Introduction of Purine Analog Benzimidazole into Nucleoside by Acid Metabolic Enzyme

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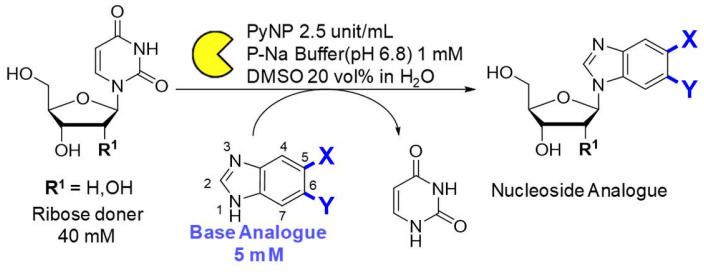
With bioactivity, unnatural nucleoside is used as an antiviral agent and anticancer. However, organic synthesis of the unnatural nucleoside tends to be lower yields. Our laboratory has been considering a way to efficiently synthesize unnatural nucleosides based on a nucleic-acid metabolism enzyme. First, the base exchange reaction using thymidine and benzimidazole as pseudo-base instead of purine was examined by PyNP, and then the maximum conversion of unnatural nucleosides in which benzimidazole was introduced into the base site of nucleosides was 99%. Next, the base exchange reaction was carried out with 2,3-dimethylbenzimidazole having a methyl group at the 2 and 3 positions of the benzene ring of benzimidazole. The conversion of this reaction was 99%. The substrate recognition ability of the benzene ring moiety of the benzimidazole was predicted to be low, and a catalytic reaction was carried out with 2,3-naphthoimidazole in which one benzene ring was extended with respect to benzimidazole. As a result, PyNP was able to exchange the base site of thymidine to produce a compound having 2,3-naphthoimidazole at the base site of the nucleoside at high conversion (99%). We considered that the imidazole moiety is very important for the substrate specificity of PyNP. Therefore, we tried to react with 4-phenylimidazole and thymidine with PyNP. We reveal that this enzymatic reaction rate was very slow, but the reaction conversion was very high (99 %). This study considered introducing various modified benzimidazole compounds, into the nucleoside structure.



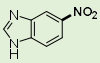
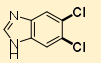
Compound		R^1	Max Conv. [%]	V_0 [mM/h]
1		-H	99	**0.96**
		-OH	99	0.037
2		-H	95	**0.024**
		-OH	(15)	0.00017
3		-H	99	0.26
		-OH	99	**0.27**

Figure 1 Substrate reactivity for modified benzimidazole

KEYWORDS
Pyrimidine nucleoside phosphorylase, Nucleoside Metabolic Enzyme, Unnatural nucleoside