Novel Applications of Tetrazoles Derived from the TMSN3-Ugi Reaction

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Summary

The distinguished properties of tetrazole moiety make it possible to be employed as bioisosteric substituent of carboxylic acid in developing biological active substances (Figure S.1). Tetrazole possesses several advantages over carboxylic acids with respect to many aspects including metabolic stability, electronic distribution, hydrogen bonding, and lipophilicity. These advantages facilitate the interactions between ligands and receptors, and potentially allow for a better cell membrane passage.

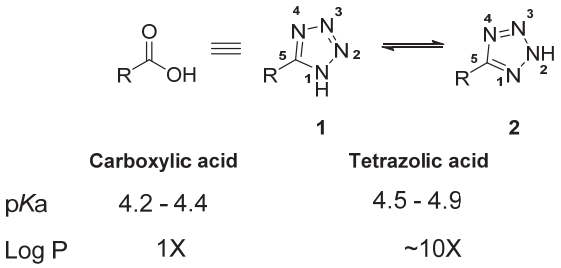
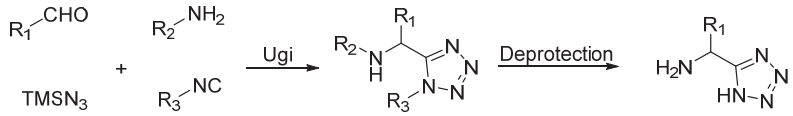


Figure S.1. Tetrazolic acids are bioisosteres of carboxylic acids.

The research presented in this thesis mainly focuses on introducing the tetrazole moiety as a structural fragment in the preparation of several series of drug-like molecules, and studies towards their related applications in pharmacology.

Chapter 2 comprehends a compact literature review on the synthesis of tetrazole derivatives via multicomponent reactions. Most of these reported tetrazole derivatives are designed and prepared aiming for the potentially pharmacological applications.

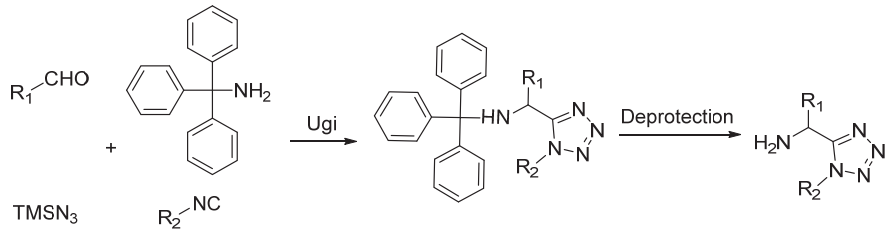


Scheme S.1. Synthesis of α-amino acid-bioisosteric α-amino tetrazoles.

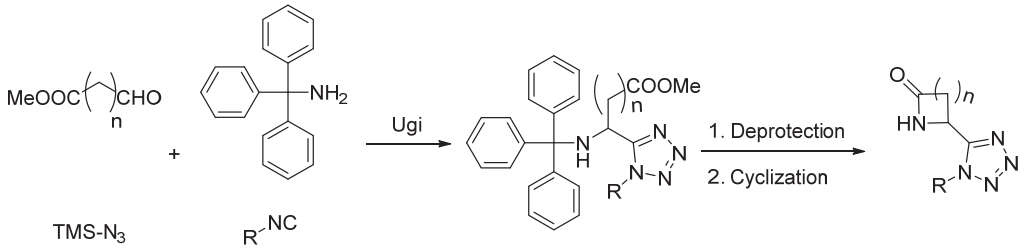
In **Chapter 3**, it is the first time to produce all endogenous natural proteinogenic α-amino acid-bioisosteric α-amino tetrazoles and 4 others by using a concise and rapid synthetic route, which includes azido-Ugi reaction and deprotection (Scheme S.1). Moreover, this is the first report that presents the tetrazole derivatives of the amino acids Thr, His, Arg, and Cys. However, due to the lack of stereo-selectivity in Ugi reaction, all obtained compounds are

presented as racemic mixtures or diastereomeric mixtures. Their related investigation of the biological activity in drug design are ongoing.

In **Chapter 4**, for the first time, tritylamine is introduced as a convenient and easily cleavable ammonia surrogate that reacts with aldehydes, TMS-azide and isocyanides, to yield *N*-trityl α-aminotetrazoles under very mild conditions. Furthermore, with the subsequent trityl deprotection, *N*-tetrazole-substituted and amino-*N*-unsubstituted α-amino tetrazoles are obtained via Ugi reaction (Scheme S.2). Although the steric hindrance of tritylamine and the failure to react with ketones and aromatic aldehydes cannot be ignored, the Ugi reaction proceeds smoothly and in good to satisfactory yields in all reported cases. This can have remarkable advantages that can be employed in investigating further synthetic applications and biological properties of new compounds.



Scheme S.2. Synthetic pathway to *N*-unsubstituted primary α-amino tetrazole using a Ugi-4CR by employing tritylamine as an ammonia surrogate.



Scheme S.3. Devised synthetic pathway to tetrazolo *N*-unsubstituted γ- and δ-lactams.

In **Chapter 5**, a fast and reliable synthetic route to 5- and 6-membered unsubstituted tetrazololactams has been designed, which employs a key azido-Ugi reaction followed by a deprotection and cyclisation step (Scheme S.3). By analyzing the scaffold in the protein data bank, it indicates that the lactam-NH can undergo multiple and strong hydrogen bonds. Currently, this scaffold is widely used in medicinal chemistry and this structure could be introduced as an important moiety in drug design.

Except all the above successful examples of employing tetrazoles in the design and synthesis of drug-like molecules and discussing their potential applications in medicinal chemistry, **Chapter 6** summarizes the structures and the inhibitory potency of all disclosed human arginase inhibitors. Furthermore, we rationalize their structure-activity relationship based on the crystallography research.

In **Chapter 7**, we design and synthesize a series of novel α-isosteric tetrazole ABH analogues as promising human arginase inhibitors using Ugi reaction for the first time. Noteworthy is that these synthetic compounds show, in the *in vitro* enzyme assay, less potent inhibition than ABH. This lower efficiency could be explained by the larger size of the tetrazole and weaker interactions between the boronate and the active site of human arginase. However, the novel α-isosteric tetrazole ABH analogue could still present a good inhibitory potency in the *in vivo* assay and clinical studies, caused by the higher lipophilicity and metabolic stability of the tetrazole.

Although many successful applications of the tetrazole in medicinal chemistry are presented, we can expect more investigations and discoveries in this field. For instance, it is attractive to further optimize the structures of the present drug molecules and develop feasible approaches for the preparation of tetrazole containing natural products by using multicomponent reactions. However, it is of the most importance to gain a good understanding of the pharmacophore and the physicochemical properties of the bioisosteres for the proper bioisosteric replacements with favorable attributes.