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Ultrasound Assisted Synthesis of 1,5-Disubstituted Tetrazoles Containing Propargyl or 2-Azidophenyl Moieties via Ugi-Azide Reaction †

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Abstract: A series of ten 1,5-disubstituted-1*H*-tetrazoles (1,5-DS-T) were synthesized via isocyanide-based multicomponent reactions (IMCR) Ugi-azide in low to good yields (30–85%), using propargyl amine or 2-azidobenzaldehyde as component using ultrasound irradiation (USI) as alternative energy source. 1,5-DS-T are useful heterocyclic moieties present in many bioactive compounds and drugs. Moreover 1,5-DS-T are used as bidentate ligands, in coordination chemistry, metal-organic framework science, bioimaging, photo-imaging, explosives, propellants, high energy materials. The generated products can be used as synthetic platforms for subsequent post-transformations.

Keywords: 1,5-disubstituted-1*H*-tetrazoles; isocyanide-based multicomponent reactions; Ugi-azide; ultrasound irradiation

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1. Introduction

MCR are chemical reactions where at least starting materials react to form a single product that containing all or most of the atoms of the starting materials. MCRs are flexible, diversity-oriented and one-pot process that can be used to prepare products with new different diversification points [1]. In this context, the isocyanide-based multicomponent reactions (IMCRs) are most relevant for the prepare synthetic platforms [2]. One type of these is the Ugi-azide reaction, between an aldehyde or ketone, an amine, the carboxylic acid used in the classical Ugi reaction is replaced by hydrazoic acid (generated in situ from NaN_3/$TMSN_3$) and an isocyanide to obtained 1,5-disubstituted-1*H*-tetrazoles (1,5-DS-T). In the same way, the 1,5-DS-T are privileged heterocycles that are bioisosteres of the *cis*-amide bond in peptides due to their similar physochemical properties in living systems. mimicking their bioactive conformations, for this reason are of high interest in medicinal chemistry. The most common methodologies for the synthesis of 1,5-DS-T are (i) the [2 + 3] azide–cyanide cycloadition reactions and (ii) Ugi-azide reaction. However, the latter allows to obtain highly functionalized products and under milder conditions [3].

Compounds with alkyne moieties are present in natural products isolated from plants and marine organisms and pharmaceuticals as important pharmacophores [4,5]. The incorporation of propargyl moiety have important application in medicinal chemistry and they are incorporated in drugs such as pargyline 1, selegiline 2, and rasagyline 3 [6,7]. Moreover, this group is used as small-molecule probes to increase the covalent interaction, detection and identification of protein targets (4) [8]. On the other hand, organic azides are not found in nature, to our knowledge, only the antiviral drug Zidovunide 5 incorporates this group (Figure 1) [9].

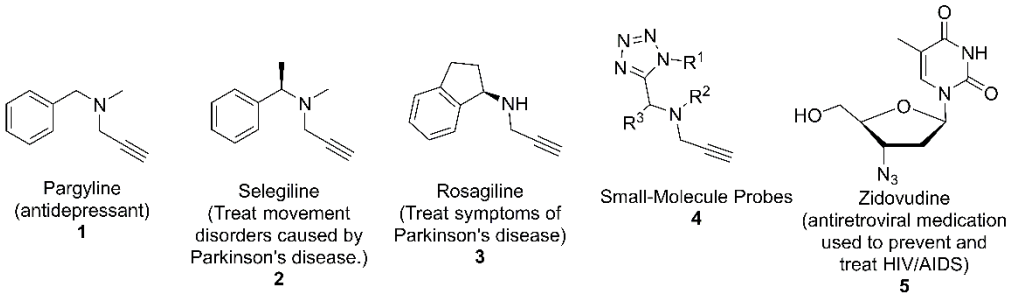


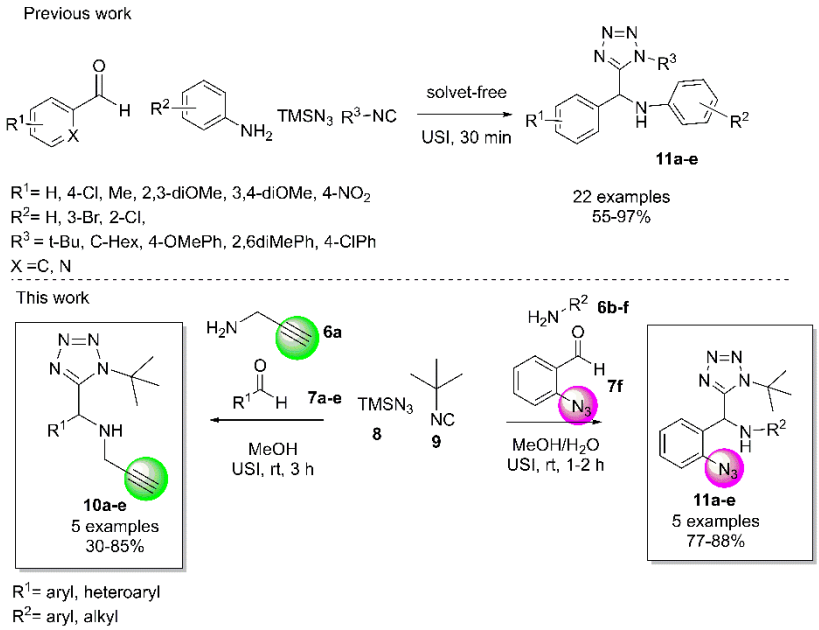
Figure 1. Selected bioactive compounds.

Compounds that incorporate azide or propargyl moeties are useful intermediates in organic synthesis and can be used as synthetic platforms for subsequent post-transformations [10–13]. In this context, multicomponent reactions (MCRs) are a powerful tool for the synthesis of compounds that incorporate these functional groups [14,15].

2. Results and Discussion

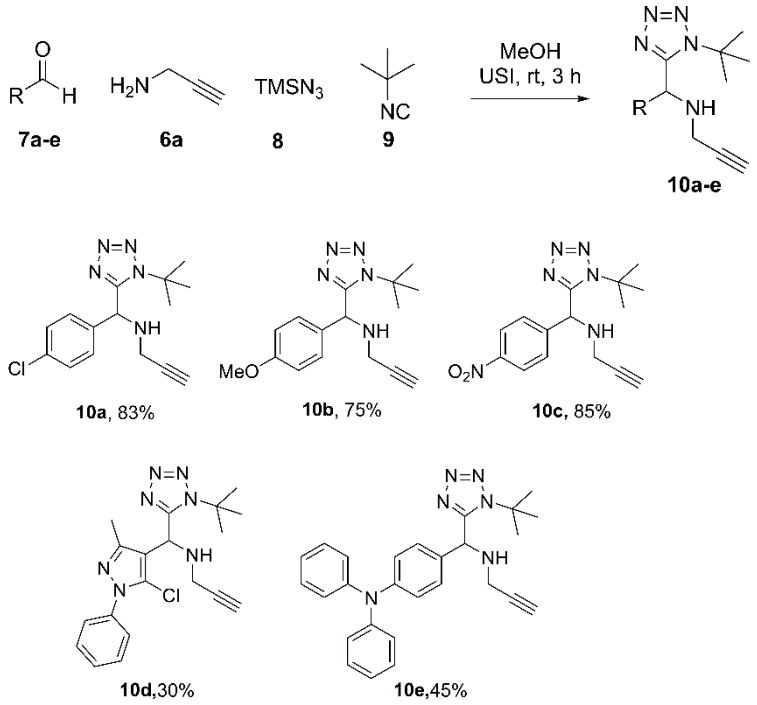
In recent years, our research group reported the first ultrasound assisted Ugi-azide and Grobke Blackburn Bienayme IMCRs and demonstrated their role in accelerates the rate of reaction and decrease reaction times frequently taking place at ambient temperature in mild conditions [16–22].

Following in this research area in 2017 we reported the first Ultrasound assisted Ugi-azide under solvent-free using benzaldehydes and anilines [23]. Herein, we describe the ultrasound assisted synthesis of 1,5-DS-T that incorporate propargyl (**10a–e**) or 2-azidophenyl (**11a–e**) moieties in yields (30–88%) via a IMCR of type Ugi-azide reaction (Scheme 1).



Scheme 1. Previous work and this work.

As depicted in Scheme 2, the 1,5-DS-T that containing propargyl moiety were obtained in 30–85% yields. Aldehydes of different steroelectronic nature were tested. The best yields were obtained using benzaldehydes (**10a–c**). Unfortunately, with 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde and 4-(diphenylamino)benzaldehyde, low yields were obtained (**10d**,**e**) (Scheme 2).



Scheme 2. 1,5-DS-T that containing propargyl moiety.

Figures 2 and 3 show the ^{1}H and ^{13}C NMR spectra of the 1,5-DS-T **10a**.

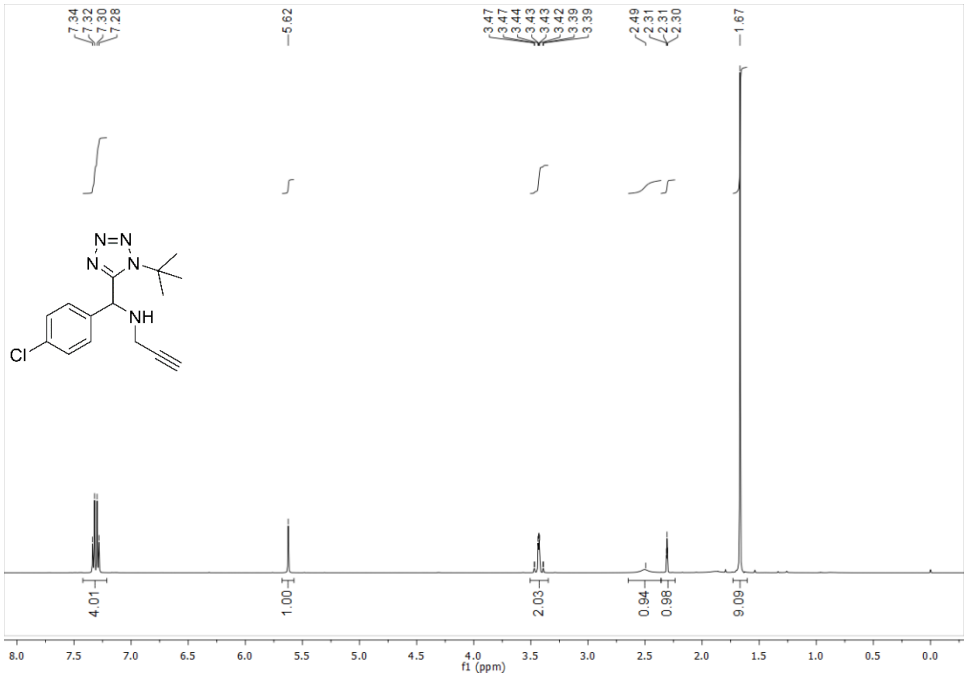


Figure 2. ^{1}H NMR spectrum of 1,5-DS-T **10a**.

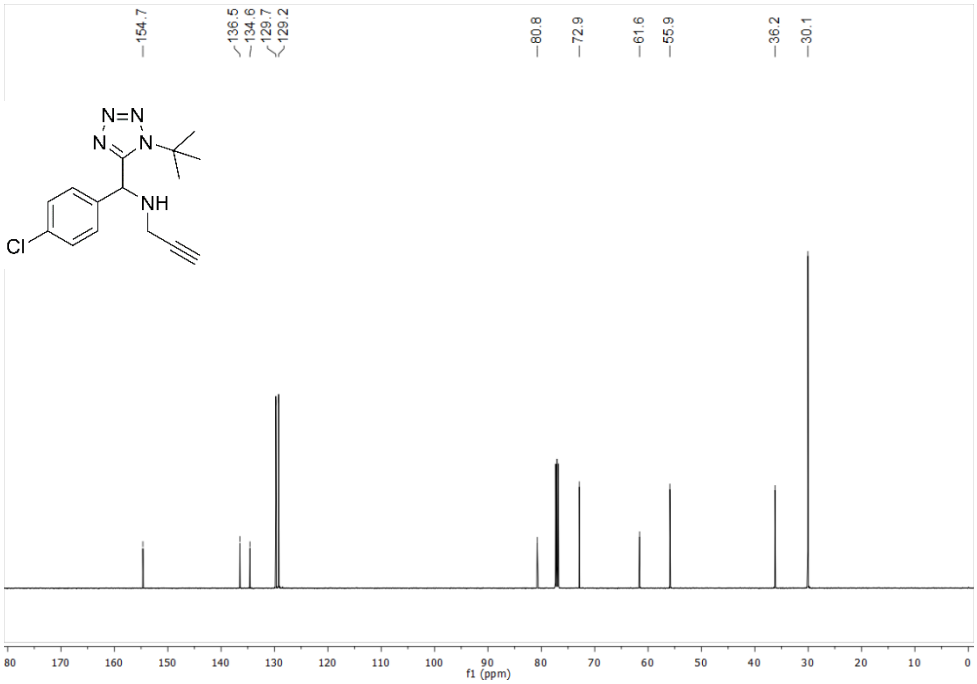
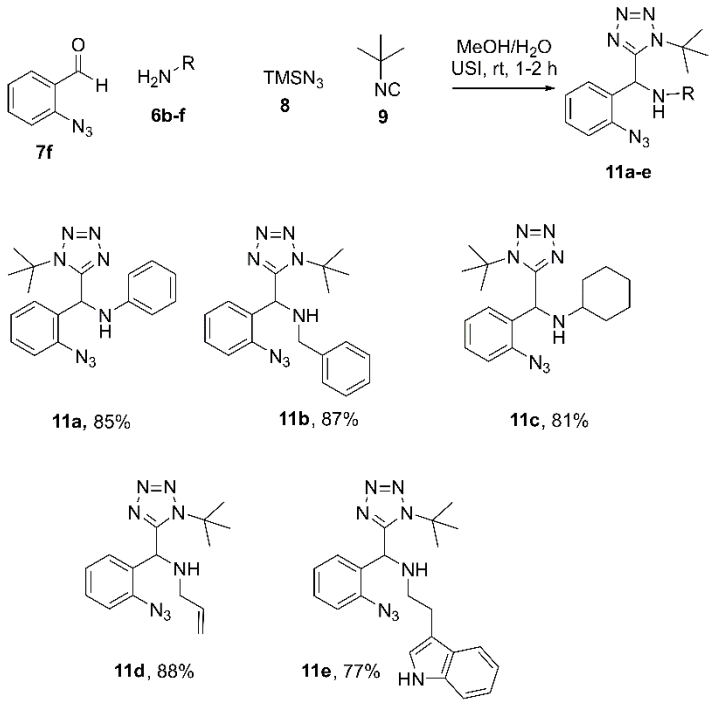


Figure 3. ^{13}C NMR spectrum of 1,5-DS-T **10a**.

1,5-DS-T that containing azidophenyl moiety were obtained in 30–85% yields (Scheme 3). For this case, amines with different steroelectronic nature were tested. The products were obtained in good yield (77–88%)



Scheme 3. 1,5-DS-T that containing azidophenyl moiety.

Figures 4 and 5 show the ^{1}H and ^{13}C NMR spectra of the 1,5-DS-Ts **11a**.

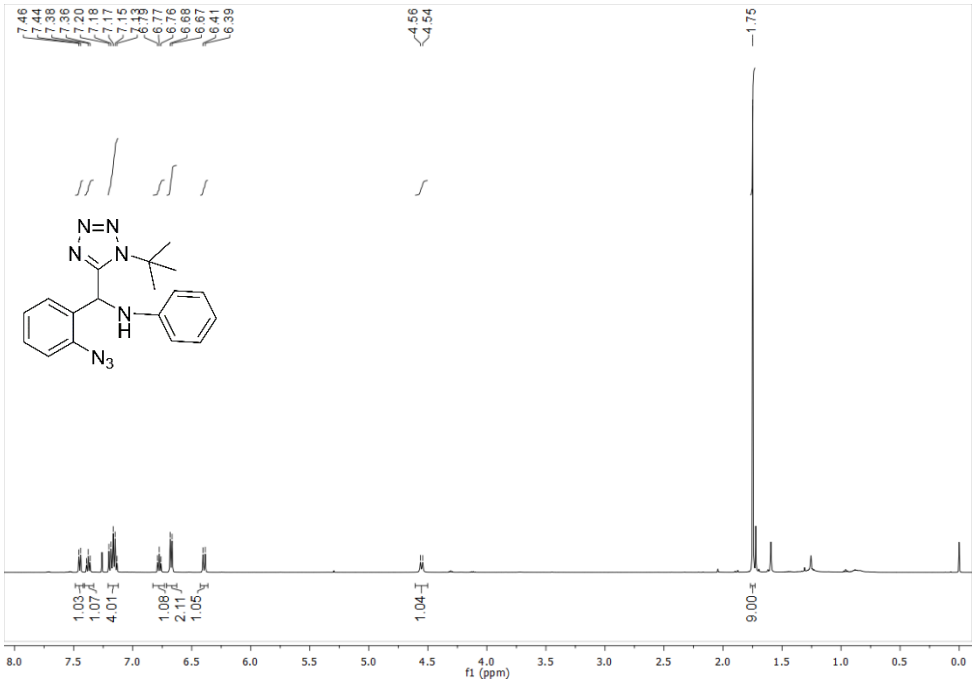


Figure 4. [1]H NMR spectrum of 1,5-DS-T **11a**.

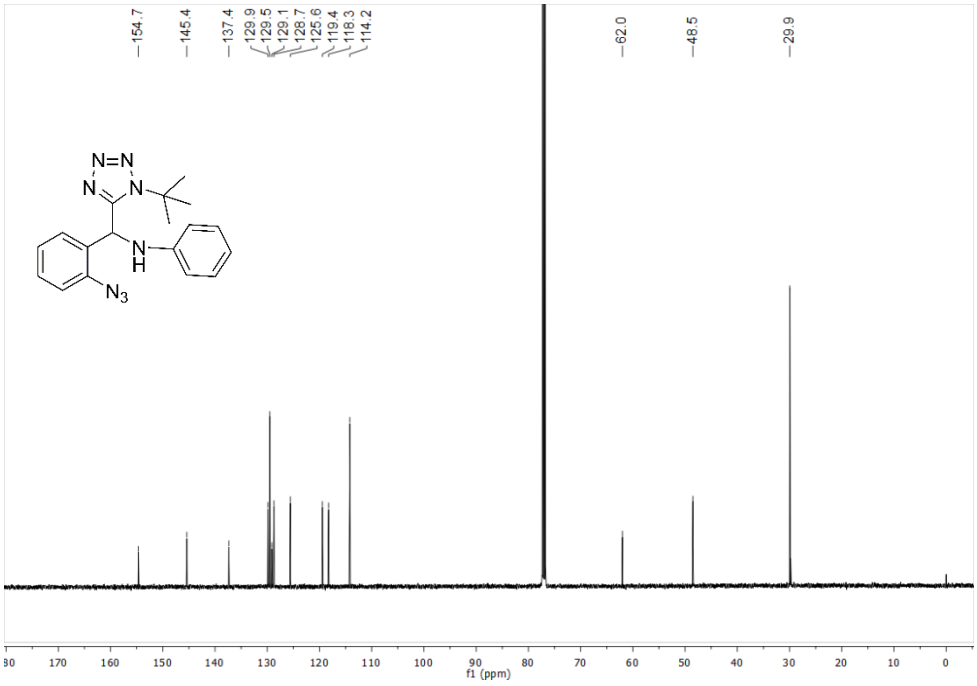


Figure 5. [13]C NMR spectrum of 1,5-DS-T **11a**.

As can be seen the generated products (**10a**–**e** and **11a**–**e**) can be used as synthetic platforms for subsequent post-transformations due to the different diversification points.

3. Conclusions

A series of ten 1,5-disubstituted-1*H* tetrazoles in low to good yields was synthesized, via one-pot Ugi-azide reaction under ultrasound irradiation at mild conditions. The products herein described may find application in various fields, but mainly in medicinal chemistry since they contain tetrazole moiety. It is noteworthy that Ugi-azide reaction can be used to prepare products with new different diversification points.

4. Experimental Section

4.1. General Information, Instrumentation, and Chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance III spectrometers (500 or 400 MHz). The solvent used was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for ^{1}H NMR spectra is trimethylsilane at 0.0 ppm. The internal reference for ^{13}C NMR spectra is $CDCl_3$ at 77.0 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1–14719. IR spectra were acquired on a Perkin Elmer 100 spectrometer using an Attenuated Total Reflectance (ATR) method with neat compounds. The absorbance peaks are reported in reciprocal centimeters (υ_{max}/cm^{-1}). Reaction progress was monitored by Thin-Layer Chromatography (TLC) on precoated silica-gel 60 F_{254} plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (EtOAc) were used to run TLC and for measuring retention factors (R_f). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane with EtOAc in different proportions (*v*/*v*) as the mobile phase. All reagents were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package. The purity for all the synthesized products (up to 99%) was assessed by NMR.

*4.2. Synthesis and Characterization of 1,5-DS-T (***10a**–**e***)*

General procedure 1 (GP1): In a 10 mL sealed CEM Discover™ microwave reaction tube containing a solution of the corresponding aldehyde (1.0 equiv.), in MeOH (1.0 M) were added sequentially propargylamine (1.1 equiv.), $TMSN_3$ (1.1 equiv.) and *tert*-butyl isocyanide isocyanide (1.1 equiv.). The reaction mixture was placed in a water bath of a sonicator cleaner. Then, the mixture was US-irradiated at room temperature for 3 h. Then, the solvent was removed to dryness under vacuum. The residue was diluted in AcOEt (5.0 mL) and washed with brine (3 × 15 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed to dryness under vacuum. The crude product was purified by flash chromatography using mixtures of hexanes–EtOAc to afford the corresponding 1,5-DS-1H-T Xx-x.

4.2.1. N-((1-(tert-butyl)-1H-tetrazol-5-yl)(4-chlorophenyl)methyl)prop-2-yn-1-amine (**10a**)

Based on *GP-1*, 0.023 g 4-chlorobenzaldehyde (0.164 mmol), 0.012 mL propargylamine (0.178 mmol), 0.025 mL azidotrimethylsilane (0.178 mmol) and 0.020 mL *tert*-butyl isocyanide (0.178 mmol) were reacted together in MeOH (0.1 mL) to afford the 1,5-DS-T **10a** (41.0 mg, 83%) as a white gum; Rf = 0.29 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 5.62 (s, 1H), 3.51–3.33 (m, 2H), 2.50 (s, 1H), 2.31 (t, *J* = 2.3 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 154.7, 136.5, 134.6, 129.7, 129.2, 80.8, 72.9, 61.6, 55.9, 36.2, 30.1.

4.2.2. N-((1-(tert-butyl)-1H-tetrazol-5-yl)(4-methoxyphenyl)methyl)prop-2-yn-1-amine (**10b**)

Based on *GP-1*, 0.023 mL 4-methoxybenzaldehyde (0.187 mmol), 0.013 mL propargylamine (0.206 mmol), 0.029 mL azidotrimethylsilane (0.206 mmol) and 0.023 mL *tert*-butyl isocyanide (0.206 mmol) were reacted together in MeOH (0.1 mL) to afford the 1,5-DS-T **10b** (42.0 mg, 75%) as a white gum; Rf = 0.27 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.59 (s, 1H), 3.79 (s, 3H), 3.51–3.32 (m, 2H), 2.47 (s, 1H), 2.29 (t, *J* = 2.4 Hz, 1H), 1.67 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 159.7, 155.1, 129.9, 129.6, 114.4, 81.1, 72.6, 61.5, 56.0, 55.3, 36.1, 30.0.

4.2.3. N-((1-(tert-butyl)-1H-tetrazol-5-yl)(4-nitrophenyl)methyl)prop-2-yn-1-amine (**10c**)

Based on *GP-1*, 0.024 g 4-nitrobenzaldehyde (0.155 mmol), 0.011 mL propargylamine (0.171 mmol), 0.024 mL azidotrimethylsilane (0.171 mmol) and 0.019 mL *tert*-butyl isocyanide (0.171 mmol) were reacted together in MeOH (0.1 mL) to afford the 1,5-DS-T **10c** (42.0 mg, 85%) as a white gum; Rf = 0.24 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 5.76 (s, 1H), 3.51–3.32 (m, 2H), 2.59 (s, 1H), 2.34 (t, J = 2.5 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 154.1, 147.9, 145.0, 129.4, 124.2, 80.4, 73.3, 61.8, 55.8, 36.4, 30.1.

4.2.4. N-((1-(tert-butyl)-1H-tetrazol-5-yl)(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)methyl)prop-2-yn-1-amine (**10d**)

Based on *GP-1*, 0.023 g 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.155 mmol), 0.008 mL propargylamine (0.115 mmol), 0.016 mL azidotrimethylsilane (0.115 mmol) and 0.013 mL *tert*-butyl isocyanide (0.115 mmol) were reacted together in MeOH (0.1 mL) to afford the 1,5-DS-T **10d** (12.0 mg, 30%) as a white gum; Rf = 0.24 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.52–7.44 (m, 4H), 7.43–7.38 (m, 1H), 5.67 (s, 1H), 3.62–3.46 (m, 2H), 2.53 (s, 1H), 2.29 (t, *J* = 2.5 Hz, 1H), 2.27 (s, 3H), 1.73 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 153.7, 148.9, 137.9, 129.1, 128.4, 126.4, 125.0, 114.0, 80.6, 72.7, 61.9, 48.2, 36.1, 29.8, 13.5.

4.2.5. 4-((1-(tert-butyl)-1H-tetrazol-5-yl)(prop-2-yn-1-ylamino)methyl)-N,N-diphenylaniline (**10e**)

Based on *GP-1*, 0.035 g 4-(diphenylamino)benzaldehyde (0.128 mmol), 0.010 mL propargylamine (0.141 mmol), 0.019 mL azidotrimethylsilane (0.141 mmol) and 0.016 mL *tert*-butyl isocyanide (0.141 mmol) were reacted together in MeOH (0.1 mL) to afford the 1,5-DS-T **10e** (25.0 mg, 45%) as a white gum; Rf = 0.27 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.29–7.20 (m, 4H), 7.20–7.13 (m, 2H), 7.08–6.98 (m, 8H), 5.56 (s, 1H), 3.53–3.38 (m, 2H), 2.27 (t, *J* = 2.3 Hz, 1H),1.69 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 155.1, 148.1, 147.3, 131.1, 129.3, 129.1, 124.7, 123.3, 123.2, 81.1, 72.6, 61.5, 56.2, 36.3, 30.0.

*4.3. Synthesis and Characterization of 1,5-DS-T (***11a**–**e***)*

General procedure 2 (GP2): In a 10 mL sealed CEM Discover™ microwave reaction tube containing a solution of 2-azidobenzaldehyde (1.0 equiv.), in a mixture MeOH:H_2O (1:1 *v*/*v*, 0.5 M) were added sequentially the corresponding amine (1.1 equiv.), $TMSN_3$ (1.1 equiv.) and *tert*-butyl isocyanide (1.1 equiv.). The reaction mixture was placed in a water bath of a sonicator cleaner. Then, the mixture was US-irradiated at room temperature for 60 min. Then, the solvent was removed to dryness under vacuum. The residue was diluted in AcOEt (5.0 mL) and washed with brine (3 × 15 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed to dryness under vacuum. The crude product was purified by flash chromatography using mixtures of hexanes–EtOAc to afford the corresponding 1,5-DS-1H-T Xx-x.

4.3.1. N-((2-azidophenyl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)aniline (**11a**)

Based on *GP-2*, 0.030 g 2-azidobenzaldehyde (0.204 mmol), 0.020 mL aniline (0.224 mmol), 0.030 mL azidotrimethylsilane (0.224 mmol) and 0.025 mL *tert*-butyl isocyanide (0.224 mmol) were reacted together in MeOH (0.2 mL) to afford the 1,5-DS-T **11a** (60.0 mg, 85%) as a white solid; Rf = 0.30 (hexanes-AcOEt = 4:1 *v*/*v*); m.p. 197–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.21–7.12 (m, 4H), 6.77 (t, *J* = 7.7 Hz, 1H), 6.40 (d, *J* = 9.7 Hz, 1H), 4.55 (d, *J* = 9.7 Hz, 1H), 1.75 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 13C NMR (126 MHz, CDCl3) δ 154.7, 145.4, 137.4, 129.9, 129.5, 129.1, 128.7, 125.6, 119.4, 118.3, 114.2, 62.0, 48.5, 29.9.

4.3.2. 1-(2-azidophenyl)-N-benzyl-1-(1-(tert-butyl)-1H-tetrazol-5-yl)methanamine (**11b**)

Based on *GP-2*, 0.030 g 2-azidobenzaldehyde (0.204 mmol), 0.024 mL benzylamine (0.224 mmol), 0.030 mL azidotrimethylsilane (0.224 mmol) and 0.025 mL *tert*-butyl isocyanide (0.224 mmol) were reacted together in MeOH (0.2 mL) to afford the 1,5-DS-T **11b** (64.0 mg, 87%) as a white solid; Rf = 0.29 (hexanes-AcOEt = 4:1 *v*/*v*); m.p. 109–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.39–7.28 (m, 6H), 7.28–7.24 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.11 (t, k = 7.7 Hz, 1H), 5.62 (s, 1H), 3.84 (d, *J* = 13.0 Hz, 1H), 3.70 (d, *J* = 13.0 Hz, 1H), 2.53 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 155.0, 138.7, 137.6, 130.1, 129.7, 18.9, 128.6, 128.3, 127.4, 125.6, 118.5, 61.4, 51.7, 51.0, 29.7.

4.3.3. N-((2-azidophenyl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)cyclohexanamine (**11c**)

Based on *GP-2*, 0.030 g 2-azidobenzaldehyde (0.204 mmol), 0.026 mL cyclohexanamine (0.224 mmol), 0.030 mL azidotrimethylsilane (0.224 mmol) and 0.025 mL *tert*-butyl isocyanide (0.224 mmol) were reacted together in MeOH (0.2 mL) to afford the 1,5-DS-T **11c**(59.0 mg, 81%) as a white solid; Rf = 0.35 (hexanes-AcOEt = 4:1 *v*/*v*); m.p. 162–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.34 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.80 (s, 1H), 2.41–2.15 (m, 2H), 1.97–1.90 (m, 1H), 1.90–1.82 (m, 1H), 1.78–1.67 (m, 2H), 1.66 (s, 9H), 1.61–1.53 (m, 1H), 1.25–1.07 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 155.8, 137.2, 130.5, 129.5, 128.9, 125.5, 118.5, 61.3, 54.8, 48.9, 33.3, 33.0, 29.8, 25.9, 24.8, 24.7.

4.3.4. N-((2-azidophenyl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)prop-2-en-1-amine (**11d**)

Based on *GP-2*, 0.030 g 2-azidobenzaldehyde (0.204 mmol), 0.017 mL allylamine (0.224 mmol), 0.030 mL azidotrimethylsilane (0.224 mmol) and 0.025 mL *tert*-butyl isocyanide (0.224 mmol) were reacted together in MeOH (0.2 mL) to afford the 1,5-DS-T **11d** (56.0 mg, 88%) as a white gum; Rf = 0.28 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.40–7.31 (m, 1H), 7.26–7.16 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 5.99–5.87 (m, 1H), 5.67 (s, 1H), 5.19–5.11 (m, 2H), 3.32 (dd, J = 13.8, 5.5 Hz, 1H), 3.17 (dd, J = 13.8, 6.8 Hz, 1H), 2.35 (s, 1H), 1.63 (s, 9H).; ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 155.0, 137.4, 135.9, 130.1, 129.7, 128.8, 125.5, 118.5, 117.2, 61.4, 51.1, 50.6, 29.8.

4.3.5. N-((2-azidophenyl)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)-2-(1H-indol-3-yl)ethan-1-amine (**11e**)

Based on *GP-2*, 0.030 g 2-azidobenzaldehyde (0.204 mmol), 0.034 g tryptamine (0.224 mmol), 0.030 mL azidotrimethylsilane (0.224 mmol) and 0.025 mL *tert*-butyl isocyanide (0.224 mmol) were reacted together in MeOH (0.2 mL) to afford the 1,5-DS-T **11e** (43.0 mg, 77%) as a white gum; Rf = 0.20 (hexanes-AcOEt = 4:1 *v*/*v*); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.12 (s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.36–7.28 (m, 3H), 7.21–7.13 (m, 5H), 7.09–6.99 (m, 3H), 5.67 (s, 1H), 2.98 (t, J = 6.5 Hz, 2H), 2.94–2.90 (m, 2H), 1.62 (s, 8H).; ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 13C NMR (126 MHz, CDCl3) δ 155.3, 137.4, 136.4, 129.9, 129.6, 128.8, 127.3, 125.5, 122.0, 119.2, 118.8, 118.3, 113.4, 111.2, 61.5, 52.3, 48.1, 29.8, 25.9.

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