Development of novel OFF-ON type alkylating reagents

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Alkylating reagents which can irreversibly modify biomacromolecules such as proteins and nucleic acids have been widely studied and utilized throughout medicinal history. DNA alkylating reagents were extensively used in chemotherapy for treating cancer. Their potent efficacy is largely attributed to the efficient suppression on functional target molecules. Meanwhile, the lack of selectivity can cause off-target effect and generate adverse side effect. Accordingly, it is challenging to develop novel alkylating reagents which react in a more controllable way for drug discovery.

The conjugation of alkylating warhead with specific binding molecule is a promising approach to increase the selectivity. We previously developed the OFF-ON type vinyl-quinazolinone (VQ) precursors as chemically reactive moiety and found the selective alkylation reactivity towards G-quadruplex (G4) structure by tethering VQ with specific binders.[1,2] It was suggested that the departure of leaving groups played a dominant role for VQ reactivity. Therefore, we could possibly modulate VQ by changing the leaving groups.

In this study, we extensively investigated the amine leaving groups and found highly reactive compounds as well as an OFF-ON type precursors for nucleic acids alkylation (Fig 1). For dimethylamine (-NMe_2) precursor, we found its highly reactive and storable properties due to the protonation-accelerated mechanism and equilibrium eliminating manner. As for monomethylamine (-NHMe), we established a prototype activating system to stimulate its reactivity. In this presentation, we will report our molecular design, synthesis and alkylation results in detail.

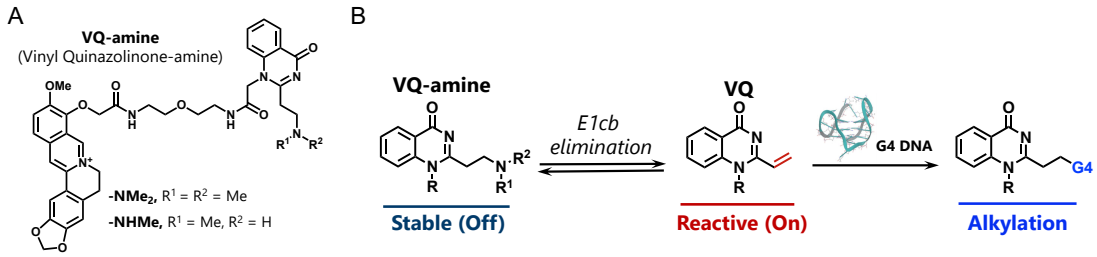

Figure 1. (A) Vinyl-quinazolinone (VQ) precursors in this study. **(B)** Schematic representation of alkylation of G4 DNA by VQ-amine precursors.

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