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Discovery and Characterization of a Short Peptide Possessing a Latent Warhead Undergoing Intramolecular Cyclization in the Aqueous Environment

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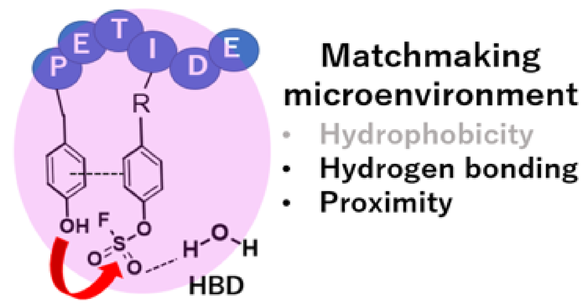
■ Abstract

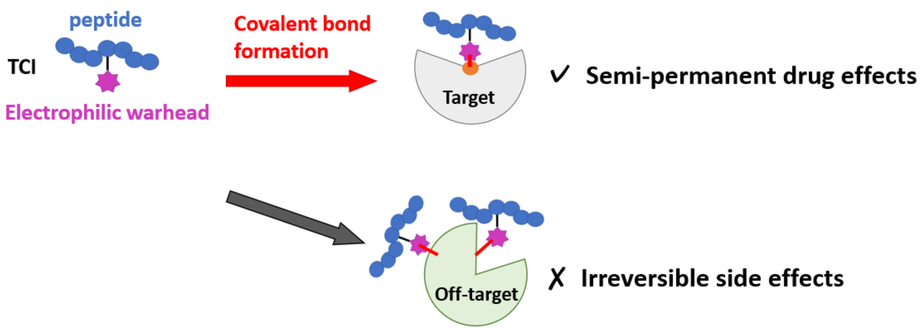
Peptidic targeted covalent inhibitor (TCI) can form a specific covalent bond to a target protein and show semi-permanent drug effects. Such a TCI should possess a latent reactive group (i.e., warhead), which can react only in a bioactive site of the target protein(i.e., matchmaking microenvironment). We hypothesize that even a simple peptide without needing a complex protein would create the matchmaking microenvironment. This peptide had a geometry in which a nucleophilic tyrosine and the electrophilic AFS are supposed to be stacked each other by π-π interaction. In addition, the reactivity of an AFS was increased in a hydrophilic environment, rather than a hydrophobic environment.



■ Background

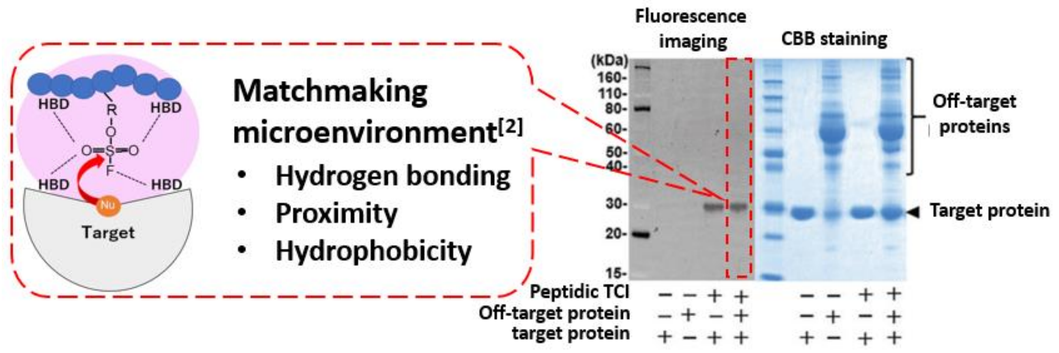
➢ Targeted Covalent Inhibitor (TCI)[1]

TCIs form a specific covalent bond to a target protein and show semi-permanent drug effects.



➢ Latent warhead[2]

Aryl-fluorosulfate has a latent reactivity; it is activated only in a matchmaking microenvironment.

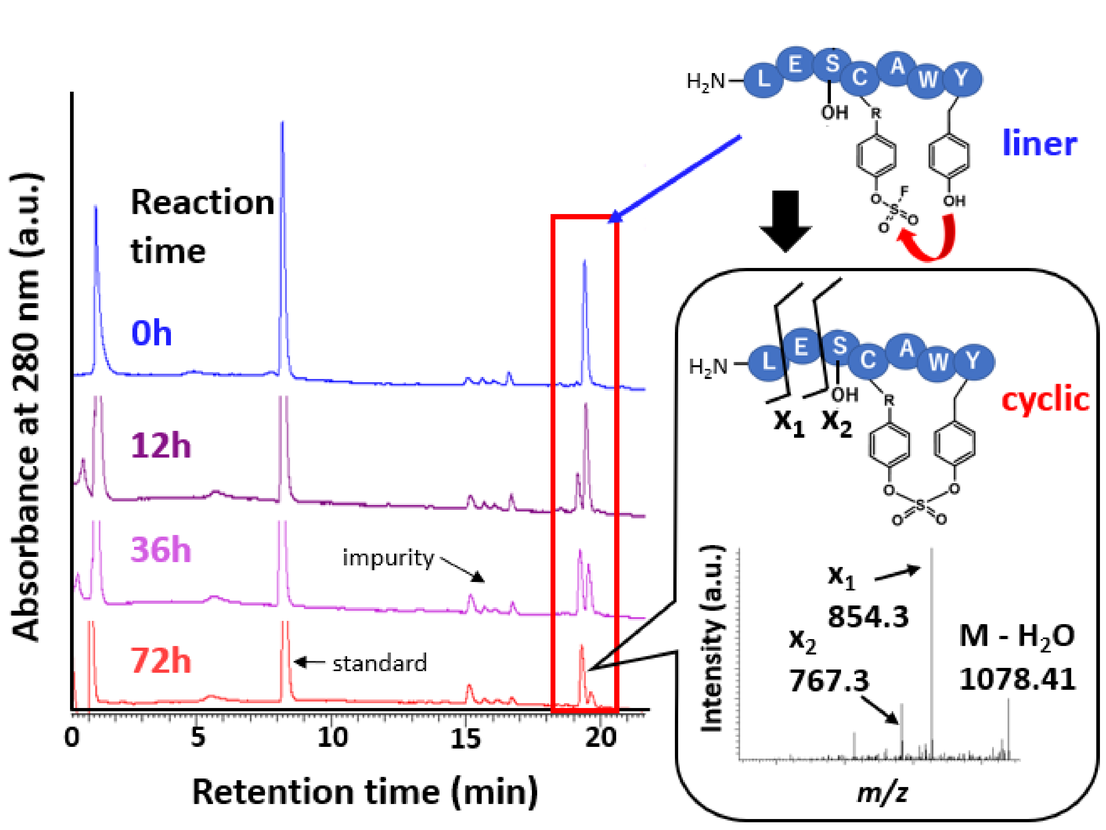


[1] Tabuchi Y., Yang J. and Taki M., *Int. J. Mol. Sci.,* **23**, 7778 (2022).

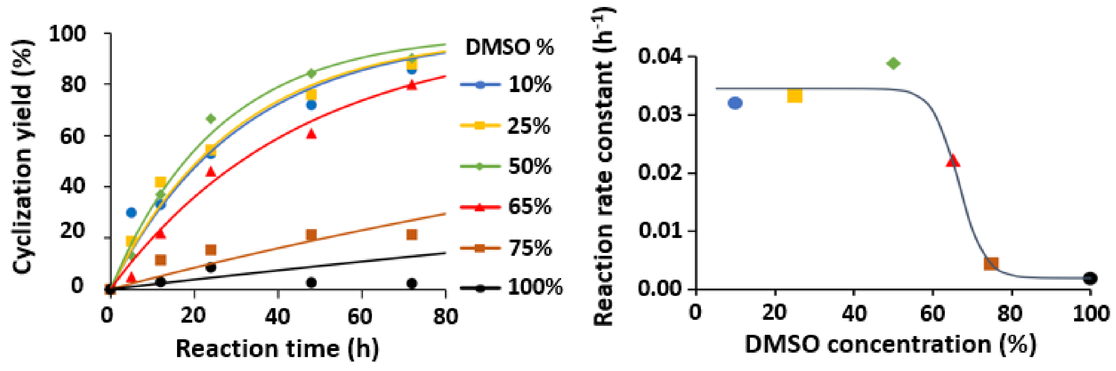
[2] Yang J., Tabuchi Y., ○**Katsuki R**. and Taki M., *Int. J. Mol. Sci.,* **24**, 3525 (2023).

■ Result and discussion

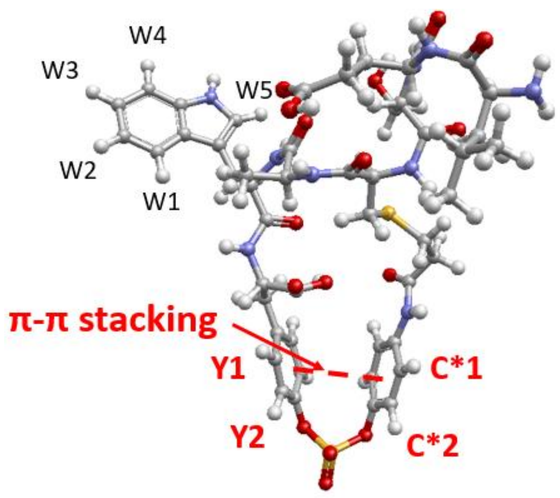
➢ Characterization of the intramolecular cyclization



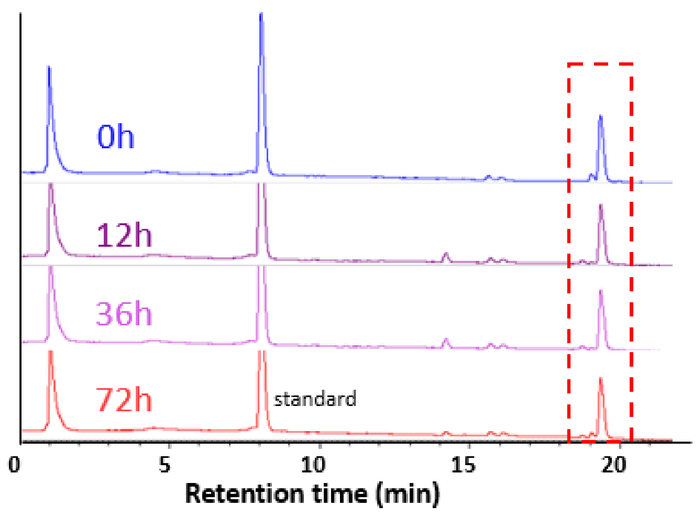
➢ Solvent effects

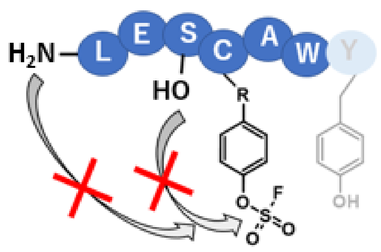


➢ MD simulation in the aqueous environment

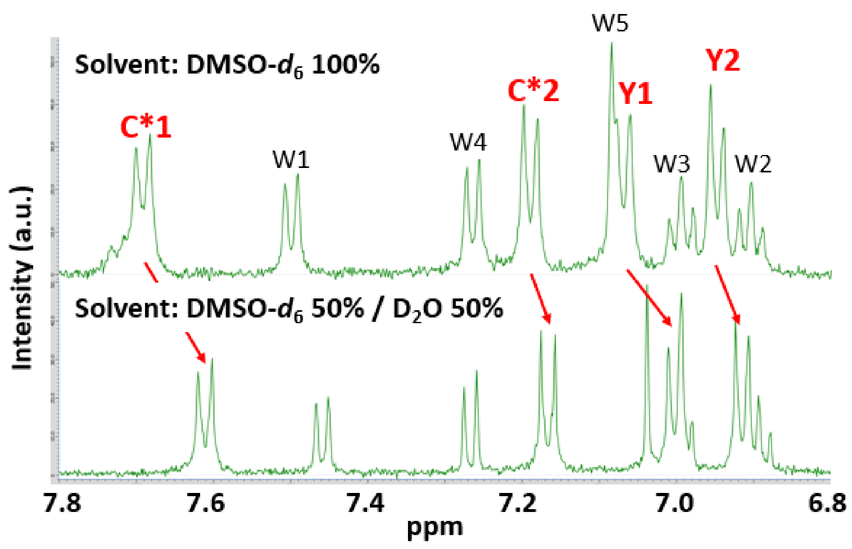


➢ Position selectivity of cyclization





➢ ^{1}H-NMR spectra of the cyclic peptide



■ Future perspective

We will investigate the sequence dependency of this activation. Also, we wonder that we would construct a staple peptide library by the demonstrated tyrosine-selective cyclization.