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## Novel Applications of Tetrazoles Derived from the TMSN3-Ugi Reaction

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2016

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Zhao, T. (2016). *Novel Applications of Tetrazoles Derived from the TMSN3-Ugi Reaction*. Rijksuniversiteit Groningen.

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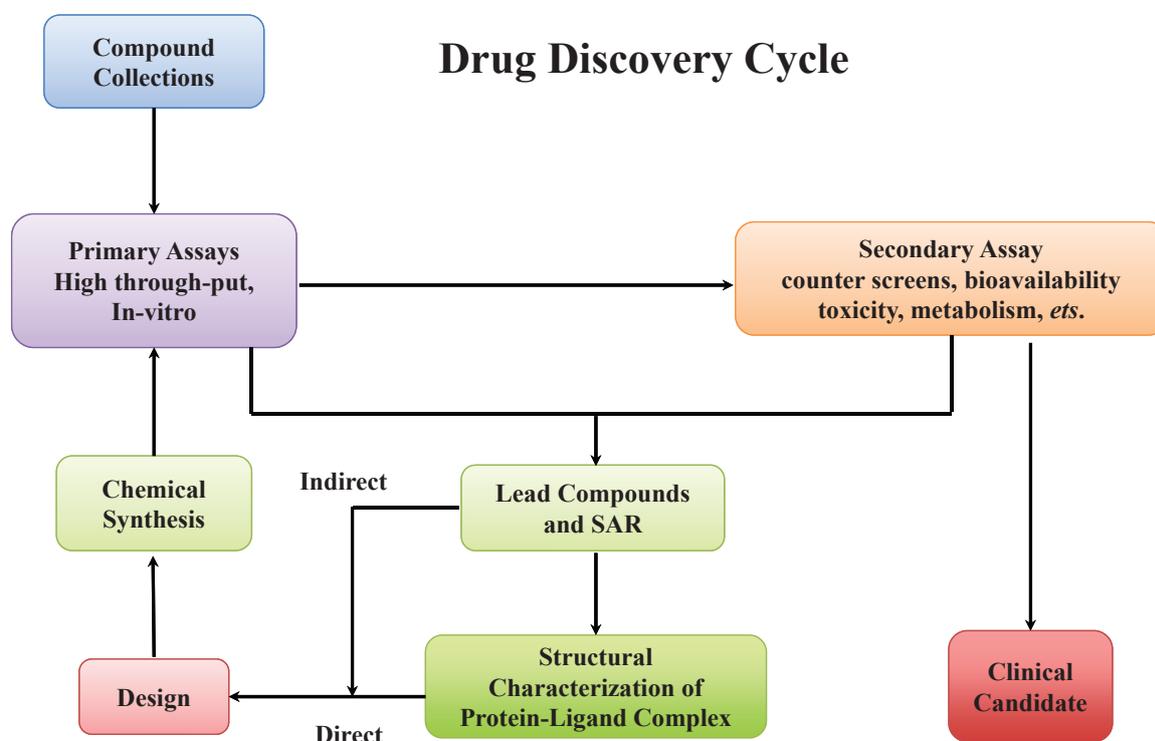
# **Chapter 1**

## **General introduction and scope of this thesis**

## 1.1 Drug discovery

Historically, drugs were discovered through a process in which the active ingredient is identified from traditional remedies or by serendipitous discovery. Later, when classical pharmacology was well established, screening chemical libraries of small molecules, natural products or extracts against targets of interest, intact cells or whole organisms to identify the desirable therapeutic effects.

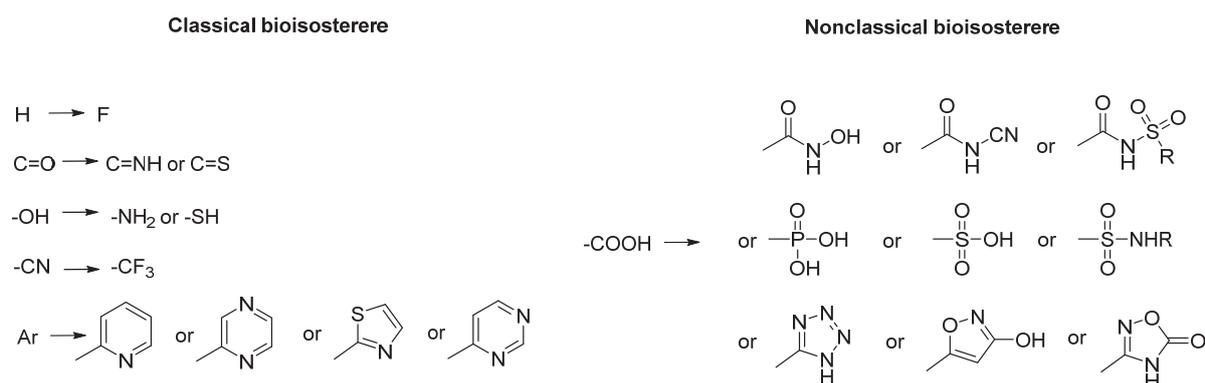
Current paradigms in drug discovery focus on generating a high degree of structural diversity within a library.<sup>1,2</sup> Furthermore, screening all compounds in the library against a panel of functional dissimilar proteins and determining the binding affinity of each compound for each protein can be achieved. In recent years, as the advancement of many new technologies such as NMR,<sup>3</sup> robotic crystallization,<sup>4</sup> and X-ray crystallography<sup>5</sup> applied in structural biology, the molecular structures of proteins can be clearly determined, and more comprehensive overview of the interactions between small molecules and proteins can be obtained. This structural biology information can facilitate the understanding how the potency or affinities are consistent with the interactions between drug molecules and receptors, and to make the modern drug design more effective and aimful (Scheme 1.1).



**Scheme 1.1.** The schematic diagram of the drug discovery cycle (adapted from [en.wikipedia.org/wiki/Drug\\_discovery](http://en.wikipedia.org/wiki/Drug_discovery)).

## 1.2 Bioisosterism

In modern drug discovery, an effective drug candidate is determined by its affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability. It is very common that a lead compound with a desired pharmacological activity may associate with some unexpected and unfavorable side effects. These side effects can limit the bioavailability and influence the absorption, distribution, metabolism, and excretion (ADME) properties.<sup>6</sup> Bioisosterism is a smart method used in drug design to rationally modify the structure of the lead compound using bioisosteres,<sup>7</sup> which could enhance the desired biological or physiological properties without significant changes in chemical structure.<sup>8</sup> Bioisosteres are commonly referred as chemical substituents such as single atoms and groups which exhibit similar volumes, shapes, and/or physicochemical properties with broadly similar biological effects.<sup>9</sup> Some typical bioisosteres are presented in Figure 1.1.



**Figure 1.1.** Selected classical and nonclassical bioisosteres in medicinal chemistry.

## 1.3 Carboxylic acid as a key determinant in drug-target interactions

Carboxylic acid moieties can be found in a wide variety of endogenous substances, for example, amino acids, triglycerides and prostanooids. This functional group plays a key role as part of the pharmacophore in diverse classes of therapeutic agents, as it can form strong electrostatic interactions and hydrogen bonds with receptors and often determines the interactions between drug and target. At present, a large number of carboxylic acid-containing drugs are commercially available on the market worldwide, including nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anticoagulants, and cholesterol-lowering statins, just to name a few.

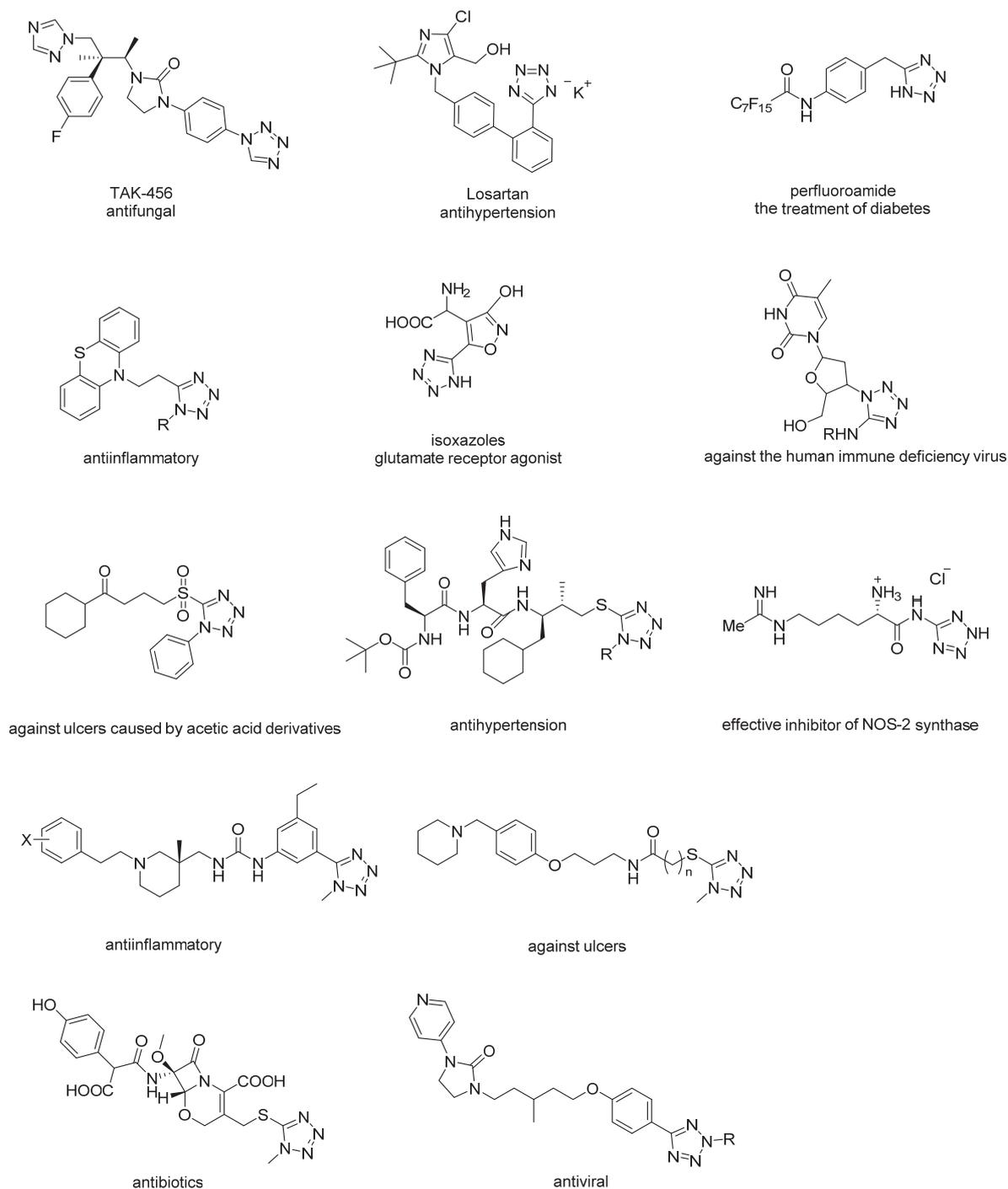
However, the introduction of carboxylate functionality in drug design sometimes induces undesired properties such as low oral bioavailability and short half-life time. For example, the presence of carboxylic acid in a drug will diminish the ability to passively diffuse across biological membranes, especially in central nervous system (CNS); and the carboxylic acid moieties present the easy metabolism which is the reason for the withdrawal of idiosyncratic drug from the market. As a result, it is appealing to replace the carboxylic acid moieties with a suitable bioisostere, for instance, carboxamide, sulfonamide or tetrazole, to improve the pharmacokinetic properties of drug candidates.

#### **1.4 Tetrazole as a nonclassical bioisostere of carboxylic acid**

Bioisosteres can be classified as two categories: classical and nonclassical.<sup>7</sup> Classical bioisosteres are generally referred to structurally simple atoms, ions or groups with the same atom numbers and/or the same valence electron numbers, while nonclassical bioisosteres are distinct in structures, which contain the different number of atoms and show varied steric and electronic properties. Some representative classical and nonclassical bioisosteres are shown in Figure 1.1.

Many tetrazole-based drugs are effective therapeutic agents for various pathogenesis, which are illustrated in Figure 1.2.<sup>10</sup>

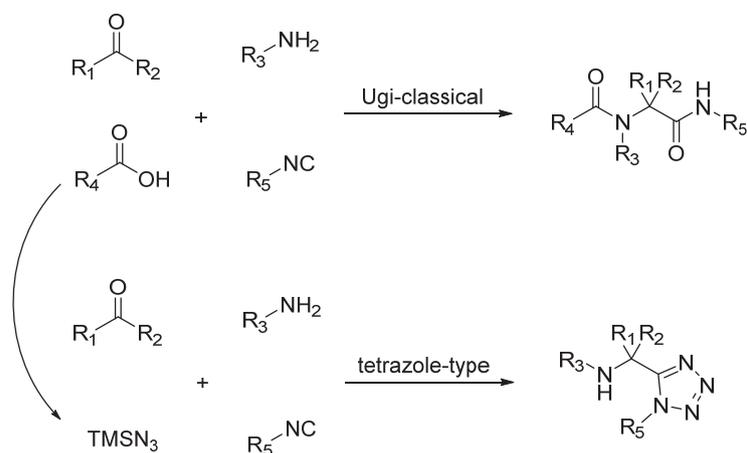
Tetrazole is the most frequently used nonclassical bioisostere of carboxylic acid moieties in biologically active molecules.<sup>11</sup> Although tetrazole and carboxylic acid moieties possess different electronic or steric characteristics, they show the similar  $pK_a$  values (4.5 – 4.9 and 4.2 – 4.4, respectively), and can be ionized at physiological pH (7.4). Moreover, with exhibiting a planar structure, tetrazole can stabilize a negative charge by delocalizing electron. This distribution of charge is probably favorable for the interaction of receptor-ligand. In addition, tetrazolate anions are more lipophilic than carboxylates, which benefits the passing of drug molecules through cell membranes. Besides, the nitrogen rich tetrazoles provide more opportunities to form hydrogen bonds with the recognition sites of receptor. Furthermore, tetrazoles are resistant to many biological metabolic degradation pathways, having a longer duration of action.



**Figure 1.2.** Selected drugs in the tetrazole series.

However, the development of tetrazole-containing drugs, aiming to improve the ADME properties while remain the biological activity, was limited due to the difficult synthetic process which required harsh reaction condition and toxic reagents. Fortunately, Ugi *et al.* found that replacing carboxylic acid with azidotrimethylsilane (TMSN<sub>3</sub>) in classical Ugi reaction could afford tetrazole derivatives with structure varieties and high yields in mild

reaction condition (Scheme 1.2). Since then, the tetrazole-containing compounds are proliferating in medicine chemistry, either in number or in structural variety.<sup>12</sup> For instance, Torrence *et al.* prepared a small library of 5-substituted pyrimidine nucleoside *N*-acylamino acid amides as potential antiviral and antileishmanial agents;<sup>13</sup> and several substituted benzyl tetrazoles as histamine H3 receptor antagonists were developed by Hallett *et al.*<sup>14</sup>



**Scheme 1.2.** The overview of classical Ugi reaction and tetrazole-type Ugi reaction.

## 1.5 Aim and scope of this thesis

In this research, we study the synthesis of tetrazole derivatives via Ugi reaction and evaluate their promising applications in pharmacology. To date, a large number of tetrazole derivatives are readily produced via classical approaches and by multicomponent reactions (Ugi and Passerini reaction), which are reported in many review articles. However, the biological information of these drug-like molecules and the systematical study of their structure-activity relationship are scarcely summarized. In **Chapter 2**, the synthesis of tetrazole derivatives via multicomponent reactions and their potential pharmaceutical applications are comprehensively discussed.

As one of the most important known classes of organic compounds,  $\alpha$ -amino acids have found diverse applications in nutrition, medicine, materials, chemistry, and biochemistry. However, in some cases,  $\alpha$ -amino acids do not have the desired physicochemical properties for a specific application and isosteric derivatives can be more suitable. As presented in **Chapter 3**, for the first time, all 20 natural proteinogenic  $\alpha$ -amino acid-isosteric  $\alpha$ -amino tetrazoles are prepared using Ugi reaction and the followed deprotection.

To enrich the tetrazole derivatives library via Ugi reaction, tritylamine is introduced as a convenient ammonia substitute. **Chapter 4** focuses on the preparation of a series of *N*-unsubstituted  $\alpha$ -aminotetrazoles using Ugi reaction followed by a simple and effective deprotection step. This is the first time that the utilization of tritylamine in Ugi reaction is addressed.

The  $\gamma$ - and  $\delta$ -lactam moiety are present in many bioactive molecules. With the well-established strategy developed in **Chapter 4**, a series of tetrazole-containing  $\gamma$ - and  $\delta$ -lactams are produced, which are difficult to access via conventional approaches (**Chapter 5**). The X-ray crystal structures of the selected compounds are studied, to reveal the intermolecular hydrogen bond formation. Moreover, this scaffold is analyzed in the protein data bank.

In addition, human arginase is a novel therapeutic target to treat diseases which are induced by the overexpression of arginase in human living systems. Until now, most of the reported human arginase inhibitors possess moderate to potent inhibitory activity. In order to understand the inhibition mechanism of human arginase by these inhibitors, their structures and the interactions with human arginase are discussed in **Chapter 6**.

2(*S*)-Amino-6-boronohexanoic acid (ABH) and some ABH analogues are potent human arginase inhibitors. However, at present, they are not applied in clinical treatments due to their poor pharmacokinetic profiles. Considering the good metabolic stability and high lipophilicity of tetrazole, tetrazole-containing ABH analogues are promising potent human arginase inhibitors. **Chapter 7** describes the design and synthesis of a series of ABH analogues containing tetrazole moiety as human arginase inhibitors. In addition, the inhibitory potency is determined by enzyme assay, and the X-ray crystallography results are presented.

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