Development of reactive OFF-ON type alkylating agents based on pyrimidine structure

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Alkylating reagents which can irreversibly modify biomolecules such as nucleic acids have been widely studied throughout medicinal history. For example, DNA alkylating agents were used in chemotherapy for cancer treatments. However, the lack of selectivity can cause off-target effect and lead to adverse side effects. Higher-ordered structure motifs of nucleic acids, such as G-quadruplex (G4), are important research targets since these structures are considered to play critical roles in gene regulation thus became a significant target for small-molecule intervention.

We previously developed the OFF-ON type vinyl-quinazolinone (VQ) as chemically reactive moiety and its precursors (VQ-X) and found the selective alkylation reactivity towards G4 structure by tethering VQ with acridine binder (Fig-A).[1,2)] Besides, it was suggested that the leaving groups played a dominant role for alkylation rate. After leaving groups screening, S(O)Me and NMe_2 showed the good reactivity.

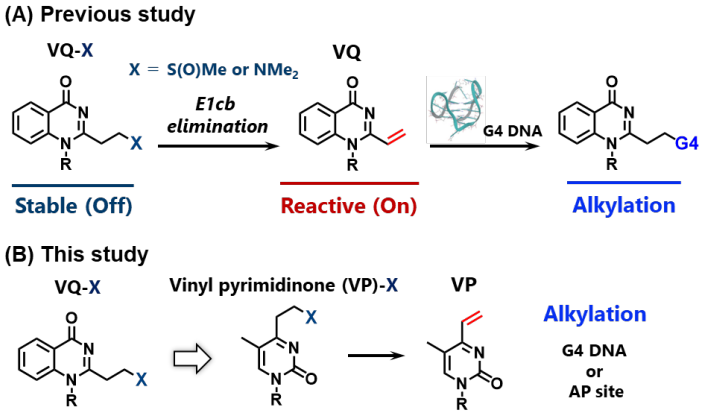

Figure. (A) Previous alkylating moiety.
(B) Newly designed alkylating moiety.

In this study, we designed a simple alkylator, Vinyl pyrinidinone-X (VP-X) based on the pyrimidine structure to reduce the size of the alkylating moiety (Fig-B). VP-X with acridine binder was successfully synthesized and the alkylation properties were investigated. VP-S(O)Me showed the good reactivity to G4 DNA and T base in AP site. In this presentation, we will report the molecular design, synthesis, and alkylation results in detail.

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2) Y. Chen, K. Onizuka, M. E. Hazemi, F. Nagatsugi, *Bioconjugate Chem.* **2022**, *33*, 2097-2102.