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The first chemical synthesis of pyrazofurin 5′-triphosphate

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ABSTRACT

As an archetype *C*-nucleoside, pyrazofurin possesses broad-spectrum antiviral and antitumor activities. However, the presence of the acidic enol in the nucleobase of pyrazofurin poses a huge challenge to the conventional NTP synthetic methods. On the basis of a selective phosphoylation method and the P(V)-N activation strategy, the first chemical synthesis of pyrazofurin 5′-triphosphate (PTP) was accomplished, which will greatly facilitate the investigation on the interactions of viral RNA polymerases and PTP, an important cellular metabolite of pyrazofurin.

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Pyrazofurin, a naturally occurring *C*-nucleoside first isolated from the fermentation of a strain of *Streptomyces candidus* in 1969,[1] is a close structural analog of a natural imidazole nucleoside, bredinin,[2] and a synthetic triazole nucleoside drug, ribavirin (Figure 1).[3] As a microbial metabolite, pyrazofurin possesses broad-spectrum antiviral activities against both RNA and DNA viruses[4] and antitumor properties.[5]

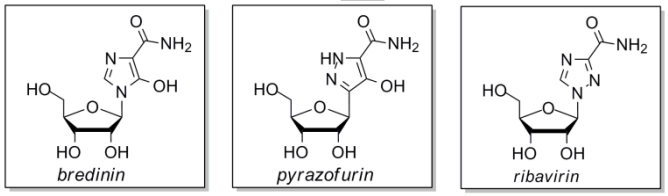

Figure 1. Structures of pyrazofurin and its analogs

In cellular metabolism, both pyrazofurin and ribavirin are converted to their monophosphates and triphosphates.[6-7] Early research on the mechanism of action of the two antiviral agents showed that pyrazofurin 5′-monophosphate (PMP) and ribavirin 5′-monophosphate (RMP) inhibit the orotidine 5′-monophosphate (OMP) decarboxylase[8] and inosine 5′-monophosphate (IMP) dehydrogenase,[9] respectively, and thus block the *de novo* pyrimidine and purine biosynthesis. In 2000, with the assistance of synthetic ribavirin 5′-triphosphate (RTP), Cameron and his coworker were able to investigate the interactions of RTP with viral RNA polymerases on the basis of a novel primer-extension assay and found that non-specific incorporation of ribavirin into viral genome leads to lethal mutagenesis of virus population.[10-12] Similarly, in the mechanistic investigation of T-705, a pyrazine nucleoside drug (favipiravir), synthetic T-705 5′-triphosphate (T-705TP) helped Furuta and coworkers reveal that the drug's antiviral activity comes from the inhibition of influenza virus RNA polymerase by T-705TP.[13] In contrast, due to the unique enol-containing nucleobase in pyrazofurin, the chemical synthesis of pyrazofurin 5′-triphosphate (PTP) has always been an unsolved problem for phosphorus chemists. But it can be envisioned that the availability of synthetic PTP will help virologists and medicinal chemists elucidate the potential roles of PTP in halting virus replication and develop effective antiviral strategies.

In recent years, our research group reported the P(V)-N activation strategy for the synthesis of nucleoside polyphosphates,[14-15] nucleoside diphosphate sugars,[16] and dinucleoside polyphosphates.[17] The high coupling efficacy and tolerance of diverse functional groups on nucleobases offer an ideal approach to PTP. We report herein the first chemical synthesis of PTP from the corresponding pyrazofurin 5′-monophosphate, which was efficiently prepared from isopropylidene-protected pyrazofurin via selective phosphorylation without enol protection.

Due to the poor commercial availability of pyrazofurin, we first synthesized the isopropylidene-protected pyrazofurin (**10**) according to a known synthetic route.[18-20] The detailed synthetic methods of certain steps were optimized to improve the practicability (Scheme 1). First, D-ribose (**1**) was treated with catalytic amount of *p*-TsOH in 2,2-dimethoxypropane and acetone. But the yield of 2,3-*O*-isopropylidene-D-ribose (**2**) was only around 70%.[21] Instead, the application of 5 mol‰ $Hf(OTf)_4$ as the catalyst afforded **2** in 93% yield within 30 min.[22] Direct tritylation of the 5-OH of **2** with TrCl in refluxing pyridine