Efficient Multicomponent Synthesis of Mono-, Bis-, and Tris-1,2,3-triazoles Supported by Hydroxybenzene Scaffolds

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Abstract: A versatile one-pot synthesis of a series of mono-, bis- and tris-1,2,3-triazoles supported by commercially available hydroxybenzene scaffolds has been developed employing click chemistry. The multicomponent copper(I)-catalyzed 1,3-dipolar cycloaddition of sodium azide, propargyl bromide, and a *para*-substituted benzyl derivative yields *N*-benzyl-functionalized triazoles featuring several electron-donating or electron-withdrawing groups. Despite the preparation of highly substituted molecules, reaction conditions that provides good yields involved room temperature, times that oscillate between 16 and 24 hours, and catalyst loads ranging from 5–10 mol%. The present methodology could be useful for the building up of multi-triazole libraries easily tunable with donor or attractor functional groups.

Key words: click chemistry, multi-triazoles, one-pot synthesis, hydroxybenzene, catalysis

1,2,3-Triazole derivatives are an important class of heterocycles constantly attracting attention due to their chemical properties, synthetic versatility, pharmacological, and agrochemical applications.[1] Even though the 1,2,3-triazole structural moiety does not occur in nature, it is located in diverse biologically active substances, displaying anti HIV,[2] antimicrobial,[3] antifungal,[4] antitumor,[5] and selective β_3-adrenergenic[6] and cannabinoid CB1 receptor antagonists.[7] Furthermore, compounds containing 1,2,3-triazoles have found industrial applications as dyes, photostabilizers, and corrosion inhibitors.[1]

The most conventional method for the preparation of triazoles relies in the Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes.[8] Even though the classical Huisgen reaction is highly exothermic (ca. 50 to 60 kcal/mol), its high activation barrier (25–26 kcal/mol for methyl azide and propyne)[9] results in slow reaction rates and conversions that occurs mostly at elevated temperatures. In addition, since the difference in HOMO-LUMO levels for both azides and alkynes are of similar magnitude, both dipole-HOMO and dipole-LUMO-controlled pathways take place in these cycloadditions. As a result, a mixture of 1,4- and 1,5-dibustituted 1,2,3-triazoles is obtained when an alkyne is unsymmetrically substituted. In 2001, Sharpless reported the outstanding efficiency and selectivity achieved with Cu-catalyzed alkyne-azide cycloaddition (CuAAC) reaction unveiling the widely known click methodology.[10] In this process, considered now as a landmark in organic synthesis, the formation of 1,4-disubstituted 1,2,3-triazoles is easy to carry out with access to high yields, negligible or no by-products are formed, several functional groups are tolerated, and the reaction is highly atom economical.

Because of the breakthrough of click chemistry in the 1,2,3-triazole motif, most of the work reported in the last ten years has focused on the synthesis optimization and functionalization of the monocyclic derivatives. Surprisingly, little attention has been placed in the preparation of bis-, and tris-1,2,3-triazole counterparts despite their evident potential as building blocks, ligands, and material precursors.

As part of our ongoing program in triazole chemistry, we have envisioned the synthesis of multi-triazoles as potential steel corrosion inhibitors and/or transition metal ligands. In the present report, we disclose an efficient general approach for the one-pot synthesis of a series of mono-, bis-, and tris-1,2,3-triazoles supported by hydroxybenzene scaffolds. The modular synthesis described herein, allows for the preparation of 1,2,3-triazoles under mild conditions, high yields, featuring several electron-attracting or -donating functional groups, and a wide range of structural topologies.

To prove the viability of the envisioned multi-triazole synthesis, the preparation of mono-1,2,3-triazoles was first explored using phenol as the starting scaffold. The first synthetic step involved the preparation of propargyloxybenzene (**I**) by deprotonation of phenol with potassium carbonate in dimethylformamide at 60 °C, followed by the addition of equimolar amounts of propargyl bromide. After workup and purification through column chromatography on silica gel, alkyne **I** was isolated in 73% yield.[11] The click reaction between **I** and sodium

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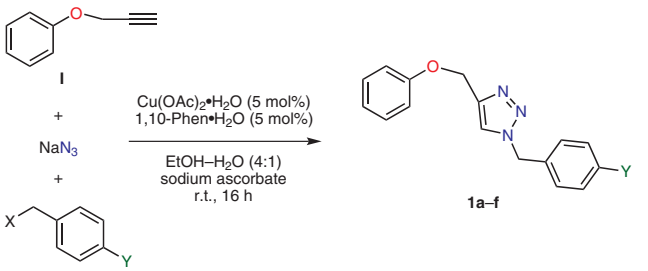
azide was carried out in a water–ethanol mixture (4:1) using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as the reagents to render the Cu(I) active catalyst. After the addition of benzyl chloride to the reaction mixture and stirring at room temperature for 20 hours, the expected 1,2,3-triazole **1a** was obtained in only 30% yield. Targeting the process yield improvement and taking advantage of our previously reported methodology for 1,2,3-triazoles synthesis,[12] we switched the copper(II) source to $Cu(OAc)_2 \cdot H_2O$ and included the addition of 1,10-phenanthroline to stabilize the in situ generated Cu(I) catalyst. Performing the one-pot reaction under the new click conditions allowed for the synthesis of **1a** in 83% isolated yield (Table 1).

Table 1 Synthesis of Mono-1,2,3-triazoles **1a–f**[a]



Entry	X	Y	Product	Yield (%)
1	Cl	H	**1a**	83
2	Cl	F	**1b**	81
3	Cl	Cl	**1c**	75
4	Br	Br	**1d**	79
5	Br	I	**1e**	69
6	Cl	OMe	**1f**	74

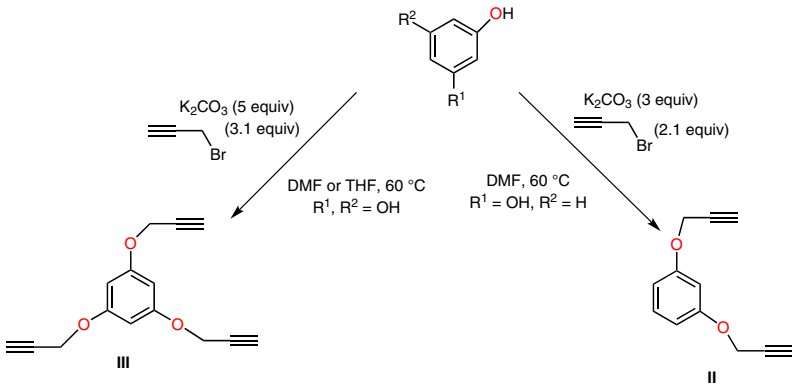
[a] Reaction conditions: **I** (0.7 mmol), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), 1,10-phenanthroline (5 mol%), sodium ascorbate (0.7 mmol), NaN_3 (0.77 mmol), *para*-substituted benzyl halogenide (0.77 mmol), EtOH–H_2O (5 mL, 4:1), stirring at r.t. for 16 h.

The scope of the method was extended with the use of several *p*-halogenide or *p*-methoxybenzylic derivatives, yielding 1,2,3-triazoles **1b–f**, which feature several electron-donating or electron-attracting groups. As depicted in Table 1, the methodology proceeds smoothly in good yields and under mild reaction conditions.

Triazoles **1a–f** were conveniently characterized by FT-IR, ^1H and ^{13}C NMR spectroscopy, and also by high-resolution mass spectrometry. The formation of the 1,2,3-triazoles was apparent from the absorption band in the 3120–3140 cm^{-1} region due to the =CH (stretching) of the triazole ring in the IR spectra. In addition, the presence of the characteristic singlet in ^1H NMR due to the triazolyl protons in the region of δ = 7.52–7.74, and the peaks at δ = 121.5–122.6 in ^{13}C NMR belonging to the C-5 atom, confirm the structure of the expected five-membered rings.

Recently, the preparation of multi-triazoles has attracted the attention of the chemical community due to their potential in areas such as materials, catalysis, and biochemistry. For instance, bis-triazole based size-specific mRNA hairpin loop binding agents have been developed targeting mRNAs coding for proteins,[13] which can be a suitable approach in drug discovery. Also, recent studies have disclosed a series of 1,2,3-bis-triazoles as potent HIV-1 protease inhibitors.[2c] The reported synthetic routes to access this highly functionalized molecules include oxidative conditions using inorganic bases,[14] sequential functionalization of mono-triazoles,[15] and one-pot click chemistry conditions.[16] Unfortunately, some of these processes present important drawbacks such as the need of several synthetic steps, difficult purification procedures, formation of secondary products, and functionalization is not always accessible. In conjunction with our interest in sustainable chemistry and encouraged by the discovery of the optimal reaction conditions for 1,2,3-triazoles formation, we decided to turn our efforts in the multicomponent one-pot synthesis of bis- and tris-1,2,3-triazoles.

The selected approach to install bis- and tris-triazoles within the same scaffold, involved the usage of 1,3-dihydroxy-, and 1,3,5-trihydroxybenzene moieties. Analogue to the preparation of **I** and following the literature procedure, 1,3-dipropargyloxybenzene (**II**)[11] and 1,3,5-tripropargyloxybenzene (**III**)[17] were obtained by deprotonation of the benzene hydroxyl groups with excess of potassium carbonate at 60 °C in DMF or THF, and the subsequent treatment with the appropriate equivalents of

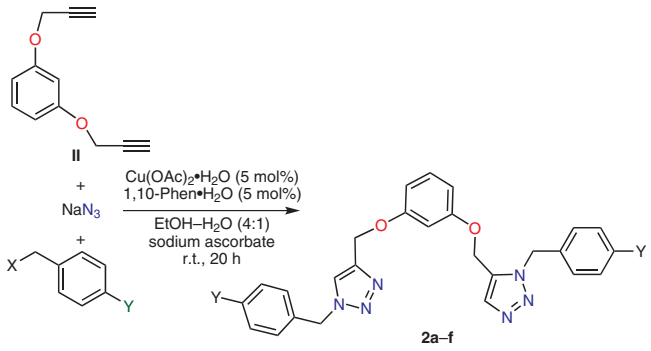


Scheme 1 Synthesis of alkynes **II** and **III**

propargyl bromide. After workup and purification, precursors **II** and **III** were isolated as yellow oils in 78 and 67% yield, respectively (Scheme 1).

The preparation of bis-1,2,3-triazoles **2a–f** followed similar click reaction conditions as those for the mono-triazoles, only differing in longer reaction times (20 h). The crude materials precipitate out from the reaction mixture after water addition, and their purification is accomplished through column chromatography on silica gel using a mixture of dichloromethane and methanol as eluent. As depicted in Table 2, the reaction scope permits the installation of several electron-attracting and -donating groups, and provides good yields employing only 2.5 mol% of the copper catalyst per each triazole formed (5 mol% overall).

Table 2 Synthesis of Bis-1,2,3-triazoles **2a–f**[a]



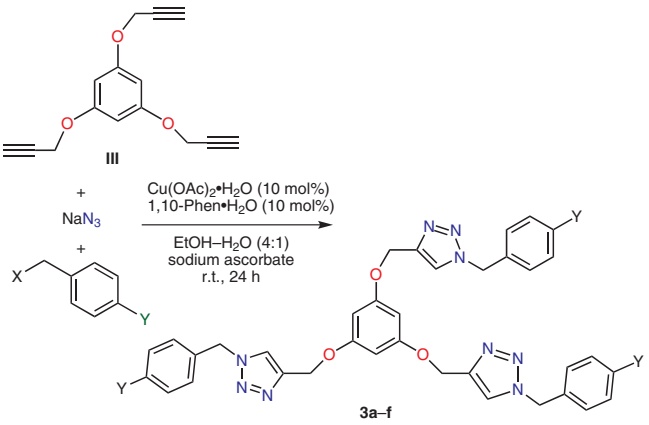
Entry	X	Y	Product	Yield (%)
1	Cl	H	**2a**	71
2	Cl	F	**2b**	76
3	Cl	Cl	**2c**	66
4	Br	Br	**2d**	62
5	Br	I	**2e**	64
6	Cl	OMe	**2f**	69

[a] Reaction conditions: **II** (0.7 mmol), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), 1,10-phenanthroline (5 mol%), sodium ascorbate (0.7 mmol), NaN_3 (1.54 mmol), *para*-substituted benzyl halogenide (1.54 mmol), EtOH–H_2O (5 mL, 4:1), stirring at r.t. for 20 h.

Bis-triazoles **2a–f** are highly soluble in chloroform and dichloromethane and slightly soluble in ethanol or methanol. Interestingly, despite their complex topology, the ^1H and ^{13}C NMR spectra of **2a–f** feature highly symmetric patterns. For instance, the two triazolyl protons are displayed as single sharp peaks in the region of δ = 7.52–7.55, while the CH and quaternary triazole signals show single peaks in the range of δ = 122.4–122.7 and 144.3–144.7, respectively. Overall, the NMR patterns for the bis-1,2,3-triazoles suggest a C_2 symmetry in solution.

As synthesis of **2a–f** was conveniently achieved using the CuAAC reaction, it was thought that this methodology could be extended to produce tris-1,2,3-triazoles starting from 1,3,5-tripropargyloxybenzene (**III**). In a first trial, the treatment of **III** with a slight excess of sodium azide and benzyl chloride and employing 5 mol% of the copper(I) catalyst system yielded tris-1,2,3-triazole **3a** in 32% yield. As the conversion of the starting materials into the final product proved low, the reaction kinetics were monitored by TLC, observing that the consumption of the starting alkyne proceeded slower compared to mono- and bis-triazoles. Noticing this behavior, the reaction time was increased to 24 and 36 hours and the temperature was raised to 40 °C, but no conversion improvement was achieved (yields were not higher than 40%). After several optimization experiments including variable modifications such as reaction times, stoichiometry, and temperature, we found that addition of 10 mol% of the copper(I) catalyst system (less than 3.5 mol% per triazole unit) afforded the best yields of the series **3a–f** as depicted in Table 3.

Table 3 Synthesis of Tris-1,2,3-triazoles **3a–f**[a]



Entry	X	Y	Product	Yield (%)
1	Cl	H	**3a**	57
2	Cl	F	**3b**	55
3	Cl	Cl	**3c**	61
4	Br	Br	**3d**	64
5	Br	I	**3e**	58
6	Cl	OMe	**3f**	49

[a] Reaction conditions: **III** (0.42 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), 1,10-phenanthroline (10 mol%), sodium ascorbate (0.84 mmol), NaN_3 (1.39 mmol), of *para*-substituted benzyl halogenide (1.39 mmol), EtOH–H_2O (10 mL, 4:1), stirring at r.t. for 24 h.

Despite the lower solubility of tris-1,2,3-triazoles **3a–f** in dichloromethane and chloroform compared with mono- and bis-triazoles, their purification can still be performed by column chromatography on silica gel using CH_2Cl_2–MeOH. In solution, the ^1H and ^{13}C NMR spectra of **3a–f** feature C_3 symmetry patterns displaying a single sharp peak for the triazolyl-CH groups in the region of δ = 8.21–8.27 and singlets for the two nonequivalent series of methylene bridges at δ = 5.06–5.08 (ArCH_2N) and δ = 5.52–

5.61 (CCH_2O). Likewise, a single set of aromatic patterns is displayed in all cases, corroborating the high symmetry of the tris-1,2,3-triazole system (see experimental section). It is noteworthy mentioning that the symmetry featured by the tris-triazoles **3a**–**f** could place them as potential G-quadruplex stabilizing ligands[15a,18] or tridentate transition-metal ligands relevant to bio-inorganic research and electron-transfer studies.[19]

All the reported 1,2,3-triazoles are obtained as white crystalline solids, and their robustness is denoted by their high stability in solution and under aerobic conditions. Additional to the wide variety of structural features, the presence of halogens at the *para*-position of the benzylic moieties in each triazole carries an extra reactive position that can be employed in further chemical transformations.

In conclusion, we have reported a convenient methodology for the synthesis of a series of mono-, bis- and tris-1,2,3-triazoles utilizing click chemistry. Despite the preparation of molecules featuring a wide variety of structural topologies, reaction conditions that provides good yields involved room temperature, reaction periods in the range of 16–24 hours and catalyst loads of 5–10 mol%. Particularly appealing is the possibility of using this strategy for the synthesis of multi-triazole libraries easily tunable with electron-donating or electron-attracting functional groups. The possible applications of the synthesized 1,2,3-triazoles are the topic of current investigation in our laboratory.

Commercially available reagents and solvents were used as received. Alkynes **I**, **II**,[11] and **III**[18] were synthesized as reported in the literature. Compounds **1a**, **1e**, and **1f** have been reported elsewhere and their spectroscopic characterization is consistent with the one described in this article. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Petroleum ether used refers to the fraction boiling in the 35–60 °C range. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha FT-IR/ATR spectrophotometer. NMR spectra were obtained with a Bruker Avance DMX-500 (500 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from Me_4Si as an internal reference; coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were recorded on JEOL JMS-SX 102a and Agilent-MSD-TOF-1069A spectrometers 41.

1,2,3-Triazoles Derived from Hydroxybenzene; 1-Benzyl-4-phenoxymethyl-1*H*-1,2,3-triazole (1a); Typical Procedure

To a 20 mL round-bottomed flask equipped with a magnetic stirrer, were charged $Cu(OAc)_2{\cdot}H_2O$ (7 mg, 0.035 mmol, 5 mol%), 1,10-phenanthroline monohydrate (7 mg, 0.035 mmol, 5 mol%), and sodium L-ascorbate (139 mg, 0.70 mmol). After the addition of a mixture of EtOH–H_2O (5 mL, 4:1 v/v), the resulting suspension was stirred for 5 min at r.t. Subsequently, **I** (93 mg, 0.70 mmol), NaN_3 (50 mg, 0.77 mmol), and benzyl chloride (0.09 mL, 0.78 mmol) were added to the reaction mixture and stirred for 16 h at r.t. H_2O (5 mL) was added to the mixture and the precipitate was collected by filtration, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 95:5 v/v); yield: 154 mg (83%); white solid; mp 120–122 °C (Table 1).

FT-IR (ATR): 3137, 3090, 3030, 3002, 2960, 2924, 2872, 1716, 1593 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 2 H, ArCH_2N), 5.55 (s, 2 H, ArOCH_2), 6.97–7.00 (m, 3 H, CH_{ar}), 7.29–7.32 (m, 4 H, CH_{ar}), 7.38–7.40 (m, 3 H, CH_{ar}), 7.55 (s, 1 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 54.2 (ArCH_2N), 62.1 (ArOCH_2), 114.8 (CH_{ar}), 121.2 (CH_{ar}), 122.6 ($CH_{triazole}$), 128.1 (CH_{ar}), 128.8 (CH_{ar}), 129.1 (CH_{ar}), 129.5 (CH_{ar}), 134.5 (C_{ar}), 144.1 ($C_{triazole}$), 158.2 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{15}N_3O + H^+$: 266.1287; found: 266.1289.

1-(4-Fluorobenzyl)-4-phenoxymethyl-1*H*-1,2,3-triazole (1b)

The procedure described for **1a** was followed using 4-fluorobenzyl chloride (0.78 mmol, 113 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 97:3 v/v); yield: 160 mg (81%); white solid; mp 88–90 °C.

FT-IR (ATR): 3142, 3106, 3066, 2951, 2890, 1596, 1584, 1507, 1498, 1468 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 2 H, ArCH_2N), 5.52 (s, 2 H, ArOCH_2), 6.98–7.00 (m, 3 H, CH_{ar}), 7.07–7.10 (m, 2 H, CH_{ar}), 7.29–7.31 (m, 4 H, CH_{ar}), 7.55 (s, 1 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.5 (ArCH_2N), 62.0 (ArOCH_2), 114.7 (CH_{ar}), 116.1 (d, *J* = 21.4 Hz, $CH_{ar\text{-}F}$), 121.2 (CH_{ar}), 122.4 ($CH_{triazole}$), 129.5 (CH_{ar}), 129.9 (d, *J* = 8.8 Hz, $CH_{ar\text{-}F}$), 130.3 (d, *J* = 3.8 Hz, $C_{ar\text{-}F}$), 144.8 ($C_{triazole}$), 158.1 (C_{ar}), 163.0 (d, *J* = 216.4 Hz, $C_{ar\text{-}F}$).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{14}FN_3O + H^+$: 284.1124; found: 284.1198.

1-(4-Chlorobenzyl)-4-phenoxymethyl-1*H*-1,2,3-triazole (1c)

The procedure described for **1a** was followed using 4-chlorobenzyl chloride (0.78 mmol, 126 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 98:2 v/v); yield: 157 mg (75%); white solid; mp 70–72 °C.

FT-IR (ATR): 3127, 3084, 3068, 2919, 2874, 1913, 1720, 1598, 1491, 1462 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 2 H, ArCH_2N), 5.51 (s, 2 H, ArOCH_2), 6.98–7.00 (m, 3 H, CH_{ar}), 7.22 (d, *J* = 7.7 Hz, 2 H, CH_{ar}), 7.29–7.31 (m, 2 H, CH_{ar}), 7.37 (d, *J* = 7.7 Hz, 2 H, CH_{ar}), 7.57 (s, 1 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.5 (ArCH_2N), 62.0 (ArOCH_2), 114.8 (CH_{ar}), 121.3 (CH_{ar}), 122.5 ($CH_{triazole}$), 129.3 (CH_{ar}), 129.4 (CH_{ar}), 129.5 (CH_{ar}), 133.0 (C_{ar}), 134.9 (C_{ar}), 144.9 ($C_{triazole}$), 158.2 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{14}ClN_3O + H^+$: 300.0898; found: 300.0905.

1-(4-Bromobenzyl)-4-phenoxymethyl-1*H*-1,2,3-triazole (1d)

The procedure described for **1a** was followed using 4-bromobenzyl bromide (0.78 mmol, 195 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 99:1 v/v); yield: 190 mg (79%); white solid; mp 108–110 °C.

FT-IR (ATR): 3133, 3096, 3059, 3041, 3002, 2938, 2875, 1597, 1585, 1486, 1463 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.22 (s, 2 H, ArCH_2N), 5.50 (s, 2 H, ArOCH_2), 6.98–7.01 (m, 3 H, CH_{ar}), 7.17 (d, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.29–7.32 (m, 2 H, CH_{ar}), 7.52 (s, 1 H, $CH_{triazole}$), 7.55 (d, 7.8 Hz, 2 H, CH_{ar}).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.5 (ArCH_2N), 62.0 (ArOCH_2), 114.8 (CH_{ar}), 121.3 (CH_{ar}), 121.5 ($CH_{triazole}$), 123.0 (C_{ar}), 129.5 (CH_{ar}), 129.7 (CH_{ar}), 132.3 (CH_{ar}), 133.5 (C_{ar}), 145.0 ($C_{triazole}$), 158.2 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{14}BrN_3O + H^+$: 344.0393; found: 344.0396.

1-(4-Iodobenzyl)-4-phenoxymethyl-1*H*-1,2,3-triazole (1e)
The procedure described for **1a** was followed using 4-iodobenzyl bromide (0.78 mmol, 232 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 99:1 v/v); yield: 189 mg (69%); white solid; mp 110–112 °C.

FT-IR (ATR): 3131, 3098, 3040, 3016, 2937, 2876, 1597, 1585, 1496, 1483, 1462 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 2 H, ArCH_2N), 5.49 (s, 2 H, ArOCH_2), 6.98–7.01 (m, 3 H, CH_{ar}), 7.04 (d, *J* = 7.6 Hz, 2 H, CH_{ar}), 7.29–7.32 (m, 2 H, CH_{ar}), 7.55 (s, 1 H, $CH_{triazole}$), 7.74 (d, *J* = 7.6 Hz, 2 H, CH_{ar}).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.7 (Ar*C*H_2N), 62.0 (ArO*C*H_2), 94.6 (C_{ar}), 114.8 (CH_{ar}), 121.3 (CH_{ar}), 122.5 ($CH_{triazole}$), 129.5 (CH_{ar}), 129.8 (CH_{ar}), 134.2 (C_{ar}), 138.3 (CH_{ar}), 145.0 ($C_{triazole}$), 158.2 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{14}IN_3O$ + H^+: 392.0215; found: 392.0257.

1-(4-Methoxybenzyl)-4-phenoxymethyl-1*H*-1,2,3-triazole (1f)
The procedure described for **1a** was followed using 4-methoxybenzyl chloride (0.78 mmol, 122 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 97:3 v/v); yield: 153 mg (74%); white solid; mp 74–76 °C.

FT-IR (ATR): 3125, 3069, 3040, 3008, 2954, 2931, 2911, 2873, 2837, 1610, 1598, 1586, 1511, 1495, 1455 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 5.20 (s, 2 H, ArCH_2N), 5.48 (s, 2 H, ArOCH_2), 6.92 (d, *J* = 7.9 Hz, 2 H, CH_{ar}), 6.93–6.98 (m, 3 H, CH_{ar}), 7.25 (d, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.28–7.30 (m, 2 H, CH_{ar}), 7.52 (s, 1 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.8 (Ar*C*H_2N), 55.4 (OCH_3), 62.1 (ArO*C*H_2), 114.5 (CH_{ar}), 114.8 (CH_{ar}), 121.2 (CH_{ar}), 122.3 ($CH_{triazole}$), 126.5 (C_{ar}), 129.5 (CH_{ar}), 129.7 (CH_{ar}), 144.6 ($C_{triazole}$), 158.2 (C_{ar}), 160.0 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{17}N_3O_2$ + H^+: 296.1354; found: 296.1392.

Bis-1,2,3-triazoles Derived from 1,3-Dihydroxybenzene; 4,4′-[1,3-phenylenebis(oxymethylene)]bis(1-benzyl-1*H*-1,2,3-triazole (2a); Typical Procedure
To a 20 mL round-bottomed flask equipped with a magnetic stirrer, were charged $Cu(OAc)_2·H_2O$ (7 mg, 0.035 mmol, 5 mol%), 1,10-phenanthroline monohydrate (7 mg, 0.035 mmol, 5 mol%), and sodium L-ascorbate (139 mg, 0.70 mmol). After the addition of a mixture of EtOH–H_2O (5 mL, 4:1 v/v), the resulting suspension was stirred for 5 min at r.t. Subsequently, **II** (130 mg, 0.70 mmol), NaN_3 (100 mg, 1.54 mmol), and benzyl chloride (0.18 mL, 1.54 mmol) were added to the reaction mixture and stirred for 20 h at r.t. H_2O (5 mL) was added to the mixture and the precipitate was collected by filtration, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 98:2 v/v); yield: 225 mg (71%); white solid; mp 160–162 °C (Table 2).

FT-IR (ATR): 3137, 3090, 3030, 3002, 2960, 2924, 2872, 1716, 1593 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.16 (s, 4 H, ArCH_2N), 5.54 (s, 4 H, ArOCH_2), 6.59–6.61 (m, 3 H, CH_{ar}), 7.18 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 7.28–7.30 (m, 4 H, CH_{ar}), 7.37–7.39 (m, 6 H, CH_{ar}), 7.55 (s, 2 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 54.2 (Ar*C*H_2N), 62.1 (ArO*C*H_2), 102.1 (CH_{ar}), 107.6 (CH_{ar}), 122.7 ($CH_{triazole}$), 128.1 (CH_{ar}), 128.8 (CH_{ar}), 129.1 (CH_{ar}), 130.0 (CH_{ar}), 134.5 (C_{ar}), 144.5 ($C_{triazole}$), 159.4 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{24}N_6O_2$ + H^+: 453.1994; found: 453.2040.

4,4′-[1,3-Phenylenebis(oxymethylene)]bis[1-(4-fluorobenzyl)]-1H-1,2,3-triazole (2b)
The procedure described for **2a** was followed using 4-fluorobenzyl chloride (1.54 mmol, 223 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 97:3 v/v); yield: 260 mg (76%); white solid; mp 109–111 °C.

FT-IR (ATR): 3141, 3080, 3006, 2938, 2927, 2874, 1907, 1771, 1728, 1592, 1510, 1490, 1455, 1333 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.13 (s, 4 H, ArCH_2N), 5.49 (s, 4 H, ArOCH_2), 6.57–6.59 (m, 3 H, CH_{ar}), 7.03–7.07 (m, 4 H, CH_{ar}), 7.16 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 7.25–7.28 (m, 4 H, CH_{ar}), 7.53 (s, 2 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.5 (Ar*C*H_2N), 62.0 (ArO*C*H_2), 102.1 (CH_{ar}), 107.6 (CH_{ar}), 116.0 (d, *J* = 21.4 Hz, $CH_{ar\text{-}F}$), 122.5 ($CH_{triazole}$), 129.9 (d, *J* = 8.8 Hz, $CH_{ar\text{-}F}$), 130.3 (d, *J* = 3.8 Hz, $C_{ar\text{-}F}$), 144.5 ($C_{triazole}$), 159.3 (CH_{ar}), 161.8 (*C*$_{ar}$), 162.8 (d, *J* = 270.2 Hz, $C_{ar\text{-}F}$).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{22}F_2N_6O_2$ + H^+: 489.1806; found: 489.1847.

4,4′-[1,3-Phenylenebis(oxymethylene)]bis[1-(4-chlorobenzyl)]-1H-1,2,3-triazole (2c)
The procedure described for **2a** was followed using 4-chlorobenzyl chloride (1.54 mmol, 248 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 98:2 v/v); yield: 241 mg (66%); white solid; mp 122–124 °C.

FT-IR (ATR): 3127, 3088, 2996, 2948, 2879, 1590, 1489, 1464, 1438, 1409 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.13 (s, 4 H, ArCH_2N), 5.49 (s, 4 H, ArOCH_2), 6.56–6.58 (m, 3 H, CH_{ar}), 7.16 (t, *J* = 7.9 Hz, 1 H, CH_{ar}), 7.20–7.36 (m, 4 H, CH_{ar}), 7.32–7.35 (m, 4 H, CH_{ar}), 7.54 (s, 2 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.6 (Ar*C*H_2N), 62.1 (ArO*C*H_2), 102.2 (CH_{ar}), 107.7 (CH_{ar}), 122.7 ($CH_{triazole}$), 129.4 (2 × CH_{ar}), 129.5 (CH_{ar}), 133.0 (CH_{ar}), 134.9 (C_{ar}), 144.7 ($C_{triazole}$), 159.5 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{22}Cl_2N_6O_2$ + H^+: 521.1215; found: 521.1254.

4,4′-[1,3-Phenylenebis(oxymethylene)]bis[1-(4-bromobenzyl)]-1H-1,2,3-triazole (2d)
The procedure described for **2a** was followed using 4-bromobenzyl bromide (1.54 mmol, 385 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 98:2 v/v); yield: 265 mg (62%); white solid; mp 136–138 °C.

FT-IR (ATR): 3126, 3087, 2945, 2934, 2877, 1591, 1498, 1488, 1464, 1437, 1400, 1382, 1291 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.13 (s, 4 H, ArCH_2N), 5.47 (s, 4 H, ArOCH_2), 6.56–6.58 (m, 3 H, CH_{ar}), 7.12–7.15 (m, 4 H, CH_{ar}), 7.16 (t, *J* = 7.9 Hz, 1 H, CH_{ar}), 7.47–7.49 (m, 4 H, CH_{ar}), 7.54 (s, 2 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.6 (Ar*C*H_2N), 62.1 (ArO*C*H_2), 102.2 (CH_{ar}), 107.7 (CH_{ar}), 122.8 ($CH_{triazole}$), 123.0 (CH_{ar}), 129.8 (CH_{ar}), 130.2 (C_{ar}), 132.4 (CH_{ar}), 133.5 (C_{ar}), 144.7 ($C_{triazole}$), 159.5 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{22}Br_2N_6O_2$ + H^+: 611.0229; found: 611.0227.

4,4′-[1,3-Phenylenebis(oxymethylene)]bis[1-(4-iodobenzyl)]-1H-1,2,3-triazole (2e)
The procedure described for **2a** was followed using 4-iodobenzyl bromide (1.54 mmol, 457 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 99:1 v/v); yield: 315 mg (64%); white solid; mp 158–160 °C.

FT-IR (ATR) : 3130, 3089, 2955, 2946, 2908, 2872, 1614, 1585, 1484, 1459, 1435, 1402 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.14 (s, 4 H, ArCH_2N), 5.46 (s, 4 H, ArOCH_2), 6.57–6.59 (m, 3 H, CH_{ar}), 7.01 (d, *J* = 7.9 Hz, 4 H, CH_{ar}), 7.16 (t, *J* = 7.9 Hz, 1 H, CH_{ar}), 7.53 (s, 2 H, $CH_{triazole}$), 7.71 (d, *J* = 7.8 Hz, 4 H, CH_{ar}).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.6 (Ar*C*H_2N), 62.1 (ArO*C*H_2), 94.6 (C_{ar}), 102.1 (CH_{ar}), 107.7 (CH_{ar}), 122.6 ($CH_{triazole}$), 129.8 (CH_{ar}), 130.1 (CH_{ar}), 134.1 (C_{ar}), 138.3 (CH_{ar}), 144.6 ($C_{triazole}$), 159.3 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{22}I_2N_6O_2$ + H^+: 704.9927; found: 704.9968.

4,4′-[1,3-Phenylenebis(oxymethylene)]bis[1-(4-methoxybenzyl)]-1H-1,2,3-triazole (2f)

The procedure described for **2a** was followed using 4-methoxybenzyl bromide (1.54 mmol, 241 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 97:3 v/v); yield: 247 mg (69%); white solid; mp 132–134 °C.

FT-IR (ATR): 3293, 3127, 3088, 3003, 2957, 2934, 2878, 2836, 1720, 1592, 1512, 1490, 1463 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 6 H, OCH_3), 5.14 (s, 4 H, ArCH_2N), 5.47 (s, 4 H, ArOCH_2), 6.58–6.60 (m, 3 H, CH_{ar}), 6.92 (d, *J* = 7.8 Hz, 4 H, CH_{ar}), 7.25 (t, *J* = 7.9 Hz, 1 H, CH_{ar}), 7.26 (d, *J* = 8.0 Hz, 4 H, CH_{ar}), 7.52 (s, 2 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 53.8 (Ar*C*H_2N), 55.3 (OCH_3), 62.1 (ArO*C*H_2), 102.1 (CH_{ar}), 107.6 (CH_{ar}), 114.5 (CH_{ar}), 122.4 ($CH_{triazole}$), 126.4 (CH_{ar}), 129.7 (C_{ar}), 130.0 (CH_{ar}), 144.3 ($C_{triazole}$), 159.5 (C_{ar}), 160.0 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{28}N_6O_4$ + H^+: 513.2206; found: 513.2247.

Tris-1,2,3-triazoles Derived from 1,3,5-Trihydroxybenzene; 1-Benzyl-4-({3,5-bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenoxy}methyl)-1*H*-1,2,3-triazole (3a); Typical Procedure

To a 50 mL round-bottomed flask equipped with a magnetic stirrer, were charged $Cu(OAc)_2·H_2O$ (8 mg, 0.042 mmol, 10 mol%), 1,10-phenanthroline monohydrate (8 mg, 0.042 mmol, 10 mol%), and sodium L-ascorbate (166 mg, 0.84 mmol). After the addition of a mixture of EtOH–H_2O (10 mL, 4:1 v/v), the resulting suspension was stirred for 5 min at r.t. Subsequently, **III** (100 mg (0.42 mmol), NaN_3 (90 mg, 1.39 mmol), and benzyl chloride (0.16 mL, 1.39 mmol) were added to the reaction mixture and stirred for 24 h at r.t. H_2O (10 mL) was added to the mixture and the precipitate was collected by filtration, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 96:4 v/v); yield: 154 mg (57%); white solid; mp 118–120 °C (Table 3).

FT-IR (ATR): 3138, 3090, 3065, 3011, 2937, 2875, 1589, 1496, 1456, 1435 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.07 (s, 6 H, ArCH_2N), 5.61 (s, 6 H, CCH_2O), 6.32 (s, 3 H, CH_{ar}), 7.31–7.33 (m, 9 H, CH_{ar}), 7.35–7.37 (m, 6 H, CH_{ar}), 8.26 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.8 (Ar*C*H_2N), 61.1 (ArO*C*H_2), 94.6 (CH_{ar}), 124.6 ($CH_{triazole}$), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.7 (CH_{ar}), 135.9 (C_{ar}), 142.8 ($C_{triazole}$), 159.8 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{36}H_{33}N_9O_3$ + H^+: 640.2740; found: 640.2779.

4-[(3,5-Bis{[1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenoxy)methyl]-1-(4-fluorobenzyl)-1*H*-1,2,3-triazole (3b)

The procedure described for **3a** was followed using 4-fluorobenzyl chloride (1.39 mmol, 201 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 95:5 v/v); yield: 160 mg (55%); white solid; mp 168–170 °C.

FT-IR (ATR): 3130, 3079, 3012, 2939, 2873, 1723, 1589, 1518, 1509, 1498, 1458, 1436, 1419, 1403 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.07 (s, 6 H, ArCH_2N), 5.60 (s, 6 H, CCH_2O), 6.31 (s, 3 H, CH_{ar}), 7.20 (dd, *J* = 8.5 Hz, 6 H, CH_{ar}), 7.40 (dd, *J* = 8.5 Hz, 6 H, CH_{ar}), 8.27 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.0 (Ar*C*H_2N), 61.1 (ArO*C*H_2), 94.5 (CH_{ar}), 115.5 (d, *J* = 21.4 Hz, $CH_{ar\text{-}F}$), 124.5 ($CH_{triazole}$), 130.2 (d, *J* = 8.8 Hz, $CH_{ar\text{-}F}$), 132.1 (d, *J* = 3.8 Hz, $C_{ar\text{-}F}$), 142.8 ($C_{triazole}$), 159.7 (C_{ar}), 161.8 (d, *J* = 246.3 Hz, $C_{ar\text{-}F}$).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{36}H_{30}F_3N_9O_3$ + H^+: 694.2457; found: 694.2491.

4-[(3,5-Bis{[1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenoxy)methyl]-1-(4-chlorobenzyl)-1*H*-1,2,3-triazole (3c)

The procedure described for **3a** was followed using 4-chlorobenzyl bromide (1.39 mmol, 224 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 96:4 v/v); yield: 190 mg (61%); white solid; mp 155–157 °C.

FT-IR (ATR): 3129, 3085, 3064, 3029, 2934, 2875, 1724, 1590, 1492, 1455, 1438, 1430 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.08 (s, 6 H, ArCH_2N), 5.61 (s, 6 H, CCH_2O), 6.31 (s, 3 H, CH_{ar}), 7.35 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 7.43 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 8.28 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.0 (Ar*C*H_2N), 61.1 (ArO*C*H_2), 94.6 (CH_{ar}), 124.6 ($CH_{triazole}$), 128.6 (CH_{ar}), 129.8 (CH_{ar}), 132.8 (C_{ar}), 134.8 (C_{ar}), 142.8 ($C_{triazole}$), 159.7 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{36}H_{30}Cl_3N_9O_3$ + H^+: 744.1586; found: 744.1589.

4-[(3,5-Bis{[1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenoxy)methyl]-1-(4-bromobenzyl)-1*H*-1,2,3-triazole(3d)

The procedure described for **3a** was followed using 4-bromobenzyl bromide (1.39 mmol, 347 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 95:5 v/v); yield: 236 mg (64%); white solid; mp 115–117 °C.

FT-IR (ATR): 3139, 3115, 3070, 2931, 2873, 1722, 1593, 1487, 1458, 1432, 1407 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.08 (s, 6 H, ArCH_2N), 5.60 (s, 6 H, CCH_2O), 6.32 (s, 3 H, CH_{ar}), 7.28 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 7.57 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 8.28 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.0 (Ar*C*H_2N), 61.1 (ArO*C*H_2), 94.5 (CH_{ar}), 121.4 (C_{ar}), 124.6 ($CH_{triazole}$), 130.1 (CH_{ar}), 131.6 (CH_{ar}), 135.3 (C_{ar}), 142.8 ($C_{triazole}$), 159.7 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{36}H_{30}Br_3N_9O_3$ + H^+: 878.0059; found: 878.0076.

4-[(3,5-Bis{[1-(4-iodobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenoxy)methyl]-1-(4-iodobenzyl)-1*H*-1,2,3-triazole (3e)

The procedure described for **3a** was followed using 4-iodobenzyl bromide (1.39 mmol, 413 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 95:5 v/v); yield: 248 mg (58%); white solid; mp 183–185 °C.

FT-IR (ATR) : 3137, 3119, 3076, 2933, 2874, 1718, 1677, 1592, 1484, 1458, 1432 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.07 (s, 6 H, ArCH_2N), 5.57 (s, 6 H, CCH_2O), 6.31 (s, 3 H, CH_{ar}), 7.13 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 7.74 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 8.26 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.2 (Ar*C*H_2N), 61.0 (ArO*C*H_2), 94.4 (CH_{ar}), 94.5 (C_{ar}), 124.6 ($CH_{triazole}$), 130.2 (CH_{ar}), 135.6 (C_{ar}), 137.4 (CH_{ar}), 142.8 ($C_{triazole}$), 159.7 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{36}H_{30}I_3N_9O_3$ + H^+: 1017.9606; found: 1017.9696.

4-[(3,5-Bis{[1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenoxy)methyl]-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole (3f)

The procedure described for **3a** was followed using 4-methoxybenzyl chloride (1.39 mmol, 218 mg). The crude product was purified by column chromatography (CH_2Cl_2–MeOH, 97:3 v/v); yield: 150 mg (49%); white solid; mp 112–114 °C.

FT-IR (ATR): 3135, 3092, 3000, 2932, 2836, 1719, 1590, 1511, 1459, 1437 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.73 (s, 9 H, OCH_3), 5.06 (s, 6 H, ArCH_2N), 5.52 (s, 6 H, CCH_2O), 6.30 (s, 3 H, CH_{ar}), 6.92 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 7.30 (d, *J* = 8.5 Hz, 6 H, CH_{ar}), 8.21 (s, 3 H, $CH_{triazole}$).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 52.3 (ArCH_2N), 55.0 (OCH_3), 61.1 (ArOCH_2), 94.5 (CH_{ar}), 114.0 (CH_{ar}), 124.2 ($CH_{triazole}$), 127.8 (C_{ar}), 129.3 (CH_{ar}), 142.7 ($C_{triazole}$), 159.1 (C_{ar}), 159.7 (C_{ar}).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{39}H_{39}N_9O_6 + H^+$: 730.3057; found: 730.3103.

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