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Chemoselective Organoclick–Click Sequence

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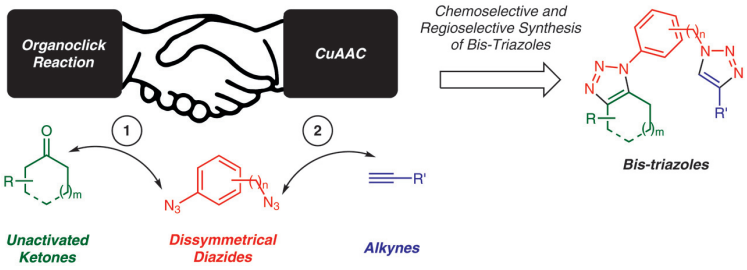
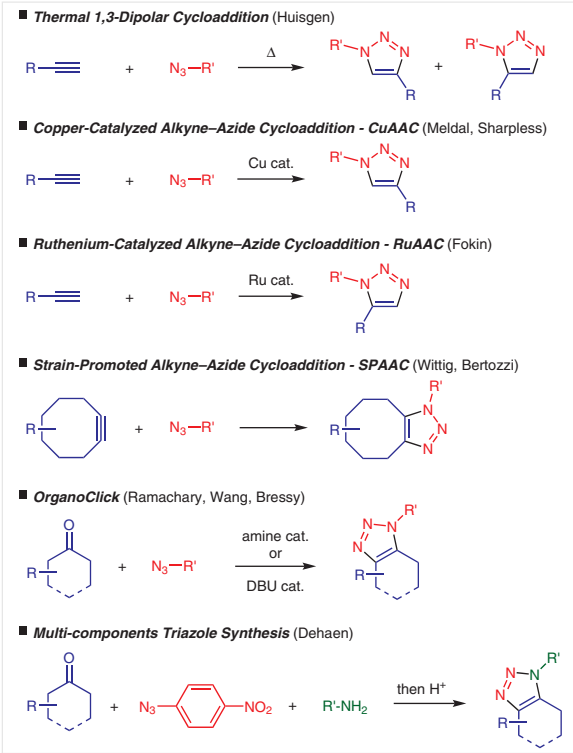


Abstract A highly chemoselective bis-triazole synthesis based on a sequence organocatalyzed click reaction/copper-catalyzed click reaction is described in this paper. A range of bis-azides react with various ketones using proline catalysis through the aryl azide moiety while the alkyl azide one remains available for a metal-catalyzed triazole synthesis.

Key words triazoles, organocatalysis, organoclick reaction, click reaction, chemoselectivity

The discovery of new chemoselective transformations is a stimulating research area in organic chemistry.[1] These reactions present the precious advantage to avoid the masking of functional group while another one is transformed. The development of such transformations represents a crucial challenge in multi-step synthesis to privilege short synthetic sequence but could also be highly valuable for sequential cross-coupling,[2] multicatalytic reactions,[3] or in ligation in various reaction media.[4]

In this last field, the preparation of triazoles played a pioneer and pivotal role (Scheme 1). Since the independent reports by the groups of Meldal[5] and Sharpless[6] about the highly regioselective copper-catalyzed alkyne–azide Huisgen cycloaddition[7] (CuAAC) under very mild conditions, the synthesis of this aromatic nitrogenated heterocycle became an intensive field of research. Indeed this reaction abusively named 'click reaction' in reference to the Sharpless concept,[8] is used as a powerful tool in material sciences[9] as well as in chemical biology.[10] The regioselectivity could be reversed towards the synthesis of the 1,5-disubstituted cycloadduct using ruthenium-catalyzed[11] (RuAAC) or base-catalyzed[12] reaction. Strain-promoted cycloadditions (SPAAC) were elegantly used in a context of bioorthogonal ligation by the Bertozzi's group[13] based on an initial report by Wittig.[14] More recently organocatalyzed triazole synthesis,[15] based on the cycloaddition between enamine,[16] enolate,[17] or nitroolefin[18] with azide, emerged. In 2016, Dehaen's group developed an efficient three-component triazole synthesis between a ketone, a primary amine, and *p*-nitrophenyl azide (Scheme 1).[19]



Scheme 1 Main triazole syntheses

Few studies examined the chemoselectivity of bis-triazole[20] synthesis through alkyne–azide cycloaddition using either diyne or diazide partners (Scheme 2). Several strategies were adopted to use chemoselectively diynes by protection of one alkyne with bulky group[21] or by activation and/or deactivation of alkynes by neighboring effect.[22] Recently Wright and Couty developed a bis-triazole synthesis using an azide bearing a latent alkyne functionality.[23] Even fewer studies were conducted on the use of diazides. An efficient double CuAAC was performed, by Zhu's group, on dissymmetrical diazides featuring a chelating group.[24]

In this paper, we describe the unprecedented chemoselective coupling between a ketone **1** and an alkyne **4** with a dissymmetrical diazide **2** using an organoclick and a click reaction (Scheme 3). In contrast to previous approaches, this strategy does not require protection/deprotection steps.

First, we determined the order of the sequence: organoclick, then click reactions, or the reverse. We planned to use diazide **2a** bearing an aryl azide and a benzyl azide moieties to evaluate the chemoselectivity of each step (Scheme 4). The CuAAC approach, performed under Zhu's conditions[25] with 1 equivalent of propargyl alcohol (**4a**), exhibits a mod-

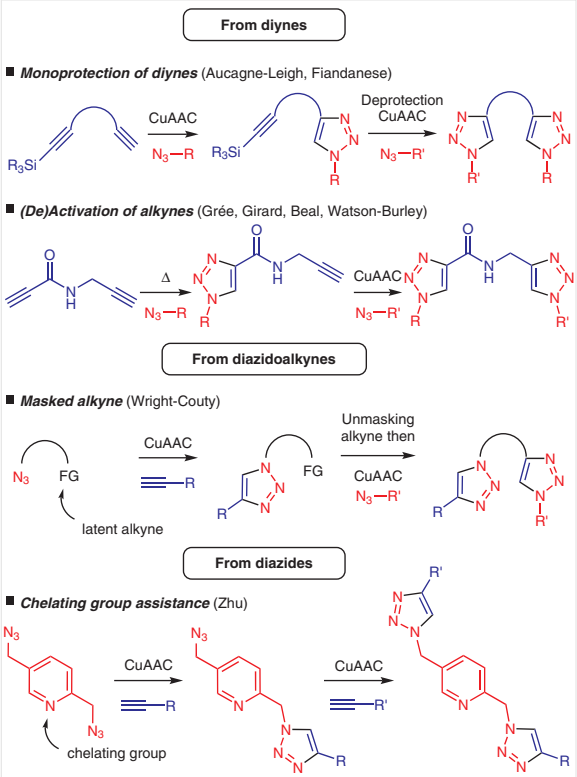
Biographical Sketches

Mokhtaria Belkheira studied at the Université d'Oran, Es-Sénia in Algeria where she obtained her Magister's degree in 2003 under the supervision of Prof. Douniazad El Abed. In 2008, she joined as doctoral student in the group of Prof. Cyril Bressy and Prof. Jean-Marc Pons in Marseille, France where she developed a new organocatalyzed triazole synthesis. She obtained her Ph.D. in 2012 and was nominated Maître de Conférences at the Université Tahri-Mohamed in Béchar-Algeria.

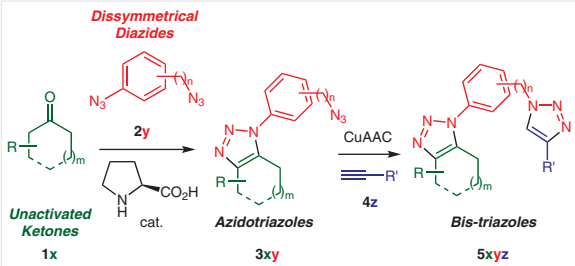
Douniazad El Abed studied at the Université d'Oran Es-Sénia where she obtained her DEA under the supervision of Prof. Fernand Texier. She then entered as an Assistant at the Université d'Oran Es-Sénia and defended a Thèse de Doctorat de 3ème Cycle in 1977. In 1982, she joined the group of Prof. Maurice Santelli in the Université d'Aix-Marseille and defended a Thèse d'Etat in 1986. Back in Algeria, she worked on the extraction of natural products and synthesis of heterocycles (triazoles and triazolines). Since 1989 she holds a position of Professor at Université d'Oran Es-Sénia. Her research focuses on synthesis of nitrogenous bioactive molecules obtained under environmentally-friendly conditions that comply with the principles of green chemistry by synthesis or extraction.

Jean-Marc Pons studied at the Université de Provence in Marseille where he obtained his Ph.D. in 1982 under the supervision of Prof. Maurice Santelli. He then entered the CNRS as Chargé de Recherches and defended a Thèse d'Etat in 1987 on low valent transition metal complexes in organic synthesis. In 1988, he spent a year as a post-doctoral fellow in the group of Prof. Philip Kocienski at Southampton, where he worked on the total synthesis of natural products. He was dean of the faculty of sciences of Aix-Marseille Université from 2008 to 2017. He is currently involved in organocatalyzed transformations.

Cyril Bressy studied at the Université Claude Bernard in Lyon where he obtained his Ph.D. in 2004 under the supervision of Prof. Olivier Piva. He then joined as a post-doctoral researcher in the group of Prof. Mark Lautens in Toronto, Canada where he developed a novel variant of the Catellani reaction. Back in France, he worked on a total synthesis project in Paris at Ecole Supérieure de Physique et Chimie Industrielle (ESPCI-ParisTech) with Prof. Janine Cossy. From 2006 he held a position of Maître de Conférences at Aix-Marseille Université (AMU). He obtained in 2012 a Habilitation à Diriger les Recherches (HDR) and was promoted as full professor in 2015 at AMU. His research focuses on total synthesis using desymmetrization strategies and organocatalyzed transformations.



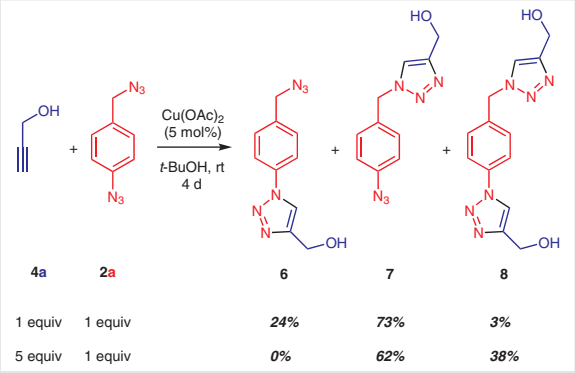
Scheme 2 Chemoselective strategies to obtain bis-triazoles



Scheme 3 Bis-triazole synthesis through organoclick–click sequence

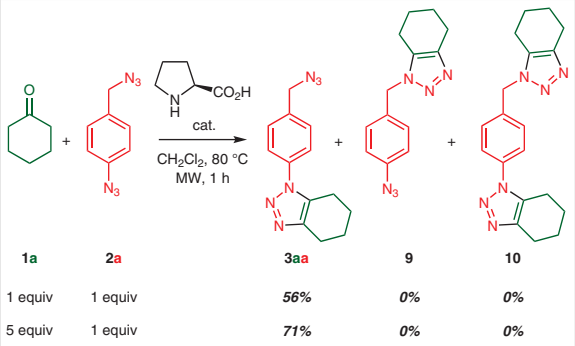
erate chemoselectivity in favor of the benzyl azide moiety (73%) leading to the formation of triazole **7**. Nevertheless significant amounts of triazole **6** were obtained through the cycloaddition involving the aryl azide function (24%). Notably, only 3% of bistriazole **8** was formed under these conditions. Using 5 equivalents of the same propargyl alcohol (**4a**) led to the formation of monotriazole **7** in 62% yield, but this was accompanied by a larger amount of bistriazole **8**.

The organoclick reaction, previously developed by our group,[16c] was tested with cyclohexanone (**1a**) and diazide **2a** (Scheme 5). The proline-catalyzed reaction, run with di-



Scheme 4 Evaluation of the click reaction chemoselectivity using propargyl alcohol (**4a**) and diazide **2a**

azide **2a** and 1 equivalent of cyclohexanone (**1a**), led exclusively to triazole **3aa** in 56% yield. The presence of regioisomer **9** or bistriazole **10** was not detected even with larger amounts of ketone (5 equiv). An excess of ketone raised the yield of aryltriazole **3aa** up to 71%.



Scheme 5 Evaluation of the organoclick reaction chemoselectivity using cyclohexanone (**1a**) and diazide **2a**

These preliminary results exhibited the complete chemoselectivity of the organoclick reaction in favor of aryl azides. As a consequence, the coupling sequence should have begun with the organoclick reaction and be followed by the click reaction. The scope of this sequence was explored using the diazides, ketones, and alkynes depicted in Figure 1.

The scope of the organoclick reaction between diazides and ketones was first examined (Scheme 6). Cyclohexanone (**1a**) was coupled with diazides **2a–e** leading to the azidotriazoles **3aa–ae**. The formation of azidoanilines **11a–e** was observed during the course of the reaction resulting from a selective reduction of the aromatic azide function. The amount of this side-product (yields between parentheses) seems to increase when the two azide functions become closer (*para* < *meta* < *ortho*). Other cyclic and acyclic ke-

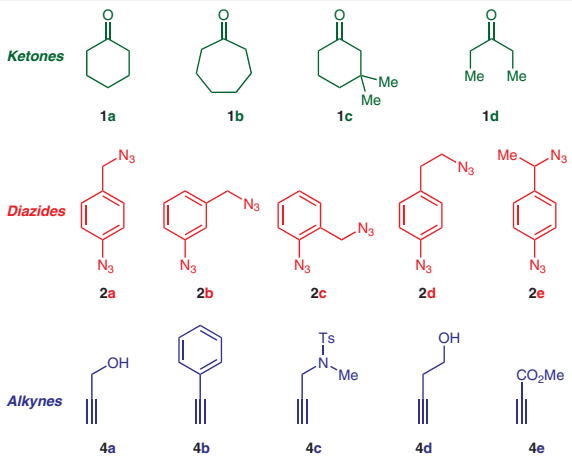
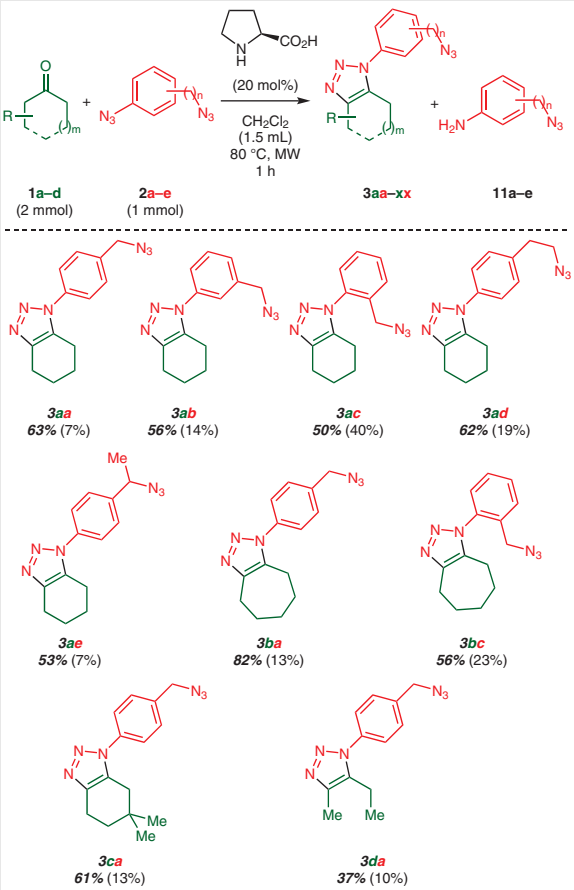


Figure 1 Partners of the organoclick–click sequence

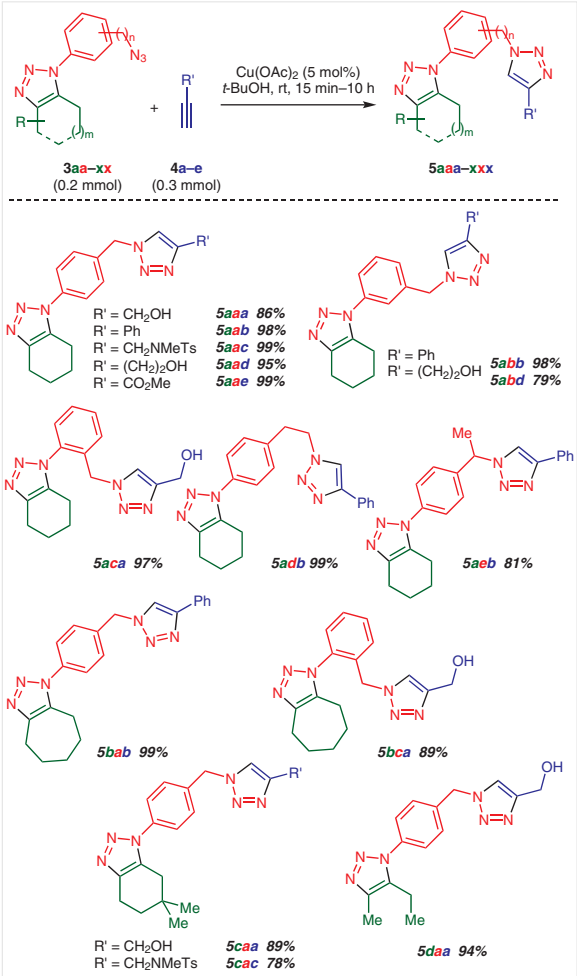


Scheme 6 Scope of organoclick reaction with diazides; yields in parentheses refer to the side-product **11** formed in the reaction

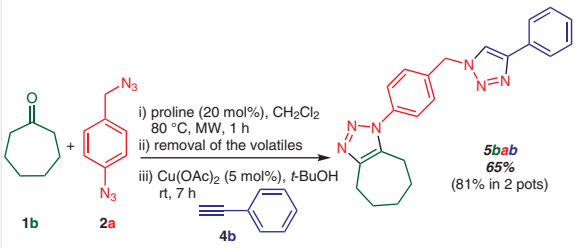
tones **1b–d** were successfully used leading in some cases, **1c** and **1d**, to dissymmetrical triazoles **3ca** and **3da** resulting from a complete regioselectivity. Complete chemoselectivity was also observed for the formation, with yields from 37% to 82%, of azidotriazoles **3** reported in Scheme 6.

Having these azidotriazoles resulting from the organoclick reaction in hand, we examined the click step of the sequence using copper acetate, as catalyst, in *tert*-butyl alcohol at room temperature. The bis-triazoles **5** obtained, in excellent yields, through this last step are represented in Scheme 7. The position of the alkyl azide moiety does not seem to influence the efficiency of this step.

Finally, a one-pot procedure, combining sequentially the two triazole syntheses without isolation of the azidotriazole intermediate **3ba** was elaborated (Scheme 8). Following the organoclick reaction, dichloromethane was removed under vacuo and changed for *t*-BuOH before the ad-



Scheme 7 Scope of bis-triazoles



Scheme 8 One-pot three-component reaction

dition of copper acetate. Bis-triazole **5bab** was formed in slightly lower yield (65%) than through the two-pot sequence (81% over 2 steps).

In conclusion, we have developed a new chemo- and regioselective synthesis of bis-triazoles based on an organoclick–click sequence. It allows the coupling of a ketone and an alkyne through a diazide linker. The organoclick step, combining the ketone and the diazide, furnishes a triazole by reaction with the aryl azide with complete regio- and chemoselectivities. The click step was revealed to be efficient and robust on a large variety of alkynes. In addition, we had shown the possibility to perform the one-pot synthesis by sequential addition of catalytic system and reagent.

Anhydrous CH_2Cl_2, Et_2O, toluene, THF, and DMSO were obtained from the Solvent Purification System BRAUN MB-SPS800. All experiments using anhydrous solvents were performed under inert atmosphere of argon, using dried apparatus and employing standard techniques for handling air-sensitive materials. All reagents were obtained from commercial suppliers, unless otherwise stated. Flash chromatography was performed using Merck 40–63 µm particle-sized silica gel (230–400 mesh) and eluted with EtOAc in petroleum ether (PE, bp 40–60 °C) or with MeOH in EtOAc, unless otherwise specified. Analytical TLC was performed using 0.20 mm silica gel 60 plates. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with various stains (e.g., *p*-anisaldehyde, phosphomolybdic acid). Melting points were determined with a Büchi Melting-point B-450 apparatus and are not corrected. High-resolution mass spectra (HRMS) were obtained from a QStar Elite spectrometer (Applied Biosystems SCIEX) by electrospray ionization. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 and at 400 MHz on a Bruker AC-400 spectrometer using as internal standard the residual $CHCl_3$ signal for ^{1}H NMR (δ = 7.26). ^{13}C NMR spectra were similarly recorded at 75.47 MHz on a Bruker AC-300 and at 100.61 MHz on a Brucker AC-400 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence and as internal standard the $CDCl_3$ solvent signal for ^{13}C NMR (δ = 77.0). Chemical shifts (δ) are reported in parts per million (ppm). Standard abbreviations are used for denoting the multiplicities. Coupling constants (*J*) are reported in hertz (Hz).

Diazides **2a**,[16c], **2b**,[26] and **2c**[27] are known compounds. For the preparation of diazides **2d** and **2e**, see the Supporting Information.

Azidotriazoles 6 and 7, and Bistriazole 8

1-Azido-4-azidomethylbenzene (**2a**; 34.80 mg, 0.2 mmol), propargyl alcohol (**4a**; 11.2 mg, 0.2 mmol), and *t*-BuOH (0.50 mL) were mixed under argon. A 0.53 M aqueous solution (19 µL) of $Cu(OAc)_2$ was then added and the resulting mixture stirred for 4 days at r.t. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) before quenching with H_2O (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under vacuo. Flash chromatography (EtOAc/MeOH 20:1) of the crude product led to azidomethylphenyltriazole **6** (11.1 mg, 24%), azidophenylmethyltriazole **7** (33.7 mg, 73%), and bistriazole **8** (1.7 mg, 3%).

Azidomethylphenyltriazole 6

White solid; mp 59 °C; R_f = 0.56 (EtOAc/PE 10:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.69 (s, 1 H), 7.94 (d, *J* = 8.5 Hz, 2 H), 7.59 (d, *J* = 8.5 Hz, 2 H), 5.33 (t, *J* = 5.5 Hz, 1 H, OH), 4.61 (d, *J* = 5.5 Hz, 2 H), 4.55 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.1, 136.3, 136.0, 129.8 (2 C), 120.9, 120.1 (2 C), 54.9, 52.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}N_6O$: 231.0989; found: 231.0997.

Azidophenylmethyltriazole 7

Yellow solid; mp 64 °C; R_f = 0.45 (EtOAc/MeOH 20:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 1 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 5.55 (s, 2 H), 5.17 (t, *J* = 5.5 Hz, 1 H, OH), 4.49 (d, *J* = 5.5 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.3, 139.2, 133.0, 129.7 (2 C), 122.6, 119.3 (2 C), 54.9, 51.9.

Bistriazole 8

White solid; mp 83 °C; R_f = 0.10 (EtOAc/MeOH 20:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.67 (s, 1 H), 8.09 (s, 1 H), 7.91 (d, *J* = 8.5 Hz, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 5.66 (s, 2 H), 5.32 (br s, 1 H, OH), 5.19 (br s, 1 H, OH), 4.60 (s, 2 H), 4.51 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.1, 148.3, 136.4, 136.3, 129.3 (2 C), 122.9, 120.9, 120.1 (2 C), 54.9, 54.8, 51.9.

Azidotriazoles 3xy; General Procedure for the Organoclick Reaction

Ketone **1** (2 mmol) and diazide **2** (1 mmol) were dissolved in CH_2Cl_2 (1.5 mL) in a sealed tube, followed by the addition of proline (20 mol%). The stirred mixture was then heated to 80 °C in a Micro-Wave reactor (CEM Discover – 1-300 W oven). After 1 h, the solvent was removed under vacuo and the crude product submitted to flash chromatography.

1-[4-(Azidomethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (3aa)

Prepared from cyclohexanone (**1a**) and 1-azido-4-azidomethylbenzene (**2a**); yield: 160 mg (63%); brown solid; 63 °C; R_f = 0.42 (EtOAc/PE 2:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.6 Hz, 2 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 4.44 (s, 2 H), 2.85 (t, *J* = 6.2 Hz, 2 H), 2.75 (t, *J* = 6.1 Hz, 2 H), 1.88 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.1, 136.7, 135.9, 132.0, 129.1 (2C), 123.3 (2 C), 54.0, 22.7, 22.3, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_6$: 255.1353; found: 255.1353.

1-[3-(Azidomethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (3ab)

Prepared from **1a** and 1-azido-3-azidomethylbenzene (**2b**); yield: 137 mg (56%); brown solid; mp 75 °C; R_f = 0.30 (EtOAc/PE 2:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 6.0 Hz, 1 H), 7.54 (t, *J* = 6.0 Hz, 1 H), 7.52 (t, *J* = 3.3 Hz, 1 H), 7.39 (d, *J* = 6.0 Hz, 1 H), 4.45 (s, 2 H), 2.85 (t, *J* = 5.7 Hz, 2 H), 2.76 (t, *J* = 5.9 Hz, 2 H), 1.89 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 137.2, 137.3, 132.0, 130.0, 128.0, 122.6, 122.5, 54.1, 22.7, 22.4, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_6$: 255.1353; found: 255.1356.

1-[2-(Azidomethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-benzo-[*d*][1,2,3]triazole (3ac)

Prepared from **1a** and 1-azido-2-azidomethylbenzene (**2c**); yield: 127 mg (50%); orange solid; mp 86 °C; R_f = 0.40 (EtOAc/PE 1:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.48 (m, 2 H), 7.47 (td, *J* = 7.0, 1.7 Hz, 1 H), 7.25 (m, 1 H), 4.28 (s, 2 H), 2.84 (t, *J* = 5.1 Hz, 2 H), 2.50 (t, *J* = 5.1 Hz, 2 H), 1.86 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 134.9, 133.8, 132.8, 130.3, 130.2, 129.1, 126.6, 50.5, 22.5, 22.4, 21.8, 20.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_6$: 255.1353; found: 255.1356.

1-[4-(2-Azidoethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (3ad)

Prepared from **1a** and 1-azido-4-(2-azidoethyl)benzene (**2d**); yield: 166 mg (62%); viscous yellow oil; R_f = 0.36 (EtOAc/PE 2:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 3.56 (t, *J* = 7.0 Hz, 2 H), 2.96 (t, *J* = 7.0 Hz, 2 H), 2.84 (t, *J* = 5.3 Hz, 2 H), 2.73 (t, *J* = 4.8 Hz, 2 H), 1.87 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 138.7, 135.7,132.0, 129.8 (2 C), 123.3 (2 C), 52.2, 34.9, 22.7, 22.5, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}N_6$: 269.1509; found: 269.1508.

1-[4-(1-Azidoethyl)phenyl]-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (3ae)

Prepared from **1a** and 1-azido-4-(1-azidoethyl)benzene (**2e**); yield: 142 mg (53%); yellow solid; mp 73 °C; R_f = 0.41 (EtOAc/PE 2:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.5 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 4.70 (q, *J* = 6.8 Hz, 1 H), 2.84 (t, *J* = 6.1 Hz, 2 H), 2.75 (t, *J* = 6.1 Hz, 2 H), 1.88 (m, 4 H), 1.58 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 141.5, 136.6, 132.0, 127.5 (2 C), 123.3 (2 C), 60.4, 22.7, 22.4, 21.9, 21.8, 21.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}N_6$: 269.1509; found: 269.1509.

1-[4-Azidomethyl)phenyl]-1,4,5,6,7,8-hexahydrocyclohepta[*d*][1,2,3]triazole (3ba)

Prepared from cycloheptanone (**1b**) and 1-azido-4-azidomethylbenzene (**2a**); yield: 219 mg (82%); yellow solid; mp 48 °C; R_f = 0.40 (EtOAc/PE 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 4.44 (s, 2 H), 2.96 (t, *J* = 5.7 Hz, 2 H), 2.74 (t, *J* = 5.6 Hz, 2 H), 1.76 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.5, 136.7, 136 .4, 135.6, 129.0 (2 C), 125.7 (2 C), 54.0, 30.8, 27.2 (2 C), 27.0, 24.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}N_6$: 269.1509; found: 269.1505.

1-[(2-Azidomethyl)phenyl]-1,4,5,6,7,8-hexahydrocyclohepta[*d*][1,2,3]triazole (3bc)

Prepared from **1b** and 1-azido-2-azidomethylbenzene (**2c**); yield: 150 mg (56%); yellow solid; mp 77 °C; R_f = 0.29 (EtOAc/PE 1:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (m, 2 H), 7.49 (m, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 4.21 (s, 2 H), 2.98 (t, *J* = 5.6 Hz, 2 H), 2.54 (t, *J* = 5.6 Hz, 2 H), 1.78 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0, 137.0, 135.0, 133.3, 130.4, 130.2, 129.1, 127.7, 50.4, 30.9, 27.2 (2C), 26.9, 24.4.

HRMS: m/z [M + H]$^+$ calcd for $C_{13}H_{14}N_6$: 269.1509; found: 269.1512.

1-[4-(Azidomethyl)phenyl]-6,6-dimethyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (3ca)

Prepared from 3,3-dimethylcyclohexanone (**1c**) and 1-azido-4-azidomethylbenzene (**2a**); yield: 172 mg (61%); yellow solid: mp 87 °C; R_f = 0.32 (EtOAc/PE 2:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.3 Hz, 2 H), 7 .47 (d, *J* = 8.3 Hz, 2 H), 4.43 (s, 2 H), 2.83 (t, *J* = 6.4 Hz, 2 H), 2.51 (s, 2 H), 1.66 (t, *J* = 6.4 Hz, 2 H), 1 .03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 136.7, 136.0, 132.0, 129.1 (2 C), 123.4 (2 C), 54.1, 35.5, 35.4, 19.1, 31.2, 27.7 (2 C).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N_6$: 283.1666; found: 283.1666.

1-[4-(Azidomethyl)phenyl]-5-ethyl-4-methyl-1*H*-[*d*][1,2,3]triazole (3da)

Prepared from pentan-3-one (**1d**) and 1-azido-4-azidomethylbenzene (**2a**); yield: 90 mg (37%); yellow oil; R_f = 0.26 (EtOAc/PE 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (m, 4 H), 4.45 (s, 2 H), 2.67 (q, *J* = 7.6 Hz, 2 H), 2.37 (s, 3 H), 1.07 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 136 .9, 136.7, 135.3, 129.0 (2 C), 125.6 (2 C), 54.0, 16.2, 13.1, 10.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_6$: 243.1353; found: 243.1343.

Bistriazoles 5xyz; General Procedure

Azidotriazole **3** (0.2 mmol) and alkyne derivative **4** (0.3 mmol) were dissolved under argon at r.t. in *t*-BuOH (0.5 mL) and then an aq 0.53 M $Cu(OAc)_2$ solution (19 µL, 5 mol%) was added. The reaction mixture was then stirred at the same temperature (from 15 min to 10 h) until complete disappearance of the starting triazole **3** (reaction followed by TLC). The mixture was then diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with H_2O (10 mL). The organic layer was dried ($MgSO_4$) and the volatiles were removed under vacuo. Bis-triazole **5** was then purified by flash chromatography on silica gel.

1-{[4-(4,5,6,7-Tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}methanol (5aaa)

Prepared from azidotriazole **3aa** and propargyl alcohol (**4a**); yield: 53 mg (86%); yellow solid; mp 179 °C; R_f = 0.12 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (s, 1 H), 7.65 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 5.68 (s, 2 H), 4.52 (d, *J* = 5.4 Hz, 2 H), 4.05 (br s, 1 H, OH), 2.73 (t, *J* = 5.5 Hz, 2 H), 2.69 (t, *J* = 5.5 Hz, 2 H), 1.78 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 148.4, 143.0, 136 .7, 136.0, 132.3, 129.1 (2 C), 123.2 (2 C), 123.0, 55.0, 52.0, 22.1, 21.9, 21.3, 20.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_6O$: 311.1615; found: 311.1610.

1-{4-[(4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl]phenyl}-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (5aab)

Prepared from azidotriazole **3aa** and ethynylbenzene (**4b**); yield: 70 mg (98%); white solid; mp 158 °C ; R_f = 0.39 (EtOAc/PE 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.5 Hz, 2 H), 7 .73 (s, 1 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 5.65 (s, 2 H), 2.82 (t, *J* = 6.0 Hz, 2 H), 2.72 (t, *J* = 6.1 Hz, 2 H), 1.86 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 144.2, 137.1, 135.2, 132.0, 130.3, 129.0 (2 C), 128.8 (2 C), 128.3, 125.7 (2 C), 123.5 (2 C), 119.6, 53.4, 22.6, 22.3, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_6$: 357.1822; found: 357.1812.

***N*,4-Dimethyl-*N*-({1-[4-(4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}methyl)benzenesulfonamide (5aac)**

Prepared from azidotriazole **3aa** and *N*-tosyl-*N*-methylpropargylamine (**4c**); yield: 94 mg (99%); white solid; mp 153 °C; R_f = 0.30 (EtOAc/PE 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.0 Hz, 2 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 7.59 (s, 1 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.58 (s, 2 H), 4.31 (s, 2 H), 2.82 (t, *J* = 4.5 Hz, 2 H), 2.75 (t, *J* = 6.0 Hz, 2 H), 2.71 (s, 3 H), 2.44 (s, 3 H), 1.88 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.21, 144.20, 137.2, 134.8, 134.1, 132.0, 129.8 (2 C), 129.1 (2 C), 127.4 (2 C), 123.5 (2 C), 123.0, 53.5, 45.6, 34.9, 22.7, 22.3, 21.9 (2 C), 21.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_7O_2S$: 478.2020; found: 478.2010.

2-{1-[4-(4,5,6,7-Tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}ethanol (5aad)

Prepared from azidotriazole **3aa** and but-3-ynol (**4d**); yield: 62 mg (95%); yellow solid; mp 114 °C; R_f = 0.16 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.39 (s, 1 H), 5.58 (s, 2 H), 3.95 (t, *J* = 5.8 Hz, 2 H), 2.95 (t, *J* = 5.8 Hz, 2 H), 2.83 (t, *J* = 4.7 Hz, 2 H), 2.73 (t, *J* = 4.7 Hz, 2 H), 1.87 (m, 4 H), 1.85 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 144.2, 137.1, 135.3, 132.0, 129.0 (2 C), 123.5 (2 C), 121.7, 61.4, 53.3, 28.7, 22.6, 22.3, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_6O$: 325.1771; found: 325.1773.

Methyl 1-[4-(4,5,6,7-Tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazolylcarboxylate (5aae)

Prepared from azidotriazole **3aa** and methyl propynoate (**4e**), yield: 67 mg (99%); white solid; mp 147 °C; R_f = 0.23 (EtOAc/PE 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.58 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 5.65 (s, 2 H), 3.92 (s, 3 H), 2.81 (t, *J* = 6.0 Hz, 2 H), 2.72 (t, *J* = 5.8 Hz, 2 H), 1.86 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 144.3, 140.4, 137.4, 134.1, 132.0, 129.3 (2 C), 127.5,123.6 (2 C), 53.7, 52.2, 22.6, 22.3, 21.8 (2 C).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_6O_2$: 339.1564; found: 339.1557.

1-{3-[(4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl]phenyl}-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (5abb)

Prepared from azidotriazole **3ab** and ethynylbenzene (**4b**); yield: 70 mg (98%); white solid; mp 125 °C; R_f = 0.34 (EtOAc/PE 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 7.2 Hz, 2.3 Hz, 2 H), 7.77 (s, 1 H), 7.51 (m, 3 H), 7.41–7.30 (m, 3 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 5.64 (s, 2 H), 2.80 (t, *J* = 5.8 Hz, 2 H), 2.67 (t, *J* = 5.6 Hz, 2 H), 1.83 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 144.2, 137.4, 136.6, 132.0, 130.2, 130.1, 128.7 (2 C), 128.1, 127.7, 125.6 (2 C), 122.8, 122.6, 119.8, 53.4, 22.6, 22.2, 21.8, 21.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_6$: 357.1822; found: 357.1814.

2-{1-[3-(4,5,6,7-Tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}ethanol (5abd)

Prepared from azidotriazole **3ab** and but-3-ynol (**4d**); yield: 51 mg (79%); white solid; mp 138 °C; R_f = 0.14 (EtOAc/MeOH 20:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1 H), 7.59 (m, 3 H), 7.42 (m, 1 H), 5.67 (s, 2 H), 4.68 (t, *J* = 5.3 Hz, 1 H, OH), 3.62 (td, *J* = 6.7, 5.3 Hz, 1 H), 2.76 (t, *J* = 6.7 Hz, 2 H), 2.70 (m, 4 H), 1.78 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 144.8, 143.1, 138.0, 136.5, 132.2, 130.0, 127.9, 122.7, 122.2, 122.1, 60.2, 51.9, 29.0, 22.1, 21.8, 21.3, 20.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}$ N_6O: 325.1771; found: 325.1772.

1-{[2-(4,5,6,7-Tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}methanol (5aca)

Prepared from azidotriazole **3ac** and propargyl alcohol (**4a**); yield: 60 mg (97%); white solid; mp 132 °C; R_f = 0.20 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (m, 3 H), 7.41 (s, 1 H), 7.24 (m, 1 H), 5.43 (s, 2 H), 4.71 (s, 2 H), 2.81 (t, *J* = 6.1 Hz, 2 H), 2.65 (br s, 1 H, OH), 2.37 (t, *J* = 6.0 Hz, 2 H), 1 .79 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.8, 143.6, 134.6, 133.9, 131.9, 130.9, 130.4, 129.6, 126.5, 122.4, 56.1, 49.9, 22.4, 22.2, 21.6, 20.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_6O$: 311.1615; found: 311.1621.

1-{4-[2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethyl]phenyl}-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]-triazole (5adb)

Prepared from azidotriazole **3ad** and ethynylbenzene (**4b**); yield: 73 mg (99%); yellow solid; mp 204 °C; R_f = 0.25 (EtOAc/PE 5:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7 .53 (s, 1 H), 7.50 (d, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 4.68 (t, *J* = 7.0 Hz, 2 H), 3.36 (t, *J* = 7.0 Hz, 2 H), 2.82 (m, 2 H), 2.71 (m, 2 H), 1.86 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 137.6, 136.0, 132.4, 132.0, 130.4, 129.8 (2 C), 128.8 (2 C), 128.1, 125.6 (2 C), 123.3 (2 C), 119.9, 51.3, 36.2, 22.7, 22.3, 21.9, 21.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_6$: 371.1979; found: 371.1977.

1-{4-[1-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethyl]phenyl}-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]-triazole (5aeb)

Prepared from azidotriazole **3ae** and ethynylbenzene (**4b**); yield: 60 mg (81%); white solid; mp 133 °C; R_f = 0.30 (EtOAc/PE 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 7.5, 1.4 Hz, 2 H), 7.72 (s, 1 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.32 (tt, *J* = 7.5, 1.4 Hz, 1 H), 5.94 (q, *J* = 7.1 Hz, 1 H), 2.83 (t, *J* = 5.3 Hz, 2 H), 2.72 (t, *J* = 4.3 Hz, 2 H), 2.08 (d, *J* = 7.1 Hz, 3 H), 1.87 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 144.2, 140.5, 137.0, 132.0, 130.4, 128.8 (2 C), 128.2, 127.6 (2 C), 125.7 (2 C), 123.5 (2 C), 118.3, 59.7, 22.7, 22.4, 21.9, 21.8, 21.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_6$: 371.1979; found: 371.1969.

1-{4-[(4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl]phenyl}-1,4,5,6,7,8-hexahydrocyclohepta[*d*][1,2,3]triazole (5bab)

Prepared from azidotriazole **3ba** and ethynylbenzene (**4b**); yield: 73 mg (99%); white solid; mp 179 °C; R_f = 0.29 (EtOAc/PE 3:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 8.2, 1.5 Hz, 2 H), 7.75 (s, 1 H), 7.51–7.43 (m, 4 H), 7.40 (m, 2 H), 7.33 (tt, *J* = 7.5, 1.2 Hz, 1 H), 5.66 (s, 2 H), 2.95 (t, *J* = 5.7 Hz, 2 H), 2.71 (t, *J* = 5.8 Hz, 2 H), 1.87–1.68 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 147.6, 136.8, 135.9, 135.6, 130.3, 128.9 (2 C), 128.8 (2 C), 128.3, 125.9 (2 C), 125.7 (2 C), 119.6, 53.5, 30.8, 27.1, 26.9 (2 C), 24.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_6$: 371.1979; found: 371.1968.

1-[4-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl)methanol (5caa)

Prepared from azidotriazole **3ca** and propargyl alcohol (**4a**); yield: 60 mg (89%); brown solid; mp 197 °C; R_f = 0.24 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (s, 1 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 7 .52 (d, *J* = 8.5 Hz, 2 H), 5.68 (s, 2 H), 5.19 (t, *J* = 5.6 Hz, 1 H, OH), 4.52 (d, *J* = 5.6 Hz, 2 H), 2.69 (t, *J* = 6.4 Hz , 2 H), 2.54 (s, 2 H), 1.59 (t, *J* = 6.4 Hz, 2 H), 0.95 (s, 6 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 148.4, 141.2, 136.7, 135.9, 132.2, 129.2 (2 C), 123.2 (2 C), 122.9, 55.0, 52.0, 34.8, 34.1, 18.5, 30.6, 27.2 (2 C).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}N_6O$: 339.1928; found: 339.1919.

***N*-({1-[4-(6,6-Dimethyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}methyl)-*N*,4-dimethylbenzenesulfonamide (5cac)**

Prepared from azidotriazole **3ca** and *N*-tosyl-*N*-methylpropargylamine (**4c**); yield: 79 mg (78%); yellow solid; mp 154 °C; R_f = 0.20 (EtOAc/PE 3:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.3 Hz, 2 H), 7.61 (s, 1 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.58 (s, 2 H), 4.31 (s, 2 H), 2.84 (t, *J* = 6.0 Hz, 2 H), 2.72 (s, 3 H), 2.53 (s, 2 H), 2.44 (s, 3 H), 1.67 (t, *J* = 6.0 Hz, 2 H), 1.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 144.3, 143.7, 137.3, 137.2, 134.8, 134.2, 129.8 (2 C), 129.1 (2 C), 127.4 (2 C), 123.6 (2 C), 123.0, 53.6, 45.6, 35.5 (2 C), 35.0, 31.2, 27.7 (2 C), 21.5, 19.1.

1-[2-(5,6,7,8-Tetrahydrocyclohepta[*d*][1,2,3]triazol-1(4*H*)-yl)benzyl]-1*H*-1,2,3-triazol-4-yl)methanol (5bca)

Prepared from azidotriazole **3bc** and propargyl alcohol (**4a**); yield: 58 mg (89%); white solid; mp 143 °C; R_f = 0.26 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.46 (m, 3 H), 7.21–7.19 (m, 1 H), 5.36 (s, 2 H), 4.72 (s, 2 H), 2.95 (t, *J* = 5.7 Hz, 2 H), 2.70 (br s, 1 H, OH), 2.42 (t, *J* = 5.7 Hz, 2 H), 1.83–1.60 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 147.3, 137.0, 134.6, 132.3, 130.8, 130.6, 129.6, 127.5, 122.4, 56.2, 49.6, 30.7, 27.0 (2 C), 26.7, 24.2.

1-{[4-(5-Ethyl-4-methyl-1*H*-1,2,3-triazol-1-yl)benzyl]-1*H*-1,2,3-triazol-4-yl}methanol (5daa)

Prepared from azidotriazole **3da** and propargyl alcohol (**4a**); yield: 56 mg (94%); white solid; mp 132 °C; R_f = 0.18 (EtOAc/MeOH 20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 7.41 (s, 4 H), 5.60 (s, 2 H), 4.79 (s, 2 H), 2.67 (q, *J* = 7.6 Hz, 2 H), 2.35 (s, 3 H), 1.85 (br s, 1 H, OH), 1.06 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 140.8, 137.1, 136.0, 135.3, 129.0 (2 C), 125.8 (2 C), 121.8, 56.4, 53.4, 16.2, 13.0, 10.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N_6O$: 299.1615; found: 299.1617.

One-Pot Preparation of Bistriazole 5bab

Cycloheptanone (**1b**; 224 mg, 2 mmol) and 1-azido-4-azidomethylbenzene (**2a**; 174 mg, 1 mmol) were dissolved in CH_2Cl_2 (1.5 mL) in a sealed tube, followed by the addition of proline (23 mg, 20 mol%). The stirred mixture was then heated to 80 °C in a Micro-Wave reactor (CEM Discover – 1-300 W oven). After 1 h, the solvent was removed under vacuo. The crude azidotriazole **3ba** formed was mixed with ethynylbenzene (**4b**; 153 mg, 1.5 mmol) in *t*-BuOH (2.5 mL) under argon at r.t., followed by the addition of an aq 0.53 M $Cu(OAc)_2$ solution (95 µL, 5 mol%). The reaction mixture was then stirred at the same temperature for 7 h until complete disappearance of the starting triazole **3ba** (reaction followed by TLC). The mixture was then diluted with CH_2Cl_2 (150 mL) and the organic layer was washed with H_2O (20 mL). The organic layer was dried ($MgSO_4$) and the volatiles were removed under vacuo. Bis-triazole **5bab** (239 mg, 65%) was obtained pure by flash chromatography on silica gel.

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