The tetrazole building block strategy
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CHAPTER 2

Tetrazole Building Block Strategy Towards Synthesis of Drug-like Molecules

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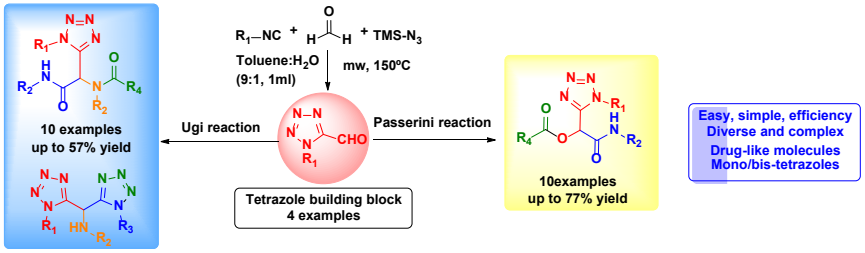
§ The authors contributed equally

In prep. for submission

Abstract



Tetrazole scaffolds are extensively used in medicinal chemistry and drug discovery to improve the drug-like qualities of molecules. The building block approach to introduce the tetrazole moiety into multicomponent reactions towards the synthesis of diverse and complex drug-like molecules is presented. The tetrazole building block was efficiently and directly accessed by using a three-component reaction between cost-efficient and commercially available starting materials. Further synthetic utility of this novel tetrazole building block was demonstrated by introducing a tetrazole moiety into different MCRs that have already found important uses in the drug discovery industry. This method subsequently fulfills the ever-increasing demand for the tetrazole-based compound libraries and novel scaffolds that are otherwise difficult to access through other methods.

Introduction

The synthetic accessibility of drug-like molecules is a prime requirement to facilitate the drug discovery process. Generating complex and diverse drug-like libraries offer an increased chance of evoking molecular recognition with broad biological targets and becomes an integral part of the structure-based drug design and high-throughput screening to find high-affinity lead molecules.[1-3] There is an ever-increasing demand for a facile and efficient synthetic method to explore diverse chemical space. However, due to the vastness of chemical space, the generation of a ready-to-screen drug-like molecules remains a key challenge in the medicinal chemistry field.[4-5]

The tetrazole is considered a privileged scaffold in pharmaceutical and medicinal chemistry, used as an acid bioisostere and cis amide mimic contributing to improvements in lipophilicity, metabolic stability, and potency.[6-8] Recently, the use of the tetrazole moiety in drug development has been increased and exhibited prevalent occurrence in the bioactive compounds; being present in more than 20 marketed drugs with a very broad range of biological activities such as anticancer, antitubercular, antibacterial, antiviral, antimalarial, antiallergic, and antihypertensive(**Figure 1a**).[6,9] In addition, tetrazoles constitute a diverse range of industrial applications and extensively used in materials, agriculture, explosives, and photography.[10-11]

Due to the high synthetic value, significant efforts have been devoted to developing methods for the preparation of the tetrazole scaffold, in particular through multicomponent reactions (MCRs) and mostly Ugi and Passerini reactions.[6-8] Accessing diverse tetrazole scaffolds from the limited number of MCRs, typically involves first de novo construction of the tetrazole scaffold and subsequent post-modifications (**Figure 1b** and **c**).[12] In stark contrast, the methods for the synthesis of drug-like tetrazole compound libraries involving a building block approach have remained elusive, with success being reported thus far only with the tetrazole amine.[12-13] Use of tetrazole building blocks in MCRs has all the advantages of the de novo approach and furthermore provides extra efficiency, complexity and diversity in the same number of steps (**Figure S1**). Also, it offers flexibility in the placement of tetrazole moiety in the scaffold and enables facile post-modifications. Additionally, the inclusion of a strategically placed tetrazole and bioisostere replacement of MCR substrate with tetrazole may give rise to molecules with improved drug-like characteristics with nominal weight or size difference. This tetrazole building block approach will allow direct access to ready to screen molecular scaffolds

for medicinal chemistry programs to investigate different biological activities.[14-16]

Motivated by the shortcomings of current methodologies for this tetrazole building block approach, we have pursued and report herein the development of a rapid synthetic approach to generate the libraries in which tetrazole ring is conveniently introduced in a scaffold rather than built up de novo for each molecule. We report the synthesis of -diverse tetrazole building blocks, which are readily prepared, and their unprecedented use in MCRs to access diverse molecular scaffolds. To do that, we first developed an efficient

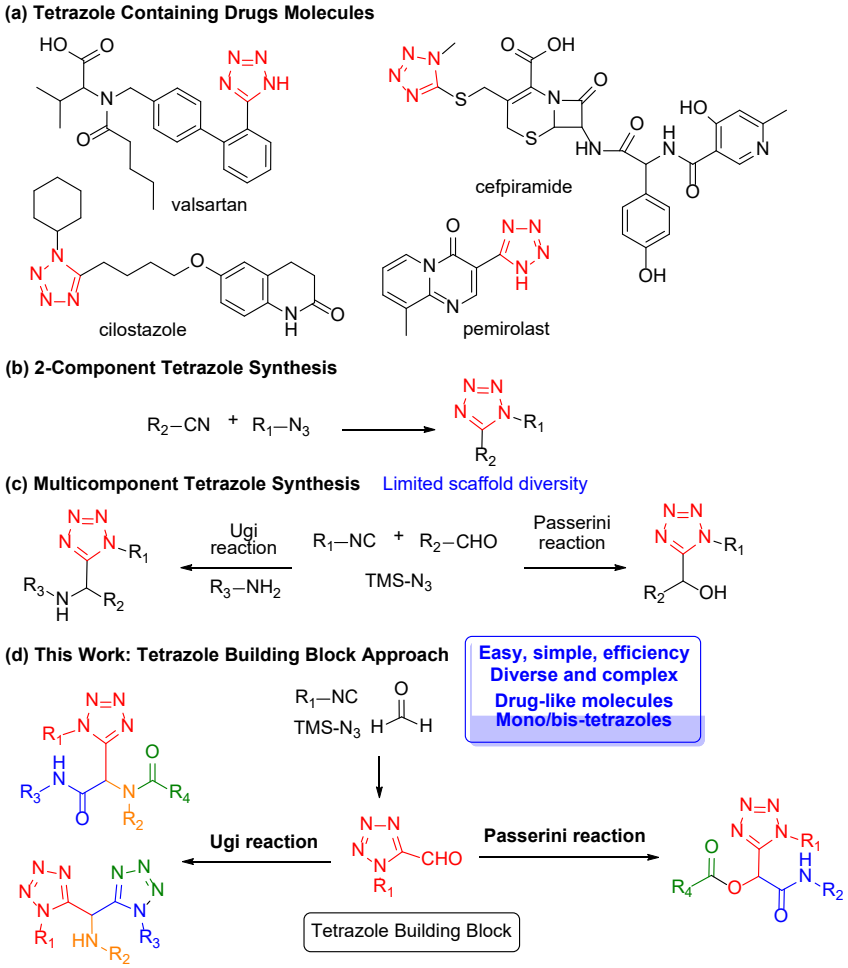


Figure 1. Cyclization strategies in chemistry.

and scalable MCR-based route in order to provide useful quantities of tetrazole building block by using isocyanide, azide, and paraformaldehyde. Then, this novel tetrazole building block was used in Passerini and Ugi reactions amenable to convenient, efficient, simple, and fast synthesis of diverse library scaffolds and can be readily elaborated to afford variously functionalized tetrazole-based drug-like molecules.

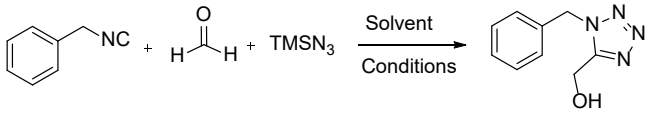
In order to achieve the synthesis of novel tetrazole building blocks and their use in organic synthesis, we envisioned the use of multicomponent reactions in both steps. The use of MCRs provides the benefits of simplicity, speed, complexity and diversity with the minimum number of steps and with an environmentally friendly nature. First, we focused on the use of the Passerini-tetrazole reaction for the synthesis of tetrazole building blocks which provides the handle of alcohol functionality. The latter after oxidation serves as an oxo-component in subsequent MCRs (**Figure 1d**). The synthesis of oxo-tetrazoles was targeted because of the prevalence of the aldehyde substrate in MCRs and their use in the medicinal chemistry literature.

Optimization

To explore the utility of the Passerini-tetrazole reaction with cost-efficient and readily available paraformaldehyde (powder form) towards higher yields, we started our investigation by using benzyl isocyanide (1 equiv.), paraformaldehyde (2 equiv.) and TMS-azide (1 equiv.) as a model substrate. However, paraformaldehyde can be a challenging substrate for MCRs and this was also the case for the synthesis of oxo-tetrazoles via a Passerini tetrazole reaction.[17] We started our optimization by using MeOH and H_2O as the solvent system at room temperature, however, it did not yield any product even after 3 days (**Table 1, entry 1**). Use of DMF to improve the solubility of the paraformaldehyde powder was also unable to improve the product yield.

Recently, microwave use in organic synthesis has been increased[18] and our previous promising studies on the microwave-assisted MCRs,[19] motivated us to use microwave conditions for further optimization. Accordingly, we investigated several sets of reaction conditions with or without solvents at low or high temperature under microwave irradiation and the results are summarized in **Table 1**. Notably, the reaction with water as a solvent provided a promising yield of 52%, whereas other solvents and conditions resulted only in trace product formation. Combining water with different co-solvents such as MeOH, DCM, CH_3CN and THF provided products with low to moderate yields

Table 1. Optimization of reaction conditions[a]



1a

Entry	Solvent	Condition	Temp,	Time (min)	Yield (%)[a]
1	MeOH/H_2O (9:1)	rt	rt	3 days	0
2	DMF	rt	rt	3 days	0
3	DCM	mw	60°C	60	<5
4	MeOH	mw	80°C	40	<5
5	MeOH	mw	100°C	20	<5
6	-	mw	100°C	10	<5
7	H_2O	mw	100°C	60	52
8	Toluene	mw	150°C	60	<5
9	MeOH/H_2O(9:1)	mw	100°C	60	29
10	MeOH/H_2O(1:9)	mw	100°C	60	50
11	DCM/H_2O(9:1)	mw	80°C	70	57
12	DCM/H_2O(9:1)	mw	80°C	80	69
13	CH_3CN/H_2O(9:1)	mw	100°C	120	51
14	THF/H_2O(9:1)	mw	100°C	80	56
15	Toluene/H_2O(9:1)	mw	80°C	60	99
16	Toluene/H_2O(9:1)	mw	100°C	60	80
17	Toluene/H_2O(9:1)	mw	150°C	60	77

[a] Isolated yields.

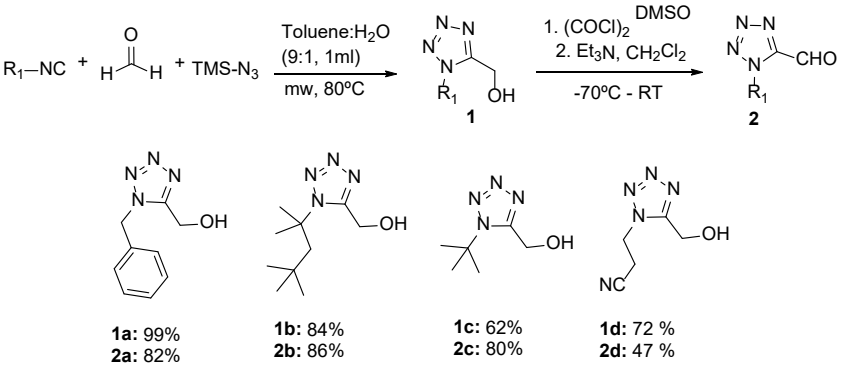
of 29-69% (**Table 1, entries 9-14**). The low yield of the desired product is either due to the formation of 1-benzyl-1H-tetrazole side product or the oxo—tetrazole component remained intact. To our delight, the use of toluene/ water (9:1) as the solvent system provided the quantitative product formation with 99% isolated yield (**Table 1, entry 15**). Upon trying to reduce the reaction time and performing the reactions at higher temperatures, the product yields were significantly reduced. Thus, the best reaction conditions were using toluene/water (9:1) as solvent in microwave at 80°C. It should also be noted that the synthesis of tetrazole building blocks under the optimized conditions could be easily scaled up to gram scale.

Restult and discussion

After establishing the optimized conditions, we next examined the substrate scope of the Passerini-tetrazole reaction by varying the isocyanide component (**Scheme 1**). Aliphatic isocyanides, such as the tert-octyl and tert-butyl (**1b** and **1c**) were well-tolerated in the Passerini-tetrazole reaction, leading to the corresponding tetrazole products in moderate to good yields of 62% and 84% respectively. β-Cyanoethyl isocyanides (**1d**) were also well tolerated providing good yields (72%). The tolerability of different isocyanides, and the possibility to remove cleavable isocyanides under different reactions conditions (acidic for the tert-octyl and tert-butyl isocyanide, basic for β-Cyanoethyl isocyanide or reductive for the Benzyl isocyanide), in the developed methodology provides multiple opportunities for various further chemical manipulations and easy access of 1H-tetrazole moieties.

First, the tetrazole building blocks were prepared on a multi-gram scale to access the free alcohol Passerini-tetrazole product. Moreover, the Swern oxidation,[20-22] which is widely exploited and has a wide tolerance of functional groups, was used to convert the tetrazole containing alcohols to aldehydes, in particular for derivatives bearing convertible isocyanides. The building blocks was well tolerated in Swern oxidation with moderate to excellent yields. Importantly, the Synthetized oxo-tetrazole building blocks are bench stable and can be easily and efficiently scaled-up to gram scale.

Scheme 1. Synthesis of Tetrazole building blocks.[a]



[a] Isolated yield

With these tetrazole building blocks in hand, our next aim was to assemble compound libraries with a high degree of complexity and skeletal diversity. Excellent functional

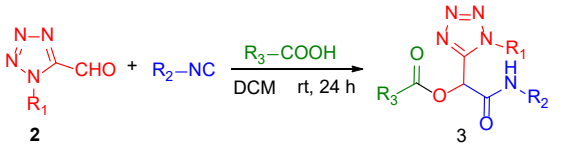
group compatibility and versatility of MCRs along with their promising impact on medicinal chemistry and drug discovery for the library generation[23-24] prompted us to further use the tetrazole building blocks in MCRs. Building on our past success with the Passerini reaction involving atypical substrates,[25] we aimed to investigate the unprecedented use of the tetrazole building block as an oxo component in the Passerini reaction to build a library that would possess drug-like properties and could be easily screened for biological activity and establishment of structure-activity relationships. We envisioned that the use of tetrazole oxo component in the Passerini reaction will provide more diversity and complexity in the same number of steps and conditions (**Scheme S1**).

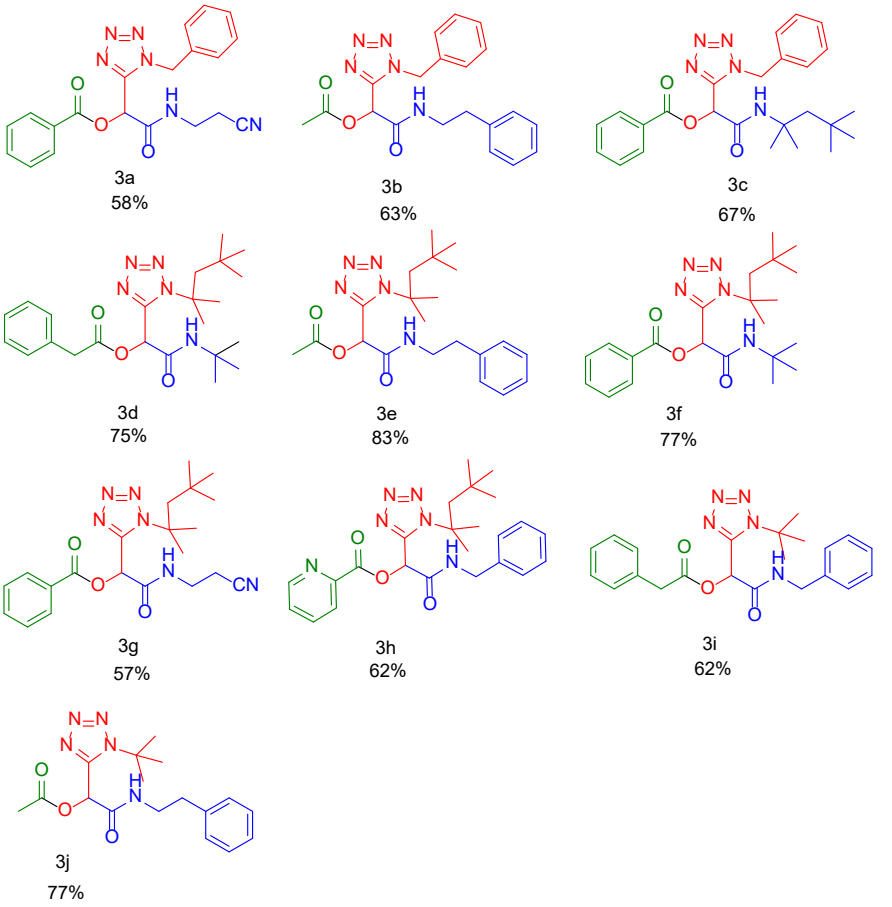
Thus, we examined the ability of the Passerini reaction to incorporate an oxo tetrazole group with a diverse panel of isocyanide and acid derivatives. To our delight various aliphatic and aromatic acid derivatives are well tolerated leading to the corresponding tetrazole products **3b** –**3i** in moderate to good yields when reactions were conducted in DCM at room temperature for 24 hours. Both aliphatic and aromatic substituents on the tetrazole ring of the oxo-component were equally well tolerated (**Scheme 2**). Aliphatic aldehydes with aliphatic and aromatic groups underwent smoothly the reaction and provided moderate to excellent yields of 58-83%. Among this, the tert-octyl substituted aldehyde **3e**, exhibited excellent product transformation with a yield of 83%. The various isocyanides such as benzyl, phenylethyl, tert-octyl and tert-butyl participated in the reaction with moderate to good yields, mainly lower yields were obtained with the β-Cyanoethyl isocyanide (**3a** and **3g**). In addition, good substrate tolerance was also achieved for the acid component with both aliphatic, aromatic, and heterocyclic acids.

The excellent overall performance of these tetrazole-aldehyde building blocks in Passerini reactions reflected the commendable feasibility of our strategy. These results pave the way to the development of the tetrazole building block approach for the other MCRs and can furnish the synthetically important tetrazole-based scaffold.

To further demonstrate the utility of the developed building block approach in the field of medicinal chemistry, we decided to incorporate an oxo-tetrazole into Ugi-four-component reaction, the most studied and versatile MCR in organic synthesis and drug discovery.[23-24] Despite tremendous exploration, finding novel substrates or bioisosteres as a starting material in the Ugi reaction remains a highly challenging and desired research area.[26-28]

Scheme 2. Substrate Scope of the Passerini Products (**3**)[a]



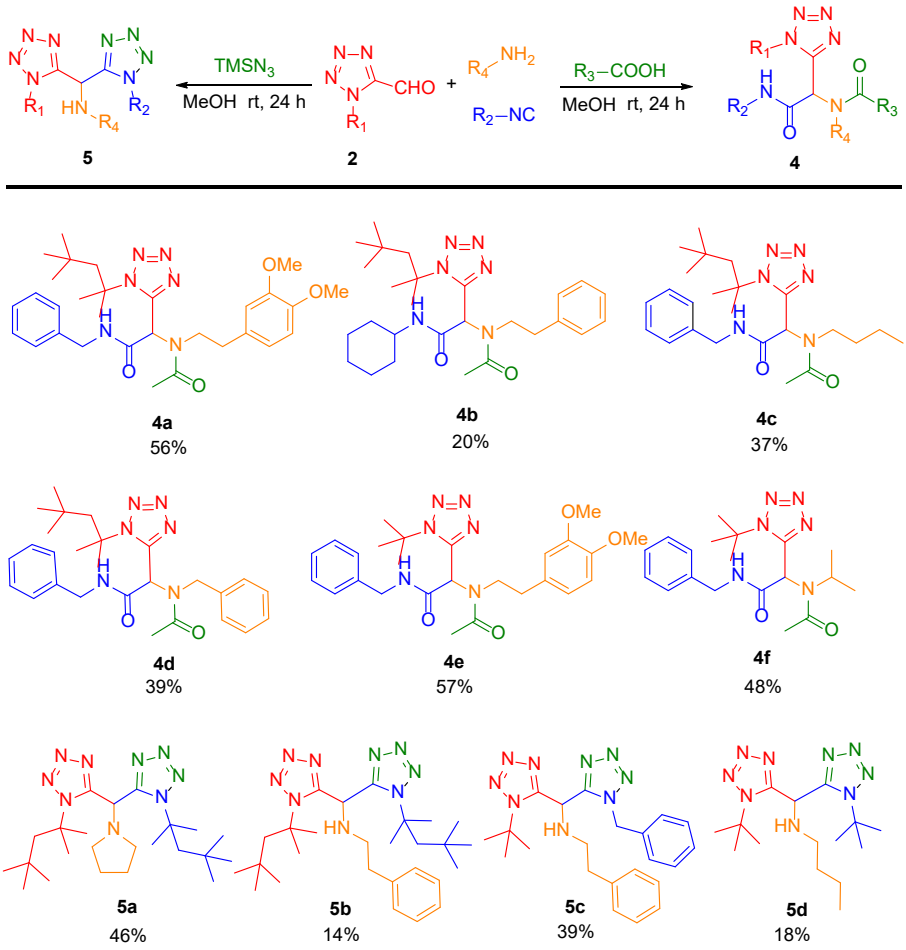


[a] Isolated yield

The use of this atypical oxo-tetrazole scaffold in Ugi reaction can be a direct and effective way to further explore the tetrazole-based vast chemical space, importantly their use in Ugi reaction can create molecules with diversity and complexity with minor effect on the molecular weight (**Figure S1**). The oxo-tetrazole scaffold proved to be successful in the incorporation to the Ugi reaction generating a diverse range of molecules having

both mono and di-tetrazole building blocks (**Scheme3**). This method is applicable to different amines, isocyanides and acid components including Ugi-four-component and Ugi-tetrazole reactions proving the desired product with low to moderate yields. The Ugi reactions were performed in MeOH at room temperature for 24 hours and without any further optimization. As this oxo-tetrazole scaffold is a challenging substrate to incorporate in the Ugi reaction and remained mostly intact during the reaction, ultimately provides lower yields as compares to the Passerini reaction (**Scheme2**).

Scheme 3. Substrate Scope of Ugi products (**4**) and (**5**)[a]



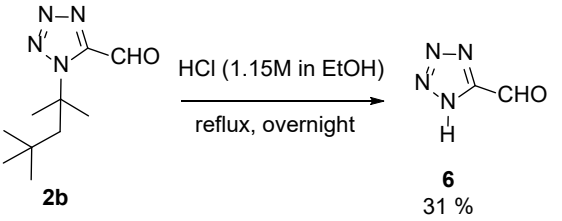
[a] Isolated yield

Although yields for the Ugi-reactions are modest with this unusual and unprecedented substrate, this simple and powerful method offers unique tetrazole based products

in a single step that could be difficult to obtain by alternative procedures. These low yields could be further improved with the optimization of individual substrates reaction regarding the solvent, temperature or assisting techniques such as sonication or microwave. Collectively, this building block strategy opens the new avenue to screen an acid bioisostere or amide bioisostere compound libraries to revisit or investigate a novel drug target. The diverse scaffold generation from this method also provides multiple opportunities for various further chemical manipulations which may allow the discovery of novel bioactive small molecule tools.

Recently, the fragment-based drug discovery (FBDD) approach has emerged as a promising starting point for the new drug discovery, which typically involves the screening of small fragments followed by building the lead molecules by combining active fragments or elaborating the molecules on this fragment. We became interested to investigate the new, easy and direct access to commercially unavailable 1H-tetrazole oxo-tetrazole fragment. We envisioned the use of tetrazole building blocks having cleavable isocyanide for the synthesis of 5-substituted 1H-tetrazoles. Tert-octyl isocyanide, which has an excellent performance in each step of this strategy, was utilized as model substrate and further treated with 1 M HCl in EtOH under refluxing over-night which provides the desired 1H-tetrazole with an acceptable yield of 31%. This easy and direct method provides further opportunities to use these fragments in FBDD or building blocks for organic synthesis.

Scheme 4. Yields of tetrazole building blocks (6)[a]



2b **6** 31 %

[a] Isolated yield

Conclusion

Indeed, the increasing use of the tetrazole scaffold in medicinal chemistry and drug molecules undoubtedly opens new vistas in drug discovery, and access to such compounds is highly desired. In summary, the building block strategy has been utilized as a versatile approach to synthesize a variety of scaffolds and expand the tetrazole based chemical space. The synthesis of tetrazole building block was first achieved by using a novel microwave-assisted three-component Passerini tetrazole reaction with high efficiency and simplicity. Furthermore, this novel tetrazole scaffold was incorporated, via building block strategy, into both Passerini and Ugi reactions for the design and synthesis of compound libraries with high skeletal diversity spanning large tracts of biologically relevant chemical space. Additionally the easily accessed 1H-tetrazole fragment can be a powerful addition to the arsenal of fragment-based drug discovery approaches.

Owing to their admirable biological, pharmaceutical, and clinical properties, we anticipate that these new, mono- and bis- tetrazole compounds will prove to be useful tools in drug discovery and optimization for novel and challenging disease targets. Many of the diverse scaffolds prepared have scope for easy further diversification which may allow the use of the tetrazole building block approach in organic and industrial applications. Work is ongoing to explore the synthetic utility of this tetrazole scaffold in other MCRs as an oxo-component and further post-modifications towards scaffold diversity generation. Additionally, investigation of these drug-like molecules in the different valuable biological targets such as p53/MDM2, PD-1/PDL-1, and IL-17A is in progress.

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Experimental section

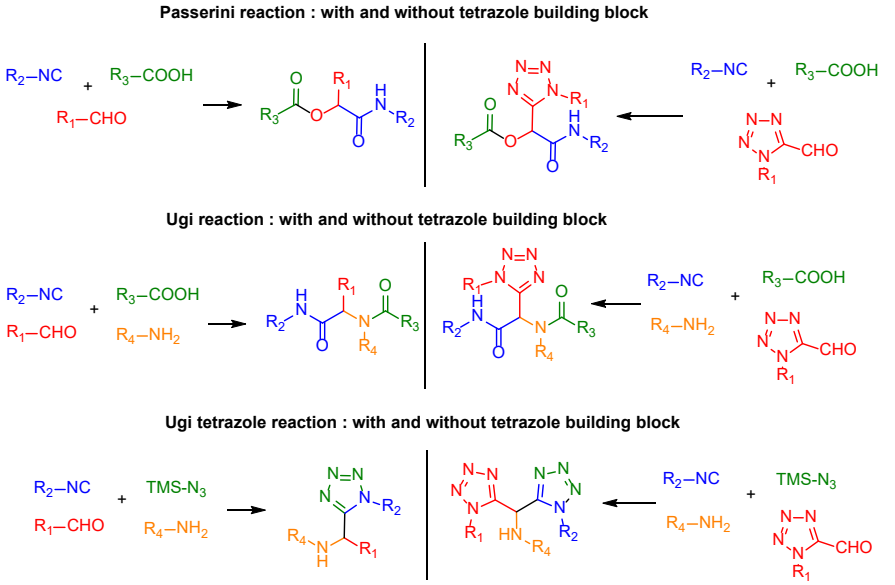


Figure S1: Scaffold diversity and complexity with tetrazole building block use in the Passerini and Ugi reaction. Use of tetrazole building block in MCRs provides an extra efficiency, complexity and diversity in the same number of reaction steps and with minor change in molecular weight.

Experimental procedures

Procedure A: General procedure for the synthesis of alcohols:

A 5 mL microwave vial equipped with a magnetic stir bar was charged with an aldehyde (1.0 mmol) and paraformaldehyde (2.0 mmol) in Toluene:H_2O (9:1 1 mL) and trimethylsilyl azide (1.0 mmol) was added slowly at room temperature. Vial was sealed with cap containing a septum and subjected to microwave heating at 80 °C [attention: during irradiation, pressure develops] till completion of reaction (reaction monitored by TLC). The solvent was removed under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent on to afford the titled product.

Procedure B: General procedure for the synthesis of aldehyds:

To a solution of oxalyl chloride (5 equiv.) and 3 Å MS in CH_2Cl_2 at -78 °C under N_2 was

added dropwise a solution of DMSO (10 equiv.) in CH_2Cl_2. After 15 min a solution of the alcohol (1 equiv.) in CH_2Cl_2 was slowly added dropwise. After 30 min, Et_3N (15 equiv.) was added dropwise. The reaction was stirred 30 min at -78 °C then slowly allowed to warm to rt. Water was added and stirred for few min to separate organic layer and extracted with DCM. The organic fraction was dried under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent on to afford the titled product.

Procedure C: General procedure for the synthesis of Passerini products:

Isocyanide (1.0 mmol) and acid (1.0 mmol) were added to a solution of aldehyde (1.0 mmol) in DCM (1 mL), and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure followed by purification by flash chromatography on silica gel using EtOAc–hexane as eluent to afford the titled product.

Procedure D: General procedure for the synthesis of Ugi products:

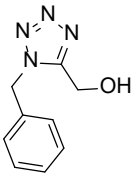
A solution of aldehyde (1.0 mmol) and amine (1.0 mmol) in methanol (1 mL) was stirred at room temperature for 30 minutes. Subsequently, isocyanide (1.0 mmol) and acid (1.0 mmol) or trimethylsilyl azide (1.0 mmol, 130 µL) were added and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure followed by purification by flash chromatography on silica gel using EtOAc–hexane as eluent to afford the titled product.

Procedure E: General procedure for the synthesis of 1H-tetrazole:

HCl in EtOH (9 eq) was slowly added to 1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazole-5-carbaldehyde. The reaction was refluxed for overnight. Water was added and stirred for few min to separate organic layer and extracted with DCM. The organic fraction was dried under reduced pressure and residue was purified by silica gel flash chromatography using MeOH:DAM (20 %) as eluent on to afford the titled product.

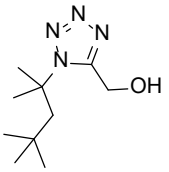
Characterization data

(1-benzyl-1H-tetrazol-5-yl)methanol (1a)



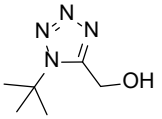
Synthesized according to procedure A from 1 mmol reaction as white solid, yield: 188 mg (99 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 3H), 7.29 (dd, *J* = 7.1, 2.0, 2H), 5.66 (s, 2H), 4.84 (s, 2H), 3.37 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 133.1, 129.2, 129.1, 128.0, 53.9, 51.4.

(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methanol (1b)



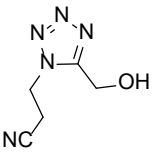
Synthesized according to procedure A from 1 mmol reaction as white solid, yield: 178mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, *J* = 6.3, 2H), 4.15 (t, *J* = 6.6, 1H), 2.02 (s, 2H), 1.83 (s, 6H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 65.1, 55.4, 53.5, 31.7, 30.6, 29.9. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.00 65.09 55.37 53.51 31.65 30.61 29.94.

(1-(tert-butyl)-1H-tetrazol-5-yl)methanol (1c)



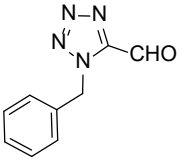
Synthesized according to procedure A from 1 mmol reaction as white solid, yield: 97mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (d, *J* = 6.6, 2H), 4.08 – 3.93 (m, 1H), 1.77 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 61.8, 55.0, 29.6.

3-(5-(hydroxymethyl)-1H-tetrazol-1-yl)propanenitrile (1d)



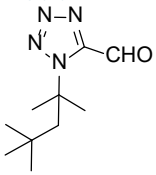
Synthesized according to procedure A from 2 mmol reaction as white solid, yield: 220 mg (72 %); ^{1}H NMR (500 MHz, MeOD) δ 4.01 (t, *J* = 2.8, 2H), 3.58 – 3.46 (m, 2H), 2.70 (td, *J* = 6.6, 2.9, 2H). ^{13}C NMR (126 MHz, MeOD) δ 175.7, 119.3, 62.5, 36.0, 18.5. MS (ESI) m/z calculated $[M+H]^+$: 154.07; found $[M+H]^+$: 154.06.

1-benzyl-1H-tetrazole-5-carbaldehyde (2a)



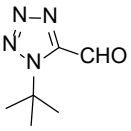
Synthesized according to procedure B from 1 mmol reaction as colorless liquid, yield: 154 mg (82 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.42 – 7.32 (m, 6H), 5.87 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 148.7, 132.9, 129.3, 129.1, 129.0, 128.6, 52.7 ppm. MS (ESI) m/z calculated $[M+H]^+$: 189.07; found $[M+H]^+$: 189.14.

1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazole-5-carbaldehyde (2b)



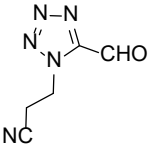
Synthesized according to procedure B from 3 mmol reaction as colorless liquid, yield: 542 mg (86 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 0.81 (s, 2H), 0.78 (s, 4H), 0.72 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 140.6, 54.3, 51.2, 30.6, 29.9, 29.5 ppm.

1-(tert-butyl)-1H-tetrazole-5-carbaldehyde (2c)



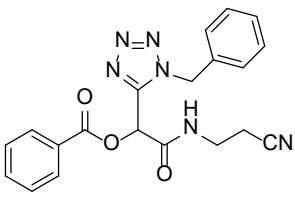
Synthesized according to procedure B from 4.87 mmol reaction as pale yellow liquid, yield: 600 mg (80 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 1.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.1, 150.6, 64.1, 28.7 ppm.

3-(5-formyl-1H-tetrazol-1-yl)propanenitrile (2d)



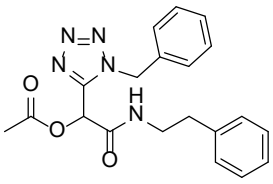
Synthesized according to procedure B from 1 mmol reaction as colorless liquid, yield: 71 mg (47 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 4.80 (t, J = 6.5, 2H), 3.13 (t, J = 6.5, 2H).

1-(1-benzyl-1H-tetrazol-5-yl)-2-((2-cyanoethyl)amino)-2-oxoethyl benzoate (3a)



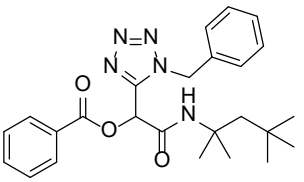
Synthesized according to procedure C from 1 mmol reaction as white viscous liquid, yield: 226 mg (58 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (t, J = 6.1, 1H), 7.75 (d, J = 7.3, 2H), 7.49 (t, J = 7.5, 1H), 7.35 – 7.27 (m, 5H), 7.23 (dd, J = 7.2, 1.7, 2H), 6.67 (s, 1H), 5.90 (d, J = 15.5, 1H), 5.81 (d, J = 15.6, 1H), 3.66 – 3.42 (m, 2H), 2.58 (t, J = 6.6, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 164.8, 164.6, 150.6, 134.2, 133.2, 130.1, 129.1, 128.8, 128.6, 127.7, 127.4, 117.9, 65.9, 52.0, 35.8, 17.9 ppm; MS (ESI) m/z calculated $[M+Na]^+$: 413.13; found $[M+Na]^+$: 413.21.

1-(1-benzyl-1H-tetrazol-5-yl)-2-oxo-2-(phenethylamino)ethyl acetate (3b)



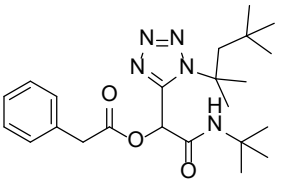
Synthesized according to procedure C from 0.5 mmol reaction as white solid, yield: 119 mg (63 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 3H), 7.28 – 7.24 (m, 4H), 7.24 – 7.17 (m, 1H), 7.16 – 7.07 (m, 2H), 6.93 (t, J = 6.0 Hz, 1H), 6.27 (s, 1H), 5.83 – 5.67 (m, 2H), 3.64 – 3.39 (m, 2H), 2.79 (t, J = 7.1 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.48, 163.80, 150.70, 138.14, 133.20, 129.04, 128.86, 128.77, 128.70, 128.67, 127.93, 126.69, 65.57, 51.89, 40.86, 35.28, 20.18. MS (ESI) m/z calculated $[M+H]^+$: 380.17; found $[M+H]^+$: 380.27.

1-(1-benzyl-1H-tetrazol-5-yl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl benzoate (3c)



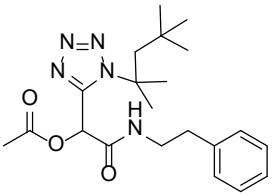
Synthesized according to procedure C from 0.5 mmol reaction as white solid, yield: 150 mg (67 %);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 2H), 7.64 – 7.51 (m, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.34 – 7.30 (m, 3H), 7.30 – 7.26 (m, 2H), 6.63 (s, 1H), 6.56 (s, 1H), 6.03 – 5.84 (m, 2H), 1.71 (q, *J* = 15.0 Hz, 2H), 1.42 (d, *J* = 7.4 Hz, 6H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.43, 162.60, 150.82, 134.12, 133.34, 129.96, 129.08, 128.74, 128.63, 127.78, 127.76, 66.49, 56.42, 51.87, 31.59, 31.32, 28.88, 28.69. MS (ESI) m/z calculated $[M+H]^+$: 450.25; found $[M+H]^+$: 450.36.

2-(tert-butylamino)-2-oxo-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)ethyl 2-phenylacetate (3d)



Synthesized according to procedure C from 1 mmol reaction as white solid, yield: 322 mg (75 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.32 – 7.29 (m, 3H), 6.54 (s, 1H), 6.06 (s, 1H), 3.75 (d, *J* = 2.0 Hz, 2H), 2.20 (d, *J* = 15.3 Hz, 1H), 2.03 (d, *J* = 15.3 Hz, 1H), 1.91 (s, 3H), 1.83 (s, 3H), 1.20 (s, 9H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.14, 163.20, 150.89, 132.53, 129.24, 129.03, 127.77, 66.68, 66.60, 54.26, 51.89, 41.00, 31.63, 30.53, 30.05, 28.28. MS (ESI) m/z calculated $[M+H]^+$: 430.28; found $[M+H]^+$: 430.40.

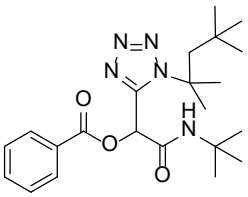
2-oxo-2-(phenethylamino)-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)ethyl acetate (3e)



Synthesized according to procedure C from 1 mmol reaction as white solid, yield: 334 mg (83 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.29 (m, 1H), 7.28 – 7.27 (m, 1H), 7.24 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 7.10 (t, *J* = 6.1 Hz, 1H), 6.66 (s, 1H), 3.68 – 3.57 (m, 1H), 3.45 – 3.35 (m, 1H), 2.82 (td, *J* = 7.1, 1.8 Hz, 2H), 2.21 (d, *J* = 15.3 Hz, 1H), 2.10 – 2.03 (m, 4H), 1.92 (s, 3H), 1.86 (s, 3H), 0.80 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.71, 164.34, 150.94, 138.28, 128.82, 128.64, 126.63, 66.78, 66.22, 54.24, 40.71, 35.33, 31.66, 30.54, 30.11, 20.45. MS (ESI) m/z calculated $[M+Na]^+$: 402.23; found $[M+Na]^+$: 424.35.

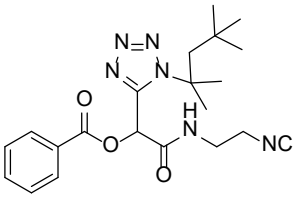
2-(tert-butylamino)-2-oxo-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)ethyl

benzoate (3f)



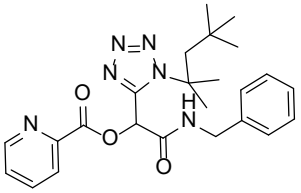
Synthesized according to procedure C from 0.5 mmol reaction as white solid, yield: 160 mg (77 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 2H), 7.63 – 7.57 (m, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 6.80 (s, 1H), 6.43 (s, 1H), 2.17 (d, *J* = 15.2 Hz, 1H), 2.05 (d, *J* = 15.2 Hz, 1H), 1.93 (s, 3H), 1.88 (s, 3H), 1.35 (s, 9H), 0.74 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.44, 163.51, 150.95, 134.34, 129.98, 128.84, 127.87, 66.95, 66.53, 54.22, 52.10, 31.62, 30.48, 30.35, 28.44. MS (ESI) m/z calculated $[M+H]^+$: 416.27; found $[M+H]^+$: 416.37.

2-((2-isocyanoethyl)amino)-2-oxo-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl) ethyl benzoate (3g)



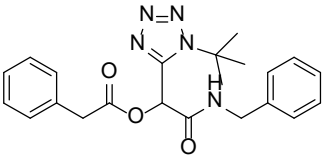
Synthesized according to procedure C from 1 mmol reaction as white solid, yield: 235 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H), 7.64 (t, *J* = 7.5, 1H), 7.47 (t, *J* = 7.8, 2H), 7.33 (t, *J* = 6.0, 1H), 6.95 (s, 1H), 3.71 – 3.61 (m, 1H), 3.59 – 3.47 (m, 1H), 2.74 – 2.54 (m, 2H), 2.14 (q, *J* = 15.3, 2H), 1.96 (s, 3H), 1.91 (s, 3H), 0.80 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 164.5, 150.4, 134.6, 130.2, 128.9, 127.5, 117.4, 66.8, 66.5, 54.4, 35.8, 31.7, 30.5, 30.4, 30.3, 18.0 ppm; MS (ESI) m/z calculated $[M-H]^-$: 411.22; found $[M-H]^-$: 411.29.

2-(benzylamino)-2-oxo-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)ethyl picolinate (3h)



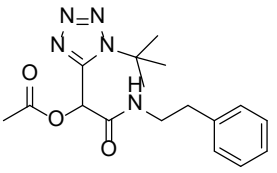
Synthesized according to procedure C from 0.5 mmol reaction as white solid, yield: 140 mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 – 8.61 (m, 1H), 8.24 – 8.16 (m, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.79 (td, *J* = 7.8, 1.8 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 6.99 (s, 1H), 4.49 (d, *J* = 6.0 Hz, 2H), 2.26 (d, *J* = 15.2 Hz, 1H), 2.14 (d, *J* = 15.2 Hz, 1H), 1.98 (s, 3H), 1.93 (s, 3H), 0.82 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.57, 163.38, 150.78, 150.05, 145.91, 137.37, 137.29, 128.61, 128.01, 127.57, 127.46, 125.86, 67.30, 66.97, 54.39, 43.47, 31.69, 30.58, 30.42, 30.11. MS (ESI) m/z calculated $[M+Na]^+$: 473.23; found $[M+ Na]^+$: 473.33.

2-(benzylamino)-1-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-oxoethyl 2-phenylacetate (3i)



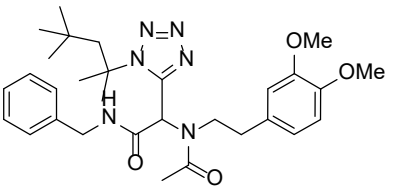
Synthesized according to procedure C from 1 mmol reaction as white solid, yield: 252 mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.25 – 7.20 (m, 6H), 7.17 (t, *J* = 6.0 Hz, 1H), 6.67 (s, 1H), 4.39 (dd, *J* = 14.8, 6.0 Hz, 1H), 4.33 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.75 (d, *J* = 15.6 Hz, 1H), 3.69 (d, *J* = 15.6 Hz, 1H), 1.77 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.53, 164.46, 150.60, 137.07, 132.50, 129.37, 129.26, 128.87, 128.73, 127.69, 127.66, 66.33, 63.32, 43.44, 40.65, 30.15. MS (ESI) m/z calculated $[M+Na]^+$: 430.19; found $[M+Na]^+$: 430.31.

1-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-oxo-2-(phenethylamino)ethyl acetate (3j)



Synthesized according to procedure C from 1 mmol reaction as white solid, yield: 266 mg (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 7.12 (t, *J* = 6.1 Hz, 1H), 6.61 (s, 1H), 3.62 – 3.56 (m, 1H), 3.51 – 3.42 (m, 1H), 2.83 (td, *J* = 7.1, 3.1 Hz, 2H), 2.10 (s, 3H), 1.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.77, 164.32, 150.78, 138.28, 128.79, 128.62, 126.61, 66.23, 63.28, 40.76, 35.31, 30.17, 20.43. MS (ESI) m/z calculated $[M+Na]^+$: 368.17; found $[M+Na]^+$: 368.30.

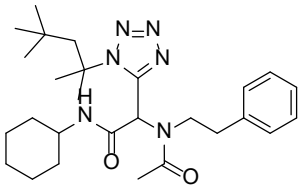
N-cyclohexyl-2-(N-phenethylacetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)acetamide (4a)



Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 308 mg (56 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.4, 2H), 7.26 – 7.21 (m, 3H), 7.15 (s, 1H), 6.77 (d, *J* = 8.1, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 8.1, 1H), 6.46 (s, 1H), 4.48 (d, *J* = 5.7, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.83 – 3.76 (m, 1H), 3.76 – 3.66 (m, 1H), 2.67 (td, *J* = 12.3, 5.2, 1H), 2.26 (s, 3H), 2.15 (td, *J* = 12.3, 5.3, 1H), 2.03 (d, *J* = 2.4, 2H), 1.88 (s, 3H), 1.80 (s, 3H), 0.79 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 165.5, 161.1, 150.5, 149.2, 148.0, 137.2, 130.1, 128.8, 128.7, 127.8, 127.8, 127.7, 127.6, 120.6, 112.0, 111.5, 66.3, 56.0, 55.9, 53.6, 52.1, 48.9, 44.2, 35.8, 31.6, 30.7, 30.2, 30.0, 21.5 ppm; MS (ESI) m/z calculated $[M+Na]^+$: 573.32; found $[M+Na]^+$: 573.40.

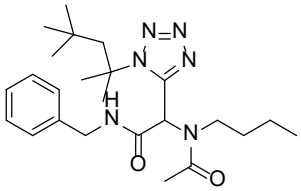
N-benzyl-2-(N-(3,4-dimethoxyphenethyl)acetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)acetamide (4b)

Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 96 mg



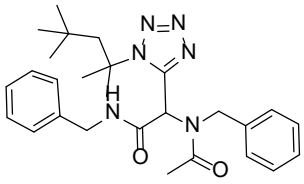
(20 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 7.21 – 7.13 (m, 2H), 7.05 (s, 1H), 6.14 (d, *J* = 8.0 Hz, 1H), 3.90 – 3.77 (m, 3H), 2.87 – 2.78 (m, 1H), 2.50 – 2.40 (m, 1H), 2.28 (s, 3H), 2.10 (d, *J* = 15.4 Hz, 1H), 2.06 (d, *J* = 15.1 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.89 (s, 3H), 1.84 (s, 3H), 1.75 – 1.55 (m, 4H), 1.43 – 1.29 (m, 2H), 1.26 – 1.06 (m, 3H), 0.83 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.89, 164.26, 150.78, 137.56, 128.77, 128.68, 126.84, 66.22, 53.52, 52.40, 49.23, 48.70, 36.26, 32.69, 32.63, 31.67, 30.72, 30.32, 30.01, 25.34, 24.60, 21.53. MS (ESI) m/z calculated $[M+Na]^+$: 505.33; found $[M+Na]^+$: 505.42.

N-benzyl-2-(N-butylacetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl) acetamide (4c)



Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 164 mg (37 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.22 (m, 3H), 7.02 (s, 1H), 4.44 (dd, *J* = 5.9, 2.1 Hz, 2H), 3.67 – 3.52 (m, 2H), 2.12 (s, 3H), 2.01 (s, 2H), 1.82 (s, 3H), 1.77 (s, 3H), 1.42 – 1.32 (m, 1H), 1.32 – 1.23 (m, 1H), 1.22 – 1.14 (m, 2H), 1.05 – 0.92 (m, 1H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.04, 165.61, 150.73, 137.39, 128.66, 127.91, 127.59, 66.04, 53.50, 52.37, 47.05, 44.08, 31.92, 31.59, 30.63, 30.03, 29.88, 21.32, 20.02, 13.50. MS (ESI) m/z calculated $[M+Na]^+$: 465.30; found $[M+Na]^+$: 465.42.

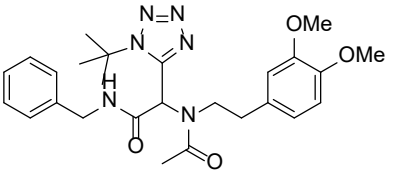
N-benzyl-2-(N-benzylacetamido)-2-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl) acetamide (4d)



Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 186 mg (39 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.24 – 7.18 (m, 4H), 7.12 (s, 1H), 7.11 – 7.03 (m, 4H), 7.03 – 6.95 (m, 1H), 5.07 (d, *J* = 17.9 Hz, 1H), 4.98 (d, *J* = 17.9 Hz, 1H), 4.24 (dd, *J* = 14.6, 6.0 Hz, 1H), 4.03 (dd, *J* = 14.6, 5.3 Hz, 1H), 2.07 (s, 3H), 2.06 – 2.01 (m, 2H), 1.79 (s, 3H), 1.76 (s, 3H), 0.78 (s, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.13, 164.98, 150.95, 137.02, 136.88, 128.73, 128.66, 127.97, 127.66, 127.43, 126.16, 66.25, 53.75, 53.57, 50.66, 44.13, 31.63, 30.65, 29.99, 29.83, 22.13. MS (ESI) m/z calculated $[M+Na]^+$: 499.28; found $[M+Na]^+$: 499.38.

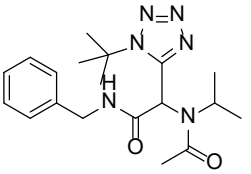
N-benzyl-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-(N-(3,4-dimethoxyphenethyl)acetamido)

acetamide (4e)



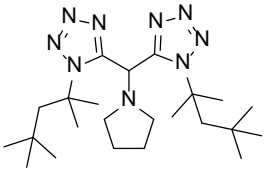
Synthesized according to procedure D from 0.5 mmol reaction as white solid, yield: 141 mg (57 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 6H), 6.81 – 6.72 (m, 2H), 6.61 (s, 1H), 6.59 (s, 1H), 5.29 (s, 1H), 4.47 (dd, *J* = 7.7, 6.1, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 – 3.75 (m, 1H), 3.75 – 3.65 (m, 1H), 2.64 (td, *J* = 12.4, 5.2, 1H), 2.22 (s, 3H), 2.10 – 2.04 (m, 1H), 1.75 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 165.5, 150.4, 149.1, 147.9, 137.3, 129.9, 128.7, 127.8, 127.7, 120.5, 111.9, 111.4, 62.6, 55.9, 55.9, 52.2, 48.9, 44.2, 35.8, 29.8, 29.7, 21.5 ppm; MS (ESI) m/z calculated $[M+Na]^+$: 517.25; found $[M+Na]^+$: 517.37.

N-benzyl-2-(1-(tert-butyl)-1H-tetrazol-5-yl)-2-(N-isopropylacetamido)acetamide (4f)



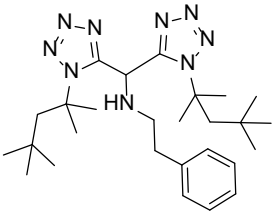
Synthesized according to procedure D from 0.5 mmol reaction as white solid, yield: 89 mg (48 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 3H), 5.30 (s, 2H), 4.51 – 4.44 (m, 2H), 2.24 (s, 3H), 1.80 (s, 2H), 1.74 (s, 9H), 1.30 (d, *J* = 7.0, 3H), 1.26 (br s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.8, 150.6, 128.8, 128.1, 127.8, 66.1, 53.4, 44.3, 43.9, 30.0, 29.9, 29.7 ppm; MS (ESI) m/z calculated $[M+Na]^+$: 395.22; found $[M+Na]^+$: 395.31.

5,5'-(pyrrolidin-1-ylmethylene)bis(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazole) (5a)



Synthesized according to procedure D from 0.5 mmol reaction as white solid, yield: 102 mg (46 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (s, 2H), 2.59 – 2.53 (m, 4H), 2.07 (s, 2H), 2.05 (s, 2H), 1.83 (s, 6H), 1.79 – 1.74 (m, 10H), 0.79 (s, 9H), 0.76 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 152.29, 140.58, 65.39, 62.84, 54.21, 53.84, 52.94, 49.78, 31.53, 31.49, 30.67, 30.58, 29.89, 29.62, 23.57. MS (ESI) m/z calculated $[M+Na]^+$: 468.35; found $[M+Na]^+$: 468.46.

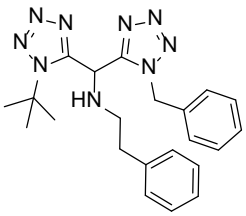
N-(bis(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)-2-phenylethan-1-amine (5b)



Synthesized according to procedure D from 0.5 mmol reaction as white solid, yield: 35 mg (14 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 5.30 (s, 1H), 4.15 (s, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H),

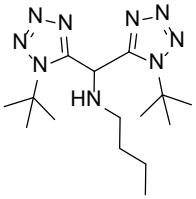
1.98 (s, 2H), 1.78 (s, 6H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.15, 139.49, 128.70, 128.56, 126.35, 64.75, 53.24, 50.75, 44.75, 36.31, 31.64, 30.67, 29.92. MS (ESI) m/z calculated $[M+Na]^+$: 518.37; found $[M+Na]^+$: 518.44.

N-((1-benzyl-1H-tetrazol-5-yl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)-2-phenylethan-1-amine (5c)



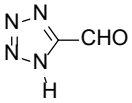
Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 162 mg (39 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 3H), 7.33 – 7.28 (m, 2H), 7.25 – 7.19 (m, 1H), 7.18 – 7.14 (m, 2H), 7.06 – 7.00 (m, 2H), 5.74 (d, *J* = 15.1 Hz, 1H), 5.67 (d, *J* = 15.1 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H), 2.87 – 2.78 (m, 1H), 2.74 – 2.62 (m, 2H), 2.57 – 2.47 (m, 1H), 2.39 – 2.27 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.55, 151.56, 139.33, 133.15, 129.24, 129.08, 128.86, 128.53, 127.94, 126.54, 62.09, 51.91, 50.72, 49.65, 36.16, 29.47. MS (ESI) m/z calculated $[M+Na]^+$: 440.23; found $[M+Na]^+$: 440.34.

N-(bis(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)butan-1-amine (5d)



Synthesized according to procedure D from 1 mmol reaction as white solid, yield: 60 mg (18 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (d, *J* = 12.4 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.52 (dt, *J* = 13.3, 6.9 Hz, 1H), 1.74 (s, 18H), 1.58 – 1.49 (m, 2H), 1.44 – 1.32 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.66, 62.52, 52.44, 48.39, 32.04, 29.56, 28.69, 20.24, 13.83. MS (ESI) m/z calculated $[M+Na]^+$: 358.24; found $[M+Na]^+$: 358.37.

1H-tetrazole-5-carbaldehyde (6)



Synthesized according to procedure E from 0.5 mmol reaction as colorless liquid, yield: 30 mg (31 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (s, 1H).