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Isoprenoid diphosphate substrates suitable for copper-free bioorthogonal conjugation through tetrazine ligation

Many non-natural isoprenoid diphosphate analogs have been shown to be substrates for Protein Farnesyltransferase (PFTase). Transferable analogs include azide and alkyne containing isoprenoid derivates which can subsequently be used as handles to perform click chemistry after modification. The limitation for bioconjugations using click chemistry is that these reactions must be completed in the presence of copper, which can degrade biological molecules. An alternative method is tetrazine ligation: a bioorthogonal reaction which proceeds through an inverse electron demand Diels-Alder mechanism at a rate comparable to copper-catalyzed click reactions, without cytotoxicity. Here we report the synthesis of cyclooctene and norbornene containing isoprenoids that are substrates for PFTase. Proteins and peptides labeled with these moieties are candidates for tetrazine ligation—a particularly useful bioconjugation method in biological environments.