Multicomponent reactions: development, scope, and applications

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Chapter 6

Convergent Three-Component Tetrazole Synthesis

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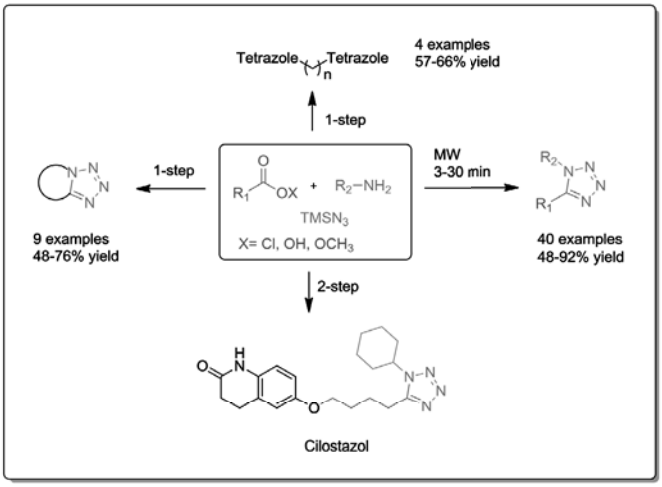


Abstract

A microwave accelerated simple and efficient method for the construction of the 1,5-tetrazole scaffold was developed. It comprises a multicomponent reaction of an amine, a carboxylic acid derivative, and an azide source. On the basis of the availabililty of the archetypical starting materials, this method provided very versatile synthetic access to 1,5-disubstituted tetrazoles. The usefulness of this method was demonstrated in the synthesis of biologically important fused tetrazole scaffolds and the marketed drug cilostazol.

Introduction

The tetrazole motif is an important synthetic scaffold that is widely use in medicine, biochemistry, pharmacology, and materials; for example, this structure is found in explosives, photography and photoimaging chemicals, rocket propellants, polymers, gas generators, and agrochemicals.[1] The first tetrazole synthesis was reported in 1885.[2] Since then, a plethora of examples has been reported, the vast majority of which rely on the use of nitriles, heterocumulenes, amides, thioamides, imidoyl chlorides, ketones, amines, and alkenes as the starting materials.[3] The increasing importance of 1,5-disubstituted tetrazoles in different applications, including as bio-active agents;[1c] drugs such as cilostazol pentylenetetrazole, and latamoxef; and cis-amide bond isosteres in peptides, has propelled the need for efficient synthetic methods. Direct access to diverse 1,5-disubstituted tetrazoles is mainly possible from amides and thioamides.[4] Other methods include the use of ketones and oximes with suitable azide sources or amidrazones with N_2O_4 or HNO_2.[5] Recently, various methods were developed for the synthesis of 1,5-disubstituted tetrazoles from amides.[3a] These methods mainly use chlorinating agents to form imidoyl chlorides, followed by the addition of an azide source to give the disubstituted tetrazoles. However, the limited availability of diverse amides as starting material compels an additional step for amide synthesis from carbonyl compounds such as acids and acetyl chlorides. Moreover, direct amide bond formation from unactivated acids is challenging and thus, multistep sequential syntheses are often the result.[6] Direct amide formation requires basic conditions, whereas tetrazole formation is favored in acidic conditions through the formation of the imidoyl chloride, which make a one-pot synthesis of tetrazoles difficult. Also the one-pot reaction for the synthesis of tetrazoles from amides is challenging, as hydrogen chloride formed in the chlorination step can have deleterious effects on acid-sensitive functionalities.[7]

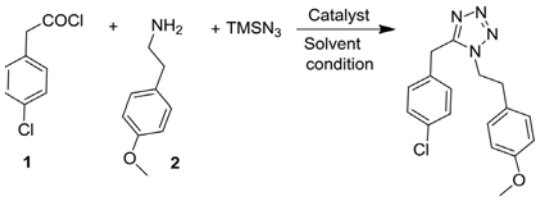
Reported methods for tetrazole formation from amides face major drawbacks, including the use of an excess amount of toxic, volatile, and highly explosive HN_3, long reaction time,[8] racemization of the product,[9] and the use of Mitsunobu reaction conditions, which require expensive reagents, long reaction times, and tedious workup procedures and with low yields.[10] The use excess of base to trap HCl generated in the reaction,[7] in addition to an excess amount NaN_3 increases the chances of toxic hydrazoic acid formation.[11,12]

The $SiCl_4/NaN_3$ combination was reported for the one-step synthesis of tetrazoles from amides, but the major drawbacks of this method are the requirement of anhydrous and inert conditions, long reaction time (50 h), and limited reported diversity.[13] Thus, the development of a straightforward, easy, safe, efficient, fast, diverse, and general method for the formation of tetrazoles form unactivated carbonyl compounds is warranted. We foresaw that the accelerating effect of microwaves could potentially lead to a multicomponent reaction (MCR) of tetrazoles among suitable carbonyl compounds, amines and azide with a chlorinating agent. We hypothesized that, in situ amide formation from amines and carbonyl compounds followed by imidoyl chloride formation and finally a tetrazole formation by azide addition would be possible in a one-pot three-component reaction (3CR). Careful choice of a suitable chlorinating reagent could trigger activation for both amide and imidoyl chloride formation as the key step of the reaction.

Results and Discussion

To test this hypothesis, optimization of the reaction was performed with hydrocinnamoyl chloride, benzylamine, and TMS-azide as starting materials with different chlorinating reagents, solvents, temperatures, microwave conditions, reaction times. Initially screening was performed at room temperature and by using conventional heating. We screened different reagents such as HCl, $AlCl_3$, $(COCl)_2$, and $SOCl_2$ at room temperature or heating, and with the use of different solvents, including CH_3CN, DMF, THF, 2,6-lutidine, but we did not get the expected product. The reactions mostly ended up in amide formation, and even refluxing for 3 days in the presence of excess amount HCl, the product was not formed. We shifted to $POCl_3$, which is safer alternative to phosgene and easier to handle than PCl_5. Encouragingly, we found a trace product formation with $POCl_3$ at room temperature after a long reaction time (3 days) (Table 1). An increase in the temperature led to a slight enhancement in the reaction conversion, but the reaction still gave the amide as the major product. The use of a base to reduce the requisite amount of HCl in the reaction did not have any effect on the reaction. The synthesis of tetrazoles by using nitriles and NaN_3 at 220 °C under microwave conditions is known,[14] and this encouraged us to try microwave conditions at higher temperature. A reaction at 150 °C gave the product but required 25 minutes to obtain complete conversion. Increasing the temperature to 180 °C accelerated the reaction to 3 minutes with 100 % conversion. We used 1.5 equivalents of TMS-azide which avoids the danger of forming hydrazide from excess azide.

Table 1. Optimization of MCR with different reaction conditions.[a]



Entry	Catalyst/Additive	Solvent	Temp °C	Time	Yield(%)[c]
1	HCl	CH_3CN	reflux	3 days	nr
2	$POCl_3$	CH_3CN	rt	3 days	trace
3	$POCl_3$	CH_3CN	80	1 day	10
4	$SOCl_2$	DCM	80[b]	20 min	nr
5	$AlCl_3$	CH_3CN	80[b]	30 min	nr
6	$(COCl)_2$ 2,6-lutidine(1.5 eq)	DCM	120[b]	50 min	trace
7	$(COCl)_2$ 2,6-lutidine(1.5 eq)	THF	120[b]	20 min	nr
8	$(COCl)_2$ 2,6-lutidine(1.5 eq)	DMF	120[b]	15 min	nr
9	$POCl_3$	CH_3CN	150[b]	20 min	70

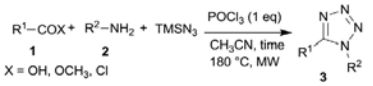
Entry	Catalyst/Additive	Solvent	Temp °C	Time	Yield(%)[c]
10	$POCl_3$	CH_3CN	180[b]	5 min	76
11	$POCl_3$ TEA (2.0 eq)	CH_3CN	180[b]	5 min	75
12	$POCl_3$ TMS-azide(3.0 eq)	CH_3CN	180[b]	5 min	72

[a]The reaction was carried out with 1mmol 1, 1 mmol 2, 1.5 mmol $TMSN_3$ and 1 mmol $POCl_3$. [b]microwave heating [c]Yield of isolated product, nr = no reaction.

With these optimized conditions at hand, we next examined the generality of this novel 3CR by treating different carbonyl compounds like acid chlorides, carboxylic acids, and esters with different amines (Table 2). The majority of the acid chlorides gave complete conversion into the corresponding tetrazoles under these optimized conditions in good to high yields (Table 2, entries **1**–**17**). Aromatic and aliphatic acid chloride compounds proved to be equally effective in this reaction. The functional group tolerance of the acid chloride (e.g., methoxy, nitro and chloro; (Table 2, entries **4**–**7** and **12**–**14**) in this protocol provides multiple opportunities for various further chemical manipulations. 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 total conversion, and moderate to good yields were provided with aliphatic and aryl esters. Esters with nitrile and chloro substituents also displayed decent reactivity in this reaction (Table 2, entries **29**–**31**). Aliphatic and aromatic amine compounds were compatible substrates for this process. Good conversions were also observed in case of sterically hindered groups, including 2-chloroaniline, 2-benzyl-aniline, and 2-methylaniline, which provided the product in good to excellent yields of 91, 80, and 72%, respectively (Table 2, entries **6**, **15**, and **17**). Amine derivatives containing both electron-withdrawing and donating functionalities such as methoxy, chloro, and nitrile were equally compatible and afforded the expected adducts. Easily cleavable groups such as cyanoethyl and benzyl were also compatible with this method, and they readily give access of 1*H*-5-tetrazoles (Table 2, entries **2**, **11**, and **26**). Bistetrazoles are also accessible via our method (Table 2, entries **37**–**40**), and these compounds are highly important in high-energy nitrogen-rich compounds and in polymerization.[15]

Table 2. Synthesis of tetrazoles from carbonyl compounds, amines and TMS-azide.[a]

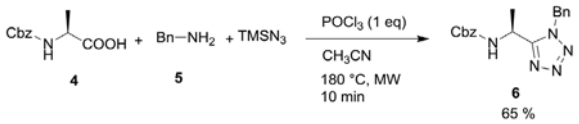


Entry	R^1	R^{2b}	Time (min)	Yield(%)[c]
	R-COCl			
1	CH_2-C_6H_5	$(CH_2)_2$-C_6H_5	4	68 (**3a**)
2	$(CH_2)_2$-C_6H_5	CH_2-C_6H_5	3	72 (**3b**)
3	$(CH_2)_2$-CH_3	$(CH_2)_2$-CH_3	4	78 (**3c**)
4	CH_2-C_6H_4-*p*-Cl	$(CH_2)_2$-C_6H_4-*p*-OCH_3	5	76 (**3d**)
5	CH_2-C_6H_4-*p*-Cl	$(CH_2)_2$-C_6H_5	5	73 (**3e**)
6	CH_2-C_6H_4-*p*-Cl	*o*-Cl-C_6H_4	5	91 (**3f**)
7	CH_2-C_6H_4-*p*-Cl	Cy	5	48 (**3g**)
8	CH_2-CH_3	CH_2-CH-CH_2	7	70 (**3h**)
9	CH_2-CH_3	$(CH_2)_2$-C_6H_5	5	73 (**3i**)
10	CH_2-CH_3	Ph	5	86 (**3j**)
11	$(CH_2)_2$-CH_3	$(CH_2)_2$-CN	10	60 (**3k**)
12	$(CH_2)_2$-Cl	$(CH_2)_2$-C_6H_5	5	71 (**3l**)
13	*m*-OCH_3-C_6H_4	Ph	4	72 (**3m**)
14	*p*-NO_2-C_6H_4	*m,p*-OCH_3-C_6H_3	7	87 (**3n**)
15	CH_2-C_6H_4-*p*-Cl	*o*-Bn-C_6H_4	7	88 (**3o**)
16	CH_2-Cl	Ph	5	73 (**3p**)
17	CH_2-Cl	*o*-CH_3-C_6H_4	5	72 (**3q**)
	R-COOH			
18	$(CH_2)_2$-C_6H_5	$(CH_2)_2$-CH_3	4	92 (**3r**)
19	$(CH_2)_2$-C_6H_5	CH_2-C_6H_5	4	72 (**3s**)
20	*m,p*-OCH_3-$CH_2C_6H_5$	*i*Pr	4	56 (**3t**)
21	CH_2-C_6H_4-p-Cl	$(CH_2)_2$-C_6H_5	5	63 (**3u**)
22	2-Naphthyl-CH_2	$(CH_2)_2$-CH_3	5	73 (**3v**)
23	Ph	Ph	5	56 (**3w**)
24	Ph	$(CH_2)_2$-C_6H_5	5	48 (**3x**)
25	*p*-OCH_3-C_6H_4	*p*-Cl-C_6H_4	4	63 (**3y**)
26	$(CH_2)_2$-CH_3	$(CH_2)_2$-CN	7	62 (**3z**)
27	$(CH_2)_2$-CH_3	$(CH_2)_2$-C_6H_5	5	71 (**3aa**)
28	$(CH_2)_2$-CH_3	CH_2-CH-CH_2	3	52 (**3ab**)
	R-$COOCH_3$			
29	CH_2-CN	$(CH_2)_2$-C_6H_5	30	67 (**3ac**)
30	CH_2-Cl	C_6H_4-*o*-Cl	30	57 (**3ad**)
31	CH_2-Cl	CH_2-C_6H_5	25	63 (**3e**)
32	CH_2CH_3	C_6H_4-*o*-Cl	25	60 (**3af**)

Entry	R^1	R^{2b}	Time (min)	Yield(%)[c]
33	$(CH_2)_2$-C_6H_5	CH_2-C_6H_5	25	69 (**3ag**)
34	$(CH_2)_2$-C_6H_5	$(CH_2)_2$-CH_3	25	60 (**3ah**)
35	CH_2-C_6H_4-p-Cl	CH_2-C_6H_4-*p*-Cl	25	70 (**3ai**)
36	Ph	CH_2-C_6H_5	30	63 (**3aj**)
	R-COCl[d]	(Bistetrazoles)		
37	CH_2-C_6H_5	C_6H_4-*o,p*-NH_2	8	60 (**3ak**)
38	$(CH_2)_2$-C_6H_5	NH_2-$(CH_2)_3$-NH_2	8	57 (**3al**)
39	CH_2-CH_3	NH_2-$(CH_2)_3$-NH_2	8	61(**3am**)
40	CH_2-C_6H_4-*p*-Cl	NH_2-$(CH_2)_3$-NH_2	8	66 (**3an**)

[a]The reaction was performed with 1 (1mmol), 2 (1 mmol), $TMSN_3$ (1.5 mmol), and $POCl_3$ (1 mmol). [b]cy = cyclohexyl, *i*Pr = isopropyl, Bn = Benzyl. [c] Yield of isolated product. [d]Acid chloride (2 equivalents), $POCl_3$ and TMS-N_3 (3 equivalents) were used.

The use of PCl_5 in the synthesis of amino acid tetrazoles often results in racemization of the products, as ketamine formation leads to racemization and careful control over the amount of base is required.[16] To check the stereochemical retention of our method, we used *N*-benzyloxycarbonyl (Cbz)-L-alanine (**4**) and benzyl amine (**5**) for the synthesis of the amino acid tetrazole **6** (Scheme 1). To our delight, the reaction proceeds under full stereoretention, as shown by chiral HPLC on a chiral stationary phase (see experimental part). Our method, therefore, provides enantiopure product likely by avoiding the use of a base. This opens the opportunity to introduce chiral tetrazoloamino acids into peptides.



Scheme 1. Synthesis of amino acid tetrazole.

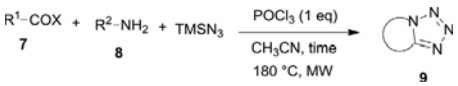
Next, we tried to access more elaborated fused tetrazole scaffolds. We envisaged a second strategy by exploiting a MCR for the synthesis of fused tetrazoles. Multicomponent reactions have lately emerged as a powerful tool in synthesis of biologically important diverse scaffolds. Even though fused tetrazole possess a wide spectrum of biological activities only very limited access to these fused tetrazole is currently possible by simple one-pot MCR.[1,17] For example, fused tetrazoles are accessible via isocyanide-based synthesis of tetrazoles followed by cyclization.[18] Using our highly flexible and robust methodology, we foresaw a quick and easy access to therapeutically interesting complex molecular structures.

According to our synthetic plan, the use of functionalized carboxylic acid with amines bearing additional functional groups would allow an anticipated domino-cyclization process in one step. The reaction of formamide, which works as an ammonia and formaldehyde surrogate, and 2-aminobenzoic acid under optimized conditions led to the formation of the tetrazolo[1,5-*c*] quinazoline scaffold in moderate yield (Table 3, entry **1**).

Biologically important tetrazolo[1,5-*a*]quinoxaline derivatives[19] were synthesized by using 2-oxoacids or their sodium salt with *o*-phenylenediamine, and they generally worked well with complete reaction conversion with good yields (Table 3, entries **2**–**4**). 4-Methyl-4,5-dihydrotetrazolo[1,5-*a*] quinoxaline was formed by the reaction of 2-chloropropanoyl chloride and o-phenylenediamine (Table 3, entry **5**). Tetrazolo[5,1-a]phthalazine (Table 3, entry **6**), for example, was reported as an anticonvulsant.[20] Using our method, the reaction between hydrazine, 2-formylbenzoic acid, and TMS-azide permitted the construction of tetrazolo[5,1-*a*]phthalazine in one step in 48% yield. Next, we attempted the synthesis of 4*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]oxazine, which is an antidepressant/ anxiolytic agent.[21] Treating 2-aminophenol with 2-chloro acetyl chloride in the presence of TMS-azide allows the preparation of a tetrazole ring fused to a benzooxazine (Table 3, entry **7**).

Pentylenetetrazole (PTZ) is a $GABA_A$ receptor antagonist and prototypical anxiogenic drug that is used experimentally as a probe to study seizure phenomena.[22] It is typically synthesized by multi-step method starting with caprolactame to form the imino ether followed by addition of hydrazine to form hydrazine derivatives, which are further treated with nitrous acid to finally affords the targets.[23] We hypothesized that PTZ could rapidly be accessed through a three-center, two-component reaction between commercially available and inexpensive 6-aminohexanoic acid and TMS-azide. We isolated this compound in a good 76% yield by using our one-pot method after reaction time of 8 min (Table 3, entry **10**).

Table 3. Synthesis of 1,5-fused tetrazole from carboxylic acid derivatives, amine and $TMSN_3$.[a]



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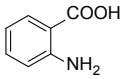
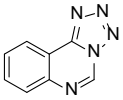
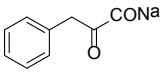
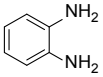
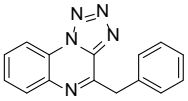
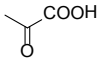
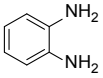
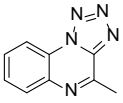
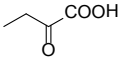
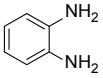
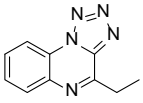
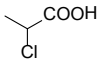
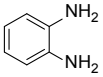
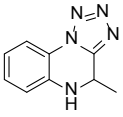
1[c]			10	50 (**9a**)	
2			25	61(**9b**)	
3			15	59 (**9c**)	
4			15	61 (**9d**)	
5			15	63 (**9e**)	

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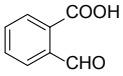
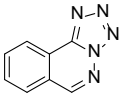
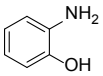
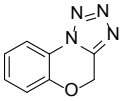
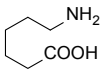
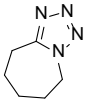
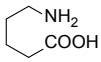
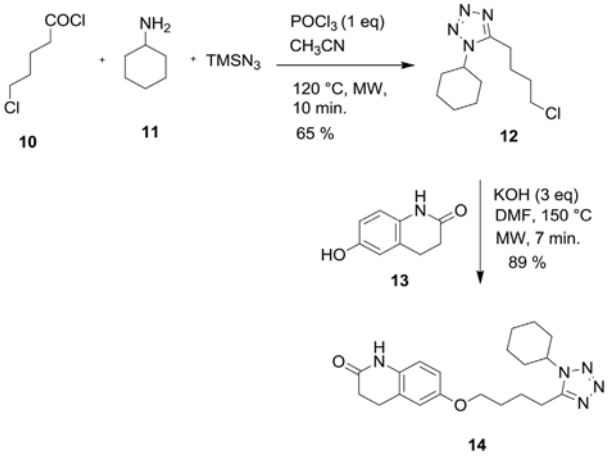
6[d]			10	48 (**9f**)	
7			7	56 (**9g**)	
8			8	76 (**9h**)	
9			5	67 (**9i**)	

[a]The reaction was performed with **7** (1 mmol), **8** (1 mmol), and $TMSN_3$ (1.5 mmol). [b]Yield of isolated product. [c] ormamide used as solvent. dExcess amount of hydrazine hydrate was used.

Finally, we validated our novel one-pot synthetic pathway towards preparation of the marketed drug Cilostazol, which targets phosphodiesterase and inhibits platelet aggregation. It is employed as a direct arterial vasodilator. Notably, this drug is usually synthesized by multistep procedures, also using toxic and explosive HN_3 and PCl_5.[24] Our rapid two-step Cilostazol synthesis involves the 3CR of 5-chloropentanoic acid chloride **10**, cyclohexyl amine **11**, and TMS-azide to form the tetrazole intermediate **12**, which was followed by coupling with commercially available 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone **13** (Scheme 2).

First, we performed the reaction of 5-chloropentanoic acid chloride **10**, cyclohexyl amine **11**, and $TMSN_3$ with $POCl_3$ at 180 °C in a microwave to form tetrazole **12**, but we observed the formation of several side products, likely involving nucleophilic substitution reactions. Then, we sequentially performed amide formation between **10** and **11** in one-pot at room temperature followed by the addition of $POCl_3$ and $TMSN_3$ and heated reaction at 120 °C for 10 minutes. Tetrazole **12** could be isolated in good yields. Coupling of 12 with 13 under microwave heating at 150 °C for 7 minutes afforded Cilostazol **14** in 89% yield (Scheme 2).



Scheme 2. Two-step synthesis of Cilostazol by our MCR methodology.

Conclusion

In conclusion, we developed a novel, efficient, safe, and general microwave-assisted first-in-class MCR-based methodology to gain access to diverse and fused tetrazoles in a single step. Multiple inter- and intramolecular examples pinpoint the versatility of the reaction. Use of $TMSN_3$ in an almost equimolar ratio makes the process safer than reported protocols. Moreover, the synthetic utility of this developed methodology was illustrated in the synthesis of biologically active 1,5-fused tetrazoles, an amino acid tetrazole and the marketed drug Cilostazol.

Experimental Procedures and Spectral Data

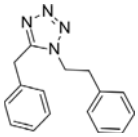
CAUTION: *Great caution should be exercised during addition of compounds as gas evolves. Proper protective measures like proper shielding and an additional safety screen in the fume hood, safety glasses, lab coat, gloves, should be used. The reactions described here were run on only 1–5 mmol scale. Use clean and scratch free microwave vial as during the reaction pressure create (up to 14 bar). Residual pressure should be relieved before opening the vessel by carefully puncturing the septum with a needle. Many tetrazole derivatives are known to be explosive. Functional groups known to be cleavable in acidic conditions like t-butyl or t-octyl (1,1,3,3-tetramethylbutyl) as amine source were avoided; as these groups may cleave under the reaction conditions and may form the free tetrazole which are explosive. Also derivatives containing a high number of nitrogens weren't pursued, as increasing the nitrogen atoms may lead to an increase in the risk for an explosion.*

General procedure for the synthesis of tetrazole:

A 20 ml microwave vial equipped with a magnetic stirring bar was charged with carbonyl compound (1.0 mmol) in CH_3CN (5 ml) and amine (1.0 mmol) was added slowly followed by phosphoryl chloride (1.0 mmol) and trimethylsilyl azide (1.5 equiv) at room temperature. The vial was sealed with a cap containing a septum and subjected to microwave heating at 180 °C [*attention: during irradiation, pressure develops*] till completion of the reaction (monitored by TLC). Then the reaction mixture was poured into 50 mL of saturated $NaHCO_3$ and extracted 3 times with 25 mL of CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane or DCM:MeOH as eluent. [*Caution: Addition of reagents and work-up must be done in a fumehood.*]

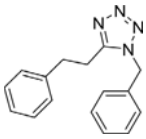
Spectral Data

5-benzyl-1-phenethyl-1*H*-tetrazole (**3a**)



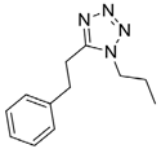
Black viscous liquid, Yield: 180 mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 6H), 7.04 (d, *J* = 7.0, 2H), 6.96 – 6.87 (m, 2H), 4.30 (t, *J* = 7.1, 2H), 3.80 (s, 2H), 2.99 (t, *J* = 7.1, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 136.4, 133.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 127.7, 127.4, 48.8, 36.1, 28.9; MS (ESI) m/z calculated $[M+H]^+$: 265.14; found $[M+H]^+$: 265.18.

1-benzyl-5-phenethyl-1*H*-tetrazole (**3b**)



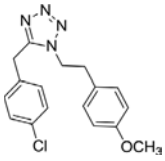
Brown solid, Yield: 190 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.30 – 7.22 (m, 3H), 7.12 – 7.01 (m, 4H), 5.20 (s, 2H), 3.01 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 139.4, 133.3, 129.3, 129.2, 128.91, 128.8, 128.4, 127.5, 127.4, 126.9, 50.5, 33.4, 25.6; MS (ESI) m/z calculated $[M+H]^+$: 263.14; found $[M+H]^+$: 263.16.

5-phenethyl-1-propyl-1*H*-tetrazole (**3c**)



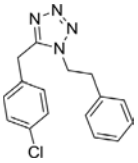
Brown liquid, Yield: 168 mg (78%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 3H), 7.13 (d, *J* = 7.2, 2H), 3.93 (t, *J* = 7.3, 2H), 3.18 (dd, *J* = 11.3, 4.4, 2H), 3.11 (dd, *J* = 11.6, 4.5, 2H), 1.78 – 1.71 (m, 2H), 0.86 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 139.5, 128.8, 128.81, 128.6, 128.4, 126.9, 126.4, 48.3, 33.7, 25.6, 22.9, 10.9; MS (ESI) m/z calculated $[M+H]^+$: 217.14; found $[M+H]^+$: 217.27.

5-(4-chlorobenzyl)-1-(4-methoxyphenethyl)-1*H*-tetrazole (**3d**)



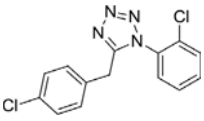
Yellow liquid, Yield: 251 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6, 2H), 6.95 (d, *J* = 8.3, 2H), 6.85 – 6.73 (m, 4H), 4.29 (t, *J* = 6.8, 2H), 3.78 (s, 3H), 3.72 (s, 2H), 3.02 (t, *J* = 6.8, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 153.5, 133.6, 132.2, 129.8, 129.7, 129.2, 128.8, 128.2, 114.4, 55.3, 49.1, 35.2, 28.3; MS (ESI) m/z calculated $[M+H]^+$: 329.11; found $[M+H]^+$: 329.15.

5-(4-chlorobenzyl)-1-phenethyl-1*H*-tetrazole (**3e**)



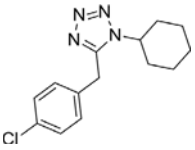
Brown liquid, Yield: 218 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 5H), 7.00 – 6.87 (m, 4H), 4.33 (t, *J* = 6.9, 2H), 3.69 (s, 2H), 3.07 (t, *J* = 6.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 136.4, 133.6, 132.2, 129.8, 129.2, 129.1, 129.1, 128.9, 128.7, 127.5, 48.9, 36.1, 28.3; MS (ESI) m/z calculated $[M+H]^+$: 299.10; found $[M+H]^+$: 299.15.

5-(4-chlorobenzyl)-1-(2-chlorophenyl)-1*H*-tetrazole (**3f**)



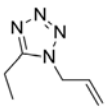
Brown solid, Yield: 279 mg (91 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.24 – 7.19 (m, 3H), 6.98 – 6.91 (m, 2H), 3.58 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 133.7, 133.1, 130.9, 130.3, 129.4, 129.3, 128.3, 127.6, 127.3, 123.5, 38.2; MS (ESI) m/z calculated $[M-H]^-$: 303.03; found $[M-H]^-$: 303.98.

5-(4-chlorobenzyl)-1-cyclohexyl-1*H*-tetrazole (**3g**)



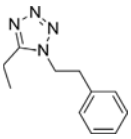
Colorless liquid, Yield: 132 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.3, 2H), 7.15 (d, *J* = 8.3, 2H), 4.26 (s, 2H), 4.11 – 3.99 (m, 1H), 1.99 – 1.83 (m, 4H), 1.79 – 1.62 (m, 3H), 1.38 – 1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 133.6, 132.8, 129.8, 129.3, 129.2, 129.0, 128.8, 128.6, 57.9, 32.6, 28.9, 25.2, 25.1, 24.7; MS (ESI) m/z calculated $[M+H]^+$: 277.11; found $[M+H]^+$: 277.24.

1-allyl-5-ethyl-1*H*-tetrazole (**3h**)



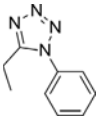
Colourless liquid, Yield: 96 mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 – 5.94 (m, 1H), 5.36 (d, *J* = 10 Hz, 1H), 5.16 (d, *J* = 15 Hz, 1H), 4.97 (d, *J* = 5 Hz, 2H), 2.89 – 2.84 (q, *J* = 15 Hz, 2H), 1.42 (t, *J* = 10 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 130.1, 119.7, 49.2, 16.8, 11.3 ppm; MS (ESI) m/z calculated $[M+H]^+$: 139.09; found $[M+H]^+$: 139.11.

5-ethyl-1-phenethyl-1*H*-tetrazole (**3i**)



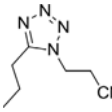
Brown liquid, Yield: 147 mg (73 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 3H), 6.98 (d, *J* = 7.7, 2H), 4.46 (t, *J* = 6.8, 2H), 3.21 (t, *J* = 6.8, 2H), 2.35 (q, *J* = 7.6, 2H), 1.17 (t, *J* = 7.6, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 136.4, 129.0, 128.8, 128.7, 127.4, 48.5, 36.3, 16.4, 11.2; MS (ESI) m/z calculated $[M+H]^+$: 203.12; found $[M+H]^+$: 203.19.

5-ethyl-1-phenyl-1*H*-tetrazole (**3j**)



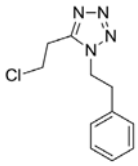
Colorless liquid, Yield: 149 mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 3H), 7.52 – 7.41 (m, 2H), 2.93 (q, *J* = 7.6, 2H), 1.38 (t, *J* = 7.6, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 133.8, 130.4, 129.9, 124.8, 17.5, 11.6; MS (ESI) m/z calculated $[M+H]^+$: 175.09; found $[M+H]^+$: 175.10.

3-(5-propyl-1*H*-tetrazol-1-yl)propanenitrile (**3k**)



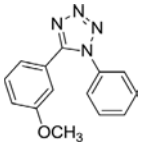
Colorless liquid, Yield: 99 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (t, *J* = 6.6, 2H), 3.13 (t, *J* = 6.6, 2H), 2.90 (t, *J* = 7.6, 2H), 1.97 – 1.81 (m, 2H), 1.06 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 116.1, 42.4, 24.8, 20.6, 18.7, 13.6; MS (ESI) m/z calculated $[M+H]^+$: 166.10; found $[M+H]^+$: 166.13.

5-(2-chloroethyl)-1-phenethyl-1*H*-tetrazole (**3l**)



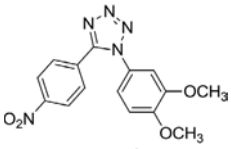
Brown liquid, Yield: 167 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, *J* = 5.1, 1.6, 3H), 7.01 – 6.93 (m, 2H), 4.54 (t, *J* = 6.7, 2H), 3.66 (t, *J* = 6.9, 2H), 3.22 (t, *J* = 6.7, 2H), 2.71 (t, *J* = 6.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 136.3, 129.1, 129.0, 128.7, 128.7, 127.5, 48.9, 40.6, 36.3, 26.3; MS (ESI) m/z calculated $[M+H]^+$: 236.08; found $[M+H]^+$: 237.29.

5-(3-methoxyphenyl)-1-phenyl-1*H*-tetrazole (**3m**)



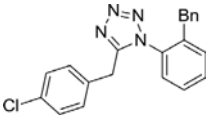
Brown liquid, Yield: 182 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, *J* = 7.8, 3H), 7.41 (d, *J* = 7.2, 2H), 7.14 (s, 1H), 7.11 – 6.95 (m, 4H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 153.5, 134.6, 130.5, 130.1, 129.9, 128.9, 125.4, 121.1, 117.6, 113.9, 55.4; MS (ESI) m/z calculated $[M+H]^+$: 253.10; found $[M+H]^+$: 253.18.

1-(3,4-dimethoxyphenyl)-5-(4-nitrophenyl)-1*H*-tetrazole (**3n**)



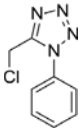
Yellow solid, Yield: 290 mg (87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.6, 2H), 7.83 (d, *J* = 8.6, 2H), 6.98 – 6.92 (m, 2H), 6.87 (dd, *J* = 8.5, 2.2, 1H), 3.98 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9, 151.1, 150.1, 149.3, 129.9, 129.7, 128.9, 126.6, 124.1, 123.7, 118.0, 111.3, 108.7, 56.4, 56.3; MS (ESI) m/z calculated $[M+H]^+$: 328.10; found $[M+H]^+$: 328.18.

1-(2-benzylphenyl)-5-(4-chlorobenzyl)-1*H*-tetrazole (**3o**)



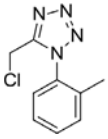
Yellow liquid, Yield: 318 mg (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (td, *J* = 7.6, 1.1, 1H), 7.41 (d, *J* = 7.6, 1H), 7.34 (td, *J* = 7.7, 1.2, 1H), 7.24 – 7.11 (m, 5H), 6.90 (dd, *J* = 7.8, 0.8, 1H), 6.86 (d, *J* = 8.4, 2H), 6.79 (d, *J* = 6.6, 2H), 3.62 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 139.1, 138.1, 133.5, 132.4, 132.3, 131.6, 131.4, 130.1, 128.9, 128.7, 128.7, 127.6, 127.4, 126.8, 37.4, 28.3; MS (ESI) m/z calculated $[M+H]^+$: 361.11; found $[M+H]^+$: 361.20.

5-(chloromethyl)-1-phenyl-1*H*-tetrazole (**3p**)



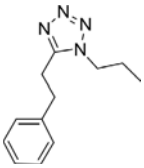
White solid, Yield: 141 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.47 (m, 5H), 4.83 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 133.1, 131.0, 130.1, 124.7, 31.2; MS (ESI) m/z calculated $[M+H]^+$: 195.04; found $[M+H]^+$: 195.26.

5-(chloromethyl)-1-(*o*-tolyl)-1*H*-tetrazole (**3q**)



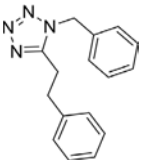
White solid, Yield: 150 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.6, 1H), 7.42 (d, *J* = 7.4, 1H), 7.38 (t, *J* = 8.0, 1H), 7.28 (d, *J* = 7.8, 1H), 4.66 (s, 2H), 2.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 135.5, 131.9, 131.6, 127.3, 126.6, 30.9, 17.3; MS (ESI) m/z calculated $[M+H]^+$: 209.05; found $[M+H]^+$: 209.26.

5-phenethyl-1-propyl-1*H*-tetrazole (**3r**)



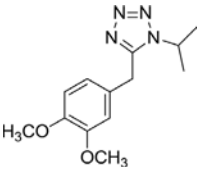
Yellow liquid, Yield: 199 mg (92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 12.9, 5.2, 2H), 7.23 (t, *J* = 7.2, 1H), 7.13 (d, *J* = 7.2, 2H), 3.93 (t, *J* = 7.3, 2H), 3.21 – 3.06 (m, 4H), 1.81 – 1.67 (m, 2H), 0.86 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 139.5, 128.8, 128.4, 126.9, 48.3, 33.7, 25.6, 22.9, 10.9; MS (ESI) m/z calculated $[M+H]^+$: 217.14; found $[M+H]^+$: 217.20.

1-benzyl-5-phenethyl-1*H*-tetrazole (**3s**)



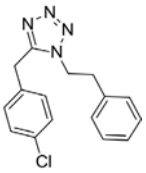
Brown solid, Yield: 190 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 3H), 7.33 – 7.23 (m, 3H), 7.15 – 7.05 (m, 4H), 5.22 (s, 2H), 3.04 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 139.4, 133.3, 129.2, 128.9, 128.8, 128.4, 127.4, 126.9, 50.5, 33.5, 25.6; MS (ESI) m/z calculated $[M+H]^+$: 265.14; found $[M+H]^+$: 265.21.

5-(3,4-dimethoxybenzyl)-1-isopropyl-1*H*-tetrazole (**3t**)



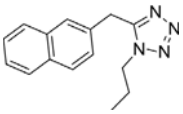
Brown solid, Yield: 148 mg (56%);^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.2, 1H), 6.71 (d, *J* = 8.3, 1H), 6.68 (d, *J* = 1.7, 1H), 4.48 (hept, *J* = 6.7, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.43 (d, *J* = 6.7, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 149.5, 148.5, 126.5, 120.4, 119.4, 111.4, 111.3, 111.1, 110.5, 55.9, 55.9, 50.7, 29.2, 22.4; MS (ESI) m/z calculated $[M+H]^+$: 263.14; found $[M+H]^+$: 263.20.

5-(4-chlorobenzyl)-1-phenethyl-1*H*-tetrazole (**3u**)



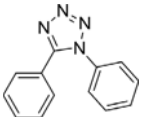
Yellow liquid, Yield: 189 mg (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 5H), 6.98 – 6.88 (m, 4H), 4.32 (t, *J* = 6.9, 2H), 3.68 (s, 2H), 3.08 (t, *J* = 6.9, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 136.4, 132.2, 129.8, 129.3, 129.1, 128.7, 127.5, 48.9, 36.1, 28.2; MS (ESI) m/z calculated $[M+H]^+$: 299.77; found $[M+H]^+$: 299.11.

5-(naphthalen-2-ylmethyl)-1-propyl-1*H*-tetrazole (**3v**)



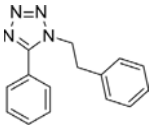
Colorless solid, Yield: 184 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.77 – 7.74 (m, 1H), 7.60 (s, 1H), 7.50 – 7.46 (m, 2H), 7.29 (dd, *J* = 8.4, 1.7, 1H), 4.43 (s, 2H), 4.07 (t, *J* = 7.4, 7.2, 2H), 1.78 – 1.67 (m, 2H), 0.79 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 133.4, 132.6, 131.3, 129.1, 127.8, 127.6, 127.1, 126.7, 126.4, 126.1, 48.9, 29.7, 22.8, 10.9; MS (ESI) m/z calculated $[M+H]^+$: 253.14; found $[M+H]^+$: 253.22.

1,5-diphenyl-1*H*-tetrazole (**3w**)



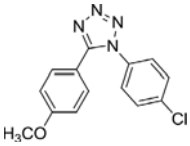
White solid, Yield: 124 mg (58%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.44 (m, 2H), 7.41 – 7.12 (m, 6H), 7.03 – 6.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 131.3, 130.5, 129.9, 129.0, 129.0, 128.9, 128.4, 125.3; MS (ESI) m/z calculated $[M+H]^+$: 223.09; found $[M+H]^+$: 223.18.

1-phenethyl-5-phenyl-1*H*-tetrazole (**3x**)



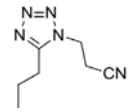
Yellow viscous liquid, Yield: 120 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 1H), 7.47 (t, *J* = 7.6, 2H), 7.32 – 7.28 (m, 3H), 7.26 – 7.20 (m, 2H), 7.01 – 6.92 (m, 2H), 4.63 (t, *J* = 7.1, 2H), 3.27 (t, *J* = 7.1, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 136.1, 131.1, 129.1, 128.9, 128.9, 128.7, 128.7, 127.3, 49.2, 36.1; MS (ESI) m/z calculated $[M+H]^+$: 251.12; found $[M+H]^+$: 251.23.

1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-tetrazole (**3y**)



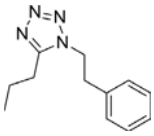
Brown soild, Yield: 180 mg (63 %); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 1H), 7.22 (d, *J* = 8.6, 2H), 7.09 (dd, *J* = 19.3, 8.6, 2H), 6.93 (d, *J* = 8.9, 1H), 6.87 – 6.76 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 146.4, 130.5, 130.2, 129.3, 126.6, 122.8, 114.9, 114.6, 114.4, 55.5; MS (ESI) m/z calculated $[M+H]^+$: 287.06; found $[M+H]^+$: 287.19.

3-(5-propyl-1*H*-tetrazol-1-yl)propanenitrile (**3z**)



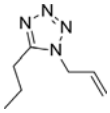
Colorless liquid, Yield: 103 mg (62%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (t, *J* = 6.6, 2H), 3.12 (t, *J* = 6.6, 2H), 2.90 (t, *J* = 7.6, 2H), 1.97 – 1.83 (m, 2H), 1.07 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 115.9, 42.4, 24.9, 20.7, 18.8, 13.7; MS (ESI) m/z calculated $[M+H]^+$: 166.10; found $[M+H]^+$: 166.26.

1-phenethyl-5-propyl-1*H*-tetrazole (**3aa**)



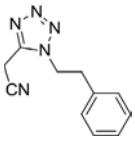
Colorless liquid, Yield: 153 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 3H), 7.02 – 6.96 (m, 2H), 4.46 (t, *J* = 6.9, 2H), 3.21 (t, *J* = 6.8, 2H), 2.31 (t, *J* = 7.6, 2H), 1.63 – 1.54 (m, 2H), 0.86 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 136.5, 128.9, 128.7, 127.4, 48.5, 36.2, 24.5, 20.3, 13.6; MS (ESI) m/z calculated $[M+H]^+$: 217.14; found $[M+H]^+$: 217.23.

1-allyl-5-propyl-1*H*-tetrazole (**3ab**)



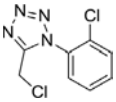
Yellow liquid, Yield: 79 mg (52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 – 5.89 (m, 1H), 5.36 (d, *J* = 10.3, 1H), 5.15 (d, *J* = 17.1, 1H), 4.96 (d, *J* = 5.6, 2H), 2.81 (t, *J* = 7.6, 2H), 1.99 – 1.76 (m, 2H), 1.03 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 130.2, 119.6, 49.2, 24.9, 20.4, 13.6; MS (ESI) m/z calculated $[M+H]^+$: 153.11; found $[M+H]^+$: 153.16.

2-(1-phenethyl-1*H*-tetrazol-5-yl)acetonitrile (**3ac**)



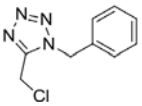
Colorless solid, Yield: 142 mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 6.96 (dd, *J* = 6.4, 2.8, 2H), 4.68 (t, *J* = 6.3, 2H), 3.24 (t, *J* = 6.4, 2H), 3.14 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 136.2, 129.5, 128.9, 128.0, 112.4, 49.9, 36.4, 12.9; MS (ESI) m/z calculated $[M-H]^-$: 212.24; found $[M-H]^-$: 212.16.

5-(chloromethyl)-1-(2-chlorophenyl)-1*H*-tetrazole (**3ad**)



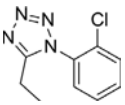
Yellow solid, Yield: 130 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0, 1.1, 1H), 7.66 – 7.61 (m, 1H), 7.59 – 7.48 (m, 2H), 4.75 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 132.9, 131.2, 130.9, 130.8, 129.1, 128.3, 31.1; MS (ESI) m/z calculated $[M+H]^+$: 229.00; found $[M+H]^+$: 229.01.

1-benzyl-5-(chloromethyl)-1*H*-tetrazole (**3ae**)



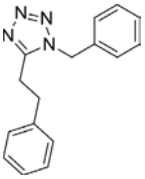
Colorless liquid, Yield: 130 mg (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 3H), 7.33 – 7.25 (m, 2H), 5.68 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 132.4, 129.4, 129.4, 127.9, 51.7, 31.4; MS (ESI) m/z calculated $[M+H]^+$: 209.05; found $[M+H]^+$: 209.05.

1-(2-chlorophenyl)-5-ethyl-1*H*-tetrazole (**3af**)



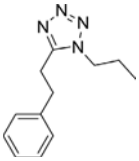
White solid, Yield: 125 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.4, 1H), 7.60 (td, *J* = 7.8, 1.6, 1H), 7.52 (td, *J* = 7.7, 1.4, 1H), 7.43 (dd, *J* = 7.8, 1.6, 1H), 2.78 (q, *J* = 7.6, 2H), 1.35 (t, *J* = 7.6, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3, 132.4, 131.6, 131.5, 130.9, 128.9, 128.2, 17.0, 11.3; MS (ESI) m/z calculated $[M+H]^+$: 209.05; found $[M+H]^+$: 209.11.

1-benzyl-5-phenethyl-1*H*-tetrazole (**3ag**)



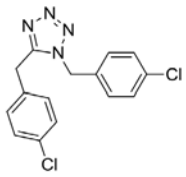
Colorless liquid, Yield: 182 mg (69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.31 – 7.20 (m, 3H), 7.12 – 7.07 (m, 2H), 7.05 (d, *J* = 7.3, 2H), 5.20 (s, 2H), 3.01 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 139.5, 133.4, 129.2, 128.9, 128.8, 128.4, 127.4, 126.9, 50.5, 33.4, 25.6; MS (ESI) m/z calculated $[M+H]^+$: 265.14; found $[M+H]^+$: 265.21.

5-phenethyl-1-propyl-1*H*-tetrazole (**3ah**)



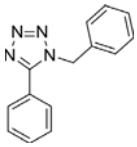
Colorless solid, Yield: 129 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.13 (d, *J* = 7.1, 2H), 3.93 (t, *J* = 7.2, 2H), 3.22 – 3.14 (m, 2H), 3.14 – 3.07 (m, 2H), 1.82 – 1.69 (m, 2H), 0.86 (t, J = 7.4, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 128.82, 128.4, 126.9, 48.3, 33.7, 25.6, 22.9, 10.9; MS (ESI) m/z calculated $[M+H]^+$: 217.14; found $[M+H]^+$: 217.16.

1,5-bis(4-chlorobenzyl)-1*H*-tetrazole (**3ai**)



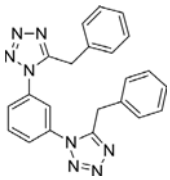
Colorless solid, Yield: 222 mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 4H), 6.98 (d, *J* = 8.3, 2H), 6.94 (d, *J* = 8.4, 2H), 5.31 (s, 2H), 4.13 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 135.1, 133.9, 131.8, 131.3, 129.7, 129.4, 129.3, 128.7, 50.3, 28.9; MS (ESI) m/z calculated $[M+H]^+$: 319.19; found $[M+H]^+$: 319.14.

1-benzyl-5-phenyl-1*H*-tetrazole (**3aj**)



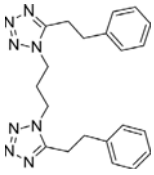
Colorless solid, Yield: 150 mg (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 3H), 7.54 – 7.47 (m, 2H), 7.38 – 7.32 (m, 3H), 7.16 (dd, *J* = 7.1, 2.2, 2H), 5.62 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 133.9, 131.4, 129.2, 129.2, 129.1, 128.9, 128.8, 127.2, 123.8, 123.5, 120.4, 51.4; MS (ESI) m/z calculated $[M+H]^+$: 237.11; found $[M+H]^+$: 237.12.

1,3-bis(5-benzyl-1*H*-tetrazol-1-yl)benzene (**3ak**)



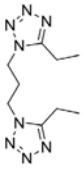
Yellow solid, Yield: 236 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, *J* = 8.1, 1H), 7.49 (dd, *J* = 8.1, 2.0, 2H), 7.26 – 7.17 (m, 7H), 7.04 (dd, *J* = 7.4, 1.4, 4H), 4.27 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 134.7, 133.6, 131.2, 129.1, 128.5, 127.8, 126.7, 121.9, 29.7; MS (ESI) m/z calculated $[M+Na]^+$: 417.17; found $[M+Na]^+$: 417.34.

1,3-bis(5-phenethyl-1*H*-tetrazol-1-yl)propane (**3al**)



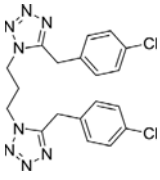
Yellow solid, Yield: 221 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 4H), 7.19 – 7.13 (m, 2H), 7.06 (d, *J* = 7.2, 4H), 3.80 (t, *J* = 6.6, 4H), 3.20 – 3.04 (m, 8H), 2.00 (p, *J* = 6.5, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 139.2, 128.8, 128.6, 128.5, 126.9, 43.2, 33.7, 28.0, 25.3; MS (ESI) m/z calculated $[M+H]^+$: 389.21; found $[M+H]^+$: 389.35.

1,3-bis(5-ethyl-1*H*-tetrazol-1-yl)propane (**3am**)



Colorless solid, Yield: 145 mg (61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (t, *J* = 6.7, 4H), 2.82 (q, *J* = 7.6, 4H), 2.57 (p, *J* = 6.6, 2H), 1.31 (t, *J* = 7.6, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 63.6, 43.5, 28.4, 16.7, 11.2; MS (ESI) m/z calculated $[M+H]^+$: 237.15; found $[M+H]^+$: 237.12.

1,3-bis(5-(4-chlorobenzyl)-1*H*-tetrazol-1-yl)propane (**3an**)

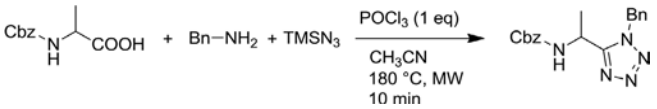


Colorless solid, Yield: 283 mg (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4, 4H), 7.09 (d, *J* = 8.4, 4H), 4.25 (s, 4H), 4.12 (t, *J* = 6.5, 4H), 2.19 (p, *J* = 6.5, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 133.9, 131.9, 129.8, 129.5, 43.7, 28.7, 28.2; MS (ESI) m/z calculated $[M+H]^+$: 429.10; found $[M+H]^+$: 429.20.

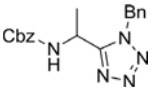
Experiments for Proving Stereochemical Retention

Synthesis of racemic compound: benzyl (1-(1-benzyl-1*H*-tetrazol-5-yl)ethyl)carbamate

Synthesized according to the general procedure.



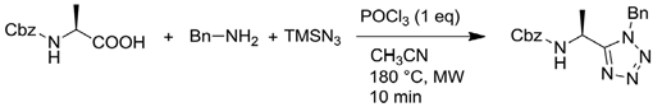
benzyl (1-(1-benzyl-1*H*-tetrazol-5-yl)ethyl)carbamate



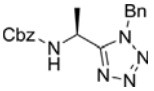
White solid, Yield: 225 mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.12 (m, 10H), 6.50 (s, 1H), 5.06 (s, 2H), 4.49 – 4.32 (m, 2H), 4.32 – 4.15 (m, 1H), 1.39 (d, J = 7.0, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 156.0, 137.9, 136.1, 128.7, 128.6, 128.3, 128.1, 127.6, 127.6, 67.1, 50.6, 43.5, 18.6; MS (ESI) m/z calculated $[M-H]^-$: 336.15; found $[M-H]^-$: 336.24. The racemate was separated on a Reprosil Chiral-OM column as described in the general methods. Enantiomer A, t_R =3.42 min (48%); Enantiomer B, t_R = 3.63 min (52%).

Synthesis of (*S*)-benzyl (1-(1-benzyl-1*H*-tetrazol-5-yl)ethyl)carbamate (**6**)

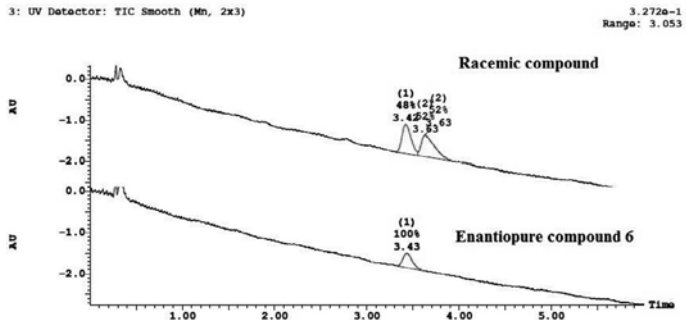
Synthesized according to the general procedure.



(*S*)-benzyl (1-(1-benzyl-1*H*-tetrazol-5-yl)ethyl)carbamate (**6**)



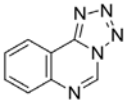
White solid, Yield: 220 mg (65%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 7H), 7.27 – 7.14 (m, 3H), 6.59 (s, 1H), 5.15 – 4.94 (m, 2H), 4.50 – 4.34 (m, 2H), 4.33 – 4.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 156.0, 137.9, 136.1, 128.7, 128.6, 128.3, 128.1, 127.6, 127.6, 67.1, 50.6, 43.5, 18.7; MS (ESI) m/z calculated $[M-H]^-$: 336.15; found $[M-H]^-$: 336.16. The enantiomeric excess was determined on a Reprosil Chiral-OM column as described in the general methods. Enantiomer A, t_R =3.43 min (>99.9%); Enantiomer B, t_R = 3.63 min (0%).



Synthesis of Fused Tetrazoles:

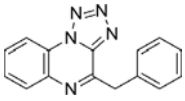
Synthesized according to the general procedure.

Tetrazolo[1,5-*c*]quinazoline (**9a**)



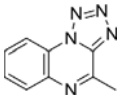
White solid, Yield: 86 mg (50%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.0, 1H), 8.15 (s, 1H), 7.87 – 7.76 (m, 2H), 7.56 (t, *J* = 7.4, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 149.0, 143.4, 135.0, 127.9, 127.4, 126.4, 122.5; MS (ESI) m/z calculated $[M+H]^+$: 172.05; found $[M+H]^+$: 172.08.

4-benzyltetrazolo[1,5-*a*]quinoxaline (**9b**)



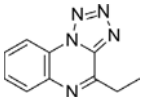
White solid, Yield: 159 mg (61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 2H), 7.31 – 7.24 (m, 5H), 7.22 – 7.17 (m, 2H), 4.24 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 136.3, 129.8, 129.6, 129.0, 129.0, 127.9, 127.3, 122.4, 35.9; MS (ESI) m/z calculated $[M+H]^+$: 262.10; found $[M+H]^+$: 262.32.

4-methyltetrazolo[1,5-*a*]quinoxaline (**9c**)



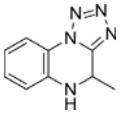
White solid, Yield: 109 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 7.5, 1.7, 1H), 8.21 (dd, *J* = 7.1, 2.1, 1H), 7.89 – 7.79 (m, 2H), 3.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 142.8, 136.8, 131.9, 130.3, 129.8, 129.7, 116.3, 21.7; MS (ESI) m/z calculated $[M+H]^+$: 186.07; found $[M+H]^+$: 186.32.

4-ethyltetrazolo[1,5-*a*]quinoxaline (**9d**)



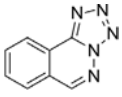
Pale yellow solid, Yield: 121 mg (61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 – 8.52 (m, 1H), 8.26 – 8.16 (m, 1H), 7.87 – 7.78 (m, 2H), 3.49 (q, *J* = 7.5, 2H), 1.58 (t, *J* = 7.5, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 136.8, 131.7, 130.7, 130.2, 129.9, 129.6, 116.2, 28.6, 11.3. MS (ESI) m/z calculated $[M+H]^+$: 200.09; found $[M+H]^+$: 200.26.

4-methyl-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline (**9e**)



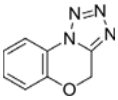
Colorless liquid, Yield: 119 mg (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.72 – 7.57 (m, 2H), 7.36 – 7.23 (m, 2H), 5.06 (q, *J* = 6.9, 1H), 1.84 (d, *J* = 6.9, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 138.3, 123.1, 115.3, 55.3, 19.2; MS (ESI) m/z calculated $[M+H]^+$: 188.09; found $[M+H]^+$: 188.13.

Tetrazolo[5,1-*a*]phthalazine (**9f**)



White solid, Yield: 82 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.76 (d, *J* = 8.0, 1H), 8.19 (d, *J* = 8.0, 1H), 8.14 (t, *J* = 7.6, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.23, 142.10, 134.88, 132.76, 128.62, 124.83, 124.58, 122.24; MS (ESI) m/z calculated $[M+H]^+$: 172.05; found $[M+H]^+$: 172.10.

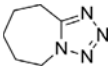
4H-benzo[b]tetrazolo[1,5-*d*][1,4]oxazine (**9g**)



Brown solid, Yield: 97 mg (56%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.4, 1H), 7.36 (td, *J* = 8.0, 1.5, 1H), 7.22 (t, *J* = 7.8, 1H), 7.18 (dd, *J* = 8.3, 0.7, 1H), 5.64 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 144.9, 130.0, 123.7, 121.9, 118.1, 117.2, 62.1; MS (ESI) m/z calculated $[M+H]^+$: 175.05; found $[M+H]^+$: 175.20.

Procedure for 9h and 9i:

A 20 ml microwave vial equipped with a magnetic stirring bar was charged with 6-aminohexanoic acid or 5-aminopentanoic acid (1.0 mmol) in CH_3CN (5 ml) and phosphoryl chloride (1.0 mmol) was added slowly followed by trimethylsilyl azide (1.5 equiv) at room temperature. The vial was sealed with a cap containing a septum and subjected to microwave heating at 180 °C till completion of reaction. [*attention: during irradiation, pressure develops*] Then the reaction mixture was poured into 50 mL of saturated $NaHCO_3$ and extracted 3 times with 25 mL of CH_2Cl_2. The solvent was removed under reduced pressure and residue was purified by silica gel flash chromatography using EtOAc–hexane or DCM:MeOH as eluent t. [*Caution: Addition of reagents and work-up must be done behind the glass-hood.*]



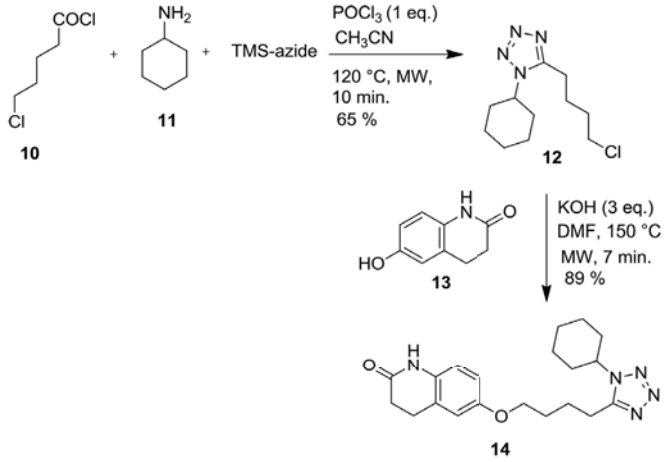
6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (**9h**)

Colorless solid, Yield: 105 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 – 4.44 (m, 2H), 3.18 – 3.05 (m, 2H), 2.07 – 1.95 (m, 2H), 1.94 – 1.85 (m, 2H), 1.84 – 1.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 49.3, 29.8, 27.1, 24.6, 24.2; MS (ESI) m/z calculated $[M+H]^+$: 139.09; found $[M+H]^+$: 139.11.

5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine (**9i**)

Colorless solid, Yield: 88 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (t, *J* = 6.1, 2H), 3.00 (t, *J* = 6.4, 2H), 2.19 – 2.07 (m, 2H), 2.06 – 1.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9, 45.5, 22.2, 20.7, 19.9; MS (ESI) m/z calculated $[M+H]^+$: 125.07; found $[M+H]^+$: 125.03.

Synthesis of Cilostazol:



Synthesis of 5-(4-chlorobutyl)-1-cyclohexyl-1H-tetrazole (**12**)

A 20 ml microwave vial equipped with a magnetic stirring bar was charged with 2-(4-chlorophenyl) acetic acid chloride (1.0 mmol), 2-phenylethanamine (1.0 mmol), and CH_3CN (5 ml) and stirred at room temperature for 30 min followed by the addition of phosphoryl chloride (1.0 mmol) at room temperature. Trimethylsilyl azide (1.5 equiv) was added in the reaction mixture and subjected to microwave heating at 120 °C for 10 minute. Then the reaction mixture was added to a 25 ml saturated $NaHCO_3$ solution and extracted in DCM. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography on silica gel (eluent: hexane/AcOEt) to afford the titled compound as a white solid. Yield: 157 mg (65%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 – 4.05 (m, 1H), 3.62 (t, *J* = 6.2, 2H), 2.89 (t, *J* = 7.5, 2H), 2.07 – 1.95 (m, 8H), 1.95 – 1.88 (m, 2H), 1.83 – 1.75 (m, 1H), 1.52 – 1.30 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 57.6, 44.2, 32.9, 31.5, 25.3, 24.8, 24.4, 22.5; MS (ESI) m/z calculated $[M+H]^+$: 243.13; found $[M+H]^+$: 243.24.

Synthesis of Cilostazol (**14**):

5-(4-chlorobutyl)-1-cyclohexyl-1*H*-tetrazole 13 (0.25 mmol) and 6-hydroxy-3,4-dihydroquinolin-2(1H)-one (0.275 mmol) were added to DMF (3 ml) in a 20 ml microwave vial followed by KOH (0.75 mmol) and subjected to microwave heating at 150 °C for 7 min. Then reaction mixture was poured into water and extracted in ethyl acetate. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography on silica gel (eluent: DCM/MeOH) to afford a cilostazol 14 as a colorless solid. Yield: 89%; 1H NMR (500 MHz, CDCl3) δ = 7.85 (s, 1H), 7.26 (s, 2H), 6.78 – 6.62 (m, 3H), 4.21 – 4.05 (m, 1H), 3.98 (t, *J* = 6.0, 2H), 3.49 (d, *J* = 5.1, 1H), 2.99 – 2.87 (m, 4H), 2.61 (m, 2H), 2.13 – 1.94 (m, 8H), 1.94 – 1.84 (m, 2H), 1.78 (d, *J* = 12.0, 1H), 1.50 – 1.32 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 154.8, 153.5, 130.8, 125.2, 116.0, 114.5, 113.1, 67.6, 57.6, 32.9, 30.6, 28.6, 25.8, 25.3, 24.8, 24.0, 23.0; MS (ESI) m/z calculated $[M+H]^+$: 370.42; found $[M+H]^+$: 370.34.

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