Reactivity modulation of reactive OFF-ON type G4-DNA alkylating reagents

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G-quadruplex (G4) is a four-stranded structure self-associated within guanine-rich DNA and RNA sequences. G4 consists of multiple planar G-quartets where four guanine bases are held together through Hoogsteen base pairing. G4-forming structures exist in many critical regions for such as oncogene promoter and 3′ single stranded overhang of telomeres. These structures are considered to play an important role in the regulation of gene expression. Therefore, G4 structures are widely investigated as a target for small molecule therapeutic intervention. One of the effective methods for increasing the affinity of a small molecule is covalent modification towards G4.

To date some G4 alkylating reagents have been exploited varied from Pt complexes to chlorambucil. To achieve efficient and selective alkylation with G4, we previously developed the reactive Off-On type reagent, vinyl-quinazolinone (VQ) precursors with a sulfoxide, thiophenyl or thiomethyl as the leaving groups (Figure 1).[1)] We demonstrated that VQ in its sulfoxide form (S(O)Me) undergoes a spontaneous vinyl generation whereas the thiophenyl (SPh, pK_a = 6.5) precursor generates a vinyl in an equilibrium manner, and the methylsulfide (SMe, pK_a = 10.5) precursor generates the vinyl site-specifically or only been triggered in the presence of G4.

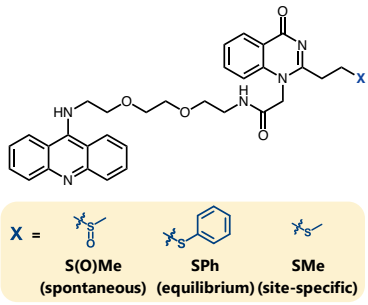

Figure 1. Vinyl-quinazolinone (VQ) precursors in previous study.

In this study, we proposed that the alkylation reactivity and VQ stability can be modulated by changing the leaving group. We synthesized a series of thiol VQ precursors with various pK_a values of leaving groups and examined the alkylation yield for each precursor. In consequence, we have obtained a reactivity trend in relation with pK_a values as expected (Figure 2). In addition to thiol derivatives, we also introduced amine precursors and discovered its fascinating reactivity. In this presentation, we will present these results in detail.

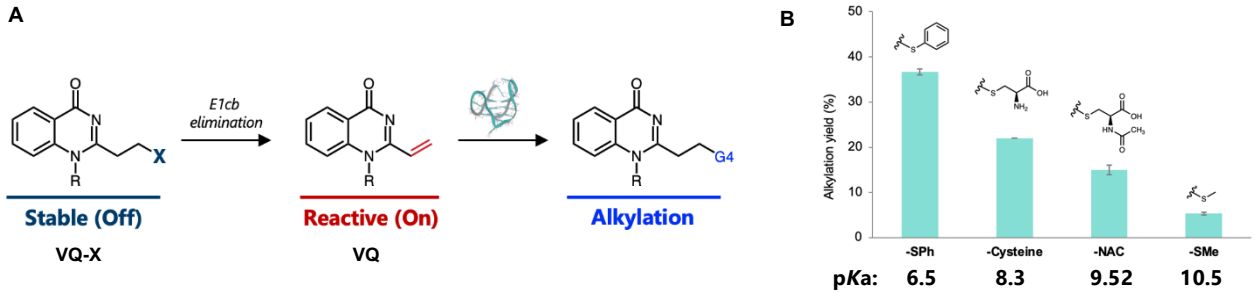

Figure 2. (**A**) Schematic representation of alkylation of G4 DNA by VQ precursors (**B**) Bar graph shows the yield (%) of thiol VQ precursors towards G4 DNA at 8 h.

1) K. Onizuka, M. E. Hazemi, N. Sato, G. Tsuji, S. Ishikawa, K. Tanno, M. Ozawa, K. Yamada, F. Nagatsugi, *Nucleic Acids Res.* **2019**, *47*, 6578-6589.