Tetrazoles via Multicomponent Reactions

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Tetrazoles via Multicomponent Reactions

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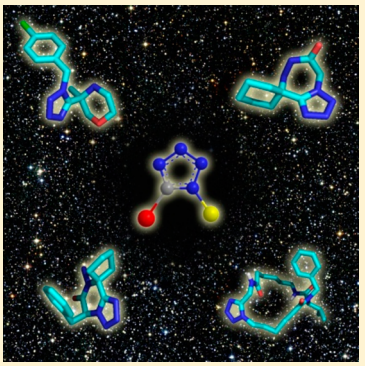
ABSTRACT: Tetrazole derivatives are a prime class of heterocycles, very important to medicinal chemistry and drug design due to not only their bioisosterism to carboxylic acid and amide moieties but also to their metabolic stability and other beneficial physicochemical properties. Although more than 20 FDA-approved drugs contain 1*H*- or 2*H*-tetrazole substituents, their exact binding mode, structural biology, 3D conformations, and in general their chemical behavior is not fully understood. Importantly, multicomponent reaction (MCR) chemistry offers convergent access to multiple tetrazole scaffolds providing the three important elements of novelty, diversity, and complexity, yet MCR pathways to tetrazoles are far from completely explored. Here, we review the use of multicomponent reactions for the preparation of substituted tetrazole derivatives. We highlight specific applications and general trends holding therein and discuss synthetic approaches and their value by analyzing scope and limitations, and also enlighten their receptor binding mode. Finally, we estimated the prospects of further research in this field.



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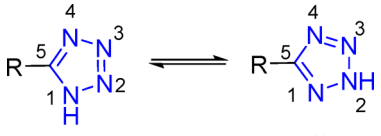
1. INTRODUCTION

Tetrazoles belong to the class of twice unsaturated five-membered ring aromatic heterocycles, consisting of one carbon and four nitrogen atoms. They do not exist in nature. Interestingly, they have the highest number of nitrogen atoms among the stable heterocycles because pentazoles are highly explosive compounds even at low temperature.[1] The first report of the synthesis of a tetrazole derivative was obtained by the Swedish chemist J. A. Bladin in 1885 at the University of Upsala.[2,3] He observed that the reaction of dicyanophenylhydrazine and nitrous acid led to the formation of a compound

Scheme 1. Tautomerism of Tetrazole Derivatives



I (1*H*) II (2*H*)

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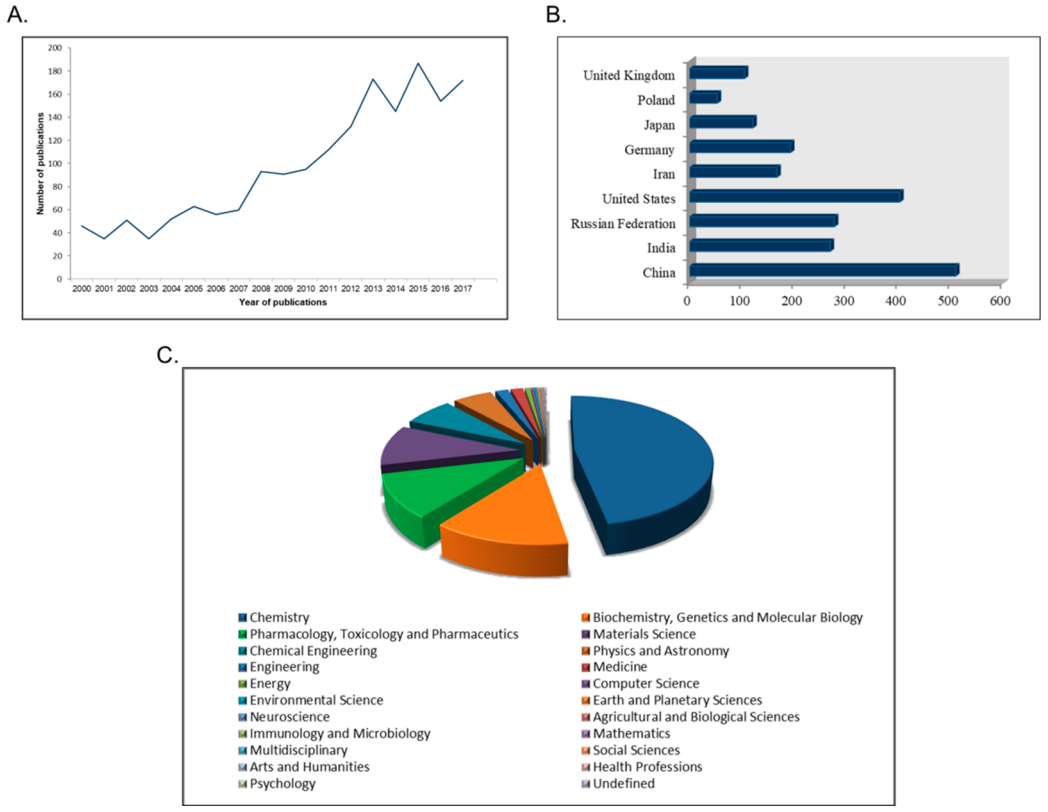

Figure 1. (A) Number of publications containing the keyword "tetrazole(s)" in the title of the articles plotted against the publication date as analyzed by Scopus (December 2018, 2707 articles). (B) Documents by country/territory of most publications contain the keyword "tetrazole(s)" in the title of the articles as analyzed by Scopus (December 2018, 2707 articles). (C) Documents by subject area as analyzed by Scopus.

with the chemical formula of $C_8H_5N_5$ which he later proposed the name "tetrazole" for the new ring structure. On the basis of the number of the substituents, tetrazoles can be classified as un-, mono-, di-, and trisubstituted. 5-Substituted tetrazoles with 6π electrons may exist in tautomeric forms as either I or II (Scheme 1). In solution, the 1*H* tautomer is the predominant form, but in the gas phase the 2*H*-tautomer is more stable.[1]

The tetrazole motif is an important synthetic scaffold that found broad applications in numerous fields such as in medicine, biochemistry, pharmacology, and in industry as materials, e.g., in photography, imaging chemicals, and military.[4−9] Indicatively, tetrazole derivatives are investigated both as a potential explosives and as rocket propellant components based on their high energy properties.[10−14] Moreover, tetrazoles, due to their high number of nitrogen atoms, could serve as an environmentally benign component of gas generators with a high burn rate and relative stability.[15] However, the most important and fruitful application of tetrazoles with many future prospects is their utility in medicinal chemistry.[16−32] Not surprisingly, the number of publications on new drugs and promising biologically active compounds containing the tetrazole moiety increased dramatically the last seven years, 2010−2017 (Scopus, SciFinder, Figure 1).

To date, Drug Bank[33] mentions 43 drugs that contain 1*H*- or 2*H*-tetrazole substituents, 23 of them FDA approved; these compounds possess hypertensive, antimicrobial, antiviral, antiallergic, cytostatic, nootropic, and other biological activities (Table 1).

Bioisosterism,[34] defined as classical or nonclassical, is a useful strategy for rational lead modification and drug design and prevail in medicinal chemistry to alter unfavorable ADME properties and/or to access free patent space. Among $-CO_2H$ isosteres,[35] 5-substituted tetrazole, which has a mobile hydrogen (on the contrary 1- or 2-substituted tetrazole have no mobile hydrogen), is of special interest because it has a comparable pK_a (tetrazole 4.5−4.9 vs carboxylic acid 4.2−4.4), a similar size, spatial arrangement of the heteroatom lone pairs, and a similar molecular electrostatic potential (Figure 2A).[36] Therefore, it often undergoes very similar receptor−ligand interactions.[37,38] However, the tetrazole group often exhibits a prolonged half-life because of the enhanced metabolic stability,[39,40] enhanced spatial delocalization of the negative charge, and better membrane penetration resulting from increased lipophilicity (tetrazoles with a mobile H are ionized at physiological pH (~7.4), but are almost 10 times more lipophilic than the corresponding carboxylates).[41,42] In addition, the high density of nitrogens in tetrazoles could provide more opportunities to form hydrogen bonds or π-stacking with the receptor recognition sites, explaining the sometimes-increased binding affinity.[43] A thorough analysis on Isostar from the Cambridge Structural Database (CSD)[44] showed the probability of occurrence and spatial characteristics of interactions between the 5-substituted tetrazole and different functional groups as −NH (aliphatic and aromatic), −OH (aliphatic, phenol, aromatic), carbonyl (ester, amide, ketones, etc.), and sp^2-N (aromatic N included). This analysis clearly demonstrates a few things: First of all, the similarity with carboxylic acids with the mobile N−H as hydrogen bond donor (Figure 2B−E). The negative charge delocalization among N2−N3−N4 of the tetrazole is obvious (Figure 2B,C), and moreover, the hydrogen bonds via the σ-lone pairs of nitrogens are almost coplanar with the tetrazole plane.[45] Finally, data mining in CSD revealed $\pi-\pi$

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Table 1. 23 FDA Approved and Selected Experimental Drugs Containing the Tetrazole Moiety

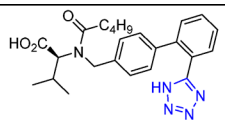
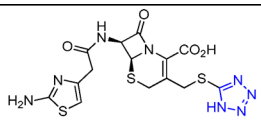
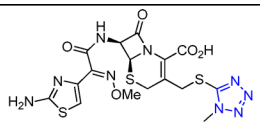
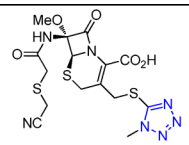
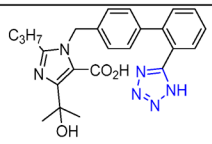
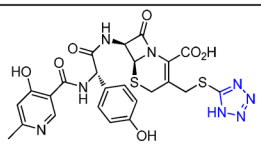
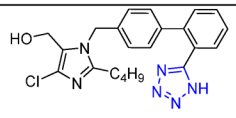
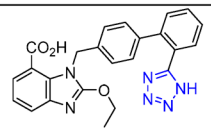
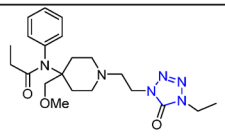
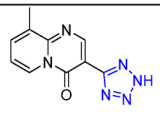
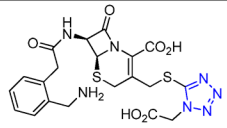
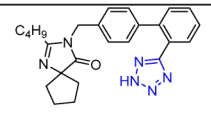
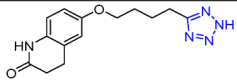
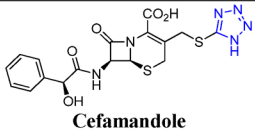
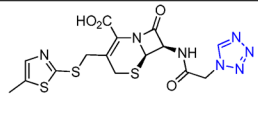
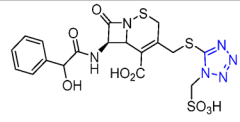
 **Valsartan** DB00177 *Antihypertensive agent, angiotensin II receptor*	 **Cefotiam** DB00229 *A broad spectrum antibiotic against both gram-positive and gram-negative microorganisms*	 **Cefmenoxime** DB00267 *A third-generation cephalosporin antibiotic*	 **Cefmetazole** DB00274 *A broad spectrum antibiotic against both gram-positive and gram-negative microorganisms*
 **Olmesartan** DB00275 *Antihypertensive agent, angiotensin II receptor*	 **Cefpiramide** DB00430 *A third-generation cephalosporin antibiotic*	 **Losartan** DB00678 *Antihypertensive agent, angiotensin II receptor*	 **Candesartan** DB00796 *Antihypertensive agent, angiotensin II receptor*
 **Alfentanil** DB00802 *A short-acting opioid anesthetic and analgesic of fentanyl*	 **Pemirolast** DB00885 *A mast cell stabilizer that acts as antiallergic agent*	 **Ceforanide** DB00923 *A second generation parenteral cephalosporin antibiotic*	 **Irbesartan** DB1029 *An angiotensin receptor blocker (ARB) used mainly for the treatment of hypertension*
 **Cilostazol** DB01166 *Intermittent claudication in individuals with peripheral vascular disease*	 **Cefamandole** DB01326 *A broad spectrum cephalosporin antibiotic*	 **Cefazolin** DB01327 *A broad spectrum antibiotic*	 **Cefonicid** DB01328 *A second generation cephalosporin*

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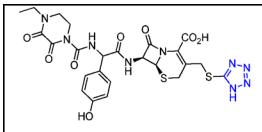
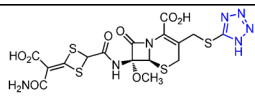
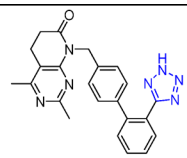
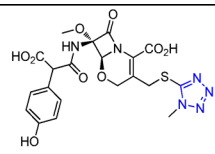
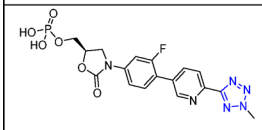
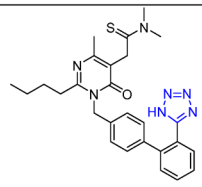
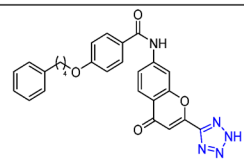
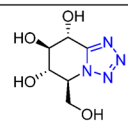
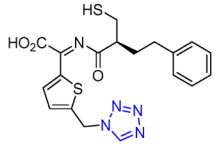
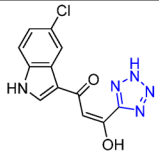
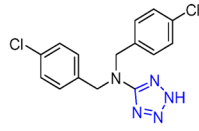
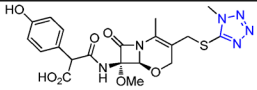
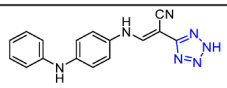
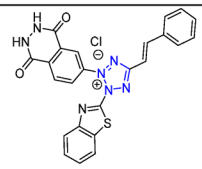
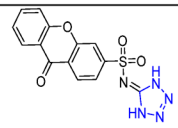
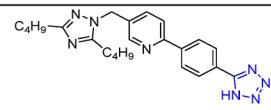
Table 1. continued

 **Cefoperazone** DB01329 *Semisynthetic broad spectrum cephalosporin*	 **Cefotetan** DB01330 *A semisynthetic cephamycin antibiotic*	 **Tasosartan** DB01349 *A long-acting angiotensin II (AngII) receptor blocker*	 **Latamoxef** DB04570 *Broad spectrum beta-lactam antibiotic*
 **Tedizolid Phosphate** DB09042 *oxazolidinone-class antibiotic prodrug*	 **Fimasartan** DB09279 *non-peptide angiotensin II receptor antagonist (ARB)*	 **Pranlukast** DB01411 *A cysteinyl leukotriene receptor-1 antagonist to antagonize or reduce bronchospasm*	 **Nojirimycine Tetrazole** DB02471 *Experimental, target: Glycogen phosphorylase, muscle form*
 DB02706 *Experimental, target: Mercaptocarboxylate Inhibitor*	 DB03118 *Experimental, target: Gag-Pol polyprotein*	 DB04037 *Experimental, target: Beta-lactamase TEM*	 DB04342 *Experimental, target: Beta-lactamase OXA-10*
 DB04430 *Experimental, target: Beta-lactamase TEM*	 DB01897 *Experimental, target: Hematopoietic prostaglandin D synthase*	 DB04698 *Experimental, target: 3-dehydroquinate dehydratase*	 **Forasartan** DB01342 *Experimental, target: angiotensin II antagonist*

interactions of the tetrazole ring with phenyl rings;[46] for the interactions between these two π systems, the T-shaped edge-to-face and the parallel-displaced stacking arrangement are predominant (Figure 2F).

In general, 5-substituted-1*H*-tetrazolic acids exhibit physical characteristics similar to carboxylic acids and are strongly influenced by the effect of substituents at the C5-position. Finally, tetrazoles are more resistant to biological metabolic degradation pathways, for example, β-oxidation or amino acid conjugation.

The same analysis on Isostar for the 1,5-disubstituted tetrazoles showed that most of the aforementioned interactions with different functional groups, due to the absence of the free NH, are focused on the electronegative sp^2 nitrogens of the tetrazole (characteristic examples are given with the −NH and −OH groups, Figure 3A,B). Furthermore, it seems that there is mostly a parallel-displaced stacking arrangement in the $\pi-\pi$ interactions with phenyl groups (Figure 3C).

The most important feature of 1,5-disubstituted tetrazoles, though, is that they are effective bioisosteres for the *cis*-amide bonds in peptidomimetics, whereas the 5-substituted tetrazoles are mostly used as surrogates for carboxylic acids.[37,47−49] In CSD, there are 20272 different crystal structures of amide-surrogates. An analysis of their torsion angle is shown in the

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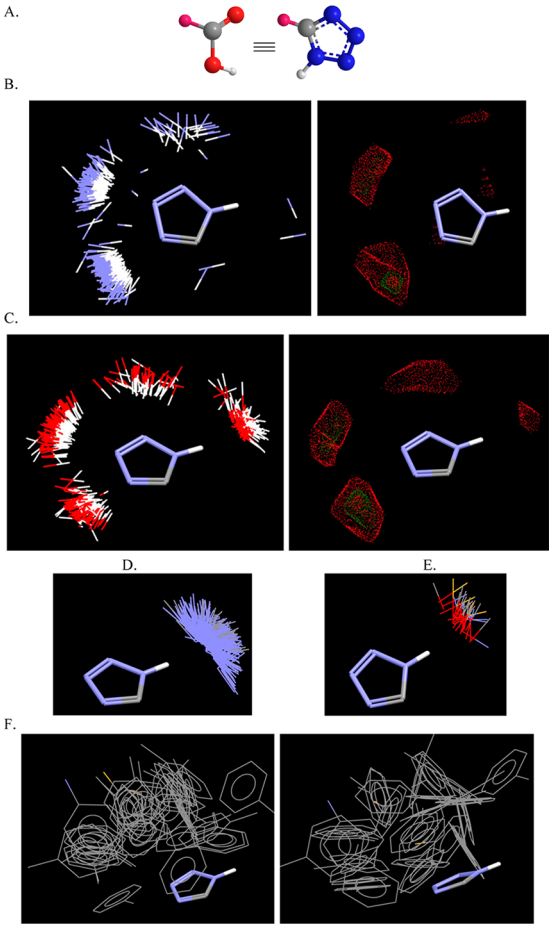

Figure 2. (A) Tetrazolic acids (5-substituted 1*H*-tetrazole or 2*H*-tetrazole) are bioisosteres of carboxylic acids. (B) The interactions of the 5-substituted 1*H*-tetrazoles with any N−H in CSD (655 different plotted compounds, left). The majority of these interactions exist around the two sp^2 3- and 4-nitrogens of the tetrazole ring as shown also by the contour surface (right). (C) The interactions of the 5-substituted 1*H*-tetrazoles with any O−H in CSD (696 different plotted compounds, left). The majority of these interactions is distributed among the sp^2 nitrogens of the tetrazole ring and the N−H, respectively, as shown also by the contour surface (right). (D) The interactions of the 5-substituted 1*H*-tetrazoles with aromatic or sp^2 N in CSD (1315 different plotted compounds), which demonstrate the acidic character of the N−H of the tetrazole. (E) Likewise, the interactions of the 5-substituted 1*H*-tetrazoles with terminal oxygen (carbonyl, amides, esters, acids, etc.) in CSD (159 different plotted compounds) depict the hydrogen bond formation of N−H···O═C. (F) $\pi-\pi$ Interactions of the 5-substituted 1*H*-tetrazoles with phenyl rings (different poses in left and right picture) in T-shaped edge-to-face and parallel-displaced stacking arrangement in CSD (50 different plotted compounds).

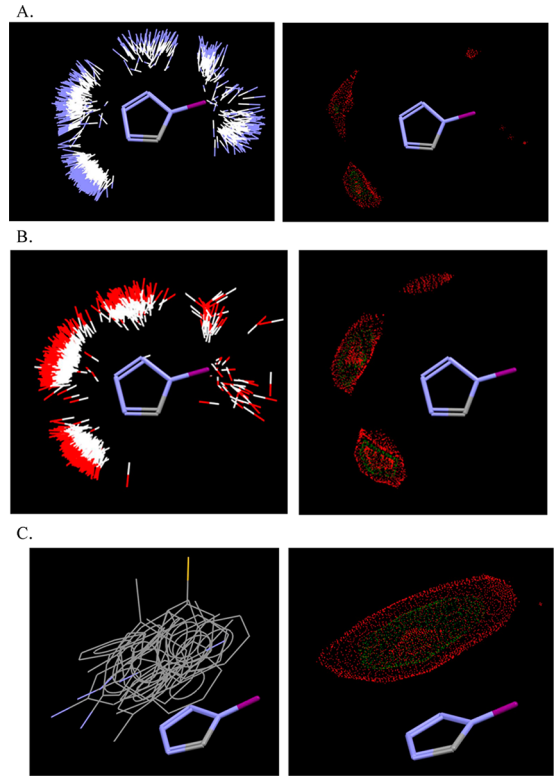

Figure 3. (A) The interactions of the 1,5-disubstituted 1*H*-tetrazoles with any N−H in CSD (2567 different plotted compounds, left). The majority of these interactions exists again around the two sp^2 3- and 4-nitrogens of the tetrazole ring as shown also by the contour surface (right). (B) The interactions of the 1,5-disubstituted 1*H*-tetrazoles with any O−H in CSD (2180 different plotted compounds, left). The majority of these interactions is distributed among the sp^2 nitrogens of the tetrazole ring and the N−H, respectively, as shown also by the contour surface (right). (C) $\pi-\pi$ Interactions of the 1,5-disubstituted 1*H*-tetrazoles with phenyl rings, mostly in parallel-displaced stacking arrangement (left) as shown also by the contour surface (right) in CSD (946 different plotted compounds).

histogram below (Figure 4A). It clearly shows that the majority of these amides are in a *trans* conformation (blue, torsion angle ±180°), and 6961 of the aforementioned structures have a *cis* conformation (red, −30° to +30°). A more close analysis on the *cis*-amide surrogates (Figure 4B) shows a normal distribution with a mean value of 0.007 °.

The average geometrical features, that derived from the inspection of 241 available crystal structures of 1,5-disubstituted tetrazoles compared with the *cis*-amide surrogates, demonstrating the similarity, are shown in Figure 5A. In Figure 5B,C, the plot of the torsion angle (C6−C5−N1-C7) of 1,5-disubstituted tetrazoles is depicted, clearly showing the favorable synperiplanar conformation. However, the distribution is not normal (Figure 5,C, mean value 0.050°). A comparison of the corresponding torsion angles of both *cis*-amide surrogates (blue) and 1,5-disubstituted tetrazoles (red) showed that the latter are more constrained as expected (Figure 5D).

For the reader to have a conclusive and spherical perspective, we made a query in CSD for 2-substituted and 2,5-disubstituted tetrazole derivatives (Figure 6A). We found 14 crystal structures of 2-substituted and 152 crystal structures of 2,5-disubstituted tetrazoles, with the average geometrical characteristics depicted in Figure 6B,C.

For all these reasons, 5-substituted tetrazole represents a first-choice bioisosteric group if the corresponding $-CO_2H$ has issues in medicinal chemistry projects. Thus, effective and time-saving synthetic methods are important to build up libraries of tetrazoles for high-throughput screening or other low-throughput pharmaceutical research applications.

Multicomponent reactions (MCRs) are chemical reactions where more than two compounds react to form a single product with several descriptive features, such as atom economy, efficiency, and convergence.[50,51] In 1961, Ugi et al.[52,53] first reported the use of HN_3 to replace carboxylic acid in the Passerini reaction[54−56] and in the Ugi reaction to form tetrazole

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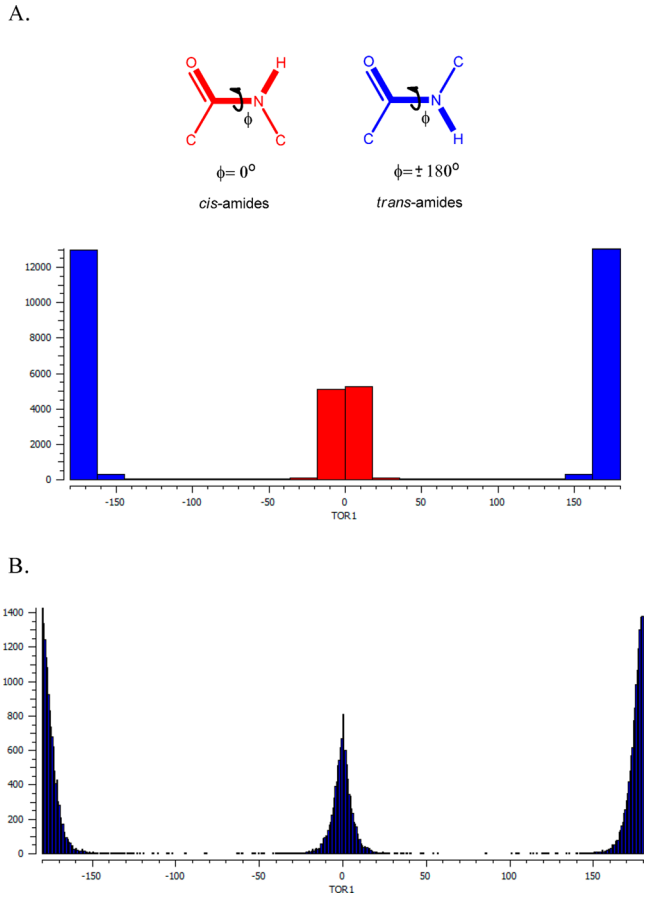

Figure 4. Geometrical features of cis and trans amides. (A) A histogram of the torsion angle analysis. (B) A close-up histogram of the torsion angle analysis.

derivatives, and since then, numerous advancements were published on the synthesis of tetrazoles via MCRs. In this review, we shortly summarize the currently mostly used synthetic routes for the preparation of tetrazole derivatives through non-multicomponent reaction, however, our focus is on the use of multicomponent reactions for the preparation of substituted tetrazole derivatives. We wish to reveal specific applications and general trends holding therein and discuss synthetic approaches and their value by analyzing scope and limitations and estimated prospects of further research in this field. Moreover, we believe that the structural understanding of this scaffold class and its 3D conformations are of uttermost importance for the process of understanding and predicting binding properties of compounds toward its receptor, e.g., in structure-based drug design and in a wider sense to predict properties of specific molecules. Therefore, in addition to synthetic accessibility, we will discuss both the 3D solid state conformations of tetrazole derivatives as well as some cocrystal structures with their protein receptors. Thus, this review covers the literature in this area reported to date as exhaustive as possible. Other published reviews on tetrazoles are more specialized on specific aspects.[57−63]

1.1. Structural Biology of Tetrazoles

As of March 2018, there are 155 tetrazole cocrystal structures present in the Protein Data Bank (PDB, Table 2).[64] Their classification according to their structures showed that the majority of them belongs to the 5-monosubstituted tetrazole derivatives (58%), followed by 1-monosubstituted (18%) and 1,5-disubstituted tetrazoles (14%, Figure 7). The PDB files can serve as excellent resource to study preferential binding poses and interactions of the tetrazole moiety toward the receptors.[65−90] These can be used to understand their bioisosteric character toward the carboxylic acids, elaborate similarities and differences, and develop guiding rules for the use of tetrazole scaffolds in medicinal chemistry (**1** and **2**, Figure 8). Understanding typical binding poses of tetrazoles in certain receptor pockets can help in the structure-based design of novel inhibitors, thus a few selected examples will be discussed.

1.1.1. Tetrazole Undergoes up to Four Hydrogen Bindings with Its Four Nitrogen σ-Lone Pairs. This is exemplified in Figure 9 of a β-lactamase inhibitor complex, where the central tetrazole moiety **3** is embedded between two serines, one threonine, and one water molecule, forming an extended hydrogen bonding network with distances between 2.7 and 2.8 Å.[91] Remarkably, the four receptor heavy atoms involved in the hydrogen bonds are almost coplanar with the tetrazole plane underlining the involvement of the σ-lone pairs of the four nitrogens. This structure also reveals the key difference between the two isosteres, carboxylic acid and tetrazole, based on their lone pairs both which can form in principle four hydrogen bonds, however with differential spatial orientation: The tetrazolyl forms four orthogonal hydrogen bonds in the plane of the five-membered ring, whereas the carboxylate forms four hydrogen bonds along the O-lone pairs in the plane spanned by the three atoms O−C−O.

1.1.2. The Tetrazole Moiety Is an Efficient Metal Chelator Similar to Carboxylate.[92] The X-ray crystal structure of the enzyme bound to the biphenyl tetrazole L-159,061 (**4**) (Figure 10) shows that the tetrazole moiety of the inhibitor interacts directly with one of the two zinc atoms in the active site, replacing a metal-bound water molecule. Two N−N polar interactions and two C−N interactions are presented in Figure 10.

1.1.3. The Tetrazolyl Unit Is Forming an Arg Sandwich.[93] The protein−protein interaction of the Keap1 with Nef2 recently became a hot target in drug discovery for neuro-inflammatory diseases.[94] The tetrazole molecule **5** was described binding to the Kelch domaine (Figure 11). Interestingly, the bioisostere carboxylic acid compound **6** (PDB 4l7B, Figure 12) is also available together with structural biology information, thus providing the opportunity for a direct comparative analysis.[95] The alignment of the two structures is very good, and only small differences in the two ligand and receptor side chain orientations can be observed (RMSD 0.142). Both acid units of **5** and **6** are sandwiched between Arg^{415} and Arg^{380}. However, tetrazole **5** is able to bury a water molecule underneath the tetrazole moiety that makes possible several close contacts to the receptor which cannot be seen with the carboxylic acid **6**. Therefore, the highly buried water molecule can be considered as part of the receptor. Moreover, the conformation of Arg415 is slightly different in **5** and **6**, placing Arg^{415} closer to the two carboxylic acid oxygens by a ∼80° turn around the C2−C3−Arg^{415} bond. Taken together, carboxylic acid **6** binds with an IC_{50} of 2.4 μM, slightly better than the tetrazole **5** with 7.4 μM.

In addition, the in vivo brain exposure was tested for both compounds and several physicochemical and DMPK properties are summarized in Table 3. None of the two compounds showed sufficient brain penetration, likely due to being substrates for efflux pumps phosphoglyco proteins (PGP).

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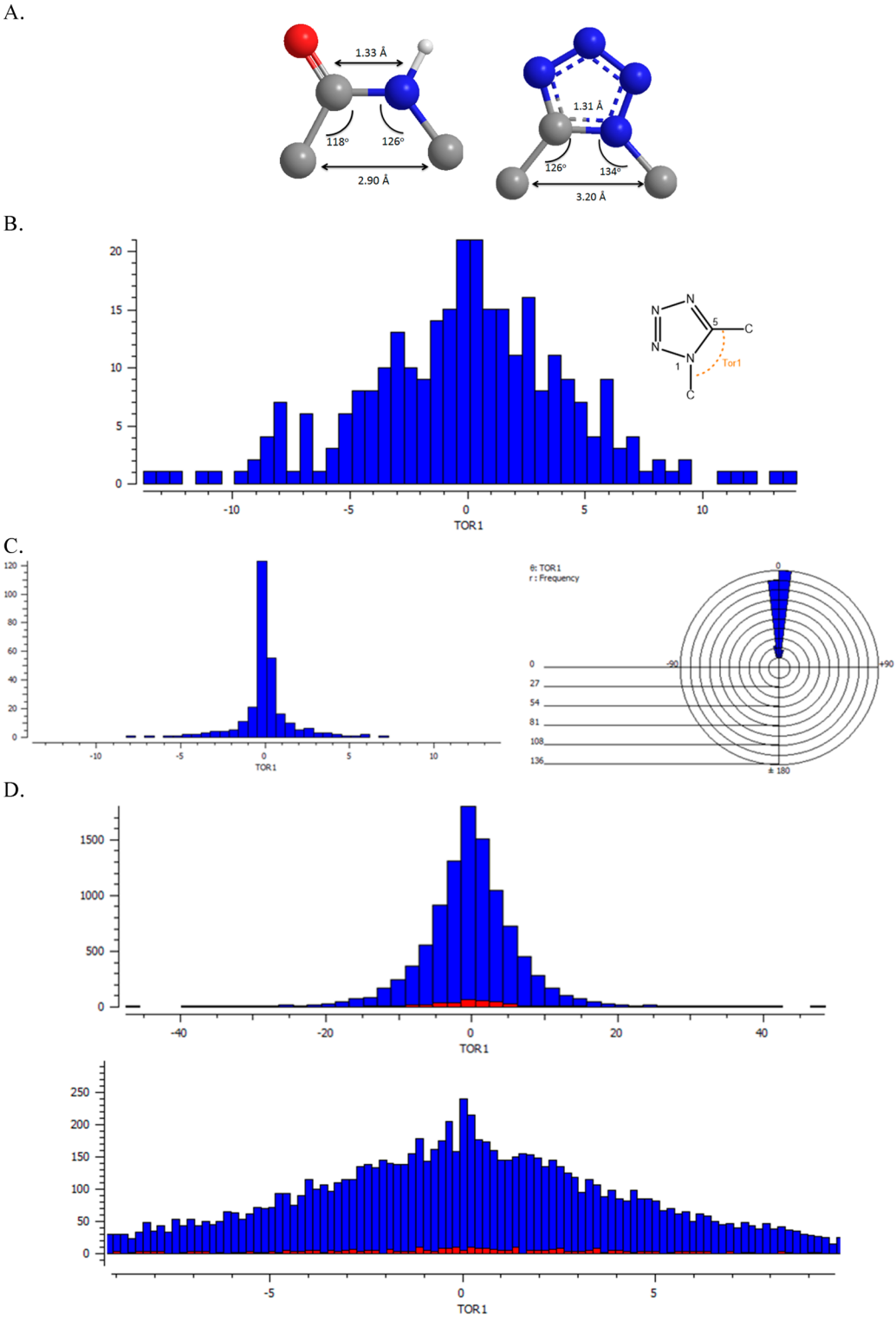

Figure 5. (A) Geometrical features of 1,5-disubstituted tetrazoles as *cis*-amides surrogates. (B) Plot of the torsion angle of 1,5-disubstituted tetrazoles. (C) Corresponding cone angle correlation (left) and the polar histogram (right) revealing the favorable synperiplanar conformation. (D) A comparison of the torsion angle (picture in bottom in zoom pose) between the *cis*-amides (blue) and 1,5-disubstituted tetrazoles (red), showing a more constrained conformation for the latter.

Yu et al.[96] designed inhibitors of the β-catenin/T-cell factor protein−protein interaction by pursuing a bioisosteric replacement approach. The available crystal structures revealed a very large protein−protein contacting surface between β-catenin and Tcf4 of ≥2800 Å^2 (PDB 2GL7). Moreover, biochemical analyses indicate that the dissociation constant (K_d) value of β-catenin/Tcf PPIs is in the 7−10 nM range. To disrupt such a large and tightly binding complex, it requires an extraordinarily high ligand efficiency of the small molecule. Biochemical analysis of truncated and mutated Tcf peptide epitopes revealed several potential hot spots for small molecule design. The Asp16 (D16) and Glu17 (E17) of human Tcf was chosen as a critical binding

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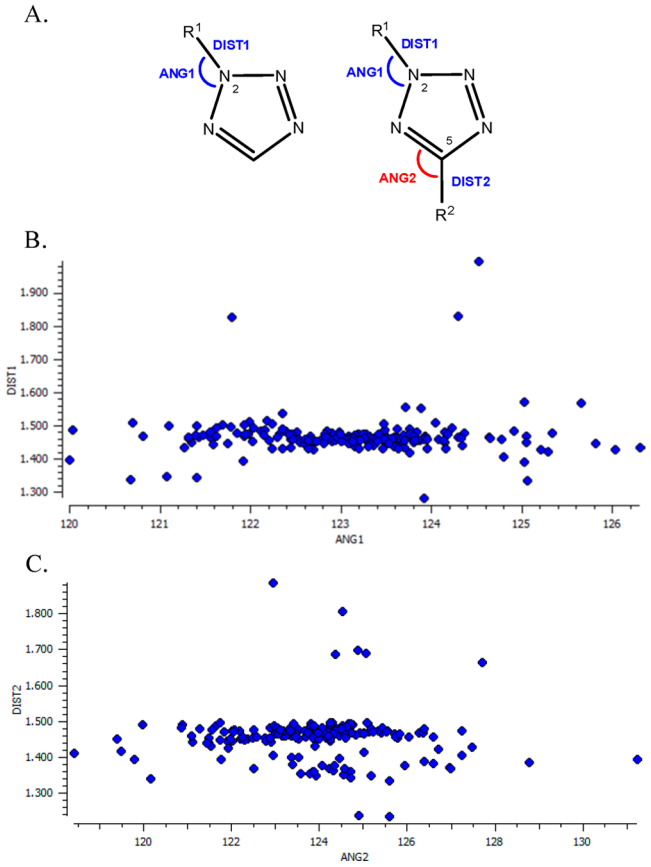

Figure 6. (A) Geometrical features of 2-substituted and 2,5-disubstituted tetrazoles. (B) Scatterplot of the distance R^1–N (DIST1, blue color) with the angle R^1–N-N (ANG1, blue color) of the 2,5-disubstituted tetrazoles with average values of 1.47 Å and 123.1°, respectively. (C) Scatterplot of the distance R^2–N (DIST2, red color) with the angle R^2–N-N (ANG2, red color) of the 2,5-disubstituted tetrazoles with average values of 1.46 Å and 123.9°, respectively.

element and converted into small molecules mimicking this key element (Figure 13).[96] The tetrazole ring (pK_a= 4.5–4.95) was used to replace the carboxyl group of Asp16 (D16) and mimic the charge–charge and H-bond interactions with Lys435 (K435) and Asn430 (N430) of β-catenin. The four lone pairs of the deprotonated tetrazole ring are evenly distributed on the five-membered ring and can form two additional H-bonds with the side chains of His470 (H470) and Ser473 (S473). These two H-bonds do not exist in the β-catenin/Tcf complex. Tetrazole derivative **7** with a molecular weight of 230 and a ligand efficiency of 0.512 has a K_d of 0.531 μM for binding to β-catenin and a K_i of 3.14 μM to completely disrupt β-catenin/Tcf interactions. Replacement of the tetrazole moiety with other carboxyl bioisosteres such as 5-oxo-1,2,4-oxadiazole and 5-thioxo-1,2,4-oxadiazole (pK_a = 6.1–6.7) decreased binding affinity dramatically. According to modeling studies, the tetrazole and the indazole-1-ol moiety mimic the Asp16 carboxylic acid and the carboxyl group of Glu17, respectively (Figure 13).

2. TETRAZOLES THROUGH NON-MULTICOMPONENT REACTION ROUTES

To date, the multitude of synthetic methods of 1,5-disubstituted tetrazoles and monosubstituted tetrazoles have been reviewed several times[58,98–103] and thus will only be briefly mentioned here.

The most common used synthesis of tetrazole derivatives is the 1,3-dipolar cycloaddition reaction between nitriles and azides (azide ion or hydrazoic acid, Scheme 2).[104–114] It was first described by Hantzsch and Vagt[115] in 1901 through a [2 + 3] cycloaddition of an azide to a nitrile (Scheme 2). Electron withdrawing groups lower the LUMO of the nitriles and thus enhance the interaction opportunities with the HOMO of the azide, leading to a smooth reaction.[116,117] However, the requirement of the strong electron withdrawing groups in the nitrile substrate somehow limits the scope of the reaction, needing, in general, high reaction temperature and catalysts. The synthesis of several ω-chloroalkyl tetrazoles and their subsequent attachment to a solid support was also described.[118] Recently, selenium-containing triazole carbonitriles were used as precursors for the corresponding tetrazole derivatives with antioxidant activity based on the aforementioned reaction.[119]

Sharpless et al.,[120–122] among the many existing methods, reported the [2 + 3] cycloaddition of an azide to the *p*-toluenesulfonyl cyanide (TsCN) with a nice substrate scope of aromatic and aliphatic azides under solvent-free conditions followed by simple isolation in good yields (**8a–c**, Scheme 2). Later, they extended this methodology to produce acyltetrazoles **9** in high yields with readily available acyl cyanides and aliphatic azides with simple purification.[123]

Moreover, fused 5-heterotetrazole ring systems **11**, **13**, and **15** were synthesized in high yields via intramolecular [2 + 3] cycloadditions of organic azides and heteroatom substituted nitriles **10**, **12**, and **14**, respectively (Scheme 3). Cyanates, thiocyanates, and cyanamides were employed, yielding various five- and six-membered heterocyclic systems fused to a tetrazole ring.[124]

In addition, the synthesis of more than 20 5-substituted 1*H*-tetrazoles (**17**) was described by Dömling et al.[125] from various, readily available cyanoacetamides **16**.[126] The combination of sodium azide, trimethylamine hydrochloride in toluene at 90 °C afforded the corresponding library in excellent yields with broad reaction scope (Scheme 4).

The 1,3-dipolar cycloaddition reaction between nitriles and azides (azide ion or hydrazoic acid) toward 1,5-disubstituted tetrazoles is well established (Schemes 2 and 3). The [2 + 3] cycloaddition of isocyanides and hydrazoic acid or trimethylsilyl azide leading to 1-monosubstituted tetrazole derivatives by Oliveri and Mandala,[127] at the beginning of 20th century, is also notable. This reaction is less known, however, it is quite general and works both with aliphatic and aromatic substrates having a broader scope than the corresponding nitrile cycloaddition (Scheme 5). Because of the in situ access to a much greater diversity of isocyanides from their formamides,[128] this method offers an alternative pathway for the synthesis of many 1-*N*-monosusbtituted tetrazoles, **18–21**. Considering the importance of this heterocycle, synthetic routes toward labeled tetrazoles have also been described.[129] Very recently, the catalytic visible-light reaction of aliphatic, aromatic, and heterocyclic aldehydes with sodium azide via 1,3-dipolar cycloaddition has been described. The azide not only behaves as three-nitrogen donor of tetrazole ring but also it converts the aldehyde into isocyanide.[130]

Elaborating the above-mentioned reaction, Dömling et al.[125] treated the *N*-substituted 2-isocyanoacetamides[131] **22** with trimethylsilyl azide with 25% cosolvent water in methanol at rt. A library of 18 1-substituted-1*H*-tetrazoles **23** was efficiently

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Table 2. Structure of Selected Tetrazoles with Their Protein Receptors and Its PDB ID

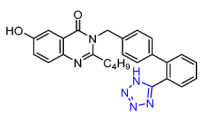
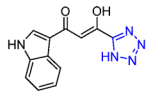
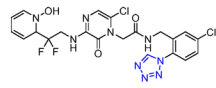
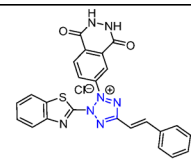
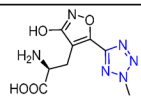
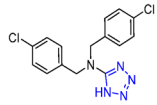
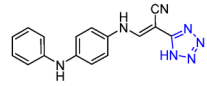
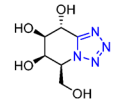
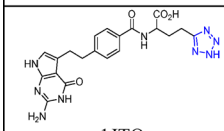
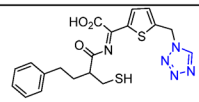
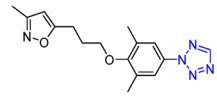
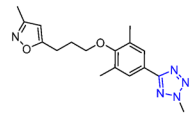
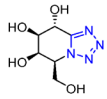
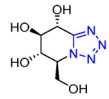
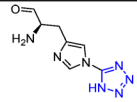
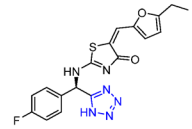
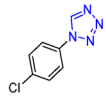
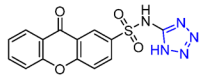
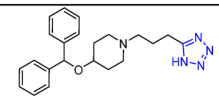
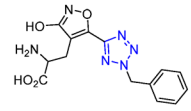
 1A8T *Metallo-β-lactamase*	 1QS4 *HIV-1 integrase catalytic domain*	 1SL3 *P1 Aryl heterocycle-based thrombin*	 1V40 *Human hematopoietic prostaglandin D synthase*
 1M5B *Glur2 ligand binding core (S1S2J)*	 1PZO *TEM-1 β-lactamase*	 1PZP *TEM-1 β-lactamase*	 1JZ6, 3VD7 *E. Coli (lacZ) β-galactosidase*
 1JTQ *Human and escherichia Coli thymidylate synthases*	 1DD6 *IMP-1 Metallo β-lactamase from Pseudomonas Aeruginosa*	 1QJX *Human rhinovirus 16*	 1QJU *Human rhinovirus 16*
 1JZ6, 3VD7 *Escherichia Coli (Lacz) β-galactosidase*	 1E6Q, 1NOI, 1NOJ, 1NOK, 1V08, 2J7B *β-glycosidase*	 1WVP *Chemically modified myoglobin*	 2I1R *HCV NS5B polymerase*
 2C90 *Thrombin*	 2C4W *Helicobacter Pylori type II dehydroquinase*	 2CVD *Human hematopoietic prostaglandin D synthase*	 2P2A *GluR2 ligand binding core (S1S2J)*

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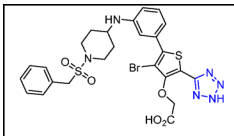
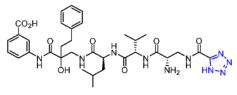
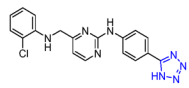
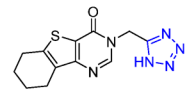
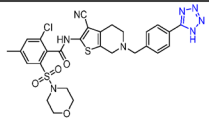
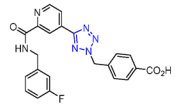
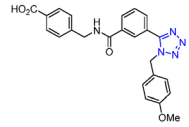
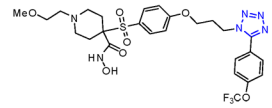
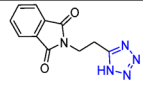
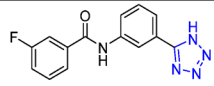
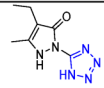
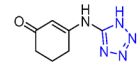
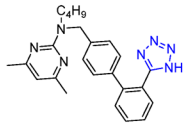
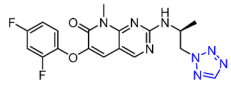
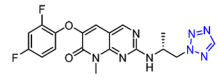
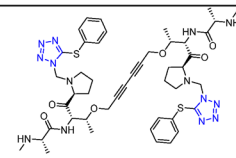
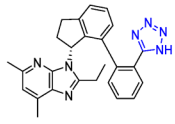
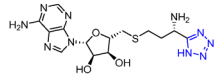
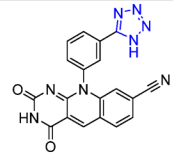
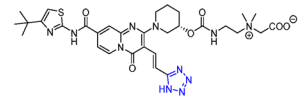
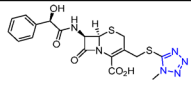
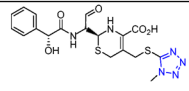
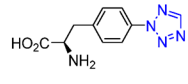
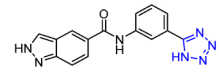
Table 2. continued

 2NT7 *Thiophene PTP1B*	 3KYR *BACE-1*	 3UOL *Aurora A*	 3G34 *CTX-M-9 class A β-lactamase*
 3ZM6 *essential peptidoglycan biosynthesis enzyme Murf*	 3KEJ *Human matrix metalloproteinase-13*	 3KEC *Human matrix metalloproteinase-13*	 3O2X *Human matrix metalloproteinase-13*
 3G32 *CTX-M-9 class A β-lactamase*	 3G35 *CTX-M-9 class A β-lactamase*	 3G2Y, 3GR2 *CTX-M-9 class A and AmpC β-lactamases*	 3G2Z *CTX-M-9 class A β-lactamase*
 3O2M *JNK1-α1 isoform*	 3FMH *p38 map kinase*	 3FMK *p38 map kinase*	 3G76 *XIAP-BIR3*
 3R8A *nuclear hormone receptor PPAR-gamma*	 5EEG *Carminomycin-4-O-methyltransferase DnrK*	 5J3S, 5J3Z *inhibitors of tyrosyl DNA phosphodiesterase 2*	 3W9H, 3W9J *bacterial multidrug exporters*
 3NY4 *BlaC-K73A*	 3N8S *BlaC-E166A*	 3N2Y *Tyrosyl-tRNA synthetase*	 4DE1 *CTX-M-9 Class A β-lactamase*

DOI: 10.1021/acs.chemrev.8b00564
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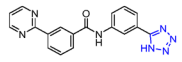
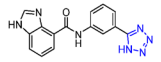
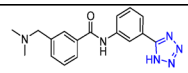
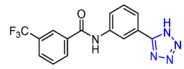
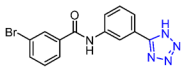
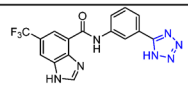
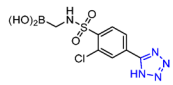
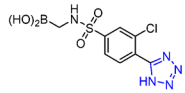
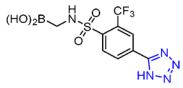
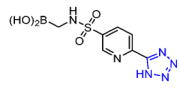
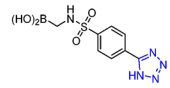
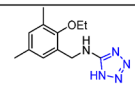
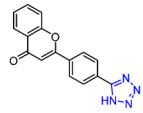
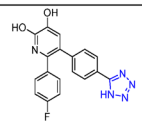
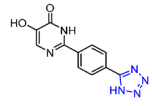
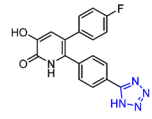
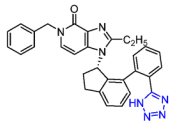
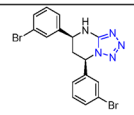
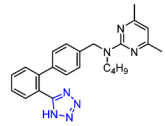
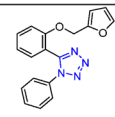
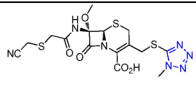
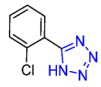
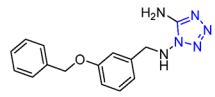
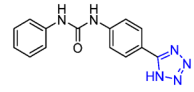
Table 2. continued

 4DDS *CTX-M-9 class A β-lactamase*	 4DE0 *CTX-M-9 class A β-lactamase*	 4DE2 *CTX-M-9 class A β-lactamase*	 4DDY *CTX-M-9 class A β-lactamase*
 4DE3 *CTX-M-9 class A β-lactamase*	 4UA7, 4UAA *CTX-M-14 class A β-lactamase*	 4E3M *AmpC β-lactamase*	 4E3L *AmpC β-lactamase*
 4E3N *AmpC β-lactamase*	 4E3K *AmpC β-lactamase*	 4E3J *AmpC β-lactamase*	 4KAC, 4KAJ, 4KYV *Haloalkane dehalogenase HaloTag7*
 4L34 *Tankyrase 2*	 4M4Q *Influenza 2009 H1N1 endonuclease*	 4W9S *Influenza 2009 H1N1 endonuclease*	 4M5U *Influenza 2009 pH1N1 endonuclease*
 4HEE *PPARgamma*	 4XT2 *High affinity heterodimer of HIF2 α and ARNT C-terminal PAS domains*	 4BXK *Angiotensin-1 converting enzyme N-domain*	 4BO9 *3-Oxoacyl-(Acyl-Carrier-Protein) Reductase (FabG) from Pseudomonas aeruginosa*
 4KOS *GNAT superfamily acetyltransferase PA4794*	 4AJ2 *Rat LDHA*	 4XOZ, 4XRJ *ERK2*	 4UAI *CXCL12 chemokine*

DOI: 10.1021/acs.chemrev.8b00564
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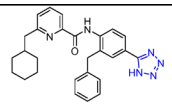
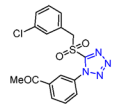
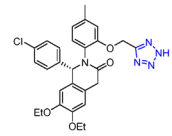
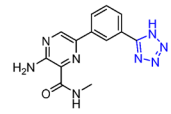
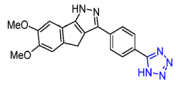
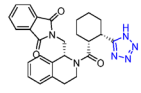
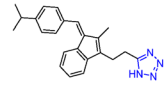
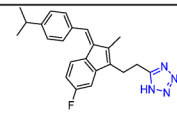
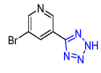
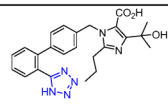
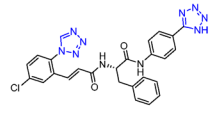
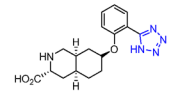
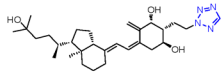
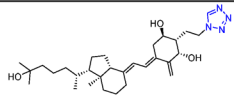
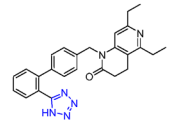
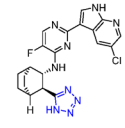
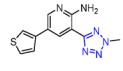
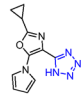
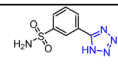
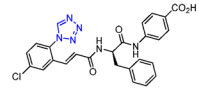
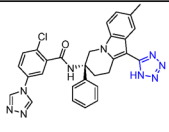
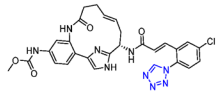
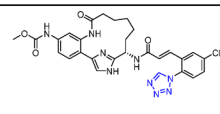
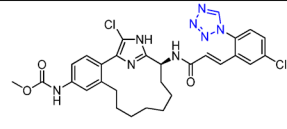
 4P3H *Kaposi's sarcoma-associated Herpesvirus (KSHV) protease*	 4XZ0 *ZAP-70-tSH2*	 4ZYC *p53-MDM2*	 4ANU *PI3Kgamma*
 4FSR *CHK1*	 4L7C *Keap1 Kelch domain*	 4N8R *RXRa LBD*	 4N5G *RXRa LBD*
 4K8A *Focal adhesion kinase*	 4ZUD *Human angiotensin receptor*	 4CRC *F1*	 4MF3 *Human GRIK1*
 4ITE *Human vitamin D receptor ligand binding domain*	 4ITF *Human vitamin D receptor ligand binding domain*	 4YAY *Human angiotensin receptor*	 4YD0 *Influenza Polymerase basic protein 2 (PB2)*
 5ALT *Epoxide hydrolase*	 5AOK *p53 cancer mutant Y220C*	 5A6N *Human death associated protein Kinase 3*	 5E2O *Factor XIa*
 5EGM *Factor Xia*	 5TKT *Factor XIa*	 5TKU *Factor XIa*	 5TKS *Factor XIa*

DOI: 10.1021/acs.chemrev.8b00564
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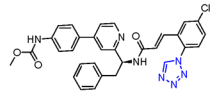
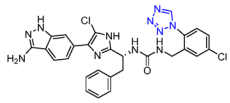
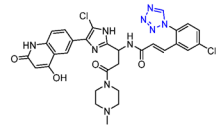
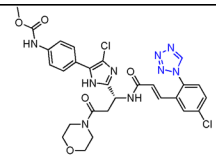
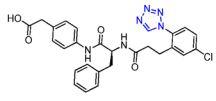
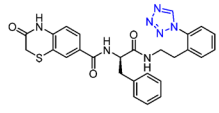
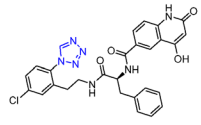
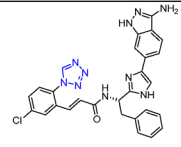
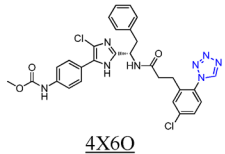
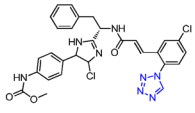
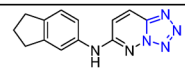
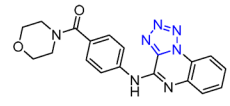
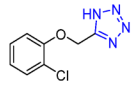
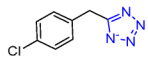
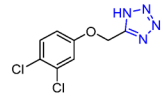
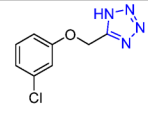
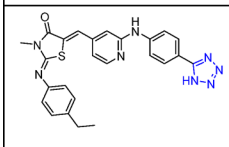
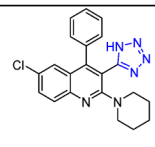
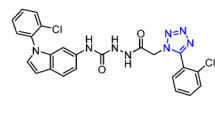
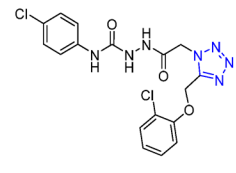
Table 2. continued

 5EXN *Factor XIa*	 4X6N *Factor XIa*	 4Y8Z *Factor XIa*	 4Y8Y *Factor XIa*
 3SOR *Factor XIa*	 3SOS *Factor XIa*	 4CRB, 5E2P *Factor XIa*	 4X6P *Factor XIa*
 4X6O *Factor XIa*	 4Y8X *Factor XIa*	 4BO7 *3-Oxoacyl-(acyl-carrier-protein) reductase (FabG) from Pseudomonas Aeruginosa*	 5DCZ *Tankyrase 2 complexed*
 5FLP *Human carbonic anhydrase II (CA II)*	 5FNG, 5FLO *Human carbonic anhydrase II (CA II)*	 5FNI, 5EH7 *Human carbonic anhydrase II (CA II)*	 5FNH *Human carbonic anhydrase II (CA II)*
 4ZTS *Aurora A kinase inhibitor*	 5HZ5 *Dual fatty acid binding protein 4 and 5 inhibitors*	 5DRY *Dot1L inhibitors*	 5DRT *Dot1L inhibitors*

DOI: 10.1021/acs.chemrev.8b00564
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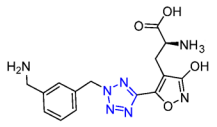
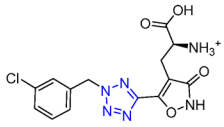
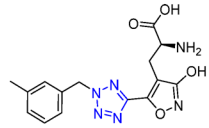
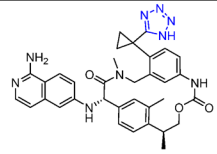
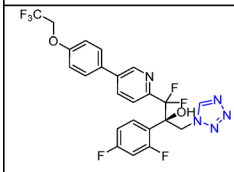
Table 2. continued

 5FHM *AMPA receptor agonist*	 5FHO *AMPA receptor agonist*	 5FHN *AMPA receptor agonist*	 5L30 *macrocyclic tissue factor-factor VIIa inhibitors*
 5AJR *Sterol 14-α demethylase (CYP51) from Trypanosoma Cruzi*			

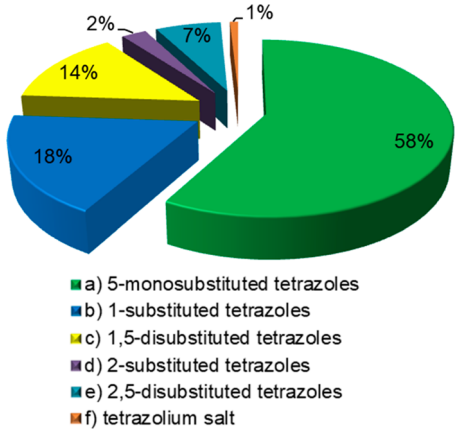


Figure 7. Classification of the selected PDB cocrystal structures of tetrazole derivatives into the categories of 5-monosubstituted tetrazoles (green), 1-substituted tetrazoles (blue), 1,5-disubstituted tetrazoles (yellow), 2-substituted tetrazoles (magenta), 2,5-disubstituted tetrazoles (cyan), and tetrazolium salt (orange).

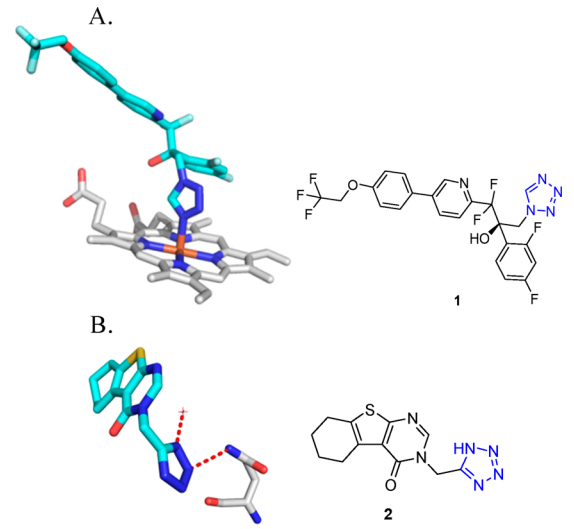


Figure 8. Examples of characteristic receptor−tetrazole binding modes found in the PDB. (A) Sterol 14α-demethylase (CYP51) from *Trypanosoma cruzi* in complex with the 1-monosubstituted-tetrazole derivative VT-1161 (**1**) (PDB 5AJR) exhibiting the metal ligand character of tetrazoles. (B) CTX-M-9 class A β-lactamase complexed with 1*H*-tetrazole **2** (PDB 3G34), exhibiting a hydrogen contact to water and one hydrogen contact to Gln[188] side chain amide.

synthesized as most of the final products were precipitated during workup (Scheme 6).

The synthesis of 1,5-diaryl-substituted tetrazoles **25** was reported by the treatment of amides **24** with tetrachlorosilane/sodium azide using a high wall (HW) pressure vessel at 90 °C in a dry MeCN (Scheme 7). The corresponding derivatives were evaluated as COX-2 inhibitors.[132,133]

3. MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF TETRAZOLES

A main focus of our review is the description of the applications of the MCR synthetic routes toward the tetrazole motif in terms of their utility in medicinal chemistry, understanding the structural behavior on specific examples and their binding properties. Thus, in the following chapter, due to the diversity of tetrazole derivatives, the MCR-based tetrazole syntheses will be classified according to the number of the overall rings, e.g., monocyclic, bicyclic, tricyclic, or polycyclic (Figure 14). Scope and limitations of its scaffold along with the 3D conformations, where available, will be given with special focus on their medicinal and pharmaceutical application.

3.1. Monocyclic Tetrazoles Derivatives

The most important approach to aminomethyl tetrazoles using MCR by far is the Ugi-4CR. Ivar Ugi described the aforementioned reaction in his seminal publication from 1959,

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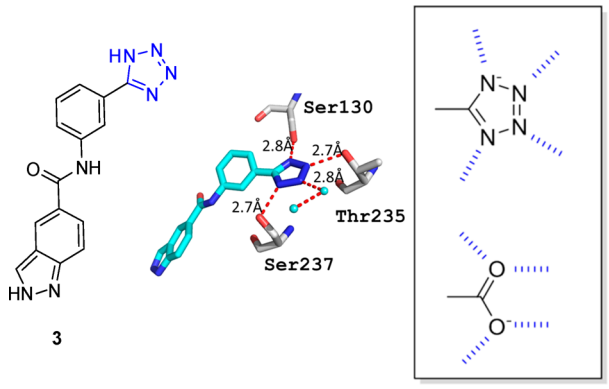

Figure 9. Comparison of the hydrogen bonding pattern of tetrazolyl and carboxyl. Example of a tetrazolyl (**3**) forming four hydrogen bonds (PDB 4DE1).[6] Ser[130] and Ser[237] form each a hydrogen bond to the tetrazole −N2 and −N5 via their side chain −OH at 2.8 and 2.7 Å, respectively. N-3 is in a 2.7 Å contact to the side chain −OH of Thr.[235] The fourth N-4 forms a close hydrogen bonding contact of 2.8 Å to a water molecule, which itself is further involved into hydrogen bonding contacts.

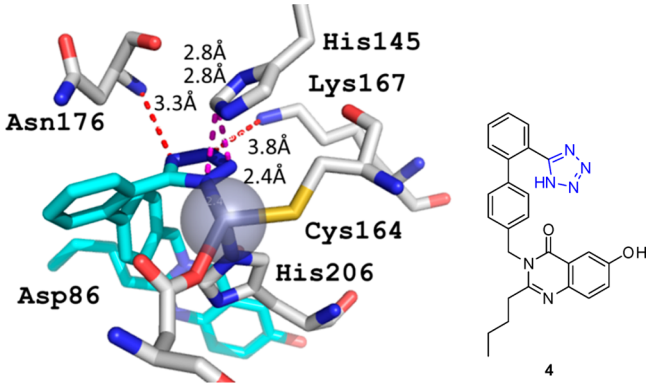

Figure 10. Tetrazole compound **4** as a ligand for the metallo-β-lactamase (PDB 1A8T).[92] The central Zn^{2+} is tetrahedrally coordinated by the ligands tetrazole-N1, the His[206] side chain N3, Asp[86] carboxyl-O, and Cys[164] side chain-S. The tetrazoloyl not only forms a bond to Zn^{2+} but forms several hydrogen bonds to the receptor, including Asn[176] backbone NH (3.3 Å), His[145] side chain NH (2.8 Å), and Lys[187] side chain NH_2 (3.8 Å). Moreover, the His[145] imidazole moiety is on top of the tetrazolyl moiety, forming an electrostatic interaction with an interplane angle of ∼30°.

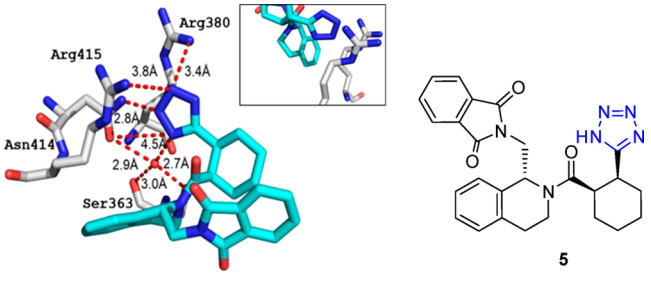

Figure 11. Kelch domain interaction of Keap1 with tetrazole **5** (PDB 4L7C). A dense network of electrostatic and hydrogen bindings contributes to the tight small molecule receptor interaction. It features an interesting sandwich charge−charge interaction driven motive between two positively charged arginines and the tetrazole moiety. The boxed figure shows the Arg sandwich from a different orientation.

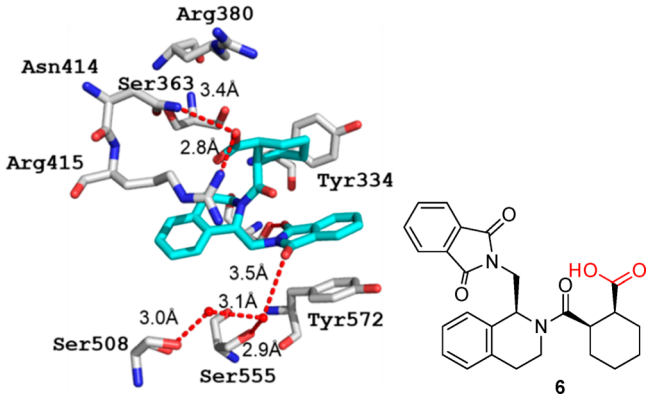

Figure 12. Kelch domain interaction of Keap1 with compound **6** (PDB 4L7B). Same as its bioisostere tetrazole **5**, a dense network of electrostatic and hydrogen bindings also contributes to the tight small molecule receptor interaction. The difference is the weaker interaction between residue Arg[380] and the carboxylic ligand, which is caused by the special orientation of carboxylic group.

Table 3. Physicochemical and DMPK Properties of Compounds 5 and 6

compd	log D^a	polar surface area (PSA) [Å^2]^b	efflux ratio (ER)^c	unbound brain-to-plasma (B_u/P_u)^d	C_u [μM]^e
5 (tetrazole)	0.69	107	NT	<0.01	<0.01
6 (carboxylic acid)	1.36	95	20	<0.01	<0.01
				0.4^a	0.18^a

^{a}Measured at pH 7.4. ^{b}Polar surface area. ^{c}Efflux ratio in MDCK-MDR1 cells (10 mm incubated up to 120 min). ^{d}Unbound brain-to-plasma ratio measured in mice. ^{e}Unbound brain concentration measured in mice at C_{max}.

where he introduced most of the today's important variation of his MCR (Scheme 8).[134] Some years later, again, Ugi was the first who introduced a Passerini MCR variation leading to α-hydroxymethyl tetrazoles,[52,53] a reaction mechanistically related to the Passerini reaction described 30 years earlier (Scheme 8). Furthermore, some other less known MCRs will be discussed. These include reactions involving for example acetylenedicarboxylates and three component reaction of isocyanides, azides, and other nucleophiles, leading to interesting 1,5-disubstituted building blocks.

3.1.1. Ugi Tetrazole Four-Component Reaction (UT-4CR). α-Aminomethyl tetrazoles are of great importance due to isosterism to α-amino acids. The classical Ugi tetrazole (UT-4CR) synthesis presents a broad scope regarding to the starting materials, i.e., isocyanides, oxo components, and amines (Figure 15). A representative set of UT-4CR adducts (**26**−**38**) that have been cited in this review is presented in Figure 16. In parallel synthesis of UT adducts, among others, in 96-well plates have also been described enabling the production of 5000−10000 compound range.[135] This also demonstrates one very attractive feature of MCRs, the relative ease of its automation. The UT-4CR differs from the classical Ugi-4CR in that the azide traps out the intermediate nitrilium ion (replacing the carboxylic acid seen in the classical Ugi variation), leading to the formation of the final 1,5-disubstituted tetrazole. The reaction is often performed in methanol, however, 2,2,2-trifluoroethanol or biphasic water chloroform mixtures were also reported.[136−139] Recently, an ultrasound accelerated UT-4CR was described without solvent

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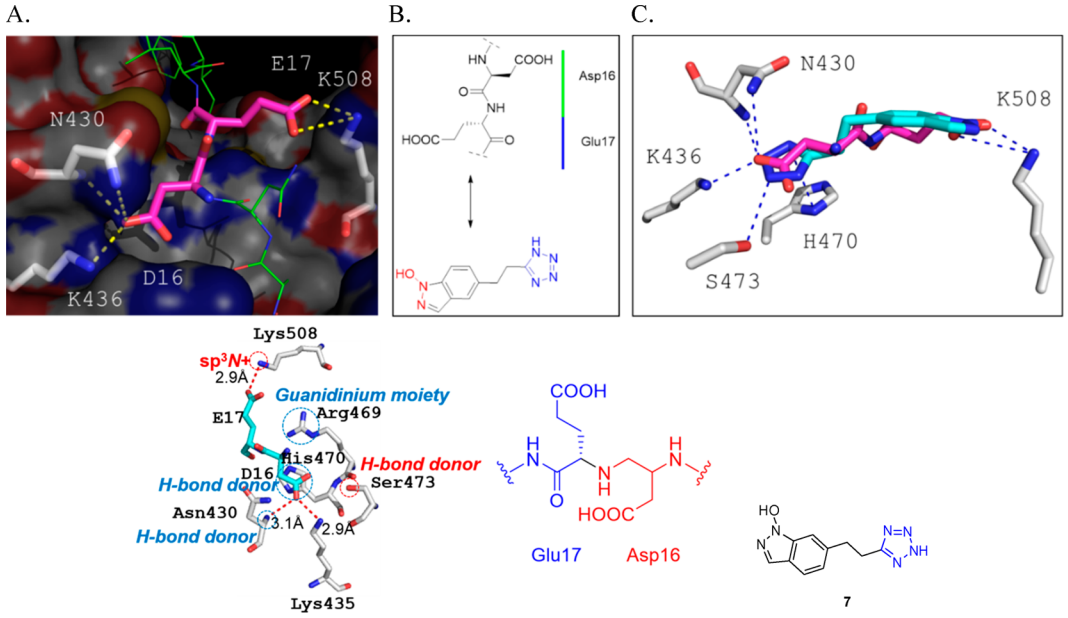
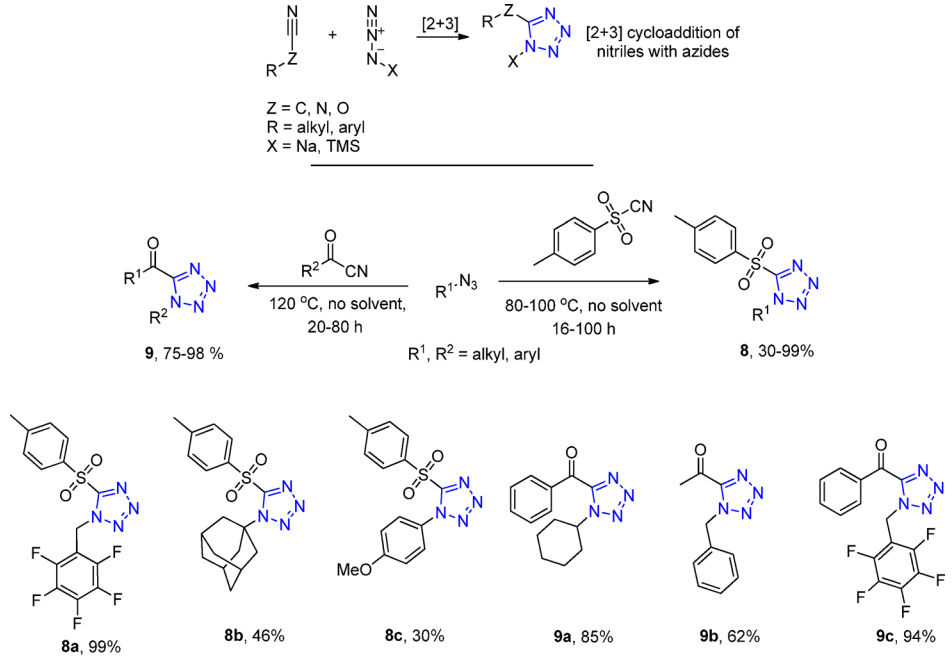


Figure 13. Bioisosteric replacement strategy for the design of β-catenin/Tcf protein protein interaction. (A) Hot spot of β-catenin/Tcf interaction showing key electrostatic interactions (PBD 2GL7).[97] Tcf peptide is shown in pink and green, and the hot spot Asp16-Glu17 is highlighted as pink sticks. β-Catenin is shown as surface representation, and interacting amino acids are shown as gray sticks. (B) Bioisosteric replacement step. (C) Close-up analysis of the aligned **7** and Asp16-Glu17 of Tcf with the β-catenin receptor. The indazole-1-ol forms H-bond and charge−charge interactions with β-catenin Lys508. The tetrazole ring was used to replace the carboxyl group of Asp16 and mimics the charge−charge and H-bond interactions with Lys435 and Asn430 of β-catenin. The deprotonated tetrazole ring with two more Lewis bases can form two additional H-bonds with the side chains of His470 and Ser473. These two H-bonds do not exist in the β-catenin/Tcf complex.

Scheme 2. Different Synthetic Routes to Tetrazoles Using Non-Multicomponent Reactions



based on a water-triggered formation of hydrazoic acid via single-proton exchange with TMS azide.[140] The reaction is generally fast at room temperature; only some special educt combinations require heating, for example, the reaction of bulky trityl amine.[141,142] The UT-4CR is considerably more exothermic than the classical Ugi four-component condensation of isocyanides, oxo components, primary amines, and carboxylic acids, yielding the α-aminoacylamides. Therefore, the addition of the components, especially on a larger scale, should proceed carefully under cooling. The order of addition of the components in the Ugi reaction in most cases does not really matter and the yields are comparable. Often the components are added to the reaction's vessel in the order of oxo component, amine, isocyanide, and finally the azide source. In the past, Ugi was using isolated hydrazoic acid in a benzene stock solution.[143] Nowadays the safer substitute trimethylsilylazide (TMS azide, $TMSN_3$) is utilized, which forms in situ the hydrazoic acid in the typically used protic alcoholic solvent. Alternatively, especially if

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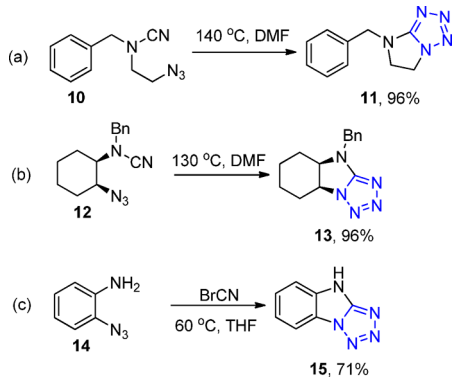
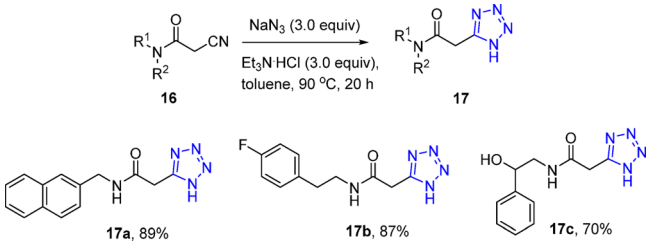
Scheme 3. Intramolecular Cycloaddition of Azidonitriles: (a) Heterocyclic Nitrile, (b) Aliphatic Nitrile, (c) Aromatic Nitrile

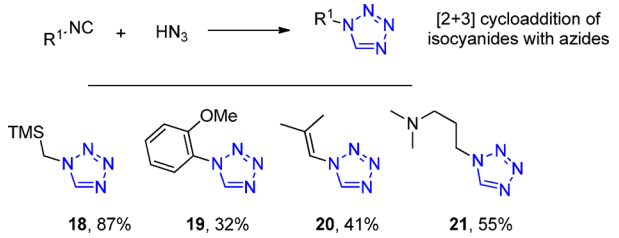


Scheme 4. Synthesis of 5-Substituted 1*H*-Tetrazoles 17 via *N*-Substituted Cyanoacetamides

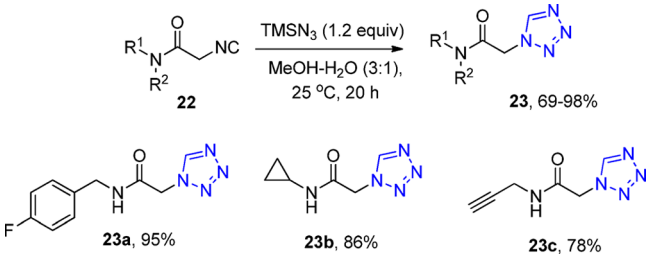


ammonium salts of the primary or secondary amines are used, the hydrazoic acid source should be sodium azide. Both aromatic and aliphatic isocyanides work well, whereas the functional groups of the isocyanide side chain are often well tolerated, e.g., the amino acid derived isocyano esters work nicely (Figures 15 and 16). However, α- and β-amino acid derived isocyano methyl esters can cyclize with the primary or secondary amine of the

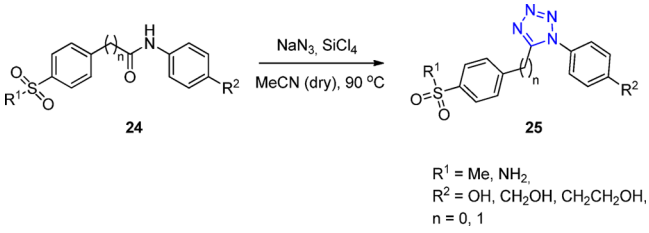
Scheme 5. Synthesis of 1-Substituted Tetrazoles by Click Reaction of Azides and Isocyanides



Scheme 6. Synthesis of 1-Substituted 1*H*-Tetrazoles 23 via *N*-Substituted Cyanoacetamides



Scheme 7. Synthesis of 1,5-Diaryl-Substituted Tetrazoles 25 via Amides 24



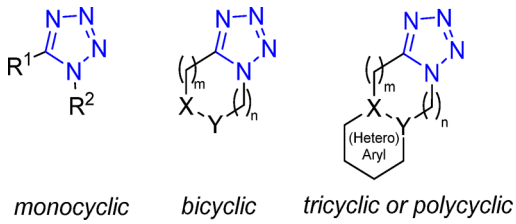
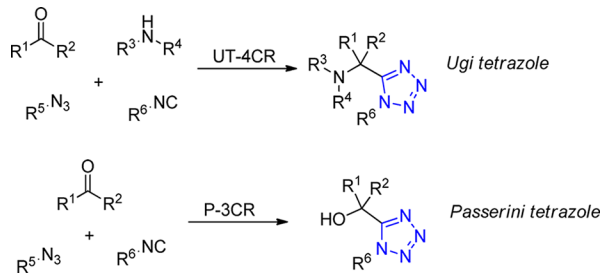


Figure 14. Classification of the MCR-based synthesis of tetrazole derivatives according to the number of cycles.

Scheme 8. Tetrazole MCRs Overview



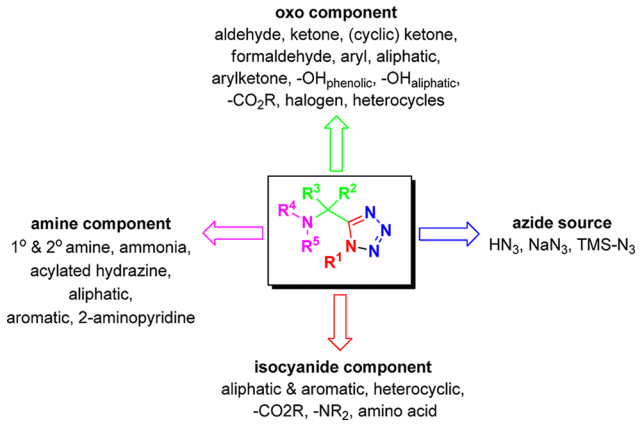


Figure 15. Scope and limitations of the UT reaction.

tetrazole side chain, forming δ-lactams. This has been advantageously used to create tetrazoloketopiperazines and will be discussed below. Oxo components can be aldehydes, ketones, and substituted variants thereof. Substituted benzaldehydes, heteroaromatic aldehydes, including formyl-ferrocene and substituted aliphatic aldehydes, glyoxals, formaldehyde, cyclic and acyclic aliphatic ketones, and monosubstituted arylketones work efficiently (Figure 15, 16).[144] In the UT-4CR, both primary and secondary amines react well, comparing with the classical U-4CR where normally only primary amines are involved.[145−151] The amines can be both aliphatic and aromatic and widely substituted. Even the super bulky trityl

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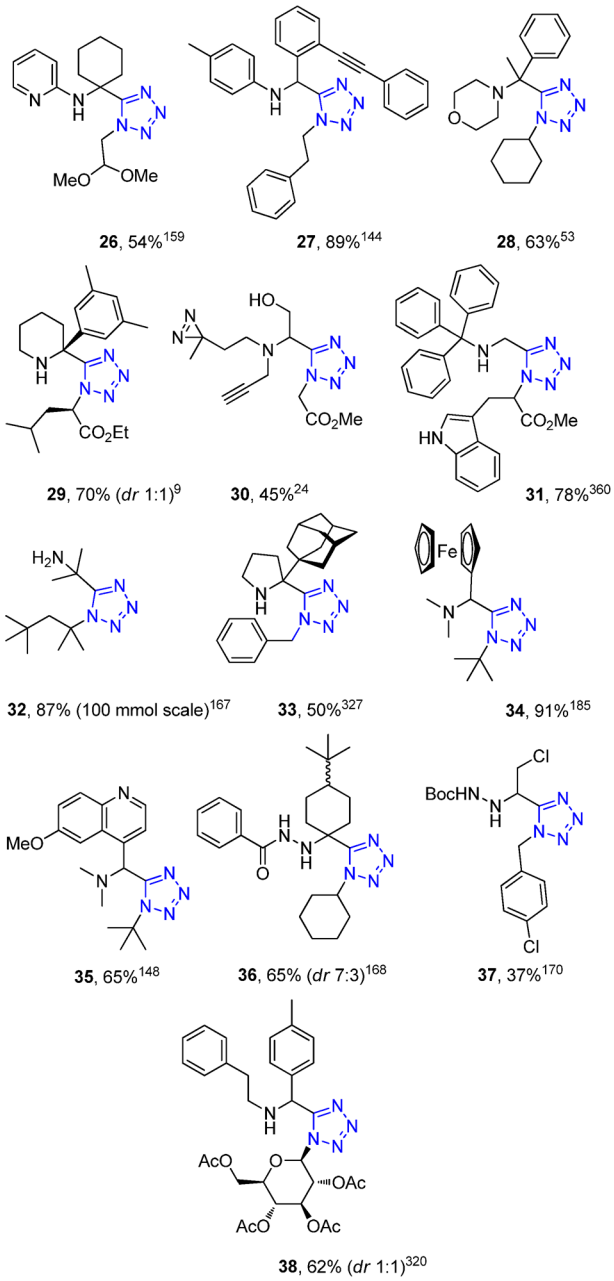
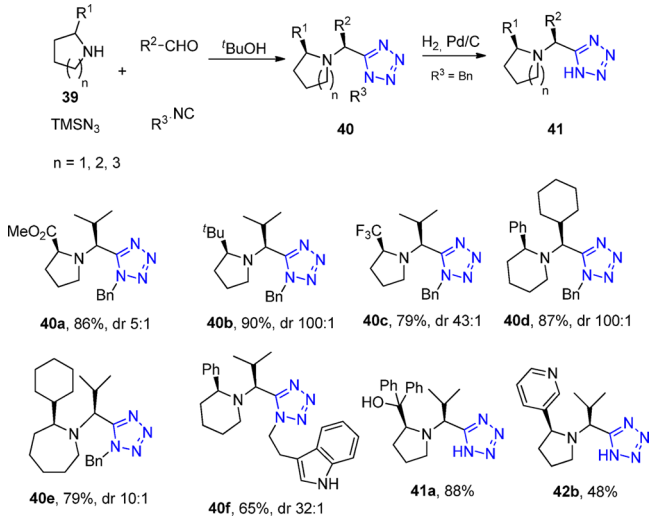


Figure 16. SAR of the UT-4CR and typical reaction products (**26**–**38**) which are cited in the current review underlining the scope of the reaction.[9,24,53,144,148,159,167,168,170,185,320,327,360]

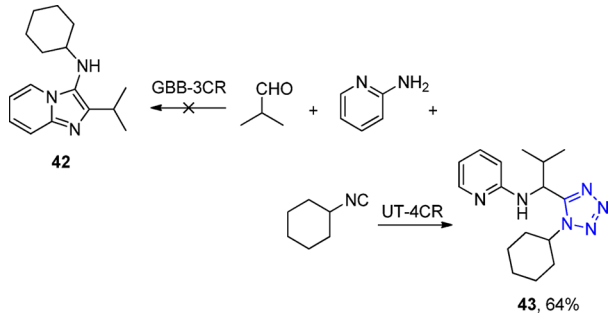
amine can react with aliphatic aldehydes to give compound **31**, however, only under microwave conditions due to the slow Schiff base formation (Figures 15 and 16).[141,142] Notably, ammonia, which causes often problems in other Ugi variations, reacts reasonably well with ketones in the UT-4CR (see compound **32**).[136,152−155] In 2007, Marcaccini and Torroba[156] described a detailed protocol for the UT-4CR, including the general mechanism and the effects of the nature of the components as well as the reaction conditions on the Ugi reaction.

Recently, Nenajdenko et al.[9,157] studied the diastereoselectivity of the UT-4CR with cyclic amines **39**, yielding the derivatives **40** and **41** (Scheme 9). They found that the reaction with α-substituted five- to seven-membered cyclic amines provided high control of diastereoselectivity (≤100% de,

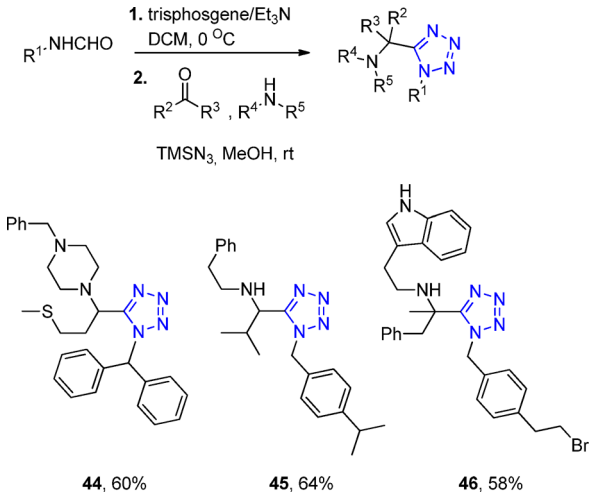
Scheme 9. Stereoselective Synthesis of Tetrazole Derivatives 40 and 41 via a Diasteroselective UT-4CR with Secondary Cyclic Amines



Scheme 10. UT-4CR vs GBB-3CR of the 2-Aminopyridine



Scheme 11. Isocyanide-less Ugi 4-CR Tetrazole Variation (UT-4CR)



≤98% yields) under mild conditions. As a matter of fact, the diastereoselectivity of the reaction depends on the ring size of the starting cyclic amines. More rigid piperidines provided the highest selectivity of the reaction.

Interestingly, the 2-aminopyridine, prone to undergo the Groebke−Blackburn−Bienaymé multicomponent reaction (GBB-3CR) with isocyanides and aldehydes in a competing

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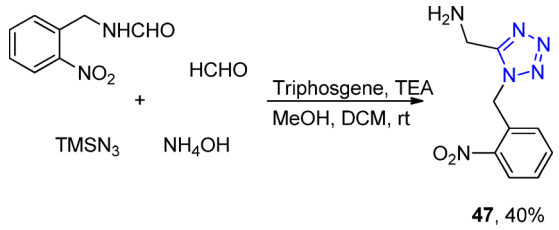
Scheme 12. Example of an Application of the Isocyanide-less UT-4CR to Synthesize the Photocleavable Tetrazole Derivative 47



reaction, reacts in the UT-4CR selectively as an amine component.[158−160] Apparently, the GBB-3CR (**42**) has slower kinetics than the UT-4CR (**43**) (Scheme 10).

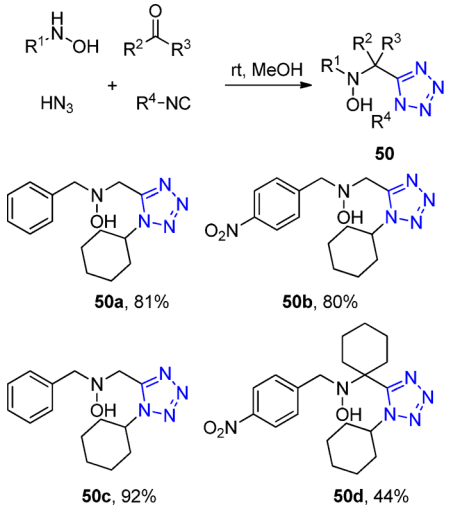
Taken together, the UT-4CR is very easy to perform[156,161] and has an amazingly great scope in all three classes of variable starting materials, especially combined with the in situ generation of the isocyanides.[128] The substrate scope includes diverse substituted aldehydes and ketones, substituted formamides, and a multitude of primary and secondary amines, yielding the 1,5-disubstituted tetrazoles, e.g., **44**−**46** in yields of 39−64% (Scheme 11). Another application of this in situ method is the access without the need of protecting group to photoinducible probe **47**, a bioisostere of the important neurotransmitter glycine. Photocleavable tetrazole was synthesized, via an UT-4CR, using the Leuckart−Wallach accessible *o*-nitrobenzyl formamide (Scheme 12). Since its first description in 1959, many researchers have used the UT-4CR, and some applications are highlighted in the following.

In 1972, Zinner et al.[162] started the early studies of UT-4CR using amine variations. In this approach, the corresponding diaziridine reacted with formaldehyde, cyclohexyl isocyanide, and HN_3 to generate diaziridine tetrazole derivatives **48**, however, in low yields. The subsequent acidic treatment opens up the diaziridine ring, giving, unexpectedly, quantitative yield of the hydrazone derivative **49** (Scheme 13).

Continuing their studies, in 1974, Zinner et al.[163] described an UT-4CR approach to 1,5-disubstituted tetrazoles using hydroxylamines as amine components. Reaction with formaldehyde in the presence of cyclohexyl isocyanide and hydrazoic acid (HN_3) afforded the corresponding 1,5-disubstituted tetrazole methylene hydroxylamines **50**. Sterically hindered cyclic ketones and different substituted benzylhydroxylamines led to the expected products at mild reaction conditions though with lower yields (Scheme 14).

The basic amino group is highly hydrophilic and also a good hydrogen bond acceptor which is of use for potential drug candidates. Ammonia and other amine-like components have been reported sporadically in Ugi reactions, however, they often afford mixed or poor yields, e.g., hydroxylamine, *N*-acylated hydrazine, *N*-sulfonated hydrazine, and unprotected hydrazine.

Scheme 14. Hydroxylamines as Amine Equivalents in UT-4CR

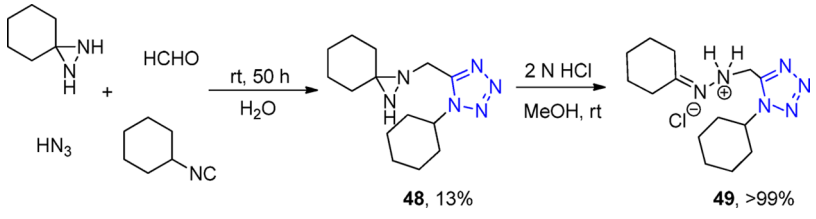


Dömling et al.[141] introduced tritylamine as a convenient ammonia substitute in the Ugi tetrazole synthesis, synthesizing 15 trityl protected 1,5-disubstituted tetrazole derivatives **51** in satisfactory to good yields. The trityl deprotecting reaction went through a mild acidic condition, with quantitative yields affording tetrazoles **52**. Ammonia, as it was expected, was found to lead to a mixture of multiple products caused by its high reactivity (Scheme 15, Figure 17); HPLC-MS analysis of the reaction of *tert*-butyl isocyanide with formaldehyde, ammonia, and TMS-azide revealed such a mixture of mono-, di-, and tri-Ugi products.

However, this problem was overcome by using ammonium chloride as the ammonia source.[164] With in-depth scope and limitation study with more than 70 oxocomponents and 15 isocyanides, it was shown that the UT with ketones, isocyanides, sodium azide, and ammonium chloride afforded the free-amino tetrazoles **53** (Scheme 16). The primary amine component of the α-amino tetrazole is a versatile starting material for further reactions because it can be converted to the tetrazole deprotected α-amino tetrazole compound[165] **54** by choosing the 1,1,3,3-tetramethylbutyl isocyanide (Walborsky's reagent).[166] As a matter of fact, Dömling et al.[167] utilized this α-amino tetrazole as the primary amine component in an U-3CR (a so-called "truncated" Ugi reaction, not involving a carboxylic acid) toward the synthesis of the compounds **55** (with more than 50 derivatives), expanding even more the chemical space, establishing a library-to-library approach (Scheme 16, Figure 18).

Balalaie et al.[168,169] reported a novel and efficient method for the diastereoselective synthesis of α-hydrazine tetrazoles **56** using cyclic ketones, TMS azide, hydrazides, and the

Scheme 13. UT-4CR to Diaziridine Tetrazole Derivative 48



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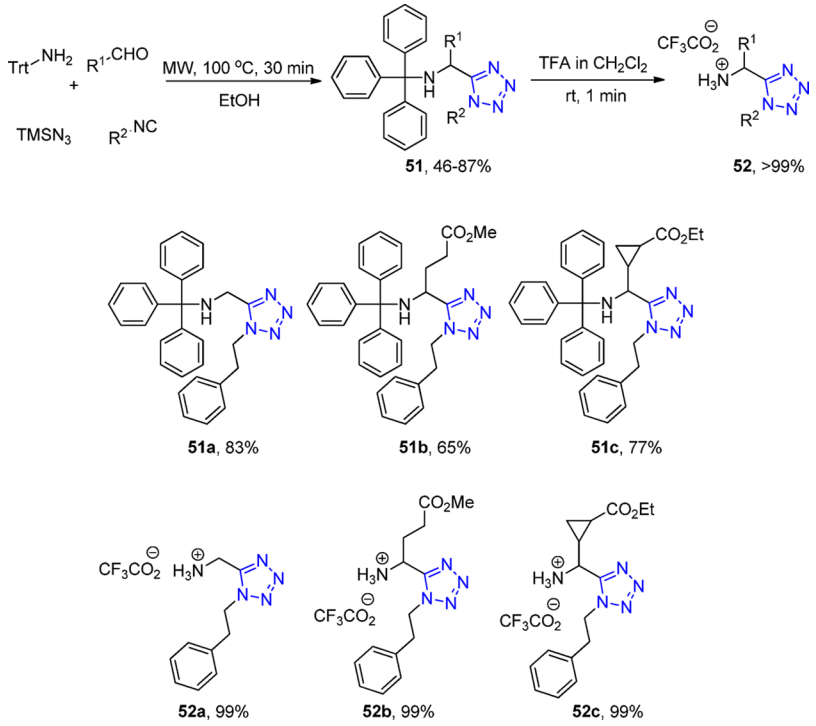
Scheme 15. A Synthetic Pathway to *N*-Unsubstituted Primary α-Aminotetrazoles 52 Using an Ugi-4CR Employing Tritylamine As an Ammonia Surrogate



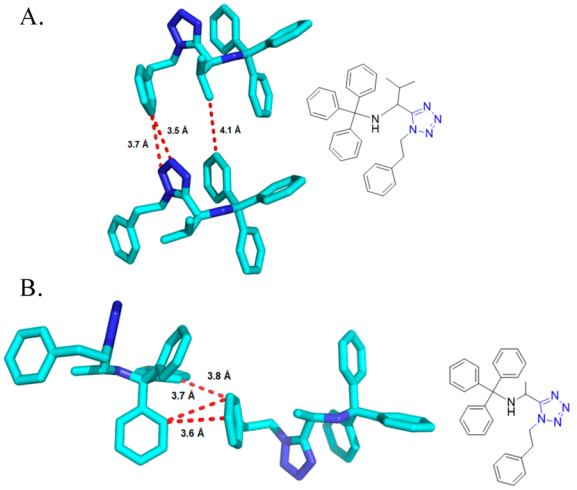


Figure 17. Crystal structures of tetrazole derivatives **50d,e**. They are dominated not only by π-stacking and hydrophobic interactions between the trityl group, the alkyl group, and the phenylethyl groups but also the tetrazole ring makes short intermolecular contacts (CCDC 903083 and 903084).

corresponding isocyanides without any catalyst via an UT-4CR in mostly good yields (Scheme 17). Two diastereomers were observed during the Ugi reaction with dr up to 4:1. On the basis of a solved X-ray structure, the major diastereomer was found to have *trans* configuration (Figure 19).

Dömling et al.[170] synthesized via a two-step procedure a series of 1-substituted 5-(hydrazinylmethyl)-1-methyl-1*H*-tetrazoles **58** by an UT-4CR using Boc-protected hydrazine, various aldehydes or ketones, isocyanides, and TMS azide with a subsequent deprotection (**57**, Scheme 18, Figure 20). To further improve the yield of the Ugi reaction, $ZnCl_2$ was used as a catalyst increasing the Schiff base formation. The straightforward access to highly substituted hydrazines is of interest because hydrazines can act as aspartic protease inhibitors interacting through charge−charge interactions with the active side aspartate residues.

An application of secondary amines in UT-4CR was reported by Dömling et al.[165] by investigating a versatile and commercially available isocyanide, the 1-isocyanomethylbenzotriazole **59** (BetMIC). Initially, BetMIC was reacted with an enamine and TMS azide in methanol to form the expected tetrazole in good yields. Moreover, in the following cleavable step, they observed the almost quantitative and mild cleavage of the Ugi product to give the expected α-aminomethyl tetrazole **60** (Scheme 19).

The concept of convertible isocyanides was introduced as early as 1963 by Ugi with cyclohexenyl isocyanide, which can be cleaved in the Ugi reaction product using acidic conditions.[171] This concept was later extended by many others.[166,172−175] Convertible isocyanides are highly useful in that they can be transformed into other functional groups during a multistep synthesis of complex molecules, e.g., natural products.[176] However, the majority of the work performed concerns the transformation of the secondary amide formed during the Ugi and Passerini reactions into esters, thioesters, ketones, carboxylic acids, and other groups. Despite the increasing popularity of using convertible isocyanides for further molecular modification, these isocyanides suffer from major disadvantages such as lengthy synthesis procedures, instability, incompatibility with delicate substrates, laborious workup, and multistep cleavage. Furthermore, these isocyanides are only applicable in one type of reactions either U-4CR or UT reactions.

Mayer et al.[177] chose two new cleavable isocyanides, the 3-isocyano-3-phenyl-ethylpropionate (**61a**) and the 2-isocyano succinic acid dimethyl ester (**61b**), in order to react with aldehydes, amines, and TMS azide synthesizing a library of UT adducts (**62**) bearing three points of diversity in good yields.

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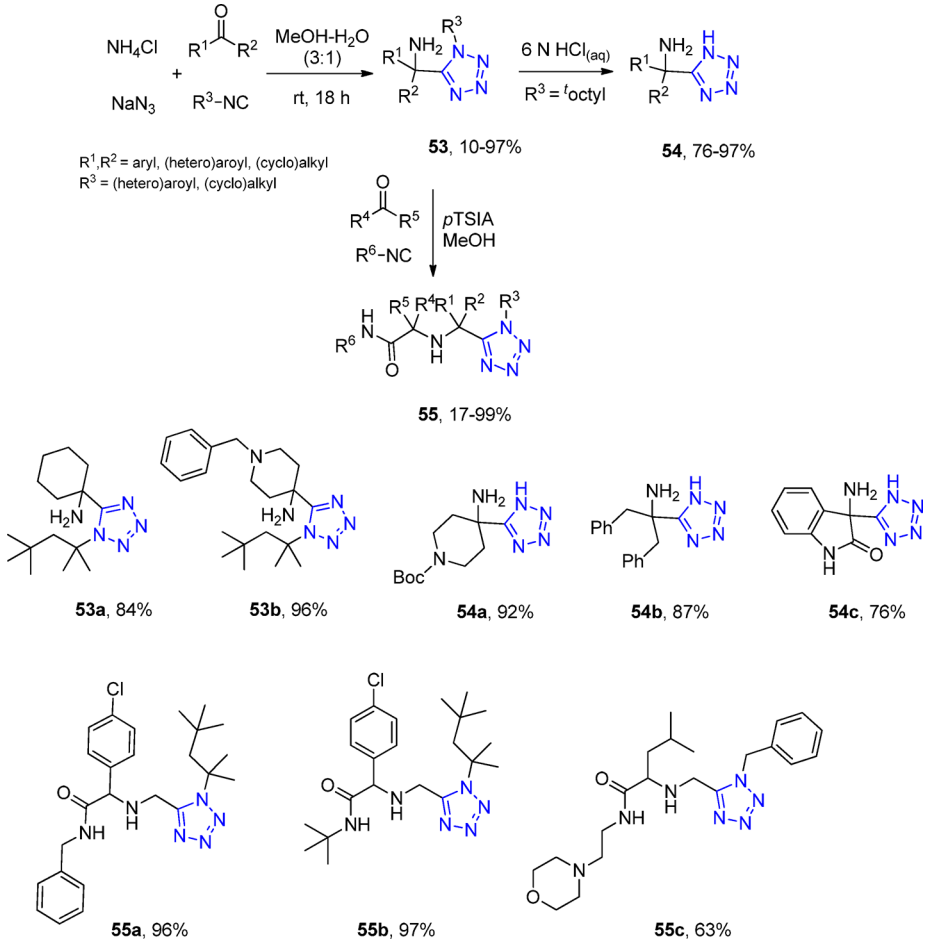
Scheme 16. A Synthetic Pathway to α,α-Disubstituted α-Aminotetrazoles 53 and 54 Using an UT-4CR Employing Ammonium Chloride as an Ammonia Surrogate and the Post-Modification Towards Tetrazoles 55



These isocyanides could be later cleaved with an alkoxide base (NaOEt, or KO^{t}Bu), affording the desired 5-substituted 1*H*-tetrazoles **63**. The two new cleavable isocyanides were both synthesized from β-amino acids (Scheme 20).

β-Cyanoethyl isocyanide (**64**) was introduced as a cleavable isocyanide in the UT-4CR, giving rise to the tetrazole derivatives **65** (Scheme 21).[178] After the UT reaction, the β-cyanoethyl moiety was cleaved under very mild basic hydrolysis conditions in only 30 min, yielding the free tetrazoles **66**.

Dömling et al.[179] employed successfully the isocyanide **67**, which bears a cleavable 2-nitrobenzyl group in both U-4CR and UT reactions using acidic and basic conditions, respectively. They demonstrated its use as a truly convertible isocyanide which performed moderately to good in the UT-4CR, affording tetrazoles **68** and compatible with diverse substrates. The cleavage was performed under basic conditions, by KO^{t}Bu, giving the adducts **69** (Scheme 22).

Tetrazoles are not only widely recognized for their pharmacological activities but also for their high chemical and thermal stabilities.[100,180] The decomposition of substituted tetrazoles normally occurs above 250 °C, and the fragmentation at lower temperatures mainly was only found during acylation of monosubstituted tetrazoles (Huisgen fragmentation).[181,182] El Kaïm et al.[183] described a Lewis acid triggered fragmentation of tetrazoles synthesized through an UT-4CR (Scheme 23). The Ugi tetrazole undergoes copper-catalyzed oxidative Schiff base formation (**70**), and then it is converted into triazoles through $Zn(OTf)_2$ catalyzed fragmentation of the tetrazole under microwave conditions toward the 1,5-disubstituted triazoles **71**. The mechanism, as proposed by the authors, is based on an electrocyclization of an intermediate α-diazo imine as the final step. Initial formation of a zinc chelate is triggering *tert*-butyl E1 elimination, which leads to the liberation of a small amount of triflic acid in the medium. This acid protonates the ring, which leads to a dearomatization of the tetrazole (Scheme 24).

Due to the fact that the C(sp^2)−Si bonds in organosilicon compounds undergo numerous transformations, Safa et al.[184] developed a library of tetrazole derivatives bearing 2,2-bis(trimethylsilyl)ethenyl groups (**73**), from the corresponding benzaldehyde (**72**), via a simple one-pot UT-4CR in the presence of catalytic amounts of $MgBr_2{\cdot}2Et_2O$ (Scheme 25). Noteworthy, primary aromatic amines with electron-donating groups such as methoxy and methyl afforded the tetrazole derivatives in slightly higher yields than amines with electron withdrawing groups such as nitro, whereas the cyclohexyl isocyanide instead of *tert*-butyl isocyanide required longer reaction times to afford similar products.

In 2012, Bazgir et al.[185] synthesized a series of ferrocenyl dialkylamino tetrazoles and ferrocenyl arylamino tetrazoles **74** via an UT-4CR without any catalyst in dichloromethane (Scheme 26). This is the first example of an efficient synthesis of ferrocenyl-fused tetrazoles. To explore the scope and limitations of the reaction, both aliphatic secondary amines and aromatic primary amines were employed, which afforded

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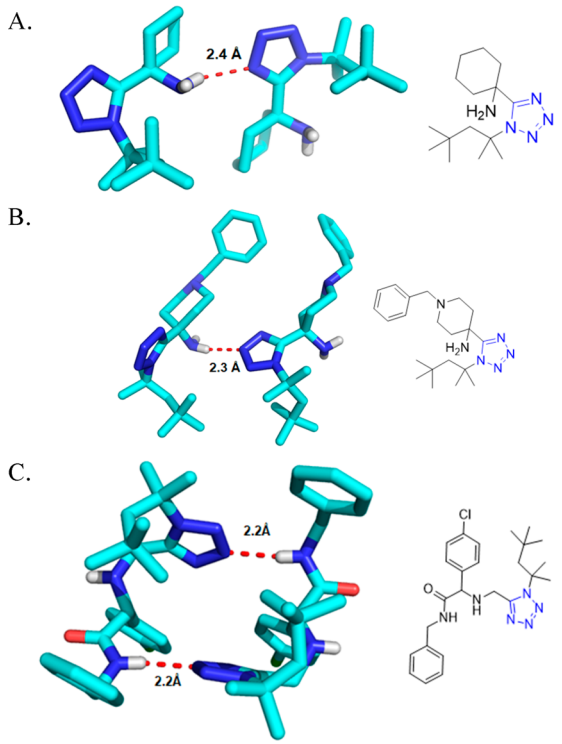
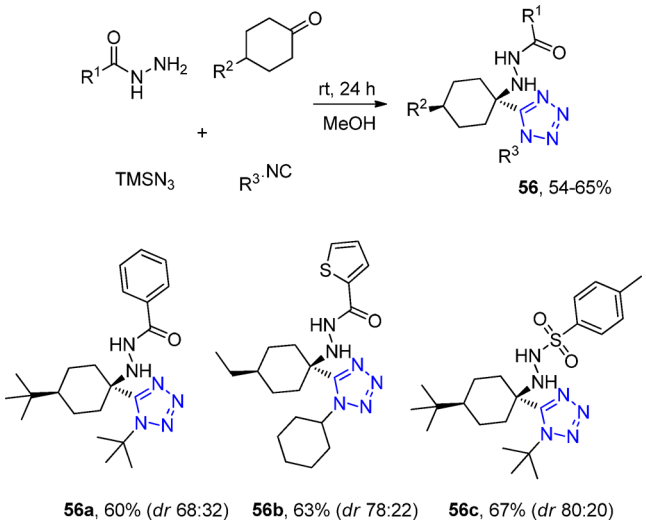


Figure 18. Structures of tetrazoles as seen in the solid-state by X-ray structure analysis. (A) Compound **53a** (CCDC 1441248) forms a hydrogen bridge of 2.4 Å length between the amine NH and the N4 of an adjacent molecule; moreover, the benzyl side chains undergo parallel and T-shaped $\pi-\pi$ interactions. (B) Compound **53b** (CCDC 1441249) forms a hydrogen bridge of 2.3 Å length between the amine NH and the N3 of an adjacent molecule. (C) Compound **55a** (CCDC 1484778) forms a hydrogen bridge of 2.2 Å length between the amine NH and the N3 of an adjacent molecule.

Scheme 17. Diastereoselective Synthesis of α-Hydrazine Tetrazoles 56 via a Facile UT-4CR



the final ferrocenyl tetrazoles in good yields. Because α-ferrocenyl-alkyl amines are important ligands in asymmetric catalysis reaction, such tetrazole derivatives could be further evaluated.[186]

The UT-4CR has found profound application in the field of medicinal chemistry. Histamine H3 receptor (H3R) acts both as an auto receptor in presynaptic histaminergic neurons and also controls histamine turnover by feedback inhibition of histamine synthesis and release.[187] Attracted by the potential of the H3R as a drug target, Davenport et al.[145] described a series of potent and subtype selective H3 receptor antagonists containing a novel tetrazole core and diamine motif. A one-pot UT-4CR was utilized to rapidly develop the structure−activity relationships (SARs) of these compounds. According to the biological screening results, the piperazine ring with small alkyl groups should be maintained. Shielding around the nitrogen, however, did not afford an improvement in metabolic stability. After modifications of the aromatic substituents and further optimization, potent derivatives (**75**) were the result (Scheme 27).

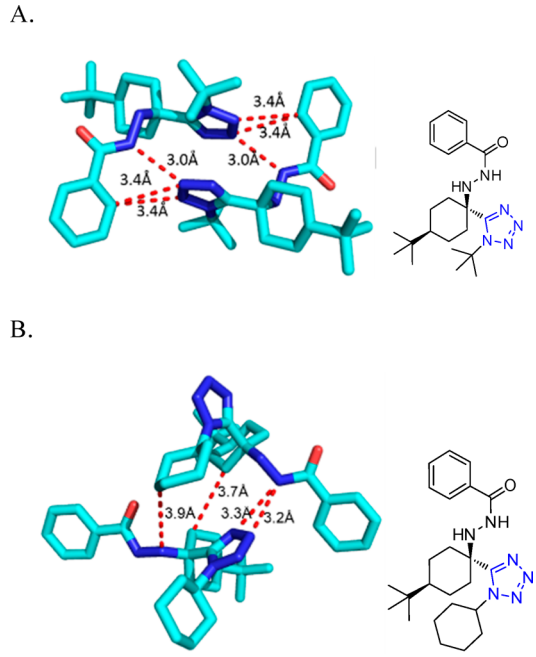


Figure 19. Crystal structures of α-hydrazine tetrazole **56a** and **56d**. (A) Hydrophobic interactions between the C of phenyl group and N(2), N(3) of tetrazole, hydrophilic interactions between N(3) of tetrazole, and the N close to C═O (CCDC 950021). (B) Hydrophobic interactions between the C of oxo component cyclohexyl groups, and hydrophilic interactions between N(3), N(4) of tetrazole, and N close to C═O (CCDC 950022).

A library of tetrazole-based diselenides and selenoquinones **77** and **78**, respectively, were synthesized via UT-4CR and a sequential nucleophilic substitution, which was evaluated against hepatocellular carcinoma.[188] Employing the corresponding diamines **76**, 18 tetrazole/naphthoquinone-based organoselenium derivatives were synthesized in good yields and their cytotoxic activity was evaluated using hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MCF-7) cancer cells and compared with their cytotoxicity in fibroblast (WI-38) cells. It was found that the selenoquinones **78** downregulated the apoptosis regulator Bcl-2 and K_i-67 expression levels and activated the expression of proapoptotic caspase-8 in HepG2 cells compared to untreated cells (Scheme 28).

The UT-4CR was also utilized in order to derivatize the anticancer drug Imatinib.[189] Under microwave irradiation, 30 adducts (**80**) with 10 different aldehydes and two isocyanides were synthesized bearing the amine **79**, which is the precursor of

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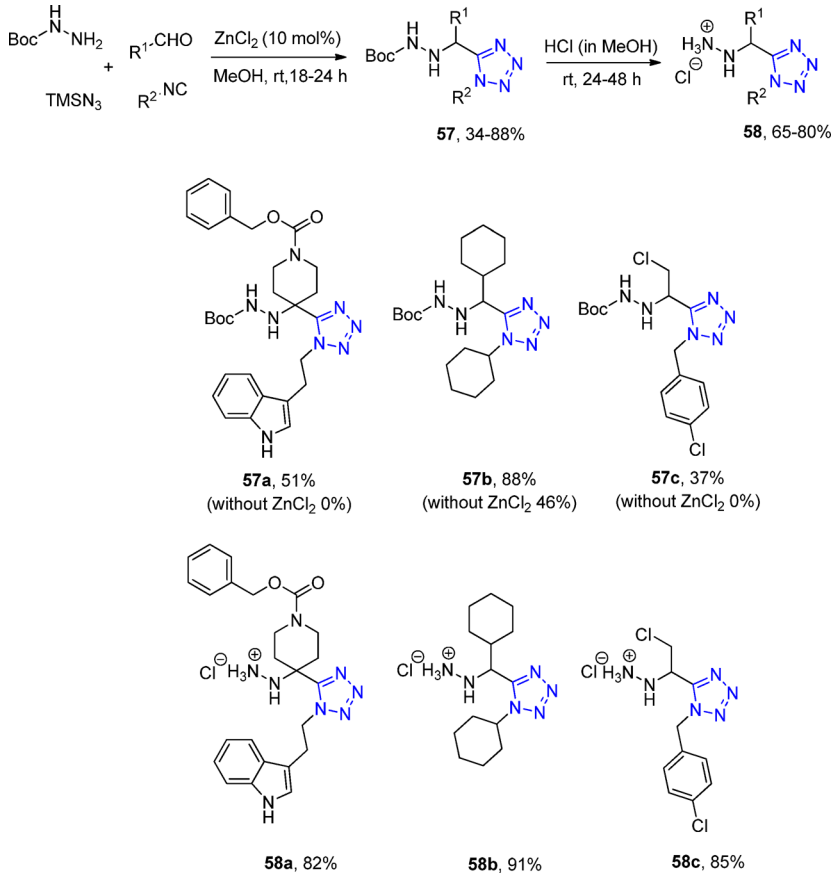
Scheme 18. Typical Two-Step Procedure Synthesis of *N*-Deprotected Tetrazole Derivatives 58



Imatinib (Scheme 29). Unfortunately no biological results were reported.

The tumor-suppressor protein p53 is the principal regulator of cell division and growth,[190,191] as it is able to control genes that are implicated in cell-cycle control, apoptosis, angiogenesis, senescence, and autophagia. Mutations in this protein are present in ∼50% of human cancers. Inhibiting the binding between wild-type (WT) p53 and its negative regulators MDM2 and/or MDMX has become an important target in oncology to restore the antitumor activity of p53.[192] In 2017, a rational design and synthesis of 1,5-disubstituted tetrazoles **81** and **82** as potent inhibitors of the MDM2-p53 interaction was reported (Scheme 30, Figure 21). An extensive SAR study was performed based on the established four-point pharmacophore model, yielding derivatives with affinity to MDM2 in the nanomolar range. Their binding affinity with MDM2 was evaluated using both fluorescence polarization (FP) assay and 2D-NMR-HSQC experiments.[193]

Considering that all receptors, metabolic enzymes, and transporters involved in GABAergic neurotransmission can be considered as valid drug targets, Wanner et al.[146] employed an UT-4CR as a key step to synthesize 1,5-disubstituted and 5-monosubstituted aminomethyltetrazole derivatives **83** and **84**, respectively, derived from glycine. All products were evaluated regarding their inhibitory potency and subtype selectivity at the four murine GABA transporter subtypes mGAT1-mGAT4. The results showed that none of the 5-monosubstituted tetrazoles has a potential for inhibition of GABA uptake, however, the 1,5-disubstituted tetrazole derivatives displayed a distinct activity, especially at the GABA transport proteins mGAT2−mGAT4. A reasonable potent and selective inhibitor of mGAT3 was found. Additionally, two more compounds were identified as potent inhibitors of mGAT2. Interestingly, up to now, only a few potent and selective inhibitors of mGAT2 that do not affect mGAT1 are known (Scheme 31).

Dysfunction of excitatory amino acid transporters (EAATs) has been implicated in the pathogenesis of various neurological disorders such as stroke, brain trauma, epilepsy, and neurodegenerative diseases among others.[194,195] EAAT2 is the main subtype responsible for glutamate clearance in the brain, having a key role in regulating transmission and preventing excitotoxicity. Therefore, compounds that increase the expression or activity of EAAT2 have therapeutic potential for neuroprotection. After a virtual screening of a library of small molecules, 10 hit molecules that interact at the proposed domain were identified as UT-4CR adducts.[196] The reaction was performed with a catalytic amount of trifluoroacetic acid in 2-propanol at 95 °C for 24 h. Further characterization of the two best ranking EAAT2 activators **85** and **86** (Figure 22) for efficacy, potency, and selectivity for glutamate over monoamine transporters subtypes and NMDA receptors and efficacy in cultured astrocytes was demonstrated. Authors also found that the EAAT2 activators interact with residues forming the interface between the trimerization and the transport domains; these compounds enhance the glutamate translocation rate, with no effect on substrate interaction, suggesting an allosteric mechanism.

Torrence et al.[197] examined the use of the Ugi reaction in the generation of new nucleosides as potential antiviral and antileishmanial agents. In that direction, starting from aldehyde

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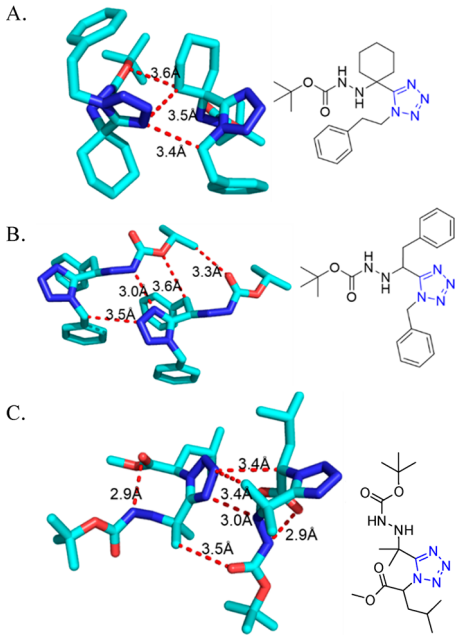


Figure 20. Crystal structures of the highly substituted 5-(Boc-hydrazinylmethyl)-1-methyl-1*H*-tetrazoles **57**. (A) Three hydrophobic interactions between carbon atom of cyclohexanyl and oxygen atom of Boc group, carbon atom of cyclohexanyl and N(4) of tetrazole, and C(1) of benzylethyl and N(4) of tetrazole (**57d**, CCDC 1438137). (B) Three hydrophobic interactions between carbon atom of methyl of isopropyl and oxygen (C═O) of Boc group, carbon atom of methylene of benzyl and oxygen of Boc group, and carbon atom of benzyl and N(3) of tetrazole, and one hydrophilic interaction between N(4) of tetrazole and N of hydrozine close to Boc group (**57e**, CCDC 1438135). (C) Four hydrophobic interactions between C(α) of isocyanide and N(3) of tetrazole, carbon atom of methyl of isopropyl and N(3) of tetrazole, and O(C═O) of Boc group and methyl of isopropyl and one hydrophilic interaction between N(4) of tetrazole and N of hydrazine close to C(α) (**57f**, CCDC 1438136).

87, they designed a series of nucleosides using the UT-4CR, which were evaluated for their activity against vaccinia virus, cowpox virus, and the parasite *Leishmania donovani*. They obtained some novel tetrazole derivatives **88** in good yields, unfortunately, without possessing any significant antiviral activity (Scheme 32).

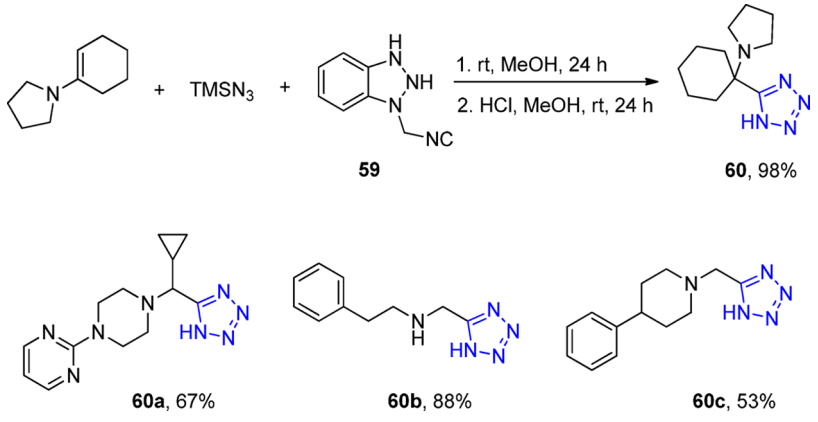
Heterocycle hybrid derivatives **90** bearing both a thiadiazole (**89**) and a tetrazole ring were designed and synthesized in 2012 by Fan et al.[198] These derivatives were formed via an UT-4CR and exhibited both broad-spectrum activity against several fungi and excellent antiviral activity (Scheme 33). A crystal structure of **90d** was reported (Figure 23).

Parasitic diseases are a global problem, affecting 30% of the world's population and much of the world's lifestock. Among parasitic diseases, malaria is one of the most devastating infectious diseases claiming many lives. There were at least 216 million cases of acute malaria reported in 2010, and about 655000 people died from malaria, 86% of which were children under 5 years of age.[199] Chibale et al.[200,201] designed new quinoline-based compounds bearing the tetrazole moiety and protonatable nitrogen(s) that have potential application in malaria. Thus, utilizing the aldehyde **91**, he synthesized in a diastereoselective way two new series of nitroimidazole and nitroimidazooxazine derivatives **92** in moderate to excellent yields using the UT-4CR. Three of these compounds appeared to be rapidly metabolized in both human and rat liver microsomes, and they had high metabolic clearance that was comparable to that of amodiaquine (Scheme 34). All synthesized tetrazole derivatives were evaluated in vitro for their antiplasmodial (against the multidrug-resistant K1 strain) and antimycobacterial activity (against the drug-sensitive H37Rv Mtb strain). Two of these compounds exhibited potent activity against the K1 strain of *Plasmodium falciparum*, with IC_{50} values in the low micromolar range.

In 2013, Chauhan et al.[202] synthesized a series of novel tetrazole derivatives **91** of 4-aminoquinolines (**93**) via an UT-4CR of primary and secondary amines, aliphatic, aromatic and ferrocene containing aldehydes, TMS azide, and isocyanides (Scheme 35). All the products were screened for their antimalarial activities against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *Plasmodium falciparum* as well as for cytotoxicity against VERO cell lines. Most of the synthesized compounds exhibited potent antimalarial activity as compared to chloroquine against the K1 strain. Some of the compounds with significant in vitro antimalarial activity were then evaluated for their in vivo efficacy in swiss mice against *Plasmodium yoelii* following both intraperitoneal (ip) and oral administration. Compounds **94a** and **94b** each showed in vivo suppression of 99.99% parasitaemia on day 4.

In addition, they introduced a novel series of 7-piperazinyl-quinolones **95** with tetrazole derivatives **96** and evaluated their antibacterial activity against various strains of *Staphylococcus*

Scheme 19. UT-4CR of BetMIC and Subsequent Acid Hydrolysis Yielding α-Aminomethyl Tetrazoles 60



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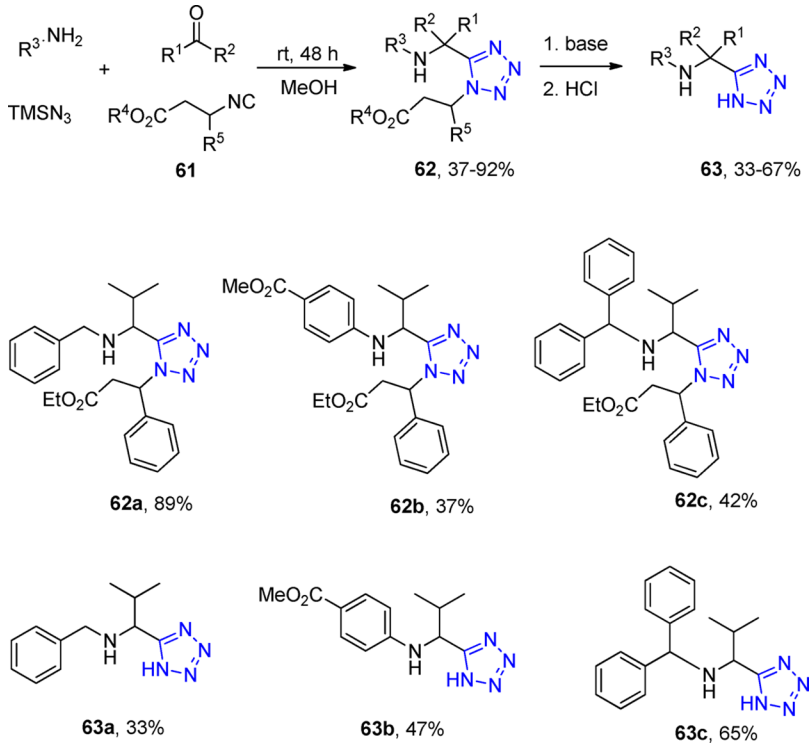
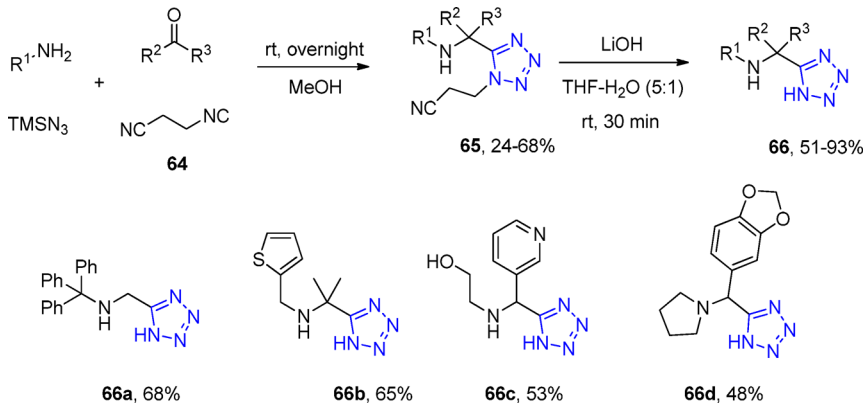
Scheme 20. Synthesis of α-Aminoalkyltetrazoles 63



Scheme 21. Synthesis of α-Aminoalkyltetrazoles 66



aureus.[151] All the compounds showed significant in vitro antibacterial activity against Gram-positive bacteria, whereas some displayed moderate activity in vivo (Scheme 36).

Sharada et al.[203] developed a facile one-pot, four-component domino reaction involving the 2-(2-bromoethyl)benzaldehyde, isocyanide, amine, and NaN_3 for the synthesis of tetrazolyl-tetrahydroisoquinoline derivatives **97** without the use of any catalyst or additive, under ambient conditions with short reaction times (Scheme 37, Figure 24). The first step is the imine formation, followed by substitution of the bromine and reaction of the resulting cyclic iminium ion with the isocyanide and the azide source. To test the generality of this methodology, various amines with both electron donating and withdrawing aromatic groups as well as aliphatic isocyanides were employed and afforded good to excellent yields. However, nitro-substituted anilines failed to give the expected products due to amine deactivation through the strong electron withdrawing features. Only one aliphatic amine, cyclohexylamine, was tested and also successfully resulted in the final ring-closed compound **97**.

In a similar fashion, the one-pot synthesis of tetrazole substituted tetrahydro-β-carbolines **98** was reported by Mukkanti et al.[204] The UT reaction of the indole-carboxaldehyde with mostly anilines (in some cases benzyl amine was utilized) and various isocyanides afforded the targeted tetrazole substituted β-carbolines in excellent yields (Scheme 38). The process involves the previous formation of a cyclic iminium ion, followed by reaction with the isocyanide and the azide.

3.1.1.1. Repetitive UT-4CR. Many proteins in nature exist as symmetrical homodimers, e.g., the HIV-protease. For that reason, symmetrical dimeric MCR reaction products might be useful to interact with the interface of symmetrical protein homodimers to stabilize such complexes.[205] Gámez-Montaño et al.[206] developed a catalyst-free UT repetitive process to quickly prepare a series of five novel bis-1,5-disubstituted-1*H*-tetrazoles **99** in excellent yields. They simply mixed one equivalent of the

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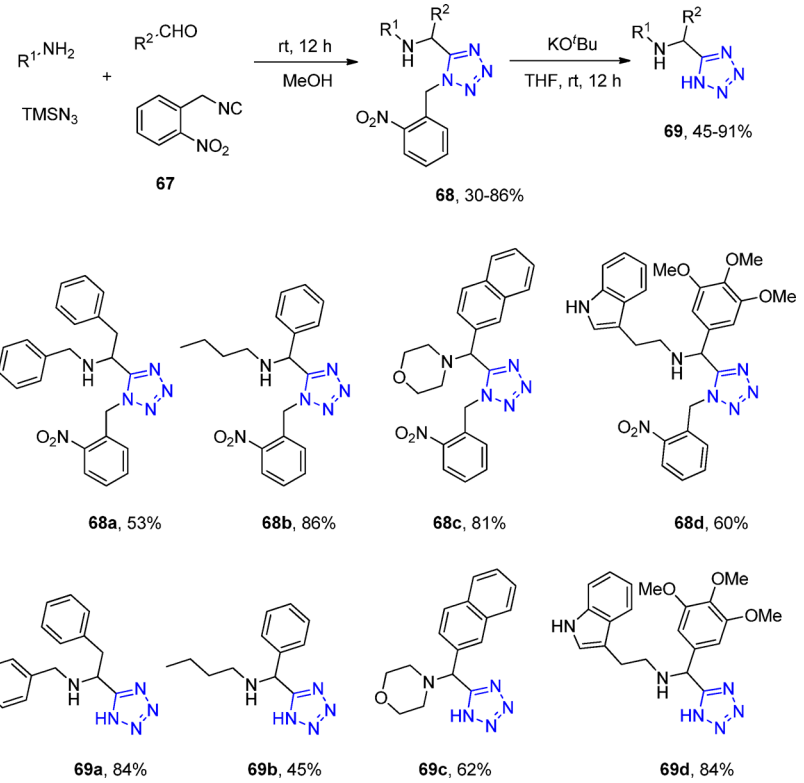
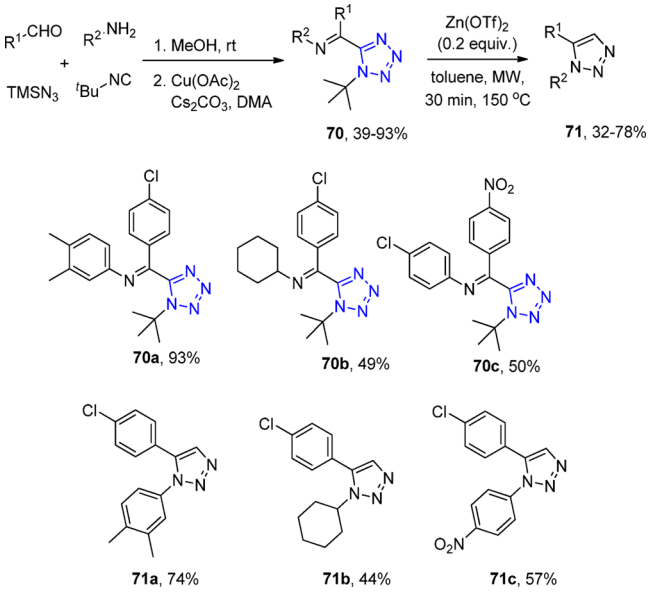
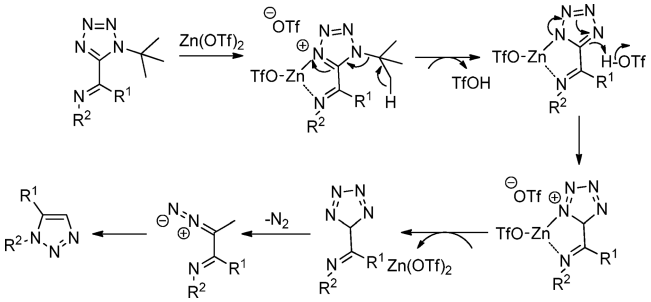
Scheme 22. Synthesis of the UT-4CR Adducts and Their Corresponding Deprotected 5-Substituted 1*H*-Tetrazoles 69



Scheme 23. Synthesis of 1,5-Disubstituted Tetrazoles 70 through Tetrazole Imine Intermediates and Their Subsequent Oxidation



Scheme 24. Plausible Mechanism of the Synthesized Triazoles through the Tetrazole Formation



corresponding primary amine and two equivalents of the corresponding aldehyde, isocyanide, and TMS azide in MeOH at room temperature. After several hours, they afforded first the mono Ugi product and then, upon further microwave heating, the repetitive Ugi products in excellent yields as a mixture of two diastereomers (in the case that R^1 is not hydrogen, Scheme 39).

Similarly to the work of Dömling et al.[170] in employing hydrazine in UT-4CR, Andrade et al.[207] reported two consecutive hydrazine UT-4CR incorporating acylhydrazines within 1,5-disubstituted tetrazoles **102**. Their strategy was based on a one-pot hydrazino UT-4CR (**100**) using protected acyl hydrazines (Boc or Cbz) followed by hydrazinolysis (**101**) by aqueous hydrazine and finally an additional hydrazino UT-4CR (Scheme 40).

Another example of a molecule with multiple tetrazole units was described by Dömling et al.[208] Reaction of cyclen **103** with formaldehyde, TMS azide, and *β*-cyanoethylisocyanide **64** quantitatively yielded compound **104** (Scheme 41). The *β*-cyanoethyl protecting group was used due to its mild deprotection conditions (LiOH in water at rt). The deprotected ligand **105** (TEMDO) was successfully metalated and crystal structures were obtained with Gd, Ln, and Eu. Moreover, the authors utilized the novel Gd-TEMDO complexes **106** in magnetic resonance imaging (MRI) in a left ventricular occlusion (LVO) mouse model (Figure 25). The overall complex and magnetic properties were compared and proved to be equivalent to most of the used Gd-DOTA complexes in the MRI field. The TEMDO synthesis is short, experimentally simple, and high yielding. In addition, in a similar fashion, many

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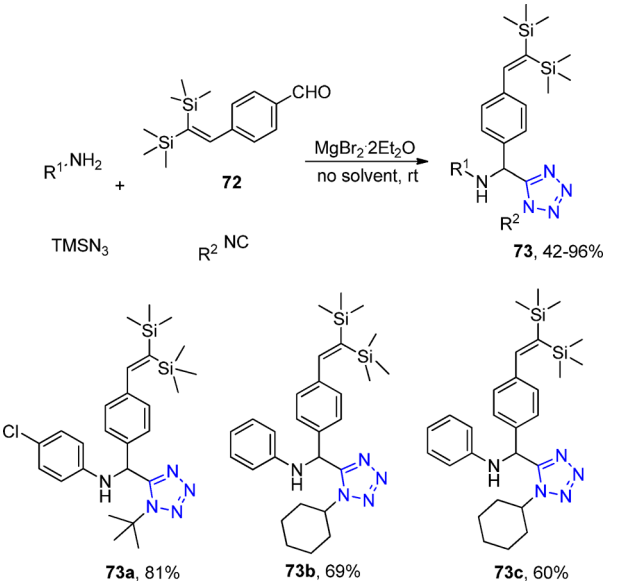
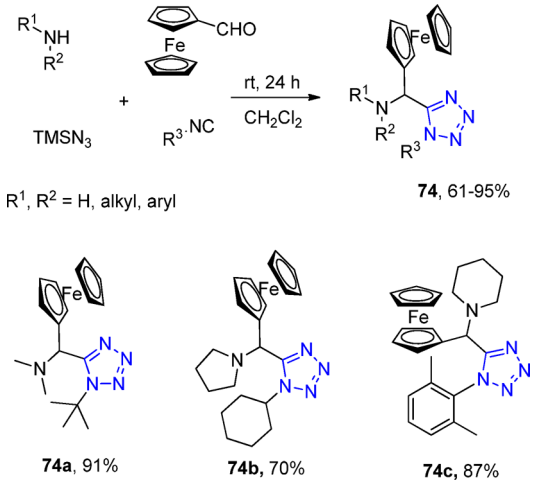
Scheme 25. Synthesis of a Series of Tetrazoles 73 Containing the 2,2-Bis(trimethylsilyl)ethenyl Group



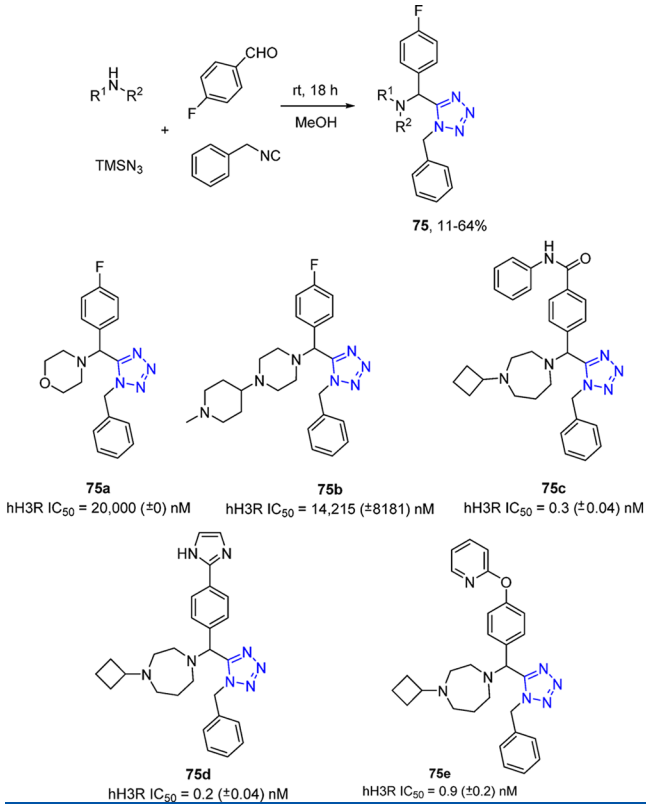
Scheme 26. Synthesis of Ferrocenyl Substituted Amino Tetrazoles 74



more oligo amino tetrazoles could be synthesized accordingly with interesting material properties.

3.1.1.2. UT-4CR on Solid Phase (UT-4CR on SP). Solid-phase synthesis (SPS) is a method in which a starting material is bound on solid support and reacts with the other reactants in solution. SPS, which has been explored by chemists for many years,[209−213] is often performed in sequential syntheses to automate synthesis and intermediate purification, e.g., in oligo-DNA or peptide synthesis. The synthetic application of solid phase in tetrazole synthesis using MCR started in 1997 when Mjalli et al.[214] first produced a small library of 1,5-disubstuted tetrazole derivatives encouraged by their success on solid phase to obtain small-ring lactams, α-(dialkylamino)amides, hydantoin 4-imides, and 2-thiohydantoin 4-imides. In their synthetic process, amines, aldehydes, NaN_3, and the supported isocyanides **107** were simply stirred for 4 days in a solvent mixture containing methanol, dichloromethane, and water (1:1:0.3) along with pyridine hydrochloride to afford the corresponding tetrazole-resin derivatives **108**. The subsequent cleavable step was

Scheme 27. Synthesis of Substituted Benzyl Tetrazoles As Histamine H3 Receptor Antagonists 75



accomplished by stirring the Ugi products **109** with 20% trifluoroacetic acid in dichloromethane after washing with methanol and dichloromethane (Scheme 42). Various amines and aldehydes could lead to the target tetrazoles by this methodology. Probably caused by poor activity of ketones in this reaction, they did not afford the corresponding tetrazoles under these conditions, but after stirring for long time, only the formamides could be detected.

Ugi et al.[215] also prepared a variety of hydantoinimide and tetrazole derivatives by the combination of two distinguished Ugi reactions in solid and liquid phases separately. Although many types of the combinations of U-4CRs and further reactions have been developed, this was the first time to employ two different types of U-4CRs with the primary amines supported by the polystyrene AM RAM or the TentaGel S Ram. In the first U-4CR, Fmoc protected amino acid **110** reacted as a carboxylic acid with aldehydes, isocyanides, and the solid supported primary amines to form the corresponding amides **111**. Subsequently, after the cleavage of Fmoc group with 20% piperidine in DMF (**112**), the second U-4CR was carried out with TMS azide as an acid component (**113**) and the removal of the resin with trifluoroacetic acid treatment led to the final tetrazole derivatives **114** formation (Scheme 43). Interestingly, the aromatic aldehydes were tolerated in the second U-4CR to form tetrazoles with good yields compared with rather low yields of the hydantoinimides. Moreover, they also compared the liquid phase combinational MCRs with that of the solid−liquid method. The results demonstrated that the former one could give higher yields.

Chen et al.[216] employed a Rink-isocyanide resin **115** as a universal platform for classical Ugi reactions to prepare a small library of five 5-substituted 1*H*-tetrazoles **116**. The cleavage of

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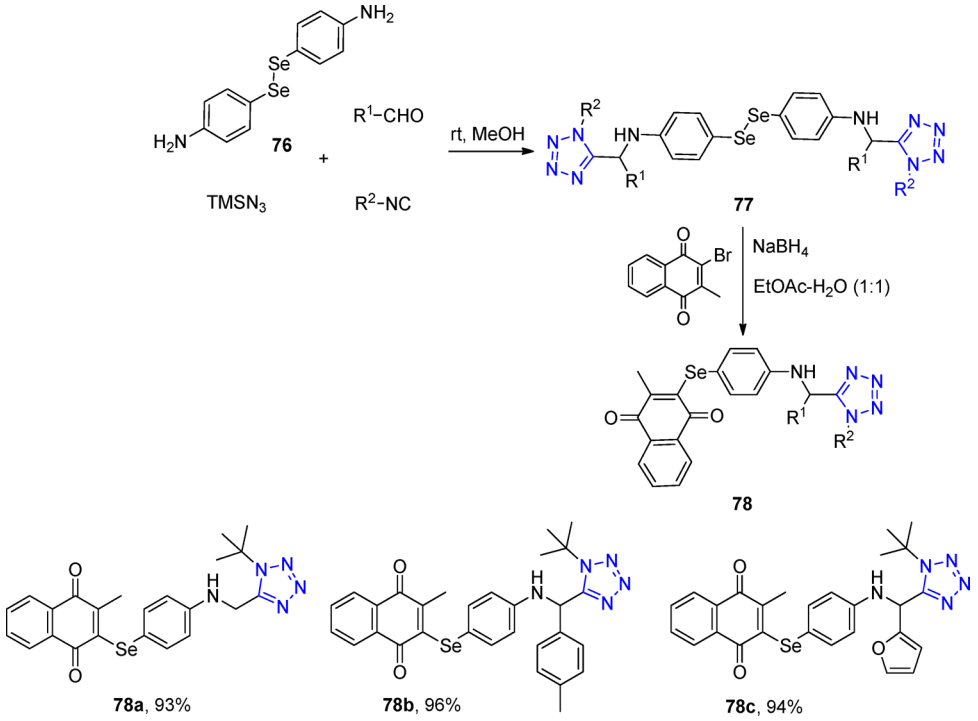
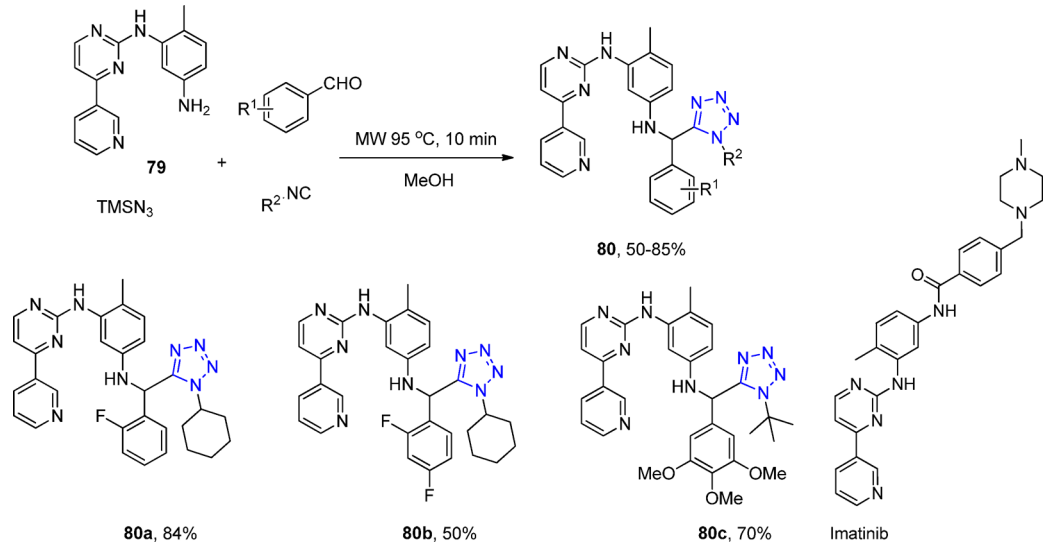
Scheme 28. Synthesis of Tetrazole/Naphthoquinone-Based Organoselenium Derivatives 78



Scheme 29. Representative Scheme for the Preparation of 1,5-Disubstituted Tetrazoles 80 Containing a Fragment of the Anticancer Drug Imatinib



the resin was performed with 15% trifluoroacetic acid in dichloromethane (Scheme 44).

Rivera et al.[217,218] reported an efficient and reproducible method implementing on-resin Ugi reactions with peptides (**117**) and its utilization in combination with peptide couplings for the solid phase synthesis of *N*-substituted and tetrazolo peptides **118** (Scheme 45).

3.1.1.3. UT-4CR Followed by Subsequent Post Cyclizations. Multicomponent reactions combine two major principles in organic synthesis, convergence, and atom economy. The combination of multicomponent reaction and post-transformation reactions is another tremendously useful tool to increment the complexity and diversity of the molecular scaffolds. An important subgroup of MCRs is the so-called unions of MCRs as coined by Dömling and Ugi,[219] where an MCR is combined with a secondary MCR.[220] The union of MCRs is the strategy for the rational design of novel MCRs combining two (or more) different types of MCRs in a one-pot process. The presence of orthogonal reactive groups in the product of the primary MCR, which is either formed during the primary MCR or present in one of the inputs, allows the union with the secondary MCR.[221]

There are many classical documented post-transformation reactions, i.e., Pictet–Spengler cyclization, intramolecular Diels–Alder reaction, Mitsunobu reaction and acyl migration, Knovenagel condensation, amide reduction, metathesis reaction, Ugi–Ugi, and Ugi–Petasis etc.[52,120,127,222–236] The strategies entailing intramolecular variants of the Ugi reaction

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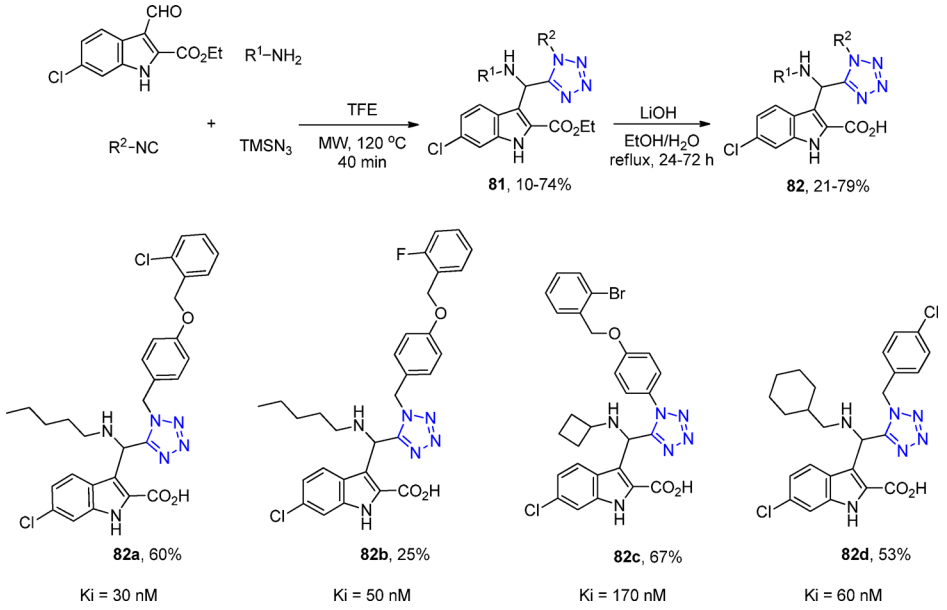
Scheme 30. Synthesis of the Potent 1,5-Disubstituted Tetrazoles 81 and 82 as p53-MDM2 Inhibitors



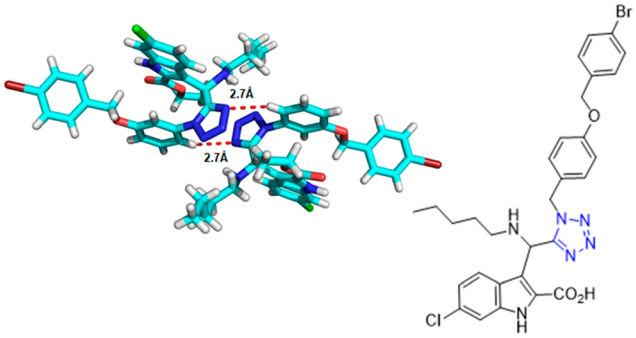


Figure 21. Crystal structure of the 1,5-disubstituted tetrazole **82e** (CCDC 1449789). The ring planes of substituents at positions 1 and 5 are almost coplanar, being constrained by tetrazole geometry and are oriented vertically to the plane of the tetrazole ring.

and post condensation modifications of the Ugi product inspire the development of methodology that enables concise access to diverse pharmacologically relevant scaffolds. These Ugi variants indeed afforded enticing structures for further diversification. The hydantoin (imidazoline-2,4-dione) scaffold is a reoccurring motif in many biologically relevant compounds with anticonvulsant, antimuscarinic, antiulcer, antiviral, and antidiabetic activities and showing strong BACE binding for potential anti-Alzheimer application.[237−242] Hulme et al.[243] described a novel methodology to elegantly obtaining new and biologically appealing 1,5-substituted tetrazole-hydantoins and thiohydantoins **120** with three points of variation (Scheme 46, Figure 26). The UT-4CR is based on the glyoxale ethylester, as a not variable oxo input, followed by the treatment of the Ugi intermediate **119** with an excess of isocyanate or isothiocyanate to generate the final scaffold in moderate to good yields. Various amines, isocyanides and isocyanates, or isothiocyanates were used to test the generality of this methodology. Because of the general availability of a large number of isocyanides, aldehydes, ketones, and iso(thio)cyanates, this reaction sequence is of high combinatorial value representing a large chemical space (Scheme 46). Furthermore, a one-step extension (but still one pot) of this methodology using a functionalized hydantoin with an internal-masked amino nucleophile previously introduced by the isocyanide input has also been reported giving imidazotetrazolodiazepinones **121** in good yields.[244] A crystal structure of the hydantoin **120c** was reported featuring an interesting intermolecular halogen bonding involving a Br and two nitrogens of the tetrazole (Figure 26).

Benzodiazepines are important drugs with a wide spectrum of biological and medicinal activities and marketed applications as anxiolytics, anticonvulsants, hypnotics, etc.[245,246] Besides these classical applications, the benzodiazepine scaffold is also of interest in numerous other areas as antagonizing the protein−protein interaction p53-MDM2,[247] GPIIbIIIa antagonists,[248] antioxidants,[249,250] and inhibitors of farnesyltransferase.[251] Multiple synthetic pathways are described toward benzodiazepines, which also include routes involving MCRs.[147,252−263] Because of the privileged scaffold character of tetrazoles and benzodiazepines, several researchers designed synthetic strategies to combine the two heterocycles.[264]

Shaabani et al.[265] reported a new class of benzodiazepine-containing tetrazole scaffold, 1*H*-tetrazol-5-yl-4-methyl-1*H*-benzo[*b*][1,4]diazepines **124**, via a two-step condensation reaction of *o*-phenylenediamines (*o*PDM), ethyl 3-oxobutanoate, or 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, an isocyanide, and TMS azide (Scheme 47, route 1). The first reaction involves the cyclocondensation of *o*-phenylenediamine with a *β*-ketoester to yield benzodiazepinone Schiff base **122**, which reacts in a second step in an UT reaction. Monosubstituted (NO_2 and CH_3) phenylenediamines reacted highly regioselectively as indicated by NMR and crystal structure (Figure 27). Moreover, they also disclosed two IMCRs,[266,267] employing 2,3-diaminomaleonitrile, ketones, isocyanides, and either sodium azide or trimethylsilyl azide in the presence of *p*TsOH·H_2O in various organic solvents and water at room temperature to afford 1*H*-tetrazolyl-1*H*-1,4-diazepine-2,3-dicarbonitriles **125** in high yields (Scheme 47, Figure 28).

o-Phenylenediamines are a limiting component in this otherwise interesting scaffold because only a few are commercially available. Therefore, Shabaani et al.[268] elaborated a second variation to this scaffold by first reacting 2-nitroanilines in the UT reaction, affording the tetrazole intermediate **123**

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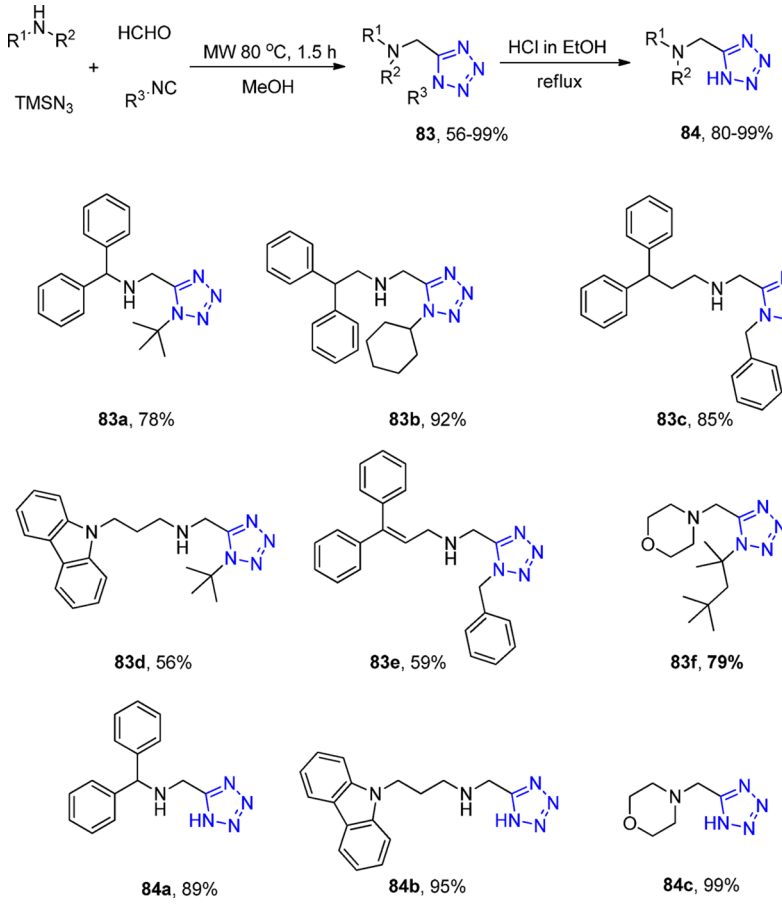
Scheme 31. Synthesis of Aminomethyltetrazoles 83 and 84



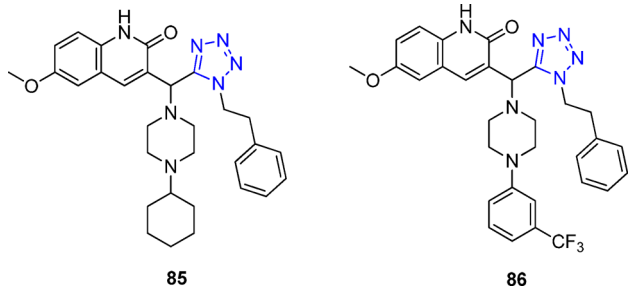
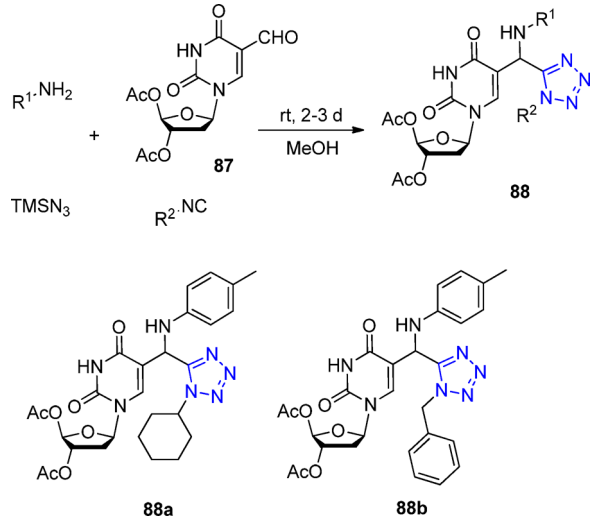


Figure 22. Two of the most potent compounds as positive allosteric modulators of EAATs.

followed by reduction of the *o*-nitro group and NaH promoted cyclization to yield compounds **124** (Scheme 47, route 2). While the second synthetic access is much more versatile in the *o*-nitroaniline component, it also involves a longer synthetic route. The overall yields are higher for the first route and also leading to short reaction times.

Isoindoline is a heterocyclic organic compound with a bicyclic structure, not found itself in nature although many of its derivatives have, with a broad structural diversity and broad-spectrum biological activities. Thus, many biologically active compounds have been discovered, i.e., endothelin-A receptor antagonists, PPARd agonists, NMDA receptor antagonists, herbicidal, anti-inflammatory, antileukemic agents, etc.[269−272] Yet, various synthetic procedures have been reported for the preparation of isoindoline core structural skeletons.

Scheme 32. Antiviral Tetrazole Desoxyribose Derivatives 88



Chauhan et al.[273] first employed a two-step combination of an UT reaction (**126**) and palladium-catalyzed cyclization with isocyanide insertion for the synthesis of tetrazole isoindolines. They constructed a series of 1,5-disubstituted-1*H* tetrazoles **127** with reaction conditions that could well tolerate a wide range of functional groups in excellent overall yields (Scheme 48).

The presence of a tetrazole N−H proton in compound **127a** was verified by D_2O exchange experiment in which an unexpected change in ^1H NMR spectrum was observed as

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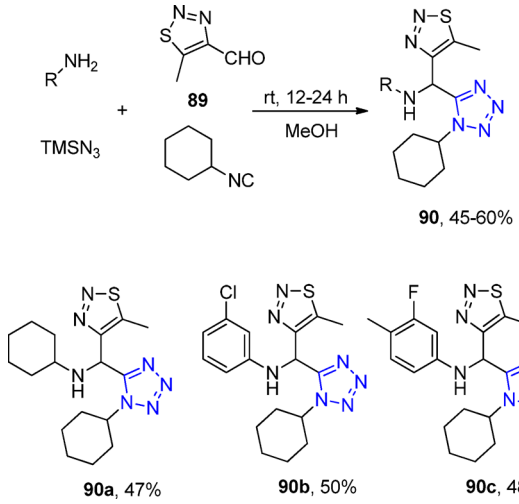
Scheme 33. Synthesis of the Thiadiazolo Tetrazole Derivatives 90



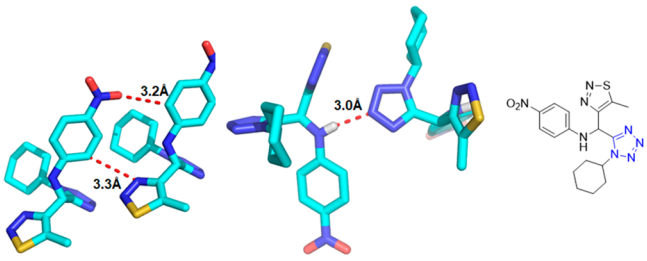
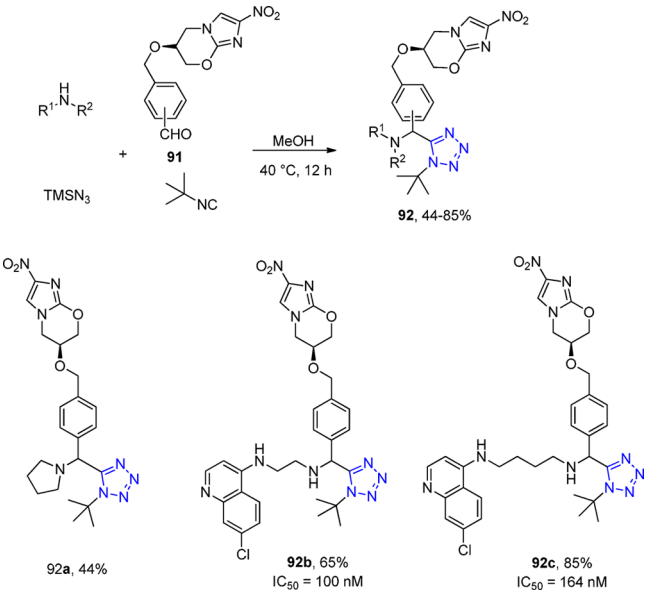
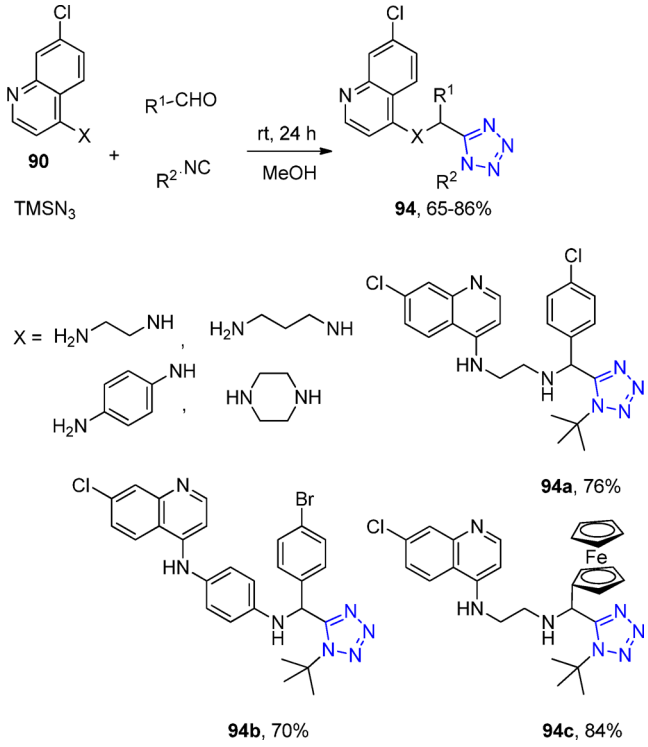


Figure 23. Crystal structure of *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)(5-methyl-1*H*-1,2,3-triazol-4-yl)methyl)-4-nitroaniline (**90d**). It shows that the dihedral angles formed between the thiadiazole and tetrazole rings, the benzene and tetrazole rings, and the thiadiazole and benzene rings are 62.59°, 86.73°, and 70.07°, respectively. Three intermolecular hydrogen bonds N(1)−H(2)···N(6), C(4)−H(4B)···O(2), and C(17)−H(17)···N(3) are identified (CCDC 859295).

Scheme 34. Synthesis of New Nitroimidazole and Nitroimidazooxazine Derivatives 92



Scheme 35. Synthesis of 4-Aminoquinoline-Tetrazole Derivatives 94



proven by X-ray structure analysis (Scheme 49). Degradation occurred, most probably provoked by water giving the isoindole-1-one **128**.

β-Carbolines are heterocyclic systems which are the key structural motif of a variety of biologically important alkaloids of natural and synthetic origin.[274,275] Tetrahydro-*β*-carbolines are often key intermediates in natural product syntheses.[276,277] Because of their structural similarity with a number of neurotransmitters, they are also incorporated in numerous compounds with biological activity. The intramolecular Mannich reaction of electron rich aromatic rings with oxo components and 1° or 2° amines, also called the Pictet−Spengler reaction, is an often used post modification in MCR.[278−285]

El Kaïm et al.[286] first prepared an array of tetrahydro-1*H*-*β*-carboline-tetrazoles in excellent overall yields using the UT/Pictet−Spengler reaction sequence. Tryptamine was used as a common starting material in the UT reaction (**129**), and the subsequent Pictet−Spengler reaction was performed with formaldehyde to form a series of 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-*β*-carbolines **130** either under refluxing conditions in methanol/toluene or under microwave conditions in the same reaction solvent with generally good to excellent yields (Scheme 50). A direct comparison of these two methods of Pictet−Spengler ring closure reveals that the yields are similar; however, the microwave variation was generally slightly less yielding.

In 2013, R. Gámez-Montaño[287] reported the synthesis of nine novel tris-heterocyclic-type 3-tetrazolyl-azepino[4,5-*b*]indol-4-ones via a sequential combination of a one-pot process (UT-4CR/*N*-acylation/S_N2)/xanthate free-radical-mediated cyclization. Thus, tryptamine was combined sequentially with the corresponding aldehydes, TMS-azide and isocyanides in MeOH as the solvent at room temperature for 24 h to give the

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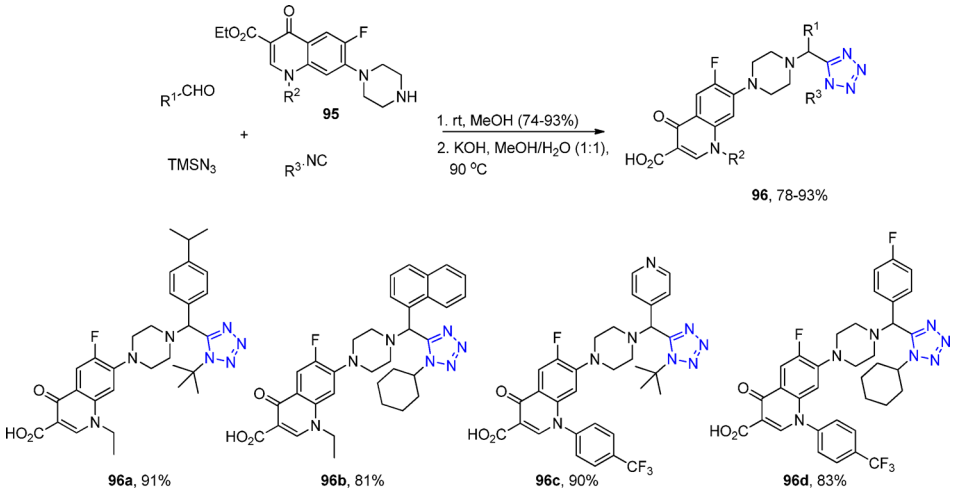
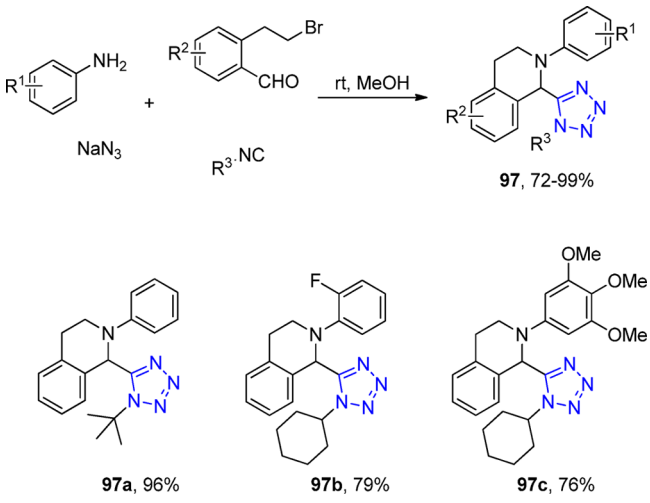
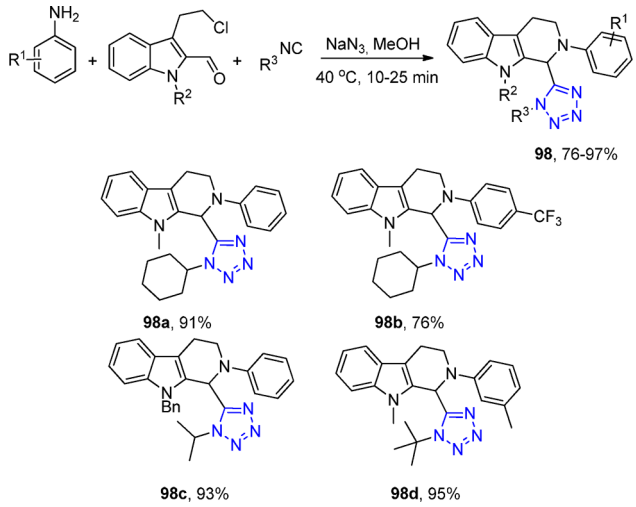
Scheme 36. Representative Scheme for the Preparation of 1*H*-Tetrazol-5-yl-(aryl)methyl Piperazinyl-6-fluoro-quinolones 96



Scheme 37. Synthesis of a Variety of Tetrazole Substituted Tetrahydroisoquinolines 97



Scheme 38. Synthesis of Tetrahydro-*β*-carbolines 98 Bearing a Tetrazole Moiety through an UT-4CR-5C



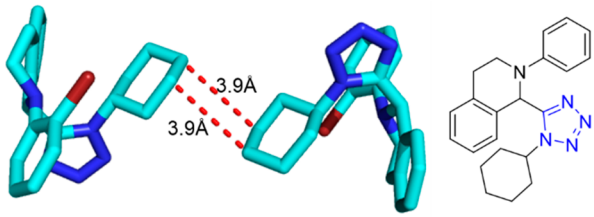


Figure 24. X-ray crystal structure of tetrahydroisoquinoline **97d** (CCDC 1012826). Two intermolecular hydrophobic interactions between the two cyclohexyl groups are observed

corresponding indole-tetrazoles **131**, which underwent a *N*-acylation with chloroacetyl chloride to give the corresponding chlorides. These latter compounds, after a S_N2 reaction with potassium ethyl xanthogenate salt, afforded the bis heterocyclic xanthates **132** in 47−71% yield. Then, DLP (dilauroyl peroxide) was added portionwise in 1,2-dichloroethane at 85 °C (using conventional or MW) to generate the azepino[4,5-*b*]indol-4-one heterocycles **133** in 45−82% yields after a favored 7-endo-trig cyclization (Scheme 51, Figure 29).

Hulme et al.[288] described a two-step methodology based on an oxidation/oxidative amidation cyclization strategy toward isatins starting from the *o*-aminoacetophenone. UT adducts **134** were successfully oxidatively cyclized through a postcondensation process utilizing selenium dioxide, affording valuable peptidomimetic-like isatins **135** (Scheme 52).

Chalcones is a class of compounds that have a wide range of biological activities[289−292] such as antidiabetic, antineoplastic, antihypertensive, antiretroviral, anti-inflammatory, etc. MCR-oxidative deamination approach was employed to access *α*-ketotetrazoles (with aromatic or aliphatic aldehydes) and *α,β*-diketotetrazoles (with glyoxals) with two diversity elements (**137**, Scheme 53, Figure 30).[293,294] Dual functionalized *α*-ketotetrazole compounds were synthesized in two steps in 25−77% yields, accessing also tetrazole chalcones **137a−d** via the UT adduct **136**. In addition, *α,β*-diketotetrazoles (**137e−h**) were formed using various glyoxals as the aldehyde component, providing a route to vicinal tricarbonyl *cis*-amide bioisosteres.

Further functionalization of the aforementioned tetrazole derivatives is presented below, giving rise to derivatives **138−140** (Scheme 54).

Tron et al.[295] discovered an attractive short synthetic approach to 5-aroyl-1-aryltetrazoles **142**, a class of compounds hardly accessible by other means. The novel and operationally simple synthetic procedure to obtain elusive 5-aroyl-1-

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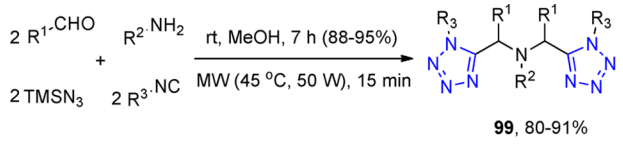
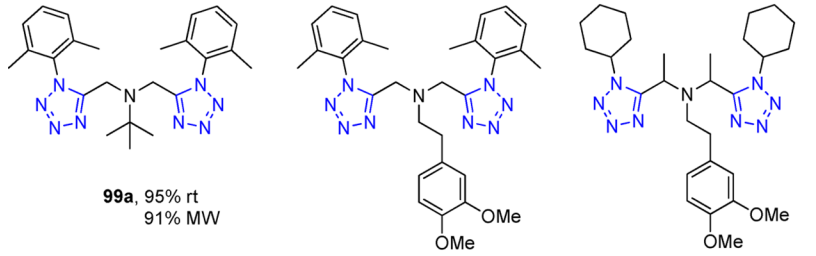
Scheme 39. Synthesis of Bis-1,5-disubstituted-1*H*-tetrazoles 99



99, 80-91%

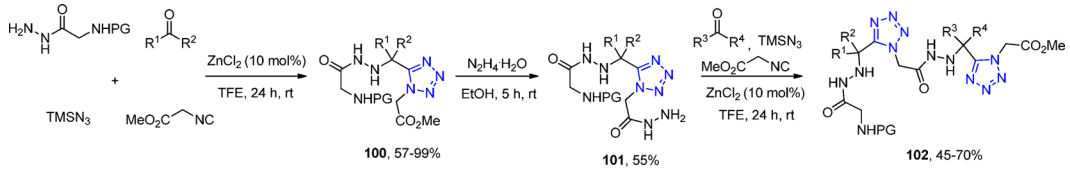


99a, 95% rt
91% MW

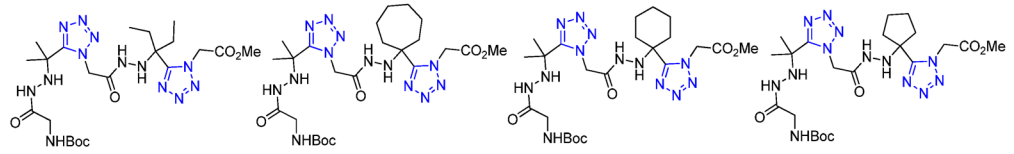
99b, 92% rt
85% MW

99c, 88% rt
80% MW

Scheme 40. Synthesis of the Acylhydrazines with 1,5-Disubstituted Tetrazoles 97 via a Two Consecutive Hydrazine UT-4CR

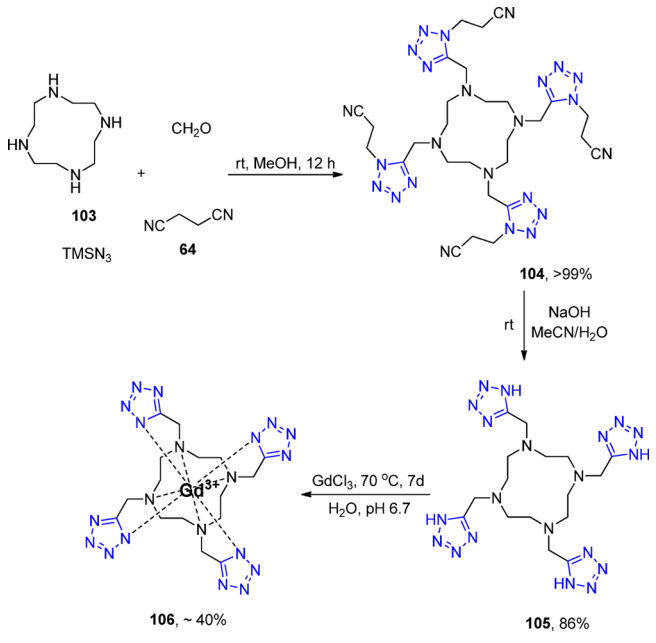


100, 57-99%
101, 55%
102, 45-70%



102a, 54%
102b, 68%
102c, 70%
102d, 45%

Scheme 41. Synthesis of the MRI Agent Gd-TEMDO 106 Involving a Key UT-MCR



103
TMSN3
64
104, >99%
105, 86%
106, ~ 40%

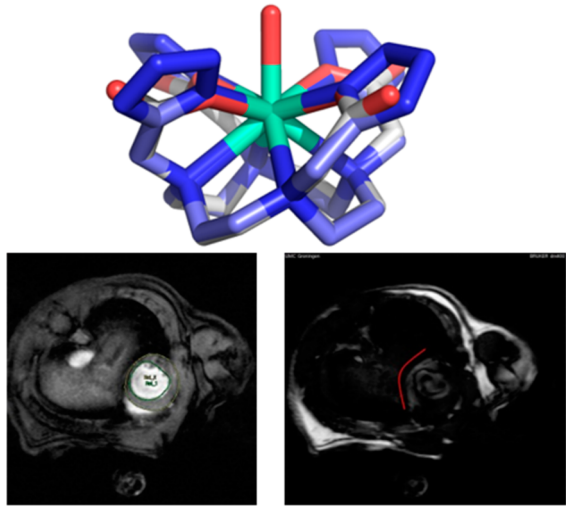


Figure 25. Left: Crystal structure of Gd-TEMDO **106**. Middle and right: LVO mouse model showing the MRI properties of Gd-TEMDO. MRI obtained from isoflurane-anaesthetized mice (middle) taken 30 min after IP administration of Gd-TEMDO (0.6 mmol/kg). Middle: the heart fully visible. Right: heart with reduced brightness; the damaged tissue remains visible due to absorbed Gd-TEMDO following the red line. Reproduced with permission from ref 208. Copyright 2016 John Wiley and Sons.

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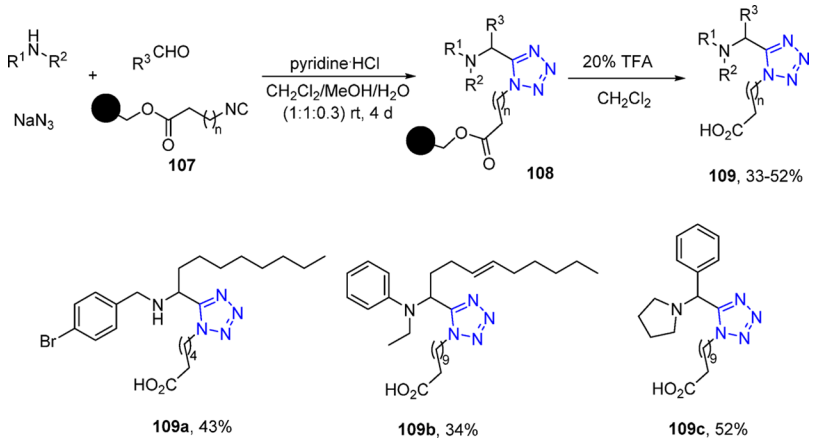
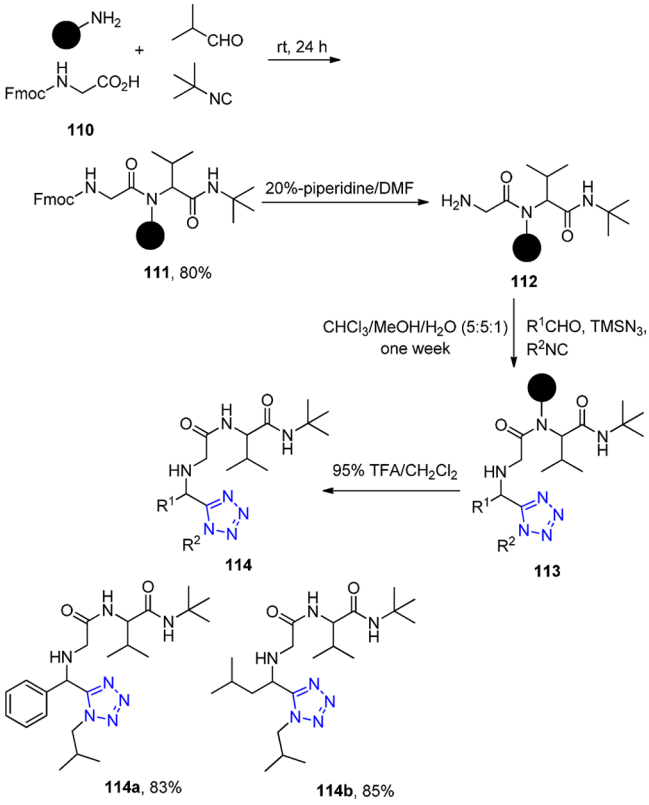
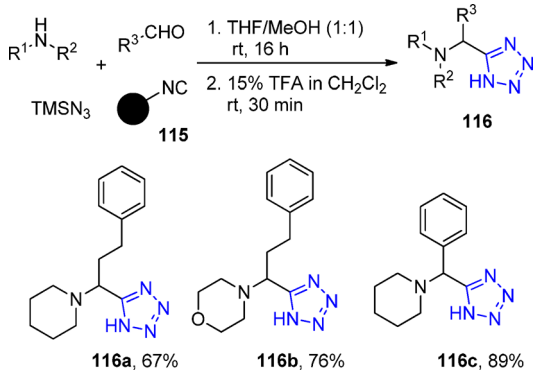
Scheme 42. Synthesis of 5-(1′-Aminoalkyl)tetrazoles 109 on Solid Phase



Scheme 43. Repetitive Ugi Reaction on the Polystyrene AM RAM



Scheme 44. Synthesis of 5-Substituted Tetrazoles 116 on the Universal Rink-Isocyanide Resin



aryltetrazoles in good yields consists of an UT adduct **141**, followed by a hydrogenolysis/transamination posttransformation (Scheme 55). This postmodification reaction sequence was based on the Rapoport procedure, which is a simple and mild biomimetic conversion to convert amines to carbonyls in the presence of 4-formyl-1-methylpyridinium benzene-sulfonate as a pyridoxal phosphate (vitamin B6) surrogate.[296,297] Different aldehydes and isocyanides with various different electron-withdrawing and electron-donating substituents were employed to demonstrate the functional group tolerance and generality of this new synthetic process. α-Keto (hetero) arynes represent a significant compound class as they have been described as covalent serine protease inhibitors or as tetrazole analogues of chalcones.

The double bond in the chalcone scaffold is commonly thought to be an important structural linker, but, for example, it is not essential for the interaction with tubulin. Yet, it may be a potential site of metabolic degradation and interaction with biological nucleophiles. To circumvent that, following the same strategy as previously described (an UT-4CR combined with the Rapoport procedure), Tron et al.[295,298] investigated the 5-aroyl-1-aryltetrazol analogues **142** for their biological antiproliferative activity. They tested these compounds and their precursors in SH-SY5Y cells, a neuroblastoma cell line. Compound **142g** was found active with an IC_{50} of 4.1 ± 0.3 μM, which was confirmed by cell cycle analysis as well by disrupting the mitotic spindle (Scheme 56).

A series of tetrazole linked imidazo[1,5-*a*]pyridines **144** were recently synthesized from simple and readily available building blocks.[299] The reaction sequence involves an Ugi tetrazole-deprotection reaction (**143**), followed by an acetic anhydride mediated *N*-acylation-cyclization process to afford the target heterocycles. The acylating agents include commercial available acid chlorides, anhydrides, and acids (Scheme 57).

Among the MCRs and postcondensation examples, mostly C−N and C−C bond formations to form monocyclic ring or fused structures were reported,[300−302] whereas N−N bond formation were rarely disclosed up to date. El Kaïm et al.[303] envisioned that a N−N bond formation as the Ugi postcondensation transformation could lead to unusual scaffolds. They selected as starting materials primary amines, *ortho*-nitrobenzaldehyde to react with TMS azide and various isocyanides to form the indazole derivatives **145** in good yields

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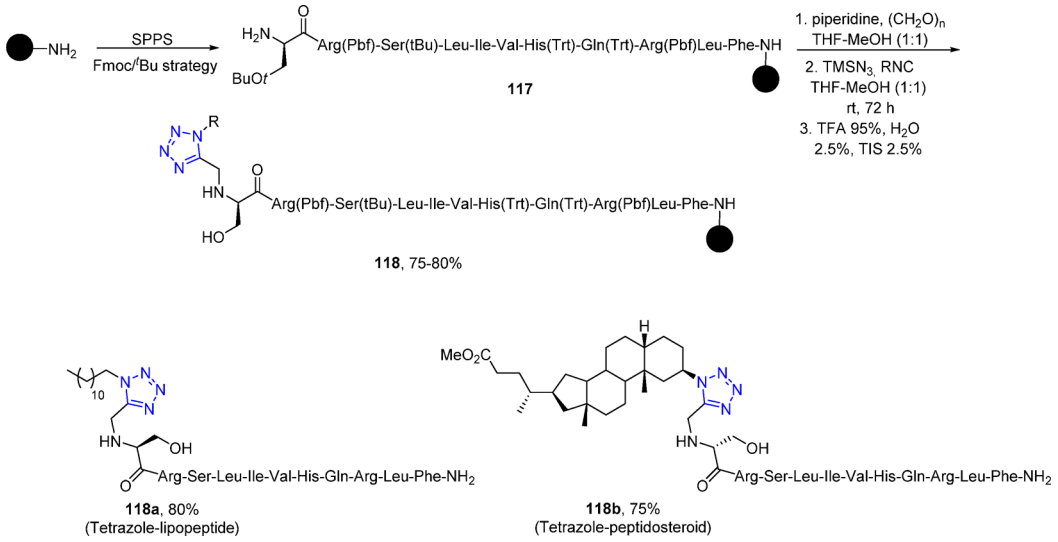
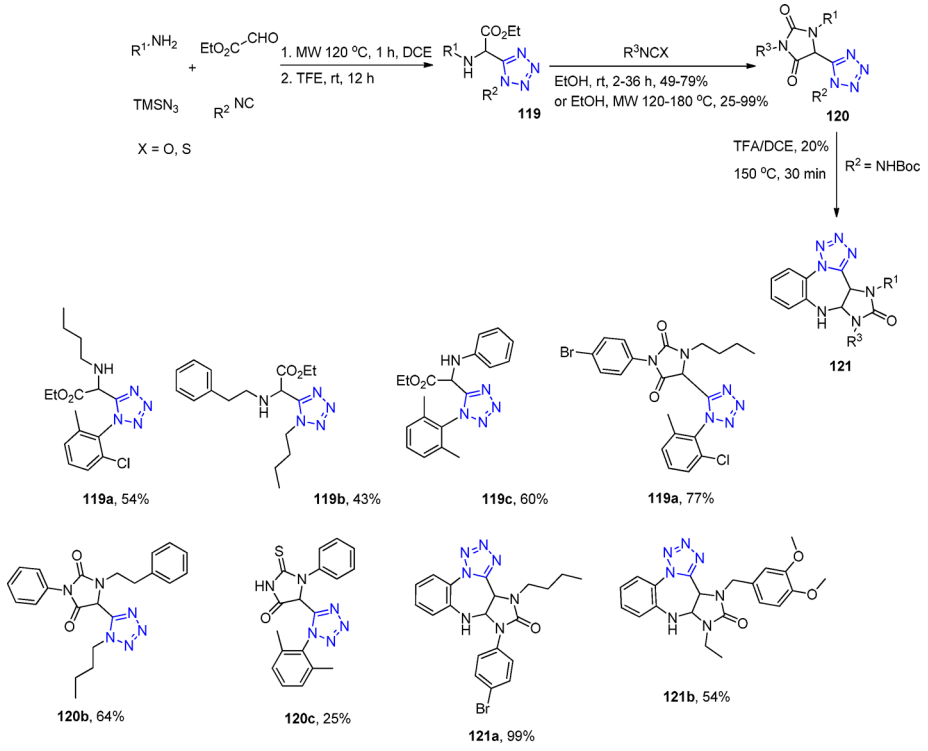
Scheme 45. On-Resin UT Reactions for the *N*-Terminal Derivatization of Peptide with Lipids and Steroids



Scheme 46. Synthesis of 1,5-Substituted Tetrazole Hydantoins and Thiohydantoins 120 and Imidazotetrazolodiazepinones 121



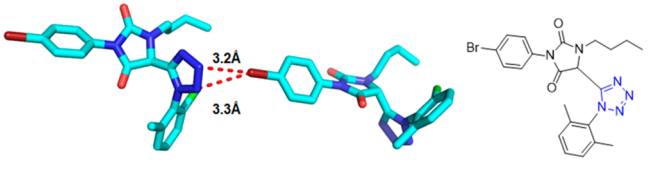


Figure 26. Crystal structure of a 4-bromophenyltetrazolohydantoin **120d** featuring two short contacts (3.2 and 3.3 Å) between the *p*-Br and N2 and N3 of an adjacent tetrazole moiety exhibiting halogen bonding character (CCDC 922820).

via a highly efficient multicomponent condensation process involving an Ugi–Cadogan cascade.[304] Indazoles are a highly underused scaffold in drug discovery.[305] The UT-4CR reactions are followed by a Cadogan reductive cyclization using triethyl phosphite as the reducing agent. A one-pot synthetic strategy was developed and compared with the two-step procedure. With no significant difference between these two methods, the one-pot sequence gave a slightly lower yield 61% compared with 62% from two-step. A variety of amines was tested, assesing the generality of this reaction. Sterically hindered amines led to the expected products with a slight decreased yield, whereas anilines gave sluggish indazole formation probably caused by the lower nucleophilicity of the nitrogen atom (Scheme 58).

Morpholines and piperazines are privileged structures, which are abundantly used as substituents in medicinal chemistry, improving the pharmacokinetic properties of molecules as water solubility and metabolic stability. These moieties belong to the

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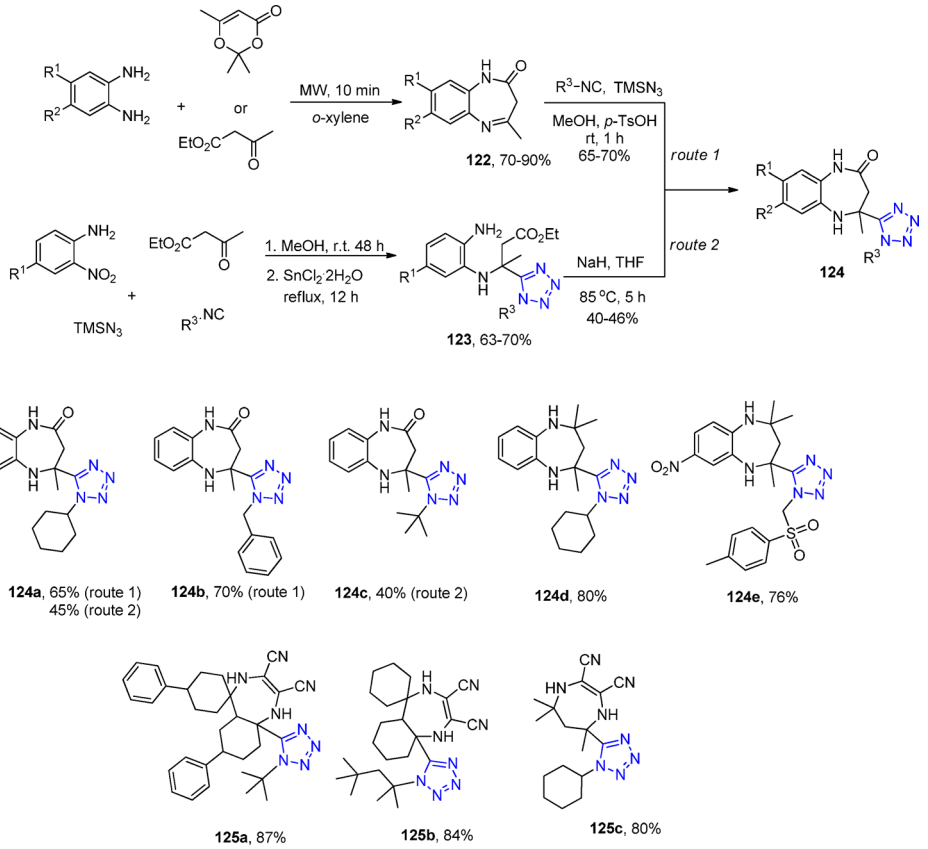
Scheme 47. Synthesis of 1*H*-Tetrazol-5-yl-4-methyl-1*H*-benzo[*b*][1,4]diazepines 124 and 1*H*-Tetrazolyl-1*H*-1,4-diazepine-2,3-dicarbonitriles 125



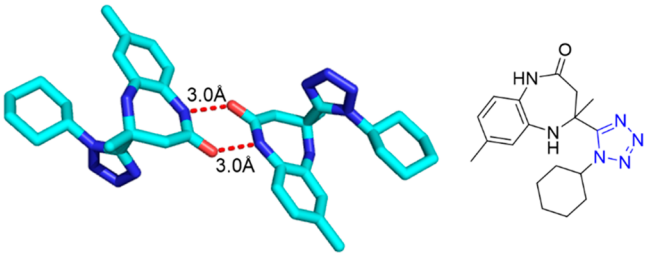


Figure 27. Crystal structure of the benzodiazepin-2-one **124f** (CCDC 900744). The symmetrical hydrogen bonding interaction between O and N was measured 3.0 Å

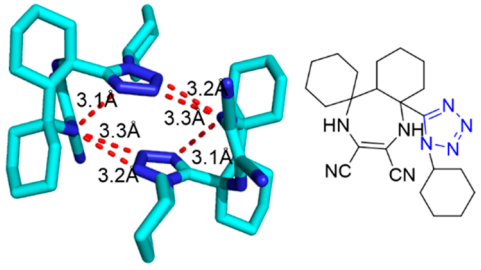


Figure 28. Crystal structure of compound **125d** (CCDC 814967). A network of intramolecular hydrogen bonds of N−H can be observed among the NH and CN groups and the tetrazole moieties varying from 3.1 to 3.3 Å

25 most frequent nitrogen heterocycles in U.S. FDA approved drugs.[306] Dömling et al.[307] reported for the first time the successful incorporation of highly substituted morpholines and piperazines in an UT-4CR. After quite a bit of optimization, the reaction of an α-hydroxy oxo-component together with an isocyanide, NaN_3, and 2-haloamine yielded the corresponding Ugi-tetrazole adduct **146**, which under treatment with NaH gave the corresponding morpholine derivative **147**. To facilitate the high throughput process, the aforementioned procedure was also performed in one pot, affording 20 morpholine-tetrazole derivatives (Scheme 59, Figure 31). In addition, underscoring the usefulness of the produced scaffolds, some further transformations of the secondary amine of morpholines and piperazines via sulfonation, acylation (**148**), urea and thiourea formation (**149**), and reductive amination (**150**) were described (Scheme 60). Similarly, the reaction of the mono-Boc protected ethylenediamine or mono-Boc *o*PDM, 2-chloroacetaldehyde, the corresponding isocyanide, and TMS azide (Scheme 61) afforded the Ugi adducts **151**, which were subsequently cyclized to the corresponding piperazine derivatives **152** after basic treatment (^{t}BuOK or NaH).

3.1.1.3.1 . *UT-4CR Followed by Cyclizations toward Tetrazole-Lactam Derivatives.* The *N*-unsubstituted γ- and δ-lactam moieties play a very important and diverse role in medicinal chemistry because they are found in many drugs, for example, in the anti-Parkinson drug Oxotremorin,[308] and in the anti-rhinoviral and enteroviral drug Rupintrivir.[309] The substitution on the lactam nitrogen position clearly affects its hydrogen bonding profile in the receptor binging site.

The general strategy of post cyclizations toward tetrazole-lactam derivatives is based on the usage of bifunctional building blocks (Scheme 62).

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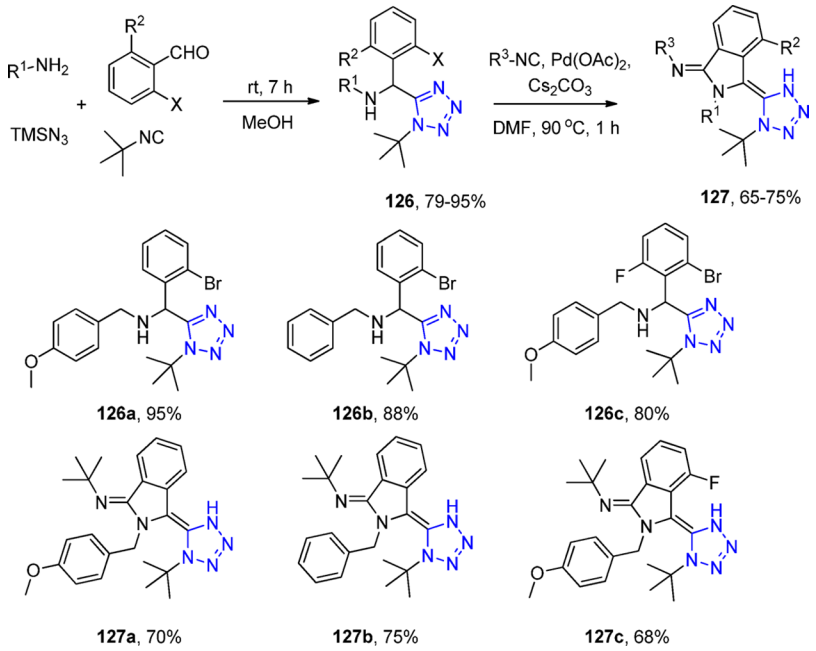
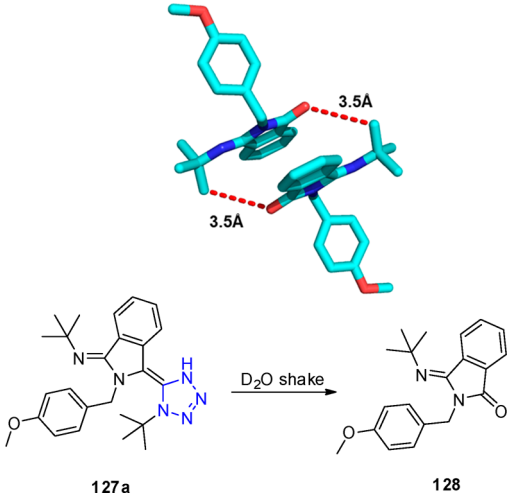
Scheme 48. General Strategy for the Synthesis of the Tetrazole-isoindolines 127



Scheme 49. Compound Degradation after D_2O Shake during NMR Experiment and ORTEP Diagram Drawn of the Crystal Structure of (*E*)-3-(*tert*-Butylimino)-2-(4-methoxybenzyl)isoindolin-1-one (128) Determined at 293 K (CCDC 959960) (The Interaction between O of Lactam and Methyl of *tert*-Butyl Was Measured as 3.5 Å



Marcaccini et al.,[310] in order to obtain heterocyclic systems by means of postcondensation modifications of the Ugi reaction, employed methyl *o*-formylbenzoates as bireactive carbonyl components and mixed it with amines, isocyanides, and TMS azide to afford the expected tetrazolyl-isoindolinones **154** with good isolated yields via a tandem Ugi tetrazole (**153**)/intramolecular amidation. In some cases, the intermediate Ugi tetrazole intermediate cyclized spontaneously, whereas in other cases the cyclization occurred only in ethanolic sodium ethoxide under refluxing conditions. Aliphatic amines generally cyclized spontaneously and also precipitated out, whereas deactivated anilines needed forced conditions for cyclization (Scheme 63).

Hulme et al.[311,312] reported bifunctional building blocks in the UT-4CR, offering an unprecedented significant scope expansion and combinatorial applications toward novel pharmacologically relevant complex bis-heterocyclic lactam-tetrazoles. They reported the reaction of suitable protected and unprotected orthogonal oxo-carboxylic acids, which yielded a great diversity of bis-heterocyclic lactam-tetrazole scaffolds, few of them containing fragments of importance in medicinal chemistry. Clearly, many of these scaffolds can be synthesized in parallel to provide libraries of interesting compounds. He established a postcondensation modification methodology which reacted keto-esters (e.g., methyl levulinate), primary amines, isocyanides, and TMS azide in one pot via the UT reaction followed by the lactam formation under acidic condition to afford a small library of novel peptidomimetic-like bispyrrolidinone tetrazoles **155**. It is noteworthy that this is the first example of a trifluoroacetic acid mediated γ-lactam formation. Sterically hindered amines gave no or low yields, such as 2,6-dichlorobenzylamine, 4-morpholinoaniline, 1-benzylpiperidin-4-amine, and cyclohexylamine. A virtual library of 400000 compounds was enumerated and compared to the NIH molecular libraries small-molecule repository (MLSMR) to show uniqueness of occupancy of chemical space by principal component analysis. Moreover, a small library of 84 compounds was obtained in 24-well plates with overall yields ranging from 2 to 84%, with 82 compounds having purity greater than 95% [as judged by UV absorbance at 214 nm, 254 nm, and evaporative light scattering (ELS)] (Scheme 64).

In 2012, Hulme et al.[252] utilized the UT to generate unique 1,5-disubstituted tetrazole with ethyl glyoxalate and mono-*N*-Boc-protected-*o*-phenylenediamine derivatives (**156**). The subsequent acid treatment and intramolecular cyclization led to bis-3,4-dihydroquinoxalinone tetrazoles **157** in just two steps but with moderate yields (Scheme 65, Figure 32). Directly catalytic oxidation using a stable solid-phase supported radical catalyst, derived from the 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) with stoichiometric ceric ammonium nitrate (CAN), generated the final targeted bis-quinoxalinone tetrazoles **158**. They also extended the research to synthesize the diazepinone derivatives **161** with *N*-Boc-2-aminobenzylamine via the UT

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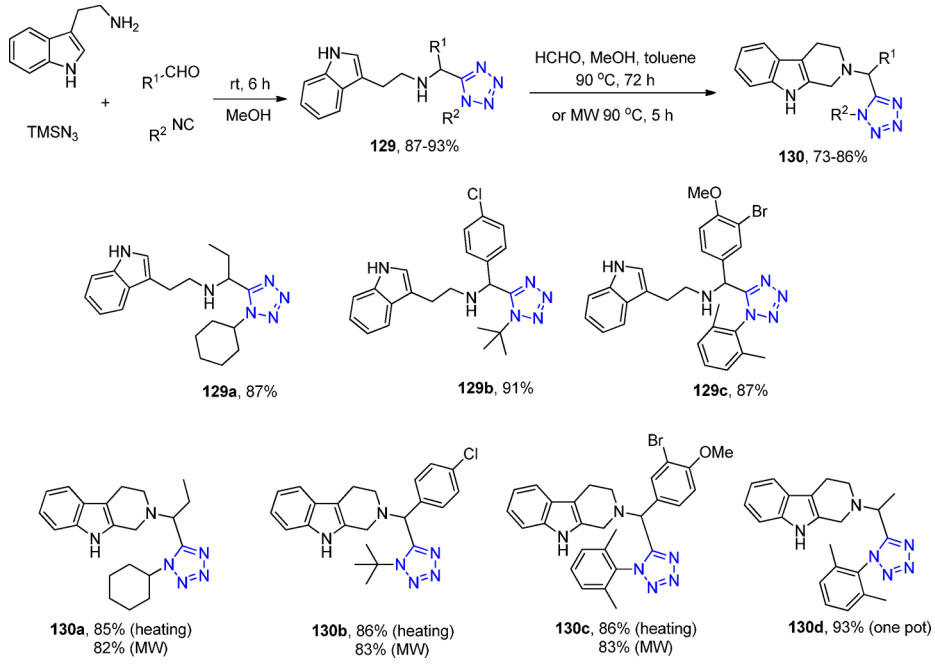
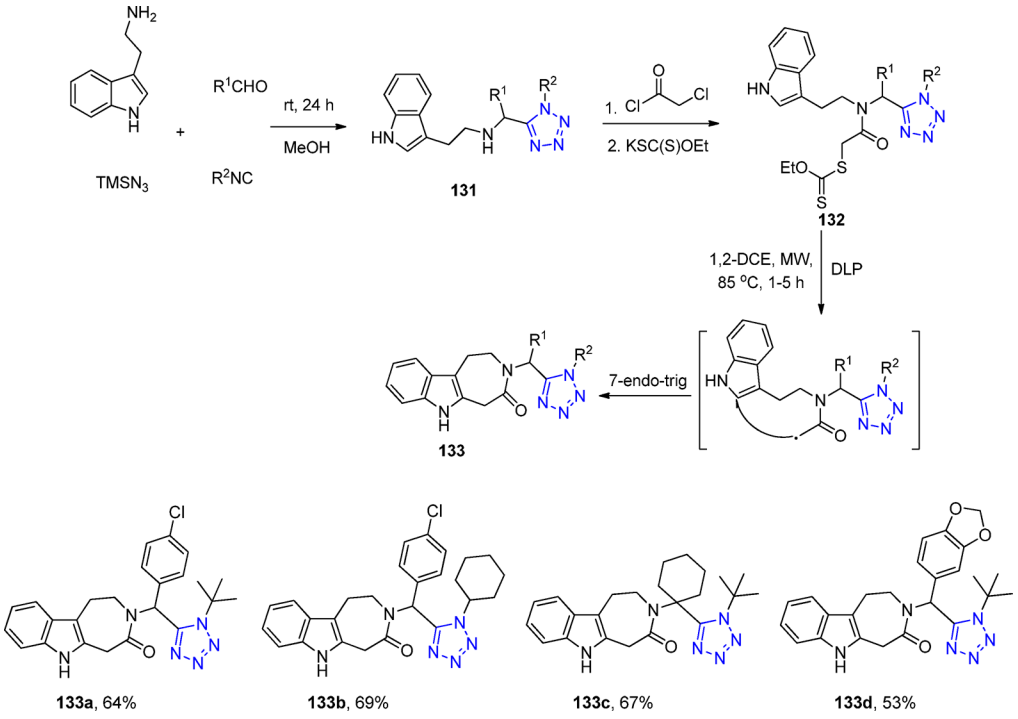
Scheme 50. Synthesis of 2-Tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines 130



Scheme 51. Synthesis of the 3-Tetrazolyl-azepino[4,5-*b*]indol-4-ones 128 via a One-Pot (UT-4CR/*N*-Acylation/S_N2)/Xanthate Free-Radical Mediated Cyclization



159 (Scheme 66). Unexpectedly, the similar acidic deprotecting procedure did not further proceed to the cyclized product and the additional aminolysis of the ester by either activating the ester or the amine failed. Therefore, a hydrolysis was performed under basic conditions (**160**) followed by an EDC-promoted intramolecular amide coupling to obtain the corresponding diazepinones **161** in 27−66% yield (Scheme 66).

Dependent on the used oxocarboxylic acid esters, quite different cyclization conditions were used. Seven series of bis-heterocyclic lactam-tetrazoles were synthesized: tetrazolyl-pyrrolidinones **162**, indolinonetetrazoles **163**, thiomorpholinone-tetrazoles **164**, 4-sulfonyl-2-piperazinone-tetrazole derivatives **165**, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one tetrazole derivatives **166**, benzo[1,4]oxazepinone derivatives **167**, and [1,4]thiazepanone derivatives **168** (Scheme 67 and Table 4). As it was previously stated,[312] in the tetrazolyl-pyrrolidinones **162** series simply trifluoroacetic acid in dichloromethane was added after completion of the Ugi tetrazole reaction. Alternatively, the Ugi intermediate was isolated, purified, and then subjected to methanolic KOH solution to

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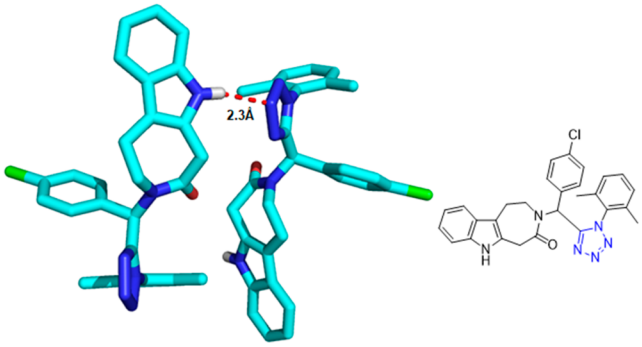
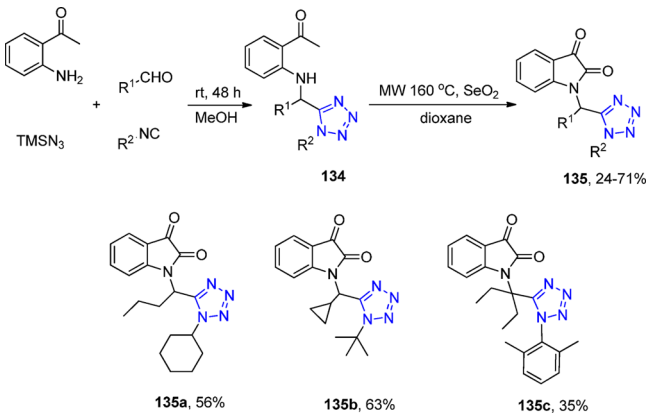


Figure 29. X-ray crystal structure of azepinoindolones **133e** (CCDC 948622). An intermolecular hydrogen bond of 2.3 Å is observed between the azepinoindole N−H and the nitrogen of the tetrazole moiety.

Scheme 52. UT Reaction of *o*-Aminoacetophenone, Aldehydes, Isocyanides, and $TMSN_3$, Followed by an Oxidation/Intramolecular Oxidative Amidation toward the Tetrazole Derivatives 135



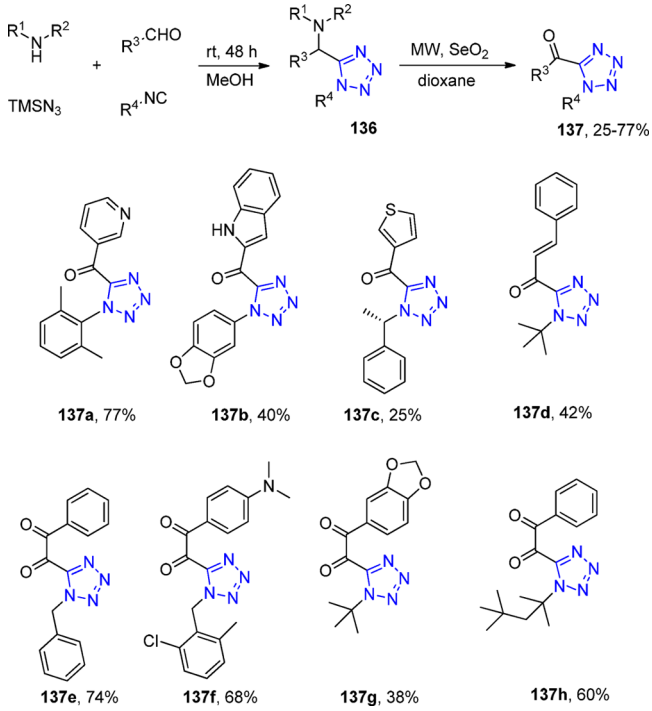
afford the tetrazolyl-pyrrolidinones. The methodology was importantly shown to be compatible with 96-well plate-based production. Yields reported for the eight isolated compounds varied between 40 and 78% (Figure 33).

Concerning the six-membered piperidinone-tetrazoles, cyclization is accomplished by KOH mediated hydrolysis of the UT methylester followed by EDC/DMAP cyclization or alternatively by thionyl chloride mediated cyclization. Interestingly, by using 5-oxo-hexanoic acid the Ugi tetrazole product **169** is formed exclusively, and no trace of the alternatively possible Ugi lactam is formed (Scheme 68).

The intermediate and not isolated Ugi tetrazole can then be cyclized in situ using DCC. The authors argue that the small and strongly nucleophilic azide ion leads to a kinetically favorable formation of the four-component Ugi tetrazole product.

Also, several seven-membered lactam motifs were introduced. Four examples of azepinone-tetrazoles were synthesized in two steps comprising consecutive basic hydrolysis and in situ acyl chloride formation. In the case of the tetrazolyl-indolinones **163**, 2-acetylbenzoate was found to be a poor substrate in the Ugi reaction, while methyl 2-formylbenzoate worked well in all eight cases in yields between 36 and 66% (Scheme 67). As described previously,[310] the cyclization occurred spontaneously at room temperature (Figure 33). The integration of a sulfur atom into the six-member ring to generate tetrazole-thiomorpholinone derivatives **164** was found to be another interesting scaffold.

Scheme 53. Dual *α*-Ketotetrazoles and *α,β*-Diketotetrazoles 137 Based on the MCR-Oxidative Deamination Approach



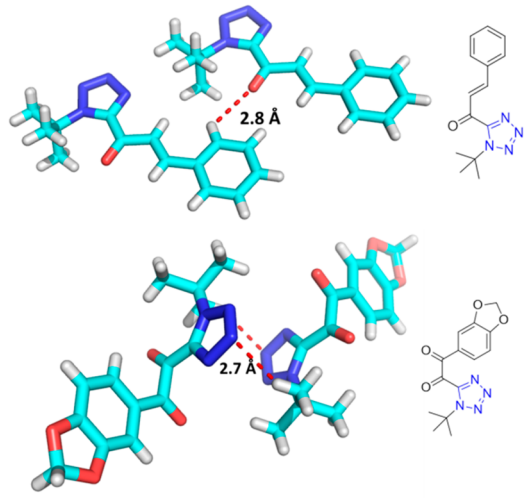


Figure 30. X-ray crystal structure and polar contacts of the tetrazole chalcone **137d** (CCDC 1531964) and the *α,β*-diketotetrazole **137g** (CCDC 1554390).

Under optimized conditions, the intermediate UT was hydrolyzed and subsequently the intramolecular amidation using $SOCl_2$ in dichloromethane afforded five isolated products in yields 22−96%. The 4-sulfonyl-2-piperazinone skeleton can be incorporated into the UT reaction sequence by choosing the appropriate starting material (Scheme 67). The 4-sulfonyl-2-piperazinone motif **165** represents an essential structural feature of human factor Xa and gene transcription inhibitors.[313,314] A series of six 4-sulfonyl-2-piperazinones were generated with yields between 16 and 74% for the UT reaction and 58−93% for the hydrolysis and cyclization step, respectively (Figure 33).

Intrigued by the potentially pharmaceutical application of unprecedented bifunctional scaffolds, a series of 4,5,6,7-

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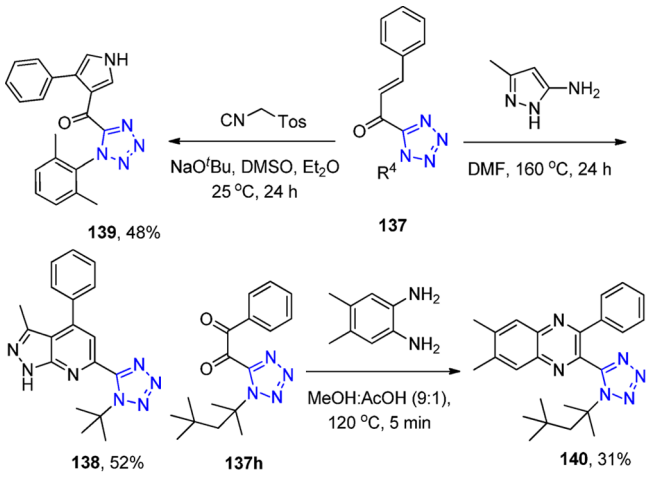
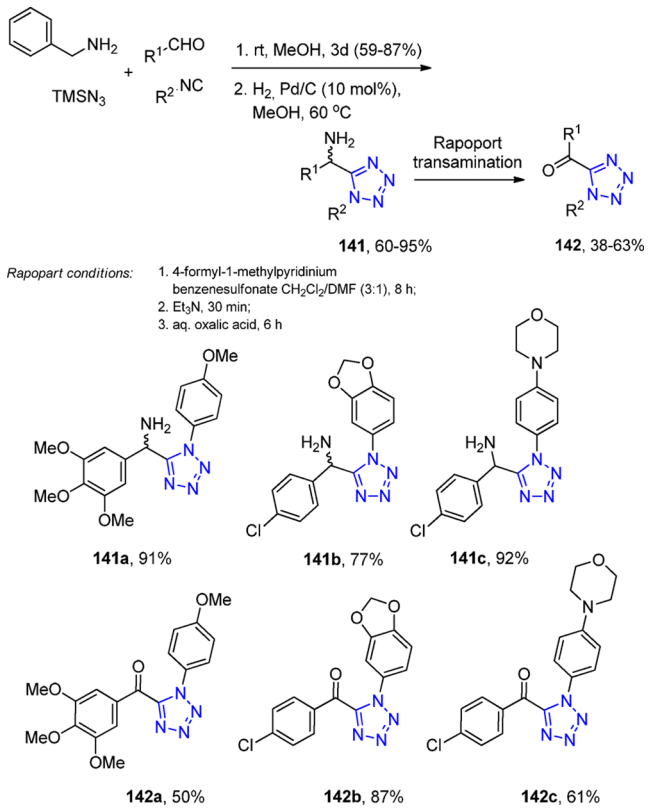
Scheme 54. Applications of Tetrazole Chalcones and α,β-Diketotetrazoles to Produce Diverse Tetrazole Chemotypes as the Derivatives 138, 139, and 140



Scheme 55. General Procedure for the Synthesis of 5-Aroyl-1-aryltetrazol Analogues 142



tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one derivatives **166** were synthesized with moderate to good isolated yields through the combination of UT-4CR and subsequent basic hydrolysis and $SOCl_2$-mediated ring closure step. Five compounds were isolated in yields between 42% and 74% and 51−78% for the UT-4CR and cyclization, respectively.

The benzo[1,4]oxazepinone motif **167** was incorporated into the UT-4CR by employing the appropriate benzaldehyde starting material. Six compounds were isolated with yields between 66% and 80% and 31−84% for the UT-4CR and cyclization, respectively (Figure 33, 34).

Last but not least, a small series of five [1,4]thiazepanones **168** was synthesized by UT-4CR, KOH hydrolysis, and $SOCl_2$ mediated cyclization in yields between 61% and 75% and 45−66% for the UT-4CR and cyclization, respectively (Figure 33).

In an analogous fashion, Stolyarenko et al.[315] used 1-ethoxycarbonyl-cycloalkane oxo compounds **170**, isocyanides and primary amines in the UT-4CR to afford the interesting class of tetrazole-substituted spirocyclic γ-lactams **171**. No spontaneous cyclization occurred under the UT-4CR conditions (MeOH, rt), but it was accomplished under acidic conditions in DCE with 10% trifluoroacetic acid under heating conditions for 10 h. A library of 20 compounds was produced with yields between 52% and 72% (Scheme 69). The substrate scope of the reaction is quite broad, including aliphatic, aromatic, and bulky isocyanides and heterocyclic, aliphatic, and aromatic primary amines. Moreover, the straightforward introduction of a spiro tetrahydro-2*H*-pyran is worth mentioning, which otherwise is very difficult to access. Tetrahydro-2*H*-pyranes are used in medicinal chemistry to improve pharmacokinetic and CYP inhibition profile of lead compounds.[316] In addition, a spirocyclic connection adjacent to an amide carbonyl might protect from spontaneous or enzymatic cleavage. Spirocyclic fragments are present in many biologically active compounds. The γ-lactam moiety is also the common structural unit for a large nootropic class of drugs, called racetames (e.g., piracetam). Racetams are memory enhancers and are hypothesized to interact with cholinergic and glutamate receptors in the central nervous system.

They also described the crystal structures of two compounds which give some ideas on the 3D conformation and intermolecular contacts (Figure 35).

Dömling et al.[317] designed and synthesized a series of *N*-unsubstituted γ- and δ-lactams **173**, which were conveniently accessed in a three-step synthesis involving an UT-4CR followed by cyclization with overall good yields. While ammonia is often troublesome in the Ugi reactions, tritylamine was introduced as a convenient ammonia surrogate.[141] However, because of the bulkiness of the trityl group, only aliphatic aldehydes afforded the corresponding products in yields between 40% and 80%. Ketones and aromatic aldehydes did not give the required Schiff base or only traces, respectively. The trityl amine tetrazole intermediate **172** was deprotected in quantitative yields using trifluoroacetic acid in dichloromethane. Optimization of the final cyclization conditions revealed that using sodium hydride is a suitable base to afford γ- and δ-lactams in most cases with reasonable to good yields (Scheme 70). A typical interaction pattern of the γ- and δ-lactam substructures was found by analyzing the PDB crystal structures. A general strong tridirectional hydrogen bond donor−acceptor interaction between the receptor amino acids and the *N*-unsubstituted γ- and δ-lactam fragment reveals a useful molecular moiety to address corresponding receptor motives (Figure 36). The same motif is generally found in the X-ray structures of small tetrazolo-lactams leading to dimerization via the γ- and δ-lactam NH−CO group.

3.1.1.4. UT-4CR toward 1,5-Disubstituted Tetrazoles Bearing a Sugar Moiety. Glycosylation is the reaction in which a carbohydrate is attached to a hydroxyl or other functional group of another molecule. Many natural products are glycosylated, and their biological activity is crucially dependent on the glycosylation, which is a form of cotranslational and post-translational modification. In living organisms, glycosylation mainly represents the enzymatic process that

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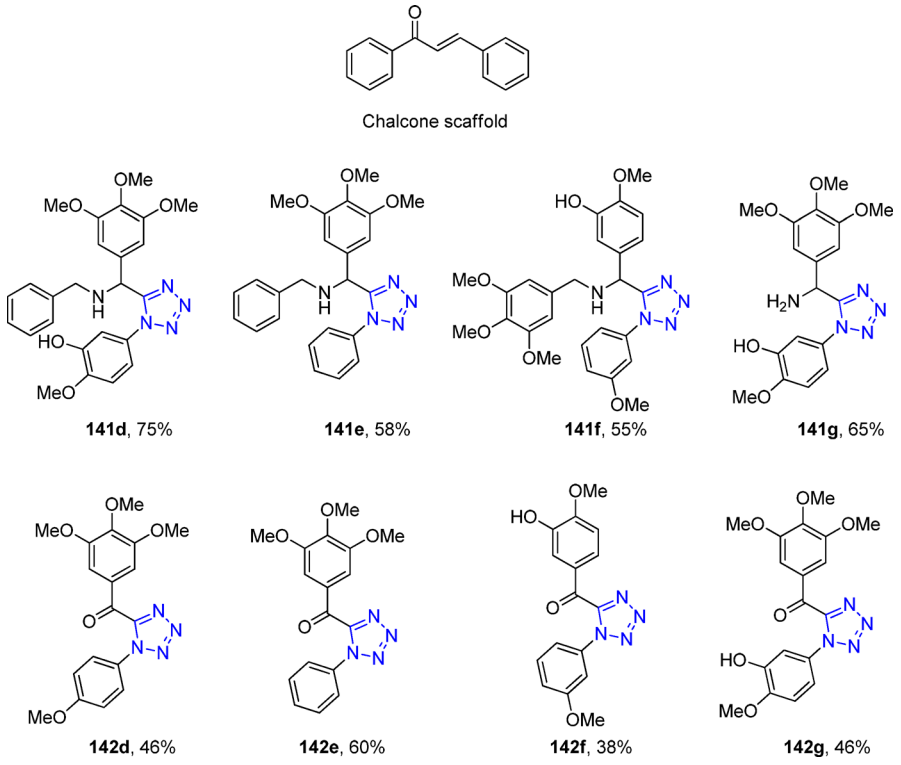
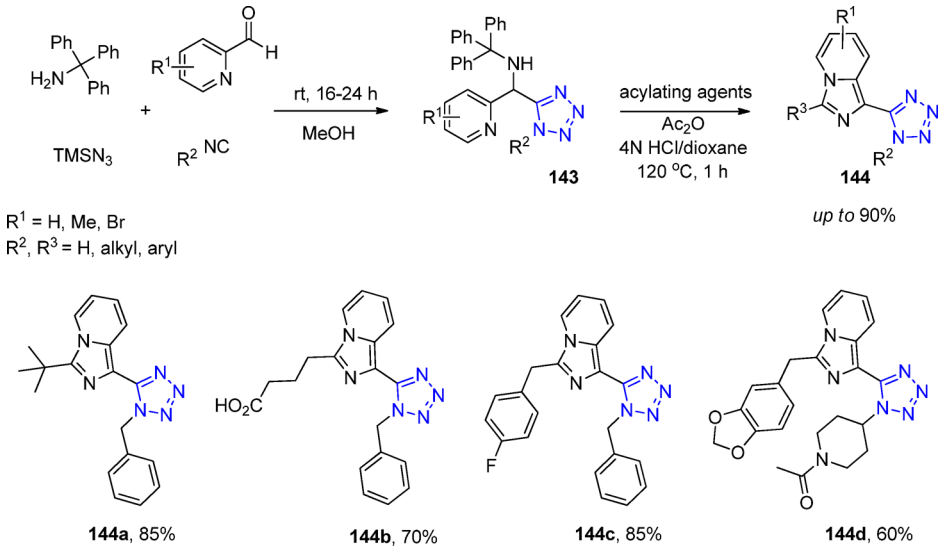
Scheme 56. General Synthesis for Tetrazolic Analogues of Chalcones 142



Scheme 57. General Synthesis for Tetrazolyl Imidazo[1,5-*a*]pyridines 144



attaches glycans to proteins, lipids, or other organic molecules.[318]

The amino sugar desosamine occurs in diverse natural products with different activities, for example, in the antibiotics tylosin with mycaminose structurally related to desosamine, erythromycin, and methymycin. In 2006, Dömling et al.[319] described the employment of desosamine into IMCRs. They prepared desosamine and the corresponding isocyanide (Scheme 71A) in a big scale by acid hydrolysis and subsequent amination from the readily available erythromycin. In addition, two syntheses were accomplished by stirring equimolar amounts of TMS azide, aldehyde, desosamine, and an isocyanide in methanol at rt for 24 h to give the disubstituted α-aminomethyl tetrazoles **174** as a mixture of diastereomers in 37% and 25% yield, respectively (Scheme 71B).

Sugar moieties in drugs are used for different purposes, e.g., the glycosyl substituent will be recognized by the receptor and contribute directly to the biological activity or it helps to improve transport properties through transporters and increase water solubility. Sugar−organic fragment chimeras are traditionally synthesized by sequential multistep synthesis. To that direction, another successful application of sugar moieties in MCRs was also presented by Dömling et al.[320] (Scheme 72). A series of anomeric sugar isocyanides (β-glycosyl and β-arabinosyl), which has been known and sporadically used in IMCRs, were synthesized via the reintroduced Leuckart−

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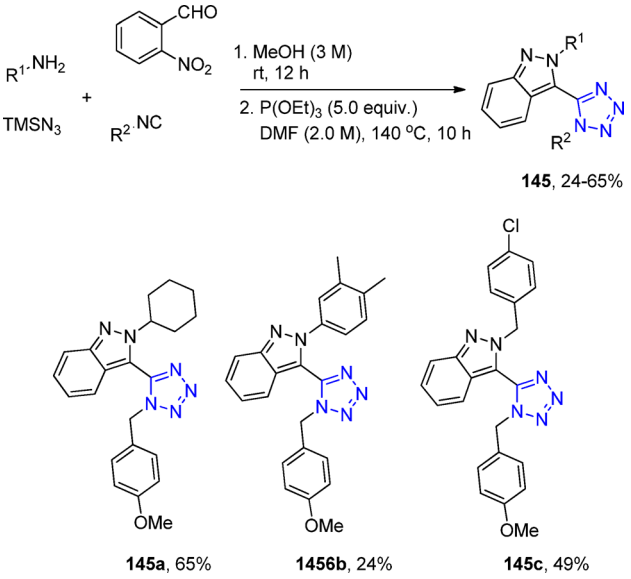
Scheme 58. One-Pot Tetrazolyl Indazole 145 Formation



145, 24-65%

145a, 65% **1456b**, 24% **145c**, 49%

Wallach approach[321,322] in good overall yields. They also reported the general usage of these two isocyanides in IMCRs to produce 1,5-disubstituted and α-alkylamino tetrazole derivatives **175** among others.

The conjugation of steroids to other biomolecules, like amino acids and proteins, is a common strategy employed both by nature and chemists to modulate the biological and chemical behavior of these molecules. Considering the growing importance of sugar/steroid hybrids in drug discovery and biological chemistry, Rivera et al.[218,323] employed multicomponent reactions for the conjugation of carbohydrates to steroidal derivatives **176** with a great level of molecular diversity and complexity generated with the low synthetic cost (Scheme 73).

Calixarenes, are a type of macrocycle or cyclic oligomer produced by the condenseation of *p*-substituted phenols with aldehydes. They have been widely used in various fields, i.e., the synthesis of multivalent/multifunctional ligands, and they are the ideal candidates for studying noncovalent interactions occurring in many biological processes based on the easy

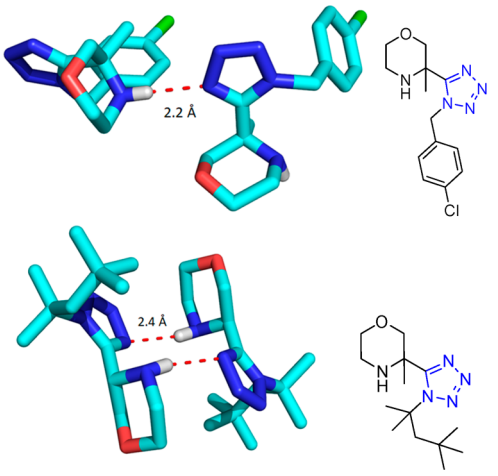
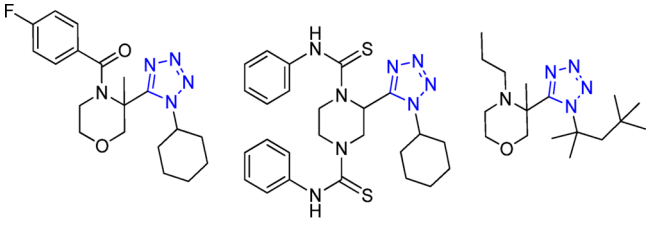


Figure 31. Crystal structures of the morpholine derivatives **138f** (CCDC 1507665) and **138a** (CCDC 1507068). An intermolecular hydrogen bond of the morpholine N−H to the N of the tetrazole can be identified at 2.2 and 2.4 Å, respectively.

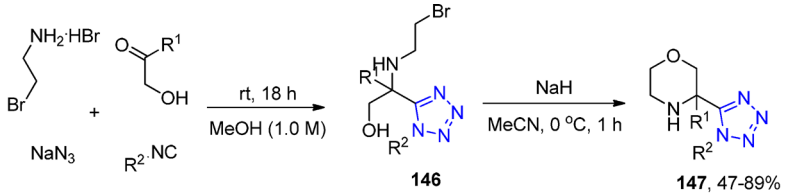
Scheme 60. Further Derivatization of the Morpholine and Piperazine Scaffolds via Acylation, Thiourea Formation, and Reductive Amination, Respectively



148, 54% **149**, 33% **150**, 72%

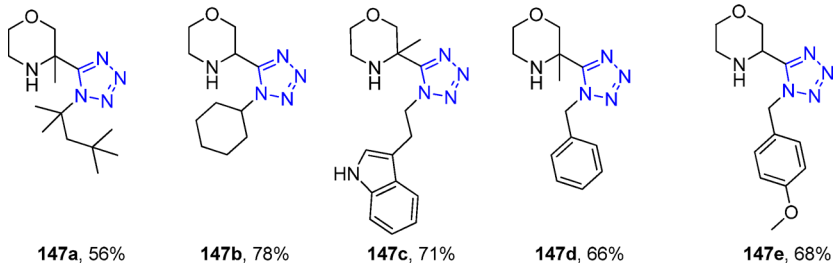
accessibility and functionalization at their wide and narrow rims. Therefore, Zadmard et al.[324] synthesized functionalized calixarenes through MCRs. They first prepared the basic precursor calixarene dihydrazide **177** using a previously reported synthetic procedure.[325] Then, α-hydrazino tetrazolocalix[4]-arene derivatives **178** were synthesized in good yields via an UT-4CR (Scheme 74, Figure 37). Metal ion binding properties of

Scheme 59. Synthesis of the Ugi Adduct 146 and the Morpholines Derivatives 147



146

147, 47-89%



147a, 56% **147b**, 78% **147c**, 71% **147d**, 66% **147e**, 68%

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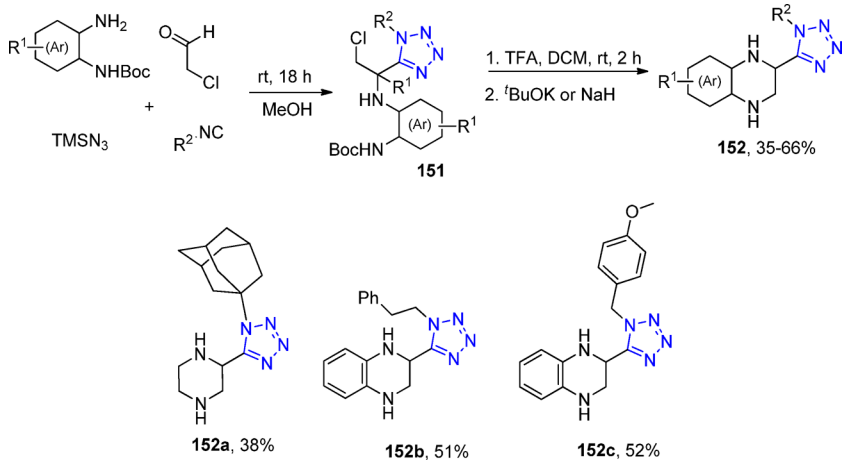
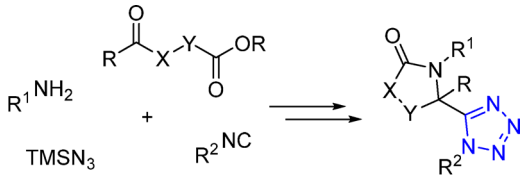
Scheme 61. Synthesis of the Ugi Adduct 151 along with the Piperazine and Tetrahydroquinoxalines Derivatives 152



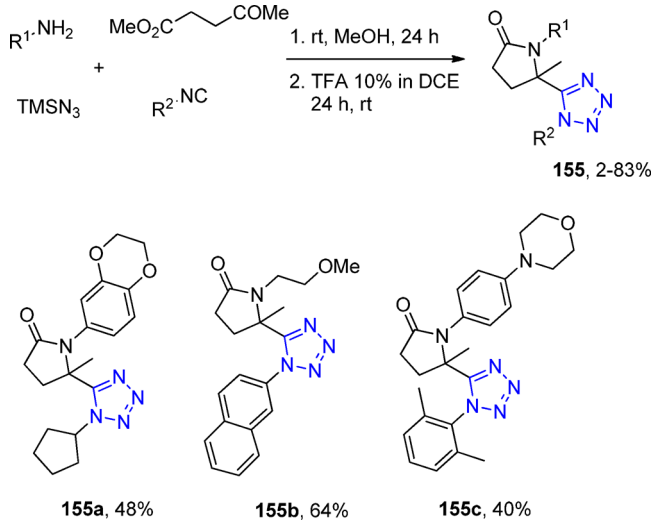
Scheme 62. General Strategy to Lactam-Tetrazoles



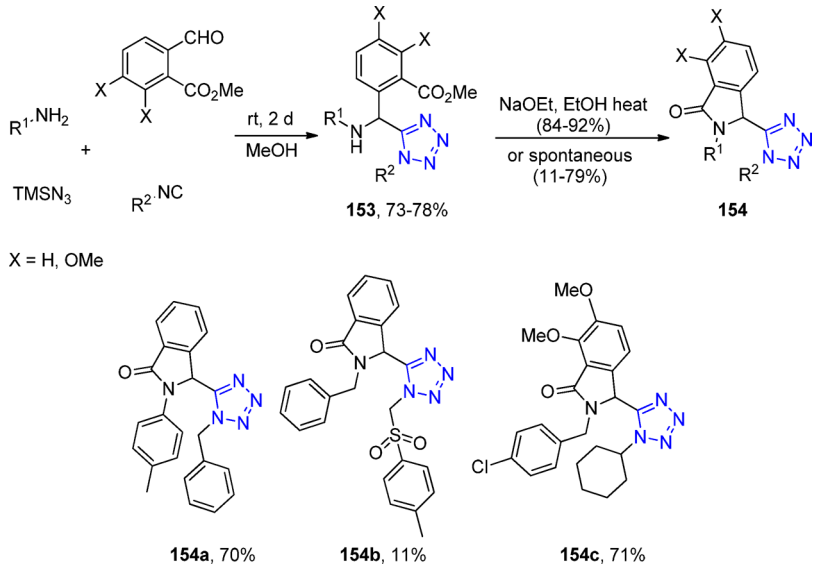
compound **178a** as the model compound were also investigated, revealing what exhibits the highest binding affinity toward Ni(II).

3.1.2. Ugi Tetrazole 3-Component Reaction (UT-3CR). The variation of an Ugi 3-component reaction can be obtained when two of the four reacting functionalities are placed in the same substrate. This is the case when, for example, cyclic imines, oxoacids, and amino acids are employed. In the tetrazole modification, there are fewer possibilities. Essentially these UT-3CR are possible with cyclic imines.

Scheme 64. General Synthetic Route to Access Bis-pyrrolidinone Tetrazole 155



Scheme 63. Synthesis of Tetrazolyl-Isoindolinones via UT-4CR/Intramolecular Amidation



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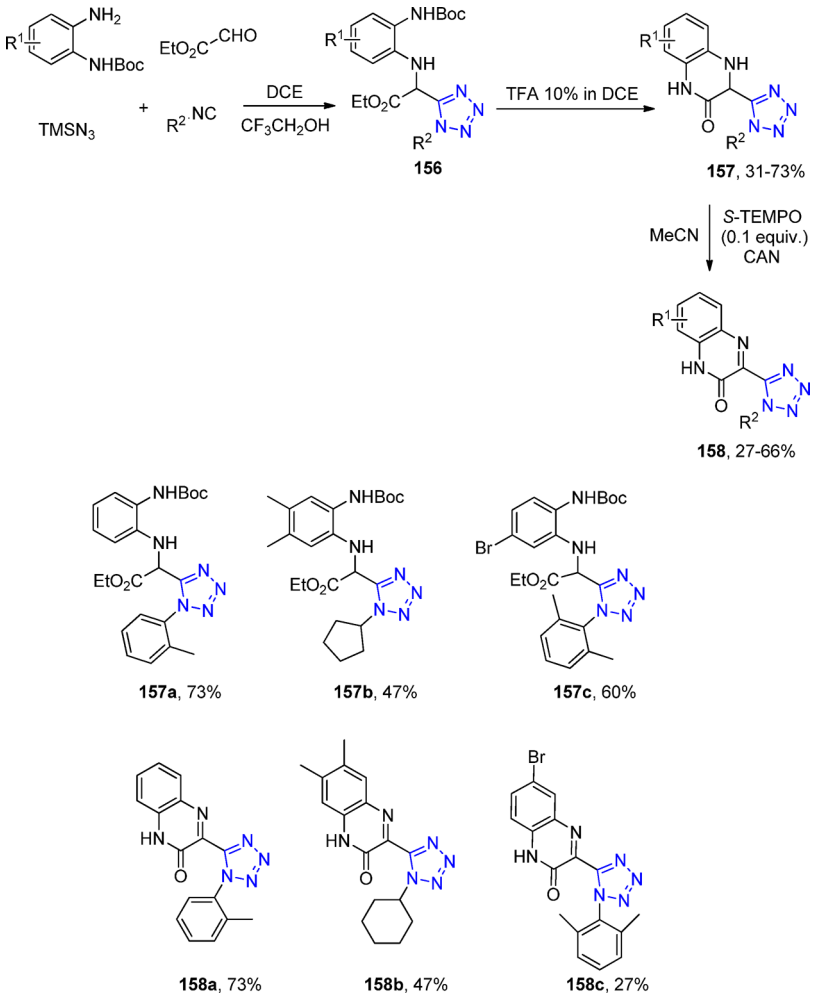
Scheme 65. Synthesis of Bis-quinoxalinone Tetrazoles 158



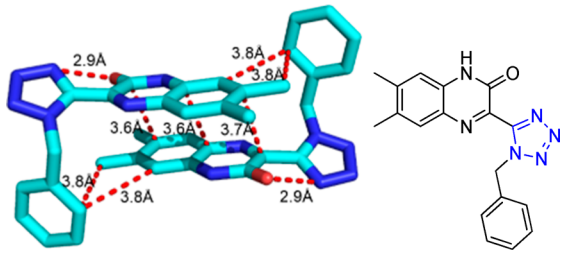


Figure 32. Crystal structure of 3-(1-benzyl-1*H*-tetrazol-5-yl)-6,7-dimethylquinoxalin-2(1*H*)-one (**158d**) exhibiting an antiparallel π stacking alignment of two adjacent quinoxaline moieties, featuring in addition a low energy antiparallel dipole dipole alignment (CCDC 932013)

Organofluorine compounds attract more and more interest due to their important properties in pharmaceutical applications and materials science.[326] The medicinal chemist often employs bioisosteres to replace the functional group in drugs to improve ADMET properties. The replacement of a hydrogen atom with a fluorine atom at a site of metabolic oxidation in a drug candidate might block metabolism without compromising biological activity and increasing half-life time. Nenajdenko et al.[327] studied the application of trifluoroalkylated cyclic imines in UT reactions. They started from different arrays of five-, six-, and seven- membered trifluoroalkylated cyclic amines to form target tetrazole derivatives of saturated nitrogen heterocycles bearing the trifluoroalkyl moieties **179**. In addition, the final 1*H*-tetrazoles **180** could easily be obtained by catalytic hydrogenation in excellent yields (Scheme 75).

In 2013, Ukaji et al.[328] first synthesized in good yields the novel 1,5-disubstituted tetrazoles **182** containing tetrahydroisoquinoline skeletons based on the UT-3CR. They utilized *C,N*-cyclic *N*′-acyl azomethine imines **181**, both aliphatic and aromatic isocyanides and in situ TMS azide generated through TMSCl and sodium azide (Scheme 76).

3.1.3. Passerini Tetrazole 3-Component Reaction (P-3CR). In 1921, a three-component reaction between carboxylic acids, oxo components, and isocyanides for the synthesis of an α-acyloxy amide was discovered by Passerini (P-3CR).[55,56] In 1961, Ugi reported the synthesis of tetrazoles via a Passerini type 3CR (P-3CR) for the first time using HN_3 and $Al(N_3)_3$.[52]

Aspartyl proteases which catalyze amide bond hydrolysis found to play a key role in many biological processes, including the development of a variety of diseases and the important therapeutic targets. Hulme et al.[225] reported the facile synthesis of analogous *cis* constrained norstatine mimetics by simply mixing an *N*-Boc-amino aldehyde **183**, an isocyanide, and TMS azide in dichloromethane affording the derivative **184**, followed by deprotection with trifluoroacetic acid and *N*-capping with TFP esters to the desired amides and sulfonamides **185** in good yields. This reaction proved to tolerate a range of functionalities

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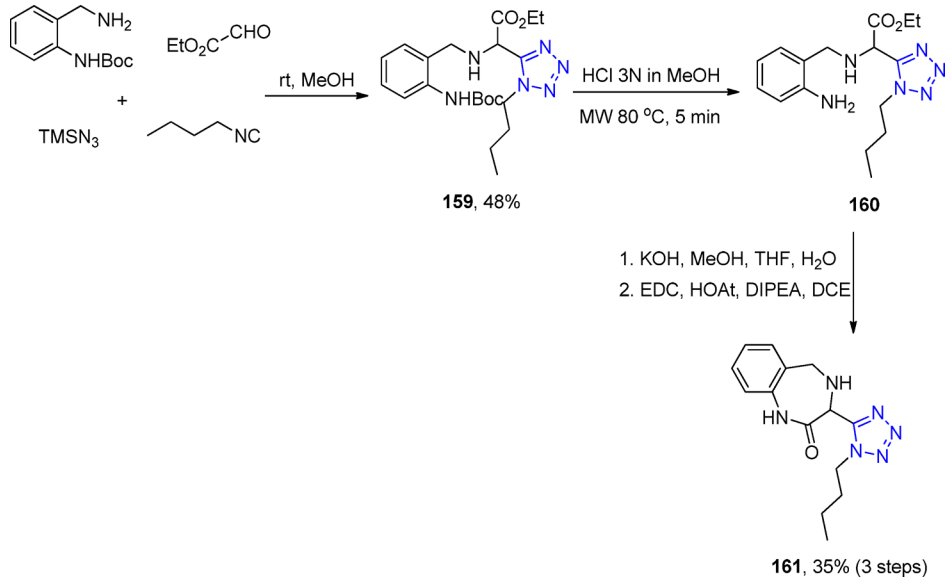
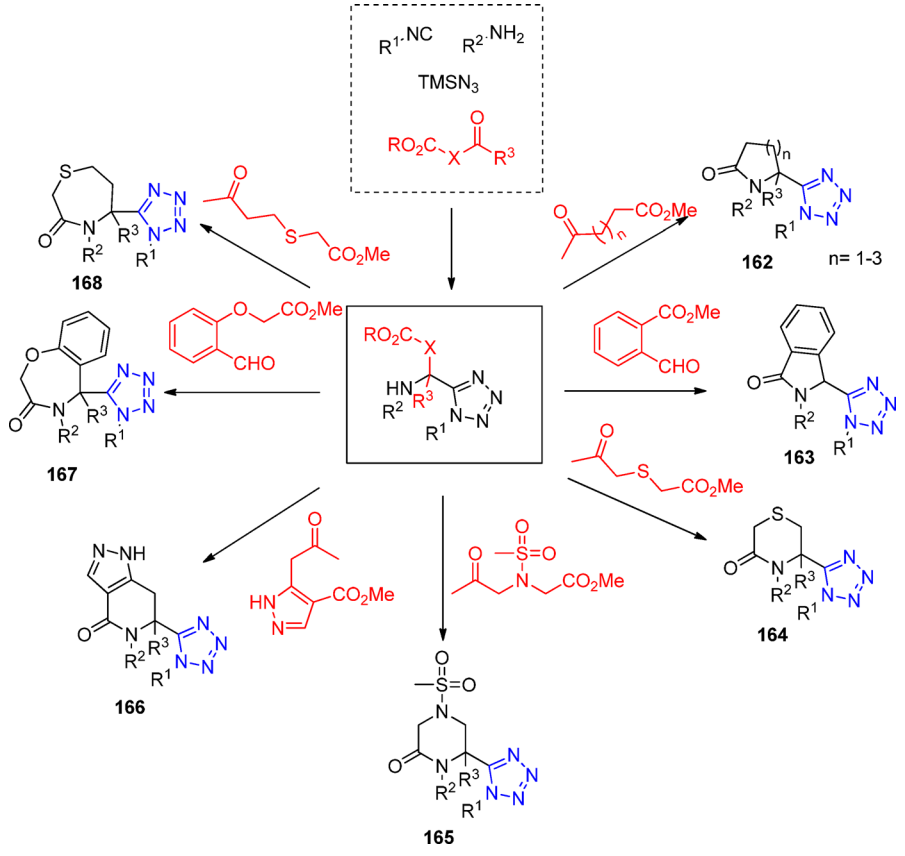
Scheme 66. Synthesis of Tetrazolobenzodiazepin-2-ones 156



Scheme 67. Diversity of Bis-heterocyclic Lactam-Tetrazoles



including a variety of isocyanides and *N*-Boc-α-amino aldehydes (Scheme 77).

Chiral 5-substituted tetrazoles have been recognized as efficient organocatalysts.[329−333] Many methods have been developed for the synthesis of 1,5-disubstituted tetrazoles, including the 5-(1-hydroxyalkyl)tetrazoles. Zhu et al.[334] first reported to synthesize enantioselective 5-(1-hydroxyalkyl)-tetrazole **186** catalyzed by a [(salen)Al^{III}Me] (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion) through Passerini-type reaction of aldehydes, isocyanides, and hydrazoic acid with good-to-excellent enantioselectivity (Scheme 78). Four different catalysts were optimized in several reaction conditions. With the optimized conditions and stoichiometry for the reaction (isobutyraldehyde/1-isocyano-4-methoxybenzene/HN_3/catalyst 1.2:1:2.5:0.1), they also examined the generality of this catalytic enantioselective process by varying the structure of the aldehyde and isocyanide. Linear and α-branched aliphatic aldehydes and aliphatic and aromatic isocyanides with

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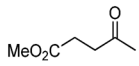
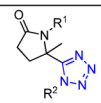
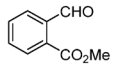
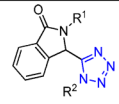
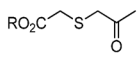
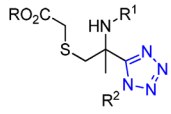
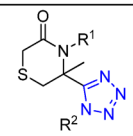
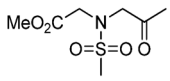
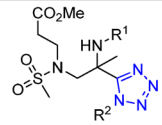
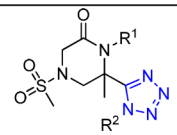
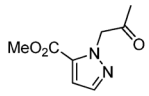
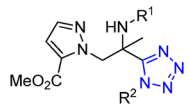
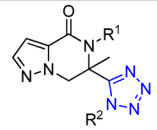
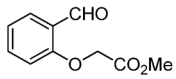
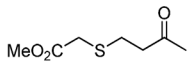
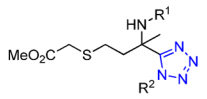
Table 4. Use of Bifunctional Building Blocks in the UT Reaction Followed by Lactamization

Oxo-component	UT product	Yield (%)	Condensation product	Yield (%)
	N/A	N/A		40-78
	N/A	N/A		29-66
		42-86		58-93
		16-74		58-93
		42-74		51-78
		63-80		45-66
		61-75		29-84

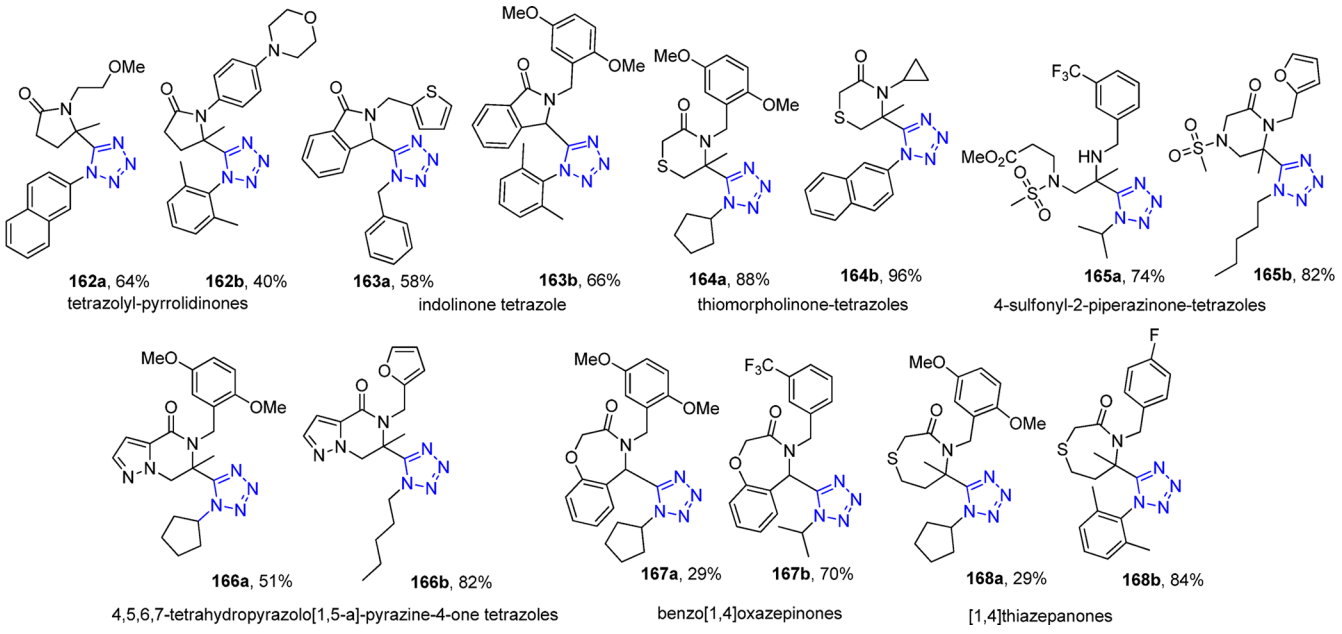


Figure 33. Examples of bis-heterocyclic tetrazolo scaffolds.

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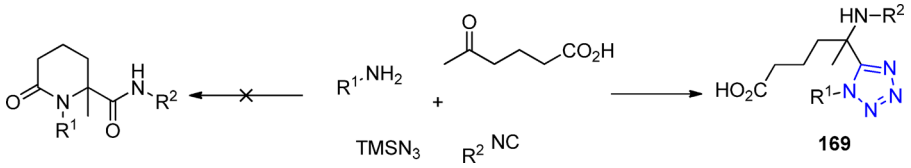
Scheme 68. Selective Tetrazole Formation over the Intramolecular Ugi Product



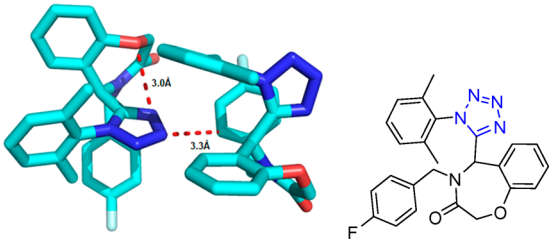


Figure 34. Crystal structure of a benzo[1,4]oxazepinone derivative **167c** (CCDC 936637). It is noteworthy that there is an intramolecular hydrogen bond (3.0 Å) between N4 and O9 and a short contact (3.3 Å) between N3 and C10

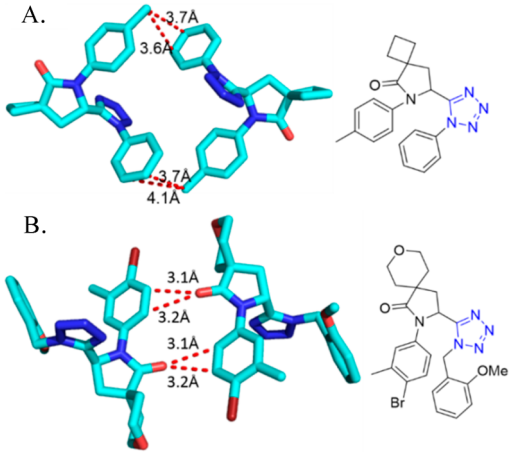


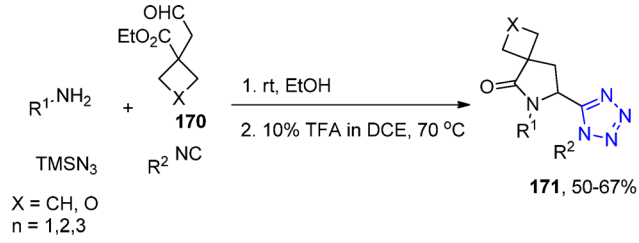
Figure 35. Crystal structure of tetrazole-substituted spirocyclic γ-lactams **171e,f** (CCDC 918594 and 918596). It is noteworthythat it is the antiparallel alignment of the phenyl units of two adjacent molecules with short contacts (3.6 Å, 3.7 Å, 4.1 Å) between C (sp^3) and C (sp^2). Similarly, there is also the semiantiparallel alignment of the phenyl units and lactam ring of two adjacent molecules with short contacts (3.1 Å, 3.2 Å) between O (C═O) and C (sp^2).

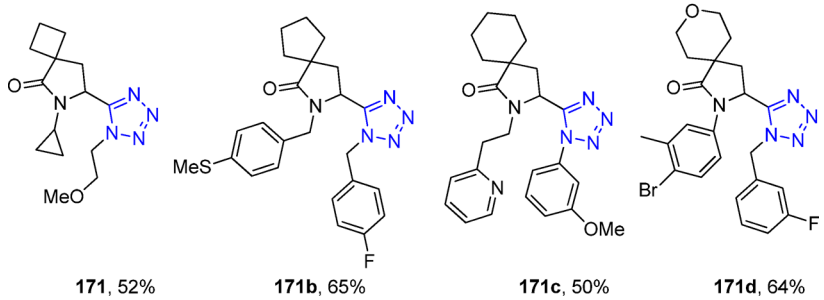
electron-donating or electronic-withdrawing groups worked nicely. However, in the case of the sterically encumbered 2,6-dimethylphenylisocyanide, yield and enantioselectivity both diminished. When α-isocyanoester was used, a spontaneous hydrolysis/lactonization sequence proceeded well. Due to the fact that salen-Al complexes catalyze the nucleophilic addition of azide to α,β-unsaturated imides and to α,β-unsaturated ketones, they were tested and found also to perform a tandem Michael addition/enantioselective P-3CR using a α,β-unsaturated aldehyde as the carbonyl substrate. The results showed that 1-(4′-methoxyphenyl)-5-(1′-hydroxy-3-azidopropyl)tetrazole could be detected with good yield and enantioselectivity (Scheme 78).

Very often, a synthetic methodology that could lead to a new class of compounds is based on the input of a component with different reactive functionalities in an already established MCR. In 2012, Yanai et al.[335] developed a novel four-component reaction of aldehydes, isocyanides, TMS azide, and free aliphatic alcohols without amines catalyzed by the Lewis acid indium(III) triflate to give rise to α-alkoxyamides **187** in good yields (direct *O*-alkylative tetrazole P-4C reaction, ATP-4CR). Aliphatic and aromatic aldehydes both were well tolerated in this synthetic methodology (Scheme 79, Figure 38).

Although MCR proved to be more environmentally benign compared with the classical tetrazole synthetic methods, people still continue to try to employ water as the reaction medium in organic synthesis. To date, its beneficial effects on a variety of organic transformations have been widely recognized.[336−338]

Scheme 69. Synthesis of Tetrazole-Substituted Spirocyclic γ-Lactams 171 by One-Pot UT-Cyclization





171, 52% **171b**, 65% **171c**, 50% **171d**, 64%

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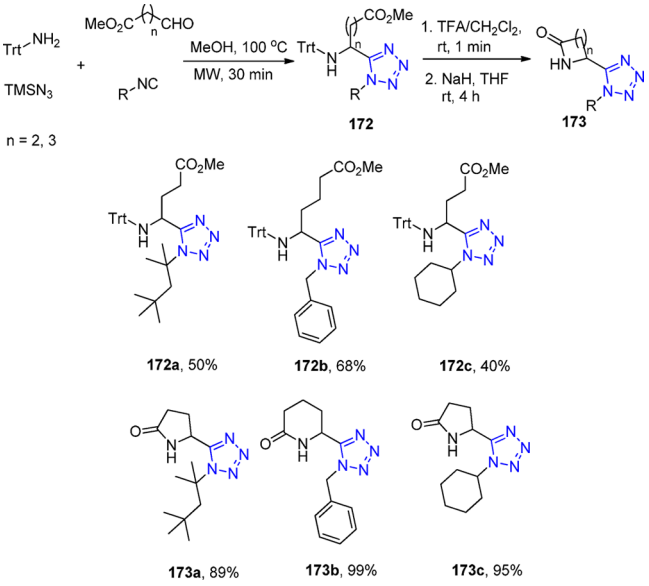
Scheme 70. Devised Synthetic Pathway to Tetrazolo *N*-Unsubstituted γ- and δ-Lactams 173



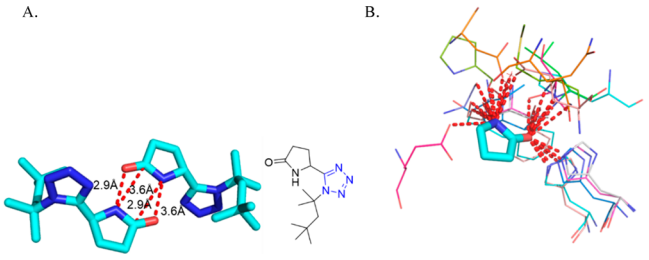


Figure 36. (A) Crystal structure of a tetrazole fused γ-lactam **173a** (CCDC 961190). It is worth mentioning that there is a pair wise hydrogen bonding with a neighbor lactam in short contacts (2.9 Å) between N6, O1 and N6′, O1′. (B) Alignment of several PDB structures (3D23, 3EWJ, 3QZR, 3RHK, 3TNT, 3UR9, 3DPM, 1H0V, 3JUC, and 3Q3Y) showing the polar interactions for 10 γ-lactam containing ligands.

High cohesion energy density, hydrogen bonding-stabilized transition state, and enhanced hydrophobic effect in the ground vs transition state, could be the reasonable resources to explain the reaction acceleration in aqueous media.[336,337,339−344] Meanwhile, there are only a few reports about the influence on the selectivity of organic reactions by adding salt. Vigalok et al.[345] demonstrated that simple sodium salts addition in Passerini reaction in aqueous media can completely reverse the product ratios. Furthermore, the use of the "salting-in" effect and a small excess of the nucleophile could lead to significantly higher yields of Passerini tetrazole products **188** instead of the Passerini adducts with different nucleophile than azide (Scheme 80).

In that direction, a sonication accelerated, catalyst free, simple, high yielding, and efficient method for the P-3CR has been developed.[346] It comprises the reaction of an oxocomponent, an isocyanide, and a TMS azide in methanol−water (1:1) as the solvent system, giving rise to derivatives **189**. The use of sonication not only accelerated the rate of the reaction but also provided good to quantitative yields (Scheme 81). The reaction has a high functional group tolerance, applicable to a broad scope of aldehydes/ketones and isocyanides, due to the very mild reaction conditions and in addition the existence of a free hydroxyl group allows various postmodifications; the authors demonstrated the possibility to synthesize fused tetrazoles **191** from the tetrazole precursors **190**, which are important scaffolds as they possess a wide spectrum of activity and vast industrial applications (Scheme 82).

3.1.4. Miscellaneous MCRs toward Monocyclic Tetrazole Derivatives. A microwave-accelerated, simple, efficient, and versatile method for the construction of the 1,5-tetrazole scaffold was developed by Dömling et al.[347] Due to the fact that the reported methods for tetrazole formation from amides face major drawbacks, such as harsh conditions, low yields, and missing substrate scope, an in situ amide formation from amines and carboxylic acid derivative followed by imidoyl chloride formation and finally tetrazole formation by azide addition as a one-pot MCR, was proposed.

The majority of the acid chlorides gave complete conversion to the corresponding tetrazoles **192** under the optimized conditions in good to high yields (Scheme 83). Aromatic and aliphatic acid chlorides proved to be equally effective in this reaction. The conversions of aromatic and aliphatic carboxylic acids were as effective as those of the acid chlorides, but these substrates delivered the products in slightly lower yields. Application of this method to esters was also successful; however, a longer reaction time was required (25−30 min) for the total conversion, and moderate to good yields were provided with aliphatic and aryl esters. Bistetrazoles **193** are also accessible and these compounds are highly important in high-energy nitrogen-rich compounds.[347]

Fused tetrazole scaffolds were also described by this methodology; the use of functionalized carboxylic acids with amines bearing an additional functional group would allow an anticipated domino cyclization process in one step. The reaction of formamide, which works both as an ammonia and formaldehyde surrogate and 2-aminobenzoic acid under the optimized conditions led to the formation of the tetrazolo[1,5-*c*]quinazoline scaffold **194** in moderate yield (Scheme 84).

The usefulness of this method was demonstrated in the synthesis of biologically important fused tetrazole scaffolds and the marketed drug cilostazol (**196**) from the halogenated tetrazole precursor **195** (Scheme 85).

Amino acids were also successfully employed with full stereoretention toward derivatives **197**, as shown by HPLC on a chiral stationary phase (Scheme 86).

Saiprathima et al.[348] described the MCR synthesis of 3-tetrazolyl oxindoles **198** from isatines by a facile intermolecular [2 + 3] cycloaddition between an azide and a nitrile group bound to quaternary center of oxindole at C3 position in water. The straightforward preparation of these compounds is the C3 functionalization by nucleophilic addition of isatins (Scheme 87). The use of TMSCN as a nucleophile allows the synthesis of 3-cyano-3-hydroxy oxindoles and their direct conversion into corresponding tetrazole derivatives **198** by facile [2 + 3] cycloaddition of azides (Figure 39). The authors also observed a one-pot four-component tetrazole formation of compound **199** using aniline as an additional component (Figure 40).

In 2011, Shaabani et al.[349] reported an efficient and simple two-step strategy for the preparation of 1,5-disubstituted tetrazole derivatives **200** and **201** containing siloxy or sulfonamide groups, respectively, by simply mixing isocyanides, dialkylacetylenedicarboxylates, and triphenylsilanol in fairly good yields. First a formal 1:1:1 addition reaction takes place selectively, yielding ketenimines containing a siloxy group in high yields. Next, an intermolecular cycloaddition reaction of

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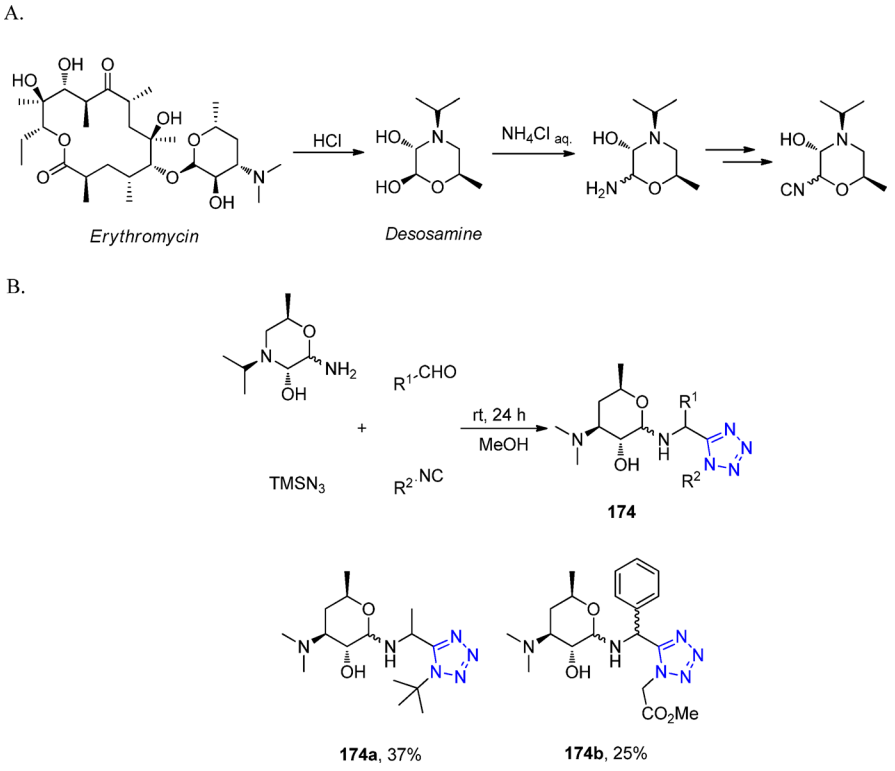
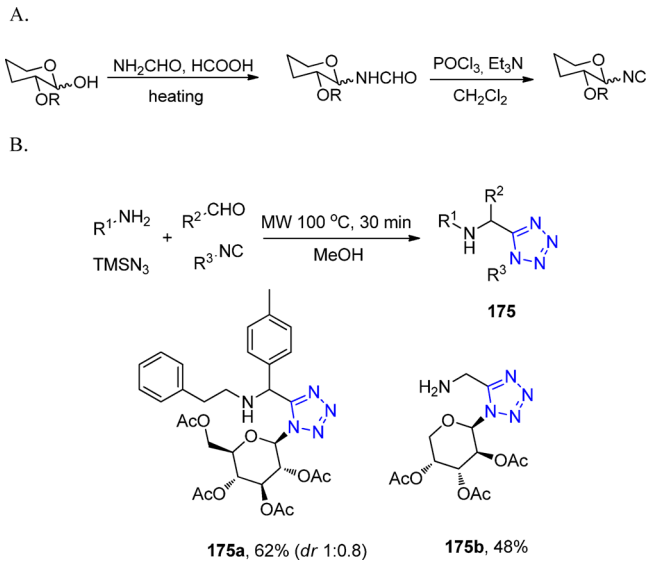
Scheme 71. (A) Acidic Hydrolysis of Erythromycin Yields Desosamine Which Is Subsequently Transforms into 1-Isocyanodesosamine; (B) Synthesis of Disubstituted α-Aminomethyl Tetrazoles 174 Based on Desosamine with UT-4CR



Scheme 72. (A) Leuckart–Wallach Approach to Sugar Isocyanides; (B) Synthesis of 1,5-Disubstituted Tetrazoles 175 Using Glycosyl Isocyanide and Arabinosyl Isocyanide



the siloxy ketenimines with TMS azide yields the corresponding 1,5-disubstituted tetrazoles **200** and **201** (Scheme 88, Figure 41).

The reaction of *N*-halo succinimide, sodium azide, and phenyl isocyanide in chloroform with a phase transfer catalyst yielded 5-halo-1-phenyltetrazoles **202** in a three-component reaction.[350−352] 5-Halo-1-substituted tetrazoles might be interested building blocks, e.g., in Pd catalyzed C−C couplings (Scheme 89). For example, the synthesis of tetrazolyl β-lactam systems **205** was described using 5-halo-1-benzyltetrazole **204** and the azetidinone **203** as a coupling building block.[353]

In 2012, Kazemizadeh et al.[354] first disclosed a three-component reaction of isocyanides, carbodiimide, and TMS azide in 1:1:1 ratio, leading to 1,5-disubstituted 1*H*-tetrazole derivatives **206**. The reaction proceeded smoothly in methanol, affording the targeted products without the need of any further purification. The mechanism is similar to the classical UT-4CR. Here, carbodiimide reacted similar to a Schiff base and was attacked by the nucleophilic addition of isocyanide. Then, the protonation of the resulting adduct led to the nitrilium intermediate, which subsequently was attacked by the azide anion to form the adduct followed by ring closure (Scheme 90).

3.2. Bicyclic Tetrazole Derivatives

3.2.1. UT-4CR toward Fused Tetrazolopyrazine Derivatives. In 1998, Bienaymé et al.[355] rigidified the basic UT-4CR scaffold of α-alkylaminotetrazole to result in the 7,8-dihydrotetrazolo[1,5-*a*]pyrazine scaffold. In this procedure, they mixed an oxo component, a primary amine, methyl-β-(*N*,*N*-methylamino)-α-isocyanoacrylate (Schöllkopf's isocyanide),[356] and TMS azide in a ratio of 1:1:1:1.4 at ambient temperature in methanol to give an intermediate UT-4CR adduct. Subsequent treatment with diluted acid catalyzes the secondary amine attack and dimethylamine substitution under ring formation to form the final bicyclic products **207**. This constitutes a sequence of an Ugi four-component reaction (U-4CR), forming an α-amino tetrazole containing a secondary amine, followed by a ring closing reaction with the dimethyl amine from the former isocyanide acting as a leaving group with overall yields fair to good (Scheme 91).

In 2000, Hulme et al.[357] disclosed an efficient one-step protocol involving an Ugi reaction followed by a postcondensation reaction to access tetrazolopiperazines **209** with three

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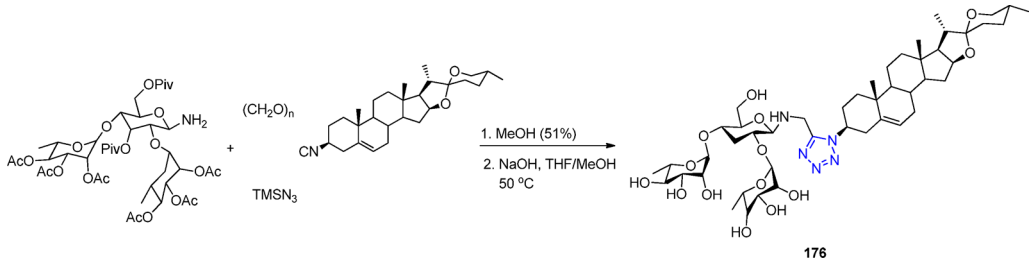
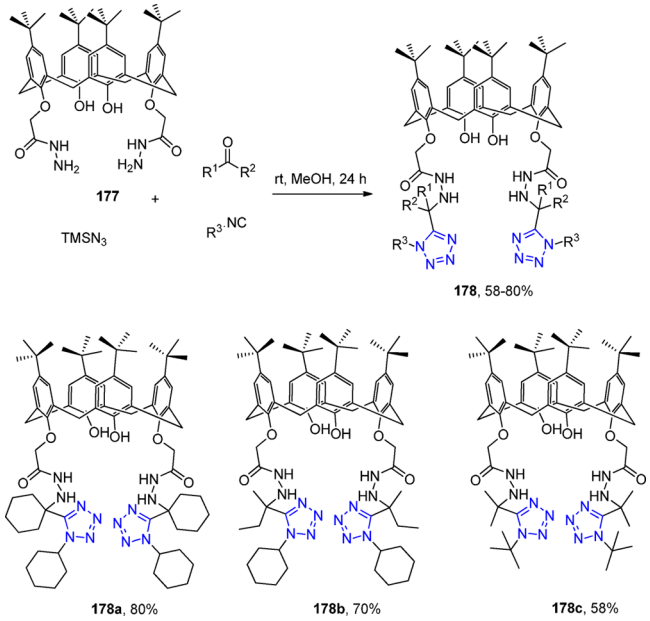
Scheme 73. Synthesis of Tetrazole-Based Spirostan Saponin Analogues 176



Scheme 74. Synthesis of Calixarene Dihydrazide 178 via UT-4CR



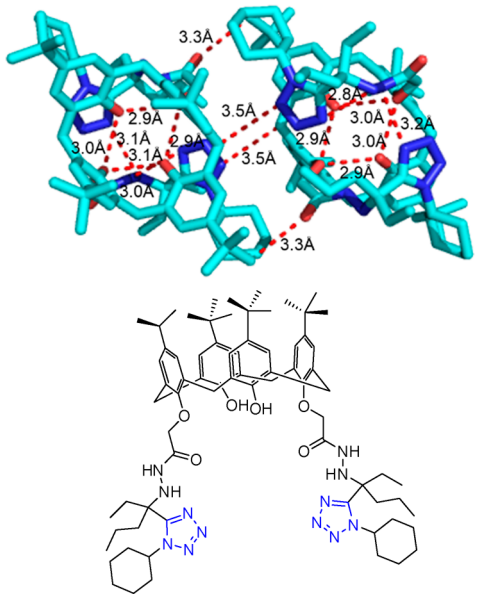


Figure 37. Crystal structure of calixarene dihydrazide **178d** (CCDC 1025095). Four hydrophobic interactions of two molecules were observed as O (C═O) and methyl, N(2), and methyl of calixarene ring. Six hydrophilic interactions consist of four interactions between N(4) of tetrazole and N of hydrazine, two interactions between hydroxyls and O of calixarene ring.

potential diversity points. α-Amino acid derived isocyano esters **208** react in the UT-4CR, and the secondary amine of the side chain spontaneously undergoes a lactamization. A range of commercially available aldehydes and aliphatic or aromatic substituted primary amines were investigated, and it was shown that more sterically hindered groups in the aldehydes or amines would largely decrease both yields (Scheme 92).

Dömling et al.[358] replaced the amine component with ammonia which provided tetrazolopyrazinones **210** in good to high yields in one-pot fashion. After quite some optimization, ammonium chloride proved to be the best ammonia source followed by treatment with catalytic amount (0.1 equiv) of ammonium hydroxide as a base at 50 °C for 18 h, giving the cyclized adducts (Scheme 93, Figure 42).

Hiller et al.[359] in 2004 employed a synthetic methodology whereby cyclization to the tetrazolopiperazine system occurs in situ via a toluolsulfonate group. It is noteworthy, that the cyclization step could proceed at rt without the addition of acid or refluxing. Simply following a classical UT-4CR procedure mixing aldehydes, primary amines, TMS azide, and 2-isocyanoethyl sulfonate in a ratio of 1:1:1.5:1.5 led to the expected fused tetrazoles **211**. The 2-isocyanoethyltoluolsulfonate building block that was employed in this versatile reaction can be synthesized in two steps from ethanolamine via selective *N*-formylation followed by *O*-tosylation and dehydration using tosyl chloride. The final products could be synthesized rapidly with two points of potential diversity (Scheme 94).

Dömling et al.[159] discovered three new different heterocyclic scaffolds easily accessible from isocyanoacetaldehyde dimethylacetal by MCRs. The initial UT-4CR with isocyanoacetaldehyde dimethylacetal yields an intermediate (**212**), which can undergo a range of condensation reactions, e.g., Pictet−Spengler (see also Schemes 103 and 104). The 7,8-dihydrotetrazolo[1,5-*a*]pyrazine scaffold **213** is formed from aliphatic or aromatic aldehyde and aliphatic amine components which cannot undergo a subsequent Pictet−Spengler reaction (Scheme 95, Figure 43). The cyclization simply runs in neat methanesulfonic acid, giving generally good to excellent yields of the 7,8-dihydrotetrazolo[1,5-*a*]pyrazines **213**.

Dömling et al.[360] also developed an effective procedure for the novel syntheses of highly substituted tetrazole-fused ketopiperazines **216** through UT/deprotection and U-4CR. First, they synthesized the *N*-unsubstituted α-aminotetrazoles **214** by using an UT-4CR; second, the *N*-unsubstituted α-aminotetrazoles **215** were then employed in a second intramolecular U-4CR to afford the desired products **216** in moderate to good yields. The UT synthesis was initially performed under Ugi azide conditions with tritylamine ($TrtNH_2$) as the amine component, various aldehydes and isocyanides derived from α-amino acids, and TMS azide (Scheme 96, Figure 44). These scaffolds are

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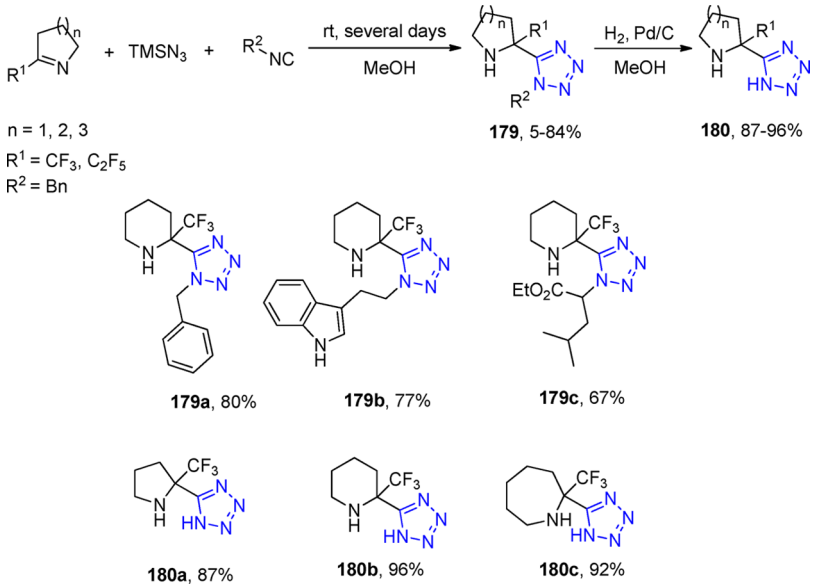
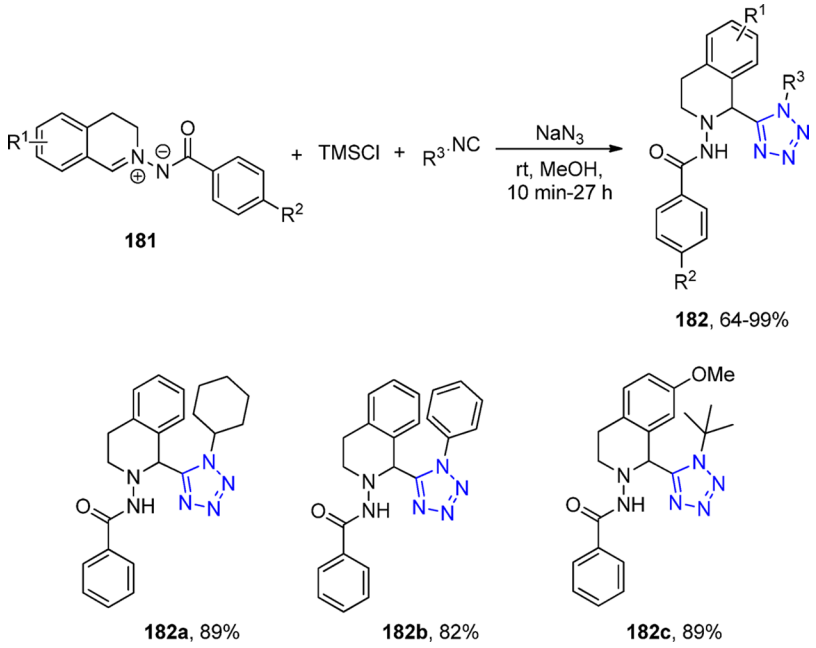
Scheme 75. UT-3CR with Trifluoroalkyl Cyclic Imines and Synthesis of *N*-Unsubstituted Tetrazoles 180



Scheme 76. Synthesis of Tetrahydroisoquinoline Tetrazoles 182



structurally related to the clinically investigated oxytocin reactor antagonists Epelsiban and Retosiban.[361]

The employment of hydrazine in UT-4CR was also reported toward the synthesis of bicyclic fused tetrazole derivatives (Scheme 97).[362] *N*-Boc protected hydrazine reacted with *α*-amino acid derived isocyanides in the UT reaction in a one-pot fashion and it was post cyclized under both acidic and basic conditions, affording 7-aminotetrazolopyrazinone (**218**) and tetrazolotriazepinone (**219**) cyclic products. The post cyclization of the isolated UT adduct **217** under basic condition could selectively afford the Boc-protected 7-aminotetrazolopyrazinone derivatives **220** in yields of 38−87%, which can be easily obtained as hydrochloric salt **221** (Scheme 97). Crystal structures of the postcyclized adducts were also obtained (Figure 45).

3.2.2. UT-4CR toward Fused Azepine-Tetrazole Derivatives. Hulme et al.[363] also described the synthesis of fused azepine-tetrazole libraries **222** in high yields via the UT-4CR (Scheme 98). Compared with their previous work leading to the tetrazolopyrazine system, they employed secondary amines together with Boc protected amino acid derived aldehydes components to enlarge the fused ring by one carbon to form azepine-tetrazoles. The first tetrazole formation was particularly well-suited for the solution phase reaction of methyl-isocyano acetate, *N*-Boc-aminoaldehydes, TMS azide, and secondary amines and generally proceeded with high yields. The subsequent Boc-deprotection was carried out with 10% trifluoroacetic acid in dichloromethane to free the amine nucleophile for the next cycloamidation step. The lactamization was promoted by proton scavenging with PS-diisopropylethylamine and reflux for 24 h. Final compound purities were

DOI: 10.1021/acs.chemrev.8b00564
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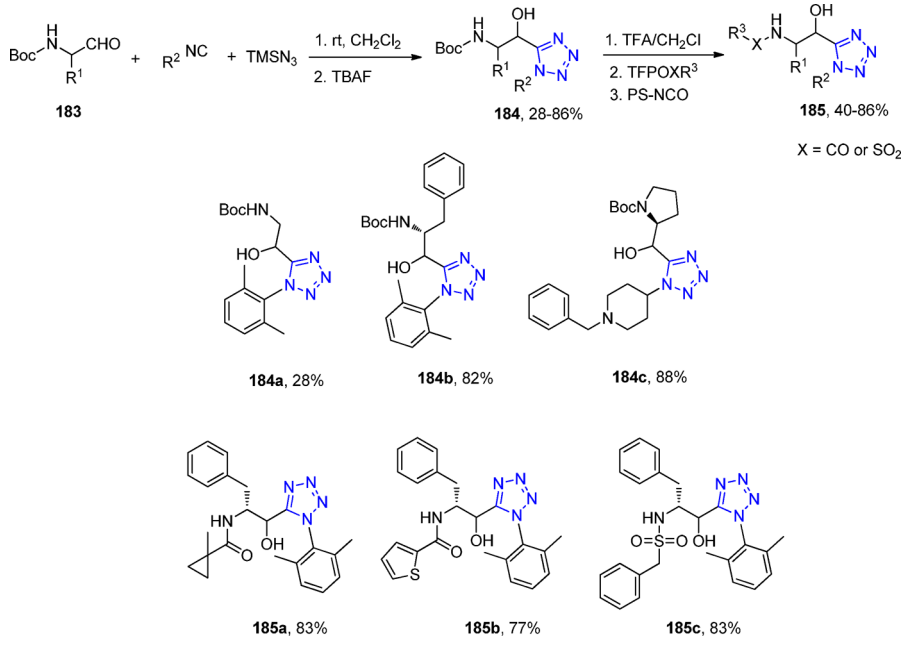
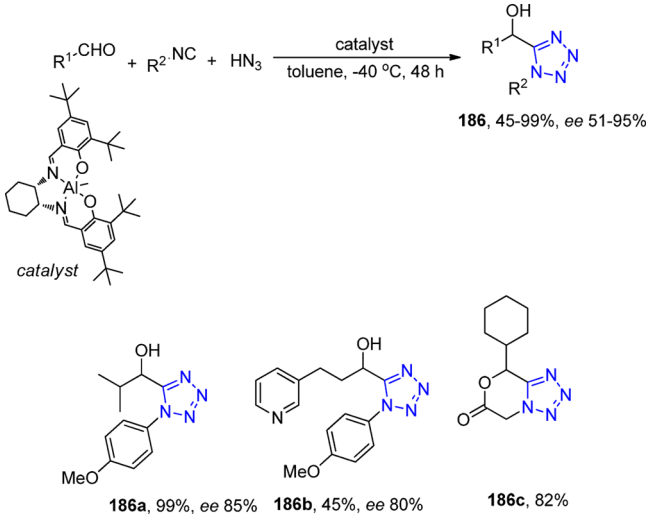
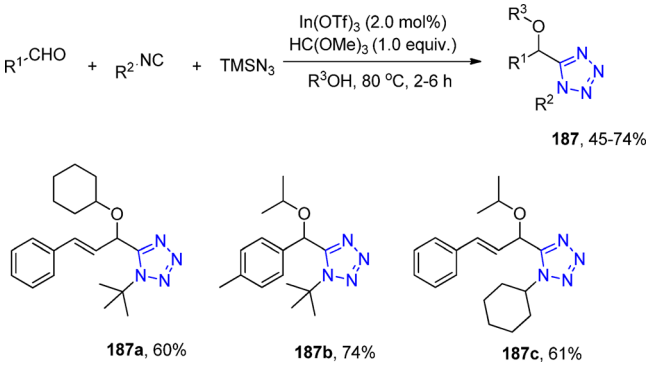
Scheme 77. Passerini Reaction Towards Tetrazole Derivatives 185



Scheme 78. Catalytic Enantioselective Synthesis of 5-(1-Hydroxyalkyl)tetrazole 186 by Three-Component Passerini Reaction (P-3CR)



Scheme 79. Synthesis of Alkoxylated 1*H*-Tetrazole Derivatives 187



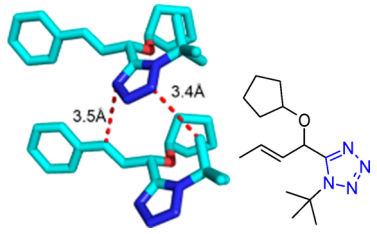
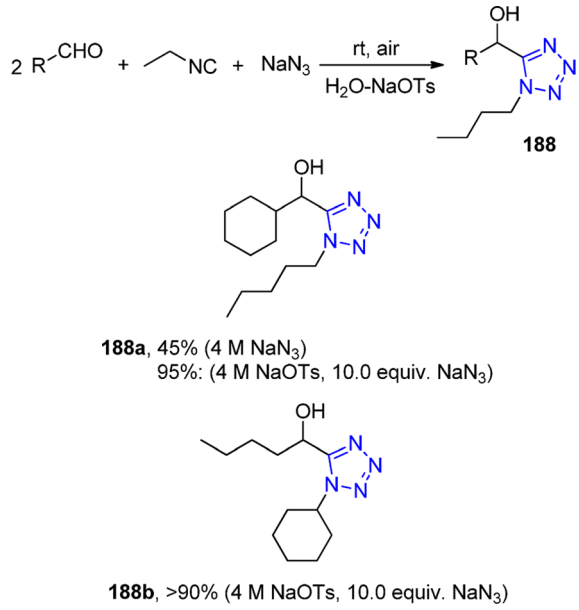


Figure 38. Crystal structure of (*E*)-1-(*tert*-butyl)-5-(1-(cyclopentyloxy)-3-phenylallyl)-1*H*-tetrazole **187d** (CCDC 862990).

Scheme 80. P-3CR under the "In Water" Or "In NaOTs" Conditions



DOI: 10.1021/acs.chemrev.8b00564
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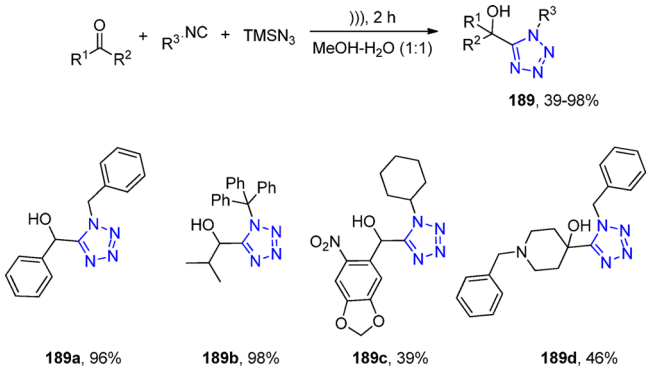
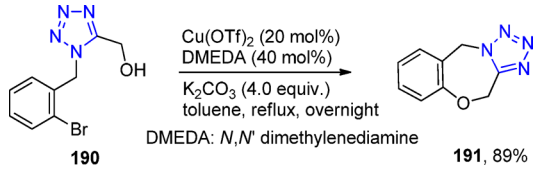
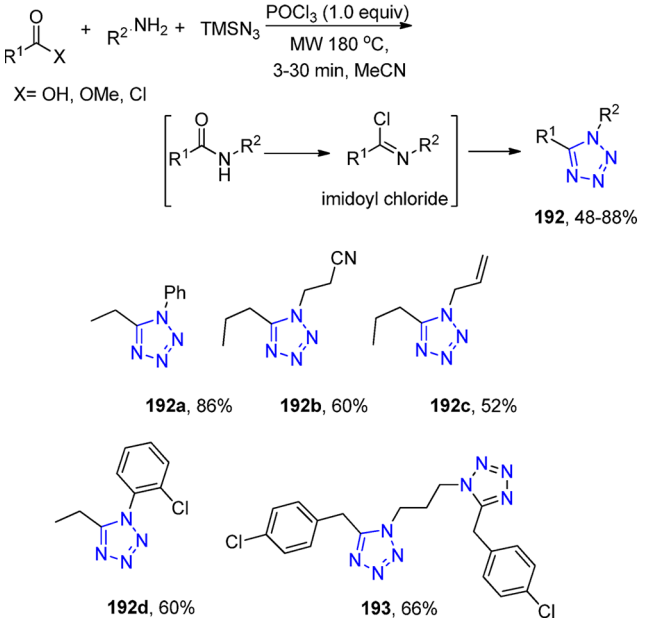
Scheme 81. A Green P-3CR under Sonication Conditions



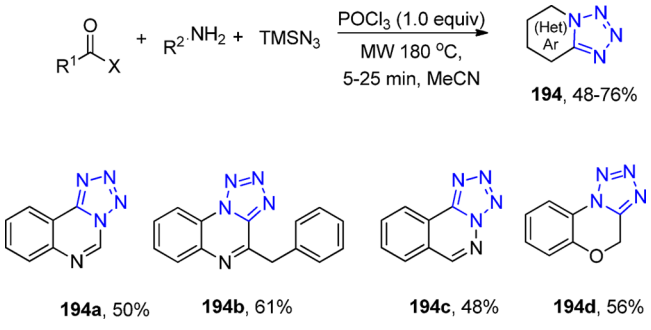
Scheme 82. Post-Modification on the Corresponding Hydroxyl Tetrazole 190 Towards the Fused Tetrazole 191



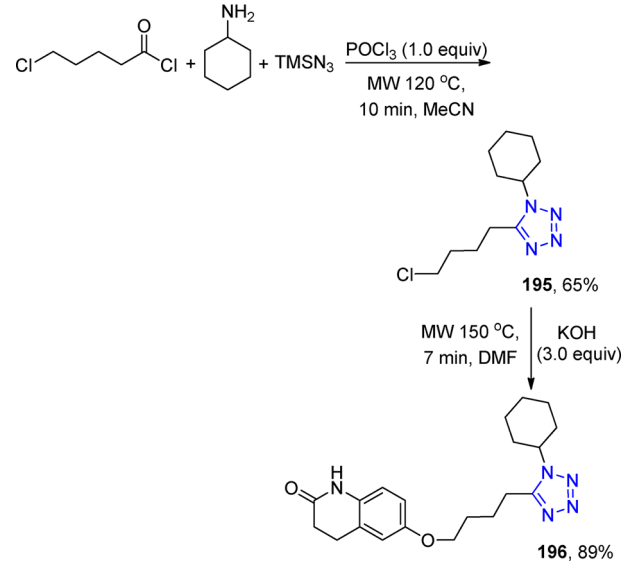
Scheme 83. Synthesis of Tetrazoles 192 and 193 from Carbonyl Compounds, Amines, and $TMSN_3$



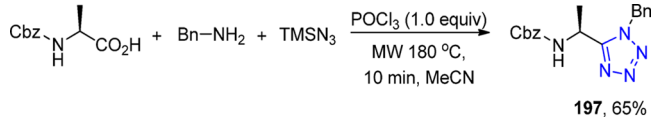
Scheme 84. Synthesis of 1,5-Fused Tetrazoles 194 from Carboxylic Acid Derivatives, Amines, and $TMSN_3$



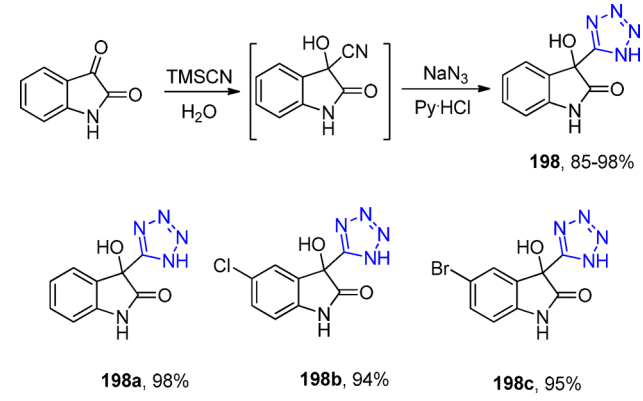
Scheme 85. Two-Step Synthesis of Cilostazol (192) by the MCR Methodology



Scheme 86. Synthesis of the Amino Acid Tetrazoles 197



Scheme 87. Synthesis of 3-Tetrazolyl Oxindoles 198 by a Facile Intermolecular [2 + 3] Cycloaddition



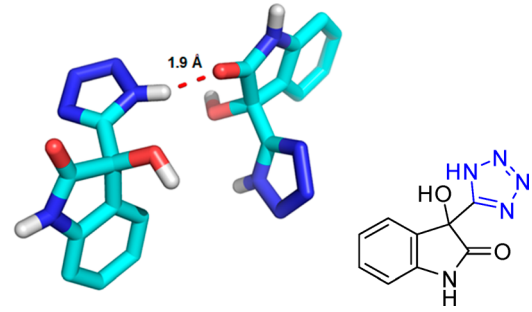


Figure 39. Solid-state structure of 3-hydroxy-3-(1*H*-tetrazol-5-yl) indolin-2-one **198a**. The oxindole-NH acts as a hydrogen bond donor toward N1 of the tetrazole (CCDC 857953).

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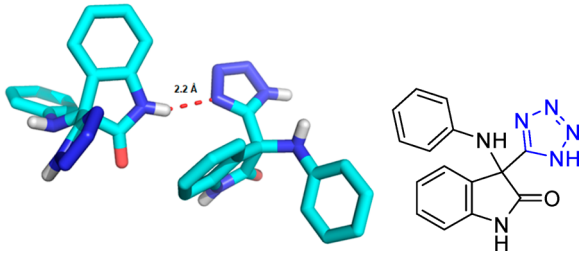


Figure 40. Solid-state structure of 3-(phenylamino)-3-(1*H*-tetrazol-5-yl)indolin-2-one **199**. The oxindole-NH acts as a hydrogen bond donor toward N1 of the tetrazole (CCDC 857954).

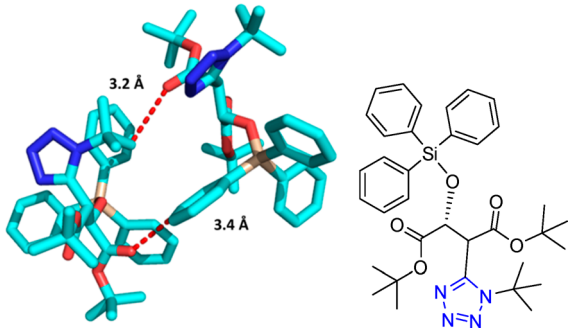


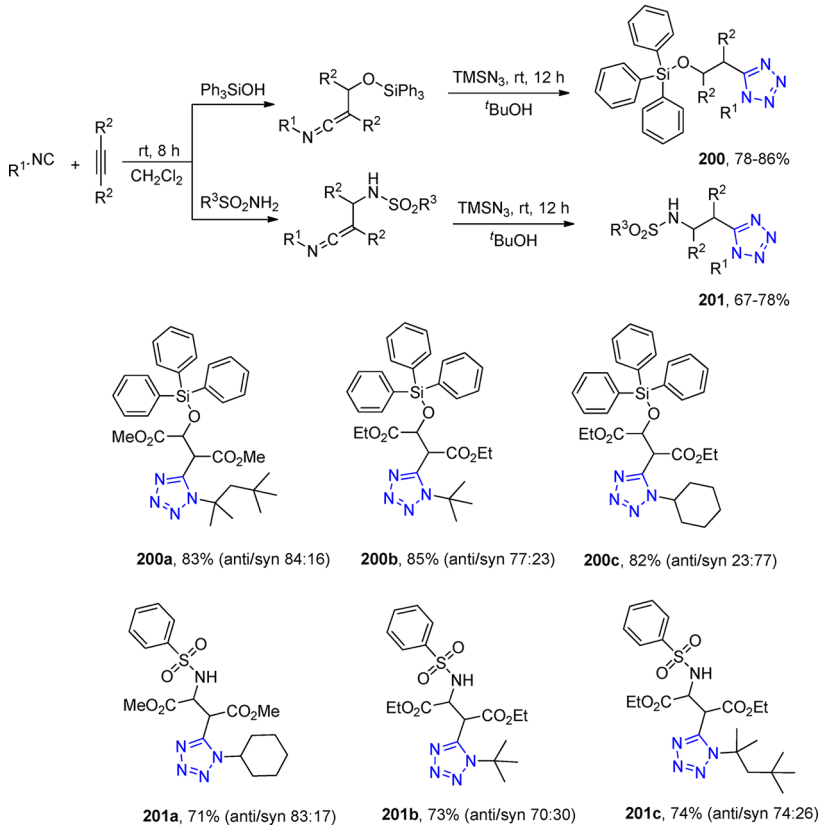
Figure 41. Crystal structure of (3*R*)-di-*tert*-butyl-2-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-3-((triphenylsilyl)oxy)succinate **200d**. It shows two short intermolecular interactions, O (C═O) and C (CH_3 in *tert*-butyl group) (CCDC 817391).

substantially improved by removal of the acyclic amine and excess aldehyde, via dissolution in THF−CH_3CHCl_2 addition of polystyrol bound scavenger resins PS-NCO and PS-TsNHNH$_2$, producing the desired fused product.

Batra et al.[367] first synthesized substituted allyl isocyanides from primary allyl amines using the Baylis−Hillman reaction (Scheme 99). The Baylis−Hillman reaction[368−370] occurs between the α-position of an activated alkene and an aldehyde or generally an electrophilic carbon to form a new C−C bond with the help of a nucleophilic catalyst as tertiary amine and phosphine. They employed this *E*-configured isocyanide in an Ugi/hydrolyze/coupling strategy (**223**, **224**) to obtain tetrazole-fused diazepinones **225** in good yields. After obtaining the expected Ugi adducts at room temperature, they also investigated a one-pot reaction combining Ugi and cyclization process without isolating the intermediate. Two cases were reported successfully with an amine and aldehyde bearing an electron withdrawing group. Noteworthy, they also found that the use of aniline instead of the primary aliphatic amines did not lead to the formation of tetrazoles.

3.2.3. UT-4CR toward 1,5-Disubstituted Tetrazoles in Macrocycles. Macrocycles represent a common motive in natural products, and several of them are marketed as drugs.[371,372] Macrocycles are a fascinating and however underrepresented class of compounds in medicinal chemistry, as they do not behave according to drug-likeliness rules and nevertheless can lead to oral bioavailability.[373] As a result of their large cycle, from 10 to 25 atoms, they show on the one hand conformational restriction but on the other hand are very flexible and can show multiple conformations.[374,375] Because of their large surface area, macrocycles are assumed to be useful to target nontraditional protein−protein interaction targets which often are large, flat, and featureless.[371,372] Currently, protein−protein

Scheme 88. Synthesis of the 1,5-Disubstituted Tetrazoles 200 and 201



DOI: 10.1021/acs.chemrev.8b00564
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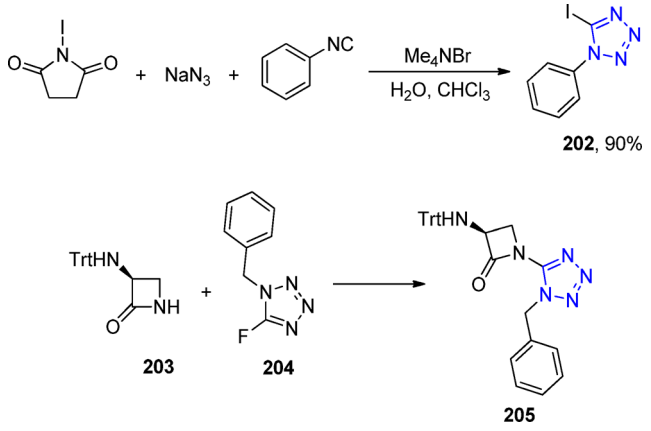
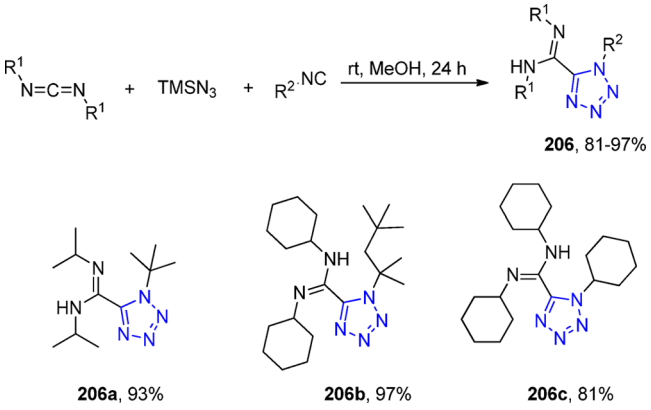
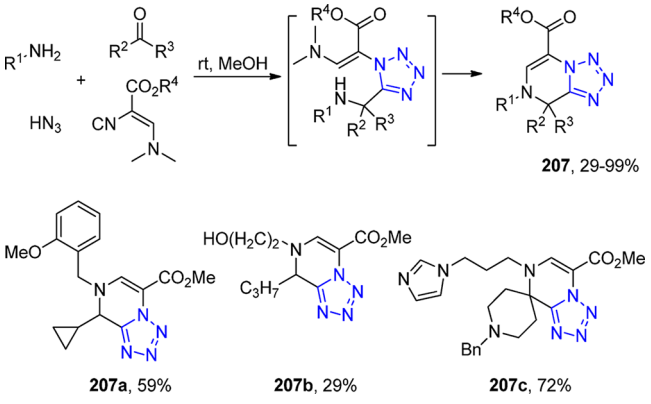
Scheme 89. 3-CR of *N*-Halo Succinimide, Sodium Azide, and Phenylisocyanide



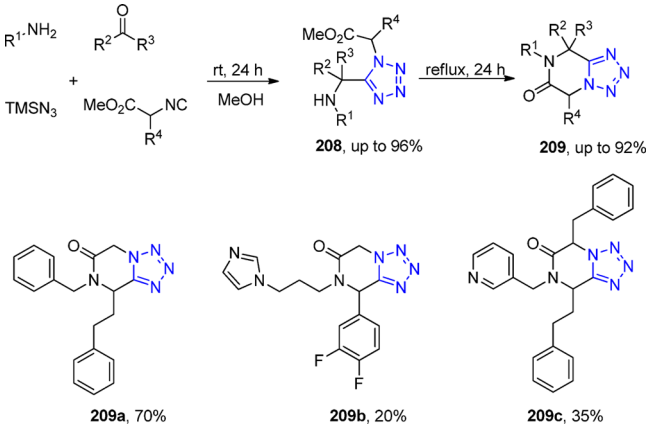
Scheme 90. Synthesis of 1,5-Disubstituted 1*H*-Tetrazole Derivatives



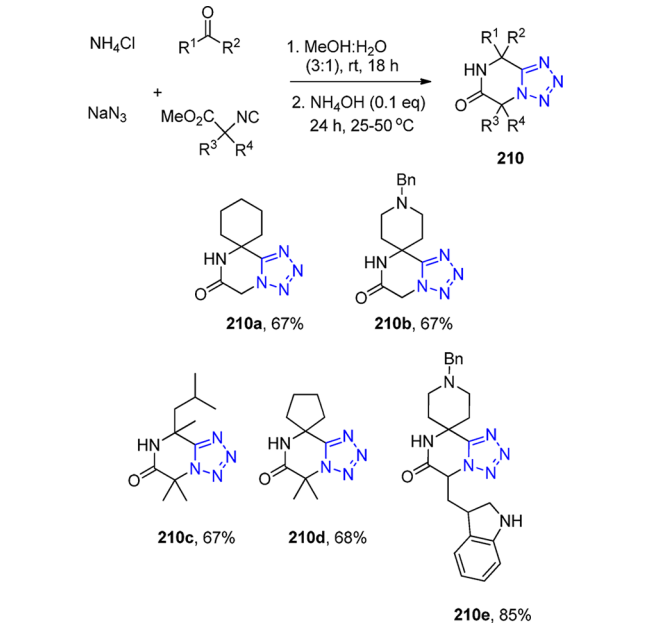
Scheme 91. Synthesis of 7,8-Dihydrotetrazolo[1,5-*a*]pyrazines 207



Scheme 92. UT-4CR and Post-Condensation to Form the Tetrazolopiperazines 209



Scheme 93. Ammonia Promoted One-Pot Tetrazolopiperidinone 210 Synthesis by UT-4CR



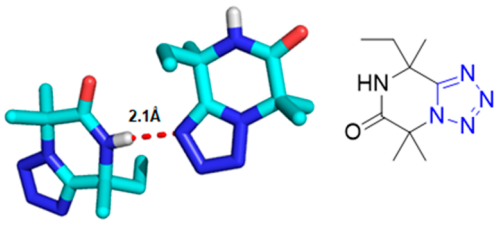


Figure 42. Crystal structure of the tetrazolopiperidinone **210f**. A hydrogen bond exhibits between the piperidinone-NH and the N-5 of a tetrazole moiety of an adjacent molecule.

interaction targets, in most cases, belong to the domain of antibodies. Therefore, artificial macrocycles have recently experienced a renaissance as scaffolds in medicinal chemistry. Unfortunately, there are few short, diverse, and general synthetic pathways toward this interesting class of compounds. Multicomponent reactions for accessing macrocycles was first reported by Failli and Immer.[376] In 2015 Dömling et al.[377] introduced α-isocyano-ω-carboxylic acids in macrocycle synthesis via Ugi reaction (U-4CR). They performed an intramolecular Ugi reaction (U-3CR) using a bifunctional α-isocyano-ω-carboxylic acid, incorporating into macrocycle **229** the other two components (a primary amine and an oxo compound), which can be widely varied. The bifunctional component has been prepared using an Ugi-tetrazole reaction (**226**−**228**, Scheme 100).

Adding to the toolkit of macrocyclizations by MCR, Dömling et al.[378] utilized for the first time a P-3CR to cyclize macrocycles and thus form artificial macrocyclic depsipeptides **230**[379] (15−

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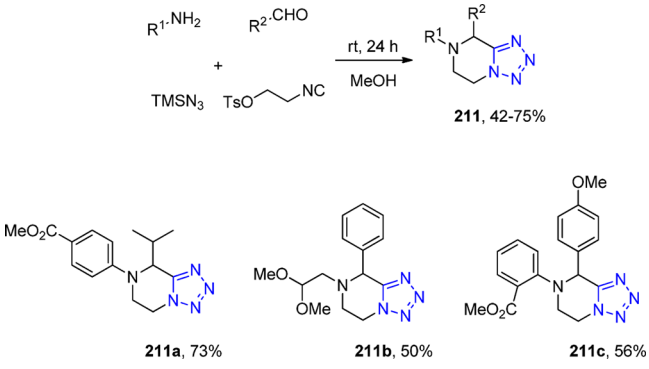
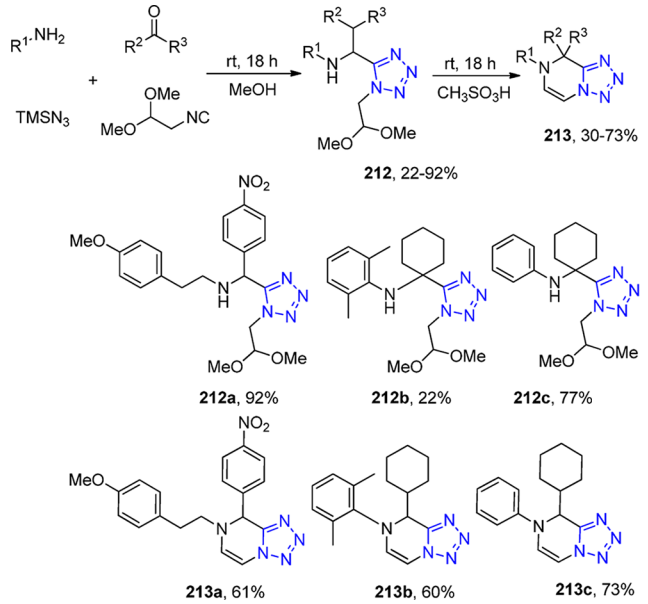
Scheme 94. Synthesis of Tetrazolopiperazines 211



Scheme 95. Designed Synthetic Pathway to Tetrazolo Piperazine Derivatives 213



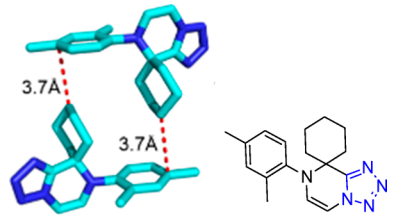


Figure 43. Crystal structures of **208d** with the cyclohexyl moiety forming a short T-shaped interaction with the adjacent phenyl group (CCDC 1017121).

20 membered). The overall sequence, which again combines two MCRs, has high diversity and broad reaction scope; it introduced different ring sizes and side chain variations in just four steps using readily available starting materials (Scheme 100). Some representative crystal structures are disclosed on Figures 46 and 47.

Moreover, bifunctional α-isocyano-ω-amines **231**, derived by a chemoselective amidation of amino acid derived isocyano carboxylic acid esters with unprotected symmetrical diamines, were employed in a concise two-step synthesis of tetrazole containing macrocycles **232**.[380] A short access to 11−19-membered macrocycles in which substituents can be independently varied at three different positions was allowed (Scheme 101, Figure 48).

3.3. Tricyclic and Polycyclic Tetrazole Derivatives

Annulated polyheterocyclic structures are interesting to the medicinal chemist due to their rigidity and often good blood−brain barrier penetration to target neurological diseases. Therefore, strategies to reduce the number of synthetic and purification steps to prepare suitably modified compounds are of special interest in medicinal/combinatorial chemistry. As it was previously described (see Scheme 95), the UT-4CR with isocyanoacetaldehyde dimethylacetal yields the intermediate

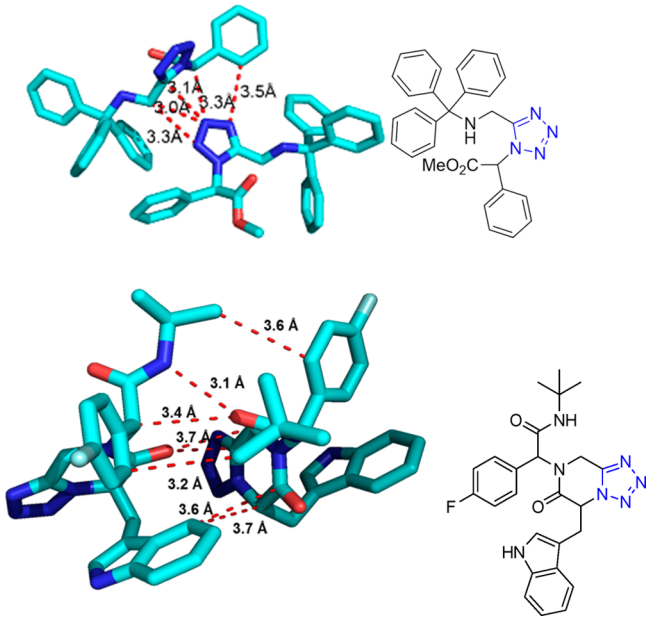


Figure 44. Crystal structures of **214d** (CCDC 986844) (top) and **216e** (CCDC 986845) (bottom). The tetrazole-fused ketopiperazine undergo three hydrogen-bonds.

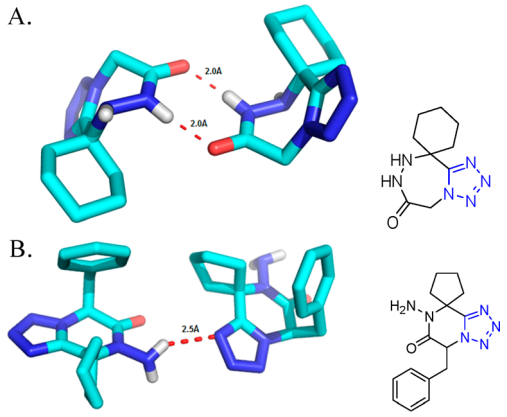


Figure 45. Crystal structures of **219b** (CCDC 1507441) and **221b** (CCDC 1507440). (A) Two intermolecular hydrogen bonds of 2.0 Å are observed between the NH and the carbonyl moiety. (B) Hydrogen bond of 2.5 Å is observed between NH_2 and the N4 of the tetrazole.

212, which can undergo a range of condensation reactions toward **233** and **234** (Scheme 102).[159]

The 11*H*-benzo[*d*]tetrazolo[1,5-*a*]azepin-11-amine scaffold **233** can be accessed from activated electron rich benzaldehydes,

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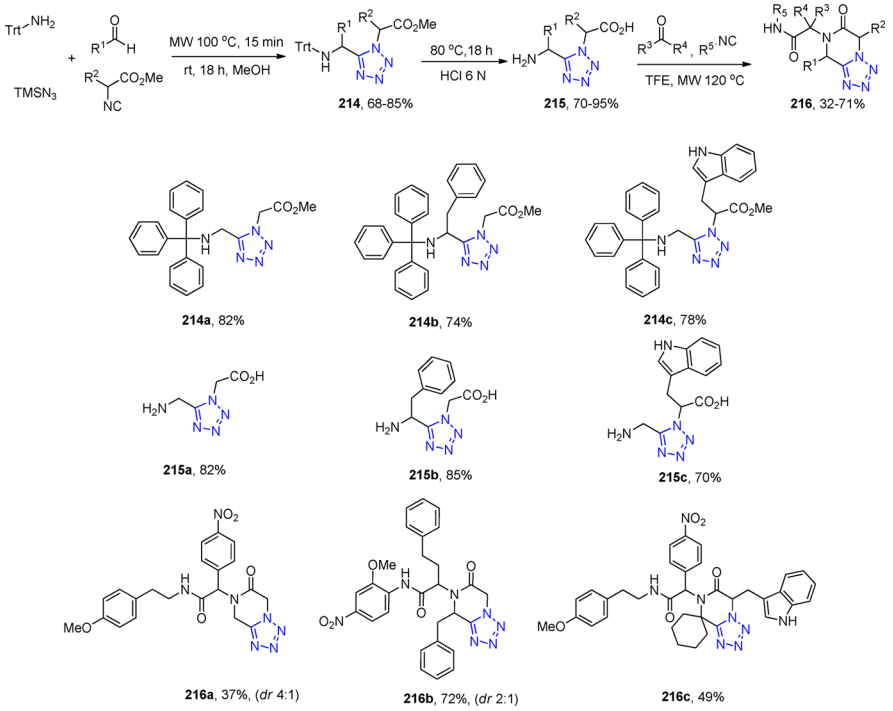
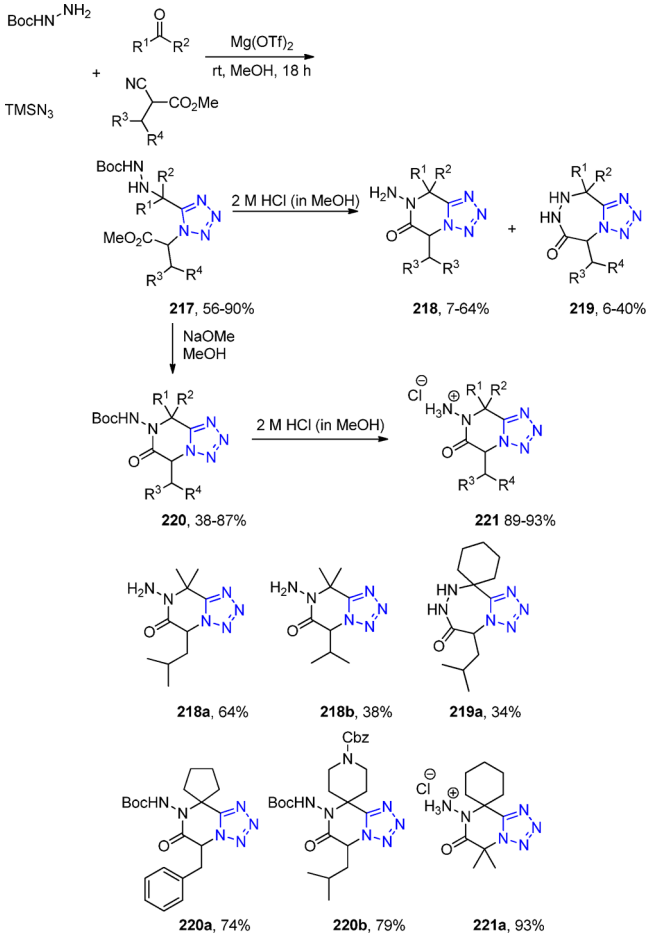
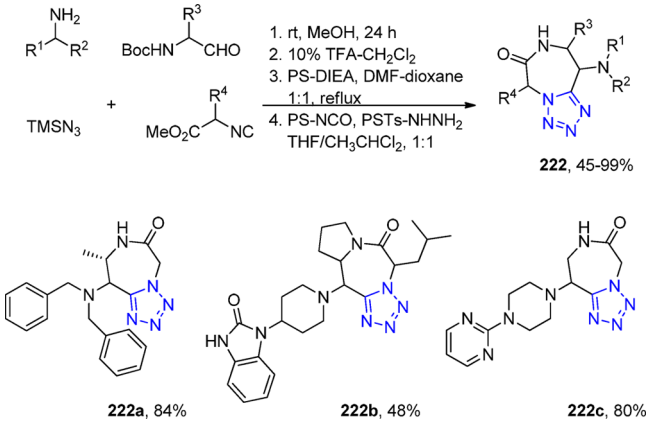
Scheme 96. Two-Step Synthesis of *N*-Unsubstituted ω-Carboxyl α-Aminotetrazoles 216



Scheme 97. Employment of Hydrazine in UT-4CR and Its Post-Cyclization



Scheme 98. Synthesis of the Azepine-Tetrazoles 222



primary or secondary amines, and isocyanoacetaldehyde dimethylacetal. The reaction sequence involves an UT-4CR (**212d–f**) followed by a condensation. The cyclization runs smoothly under methanesulfonic acid (MSA) in neat conditions in good to excellent yields (Scheme 103).

When using electron-rich substituted (hetero)phenylethyl amines, polyfused tetrazoles **234** can be accessed in great diversity (Scheme 104). The intermediate UT-4CR product (**212g–i**) can undergo a Pictet–Spengler type condensation under MSA room temperature conditions, in decent to excellent yields.[279] The reaction involves an acid induced dimethylacetal deprotection, followed by a imine formation and attack onto the nucleophilic (hetero)aromatic ring. Phenylethyl amines and tryptamines lead to the alkaloid-type scaffolds of isoquinolines and ibogaine, respectively. Libraries of >1000 compounds per scaffold have been synthesized and are part of the screening collection of the European Lead Factory.

The 3D structures and other physicochemical properties of each of the aforementioned scaffolds **233** and **234** were also

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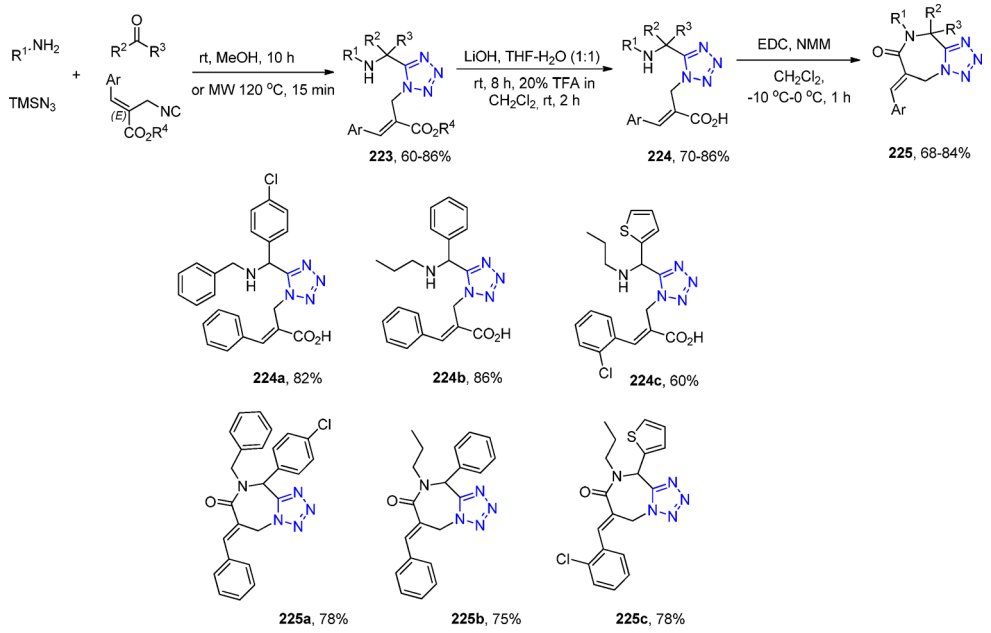
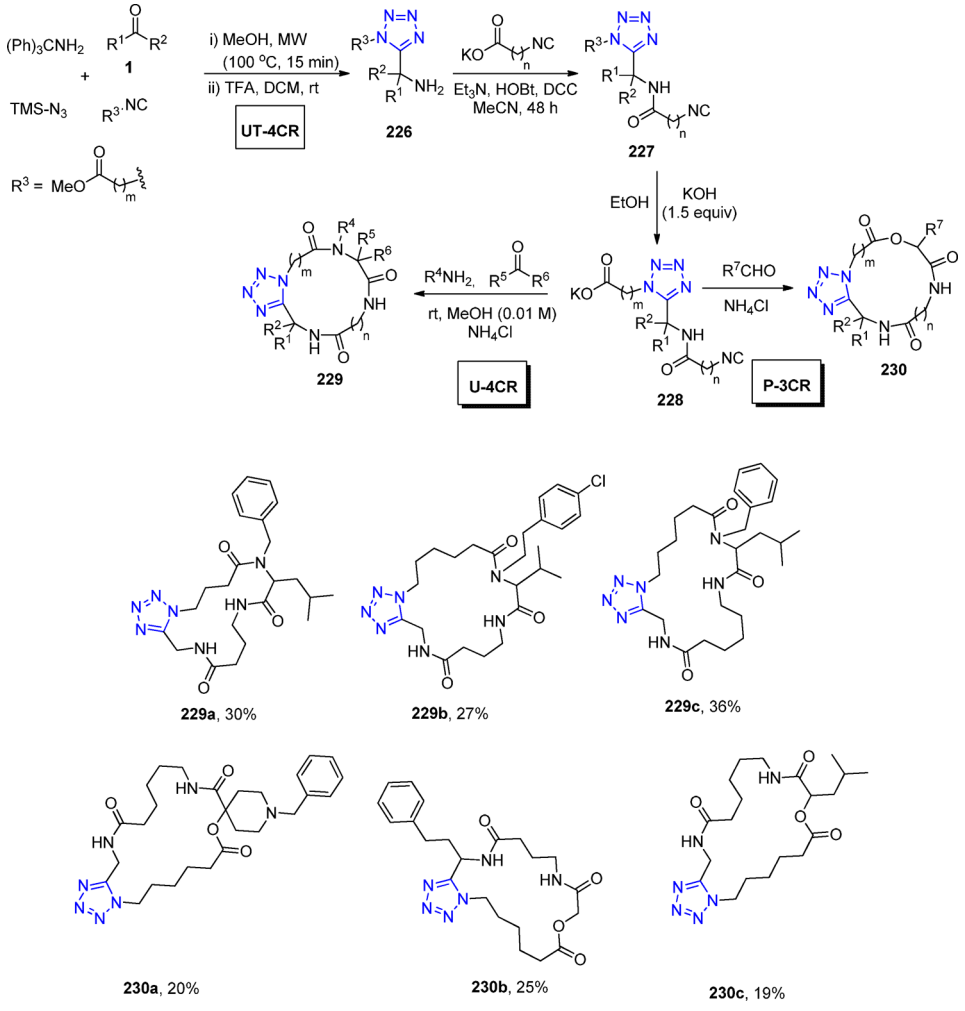
Scheme 99. Synthesis of Tetrazole-Fused Diazepinones 224



Scheme 100. UT-4CR/U-4CR/P-3CR Derived Macrocycle Synthesis Strategies



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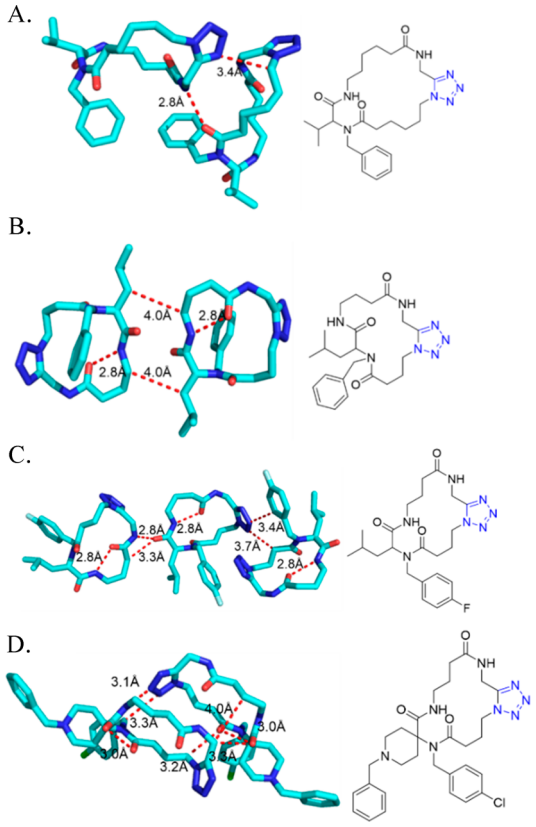


Figure 46. Four X-ray structures of the macrocycles **229** of different size involving different MCR assembly routes and different substituents (CCDC 1408649, 1408650, 1408653, 1408654). The most occupied interactions are included in the interactions between N of tetrazole and C of cycles, O and C of cycles, and C and C of cycles. The intramolecular bindings are mostly between O and N.

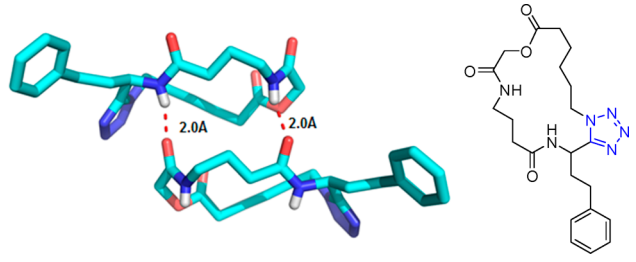
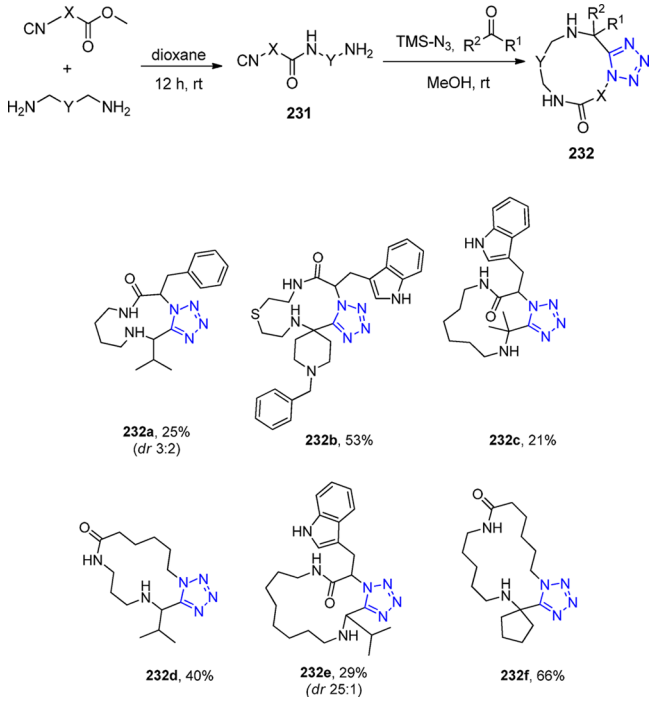


Figure 47. Two secondary amides form intermolecular hydrogen bonds to a neighbor macrocycle, whereas the *cis*-amide bioisosteric tetrazole moiety is not involved with hydrogen bonding. Looking into the different modules of compound **230b** (CCDC 1442896), one can define the two amide groups, the tetrazole, and the lactone group as rigid elements which are separated by flexible sp^3 center-based C1, C3, and C5 chain elements. These linker fragments ultimately will determine the flexibility of the overall macrocyclic conformations in aqueous and lipophilic environments, which will be a determinant of the passive diffusion through cell membranes

extensively discussed. Unexpectedly, they possess very different characteristics even though these scaffolds are all derived from the same first UT-4CR in terms of their chemical space due to their connectivity, substitution pattern, and ring sizes (Figure 49).

Kalinski et al.[381] described an UT reaction (**236**) followed by a nucleophilic aromatic substitution for the preparation of a library of polysubstituted fused 4,5-dihydrotetrazolo[1,5-*a*]-

Scheme 101. α-Isocyano-ω-amine 231 Synthesis and UT-4CR Derived Macrocycle 232 Synthesis Pathway



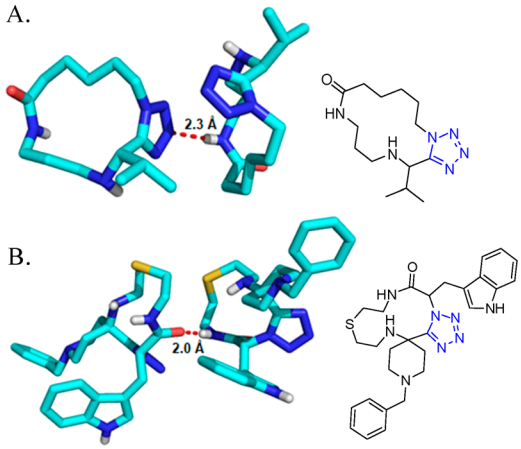
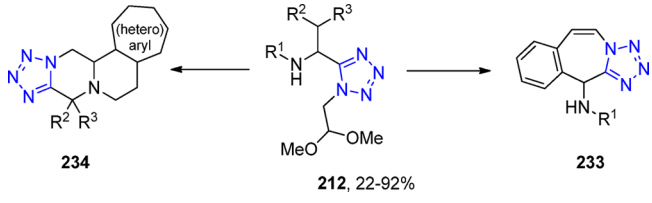


Figure 48. Crystal structures of the MCR-derived 14-membered **232d** (CCDC 1548701) and 12-membered **232b** (CCDC 1548704) macrocycles in solid state featuring intermolecular hydrogen bonding contacts of 2.3 and 2.0 Å, respectively.

Scheme 102. Diversity of Ring Fused Tetrazole Scaffolds from the Common Precursor Building Block Isocyanoacetaldehyde Dimethylacetal



quinoxalines **237**. The first synthetic step corresponds to a classical UT-4CR, exploring 2-fluorophenylisocyanide as a new bifunctional starting material, yielding tricyclic tetrazoles with two points of diversity (Scheme 105). 2-Fluorophenylisocya-

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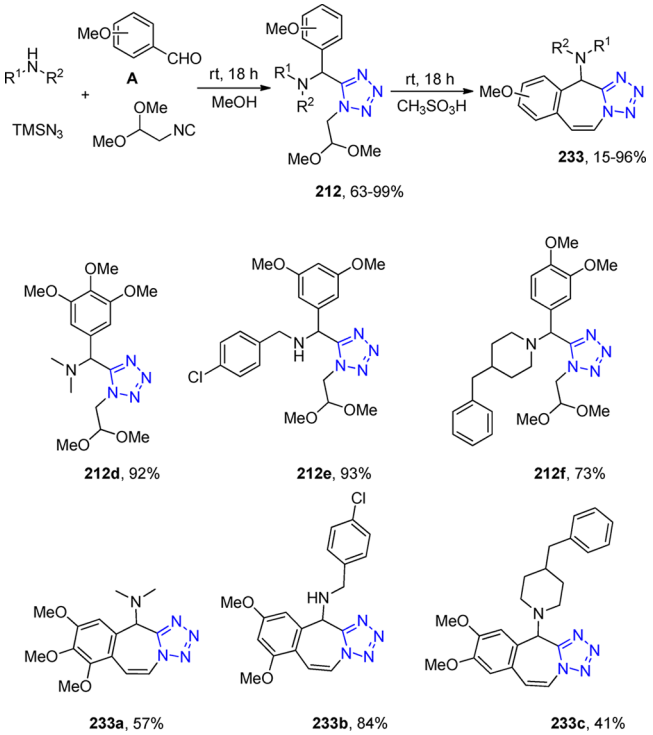
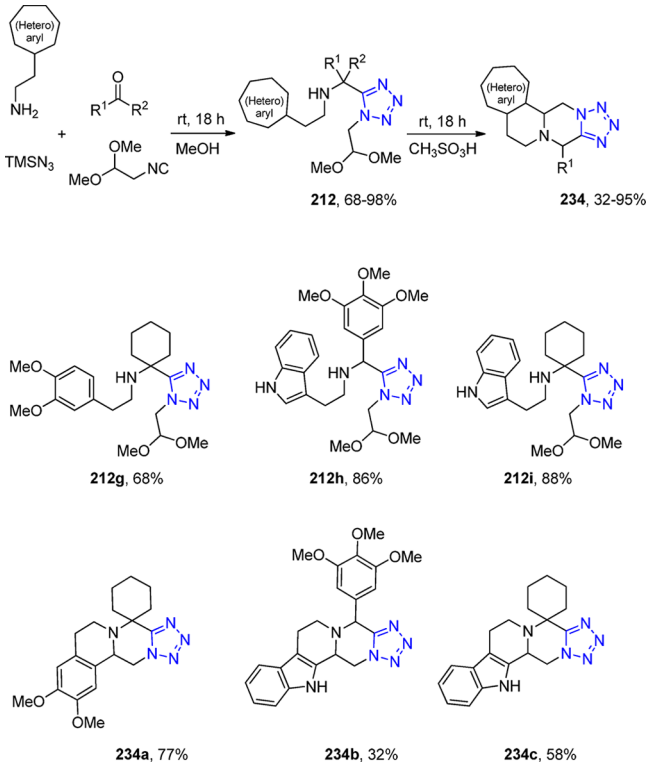
Scheme 103. Designed Synthetic Pathway to the Polyfused Tetrazolo Scaffolds 233



Scheme 104. Synthesis of Tetracyclic Piperazinotetrazoles 234



nide (**235**) allows for a subsequent nucleophilic aromatic substitution (SN_{Ar}) in a second step, thus forming a ring. They found that the best yield could be reached by mixing the four components amine/aldehyde/TMS azide/isocyanide in a ratio of 1:1:1.5:1.5 in the Ugi reaction. The nucleophilic aromatic

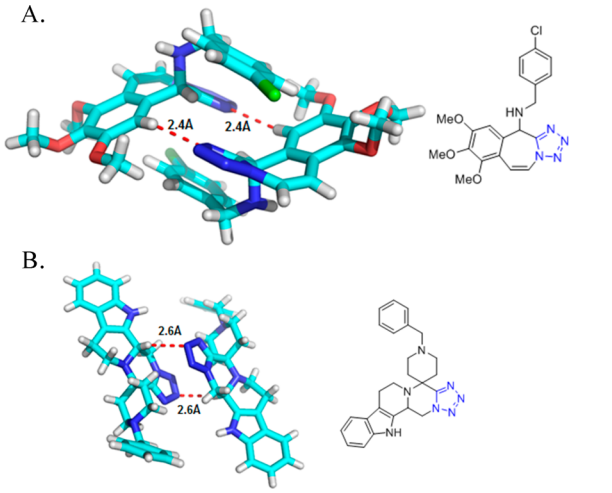
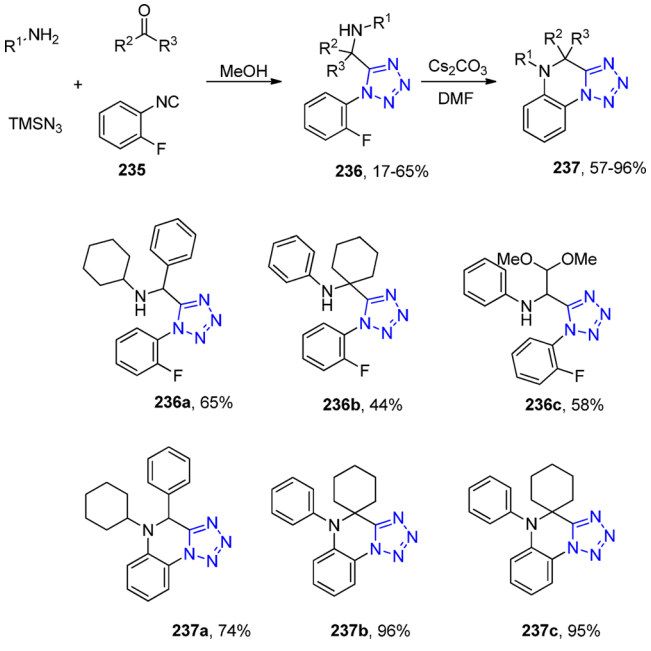


Figure 49. Crystal structures of **233d** and **234d** (CCDC 1017123 and 1017122 and some characteristic short contacts of 2.4 and 2.6 Å, respectively).

Scheme 105. Synthesized Fused 4,5-Dihydrotetrazolo[1,5-*a*]quinoxalines 237



substitution−cyclization conditions were optimized by using Cs_2CO_3 in DMF as the best conditions. They also exploited a range of amines and aldehydes for this strategy, finding that amines and carbonyls can be varied broadly, yielding tricyclic tetrazoles with two potential diversity points.

A series of 18 fused tetrazolo-quinolines **238** featuring two tetrazoles were synthesized in 21−90% yields via a novel one-pot UT/SN_{Ar}/ring−chain azido-tautomerization process under microwave irradiation or ultrasound and catalyst-free conditions (Scheme 106).[382] The overall procedure has a good substrate scope and functional group tolerance.

The compound class of 1,4-benzodiazepines are among the most widely used drugs with potent tranquilizer, muscle relaxant, anticonvulsant, antiseizure, and sedative-hypnotic activities.[246] In 2010, Voskressensky et al.[364] developed an effective procedure for the syntheses of substituted tetrazolo-

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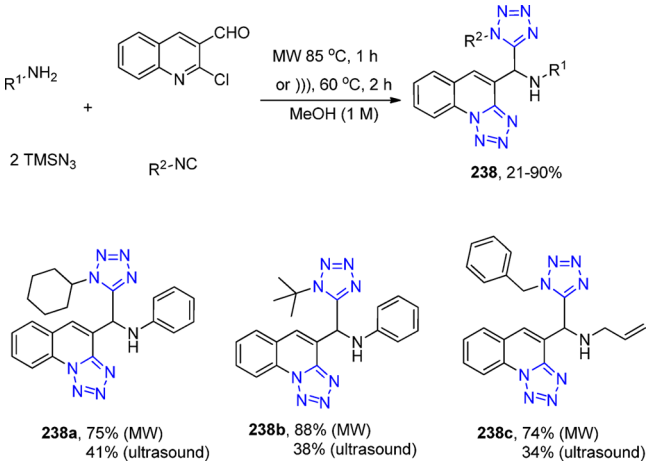
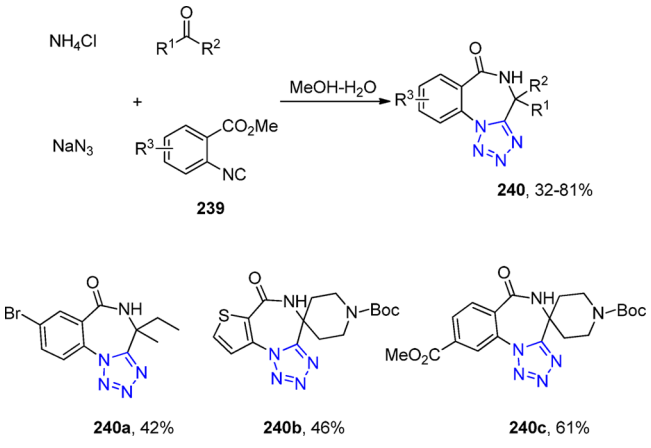
Scheme 106. Synthesis of the Bis-tetrazolo Quinolones 238



Scheme 107. Fused Tetrazolodiazepines 240 Synthesized by UT



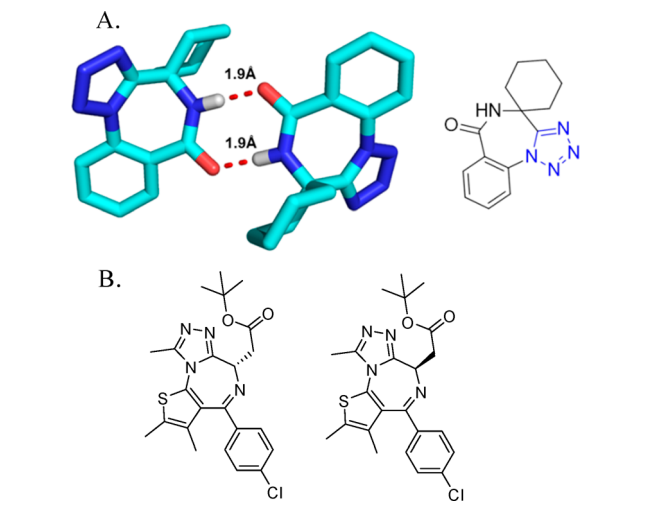


Figure 50. (A) Crystal structure of **240d** (CCDC 780553). Two hydrogen bonds of 1.9 Å are shown between the amides of the diazepineone moieties. (B) Structures of the two JQ-1 stereoisomers.

[1,5-*a*][1,4]benzodiazepines **240** via an UT reaction, followed by an amidocyclization (Scheme 107). The tetrazolodiazepines **240** were synthesized by simply mixing ketone, sodium azide, ammonium chloride, and the corresponding anthranilic acid derived isocyanide **239** in aqueous methanol. After 24−48 h of vigorous stirring at room temperature, the target products precipitated from the reaction mixture. The reaction's scope was investigated, with symmetrical and unsymmetrical, cyclic and acyclic, and sterically not hindered and very bulky (e.g., adamantyl ketone) ketones being good substrates. Interestingly, all attempts to isolate the corresponding products from aldehydes failed. Moreover, the reaction with methylamine hydrochloride instead of ammonium chloride aiming to yield the *N*-methyl substituted benzodiazepines stopped at the intermediate Ugi tetrazole stage, and no cyclization was observed under the reaction conditions.

A crystal structure showing the 3D structure of **240d** in the solid stage is shown in Figure 50, in which the overall 3D structure comprises a butterfly shape with the cyclohexyl and benzene rings presenting the wings. In general heterocyclic-conjugated benzodiazepines emerged as an important class of epigenetic drugs,[364,365] as similar structures are potent inhibitors of the BET family of proteins, e.g., JQ-1.[366]

4. TETRAZOLES IN VIRTUAL SCREENING

A pharmacophore-based virtual screening platform, ANCHOR.QUERY, was introduced to bring interactive virtual screening of novel protein−protein inhibitors to the desktop (Figure 51).[383,384] More than 2 billion 3D conformers of unprecedented compounds based on one-pot MCR can be efficiently and web-based screened against protein targets. A typical project encompasses building of a 3D pharmacophore model based on a PDB structure, query against 2 billion conformers, ranking, synthesis of best hits, and biophysical screening. Twenty-three different MCR scaffolds are enumerated, among them two tetrazole backbones (e.g., compound **241**, Figure 51). The substituents are chosen based on commercial availability of the corresponding building blocks and on previous experience to yield the products with high confidence. In fact, the success rate of synthesis of the virtual compounds is very high exceeding 90%.

Multiple successful applications of ANCHOR.QUERY have been recently published.[193,385,386] Among them α-amino tetrazoles were found to be potent antagonists of the protein protein interaction of p53-MDM2.[193] The virtual screening of very large MCR compound libraries is an interesting, fast, and cost-effective alternative to high throughput screening.

5. CONCLUSIONS AND OUTLOOK

More than 225 tetrazole-based scaffolds have been presented in this review which can be convergently and easily synthesized by using multicomponent reactions. Especially the Ugi variation UT-4CR of tetrazole synthesis is very fruitful in accessing many different drug-like scaffolds. Thus, among of all organic chemistry methods, clearly MCR stands out and provides the most versatile access to this class of heterocycles. Tetrazole derivatives will continue to be a prime class of heterocycles due to their isosteric character to carboxylic acid and *cis*-amide moieties and due to their metabolic stability and other physicochemical properties. Efficient synthetic access to a wide variety of derivatives is therefore the key to leverage the potential of tetrazoles to generate lead compounds.

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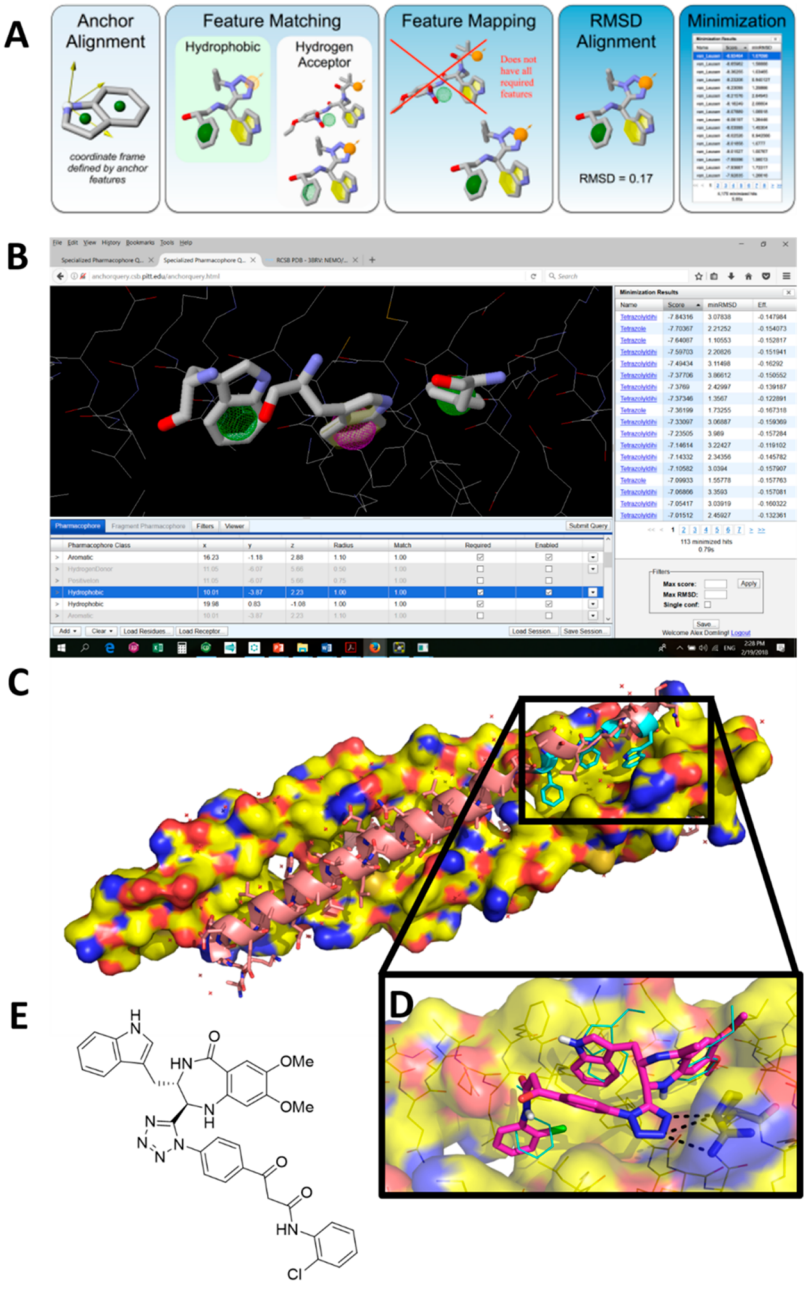

Figure 51. The ANCHOR.QUERY virtual screening platform. (A) General sequence of steps to interrogate 2 billion MCR derived conformers. (B) Screen shot of ANCHOR.QUERY to search for inhibitors of the protein protein interaction NEMO/IKK-β. (C) View of the protein protein interaction NEMO/IKK-β with NEMO as yellow surface and IKK-β as pink α-helix (PDB 3BRV). (D) Close-up view of the hot spot formed by Trp741, Trp739, and Phe734 and the aligned to hit tetrazole in red sticks. Remarkably, the close alignment with the query amino acids and the hydrogen bonding cluster of the tetrazole with the Arg101. (E) 2D structure of the top hit **241**. Reproduced with permission from ref 384. Copyright 2017 John Wiley and Sons.

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Notes

The authors declare no competing financial interest.

Biographies

Constantinos G. Neochoritis received his Ph.D. in Organic Chemistry under the guidance of Professors J. Stephanidou Stephanatou and C. Tsoleridis in the Department of Chemistry at Aristotle University of Thessaloniki in 2011. Being fascinated by the applied multicomponent reaction (MCR) chemistry, he joined the research group of Prof. Alexander Dömling in the Drug Design Group at the University of Groningen. He specialized in computational-aided drug design utilizing MCR chemistry. In 2014, he cofounded the biotech company TelesisPharma BV. Very recently, he was appointed as assistant professor in the chemistry department of the University of Crete in

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Greece. His research interests include bioactive heterocycles, multicomponent reactions, novel materials, and high throughput synthesis. He has published more than 40 peer-reviewed papers and book contributions.

Ting Zhao, received her Bachelor's degree in 2006 and Master's degree in 2011 at Lanzhou University. Then she moved to Groningen and joined Prof Dömling's research group as a Ph.D. candidate under the prestigious CSC fellowship. She focused on discovering concise and rapid routes towards novel drug-like molecules bearing tetrazole moieties, using MCR chemistry. In 2016, she graduated and moved to Norway.

Alexander Dömling studied chemistry and biology at the Technische Universität Munich and obtained his Ph.D. under the guidance of Ivar Ugi. After a postdoc under a Humboldt Fellowship in the group of the Nobel Laureate Barry Sharpless, he founded the biotech company Morphochem, later Carmolex Inc., and most recently, TelesisPharma and SMIO BV. After his habilitation, he worked as full professor at the University of Pittsburgh in the School of Pharmacy. He has held the chair for Drug Design at the University of Groningen since 2011. His interests are centered on MCR chemistry and its application to problems in drug discovery. His special focus is centered on the question of how to leverage the huge MCR space. Thus, he is working on MCR centered pharmacophore methods, structure-based drug design, and MCR-centered fragment-based drug design methods and extreme miniaturization to library synthesis. He is the author of more than 200 scientific articles, reviews, and book contributions. He has applied for more than 30 patents. His long-term vision is to bring a novel drug to patients in an indicated area of unmet medical needs.

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ABBREVIATIONS

Ac acetyl
ADME absorption, distribution, metabolism, and excretion
BET bromodomain and extraterminal domain
Boc *tert*-butyloxycarbonyl protecting group
CAN ammonium nitrate
Cbz carboxybenzyl
DCC *N*,*N*′-dicyclohexylcarbodiimide
DCE dichloroethane
DCM dichloromethane
DIEA *N*,*N*-diisopropylethylamine
DMA dimethylacetamide
DMF dimethylformamide
DMPK drug metabolism and pharmacokinetic
*o*PDM *o*-phenylenodiamine
PDB Protein Data Bank
PS polystyrol
*p*TSIA *p*-toluenesulfinic acid
*p*TsOH *p*-toluenesulfonic acid
TBAF tetra-*n*-butylammonium fluoride
TEMPO 2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf triflate
TFA thrifluoroacetic acid
TFE trifluoroethanol
TFP tetrafluorophenyl
THF tetrahydrofuran
TMS trimethylsilyl
^{t}Octyl 1,1,3,3-tetramethylbutyl
Trt trityl
Ts tosyl

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