OIST | Innovation

Selective protein functionalization platform using spirooxindole oxirane derivatives

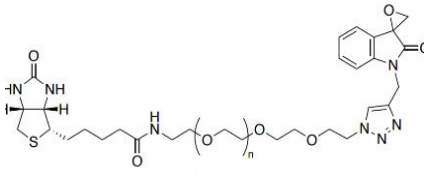
Summary

The chemical modification of proteins and peptides, e.g. for biotinylation and to produce antibody-drug conjugates, is key to the development of therapeutic and diagnostic tools in biomedical research. Traditional protein modification approaches such as the reaction of lysine amino groups with N-hydroxysuccinimide (NHS) ester derivatives, often results in the formation of a mixture of products, with different lysine positions modified. NHS esters are also relatively unstable in aqueous buffers.

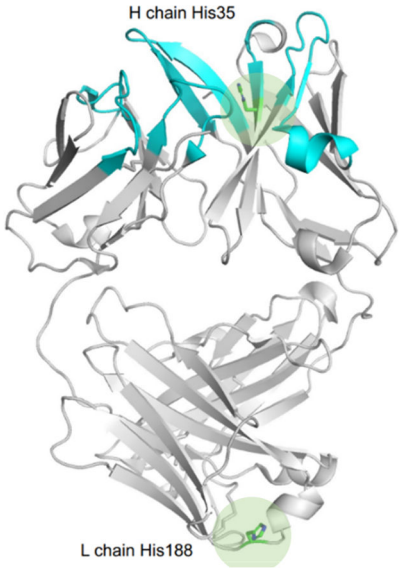
A team of researchers led by Prof Fujie Tanaka has developed a novel protein-modification platform that uses spirooxindole derivatives as the linking group between a protein and any functional molecule. The oxirane group only reacts at specific histidine residues, offering high selectivity and minimizing interference with the active site.

Technology

There are fewer histidine residues on protein surfaces than lysine residues and there is only a single N-terminus amino group per polypeptide chain. Therefore, modifications targeting histidine residues or the N-terminus amino group afford more selective functionalization. In this approach, the epoxide moiety is conjugated with a lactam amide carbonyl group, which is electron-withdrawing, affording an efficient reaction with proteins and peptides. The desired functional group is linked to the nitrogen of the lactam amide of the oxindole structure. Tuning the reactivity and/or the steric bulk of the spirooxindole oxirane allows selective modification at specific histidines, without reacting at functionally important histidine residues.



1b: n = 1
1c: n = 2



Spirooxindole oxirane derivatives can be linked to a functional label, such as biotin, and used to selectively add functionality to proteins
(e.g. pictured anti-CD20 antibody Fab)

Applications

- Drug development
- Biosensing
- Protein engineering

Advantages

- Histidine/N-terminus selectivity
- Covalent bond with protein
- Versatile: can be used on any histidine-containing protein, to add any functionality

Category:
Chemistry & Materials Science

Lead Researcher:
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Intellectual Property:
Patent Pending

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