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# One-Pot Synthesis of an AZT Boranophosphate Conjugated with Tyrosine: A Potential Prodrug Candidate

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## One-Pot Synthesis of an AZT Boranophosphate Conjugated with Tyrosine: A Potential Prodrug Candidate

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#### ABSTRACT

A one-pot synthesis of *P*-tyrosinyl(*P*-*O*)-5'-*P*-AZT boranophosphate 7 via a phosphoramidite method is described. The P-boranophosphate diastereomers were separated by RP-HPLC, and their structures were confirmed by NMR and MS.

Key Words: Nucleotide prodrug; Boranophosphate; AZT; Tyrosine.

Most anti-HIV drugs targeted at reverse transcriptase are 2',3'-dideoxynucleoside (ddN) analogues. For example, 3'-azido-3'-deoxythymidine (AZT) was the first drug approved by the FDA for the treatment of HIV infection. In most cases, conversion of the nucleoside analogues to their 5'-monophosphates (ddNMPs) can be considered as the bottleneck in the overall metabolic pathway leading to the formation of the active 5'-triphosphate metabolites (ddNTP).<sup>[1]</sup> Therefore, prodrug approaches have been employed to design 2',3'-dideoxynucleoside 5'-monophosphates that will deliver the 5'-monophosphate derivatives into the HIV-affected cells.

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This process circumvents the initial nucleoside-kinase dependency step.<sup>[1]</sup> We propose to use nucleoside boranophosphate conjugated with tyrosine as a candidate for such a prodrug.

P-Tyrosinyl(P-O)-5'-P-AZT boranophosphate 7 was synthesized according to the following scheme using a phosphoramidite method. Commercially available tyrosine 1 was protected with a 4-nitrobenzyl group to give compound 2. Phosphoramidite 3 was formed by phosphitylating compound 2 with N, N, N', N'-tetraisopropylphosphane in the presence of 1H-tetrazole. After the reaction mixture was stirred for 40 min, AZT and another portion of 1H-tetrazole were added simultaneously to the mixture. The coupling reaction was completed in 15 min as monitored by <sup>31</sup>P NMR, in which the singlet at 148 ppm for phosphoramidite 3 disappeared and two new singlets, corresponding to the diastereomers of phosphotriester 4, appeared around 135 ppm. Phosphotriester 4 was then boronated with excess dimethyl sulfideborane to yield AZT boranotriester 5, which showed a characteristic broad peak centered at 116 ppm.<sup>[2]</sup> Compound 5 was then treated with concentrated NH<sub>4</sub>OH, hydrolyzing the cyanoethyl and 4-nitrobenzyl groups to yield boranophosphate 6. Further treatment of  $\mathbf{6}$  with trifluoroacetic acid in acetonitrile afforded the title compound P-tyrosinyl(P-O)-5'-P-AZT boranophosphate 7. The boron-modified P-diastereomers of 7 were separated in a 1:1 ratio by RP-HPLC on a C<sub>18</sub> column eluted with a 0.01 M solution of triethylammonium bicarbonate (TEAB) containing 15 to 25% acetonitrile; 7a (19.0 min) and 7b (19.8 min) were the faster and slower eluting diastereomers, respectively.



#### AZT Boranophosphate Conjugated with Tyrosine

In summary, we synthesized the first nucleoside boranophosphate conjugated with tyrosine by a one-pot reaction in good yield (from **2** to **7**, 42% yield). Introduction of a BH<sub>3</sub> group in such a conjugate is expected to confer on the conjugate good substrate properties<sup>[3]</sup> and to increase lipophilicity<sup>[3]</sup> and stability toward drug resistance,<sup>[4]</sup> relative to the unboronated prodrug.

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