Synthesis and the properties of naphthyridine-azaquinolone dimer (**NAD**) targeting CAG-repeat RNA

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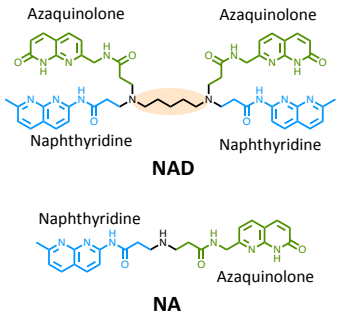
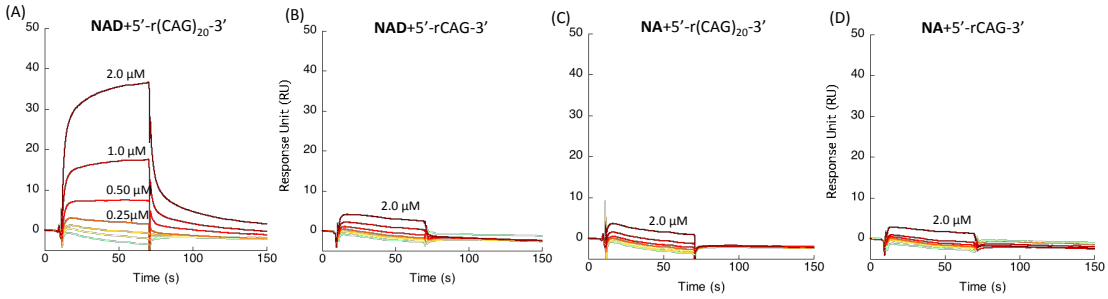
keywords: Trinucleotide repeat disease; mismatch binding ligand; A-A mismatch; RNA targeting



Abnormal expansion of CAG-repeats in some exons can cause various fatal neurodegenerative diseases, known as trinucleotide repeat disorders (TNDs). The molecular basis for the CAG-repeat expansion likely involves the formation of a metastable hairpin structure, consisting of repeating the A-A mismatches, flanked by two C-G base pairs. Because the CAG repeats encode long polyQ tracts in the respective proteins, they are also called polyQ diseases, which include Huntington's disease (HD) and several spinocerebellar ataxias (SCAs). Although the neurodegeneration caused by misfolding and aggregation of mutant proteins with expanded polyQ chains have been considered to be the sole cause of polyQ diseases, recent studies showed the gain-of-function of expanded-CAG RNAs is also involved in the pathogenesis of polyQ diseases.[1] Thus ligands that targeting CAG-repeat RNA can be potential probes to clarify the mechanisms of polyQ diseases and therapies to improve the relevant patients' QOL in future.

Naphthyridine-Azaquinolone (**NA**) can bind to A-A mismatch in CAG repeat DNA.[2] However, **NA** almost lost all of the binding towards CAG repeated RNA. In this study, a new CAG-repeat RNA binding molecule **NA** dimer (**NAD**), in which two **NA** moieties connected with a flexible 5-methylene linker, would be reported. The SPR results showed a strong binding response and high selectivity of **NAD** to CAG-repeated RNA (shown below). The binding studies of **NAD** would be reported in detail.



(1) Bogomazova, A.N., Eremeev, A. V., Pozmogova, G.E., and Lagarkova, M.A. *Mol. Biol.*, **2019**, **53**, 838–849. (2) Nakatani, K., Hagihara, S., Goto, Y., Kobori, A., Hagihara, M., Hayashi, G., Kyo, M., Nomura, M., Mishima, M., and Kojima, C. *Nat. Chem. Biol.*, **2005**, **1**, 39–43.

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