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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 Ugi-azide isocyanide-based multicomponent reactions (IMCR) in low to good yields (30–85%), using propargyl amine or 2-azidobenzaldehyde as a component, and using ultrasound irradiation (USI) as an 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, and 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 the starting materials react to form a single product, containing all or most of the atoms of the starting materials. MCRs are flexible, diversity-oriented, and a one-pot process that can be used to prepare products with new diversification points [1]. In this context, the isocyanide-based multicomponent reactions (IMCRs) are the most relevant for the preparation of 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 obtain 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, and for this reason they are of great 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 obtaining highly functionalized products, as well as 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 a propargyl moiety has important applications in medicinal chemistry and they are incorporated in drugs such as pargyline 1, selegiline 2, and rasagyline 3 [6,7]. Moreover, this group are 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].

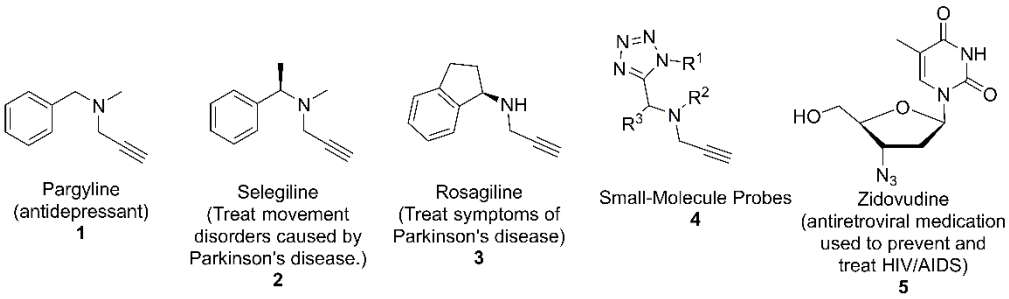


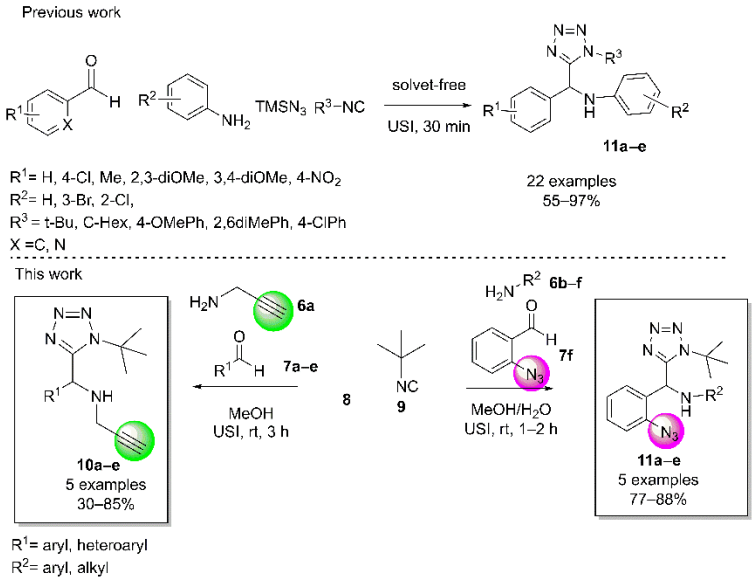
Figure 1. Selected bioactive compounds.

Compounds that incorporate azide or propargyl moieties 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

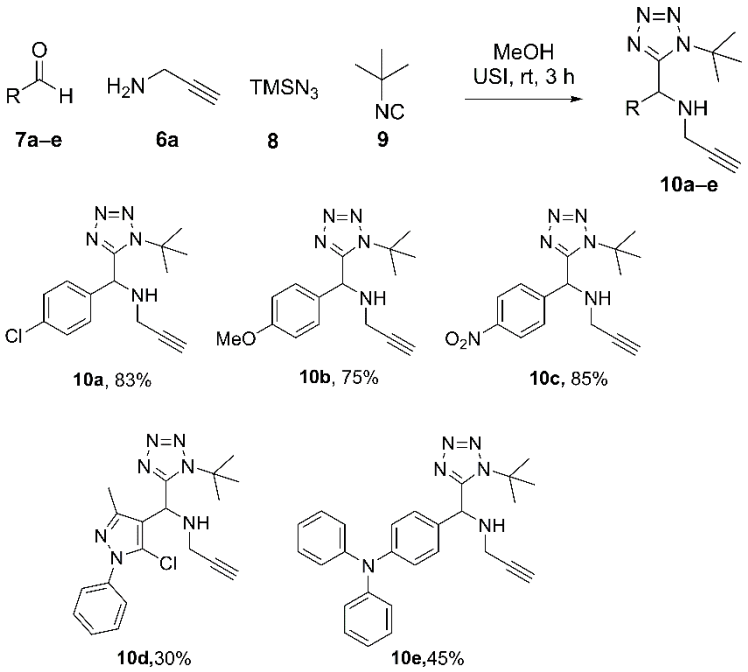
In recent years, our research group reported the first ultrasound assisted Ugi-azide and Grobke Blackburn Bienayme IMCRs and demonstrated their role in accelerating the rate of reaction and decreasing the reaction times, frequently taking place at ambient temperature and in mild conditions [16–22].

Subsequently, 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 incorporates propargyl (**10a–e**) or 2-azidophenyl (**11a–e**) moieties in yields (30–88%) via a IMCR Ugi-azide-type reaction (Scheme 1).



Scheme 1. Previous work and this work.

As depicted in Scheme 2, the 1,5-DS-T containing a 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 containing a propargyl moiety.

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

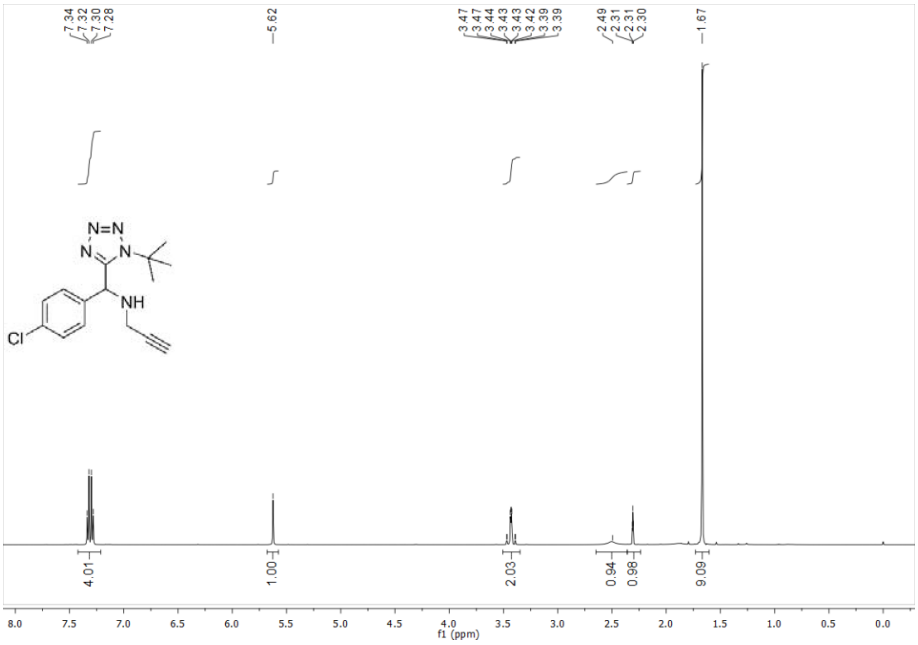


Figure 2. ^{1}H NMR spectrum of 1,5-DS-T **10a**.

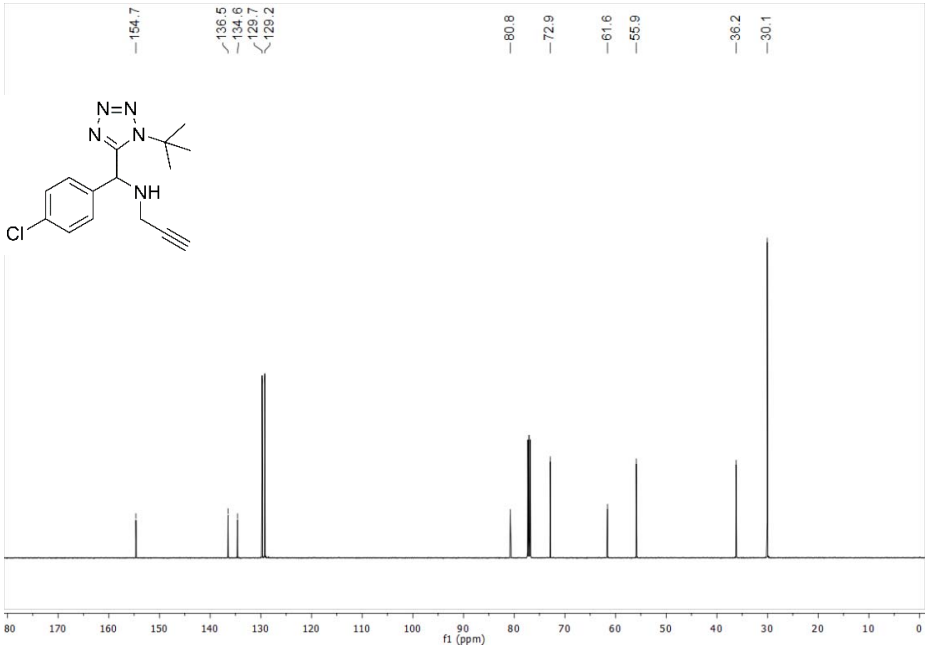
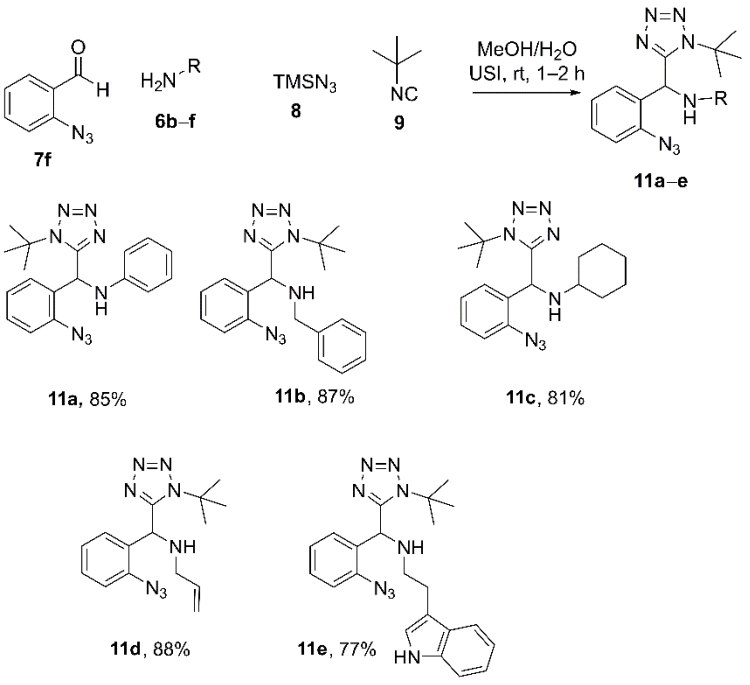


Figure 3. ^{13}C NMR spectrum of 1,5-DS-T **10a**.

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



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

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

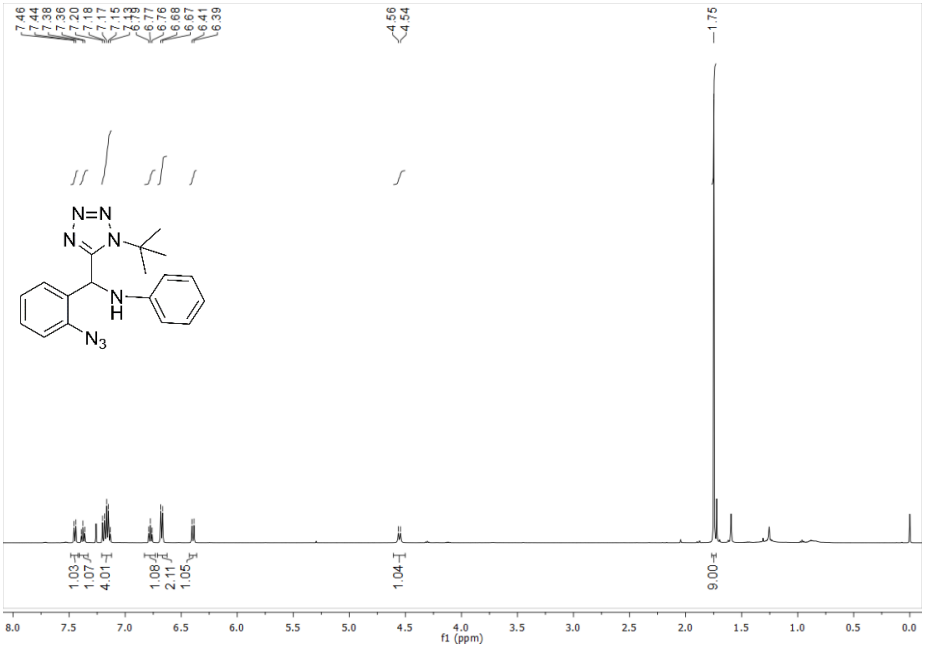


Figure 4. ^{1}H NMR spectrum of 1,5-DS-T **11a**.

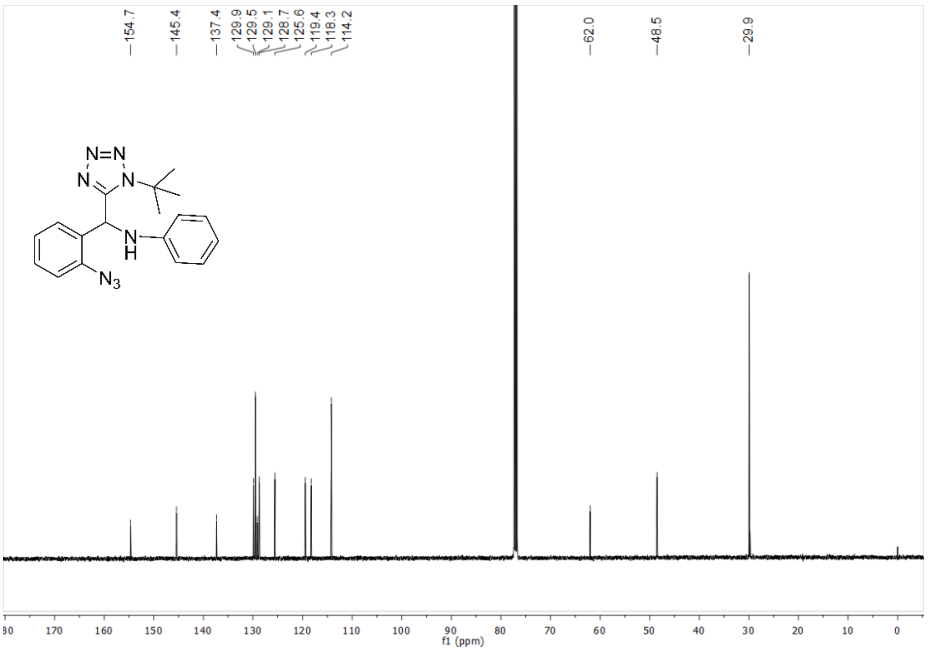


Figure 5. ^{13}C NMR spectrum of 1,5-DS-T **11a**.

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 were synthesized, via a one-pot Ugi-azide reaction under ultrasound irradiation at mild conditions. The products herein described may find applications in various fields, but mainly in medicinal chemistry, since they contain a tetrazole moiety. It is noteworthy that the Ugi-azide reaction can be used to prepare products with new 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}). The 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), with 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 of 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^{TM} microwave reaction tube containing a solution of the corresponding aldehyde (1.0 equiv.), to MeOH (1.0 M) were sequentially added propargylamine (1.1 equiv.), $TMSN_3$ (1.1 equiv.), and *tert*-butyl isocyanide isocyanide (1.1 equiv.). The reaction mixture was placed in the water bath of a sonicator cleaner. Then, the mixture was US-irradiated at room temperature for 3 h. Then, the solvent was removed to dry 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 dry under vacuum. The crude product was purified by flash chromatography using mixtures of hexanes–EtOAc to afford the corresponding 1,5-DS-1*H*-T Xx-x.

4.2.1. N-((1-(*tert*-Butyl)-1*H*-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; R_f = 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)-1*H*-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; R_f = 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)-1*H*-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; R_f = 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)-1*H*-tetrazol-5-yl)(5-chloro-3-methyl-1-phenyl-1*H*-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; R_f = 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)-1*H*-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; R_f = 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^{TM} microwave reaction tube containing a solution of 2-azidobenzaldehyde (1.0 equiv.), to a mixture of MeOH:H_2O (1:1 *v*/*v*, 0.5 M) were sequentially added the corresponding amine (1.1 equiv.), $TMSN_3$ (1.1 equiv.), and *tert*-butyl isocyanide (1.1 equiv.). The reaction mixture was placed in the water bath of a sonicator cleaner. Then, the mixture was US-irradiated at room temperature for 60 min. Then, the solvent was removed to dry 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 dry under vacuum. The crude product was purified by flash chromatography using mixtures of hexanes–EtOAc to afford the corresponding 1,5-DS-1*H*-T Xx-x.

4.3.1. *N*-((2-Azidophenyl)(1-(*tert*-butyl)-1*H*-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; R_f = 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)-1*H*-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; R_f = 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)-1*H*-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; R_f = 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)-1*H*-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; R_f = 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)-1*H*-tetrazol-5-yl)methyl)-2-(1*H*-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; R_f = 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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