GS04-4 **Structural-based drug design and synthesis of novel multisubstrate analoue inhibitors against PNP**

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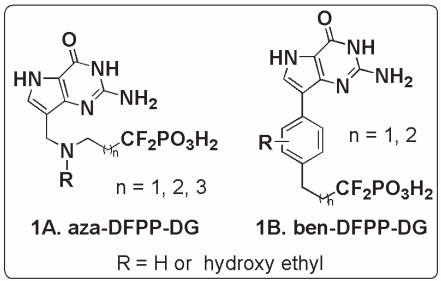
Introduction : Purine nucleoside phosphorylase (PNP) is a ubiquitous enzyme of purine metabolism that functions in the salvage pathway, and it is deeply related to the synthesis of DNA and RNA in T-cell. Inhibitors of PNP may be useful in the treatment of various autoimmune diseases, other T-cell proliferative disorders, and T-cell cancers. In our previous studies, we have designed and synthesized 9-(5',5'difluoro-5'-phosphono pentyl)-9-deazaguanine (**DFPP-DG**) as a multi-substrate analogue inhibitor against PNP. On the basis of X-ray differentiation data for a binary complex of **DFPP-DG** with calf-spleen PNP, we newly designed novel **DFPP-DG** analogues (**1A**, **1B**) for improvement of the inhibitory activity.



Result : We believed that analogues **1A** and **1B** colud be synthesized by ligation reaction of 9-deazaguanine (**9-DG**) derivatives and difluoromethylene phosphonic acid (**DFMP**) derivatives. Analogues **1A** were synthesized by several steps reactions after reductive amination between **9-DG** derivatives (R_2 = CHO) and azide alkyl units having a **DFMP** ester. Precursors of **1B** were synthesized by Suzuki-Miyaura coupling between **9-DG** derivatives (R_2 = I) and boronic acids having a **DFMP** ester. Synthetic methods of **1A** , **1B** and inhibitory activities of **1A** will be reported in this presentation.