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Triple, Mutually Orthogonal Bioorthogonal Pairs through the Design of Electronically Activated Sulfamate-Containing Cycloalkynes

J. Am. Chem. Soc. **2020**, *142*, 18826–18835, DOI: 10.1021/jacs.0c06725.

Teaching Old Clicks New Tricks

Significance: The introduction of bioorthogonal reactions has enabled tremendous advances in chemical biology. The authors designed two new, mutually orthogonal pairs by electronic tuning of S-, N-, and O-containing cyclooctynes (SNO-OCTs). The reported system should prove to be a useful tool for future *in cellulo* investigations.

Comment: Using computational and experimental studies, the authors were able to design cyclooctynes with orthogonal reactivities. By including a previously reported boronic acid/hydrazine pair, the authors were able to obtain a triple ligation system and demonstrated its utility through protein and cellular labeling assays.

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Synfacts 2021, 17(01), 0091 Published online: 16.12.2020
DOI: 10.1055/s-0040-1719253; Reg-No.: T14520SF

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Category

Chemistry in
Medicine and
Biology

Key words

bioorthogonal
chemistry

click chemistry

cyclooctynes

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