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# Recent Developments in Tetrazine Ligation Tools for Pretargeted Nuclear Imaging

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## Introduction

Tetrazine ligation has recently gained popularity as a bio-orthogonal chemistry tool. Tetrazine ligation is currently being investigated in nuclear medicine for pretargeted approaches, which have the potential to revolutionise state-of-the-art theranostic strategies. Pretargeting has been shown to increase target-to-background ratios for nanomedicine-based radiopharmaceuticals, particularly in early timeframes. This enables the use of radionuclides with short half-lives, which are more appropriate for clinical applications. Pretargeting has the potential to both increase the therapeutic dose delivered to the target and decrease the dose delivered to healthy tissue. When combined with the ability to be used for diagnostic imaging, pretargeting may be ideal for theranostic approaches. We highlight efforts to radiolabel tetrazines with an emphasis on imaging in this review [1].

## Description

Transformations that occur in living organisms without interfering with biochemical processes are known as bio-orthogonal reactions. They've been used for things like pretargeting. Pretargeting can be used to improve imaging contrast of nanomedicines, reduce radiation doses to healthy tissue, or trigger drug release, among other things. Several bio-orthogonal reactions have been described over the years, each with its own set of advantages and disadvantages. The majority of reactions found applications *in vitro*; However, only a few were successful in a real-world in vivo setting. Saxon and Bertozzi created the first bio-orthogonal reaction, the Staudinger ligation, in 2000. Soon after, in 2004, the strain-promoted alkyne-azide cycloaddition was described and successfully applied.

The required concentrations of the Staudinger ligation or the SPAAC are typically not reachable, particularly in nuclear molecular imaging applications where tracer amounts are typically used. It proposed a new bio-orthogonal reaction, the tetrazine ligation between an electron-deficient tetrazine and a strained trans-cyclooctene derivative. The tetrazine ligation is the ideal tool for in vivo applications due to its high specificity, inertness to biological media, and impressive rate constant of up to 107 M1 s1 when compared to other bio-orthogonal reactions. The bispecific antibody and hapten recognition, as well as the avidin-biotin interaction, have comparable rate constants when compared to clinically used pretargeting pairs [2,3].

Tz ligation, on the other hand, results in the formation of covalent bonds and is thus completely irreversible. In contrast, noncovalent high affinity interactions drive bispecific antibody and hapten recognition, as well as the (strep)avidin-biotin interaction, making them partially reversible in vivo. Another advantage of Tz ligation is that it is based on small molecules, which can be easily upscaled, have their rate constants manipulated, and have their physiochemical properties tailored to specific applications, such as entering the brain. Tz ligation can also be used for "click-to-release" strategies, which have recently been shown to be more effective than traditional methods. In rodents, bio-orthogonal drug release increased median survival from 26 to 50 days.

By conjugating electron donating groups to the TCO moiety, the reactivity of TCOs can be increased. This raises both the HOMO and the TCO to a higher energy level, reducing the energy gap between the TCO's highest occupied molecular orbital and the Tz's lowest unoccupied molecular orbital. Increasing the strain of the diene is another way to increase its reactivity. TCOs are significantly more reactive than cis-cyclooctenes because of this. Additional ring strain raises the reactivity even more. However, TCO stability usually correlates with reactivity, limiting the possibility of maximising the latter, particularly for in vivo applications.

Nuclear medicine has become an important tool for the early detection and treatment of diseases in oncology, cardiology, and neurology. Molecular imaging techniques, such as positron emission tomography or single-photon emission computed tomography, enable the visualisation of biological processes in living organisms by using appropriate radiolabeled derivatives. These methods are noninvasive, highly sensitive, and provide isotropy. Unlike SPECT, PET allows for a quantitative measurement of the tracer delivered to the target. This is primarily due to clinical PET cameras' higher spatial and temporal resolution, which are at least ten times more sensitive. As a result of these factors, PET images have higher quality and contrast at lower radiation doses. The choice between PET and SPECT imaging is determined by the properties of the radionuclides and the corresponding structure [4,5].

## Conclusion

Tz ligation has emerged as one of the most promising in vivo pretargeted tools. This is due to its superior reaction kinetics, selectivity, and yield. This click reaction makes it possible to label nanomedicines in live cells and even in vivo. As a result, Tzs radiolabeling has gained attention. Several methods, ranging from chelator to nucleophilic substitution approaches, have been developed in the last decade. However, few methods for radiolabeling Tzs with therapeutic nuclides have been described. We believe that new therapeutic and theranostic Tzs will emerge in the coming years for pretargeting strategies. More importantly, the first clinical phase I trial based on tetrazine ligation was launched in late 2020. We believe that radiolabeled Tzs with suitable properties for in vivo pretargeting could be a useful tool for quantifying chemotherapeutic release and/or achieving an additional therapeutic effect. In general, tetrazine ligation and its unique reaction properties are still being explored; its potential for diagnostic or therapeutic applications could revolutionise theranostic applications in nuclear medicine.

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