



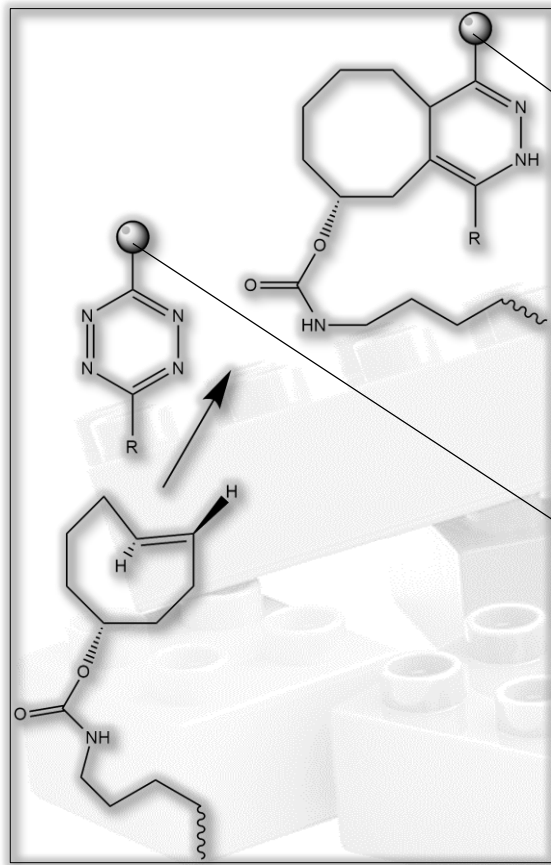
Polyfunctional clickable compounds as a useful tool for bioactive molecules labeling



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Abstract

The coming age of personalized medicine needs reactions and reagents with fast kinetics, excellent orthogonality and biocompatibility. Click-chemistry processes such as inverse-electron demand Diels-Alder (IEDDA) reaction - have become extremely popular with promises to revolutionize chemical biology, radiochemistry and materials science. The exceptional fast kinetics of this catalyst-free reaction, using low concentrations of highly strained unsaturated dienophiles and 1,2,4,5-tetrazines coupling agents, make it appropriate for in vivo radiolabelling using pretargeting methodologies. The IEDDA reaction can be tuned to reach rate constants from 1 up to $10^6 \text{ M}^{-1} \text{ s}^{-1}$ by changing the electron deficiency of the 1,2,4,5-tetrazine precursors (Tz), or by manipulating the ring strain and electronic effects on the dienophiles (TCO). Significant efforts have focused on accelerating the reaction rate by synthesizing new derivatives of TCO and Tz. The present study is aimed to the synthesis of new TCO and Tz moieties appropriate for further bioconjugation via oxime or hydrazone formation.



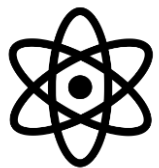
Biomolecules
(proteins,
antibodies, nucleic
acids, glycans,
lipids, small
bioactive
molecules);
Radiolabeled
molecules;
Fluorescent
molecules etc.

Inverse-electron demand Diels-Alder reaction - "Click reaction"

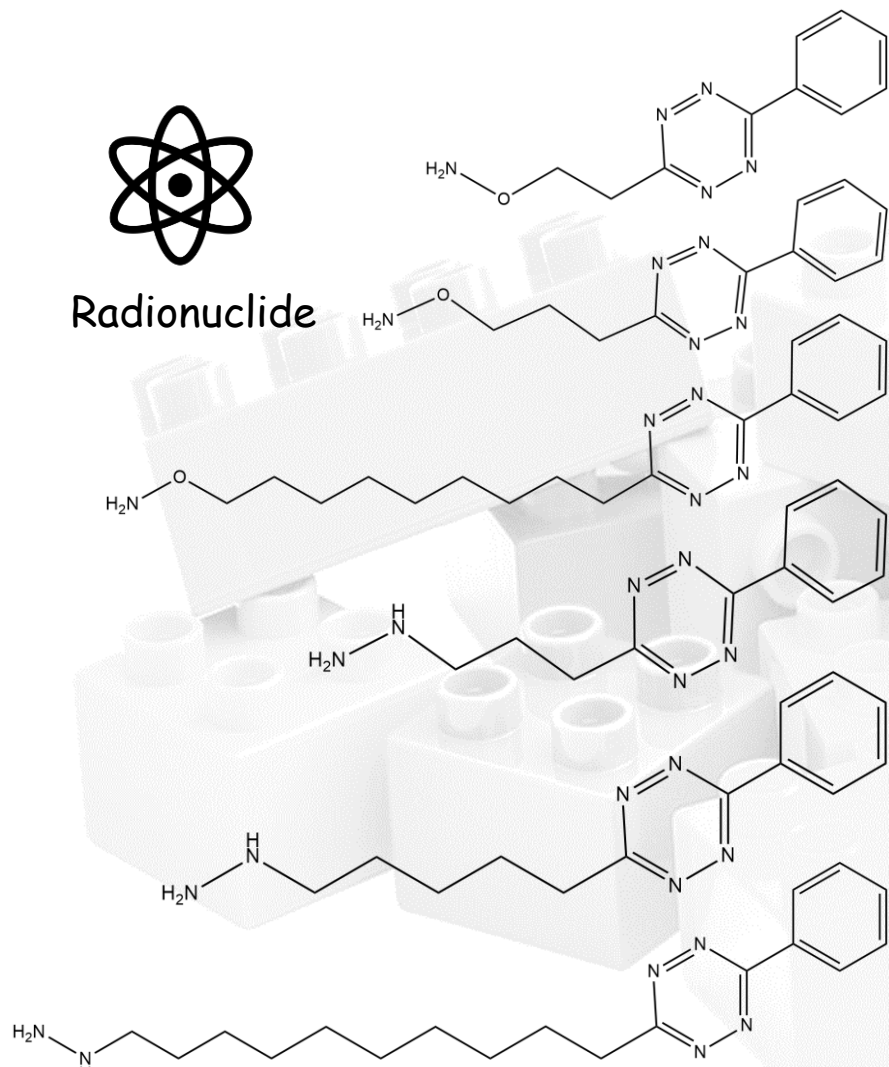
Staudinger ligations Phosphine oxidation Ref 2	 Ketone/aldehyde condensations Acidic pH Ref 1	$k \sim 10^{-3} \text{ M}^{-1}\text{s}^{-1}$	$k \sim 10^{-4} - 10^{-3} \text{ M}^{-1}\text{s}^{-1}$
Metal catalysis [Ru] Cat	Only for <i>in vitro</i> testing Ref 3		
SPAAC cycloadditions -N=N=N	Reactivity with thiols Ref 4		
SPANC cycloadditions -N=N=N	Live cells, nitrones unstable Ref 5		
Photoclick 1,3-dipolar cycloadditions -N=N=N	Spatiotemporal control, only for <i>in vitro</i> studies Ref 6		
CuAAC cycloadditions -N=N=N [Cu] ligand	Cu ^I -ligands reduce Cu toxicity Chelating N ₃ acelarate reaction Ref 7		
IEDDA cycloadditions -N=N=N	Fast, fluorogenic, catalyst-free, allows <i>in vivo</i> reactions Ref 8		

Useful biorthogonal reactions for bioconjugation and their rate constants

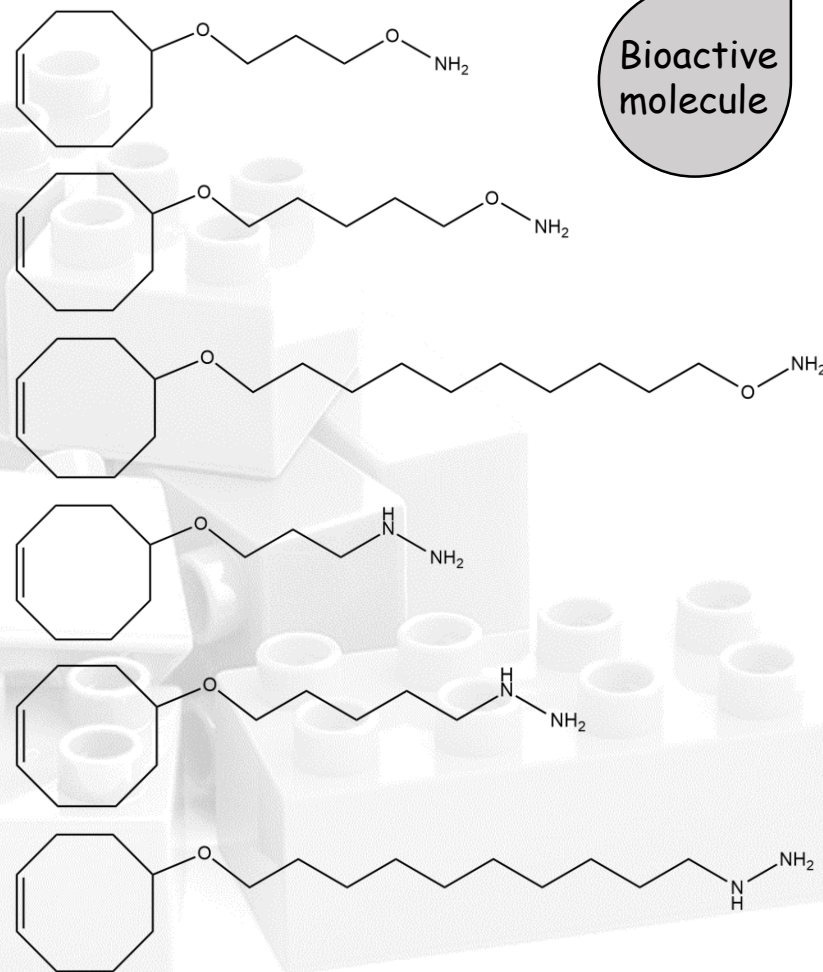
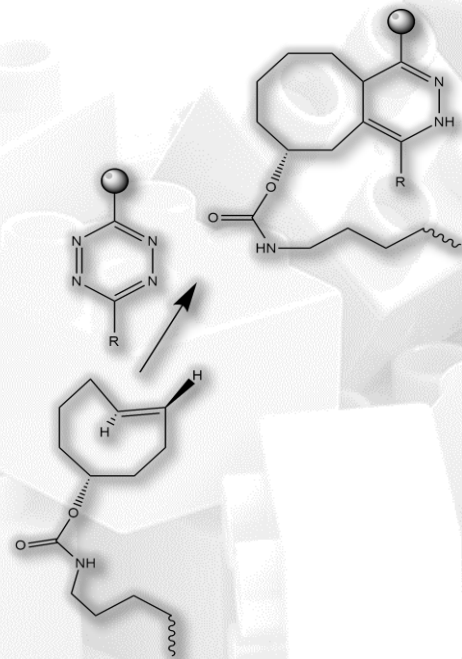
Results and discussion



Radionuclide



Newly synthesized "Click" molecules



Acknowledgement

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