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A One-Pot Three-Component Double-Click Method for Synthesis of [^{67}Cu]-Labeled Biomolecular Radiotherapeutics

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Abstract

© 2017 The Author(s). A one-pot three-component double-click process for preparing tumor-targeting agents for cancer radiotherapy is described here. By utilizing DOTA (or NOTA) containing tetrazines and the TCO-substituted aldehyde, the two click reactions, the tetrazine ligation (an inverse electron-demand Diels-Alder cycloaddition) and the RIKEN click (a rapid 6π-azaelectrocyclization), could simultaneously proceed under mild conditions to afford covalent attachment of the metal chelator DOTA or NOTA to biomolecules such as to albumin and anti-IGSF4 antibody without altering their activities. Subsequently, radiolabeling of DOTA-or NOTA-attached albumin and anti-IGSF4 antibody (an anti-tumor-targeting antibody) with [67 Cu], a β --emitting radionuclide, could be achieved in a highly efficient manner via a simple chelation with DOTA proving to be a more superior chelator than NOTA. Our work provides a new and operationally simple method for introducing the [67 Cu] isotope even in large quantities to biomolecules, thereby representing an important process for preparations of clinically relevant tumor-targeting agents for radiotherapy.

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