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Novel ion-binding C3 symmetric tripodal triazoles: synthesis and characterization

Research Article

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Abstract: Novel C_3 symmetric tripodal molecules were synthesized from cyclohexane 1,3,5-tricarboxylic acid. Utilizing click and Sonogashira reactions, ion-binding triazole and pyridazin-3(2H)-one units were incorporated to form polydentate ligands for ion complexation. The structures of the novel C_3 symmetric derivatives were extensively characterized by ^1H, ^{13}C and 2D NMR techniques along with HRMS and IR. The copper(I)-binding potentials of these ligands were investigated by using them as additives in model copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reactions. The copper(I) complexation ability of our compound was also proved by different spectroscopic methods, such as mass spectrometry, UV and NMR spectroscopy. Based on the mass spectrometric data all of the C_3 symmetric ligands formed 1:1 complex with copper(I) ion. The specific role of C_3 symmetric polydentate form in the complexation process was also discussed.

Keywords: *Cycloaddition • NMR spectroscopy • CuAAC • RuAAC • Sonogashira reaction*

1. Introduction

A large number of C_3 symmetric tripodal compounds have recently been synthesized with a wide variety of structures for a number of applications such as chelating cations [1-5] and anions [1,6,7], organocatalysts [8], chemosensors [2,9,10] or contrast agents [11] *etc*. Symmetric molecules with ion-binding functionalities have great potential in ion-recognition or in catalysis as polydentate complexing agents. One of the highly capable moieties for metal ion complexation is 1,2,3-triazole.

Concerning the preparation of triazoles, the well-known limitations of the Huisgen 1,3-dipolar cycloadditon (elevated temperature, long reaction time and the lack of regioselectivity) [12,13] were overcome by the introduction of the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) in 2002 [14,15]. Due to its regioselectivity, mild reaction conditions and excellent yields, CuAAC is the most effective tool to prepare 1,4-substituted triazoles from terminal alkynes and azides (click reaction). With this process the synthesis of triazoles became a highly investigated field of organic chemistry with over a hundred related reports. Several highly active copper(I)-catalysts have been developed since 2002 [16-18]. Because of the high oxidability and low solubility of copper(I)-salts, usually additional reducing agent or nitrogen base as ligand is used. The complexation of copper(I) by nitrogen-containing ligands results in improved solubility and minimized oxidation.

The ruthenium(II)-catalysed azide-alkyne cycloaddition (RuAAC) was published in 2005 [19], which raised the possibility to make 1,5-substituted triazoles from terminal alkynes and to couple internal alkynes and azides to 1,4,5-substituted triazoles as well.

With these robust methods, triazole could be an easy-to-make building block with a wide variety of substituents. In the structures of reported C_3 symmetric triazole derivatives, the central elements were benzene [20-23], triazine [24], phosphorus [25] or no central element at all: cyclic pseudohexapeptide [26] and homooxacalix [3] arene [10,27] structures. C_3 tripodal triazole derivatives

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with nitrogen core have also been developed especially for ligands to enhance CuAAC reactions [16].

Based on all these facts, we aimed at designing triazole containing C3 symmetric ion-binding compounds with a cyclohexane core (**20, 21, 22, 23, 24, 25**). The potential advantage of the cyclohexane scaffold is its flexibility compared to the rigid benzene scaffold. The flexible, conformational motions (often important for ion-binding) can enhance the complexation processes of many ions. The copper(I) complexation potential of these ligands was investigated in a model CuAAC reaction and by various spectroscopic methods.

2. Experimental procedure

All solvents and chemicals were obtained commercially and were used without further purification. Reaction progress was observed by thin-layer chromatography on commercial silica gel plates (Merck silica gel F254 on aluminum sheets) using different mobile phases. For column chromatography, Kieselgel 60 (particle size 0.040–0.063 mm) was employed. High-resolution accurate masses were determined with an Agilent 6230 time-of-flight mass spectrometer. Samples were introduced by the Agilent 1260 Infinity LC system, and the mass spectrometer was operated in conjunction with a Jet Stream electrospray ion source in positive ion mode. Reference masses of m/z = 121.050873 and 922.009798 were used to calibrate the mass axis during analysis. Mass spectra were processed using Agilent MassHunter B.02.00 software.

Melting points were taken on a Stuart SMP-3 apparatus. IR spectra were recorded in the range of 4000–650 cm^{-1} by means of a Perkin Elmer Spectrum 400 FT-IR/FT-NIR spectrometer and Perkin Elmer Spectrum Software version 6.3.1. UV spectra were recorded on a Jasco V-550 spectrometer in 1 cm cuvettes at 25°C using diode-array detector. Absorption spectra were measured in the range of 220-360 nm. NMR spectra were recorded on a VARIAN VNMRS spectrometer (599.9 MHz for ^{1}H, 150.9 MHz for ^{13}C) with a dual 5 mm inverse-detection gradient (IDPFG) probehead in DMSO-d_6 or chloroform-d_1 solutions. Chemical shifts are expressed in ppm with TMS as internal standard. ^{1}H and ^{13}C NMR signals were assigned on the basis of one- and two-dimensional homo- and heteronuclear experiments (COSY, HMBC and HSQC).

Conversion rates of **1** and **28** to **29** in CuAAC reactions were monitored by reversed-phase HPLC method. HPLC analysis was performed by an Agilent 1260 Infinity LC system. Agilent Zorbax SB C18, 1.8 µm, 2.1×50 mm column was used; the column temperature was maintained at 25°C. The mobile phase consisted of methanol:water 50:50. The flow rate was 0.2 mL min^{-1} and the detector wavelength was set to 210 nm for the analysis. Spectra were processed using Agilent MassHunter B.02.00 software. The purity of the final compounds was determined using the above mentioned HPLC system in conjunction with an Agilent 6460 triple-quadrupole mass spectrometer. The mass spectrometer was used in positive ion mode with Jet Stream electrospray source scanning from 100 to 1500 Da. ESI was carried out at 300°C, with a nebulizer pressure of 70 psi and nitrogen dry gas flow rate of 12 L min^{-1}. The fragmentor voltage was set at 100 V.

2.1. General CuAAC procedure for 2, 4, 7

To $Cu(OAc)_2 \cdot H_2O$ (0.01 equiv.) and PPh_3 (0.02 equiv.) in CH_2Cl_2 (V_1) propargyl alcohol (n_1) and the appropriate azide (**1**, **3** or **6**; n_1) were added. After overnight stirring at room temperature and workup, the title products (**2**, **4**, **7**) were obtained.

***(1-benzyl-1H-1,2,3-triazol-4-yl)methanol* (2)**

V_1= 8 mL, n_1= 4.9 mmol. Workup: evaporated to dryness, then purified by column chromatography (silica gel, EtOAc eluent). Yield: 78%, off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) 7.45(s, 1H, 3-H), 7.35(m, 2H, 10-H and 12-H), 7.34(m, 1H, 11-H), 7.25(m, 2H, 9-H and 13-H), 5.49(s, 2H, 7-H_2), 4.74(s, 2H, 1-H_2), 3.06(s, 1H, 1-O*H*); ^{13}C NMR (150 MHz, $CDCl_3$) 148.7(C2), 135.1(C8), 129.8(C10 and C12), 129.5(C11), 128.8(C9 and C13), 122.4(C3), 57.0(C1), 55.0(C7); HRMS (ESI) calcd for $C_{10}H_{12}N_3O$ $[M+H]^+$ 190.0975, found 190.0969. Data was consistent with reported analyis [28].

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

V_1= 2.5 mL, n_1= 1.4 mmol. Workup: precipitated from the reaction mixture with Et_2O, filtered, then extracted from H_2O (15 mL) with CH_2Cl_2 (3×15 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Yield: 64%, off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) 7.69(s, 1H, 3-H), 7.50(s, 1H, 9-H), 7.37 and 7.38(m, 3H, 16-H, 17-H and 18-H), 7.27(m, 2H, 15-H and 19-H), 5.62(s, 2H, 7-H_2), 5,50(s, 2H, 13- H_2), 4.76(d, 2H, J=5.8 Hz, 1- H_2), 2.31(t, 1H, J=5.8 Hz, 1-O*H*); ^{13}C NMR (150 MHz, $CDCl_3$) 148.7 (C2), 142.7(C8), 134.6(C14), 130.0 and 129.8(C16, C17 and C18), 129.0(C15 and C19), 123.6(C9), 122.6(C3), 57.3(C1), 55.2(C13), 46.1(C7); HRMS (ESI) calcd for $C_{13}H_{14}N_6NaO$ $[M+Na]^+$ 293.1121, found 293.1114. Data was consistent with reported analysis [29].

5-{3-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl] propyl}-2-methyl-2,3-dihydropyridazin-3-one (7)

V_1=3.0 mL, n_1=1.4 mmol. Workup: evaporated to dryness, extracted from brine (15 mL) with CH_2Cl_2 (5×15 mL), dried over Na_2SO_4, filtered and subsequently

evaporated. The residue was precipitated with Et_2O, filtered and dried. Yield: 67%, off-white solid. TLC: R_f = 0.03 (eluent: EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.60(d, 1H, J= 2.2 Hz, 15-H), 7.57(s, 1H, 3-H), 6.61(m, 1H, 11-H), 4.79(s, 2H, 1-H_2), 4.43(t, 2H, J= 6.6 Hz, 7-H_2), 3.75(s, 3H, N13-CH_3), 2.88(bs, 1H, 1-*OH*), 2.54(t, 2H, J= 7.6 Hz, 9-H_2), 2.26(m, 2H, 8-H_2); ^{13}C NMR (150 MHz, $CDCl_3$) 161.3(C12), 149.2(C2), 145.4(C10), 138.1(C15), 126.9(C11), 122.7(C3), 57.3(C1), 49.9(C7), 40.6(N13-*CH3*), 29.7(C9), 29.6(C8); HRMS (ESI) calcd for $C_{11}H_{15}N_5NaO_2$ $[M+Na]^+$ 272.1118, found 272.1120.

5-(dimethylamino)-N-{2-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]ethyl}naphthalene-1-sulfonamide (9)

To the solution of **8** (2.0 mmol) in MeCN (5 mL) and H_2O (5 mL), propargyl alcohol (1.1 equiv.), Et_3N (2.0 equiv.) and CuI (0.1 equiv.) were added. After overnight stirring at room temperature, the reaction mixture was concentrated in vacuo. H_2O (10 mL) was added and extracted with CH_2Cl_2 (3×15 mL), the organic layer was dried over Na_2SO_4, and evaporated to dryness. The oily residue was purified by column chromatography (silica gel, EtOAc eluent). Yield: 97%, green solid. TLC R_f = 0.19 (eluent: EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 8.55(dm, 1H, *J*= 8.5 Hz, 14-H), 8.24(m, 2H, 12-H and 19-H), 7.52(dd, 1H, *J*= 8.5, 7.3 Hz, 13-H), 7.51(s, 1H, 3-H), 7.49(dd, 1H, *J*= 8.5, 7.6 Hz, 18-H), 7.16(dm, 1H, *J*= 7.6 Hz, 17-H), 7.00(t, 1H, *J*= 6.2 Hz, N9-*H*), 4.67(d, 2H, *J*= 2.9 Hz, 1-H_2), 4.41(m, 2H, 7-H_2), 3.49(m, 1H, 1-*OH*), 3.45(dd, 2H, *J*= 10.9, 6.0 Hz, 8-H_2), 2.88(s, 6H, 16-N(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) 152.7(C16), 147.9(C2), 135.3(C11), 131.4(C14), 130.6(C15), 130.1(C20), 129.9(C12), 129.2(C18), 124.4(C3), 123.8(C13), 119.5(C19), 116.1(C17), 56.7(C1), 51.4(C7), 46.1(16-N(CH_3)$_2$), 43.4(C8); HRMS (ESI) calcd for $C_{17}H_{22}N_5O_3S$ $[M+H]^+$ 376.1438, found 376.1421.

2.2. General RuAAC procedure for 14-17

Cp*RuCl(COD) (0.02 equiv.) was dissolved in CH_2Cl_2 (V_2) at room temperature under a nitrogen atmosphere. The appropriate internal alkyne (**11** or **13**, n_2) and benzyl azide (**1**, n_2) was added. The reaction mixture was stirred overnight, evaporated to dryness, and the components contained (**14** and **15**, or **16** and **17**) was separated by column chromatography on silica gel.

[1-benzyl-4-(4-methylphenyl)-1H-1,2,3-triazol-5-yl]methanol (14)

V_2= 22 mL, n_2= 3.0 mmol. The column chromatography eluent was the mixture of *n*-hexane and EtOAc (1:1). Yield: 60%, beige solid. TLC: R_f = 0.32 (eluent: *n*-hexane-EtOAC (1:1)); ^{1}H NMR (600 MHz , $CDCl_3$) 7.57(d, 2H, *J*= 8.6 Hz, 15-H and 19-H), 7.33(m, 2H, 10-H and 12-H), 7.31(m, 1H, 11-H), 7.25(d, 2H, *J*= 7.2 Hz, 9-H and 13-H), 6.91(d, 2H, *J*= 8.6 Hz, 16-H and 18-H), 5.61(s, 2H, 7-H_2), 4.65(s, 2H, 1-H_2), 3.81(s, 3H, 17-OCH_3), 2.72(bs, 1H, 1-*OH*); ^{13}C NMR (150 MHz, $CDCl_3$) 160.4(C17), 146.9(C3), 135.7(C8), 131.8(C2), 129.73(C10 and C12), 129.66(C15 and C19), 129.2(C11), 128.2(C9 and C13), 123.7(C14), 114.9(C16 and C18), 56.0(17-OCH_3), 53.24(C1), 53.20(C7); HRMS (ESI) calcd for $C_{17}H_{18}N_3O_2$ $[M+H]^+$ 296.1394, found 296.1394.

[1-benzyl-5-(4-methylphenyl)-1H-1,2,3-triazol-4-yl]methanol (15)

Yield: 18%, pale yellow solid. TLC : R_f = 0.10 (eluent: hexane - EtOAc (1:1)); ^{1}H NMR (600 MHz, $CDCl_3$) 7.26(m, 3H, 10-H, 11-H and 12-H), 7.17(d, 2H, *J*= 8.7 Hz, 15-H and 19-H), 7.06(m, 2H, 9-H and 13-H), 6.94(d, 2H, *J*= 8.7 Hz, 16-H and 18-H), 5.44(s, 2H, 7-H_2), 4.66(s, 2H, 1-H_2), 3.83(s, 3H, 17-OCH_3), 2.59(bs, 1H, 1-*OH*); ^{13}C NMR (150 MHz, $CDCl_3$) 161.3(C17), 145.5(C2), 136.5(C3), 136.1(C8), 131.7(C15 and C19), 129.5(C10 and C12), 128.8(C11), 128.0(C9 and C13), 118.9(C14), 115.2(C16 and C18), 56.3(C1), 56.1(17-OCH_3), 52.1(C7). HRMS (ESI) calcd for $C_{17}H_{18}N_3O_2$ $[M+H]^+$ 296.1394, found 296.1394.

5-[1-benzyl-5-(hydroxymethyl)-1H-1,2,3-triazol-4-yl]-2-methyl-2,3-dihydropyridazin-3-one (16)

V_2= 20 mL, n_2= 2.2 mmol. Workup: separation by two consecutive column chromatographies using the mixture of *n*-hexane, CH_2Cl_2 and acetone (2:5:5) as eluent. Nominal yield: 70%, separated yield: 53%, white solid. TLC : R_f = 0.43 (eluent: hexane - CH_2Cl_2 - acetone (2:5:5)); ^{1}H NMR (600 MHz, $CDCl_3$) 8.46(d, 1H, *J*= 2.0 Hz, 15-H), 7.36(m, 3H, 10-H, 11-H and 12-H), 7.30(m 2H, 9-H and 13-H), 7.27(d, 1H, *J*= 2.0 Hz, 19-H), 5.73(s, 2H, 7-H_2), 4.73(s, 2H, 1-H_2), 3.78(s, 3H, N17-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 161.7(C18), 140.5(C3), 137.0(C15), 136.0(C2), 135.8(C14), 135.0(C8), 129.9 and 129.5(C10, C11 and C12), 128.2(C9 and C13), 124.5(C19), 53.4(C7), 52.8(C1), 40.9(N17-CH_3). HRMS (ESI) calcd for $C_{15}H_{16}N_5O_2$ $[M+H]^+$ 298.1299, found 298.1299.

5-[1-benzyl-4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl]-2-methyl-2,3-dihydropyridazin-3-one (17)

Nominal yield: 15%, separated yield: 0.5%. TLC : R_f = 0.31 (eluent: hexane - CH_2Cl_2 - acetone (2:5:5)); ^{1}H NMR (600 MHz, $CDCl_3$) 7.64(d, 1H, *J*= 2.2 Hz, 15-H), 7.32(m, 3H, 10-H, 11-H and 12-H), 7.09(m, 2H, 9-H and 13-H), 6.85(d, 1H, *J*= 2.2 Hz, 19-H), 5.57(s, 2H, 7-H_2), 4.75(s, 2H, 1-H_2), 3.81(s, 3H, N17-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 160.0(C18), 147.4(C2) 135.9(C15), 134.8(C8), 132.1(C14), 130.3(C3), 129.9 and 129.6(C10, C11 and C12), 129.8(C19), 127.8(C9 and C13), 56.3(C1), 53.7(C7), 41.0(N17-CH_3). HRMS (ESI) calcd for $C_{15}H_{16}N_5O_2$ $[M+H]^+$ 298.1299, found 298.1299.

2.3. General esterification procedure for 20-25, 27

To cyclohexane 1,3,5-tricarboxylic acid (**18**, n_3) in CH_2Cl_2 (V_3) oxalyl chloride (6 equiv.) and DMF (1 drop) were added. The reaction mixture was stirred at reflux for 1 hour, then evaporated to dryness. The oily orange residue was dissolved in CH_2Cl_2 (V_4), the appropriate triazole alcohol (**2**, **4**, **7**, **9**, **14** or **16**, 3 equiv.) and Et_3N (3.3 equiv.) was added. After overnight stirring at room temperature and workup, the title products (**20**-**25)** were obtained. **27** was prepared according to the same procedure from cyclohexanecarboxylic acid (**26,** n_3) and **14**.

1,3,5-tris(1-benzyl-1H-1,2,3-triazol-4-yl)methyl (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (20)

n_3= 0.5 mmol, V_3= 3 mL, V_4= 8 mL. Workup: evaporated to dryness, extracted from H_2O (20 mL) with CH_2Cl_2 (2×15 mL), dried over Na_2SO_4, filtered and subsequently evaporated. The residue was precipitated with EtOAc, filtered and dried. Yield: 54%, off-white solid. M.p.: 151-153°C; TLC : R_f = 0.51 (eluent: EtOAc); IR: ν = 1741, 1722, 1240, 1155, 1051, 721 cm^{-1}; ^1H NMR (600 MHz , $CDCl_3$) 7.49(s, 3H, 3-H), 7.38(m, 6H, 10-H and 12-H), 7.37(m, 3H, 11-H), 7.27(dd, 6H, *J*= 7.8, 1.4 Hz, 9-H and 13-H), 5.52(s, 6H, 7-H_2), 5.17(s, 6H, 1-H_2), 2.33(m, 3H, 1'-H, 3'-H and 5'-H), 2.18(d, 3H, *J*= 13.0 Hz, 2'-H, 4'-H and 6'-H), 1.44(ddd, 3H, *J*= 13.0, 12.8, 12.8 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz, $CDCl_3$); 174.3(C7', C8' and C9'), 143.6(C2), 135.0(C8), 129.9(C10 and C12), 129.5(C11), 128.8(C9 and C13), 124.3(C3), 58.5(C1), 54.9(C7), 42.2(C1', C3' and C5'), 30.8(C2', C4' and C6'); HRMS (ESI) calcd for $C_{39}H_{40}N_9O_6$ $[M+H]^+$ 730.3102, found 730.3111.

1,3,5-tris({1-[(1-benzyl-1H-1,2,3-triazol-4-yl) methyl]-1H-1,2,3-triazol-4-yl}methyl) (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (21)

n_3= 0.27 mmol, V_3= 2 mL, V_4= 7 mL. Workup: evaporated, precipitated with CH_2Cl_2-Et_2O mixture, filtered. The precipitate was extracted from H_2O (20 mL) with CH_2Cl_2 (3*20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Yield: 99%, off-white solid. M.p.: 168-170°C. TLC : R_f = 0.05 (eluent: EtOAc); IR: ν = 1728, 1454, 1225, 1160, 1051, 716 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) 8.23(s, 3H, 9-H), 8.16(s, 3H, 3-H), 7.36(m, 6H, 16-H and 18-H), 7.31(m, 9H, 15-H, 17-H and 19-H), 5.68(s, 6H, 7-H_2), 5.59(s, 6H, 13-H_2), 5.11(s, 6H, 1-H_2), 2.50(m, 3H, 1'-H, 3'-H and 5'-H), 2.06(d, 3H, *J*= 12.7 Hz, 2'-H, 4'-H and 6'-H), 1.28(ddd, 3H, *J*= 12.8, 12.8, 12.7 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz, DMSO-d_6) 173.4(C7', C8' and C9'), 141.9(C2), 141.7(C8), 135.8(C14), 128.7(C16 and C18), 128.2(C17), 128.0(C15 and C19), 124.8(C3), 124.3(C9), 57.3(C1), 52.9(C13), 44.5(C7), 40.1(C1', C3' and C5'), 29.9(C2', C4' and C6'); HRMS (ESI) calcd for $C_{48}H_{49}N_{18}O_6$ $[M+H]^+$ 973.4077, found 973.4077.

1,3,5-tris({1-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)propyl]-1H-1,2,3-triazol-4-yl} methyl) (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (22)

n_3= 0.28 mmol, V_3= 2 mL, V_4= 7 mL. Workup: brine (15 mL) was added, extracted with CH_2Cl_2 (3×15 mL), dried over Na_2SO_4, filtered and evaporated. The oily residue was purified by column chromatography (silica gel, acetone eluent). Yield: 38%, colourless oil. TLC: R_f = 0.10 (eluent: acetone); ^1H NMR (600 MHz, $CDCl_3$) 7.60(m, 6H, 3-H and 15-H), 6.71(m, 3H, 11-H), 5.20(s, 6H, 1-H), 4.42(t, 6H, *J*= 6.9 Hz, 7-H_2), 3.75(s, 9H, N13-CH_3), 2.53(t, 6H, *J*= 7.4 Hz, 9-H_2), 2.38(m, 3H, 1'-H, 3'-H and 5'-H), 2.25(m, 6H, 8-H_2), 2.23(m, 3H, 2'-H, 4'-H and 6'-H), 1.48(ddd, 3H, *J*= 13.0, 12.9, 12.9 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz, $CDCl_3$) 174.4(C7', C8' and C9'), 161.3(C12), 145.6(C10), 143.5(C2), 138.2(C15), 127.1(C11), 124.6(C3), 58.4(C1), 49.9(C7), 42.2(C1', C3' and C5'), 40.6(13-CH_3), 30.8(C2', C4' and C6'), 29.7(C8), 29.6(C9); HRMS (ESI) calcd for $C_{42}H_{52}N_{15}O_9$ $[M+H]^+$ 910.4067, found 910.4065.

1,3,5-tris(1-{2-[5-(dimethylamino)naphthalene-1-sulfonamido]ethyl}-1H-1,2,3-triazol-4-yl)methyl (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (23)

n_3= 0.58 mmol, V_3= 3 mL, V_4= 8 mL. Workup: washed with H_2O (15 mL), the inorganic layer extracted with CH_2Cl_2 (2×15 mL), combined organic layers were dried over Na_2SO_4, filtered and evaporated. The green, solid residue was purified by column chromatography (silica gel, EtOAc eluent), then precipitated with Et_2O. Yield: 36%, yellow solid. M.p.: 133-136°C; TLC : R_f = 0.12 (eluent: EtoAc); IR: ν = 1733, 1575, 1457, 1323, 1161, 1142, 788 cm^{-1}; ^1H NMR (600 MHz , $CDCl_3$) 8.50(d, 3H, *J*= 8.3 Hz, 14-H), 8.18(m, 3H, 19-H), 8.16(m, 3H, 12-H), 7.57(s, 3H, 3-H), 7.47(t, 3H, *J*= 8.0 Hz, 13-H), 7.43(t, 3H, *J*= 8.0 Hz, 18-H), 7.11(d, 3H, *J*= 7.5 Hz, 17-H), 6.51(t, 3H, *J*= 6.0 Hz, N9-H), 5.05(s, 6H, 1-H_2), 4.37(s, 6H, 7-H_2), 3.39(m, 6H, 8-H_2), 2.84(s,18H, 16-N(CH_3)$_2$), 2.32(m, 3H, 1'-H, 3'-H and 5'-H), 2.17(d, 3H, *J*= 12.4 Hz, 2'-H, 4'-H and 6'-H), 1.42(ddd, 3H, *J*= 12.7, 12.7, 12.4 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz , $CDCl_3$) 174.4(C7', C8' and C9'), 152.6(C16), 143.0(C2), 135.0(C11), 131.3(C14), 130.5(C15), 130.04 and 130.02(C12 and C20), 129.2(C18), 125.8(C3), 123.8(C13), 119.3(C19), 116.0(C17), 58.3(C1), 50.7(C7), 46.0(16-N(CH_3)$_2$), 43.4(C8), 41.9(C1', C3' and C5'), 30.7(C2', C4' and C6'); HRMS (ESI) calcd for $C_{60}H_{70}N_{15}O_{12}S_3$ $[M+H]^+$ 1288.4491, found 1288.4480.

1,3,5-tris[1-benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazol-5-yl]methyl (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (24)

n_3= 0.23 mmol, V_3= 2 mL, V_4= 4 mL. Workup: CH_2Cl_2 (10 mL) was added, washed with H_2O (15 mL), the inorganic layer extracted with CH_2Cl_2 (15 mL), combined organic layers were dried over Na_2SO_4, filtered and evaporated. The orange solid residue was purified by column chromatography (silica gel, *n*-hexane-EtOAC 1:2 mixture as eluent). Yield: 78%, off-white solid. M.p.: 107-109°C; TLC : R_f = 0.45 (eluent: hexane – EtoAc (1:2)); IR: ν = 1732, 1616, 1508, 1248, 11177, 836, 723 cm^{-1}; ^1H NMR (600 MHz , $CDCl_3$) 7.65(d, 6H, *J*= 8.8 Hz, 15-H and 19-H), 7.27(m, 6H, 10-H and 12-H), 7.24(m, 3H, 11-H), 7.16(d, 6H, *J*= 7.2 Hz, 9-H and 13-H), 6.97(d, 6H, *J*= 8.8 Hz, 16-H and 18-H), 5.66(s, 6H, 7-H_2), 5.15(s, 6H, 1-H_2), 3.81(s, 9H, 17-OCH_3), 2.02(m, 3H, 1'-H, 3'-H and 5'-H), 1.92(d, 3H, *J*= 12.8 Hz, 2'-H, 4'-H and 6'-H), 1.23(ddd, 3H, *J*= 12.8, 12.6, 12.6 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz, $CDCl_3$) 173.5(C7', C8' and C9'), 160.6(C17), 148.5(C3), 135.7(C8), 129.6(C10), 129.4(C15), 129.0(C11), 127.7(C9), 127.3(C2), 123.4(C14), 115.0(C16), 56.0(17-OCH_3), 54.7(C1), 53.2(C7), 41.7(C1', C3' and C5'), 30.4(C2', C4' and C6'); HRMS (ESI) calcd for $C_{60}H_{58}N_9O_9$ $[M+H]^+$ 1048.4352, found 1048.4335.

1,3,5-tris[1-benzyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-1H-1,2,3-triazol-5-yl]methyl (1R,3S,5S)-cyclohexane-1,3,5-tricarboxylate (25)

n_3= 0.18 mmol, V_3= 2 mL, V_4= 6 mL. Workup: H_2O (15 mL) was added, extracted with CH_2Cl_2 (3×15 mL), dried over Na_2SO_4, filtered and evaporated, then precipitated with Et_2O. The off-white solid residue was purified by column chromatography (silica gel, EtOAC-acetone 2:1 mixture as eluent). Yield: 45%, white solid. M.p.: 149-151°C; TLC : R_f = 0.34 (eluent: EtOAc – acetone (2:1)); IR: ν = 1738, 1655, 1604, 1248, 1151, 998, 933, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 8.46(d, 3H, *J*= 2.0 Hz, 15-H), 7.33(m, 6H, 10-H and 12-H), 7.31(m, 3H, 11-H), 7.21(m, 6H, 9-H and 13-H), 7.19(d, 3H, *J*= 2.0 Hz, 19-H), 5.78(s, 6H, 7-H_2), 5.17(s, 6H, 1-H_2), 3.81(s, 9H, N17-CH_3), 2.17(m, 3H, 1'-H, 3'-H and 5'-H), 2.01(d, 3H, *J*= 13.0 Hz, 2'-H, 4'-H and 6'-H), 1.27(ddd, 3H, *J*= 13.0, 12.8, 12.8 Hz, 2'-H, 4'-H and 6'-H); ^{13}C NMR (150 MHz, $CDCl_3$) 173.3(C7', C8' and C9'), 161.1(C18), 142.3(C3), 135.9(C15), 135.1(C8), 134.8(C14), 131.2(C2), 129.9(C10 and C12), 129.5(C11), 127.9(C9 and C13), 124.8(C19), 53.8(C1), 53.6(C7), 41.3(C1', C3' and C5'), 40.9(N17-CH_3), 30.3(C2', C4' and C6'); HRMS (ESI) calcd for $C_{54}H_{52}N_{15}O_9$ $[M+H]^+$ 1054.4067, found 1054.4071.

***[1-benzyl-4-(4-methylphenyl)-1H-1,2,3-triazol-5-yl]methyl-cyclohexanecarboxylate* (27)**

n_3= 0.32 mmol, V_3= 3 mL, V_4= 6 mL. Workup: Workup: H_2O (15 mL) was added, extracted with CH_2Cl_2 (3×15 mL), dried over Na_2SO_4, filtered and evaporated. The orange solid residue was purified by column chromatography (silica gel, *n*-hexane-EtOAC 1:1 mixture as eluent). Yield: 62%, yellow solid. TLC: R_f= 0.41 (eluent: *n*-hexane-EtOAC (1:1)); ^1H NMR (600 MHz, $CDCl_3$) 7.64(d, 2H, *J*= 8.7 Hz, 15-H and 19-H), 7.36(m, 2H, 10-H and 12-H), 7.34(m, 1H, 11-H), 7.30(d, 2H, *J*= 7.2 Hz, 9-H and 13-H), 6.99(d, 2H, *J*= 8.7 Hz, 16-H and 18-H), 5.69(s, 2H, 7-H_2), 5.09(s, 2H, 1-H_2), 3.84(s, 3H, 17-OCH_3), 2.39(m, 1H, 1'-H), 1.95(m, 2H, 2'-H and 6'-H (equatorial)), 1.77(m, 2H, 3'-H and 5-H' (eq.)), 1.66(m, 1H, 4'-H (eq.)), 1.47(m, 2H, 2'-H and 6'-H (axial)), 1.28(m, 2H, 3'-H and 5'-H (ax.)), 1.22(m, 1H, 4'-H (ax.)) ^{13}C NMR (150 MHz, $CDCl_3$) 175.4 (C7'), 160.1(C17), 146.7(C3), 134.4(C8), 132.0(C2), 129.33(C10 and C12), 129.10(C15 and C19), 128.8(C11), 127.5(C9 and C13), 122.8(C14), 114.6(C16 and C18), 55.5(17-OCH_3), 53.6(C1), 52.8(C7), 42.8 (C1'), 29.0 (C2' and C6'), 25.8 (C3' and C5') 25.4 (C4'); HRMS (ESI) calcd for $C_{24}H_{28}N_3O_3$ $[M+H]^+$ 406.2131, found 406.2141.

3. Results and discussion

3.1. Synthesis of C_3 tripodal triazoles and their constituents

Several 1,2,3-triazole alcohols (**2, 4, 7, 9, 14, 15, 16, 17**) were prepared by coupling alkynes (propargyl alcohol, **11, 13**) with azides (**1, 3, 6, 8**) in an azide-alkyne cycloaddition with copper(I) catalyst [30,31] for terminal alkynes (propargyl alcohol) and a ruthenium(II) catalyst [32] for internal alkynes (**11, 13**).

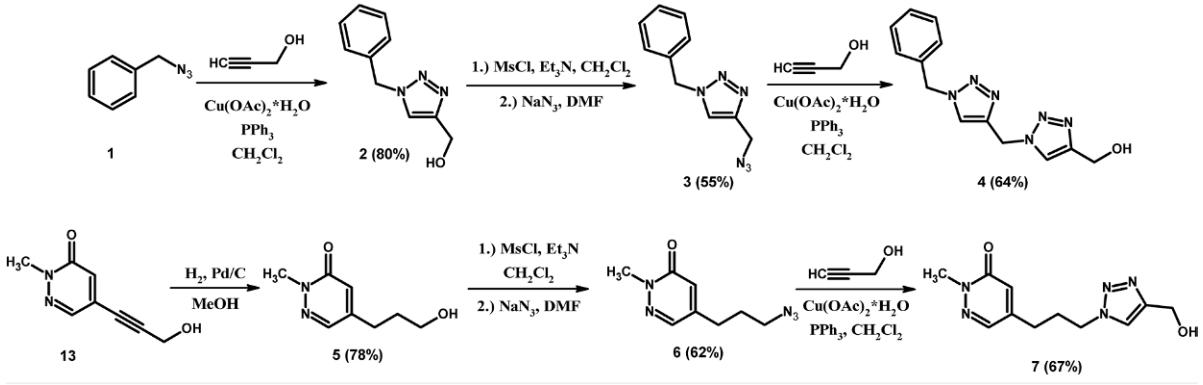
Benzyl azide (**1**) was prepared from benzyl chloride by refluxing with 1.1 equivalents of NaN_3 and 0.01 equivalents of KI in an acetone-water (2:1) mixture. Azides **3** and **6** were synthesized from the appropriate alcohol (**2, 5**) by first treating with mesyl chloride and Et_3N in CH_2Cl_2, followed by stirring with NaN_3 in DMF at room temperature. **8** was synthesized according to literature procedure [30]. Compound **13** (Scheme 3) was reduced to alcohol **5** with catalytic hydrogenation on Pd-charcoal in methanol (Scheme 1).

CuAAC reactions to get **2, 4, 7** were carried out by coupling of azide and alkyne (1 equiv.) in dichloromethane with 0.01 equivalents of $Cu(OAc)_2 \cdot H_2O$ and 0.02 equivalent of PPh_3 [31] (Scheme 1), to get **9** 0.1 equivalent of CuI was used with 2 equivalents of Et_3N in acetonitrile-water (1:1) mixture [30] (Scheme 2).

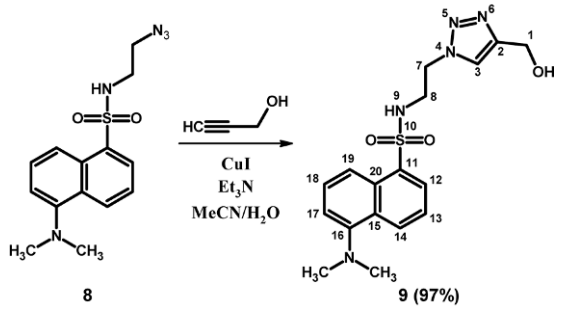
Internal alkynes (**11, 13**) were obtained via the Sonogashira reaction (Scheme 3). Based on the literature procedure, [32] iodoanisol (**10**) or 5-iodo-2-methylpyridazin-3(*2H*)-one (**12**) and propargyl alcohol were coupled with $Pd(PPh_3)_2Cl_2$, CuI and Et_3N. Besides DMF, lower boiling point solvents, such as THF and acetonitrile, were also tested. Acetonitrile proved to be the best solvent in these cases (Table 1). Beginning with the Sonogashira reaction of **12** (Scheme 3), pyridazinone moiety as another heterocyclic component was incorporated to two C_3 symmetric molecules (**22, 25**).

RuAAC reactions of the internal alkynes (**11, 13**) were performed in dichloromethane with 0.02 equivalents of Cp*RuCl(COD) catalyst [33] (Scheme 4). In each case both possible regioisomers (**14, 15** and **16, 17**) were formed. The major product **14** was completely separated from the minor **15** with a single column chromatography, whereas the minor product **17** co-eluted with a part of **16** even after several column chromatographic steps. Their yields were therefore determined by HPLC. **14** and the isolated part of **16** were used in further reactions.

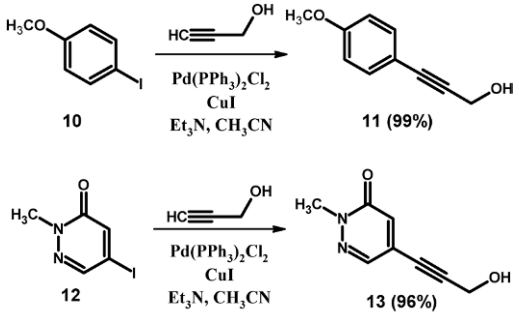
The final step in each case was an esterification of three equivalents of the appropriate triazole alcohol (**2, 4, 7, 9, 14, 16**) with the acid chloride **19** prepared from cyclohexane 1,3,5-tricarboxylic acid (**18**)



Scheme 1. Synthesis of mono- (**2**), bis-triazole (**4**) and pyridazinone (**7**) derivatives.



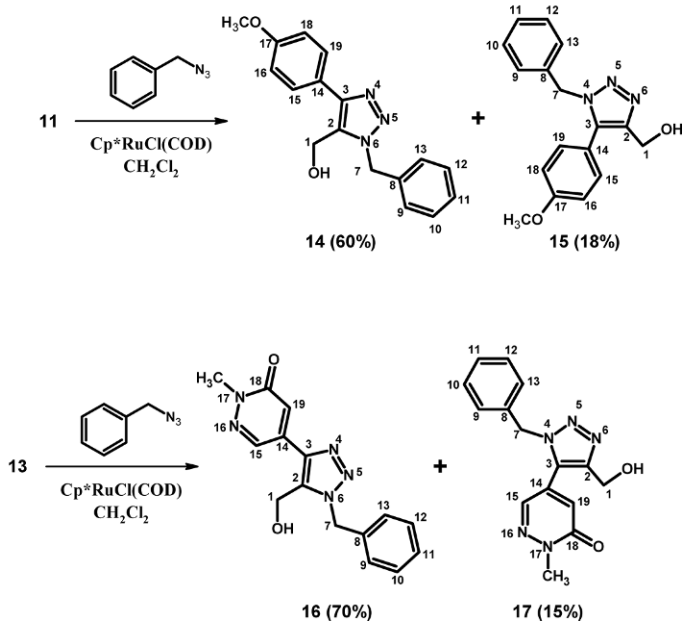
Scheme 2. Synthesis of the fluorescent dansyl derivative (**9**).



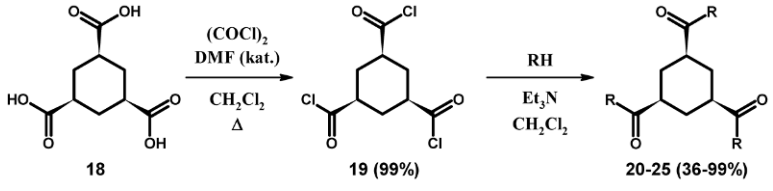
Scheme 3. Sonogashira reactions from iodoanisol (**10**) and 5-iodo-2-methylpyridazin-3(*2H*)-one (**12**).

Table 1. Sonogashira reaction with **10** and **12** in different solvents.

Iodo derivative	Propargyl alcohol	$Pd(PPh_3)_2Cl_2$	CuI	Et_3N	Solvent	Product	Yield (%)
10	1.5 equiv.	0.02 equiv.	0.02 equiv.	2.1 equiv.	THF	11	10
10	3.5 equiv.	0.02 equiv.	0.04 equiv.	3.8 equiv.	THF	11	42
10	3.5 equiv.	0.02 equiv.	0.04 equiv.	3.8 equiv.	DMF	11	78
10	3.5 equiv.	0.02 equiv.	0.04 equiv.	3.8 equiv.	MeCN	11	99
12	1.5 equiv.	0.02 equiv.	0.02 equiv.	2.1 equiv.	DMF	13	96
12	1.2 equiv.	0.02 equiv.	0.04 equiv.	1.8 equiv.	MeCN	13	96

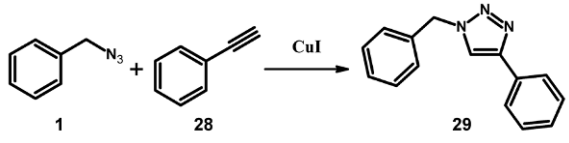


Scheme 4. RuAAC reactions of the internal alkynes **11** and **13**.



RH	Product	Yield (%)
2	20	54
4	21	99
7	22	38
9	23	36
14	24	78
16	25	45

Scheme 5. Synthesis of C_3 symmetric esters from cyclohexane 1,3,5-tricarboxylic acid (**18**).



Scheme 6. Model CuAAC reaction.

(Scheme 5). Cyclohexanecarboxylic ester (**27**) of **14** was also synthesized to investigate a role of ester function in the complexation processes.

3.2. Investigation of copper(I)-binding potentials – a model CuAAC reaction

All final products (**20, 21, 22, 23, 24, 25**) were tested in a CuAAC reaction, in which phenylacetylene (**28**) and benzyl azide (**1**) 1:1 were reacted (Scheme 6) in the presence of 0.02 equiv. CuI and 0.02 equiv. of the appropriate ligand (**20, 21, 22, 23, 24, 25**), in two different solvent systems (acetonitrile-water 25:2 and dichloromethane).

Samples were analyzed after 1, 5 and 24 hours in acetonitrile-water, and after 5 and24 hours in dichloromethane, conversion rates were determined by HPLC (Supplementary Fig. 1 in Supplementary Material). As a reference, the CuAAC reaction was also performed without any ligands. The reactions did not proceed in dichloromethane in the lack of the ligands, but 50% conversion was observed in acetonitrile-water, due to the much better solubility of CuI in acetonitrile.

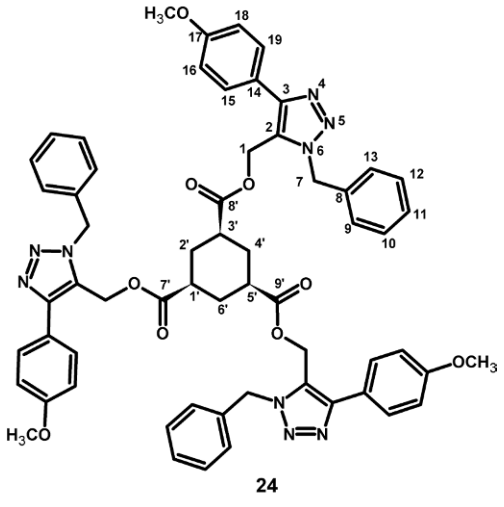
Best results were found in acetonitrile-water with **21** and **24**, in dichloromethane with **20** and **24**. To prove the beneficial effect of the C_3 symmetric molecule **24**, its constituent (**14**) and their cyclohexanecarboxylic ester (**27**) was also tested in dichloromethane, and no conversion was found for both molecules even after 24

Table 2. Conversion rates in MeCN-H_2O and in CH_2Cl_2.

Ligand (0.02 equiv.)	Conversion (%)				
	MeCN-H_2O 25:2			CH_2Cl_2	
	1 h	5 h	24 h	5 h	24 h
-	2	7	51	0	0
20	2	8	55	1	23
21	5	22	80	0	9
24	9	49	95	15	75
0.02 equiv. 14	-	-	-	0	0
0.06 equiv. 14	-	-	-	0	0
27	-	-	-	0	0
22	4	13	66	0	4
25	2	8	60	0	5
23	2	7	51	0	2

Table 3. HRMS data of copper(I)-complexes.

	measured mass [M^+]	calculated mass [M^+]	diff. (ppm)	Formula
20	792.2338	792.2314	-2.41	$[C39H39CuN9O6]^+$
21	1035.3330	1035.3295	-3.24	$[C48H48CuN18O6]^+$
22	972.3317	972.3285	-3.57	$[C42H51CuN15O9]^+$
23	1350.3726	1350.3703	-1.64	$[C60H69CuN15O12S3]^+$
24	1110.3570	1110.3572	-0.66	$[C60H57CuN9O9]^+$
25	1116.3274	1116.3285	0.79	$[C54H51CuN15O9]^+$
27				
14	No Cu(I) complex was detected			
7				



24

Figure 1. Structure and numbering of the final product **24**.

hours. This observation indicates the specific role of **24** as C_3 symmetric polydentate ligand. Conversion rates are summarized in Table 2.

The high conversion rate of **21** containing six triazole rings was expected, the even higher activity of the sterically hindered **24** was therefore surprising. The successful utilization of **24** could be interpreted in terms of its better solubility and the increased electron density of its triazole rings attached directly to the electron rich methoxyphenyl group (Fig. 1).

3.3. Investigation of copper(I)-binding potentials – spectroscopic methods

The copper(I) complexation ability of the compounds was also investigated by different spectroscopic (UV and NMR) and spectrometric (MS) methods. All of these methods prove that these ligands form a complex with copper(I)-ion.

Table 4. Proton and carbon chemical shifts of free and Cu(I) complexed **24** in ACN-d_3.

proton	free	complex	change	carbon	free	complex	change
15-H, 19-H	7.635	7.629	-0.006	C15, C19	129.15	129.03	-0.12
10-H, 12-H	7.249	7.250	0.001	C10, C12	129.18	129.25	0.07
11-H	7.193	7.192	-0.001	C11	128.47	128.42	-0.05
9-H, 13-H	7.156	7.161	0.005	C9, C13	127.88	128.01	0.13
16-H, 18-H	6.999	6.999	0	C16, C18	114.63	114.69	0.06
7-CH_2	5.629	5.644	0.015	C7	52.19	52.49	0.30
1-CH_2	5.196	5.187	-0.009	C1	54.32	53.91	-0.41
17-O-CH_3	3.810	3.808	-0.002	C17	55.40	55.44	0.04
1'-H, 3'-H, 5'-H	1.950	1.941	-0.009	C1', C3', C5'	41.07	40.82	-0.25
2'-H, 4'-H, 6'-H	1.725	1.713	-0.012	C2', C4', C6'	29.84	29.57	-0.27
2'-H, 4'-H, 6'-H	1.019	1.001	-0.018	C7', C8', C9'	173.33	173.02	-0.31

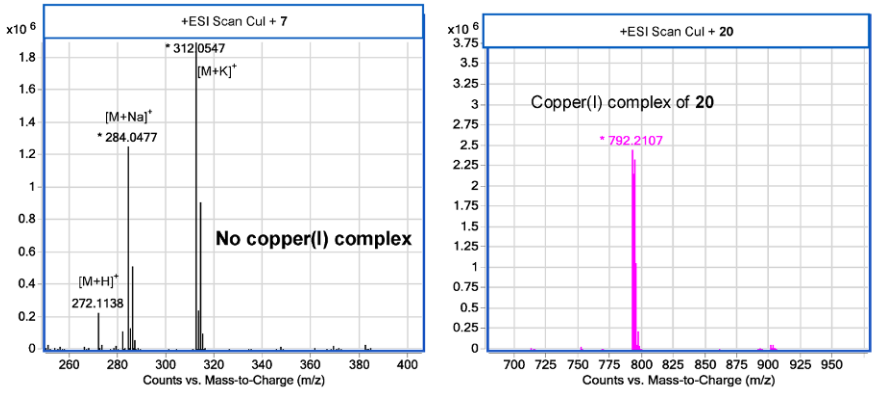


Figure 2. HRMS spectrum of 7 with CuI (left) and 20 with CuI (right). Only the C_3 symmetric tripodal ligand (20) show copper(I)-binding.

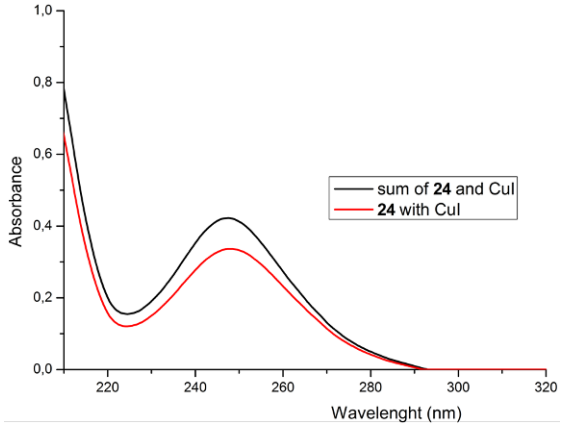


Figure 3. The sum of the UV spectra of 24 and CuI (black) and UV spectra of copper(I) complex of 24 (red).

In mass spectrometric study the exact, high resolution mass of the ligand:CuI (1:5) mixture dissolved in acetonitrile-water was determined. The measured data are summarized in Table 3.

The data in Table 3 clearly show that all of the C_3 tripodal ligands form a copper (I) complex with a 1:1 stoichiometry. Moreover, it can be seen - in accordance with investigation of a model CuAAC reaction – that the triazole alcohol constituents itself and their cyclohexanecarboxylic ester cannot bind the copper(I)-ion (Fig. 2); only the polydentate ligands show copper(I)-binding.

The UV investigation is a challenge due to the significant UV absorption of CuI compared to the triazoles. The UV intensities in the case of the complex of CuI and the tripodal ligands are lower in the entire UV range examined compared to the sum of the absorbances of CuI and the ligands recorded separately due to the reduced absorbtivity of the complex compared to the ligand [5,34]. These changes provide further evidence of complexation as shown in the case of compound **24** (see Fig. 3).

The molecular interaction of copper(I) and **24** (Fig. 1) was also analysed by NMR spectroscopic

method in $CDCl_3$ and in ACN-d_3. In the presence of CuI significant chemical shift changes were observed compared to the ^1H and ^{13}C NMR spectrum of **24** alone proving the copper(I)-binding property of **24**. The chemical shift changes at the positions nearby the triazole ring (1-CH_2, 15-H, 19-H and C1, C15, C19) prove the role of the triazole moiety in the copper(I)-complexation (Table 4, Supplementary Fig. 2) while the chemical shift changes of cyclohexane protons and carbons verify the specific role of **24** as C_3 symmetric polydentate ligand in the copper(I)-complexation. Moreover the chemical shift differences at positions 1'-H, 3'-H, 5'-H and C7', C8', C9' support the possible interaction between the ester function and Cu(I), however for detectable complexation more than one triazole moieties are needed.

4. Conclusions

We have synthesized six novel triazole alcohols (**7, 9, 14, 15, 16, 17**), including three new chemical entities (**7, 16, 17**). We have also prepared six novel C3 symmetric compounds with cyclohexane core (**20, 21, 22, 23, 24, 25**). Their structures were fully characterized by NMR spectroscopy and HRMS. Investigation of a model CuAAC reaction and several spectroscopic examples confirmed the copper(I) binding ability of our novel polydentate triazoles.

Acknowledgments

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Supplementary Materials

(1) HPLC separation of phenylacetylene (28), benzyl azide (1) and 29; (2) ^1H NMR spectra of **24** and **24** with CuI in ACN-d_3; (3) ^1H NMR spectra of compounds 7,9, 14-17, 20-25; (4) ^{13}C NMR spectra of compounds 7,9, 14-17, 20-25; (5) HPLC-MS chromatogram of compounds 20-25, (6) IR spectra of compounds 20,21,23,24,25.

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