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Synthesis and Characterization of the Azido-Functionalized Ruthenocene Analogue [TpmRu(*p*-$N_3C_6H_4$)Tp]Cl and Its Attachment to Biomolecules by Copper-Catalyzed Azide–Alkyne Cycloaddition

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The mixed-ligand tris(pyrazolyl)borate sandwich compound [TpmRuTp′]Cl (**2**) was prepared by microwave-assisted synthesis from Tp′Ru(COD)Cl (**1**) [Tp = tris(pyrazolyl)borate; Tp′ = *p*-bromophenyltris(pyrazolyl)borate; Tpm = tris(pyrazolyl)-methane; COD = 1,4-cyclooctadiene]. Subsequently, **2** was converted to the azide-functionalized [TpmRu(*p*-$N_3C_6H_4$Tp)] (**3**), which can be readily coupled to biomolecules by Cu-catalyzed azide–alkyne cycloaddition (Cu-AAC) in solution, as exemplified by the covalent attachment to pentyne-functionalized HC$(CH_2)_2$–CO–Val–O*t*Bu (**4**), and an alkyne derivative of the neuropeptide enkephaline HC$(CH_2)_2$–CO–ENK–OH (ENK = enkephaline, Tyr–Gly–Gly–Phe–Leu). The resulting triazole compounds [TpmRu({*p*-C_2N_3H–$(CH_2)_2$–CO–Val–O*t*Bu}Tp)]Cl (**5**) and [TpmRu({*p*-C_2N_3H–$(CH_2)_2$–CO–ENK–OH}Tp)]Cl (**6**), represent the first [3+2] cycloaddition products of azide-functionalized Tp compounds. They were characterized by NMR spectroscopy and mass spectrometry. Furthermore, **1**, **2**, and **3** as well as the reaction intermediate [(κ^2-*N*,*N*′-Tpm)RuCl(Tp′)] (**2a**) were characterized in the solid state by single-crystal X-ray diffraction.

Introduction

Recent years have seen an increasing interest in the labelling of biomolecules with transition metal complexes as the resulting bioconjugates offer new opportunities for the development of drugs and diagnostic tools.[1] One class of compounds frequently employed for such purposes due to their high stability, facile derivatization, and their suitability as electrochemical probes, are metallocenes, in particular ferrocene Cp_2Fe (Cp = cyclopentadienyl),[2–4] and, to a much lesser extent, ruthenocene (Cp_2Ru).[5,6] Remarkably, the use of analogues of these compounds, whether homo- or heteroleptic, has not been investigated to any serious extent. Accordingly, we have been interested in employing analogues of group 8 metallocenes in bioorganometallic applications.

One ligand system regularly employed as a Cp surrogate is the tris(pyrazolyl)borate anion [$HB(pz)_3$ or Tp][7] because it is isoelectronic,[8] shows comparable complexation behavior, and allows facile derivatization. To this end, third-generation derivatives have been developed, which allow functionalization with biomolecules on the boron atom.[9] Recent investigations in our group revealed the functionalized *p*-bromophenyltris(pyrazolyl)borate (*p*-BrC_6H_4Tp or Tp′)[10] ligand to be suitable for the preparation of various half and mixed sandwich complexes,[11–13] including the ruthenocene analogues Cp^{iPr}RuTp′[14] and TpRuTp′.[13] Functional conversion of these complexes was achieved by a sequence of lithiation, addition of solid CO_2, and workup with hydrochloric acid, which provided access to their carboxylic acid-functionalized derivatives. These carboxylates were successfully employed in the syntheses of small peptide bioconjugates by amide bond formation. However, this particular Tp′ acid functionalization was found to limit their application to: a) biomolecules that provide a suitable synthetic handle, such as amino or alcohol functions, and b) to complexes or co-ligands that withstand the treatment with reagents such as butyllithium. Inspired by recent developments in the functionalization of biomolecules, in particular peptides, by copper-catalyzed azide–alkyne cycloaddition (Cu-AAC, also referred to as click chemistry),[15,16] we were eager to investigate possible azide functionalization of mixed sandwich Tp–ruthenium complexes and their subsequent attachment to alkynyl-functionalized biomolecules. To enhance the solubility of the ruthenium complex in polar solvents usually used in azidonation and Cu-AAC reactions, we assumed that the uncharged tris(pyrazolyl)methane might prove advantageous as a spectator ligand. More-

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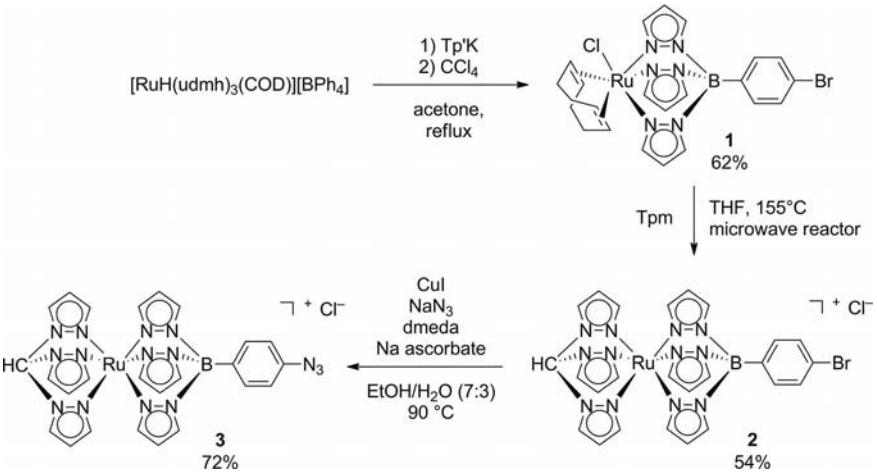


Scheme 1. Synthetic pathway to **3** (udmh = *N*,*N*-dimethylhydrazine; dmeda = *N*,*N*′-dimethylethane-1,2-diamine).

over, a charged complex may contribute to properties such as solubility and cellular uptake of the resulting bioconjugates. Herein, we report the syntheses of the positively charged ruthenocene analogue [TpmRuTp′]Cl (**2**) and its subsequent conversion to azido-functionalized [TpmRu(*p*-$N_3C_6H_4$Tp)]Cl (**3**) by the synthetic pathway outlined in Scheme 1.

Furthermore, we demonstrate the application of **3** in the labeling of biomolecules employing Cu-AAC by coupling to the pentyne-functionalized amino acid $HC(CH_2)_2$–CO–Val–O*t*Bu (**4**) and the pentyne-functionalized peptide Enkephaline (penty–ENK–OH) in solution.

Results and Discussion

Synthesis of Mixed Tp/Tpm Sandwich Azide 3

Of the two possible options for the assembly of a mixed sandwich Tpm/Tp′ ruthenium complex suitable for our purposes, the introduction of the Tp′ ligand prior to the Tpm ligand was found to be the most favorable method. Although half sandwich [TpmRu(COD)Cl]Cl can be accessed by heating a mixture of Tpm and $[RuCl_2(COD)]_x$ in ethanol for 7 h,[17] comparable yields of pure TpRu(COD)Cl are accessible in 2 h by reaction of [RuH(udmh)$_3$(COD)][X] (X = PF_6, BPh_4; udmh = *N*,*N*-dimethylhydrazine)[18] with a Tp transfer agent and subsequent addition of tetrachloromethane.[19,20] Thus, the functionalized half sandwich compound Tp′Ru(COD)Cl (**1**) was synthesized by modification of literature preparations for TpRu(COD)Cl.[20] Heating equimolar amounts of [RuH(udmh)$_3$(COD)][BPh_4] and Tp′K in acetone for 1.5 h afforded the hydride complex Tp′Ru(COD)H, which was converted to **1** in situ by addition of CCl_4 and another 30 min of heating. As reported for TpRu(COD)Cl, pure **1** was isolated by extraction into dichloromethane. Characterization of **1** by ^{1}H NMR shows sets of signals comparable to the parent TpRu(COD)Cl, with the signals of the Tp ligand split into two sets (2:1 ratio) due to the unsymmetric coordination pattern around the central ruthenium atom. The structural resemblence of **1** to TpRu(COD)Cl is further supported by its solid state structure. As shown in the ORTEP plot in Figure 1, the Tp′ ligand occupies three coordination sites on ruthenium, resulting in a local C_{3v} symmetry with Ru–N bond lengths of 2.120–

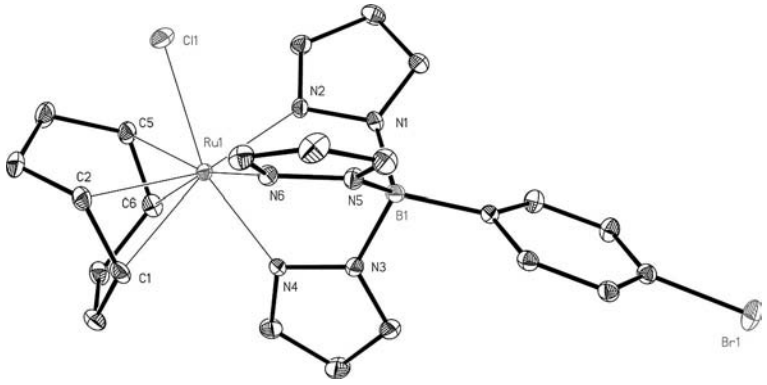


Figure 1. ORTEP plot of **1**·CH_2Cl_2 (ellipsoids at 30% probability, hydrogen atoms and CH_2Cl_2 omitted). Selected bond lengths [Å]: Ru1–C1 2.232(8), Ru1–C2 2.226(9), Ru1–C5 2.233(7), Ru1–C6 2.239(3), Ru1–N2 2.131(1), Ru1–N4 2.125(1), Ru1–N6 2.120(6), Ru1–Cl1 2.441(3). Selected angles [°]: N4–Ru1–C6 79.91(15), N4–Ru1–C1 82.81(15), N6–Ru1–C2 93.54(16), N6–Ru1–N2 87.13(15), N2–Ru1–C5 93.18(16), C2–Ru1–C5 79.35(15), C1–Ru1–C6 78.10(16), N4–Ru1–Cl1 159.76(10), N2–Ru1–Cl1 82.40(10).

2.131 Å [2.110–2.164 Å for TpRu(COD)Cl] and an average N–Ru–N angle of 84.6° (85.0° for the parent compound).[21] The COD moiety adopts a typical twisted boat conformation of C_2 symmetry, causing the Ru–C bond lengths to be in a narrow range of 2.226–2.233 Å (2.213–2.229 Å for the parent compound). Considering the two π-bound CH=CH of COD each as single ligands, the geometry at ruthenium is approximately octahedral with Ru–Cl being the longest bond (2.441 Å).

In close analogy to the synthesis of Tp′RuTp,[13] the Tp′ half sandwich **1** was treated with tris(pyrazolyl)methane in THF at 155 °C for one hour utilizing a microwave reactor. The complex salt [TpmRuTp′][Cl] (**2**) precipitated readily upon cooling and was isolated by filtration as a bright yellow solid in 54% yield. Characterization of **2** by ^{1}H NMR shows two sets of signals for the pyrazole groups comparable to C_{3v} symmetric Tp′RuTp. Additional signals are found for the AA′BB′ system of the *p*-BrC_6H_4 group and the CH moiety of the Tpm ligand, the latter being strongly shifted downfield due to the deshielding by three pyrazole groups. The solid state structure of **2** was determined by X-ray diffraction (Figure 2). The structure is similar to that of unsubstituted $RuTp_2$ as well as Tp′RuTp,[13,22,23] showing local C_{3v} symmetry at ruthenium with an average Ru–N distance of 2.059 Å (2.061 Å for $RuTp_2$, 2.057 Å for Tp′RuTp) and an average N–Ru–N angle of 86.2° (87.0° for Tp′RuTp).

However, in several ^{1}H NMR spectra of crude **2**, unidentifiable signals were observed that vanished upon repeated washing of the crude product with THF. Removal of THF from the washings gave a microcrystalline, dark yellow solid **2a**, which crystallized as orange-yellow needles from acetone. As ^{1}H NMR spectra of **2a** showed a 2:1 splitting of the pyrazole H signals reminiscent of that observed in **1** and other unsymmetric Tp^RRuL_2X (Tp^R = Tp, Tpm) complexes,[20,24] we assumed that **2a** must contain a similar co-

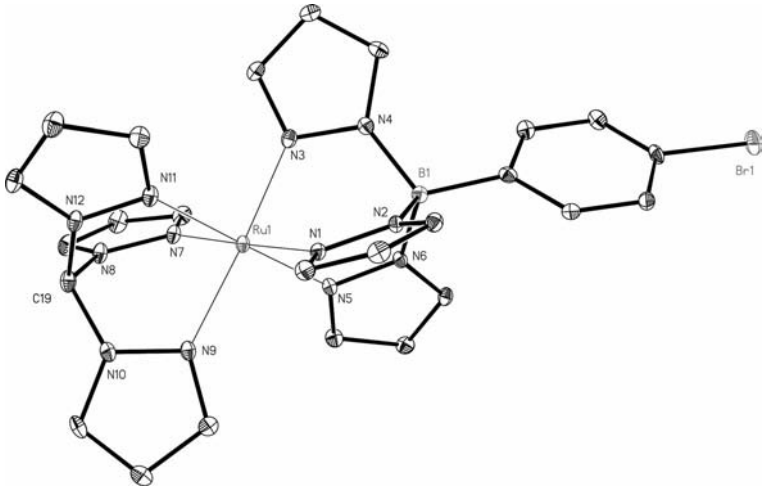


Figure 2. ORTEP plot of **2** (ellipsoids at 30% probability, hydrogen atoms and counterion omitted). Selected bond lengths [Å]: Ru1–N1 2.073(19), Ru1–N3 2.042(19), Ru1–N5 2.046(19), Ru1–N7 2.062(2), Ru1–N9 2.074(19), Ru1–N11 2.060(19). Selected angles [°]: N_{Tpm}–Ru1–N_{Tpm} 84.03(8)–86.65(7), N_{Tp}–Ru1–N_{Tp} 85.90(7)–87.96(8).

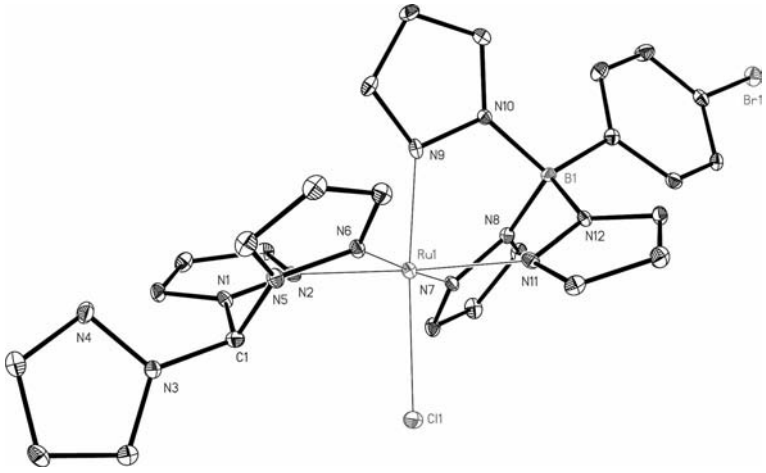


Figure 3. ORTEP plot of **2a** (ellipsoids at 30% probability, hydrogen atoms and acetone omitted). Selected bond lengths [Å]: Ru1–Cl1 2.4432(8), Ru1–N7 2.028(2), Ru1–N9 2.042(2), Ru1–N2 2.060(2), Ru1–N11 2.062(2), Ru1–N6 2.073(2), N1–C1 1.466(4), N3–C1 1.425(4), N5–C1 1.463(4). Selected angles [°]: N7–Ru1–N9 86.83(9), N7–Ru1–N11 87.30(9), N9–Ru1–N11 85.50(9), N2–Ru1–N6 86.20(9).

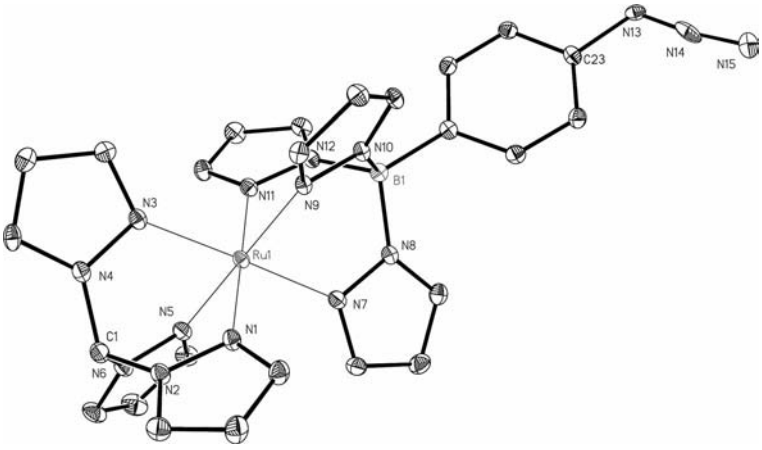


Figure 4. ORTEP plot of **3** (ellipsoids at 30% probability, hydrogen atoms and counterions omitted). Selected bond lengths [Å]: Ru1–N1 2.055(2), Ru1–N 32.068(2), Ru1–N5 2.059(2), Ru1–N7 2.042(2); Ru1–N9 2.037(2), Ru1–N11 2.053(2). Selected angles [°]: N_{Tp}–Ru1–N_{Tpm} 92.8(9)–94.5(9), N_{Tp}–Ru1–N_{Tp} 85.4(8)–86.1(9), N_{Tpm}–Ru1–N_{Tpm} 86.5(9)–87.0(9), C23–N13–N14 116.7(2), N13–N14–N15 171.7(3).

ordination motif. This assumption was confirmed by single-crystal X-ray diffraction, which revealed **2a** to be a coordination isomer of **2**, likely representing a stable intermediate of the ligand exchange reaction (Figure 3). The Tpm ligand in the neutral complex **2a** is coordinated to ruthenium in a bidentate fashion with Ru–N bond lengths of 2.060 and 2.073 Å, which are commensurable with those found for [κ^3-*N*,*N*′,*N*′′-TpmRu] compounds containing additional N donor ligands (Ru–N 2.063–2.084 Å).[25–27]

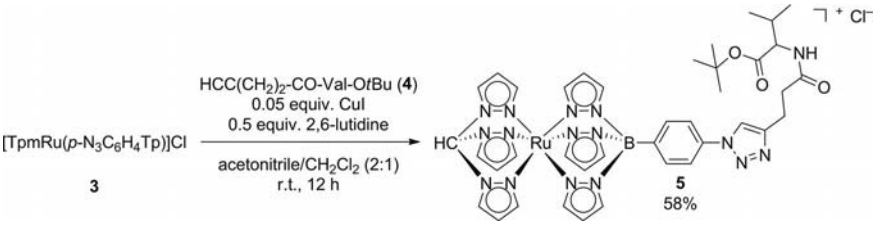
The third pyrazole ring, pointing away from Ru, is void of any interaction. The Tp′ ligand shows the expected C_{3v} symmetric κ^3 coordination with Ru–N bond lengths of 2.028–2.062 Å, slightly shorter than those found in Tp′RuTp (2.043–2.086 Å)[13] and the isomer **2**. The distorted octahedral coordination geometry at ruthenium is completed by a chloride ligand, bound to ruthenium with the same metrical parameters (Ru–Cl 2.443 Å) as in the starting material **1** (Ru–Cl 2.441 Å).

Subsequently, **2** was further functionalized by a copper iodide-catalyzed azidonation. The progress of the reaction was monitored by a shift of the AA′BB′ signals in the ^{1}H NMR spectrum, and the appearance of two signals at 2085 [ν(N≡N_{asym})] and 1258 cm^{-1} [ν(N≡N_{sym})] in the IR spectrum.[28] Just as previously reported for the syntheses of various phenylazides from phenyl bromides, 100% conversion of **2** was only observed upon addition of *N*,*N*′-dimethylethane-1,2-diamine (dmeda, 0.3 equiv.) and sodium ascorbate (0.03 equiv.).[29] Azide-functionalized **3** precipitated readily from the reaction mixture upon addition of water, was separated by filtration, and obtained in 72% yield after drying. Characterization by ESI-MS showed two signals corresponding to the molecule cation (*m*/*z* = 645.95) and formation of a NH_2-functionalized species by loss of N_2 (*m*/*z* = 620.02). Although the elemental analysis of **3** indicated the pure compound with a chloride counterion, the solid state structure obtained by XRD of a different batch of **3** showed the existence of both a chloride and a bromide counterion in a 2:3 ratio. Apart from this partial replacement, presumably a result of the salt metathesis with NaN_3, the solid state structure of **3**, as depicted in the ORTEP plot (Figure 4), indicates little change of the Tp coordination in comparison to the starting material **2**. Thus, the Ru–N distances (2.042–2.068 Å) and N–Ru–N angles (85.4–86.7°) remain unaffected by the azidonation. The metrical parameters found for the *p*-$N_3C_6H_4$ group, in particular the C–N–N (116.7°) and N–N–N (171.7°) angles, compare well with those of representative aromatic azides (C–N–N 115.2–118.1°; N–N–N 171.3–173.0°).[30–32]

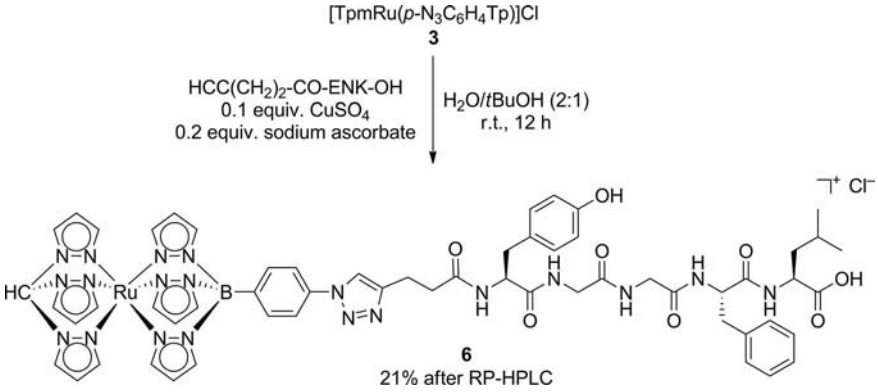
Application of 3 in Cu-AAC

In order to test the suitability of **3** for copper-catalyzed [3+2] cycloaddition reactions, it was coupled to pentyne-functionalized HCC(CH_2)$_2$–CO–Val–O*t*Bu (**4**) to give triazole **5** as depicted in Scheme 2.

For reasons of solubility of **3**, and ease of synthesis, we considered the use of copper(I) iodide in acetonitrile/dichlo-



Scheme 2. Copper-catalyzed synthesis of **5**.



Scheme 3. Copper-catalyzed synthesis of **6**.

romethane (2:1) over the widely employed $Cu^{II}SO_4$ in H_2O/*t*BuOH (2:1).[15] While the Cu^{II} system requires a reducing agent such as sodium ascorbate, Cu^{I} salts have been reported to give the desired products in comparable yields and purity upon addition of 2,6-lutidine and exclusion of oxygen.[33] Formation of the triazole **5** was unambiguously supported by observation of an additional singlet at δ = 8.01 ppm (s, 1 H), a downfield shift of the AA′BB′ signals in ^{1}H NMR spectroscopy, as well as a signal at *m*/*z* = 899.13 [M^+] in ESI-MS spectra.

In an additional synthesis, **3** was coupled to the pentyne-functionalized neuropeptide enkephaline (penty–ENK–OH)[40,41] in solution to give triazole **6** as outlined in Scheme 3.

Preliminary experiments revealed that copper iodide in CH_2Cl_2/acetonitrile did not catalyze the reaction, presumably due to interaction of Cu^{I} with the carboxy group of penty–ENK–OH. The cycloaddition reaction was therefore performed in H_2O/*t*BuOH with $CuSO_4$ and sodium ascorbate.[15] The resulting triazole bioconjugate [TpmRu({*p*-C_2N_3H–$(CH_2)_2$–CO–ENK–OH}C_6H_4Tp)]Cl (**6**) was purified by reverse phase (RP)-HPLC and characterized by MS and ^{1}H NMR spectroscopy. ESI-MS of **6** in positive mode shows two major signals, corresponding to the molecular ion (*m*/*z* = 1281.03) and the dication $[M + H]^{2+}$ (*m*/*z* = 641.23). Additional signals at *m*/*z* = 1151.06, 1004.06, 947.07, and 890.09, each showing a ruthenium isotope pattern, result from b-type fragmentation in close correspondance to the amino acid sequence of enkephalin.[34,35] All ^{1}H NMR signals could be assigned by comparison with literature data for unsubstituted enkephalin and match the proposed composition of **6**.[36]

Conclusions

This work represents a new aspect in the chemistry of functionalized, Tp-containing ruthenocene analogues and their application in bioconjugate chemistry. Modification of known procedures allowed the synthesis of the Tp′ half sandwich ruthenium complex Tp′Ru(COD)Cl (**1**), which was readily converted into the mixed Tpm/Tp′ ruthenium sandwich compound [TpmRuTp′]Cl (**2**) in a microwave-assisted synthesis. Azide-functionalized [TpmRu(*p*-$N_3C_6H_4$Tp)]Cl (**3**) was readily prepared by copper-catalyzed azidonation of **2**, and subsequently coupled to the alkyne-functionalized amino acid **4** by Cu-AAC to provide the triazole compound [TpmRu({*p*-C_2N_3H–$(CH_2)_2$–CO–Val–O*t*Bu}Tp)]Cl (**5**). In a similar preparation, **3** was coupled to a pentyne-functionalized enkephaline derivative, giving [TpmRu({*p*-C_2N_3H–$(CH_2)_2$–CO–ENK–OH}C_6H_4Tp)]Cl (**6**) as the first example of a mixed Tpm/Tp ruthenium bioconjugate comprising a triazole linkage. This report demonstrates the first use of third generation scorpionate *p*-BrC_6H_4Tp as a precursor for azide-functionalized transition metal complexes, thereby further extending the application of Tp_2-type ruthenium compounds as metallocene surrogates in bioinorganic chemistry and providing access, through click chemistry, to new peptide bioconjugates.[37]

Experimental Section

General Remarks: Unless noted otherwise, all preparations were carried out under an inert atmosphere of argon or N_2 utilizing standard Schlenk techniques and an MBraun (Germany) glovebox. All reagents and anhydrous solvents were purchased from commercial sources and used as received. [RuH(udmh)$_3$(COD)][BPh_4],[18] Tpm,[38,39] and Tp′K[10] were prepared according to literature methods. Pentynoic acid-functionalized enkephalin (penty–ENK–OH) was prepared by modification of published procedures on Wang resin (Iris Biotech, Germany), cleaved by treatment with 95% TFA in DMF, and used after washing with ethyl ether.[40,41] NMR spectra were recorded at ambient temperature with Bruker DPX-250 and DRX-400 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual proton chemical shifts of the solvents set relative to external TMS. Absolute values of the coupling constants are given in Hertz [Hz]. $^{13}C\{^1H\}$ assignments were obtained from standard attached proton test experiments. ESI-MS were recorded with a Bruker Esquire 6000 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a Pike MIRacle Micro ATR accessory as solid samples. Microwave syntheses were performed with a CEM Discover LabMate Synthesizer. Analytical and preparative RP-HPLC of **6** were both carried out with a Knaur instrument using a RP Varian Dynamax column (C18 microsorb 60 Å, diameter 10 mm, length 250 mm). Eluents were water/acetonitrile

(95:5%, buffer A) and acetonitrile/water (95:5%, buffer B), both containing 0.1% v/v TFA, using a linear gradient of 0–100% buffer B for 25 min at a flow rate of 7.5 mL/min. Elemental analyses of ruthenium-containing compounds were carried out at the Laboratory for Microanalytics and Thermal Analyses, University of Essen (Inorganic Chemistry Department). Elemental analysis of **4** was carried out at the RUBiospek Biospectroscopy Department, Ruhr-University of Bochum.

Tp′Ru(COD)Cl (1): A mixture of Tp′K (3.44 g, 8.45 mmol) and [RuH(udmh)$_3$(COD)][BPh$_4$] (6.00 g, 8.45 mmol) in acetone (70 mL) was heated to reflux for two hours. CCl_4 (15 mL) was added and the mixture heated to reflux for an additional 45 min. Cooling to –20 °C resulted in the formation of a yellow precipitate of **1** and KCl, which was isolated by filtration, dried, and extracted into CH_2Cl_2 (2 × 30 mL). Removal of the solvent and drying under reduced pressure gave analytically pure **1** as a bright orange solid (3.23 g, 0.53 mmol, 62%). $C_{23}H_{25}BBrClN_6Ru$ (612.73): calcd. C 45.09, H 4.11, N 13.72; found C 45.05, H 4.19, N 13.70. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.27 (d, J = 2.2 Hz, 1 H, pz-H3), 7.88 (d, J = 8.4 Hz, 2 H, part of AA′BB′), 7.72–7.68 (m, 6 H, pz-H3, pz-H5 and part of AA′BB′), 7.40 (d, J = 2.2 Hz, 1 H, pz-H5), 6.27 (t, J = 2.2 Hz, 1 H, pz-H4), 6.22 (t, J = 2.2 Hz, 2 H, pz-H4), 4.94 (m, 2 H, olefinic H of COD), 4.14 (m, 2 H, olefinic H of COD), 2.97 (m, 2 H, COD), 2.63 (m, 2 H, COD), 2.45 (m, 2 H, COD), 2.28 (m, 2 H, COD) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 146.1 (pz-C5), 143.5 (pz-C5), 138.6 (C-B), 137.0 (pz-C3), 135.5 (pz-C3), 131.6 (part of AA′BB′), 123.4 (C-Br), 106.2 (pz-C4), 106.0 (pz-C4), 95.48 (olefinic C of COD), 87.6 (olefinic C of COD), 30.7 (aliphatic C of COD), 29.9 (aliphatic C of COD) ppm.

Solid-State Structure of 1·CH_2Cl_2: A crystal of **1**·CH_2Cl_2 (orange needle), obtained by slow evaporation of a CH_2Cl_2 solution of **1**, was placed on a glass capillary in perfluorinated oil and measured in a cold gas flow. The intensity data were measured using a Bruker axs area detector (Mo-K_α radiation 0.71073, ω scan) at –50 °C. $C_{24}H_{27}BBrCl_3N_6Ru$ (M = 697.66), triclinic, a = 10.226(5) Å, b = 10.664(5) Å, c = 12.763(6) Å, α = 72.565(9)°, β = 87.041(8)°, γ = 83.228(8)°, V = 1318.4(10) Å^3, space group $P\bar{1}$, Z = 2, 10468 reflections collected, 4595 unique (R_{int} = 0.0437), $wR(F^2)$ = 0.1350 (all data). Structure solution with direct methods (SHELXS97),[42] and refined against $F2$ with all measured reflections (SHELXL97 and Platon/Squeeze).[42,43] CCDC-797019 contains the supplementary crystallographic data for this compound, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[TpmRuTp′]Cl (2): A mixture of **1** (613 mg, 1 mmol), Tpm (214 mg, 1 mmol), and THF (5 mL) was prepared under an argon atmosphere and heated to 155 °C by microwave irradiation in a pressure-tight reaction vessel for 1 h. Cooling to room temperature resulted in the formation of a bright yellow solid, which was isolated by filtration, washed with pentane (2 × 5 mL), and dried under reduced pressure to give analytically pure **2** (385 mg, 0.54 mmol, 54%). $C_{25}H_{23}BBrClN_{12}Ru$ (718.77): calcd. C 41.78, H 3.23, N 23.38; found C 41.85, H 3.25, N 23.30. ^{1}H NMR (250 MHz, [D$_6$]-DMSO): δ = 10.51 [s, 1 H, (pz)$_3$C*H*], 8.71 (d, J = 2.2 Hz, 3 H, pz-H3), 8.01 (d, J = 8.4 Hz, 2 H, part of AA′BB′), 7.82 (d, J = 8.4 Hz, 2 H, part of AA′BB′), 7.77 (d, J = 2.2 Hz, 3 H, pz-H3), 7.26 (broad s, 3 H, pz-H5), 6.91 (broad s, 3 H, pz-H5), 6.63 (t, J = 2.2 Hz, 3 H, pz-H4), 6.34 (t, J = 2.2 Hz, 3 H, pz-H4) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 146.0 (CH, pz-C5), 143.6 (CH, pz-C5), 136.9 (CH, pz-C3), 136.2 (CH, pz-C3), 134.9 (CH of AA′BB′), 131.2 (CH of AA′BB′), 122.4 (C-Br), 108.9 (CH, pz-C4), 106.8 (CH, pz-C4), 75.7 (CH of Tpm) ppm. ESI-MS (pos. mode): m/z = 684.82 [M]$^+$, exact mass of complex cation: 683.05.

Solid-State Structure of 2·THF: A crystal of **2**·THF (yellow needle), obtained by slow diffusion of THF into an acetone solution of **2**, was placed on a glass capillary in perfluorinated oil and measured in a cold gas flow. The intensity data were measured using a Oxford Diffraction Sapphire2-CCD device (Mo-K_α radiation 0.71073, ω scan) at –160 °C. Note: Cocrystallized solvent molecules were found to be severely disordered and could not be modeled reasonably. Thus, its contributions were removed from the diffraction data using Platon/Squeeze.[43] $C_{25}H_{23}BBrClN_{12}Ru$ (M = 718.79), triclinic, a = 7.7245(2) Å, b = 14.4789(3) Å, c = 17.0407(4) Å, α = 91.823(2)°, β = 101.008(2)°, γ = 103.716(2)°, V = 1811.51(7) Å^3, space group $P\bar{1}$, Z = 2, 6363 reflections collected, 5821 unique (R_{int} = 0.0314), $wR(F^2)$ = 0.0825 (all data). Structure solution with direct methods (SHELXS97),[42] and refined against $F2$ with all measured reflections (SHELXL97 and Platon/Squeeze).[42,43] CCDC-804163 contains the supplementary crystallographic data for this compound, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[(κ^2-*N*,*N*′-Tpm)RuCl(Tp′)] (2a): One of the major byproducts in the synthesis of **2** was identified as (κ^2-*N*,*N*′-Tpm)RuCl(Tp′) (**2a**), presumably formed as a stable intermediate in the microwave synthesis. It was found to have good solubility in THF and was recrystallized from acetone. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.75 (s, 1 H, (pz)$_3$C*H*), 8.12 (d, J = 2.2 Hz, 1 H, pz-H3), 8.10 (s, 1 H, pz-H3), 8.00 (d, J = 8.4 Hz, 2 H, part of AA′BB′), 7.90 (broad s, 2 H, pz-H3), 7.73–7.68 (m, 5 H, pz-H3, pz-H5, part of AA′BB′), 7.59 (d, J = 2.2 Hz, 1 H, pz-H5), 7.51 (broad s, 1 H, pz-H5), 7.06 (broad s, 2 H, pz-H5), 6.64 (t, J = 2.2 Hz, 1 H, pz-H4), 6.29 (t, J = 2.2 Hz, 3 H, pz-H4), 5.92 (broad s, 2 H, pz-H4) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 146.3 (CH, pz-C5), 145.2 (CH, pz-C5), 144.7 (CH, pz-C5), 143.8 (CH, pz-C5), 136.9 (CH, pz-C3), 135.9 (CH, pz-C3), 134.8 (CH of AA′BB′), 132.1 (CH, pz-C3), 131.4 (CH of AA′BB′), 123.1 (C-Br), 108.3 (CH, pz-C4), 107.57 (CH, pz-C4), 106.21 (CH, pz-C4), 105.8 (CH, pz-C4), 80.6 (CH of Tpm) ppm.

Solid-State Structure of 2a·Acetone: A crystal of **2a**·acetone (yellow needle), obtained by slow evaporation of an acetone solution of **2a**, was placed on a glass capillary in perfluorinated oil and measured in a cold gas flow. The intensity data were measured using a Oxford Diffraction Sapphire2-CCD device (Mo-K_α radiation 0.71073, ω scan) at –160 °C. $C_{28}H_{29}BBrClN_{12}ORu$ (M = 776,85), triclinic, a = 10.7878(5) Å, b = 11.8810(7) Å, c = 12.4405(7) Å, α = 75.555(5)°, β = 82.523(4)°, γ = 89.662(4)°, V = 1530.38(14) Å^3, space group $P\bar{1}$, Z = 2, 5372 reflections collected, 4218 unique (R_{int} = 0.0382), $wR(F^2)$ = 0.0639 (all data). Structure solution with direct methods (SHELXS97),[42] and refined against $F2$ with all measured reflections (SHELXL97 and Platon/Squeeze).[42,43] CCDC-797020 contains the supplementary crystallographic data for this compound, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[TpmRu(*p*-$N_3C_6H_4$Tp)]Cl (3): To a mixture of **2** (385 mg, 0.54 mmol), sodium azide (112 mg, 1.72 mmol), and copper(I) iodide (10 mg, 0.05 mmol) was added ethanol/water (7:3, 10 mL). The solution was degassed and backfilled with argon. After addition of *N*,*N*′-dimethylethane-1,2-diamine (17 μL, 0.30 mmol) and sodium ascorbate (3 mg, 0.01 mmol), the flask was covered with aluminium foil and the mixture was heated to 90 °C overnight. Addition of water (20 mL) to the mixture produced a yellow precipitate that was isolated by filtration and washed with water (2 × 5 mL) and hexanes (2 × 5 mL). Drying under reduced pressure gave **3** as a light yellow solid (265 mg, 0.39 mmol, 72%). An analytically pure sample of **3**·CH_2Cl_2 was obtained by recrystallisation

from CH_2Cl_2. $C_{26}H_{25}BCl_3N_{15}Ru$ (765.82): calcd. C 40.78, H 3.29, N 27.43; found C 40.53, H 3.26, N 27.35. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 10.08 [s, 1 H, (pz)$_3$C*H*], 8.66 (d, *J* = 2.2 Hz, 3 H, pz-H3), 8.10 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 7.77 (d, *J* = 2.2 Hz, 3 H, pz-H3), 7.37 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 7.27 (broad s, 3 H, pz-H5), 6.92 (broad s, 3 H, pz-H5), 6.64 (t, *J* = 2.2 Hz, 3 H, pz-H4), 6.34 (*J* = 2.2 Hz, 3 H, pz-H4) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 145.9 (pz-C5), 143.5 (pz-C5), 139.5 (C-N$_3$), 136.4 (pz-C3), 136.2 (pz-C3), 134.8 (CH of AA′BB′), 119.0 (CH of AA′BB′), 108.8 (pz-C4), 106.7 (pz-C4), 75.7 (*C*H of Tpm) ppm. IR (solid): $\tilde{\nu}$ = 2085 (azide N≡N asym.), 1258 (azide N≡N sym.) cm^{-1}. ESI-MS (pos. mode): *m*/*z* = 645.95 [M]$^+$, 620.02 [M – N$_2$ + 2H]$^+$ exact mass of complex cation: 646.14.

Solid State Structure of 3: A crystal of **3** (yellow needle), obtained by slow evaporation of an acetone solution of **3**, was placed on a glass capillary in perfluorinated oil and measured in a cold gas flow. The intensity data were measured using a Oxford Diffraction Sapphire2-CCD device (Mo-K_α radiation 0.71073, ω scan) at –160 °C. $C_{25}H_{23}BBr_{0.6}Cl_{0.4}N_{15}Ru$ (*M* = 707.59), monoclinic, *a* = 15.0766(2) Å, *b* = 13.5560(2) Å, *c* = 16.1782(2) Å, $\alpha = \gamma = 90°$, β = 102.555(1)°, *V* = 3227.41(8) Å^3, space group $P2_1/c$, *Z* = 4, 5652 reflections collected, 5211 unique (R_{int} = 0.0324), $wR(F^2)$ = 0.0829 (all data). Structure solution with direct methods (SHELXS97),[42] and refined against *F*2 with all measured reflections (SHELXL97 and Platon/Squeeze).[42,43] CCDC-804164 contains the supplementary crystallographic data for this compound, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

HCC(CH$_2$)$_2$CO–Val–O*t*Bu (4): 4-Pentynoic acid (980 mg, 10 mmol) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (3.21 g, 10 mmol) were stirred in dichloromethane (30 mL) for 15 min. Triethylamine (9.7 mL, 70 mmol) was added and the resultant homegenous solution stirred for 10 min. H–Val–O*t*Bu·HCl (2.10 g, 10 mmol) was added and the mixture stirred at room temperature overnight. After removal of the volatiles, the remaining oil was dissolved in ethyl acetate (40 mL) and the solution washed with aqueous $KHSO_4$ (1 N, 2 × 40 mL), $NaHSO_4$ (5%, 2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried with $MgSO_4$ and the solvents evaporated to dryness to give **4** as an off-white solid (2.03 g, 8 mmol, 80%). $C_{14}H_{23}NO_3$ (253.34): calcd. C 66.37, H 9.15, N 5.53; found C 66.14, H 9.06, N 5.51. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.15 (d, *J* = 6.6 Hz, 1 H, N*H*CO), 4.48 (m, 1 H, α-C*H*), 2.58–2.42 [m, 4 H, (C*H*$_2$)$_2$], 2.14 [m, 1 H, C*H*(CH$_3$)$_2$], 2.00 [s, 1 H, *H*CC(CH$_2$)$_2$], 1.46 [s, 9 H, OC(C*H*$_3$)$_3$], 0.93 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.90 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR ($CDCl_3$): δ = 171.4 (CONH), 170.9 (CO$_2$*t*Bu), 83.1 (HC*C*CH$_2$), 82.2 [*C*(CH$_3$)$_3$], 69.5 (H*C*CCH$_2$), 57.5 (α-*C*H), 35.7 (HCCCH$_2$*C*H$_2$), 31.7 [*C*H(CH$_3$)$_2$], 28.2 [C(*C*H$_3$)$_3$], 19.1 [CH(*C*H$_3$)$_2$], 17.8 (HCC*C*H$_2$CH$_2$) ppm.

TpmRu((*p*-C$_2$N$_3$H–(CH$_2$)$_2$–CO–Val–O*t*Bu)Tp) (5): To a mixture of **3** (396 mg, 0.58 mmol), **4** (174 mg, 0.69 mmol), and copper(I) iodide (3 mg, 0.03 mmol) was added acetonitrile/CH_2Cl_2 (2:1, 9 mL). After addition of 2,6-lutidine (20 μL, 0.30 mmol), the solution was degassed and backfilled with argon, and the reaction mixture stirred for 12 h in the dark. Removal of the volatiles gave a light green solid, which was dissolved in methanol (3 mL). Addition of water (≈ 20 mL) produced a yellow precipitate, which was isolated by filtration, washed with water (2 × 5 mL) and *n*-hexane (2 × 5 mL) and dried under reduced pressure (314 mg, 0.34 mmol, 58%). An analytically pure sample of **5**·CH_2Cl_2 was obtained by recrystallisation from CH_2Cl_2. $C_{40}H_{48}BCl_3N_{16}O_3Ru$ (1019.16): calcd. C 47.14, H 4.75, N 21.99; found C 47.92, H 5.11, N 21.52. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 12.09 [s, 1 H, *H*C(pz)$_3$], 9.06 (broad s, 3 H, pz-H3), 8.29 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 8.01 (s, 1 H, triazole-H), 7.98 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 7.77 (d, *J* = 2.2 Hz, 3 H, pz-H3), 7.20 (d, *J* = 2.2 Hz, 3 H, pz-H5), 6.92 (d, *J* = 2.2 Hz, 3 H, pz-H5), 6.46 (broad s, 3 H, pz-H4), 6.24 (t, *J* = 2.2 Hz, 3 H, pz-H4), 6.08 (d, *J* = 6.6 Hz, 1 H, CON*H*), 4.46 (m, 1 H, α-C*H*), 2.83–2.44 [m, 4 H, (C*H*$_2$)$_2$], 2.14 [m, 1 H, C*H*-(CH$_3$)$_2$], 1.47 [s, 9 H, OC(C*H*$_3$)$_3$], 0.92 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.88 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.8 (CONH), 171.3 (CO$_2$*t*Bu), 145.8 (pz-C5), 143.9 (pz-C5), 137.5 (C-B), 136.5 (pz-C3 and CH of AA′BB′), 134.8 (pz-C3) 134.4 (CH of AA′BB′), 120.2 (triazole-*C*H), 120.1 (CH of AA′BB′), 108.8 (pz-C4), 106.6 (pz-C4), 82.2 [*C*(CH$_3$)$_3$], 57.6 (α-*C*H), 35.9 (HCCCH$_2$*C*H$_2$), 31.5 [*C*H(CH$_3$)$_2$], 28.2 [C(*C*H$_3$)$_3$], 21.4 (HCC*C*H$_2$CH$_2$), 19.1 [CH(*C*H$_3$)$_2$], 17.8 [C(*C*H$_3$)$_3$] ppm; signals for Tpm-CH and Phenyl-C-N$_{triazole}$ were not observed. ESI-MS (pos. mode): *m*/*z* = 899.13 [M]$^+$, exact mass of complex cation: 899.31.

[TpmRu({*p*-C$_2$N$_3$H–(CH$_2$)$_2$–CO–ENK–OH}C$_6$H$_4$Tp)]Cl (6): To a mixture of penty–ENK–OH (85 mg, 0.14 mmol), **3** (93 mg, 0.14 mmol), and $CuSO_4$·5H_2O (4 mg, 0.014 mmol) in *t*-butanol (1 mL) was added a freshly prepared solution of sodium ascorbate (14 mg, 0.07 mmol) in water (2 mL). The resulting solution was degassed, backfilled with argon, and stirred in the dark for 12 h. Subsequent removal of the solvents yielded a greenish solid, which was washed with water (2 × 4 mL), and dried under reduced pressure. Purification by RP-HPLC yielded **6** as a light yellow solid (35 mg, 0.03 mmol, 21%). ^{1}H NMR (400 MHz, CD_3OD) note: The resonances of one α-CH and two β-CH_2 groups are obscured by the solvent peaks. Assignments are based upon comparison with literature data for Leu–Enkephalin.[36] δ = 9.73 [s, 1 H, *H*C(pz)$_3$], 8.56 (d, *J* = 2.2 Hz, 3 H, pz-H3), 8.38 (s, 1 H, triazole-H), 8.30 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 8.10 (d, *J* = 8.4 Hz, 2 H, part of AA′BB′), 7.87 (d, *J* = 2.2 Hz, 3 H, pz-H3), 7.30 (d, *J* = 2.2 Hz, 3 H, pz-H5), 7.26–7.13 (m, 5 H, Phe), 7.05 (d, *J* = 8.4 Hz, 2 H, AA′BB′ of Tyr), 6.97 (d, *J* = 2.2 Hz, 3 H, pz-H5), 6.70 (d, *J* = 8.4 Hz, 2 H, AA′BB′ of Tyr), 6.63 (t, *J* = 2.2 Hz, 3 H, pz-H4), 6.31 (t, *J* = 2.2 Hz, 3 H, pz-H4), 4.66 (dd, *J* = 9.0, 5.5 Hz, 1 H, α-C*H*), 4.52 (m, 1 H, α-C*H*), 4.41 (m, 1 H, α-C*H* of Leu), 3.90 (m, 2 H, α-C*H*$_2$ of Gly), 3.90 (m, 2 H, α-C*H*$_2$ of Gly), 3.75 (m, 2 H, α-C*H*$_2$ of Gly), 3.21–3.04 (m, 4 H, β-C*H*$_2$ and CH$_2$C*H*$_2$-triazole), 2.99–2.86 (m, 2 H, C*H*$_2$CH$_2$-triazole), 2.70 (m, 2 H, β-C*H*$_2$), 1.63 (m, 3 H, β-C*H*$_2$ and γ-C*H* of Leu), 0.91 (d, *J* = 6.3 Hz, C*H*$_3$ of Leu), 0.87 (d, *J* = 6.3 Hz, C*H*$_3$ of Leu) ppm. ESI-MS (pos. mode): *m*/*z* = 1281.03 [M]$^+$, 1151.06 [M – Leu]$^+$, 1004.06 [M – (Phe–Leu)]$^+$, 947.07 [M – (Gly–Phe–Leu)]$^+$, 890.09 [M – (Gly–Gly–Phe–Leu)]$^+$, 641.23 [M + H]$^{2+}$, exact mass of complex cation: 1281.44.

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