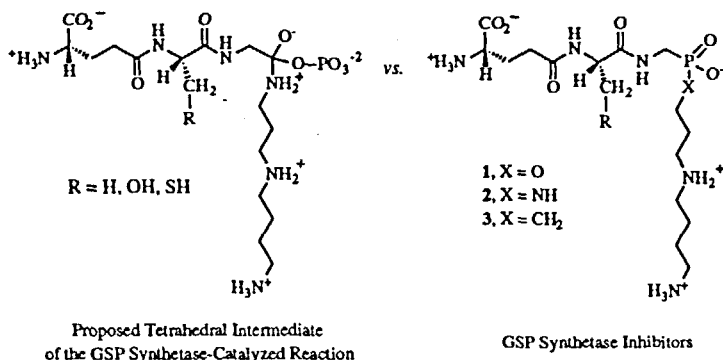


FIGURE 1 GSP Synthetase: Tetrahedral Intermediates vs. Tetrahedral Mimics

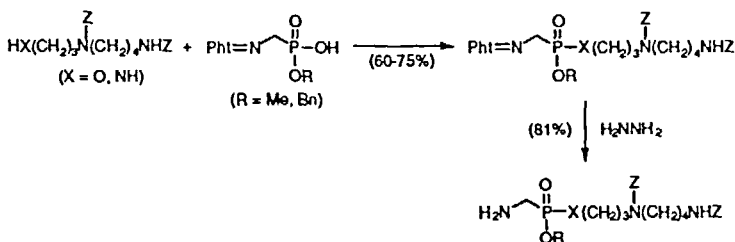


FIGURE 2 Synthesis of Phosphonate and Phosphonamidate Precursors

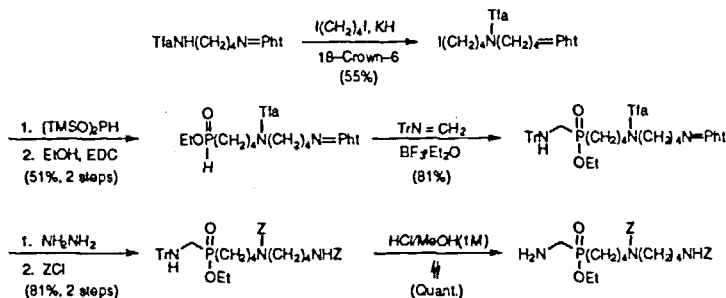


FIGURE 3 Synthesis of Phosphinate Precursors

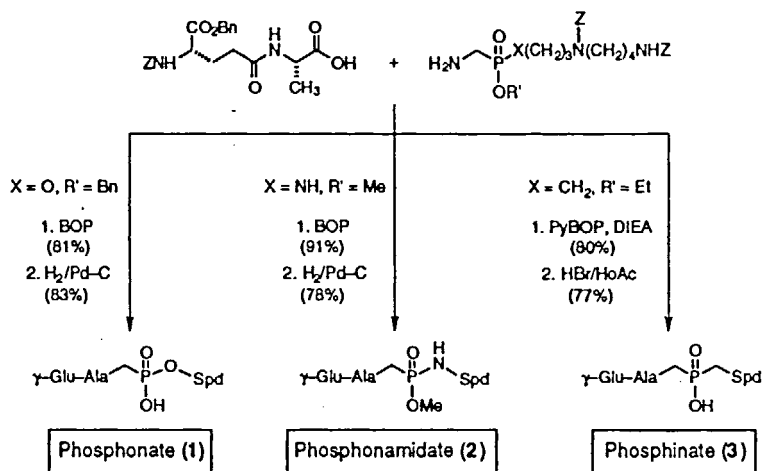
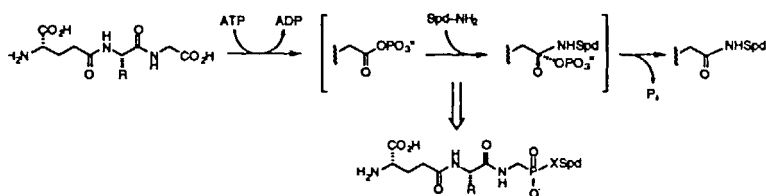


FIGURE 4 Synthesis of Phosphapeptide Tetrahedral Mimics

substrates, glutathione (GSH). The phosphapeptides, especially those in the phosphinate class (3) are potent inhibitors of Gsp synthetase (Table I). These data are summarized below (Table I).<sup>4-6</sup>

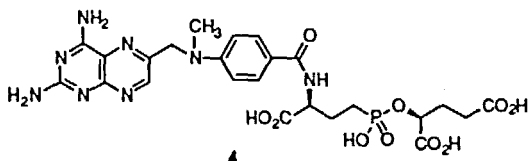
TABLE I Substrate and Inhibitor Kinetics - GSP Synthetase



R	$K_m$ , mM	$k_{cat}$ , s <sup>-1</sup>	X	$K_i$ , $\mu$ M	$K_i'$ , $\mu$ M	$K_i''$ , nM	ATP-depend.
CH <sub>3</sub>	10.0	6.4	O	6.0	14	—	No
CH <sub>3</sub>	—	—	NH <sup>a</sup>	24.0	—880	—	No
CH <sub>3</sub>	—	—	CH <sub>2</sub>	3.2	—	7.8	Yes
CH <sub>2</sub> OH	3.2	0.013	CH <sub>2</sub>	4.8	—	9.2	Yes
CH <sub>2</sub> SH	0.8	6.3	CH <sub>2</sub>	2.1	—	3.1	Yes

<sup>a</sup> Inhibitor assays with P-(OCH<sub>3</sub>) ester; free acid, P(OH), is unstable in aqueous media.

A second ATP-dependent ligase that has been investigated in our laboratory in collaboration with Dr. John McGuire, Roswell Park Cancer Institute, is folylpolyglutamate synthetase (FPGS), an enzyme of considerable importance in regulating the concentration and binding affinity of intracellular folates and antifolates. Research on the synthesis and phosphoamino acids and phosphapeptides related to glutamic acid and  $\gamma$ -glutamyl peptides<sup>7</sup> led to the synthesis of a **4**, a phosphonate analog of pteroylglutamate- $\gamma$ -glutamate.<sup>8</sup> This compound proved to be a potent inhibitor of FPGS ( $K_i = 46$  nM).



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