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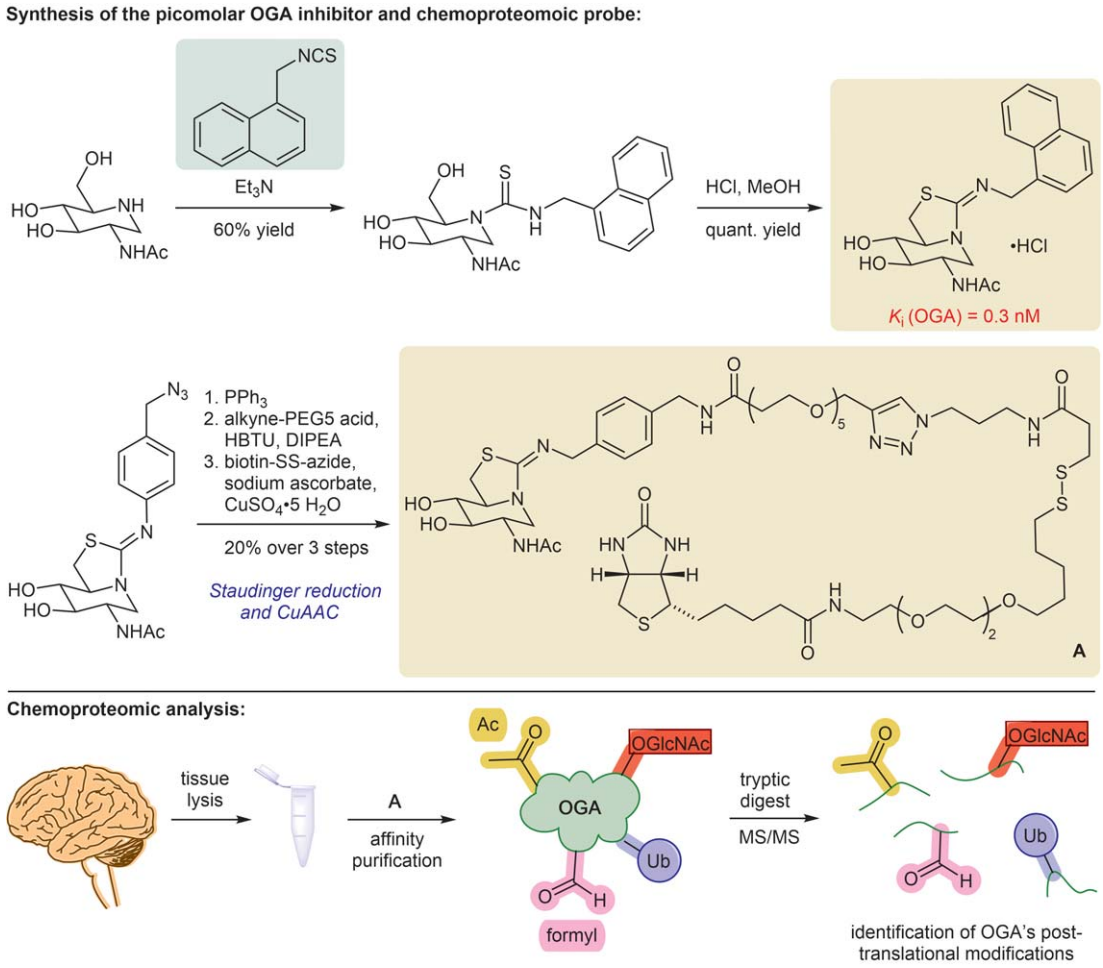
Bicyclic Picomolar OGA Inhibitors Enable Chemoproteomic Mapping of Its Endogenous Post-Translational Modifications
J. Am. Chem. Soc. **2022**, *144*, 832–844, DOI: 10.1021/jacs.1c10504.

A Novel Thiazolidine Scaffold that Inhibits O-GlcNAcase (OGA)



Significance: O-Linked *N*-acetylglucosamine (O-GlcNAc) is an important post-translational modification (PTM) that regulates many cellular processes. In contrast to numerous kinases and phosphatases controlling the phosphorylation state of the proteome, only two enzymes are responsible for O-GlcNAc installation (O-GlcNAc transferase, OGT) and removal (O-GlcNAcase, OGA). The regulation of OGA activity remains poorly understood despite a dysregulation being linked to various neurodegenerative diseases.

Comment: The authors developed a novel series of OGA inhibitors with picomolar binding affinity that are based on the aminosugar dideoxynojirimycin. Structural mimicry of the hydrolyzing transition state guided the search toward the bicyclic iminothiazolidine scaffold. Furthermore, a biotin-conjugate was synthesized, which served as an affinity-purification tag and revealed new PTMs of OGA from brain cell tissue lysates. Both inhibitors and probes could serve as important tools to elucidate the regulatory mechanism of OGA.

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Category
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Key words
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O-linked *N*-acetylglucosamine
Staudinger reduction
biotin

Synfact of the Month