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CYSTEINE CATALYZED WATER MEDIATED ECO-FRIENDLY APPROACH FOR THE SYNTHESIS OF 5-SUBSTITUTED 1*H*-TETRAZOLE AND ITS DERIVATIVES

Vikas V. Borge,[a] Ramchandra G. Thorat,[a] Arun K. Kadu,[a] Vikas M. Bangade,[b] Parag S. Panse,[c] Gangadhar A. Meshram,[a] and Bhushan B. Popatkar[a]*

[a] Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai, Maharashtra 400 098, India.
[b] Department of Chemistry, The Institute of Science, Mumbai, Dr. Homi Bhabha State University, 15, Madame Cama Road, Mumbai, Maharashtra 400 032, India.
[c] Department of Chemistry, Dr. Ambedkar College, Deekshabhoomi, Nagpur, Maharashtra 440 010, India.
***Email: bpopatkar@chemistry.mu.ac.in

Abstract – Cysteine catalyzed, water mediated, one-pot multi-component protocol for the synthesis of 5-substituted 1*H*-tetrazole and its functional derivatives has been developed. The reaction between various aldehydes, hydroxylamine hydrochloride and sodium azide under the optimized reaction condition affords desired product(s). The utilization of water as a green solvent for the synthesis of the titled compounds is an important feature of this process. The moderate to high yield of the product, reaction at room temperature, exclusion of volatile toxic organic solvent and an operational simplicity are some of the advantages of this methodology.

Multi-component reactions (MCRs) all together involve three or more reactants which end up in the product and unite the elements of all starting materials in their frameworks. In present time, MCRs are considered to be an efficient strategy for the synthesis of small heterocyclic compounds.[1] MCRs continued as an important tool in the field of synthetic organic chemistry because of its advantages such as, atom economy, less reaction time, one-step, one-pot, energy saving, eco-friendly and leads to a targeted synthesis.[2]

Tetrazoles are synthetic five-membered aromatic heterocyclic ring which consists of one carbon and four nitrogen atoms.[3] Tetrazoles have the highest number of nitrogen atoms among the stable five membered

heterocycles because the pentazoles are highly explosive compounds even at low temperature.[4] Heterocyclic compounds inbuilt tetrazole skeleton have wide range of applications in the fields of chemical, material, medicinal and biological sciences.[5] Amongst, some of the tetrazole derivatives are recognized as antihypertensive, antiallergic, antibiotic,[6] anticonvulsants,[7] antibacterial,[8] antitumor,[9] antifungal,[10] anti-HIV,[11] antidiabetic,[12] antiviral,[13] antagonist,[14] anti-arrhythmic,[15] etc. in the field of medicinal chemistry. In addition to this, some known drugs such as Pemiroplast, Valsartan, Losartan, Candesartan, and Zolarsartan holds tetrazolyl moieties in their framework[16a-b] (Figure 1).

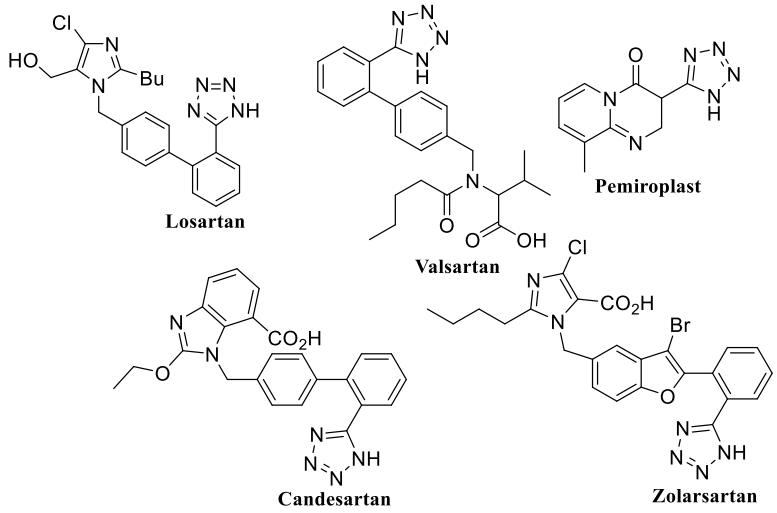


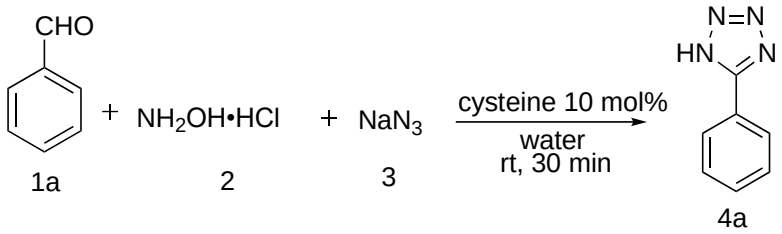
Figure 1. Structures of some of the known drugs contains tetrazole moiety

Furthermore, tetrazole scaffold is also used as an important ligand in the field of co-ordination chemistry,[17] information-recording systems,[18] explosives,[19] propellants,[20] stabilizers in photography,[21] anti-wears,[22] plant growth regulators, herbicides and fungicides,[23] high energy dense materials,[24] and in organocatalysis.[25]

By looking to the applications of tetrazole and its derivatives, abundant synthetic methodologies are available in the literature.[26,27] Among these, the [3+2] cycloaddition reaction between nitriles and sodium azide considered to be a fascinating and handy method. Beside this, the transition metal based salts/oxides such as $InCl_3$,[28a] ZnO,[28b] $Fe(OAc)_2$,[28c] $CdCl_2$,[28d] $ZrOCl_2$,[28e] $CuFe_2O_4$,[28f] Cu_2O,[28g] $TiCl_3$[16a] etc., inorganic complexes[29] of Fe, Co, Ni, Cu, Zn and Pd, metal-modified montmorillonites and zeolite[30] were successfully used as a catalysts in the synthesis of tetrazole. Likewise, Bronsted acids,[31] Lewis acids including $BF_3{\cdot}OEt_2$,[32a] $AlCl_3$,[32b] Amberlyst-15,[32c] organocatalyst like β-cyclodextrin[32d] and nanomaterials such as Mw-Pd/Co@CNT NPs,[32e] Fe_3O_4@SiO_2-TCT-PVA-Cu(II),[32f] Pt-NPs@VC[32g] and silica supported lanthanum triflate [$Ln(OTf)_3$-SiO_2][32h] were also employed as a catalyst in the synthesis of titled product.

Although, the literature is full with the several procedures which affords the tetrazole scaffold, but many above cited methodologies uses metal based expensive catalyst, toxic organic solvent and reflux reaction condition. As our interest is to developed an eco-friendly methodologies towards the synthesis of common heterocyclic compounds.[33a-d] Herein we wish to report cysteine catalyzed water mediated synthesis of 5-substituted 1*H*-tetrazole and its derivatives, under this condition the desired product(s) were obtained in moderate to high yield.

We initiated with a model reaction between benzaldehyde (1.0 mmol), hydroxylamine hydrochloride (1.0 mmol), sodium azide (1.0 mmol) and catalytic amount of cysteine (10 mol%) in aqueous medium at room temperature (Scheme 1). After 30 min, the progress of reaction was monitored on TLC and identified that, benzaldehyde was not consumed completely. Hence, the reaction condition was modified as benzaldehyde (1.0 mmol), hydroxylamine hydrochloride (1.5 mmol) and sodium azide (1.5 mmol) under this condition the benzaldehyde disappeared on TLC in a mentioned time (Scheme 1). After the completion of reaction the product was extracted in ethyl acetate. Then the solvent was evaporated thus to obtained a product in moderate yield. Here, we have investigated an effect of various solvents and the concentration of various catalysts on the model reaction (Scheme 1). To improvise the reaction condition, screening of various solvent and study of percent loading of the catalyst was done. It was noticed that, the reaction in water gives less yield when 5 mol% of the catalyst added (Table 1, ent. 1) as the loading % of catalyst increases, surprisingly the chemical yield of expected product marginally increased under the given reaction condition with less reaction time (Table 1, ent. 10). Subsequently, in absolute ethanol and in methanol under the mentioned reaction condition the yield of 5-phenyl-1*H*-tetrazole received in lesser amount (Table 1, ent. 3, 5). Later, absolute ethanol/water and methanol/water (1:1) ratio solvent system was prepared and screened for its efficacy but again the received product yield was in less amount (Table 1, ent. 2,4). Also, the reactions were carried out in various organic solvents and noticed the formation of expected product in good to moderate yield (Table 1, ent. 6, 7, 8, 9). With increase in the % loading of the catalyst, the product yield was increased slightly (Table 1, ent. 11, 12). The reactions were also been carried out under the refluxed and without catalyst condition but results not changed significantly (Table 1, ent. 13, 14). Similarly, the reaction was also carried out with the addition of glycine as a catalyst and observed the formation of expected product in the moderate yield (Table 1, ent. 15). Lastly, *p*- toluenethiol and 1-decanethiol catalytic reactivity was checked under the given reaction condition (Scheme 1) but the time took to complete the reaction was more with less yield of the desired product which was further decreased in case of 1-decanethiol may be due to its solubility in the water (Table 1, ent. 16, 17). Hence, we selected (Table 1, ent. 10) as optimized reaction condition for the synthesis of 5-phenyl-1*H*-tetrazole and its derivatives.



Scheme 1. Cysteine catalyzed, water mediated green synthesis of 5-phenyl-1*H*-tetrazole

Table 1. Effect of various solvents and the concertation of the various catalysts on the model reaction (Scheme 1)

Entry[a]	Catalysts	Solvent (ml)	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	cysteine	H_2O	5	40	62
2	cysteine	EtOH: H_2O (1:1)	5	50	60
3	cysteine	EtOH	5	35	62
4	cysteine	MeOH:H_2O (1:1)	5	35	64
5	cysteine	MeOH	5	40	60
6	cysteine	DMF	5	42	71
7	cysteine	DMSO	5	40	68
8	cysteine	THF	5	45	72
9	cysteine	DCM	5	55	68
10	**cysteine**	**H_2O**	**10**	**30**	**77**
11	cysteine	H_2O	15	30	78
12	cysteine	H_2O	20	30	78
13	cysteine	H_2O[c]	10	30	78
14	nc[d]	H_2O	-	38	47
15	glycine	H_2O	10	36	62
16	*p*-MeC_6H_4SH	H_2O	10	38	50
17	$C_{10}H_{21}SH$	H_2O	10	42	30

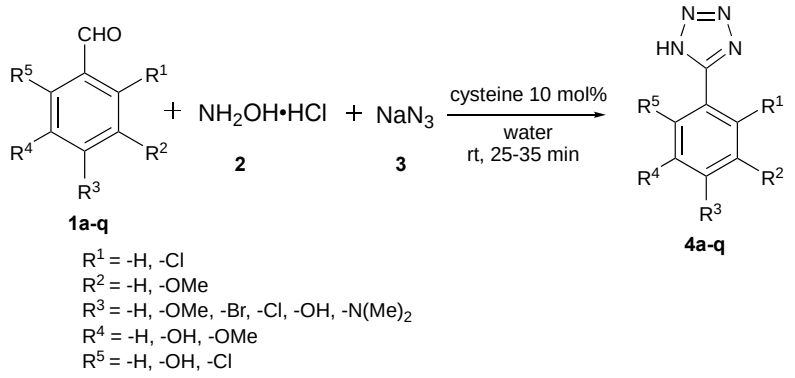
[a] Reaction of benzaldehyde (1 mmol), hydroxylammine hydrochloride (1.5 mmol), sodium azide (1.5 mmol) in presence of various catalyst as well as in absence of cysteine in 5 mL H_2O at room temperature and under reflux condition

[b] Isolated yield of the product

[c] Reaction was carried out under refluxed condition

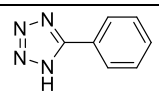
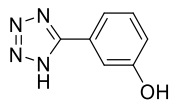
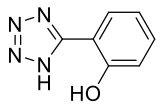
[d] No catalyst

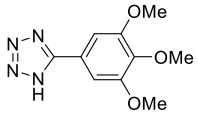
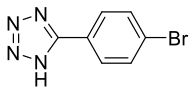
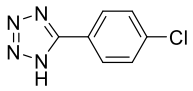
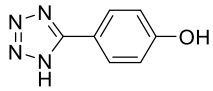
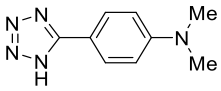
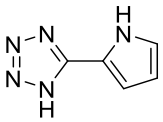
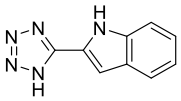
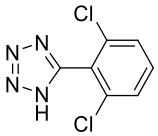
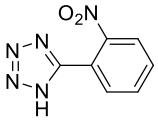
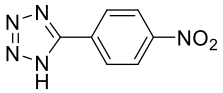
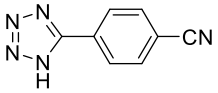
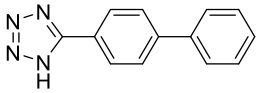
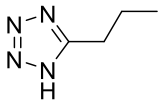
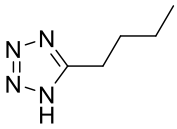
Under the optimized reaction condition (Table 1, ent. 10) the aromatic, heterocyclic and aliphatic aldehydes are evaluated for substrates scope. (Table 2, ent. 4a-4q). As a whole, various substituted aldehydes reacted smoothly with hydroxylamine hydrochloride and sodium azide which resulted into its corresponding tetrazole derivatives with moderate to high yield. The reaction of benzaldehyde and biphenylaldehyde under the given circumstance (Scheme 2) affords moderate yield of the product (Table 2, ent. 4a & 4o). The aldehyde carrying electron donating groups to the aromatic ring such as hydroxy, methoxy, *N*,*N*-dimethyl groups (Table 2, ent. 4b, 4c, 4d, 4g & 4h) were able to give considerably lesser yield, but when aldehyde holds electron withdrawing groups such as bromo, chloro, nitro and cyano then the obtained yield of the product was increased (Table 2, ent. 4e, 4f, 4m & 4n). But, in case of 2,6-dichlorobenzaldehyde and 2-nitrobenzaldehyde the final yield of the product was comparatively less (Table 2, ent. 4k & 4l) this result in low yield of the product may be due to the steric hindrance. Furthermore, heterocyclic aldehydes *viz.*, pyrrole-2-carboxaldehyde and indole-2-carboxaldehyde also reacted efficiently and affords the related tetrazole analogues in appreciable yield (Table 2, ent. 4i & 4j). Lastly, to check the reactivity of aliphatic aldehydes we used *n*-propanal and *n*-butanal which reacted sluggishly with hydroxylamine hydrochloride and sodium azide and gave very low chemical yield of the corresponding product (Table 2, ent. 4p & 4q).



Scheme 2. Cysteine catalyzed, water mediated green synthesis of 5-phenyl-1*H*-tetrazole and its derivatives

Table 2. Synthesis of tetrazole derivatives under the optimized reaction condition (Scheme 2)

Entry[a]	Product	Time (min)	Yield[b] (%)	Melting Point (°C)[Lit.]
4a		30	77	217–219[34a-b]
4b		33	76	149-150[34c]
4c		33	72	224–225[34d]

4d		35	70	202-203[28f]
4e		28	81	234-235[34g]
4f		25	83	264–265[34f]
4g		28	74	234–235[34e]
4h		35	71	132-134[34c]
4i		32	75	224-226[34h]
4j		32	76	161-163[34c]
4k		34	75	112-115[34g]
4l		35	72	155[34h]
4m		30	82	216[34h]
4n		32	78	255-258[34i]
4o		29	78	248-249 [34j]
4p		38	35	65-67[34l]
4q		40	25	42-43[34k]

[a]Reaction was carried at room temperature.

[b]Isolated yield of the product

We have established cysteine catalyzed water mediated simple, efficient and environmentally benign one-pot three-component methodology for the synthesis of 5-substituted 1*H*-tetrazole and its derivatives. Aldehyde owning electron withdrawing and donating groups under the optimized reaction condition resulted into high to moderate product yield respectively. The ease of handling of catalyst, easy workup procedure, inclusion of water as eco-friendly solvent, overall mild reaction condition and moderate to high yield of the products are the noteworthy features of this process. Consequently, it represents a convenient, economic, green and efficient development for the synthesis of 5-substituted 1*H*-tetrazole and its derivatives.

EXPERIMENTAL

General: All the required chemicals and catalyst were purchased from Merck and used directly without further purification. Crude solvents were distilled prior to use. The progress of reactions was monitored by thin layer chromatography with TLC Silica gel 60 F_{254} purchased from Merck. Column chromatography was performed on silica gel (60-120 mesh). Melting points were recorded by an *open glass capillary sealed at one end melting point tube* and are uncorrected. The IR spectra were recorded on PerkinElmer Frontier FT-IR spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Ultra shield, Avance II model NMR spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in $CDCl_3$/DMSO-d_6 as a solvent. Mass spectra were recorded on AB SCIEX QTRAP 3200 model LC-MS spectrophotometer.

General procedure for the synthesis of tetrazoles: In 50 mL round bottom flask, substituted aldehydes (1 mmol), hydroxylamine hydrochloride (1.5 mmol), sodium azide (1.5 mmol), water as a solvent (10 mL) and cysteine (0.01 g, 10 mol%) as a catalyst were added. The reaction was stirred at room temperature for 25-40 min. The progress of reaction was monitored by TLC using EtOAc: pet ether system (30:70). After the completion of reaction (as followed by TLC), the product was extracted in EtOAc. The crude product thus obtained was recrystallized from EtOH to afford desired product in pure form.

5-Phenyl-1*H*-tetrazole (4a): White solid; mp 216-217 °C[34a-b]; IR (solid, neat, ν_{max}, cm^{-1}) 3063, 3178, 2982, 2220, 1713, 1598, 1381, 749; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.00 (d, 12.2 Hz, 3H), 6.72 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.45, 129.47, 117.94, 116.61, 112.99; LC-MS *m/z* (M+1) 147.5; Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.40; H, 4.05; N, 38.26.

3-(1*H*-Tetrazol-5-yl)phenol (4b): White solid; mp 149-150 °C[34c]; IR (solid, neat, ν_{max}, cm^{-1}) 3280, 1677, 1581, 1451, 1156, 940, 779; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.91 (s, 1H), 7.19-6.82 (m, 3H), 6.72 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.45, 148.47, 134.18, 129.47, 117.94, 116.60, 112.99; LC-MS *m/z* (M-1) 161.4; Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.74; H, 3.66; N, 34.47.

2-(1*H*-Tetrazol-5-yl)phenol (4c): White solid; mp 224–225 °C[34d]; IR (solid, neat, ν_{max}, cm^{-1}) 3344, 1617, 1578, 1491, 1259, 987, 751; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.88 (s, 1H), 7.34-7.23 (m, 1H), 7.18 (d, *J* = 7.6, 1H), 7.04-6.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.04, 153.01, 131.32, 130.78, 119.87, 116.70, 116.39; LC-MS *m/z* (M-1) 161.3; Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.73; H, 3.64; N, 34.45.

5-(3,4,5-Trimethoxyphenyl)-1*H*-tetrazole (4d): Brown solid; mp 202-203 °C[28f]; IR (solid, neat, ν_{max}, cm^{-1}) 3558, 3469, 3255, 2973, 2946, 2845, 1714, 1584, 1330, 1120, 965, 710; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 2H), 5.23 (s, 1H), 3.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.67, 148.81, 137.41, 132.37, 131.73, 124.47, 121.45, 114.58, 63.86, 55.62; LC-MS *m/z* (M-1) 235.2; Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.76; H, 5.05; N, 23.61.

5-(4-Bromophenyl)-1*H*-tetrazole (4e): Yellow solid; mp 234-235 °C[34g]; IR (solid, neat, ν_{max}, cm^{-1}) 3096, 3067, 2876, 1700, 1530, 1349, 1199, 728; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 9.3 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.67-7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.27, 134.65, 129.07, 128.21, 124.53; LC-MS *m/z* (M^+) 223.6; Anal. Calcd for $C_7H_5BrN_4$: C, 37.36; H, 2.24; Br, 35.51; N, 24.90. Found: C, 37.26; H, 2.22; Br, 35.42; N, 24.81.

5-(4-Chlorophenyl)-1*H*-tetrazole (4f): Brown solid; mp 252–253 °C[34f]; IR (solid, neat, ν_{max}, cm^{-1}) 3280, 3096, 2996, 2114, 1701, 1530, 1349, 1085, 933, 666; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76-8.70 (m, 1H), 8.50 (d, *J* = 8.7, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.21, 148.80, 137.40, 134.69, 130.42, 129.03, 128.61, 128.19, 124.48; LC-MS *m/z* (M-1) 179.7; Anal. Calcd for $C_7H_5ClN_4$: C, 46.56; H, 2.79; Cl, 19.63; N, 31.02. Found: C, 45.26; H, 2.71; Cl, 19.52; N, 30.94.

4-(1*H*-Tetrazol-5-yl)phenol (4g): White solid; mp 234–235 °C[34e]; IR (solid, neat, ν_{max}, cm^{-1}) 3361, 3137, 2987, 1604, 1515, 1271, 947, 640; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 3H), 6.83 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.69, 150.12, 132.50, 128.74, 124.39, 115.83; LC-MS *m/z* (M^+) 162.9; Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.74; H, 3.64; N, 34.47.

***N*,*N*-Dimethyl-4-(1*H*-tetrazol-5-yl)aniline (4h):** White solid; mp 132-134 °C[34c]; IR (solid, neat, ν_{max}, cm^{-1}) 3363, 3132, 2856, 1601, 1515, 1360, 1165, 950, 808; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 10.6 Hz, 2H, 1H), 8.22 (d, *J* = 7.6 Hz, 2H, 1H), 7.79 (s, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 2.97 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.48, 150.36, 148.69, 137.33, 134.81, 130.43, 128.54, 128.25, 124.28, 119.49, 111.86, 40.10; LC-MS *m/z* (M^+) 189.5; Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.05; H, 5.74; N, 36.92.

5-(1*H*-Pyrrol-2-yl)-1*H*-tetrazole (4i): White solid; mp 224-226 °C[34h]; IR (solid, neat, ν_{max}, cm^{-1}) 3363, 3178, 2982, 2220, 1713, 1598, 1381, 1036, 749; ^1H NMR (300 MHz, $CDCl_3$) δ 13.05 (s, 1H), 7.42 (s, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 6.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.09, 161.02, 134.81, 131.63,

130.49, 127.10, 114.41, 108.36; LC-MS *m/z* (M^+) 135.5; Anal. Calcd for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.35; H, 3.65; N, 51.71.

2-(1*H*-Tetrazol-5-yl)-1*H*-indole (4j): White solid; mp 161-163 °C[34c]; IR (solid, neat, ν_{max}, cm^{-1}) 3384, 3354, 3156, 3051, 3010, 1681, 1633, 1518, 1452, 1097, 928, 743; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.16 (s, 1H), 7.59 (s, 2H), 7.31 (s, 1H), 7.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.47, 135.06, 130.57, 129.36, 128.16, 126.26, 121.82, 119.97, 117.71, 111.71, 106.32; LC-MS *m/z* (M^+) 185.7; Anal. Calcd for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.25; H, 3.72; N, 37.75.

5-(2,6-Dichlorophenyl)-1*H*-tetrazole (4k): Brown solid; mp 112-115 °C[34g]; IR (solid, neat, ν_{max}, cm^{-1}) 3378, 3074, 2974, 1694, 1615, 1513, 1301, 1275, 1024, 956, 850, 683; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 1H), 6.52 (s, 1H), 6.42 (d, *J* = 8.7 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.18, 144.82, 126.11, 118.71, 118.35; Anal. Calcd for $C_7H_4Cl_2N_4$: C, 39.10; H, 1.88; Cl, 32.97; N, 26.06. Found: C, 38.91; H, 1.12; Cl, 32.85; N, 25.96.

5-(2-Nitrophenyl)-1*H*-tetrazole (4l): Yellow solid; mp 155 °C[34h]; IR (solid, neat, ν_{max}, cm^{-1}) 3329, 2920, 2850, 2358, 1716, 1456, 1348, 750, 705, 669; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, *J* = 9.8 Hz, 1H), 7.73 (d, *J* = 14.7 Hz, 1H), 7.52 (s, 1H), 5.97 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6): δ 166.85, 154.36, 153.77, 142.37, 139.85, 138.38, 132.57, 130.87, 129.68, 129.64, 128.88, 127.98; Anal. Calcd for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64; O, 16.74. Found: C, 43.91; H, 2.57; N, 36.55; O, 16.65.

5-(4-Nitrophenyl)-1*H*-tetrazole (4m): Yellow solid; mp 216 °C[34h]; IR (solid, neat, ν_{max}, cm^{-1}) 3321, 2972, 2883, 2358, 1591, 1541, 1377, 1087, 879, 669; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, *J* = 9.8 Hz, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 6.04 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 1H NMR (75 MHz, DMSO) δ 157.78, 151.72, 142.61, 131.34, 129.66; Anal. Calcd for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64; O, 16.74. Found: C, 43.89; H, 2.55; N, 36.57; O, 16.67.

4-(1*H*-Tetrazol-5-yl)benzonitrile (4n)[34i]: White solid; mp 255-258 °C; IR (solid, neat, ν_{max}, cm^{-1}) 2920, 2850, 2358, 1535, 1448, 1184, 1078, 960, 686; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.0 Hz, 2H), 7.61 (s, 2H), 6.56 (s, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 161.02, 134.81, 131.63, 130.49, 127.10, 114.41, 108.36; Anal. Calcd for $C_8H_5N_5$: C, 56.14; H, 2.94; N, 40.92. Found: C, 56.08; H, 2.86; N, 40.87.

5-(Biphenyl-4'-yl)-1*H*-tetrazole (4o): White solid; mp 248-249 °C[34j]; IR (solid, neat, ν_{max}, cm^{-1}) 2970, 2920, 2360, 1614, 1541, 1309, 1124, 829, 715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 16.7 Hz, 1H), 7.35 (s, 2H), 7.15-7.28 (m, 4H), 7.04 (d, *J* = 3.9 Hz, 2H), 6.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.45, 141.23, 139.08, 129.93, 129.84, 129.20, 128.78, 128.25; Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.19; H, 4.48; N, 25.13.

5-Propyl-1*H*-tetrazole (4p): White solid; mp 65-67 °C[34l]; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 2H), 1.43-1.39 (m, 2H), 1.23-1.16 (m, 3H); Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.96. Found: C, 42.92; H, 7.25; N, 49.98.

5-Butyl-1*H*-tetrazole (4q): White solid; mp 42-43 °C[34k]; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 2H), 1.46-1.28 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H); Anal. Calcd for $C_5H_{10}N_4$: C, 47.60; H, 7.99; N, 44.41. Found: C, 47.72; H, 8.06; N, 44.53.

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