Novel triazole-based ligands and their zinc(II) and nickel(II) complexes with a nitrogen donor environment as potential structural models for mononuclear active sites†

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Three new 1,2,3-triazole-based ligands with an N,N,N coordination core were prepared using a convergent synthetic protocol starting from racemic 2-amino-1-phenylethanol. They were tested as chelators for biorelevant ZnII or NiIII ions. An N,N,N ligand with a terminal amino functionality coordinated the ZnII in a bidentate fashion, not including the triazole nitrogen. The ligand with two pendant 2-pyridyl groups acted as a tridentate ligand without an N2-triazole coordination to ZnII, while the ligand containing one 2-pyridyl group acted as an inverse-click chelator for NiIII ions.

They can be relatively easily prepared and modified.10,11 Reinaud and coworkers reported, in many papers over the past decade, on calixarene- and resorcinarene-based supramolecular biomimetic models of the trihistidine mononuclear active site, which not only mimic the first, but also the second and third coordination spheres of the catalytic metal.12 A triazole ring, on the other hand, can be regarded as an aza-analogue of imidazole, a nitrogen donor present in the histidine-containing active sites of many metalloenzymes. 1,2,3-Triazoles also act as N-donors and thus effectively coordinate metals, creating coordination materials with attractive physico-chemical properties.13 Of particular interest are the 1,4-disubstituted 1,2,3-triazole-based mono-, bi- or multidentate chelating ligands, which are employed in many fields, such as drug therapy, bioimaging and sensing, fluorescence, and catalysis.14 This is mainly because both the N2 and N3 atoms of the triazole nucleus can participate in metal coordination, while additional coordination sites can be readily introduced into 1- or 4-substituents using very efficient and selective “click reactions”.15 The majority of the 1,4-disubstituted 1,2,3-triazole ligands use their more Lewis basic N3 atom together with the pendant pyridyl group at position 4 (regular click chelators) to form planar or nonplanar pockets for the complexation of transition metals, such as ReI,16 PdII,17 FeII,18 CuIII,19 ZnII,20 and RuII,18,21. There are few 1,2,3-triazole-based chelating ligands that coordinate to the metal through the triazole N3 atom and the sp3N donor (e.g., sec-amino) in the side chain at position 4.22,23 Despite the fact that the N2 atom in a 1,2,3-triazole has a much lower electron density compared to N3,23 numerous stable complexes with the coordinating N2 atom have been prepared using suitable bi(or multi)dentate ligands with the 2-pyridyl group as the nitrogen donor, directly or remotely attached to the N1 atom of the 1,2,3-triazole ring (inverse click chelators).24 When instead of

Introduction

Mimetics of the active site of an enzyme are useful to better understand the structural features and how a donor array modulates the chemistry around the metal centre in the catalytic site.1 For instance, Rivas et al. have designed ligands that provide N4O, N2S2O and N2O coordination spheres for zinc and have observed that a nitrogen coordination environment is more efficient than mixed nitrogen/sulphur ligation in promoting amide cleavage,2 which would explain the predominant more efficient than mixed nitrogen/sulphur ligation in promoting

**Notes**

† CCDC 1011293–1011295. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c4nj01642d

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Received (in Victoria, Australia) 23rd September 2014, Accepted 29th October 2014

DOI: 10.1039/c4nj01642d

www.rsc.org/njc

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the pyridyl group, an aminoalkyl group is grafted at the N1 position of the 1,2,3-triazole ring, no complexation with metal occurs. Kuang et al. reported on utility of pyridyl or quinolinyl containing azides to accelerate the Cu-catalyzed cycloaddition with alkynes. The resulting 1,2,3-triazole ligands were demonstrated to chelate CuII or ZnII ions in a tridentate manner, including the N2 nitrogen of the triazolyl group. The successful 5-step synthesis and isolated in an overall yield of 49% (Scheme 1).

Scheme 1 Synthesis of 1,2,3-triazole 6. (i) CICO2Bn (1.2 equiv.), NEt3 (1.5 equiv.), CH2Cl2, r.t., overnight, 81%; (ii) MeSO2Cl (1.2 equiv.), NEt3 (1.5 equiv.), CH2Cl2, 0 °C, 0.5 h and r.t., 1 h, 97%; (iii) NaN3 (5 equiv.), DMF, r.t, 3 h, 92%; (iv) PhCCH (1.5 equiv.), CuSO4 (0.01 equiv.), Na-ascorbate (0.1 equiv.), t-BuOH/H2O (1 : 1), r.t., 20 h, 70%; (v) H2 (60 psi), Pd/C (20 mol%), MeOH, r.t., 8 h, 96%.

The identity of compound 6 was confirmed by NMR and IR spectroscopy, high-resolution mass spectrometry, and elemental analysis. The diastereotopic methylene protons of 6 show in the 1H NMR spectrum in DMSO-d6 two well-separated doublets of doublets at 3.33 and 3.58 ppm. Correspondingly, the signal of the proton at the chiral centre appears as a doublet of doublets. The characteristic signal of the triazole ring appears at 8.79 ppm.

In the next step, the ligand arm of the triazole 6 was elongated in order to introduce the third coordination donor. Since the direct reaction of 6 with 2-bromoethylamine hydrobromide as an aziridine precursor under basic conditions led to a complex mixture of products, the phthalate-protected reagent 7 was used. The heating of 6 with 7 in the presence of diisopropylethylamine (DIPEA) yielded N-substituted phthalimide 8, which after hydrazinolysis gave the target compound 9 in a 33% yield over two steps (Scheme 2).

Scheme 2 Synthesis of N,N,N ligand 9.

Due to the positive effect of pyridyl groups in inverse-click 1,2,3-triazole-based chelators, a potential hybrid sp2N–sp3N–sp2N ligand was also designed. When triazole 6 was reacted with a slight excess of 2-picolyl bromide hydrobromide, both the dipyridyl and monopyridyl products 10 and 11 were obtained, together with starting triazole 6, while the employment of 2.1 equivalents of 2-picolyl bromide hydrobromide selectively afforded the dipyridyl product 10 (Scheme 3). The selective synthesis of 11 was achieved by the reductive amination of 6. An in situ formed imine of 6 and pyridine-2-carboxaldehyde was reduced with sodium cyanoborohydride and the desired product 11 was isolated by chromatography in a low yield of 22% (Scheme 3). The NMR spectroscopy investigation in DMSO-d6 revealed that both picolyl groups in the ligand 10 are equivalent and that their methylenic protons display a well-resolved AB spin system (two doublets at 3.81 and 3.92 ppm, J = 14.5 Hz). Similarly, the methylenic protons of the picolyl group in 11 in DMSO-d6 are also magnetically nonequivalent.

Results and discussion

Ligand design

On the basis of geometrical preferences we envisaged that ligands comprising a 1,2,3-triazole N2 donor and two additional coordination sites in the substituent attached to the N1 atom of the triazole unit could be suitable ligands for coordination to metals in a tridentate fashion. The retrosynthetic approach to the tridentate 1,2,3-triazole-based ligands with non-planar coordination pockets containing three nitrogens or mixed nitrogen/oxygen donors is depicted in Fig. 1. The embedment of a chiral centre is designed for the potential use of these edifices in asymmetric transformations.

2-Amino-1-phenylethanol (1) was used as a starting material for the synthesis of triazole ligands. First, the hydroxyl group of amino alcohol 1 was transformed into the azido group. This was achieved via carbamate-protected methane sulphonate 3, which underwent a smooth substitution with sodium azide to yield the organic azide 4. A well-established Cu-catalyzed [3+2] cycloaddition of 4 with phenylacetylene selectively furnished 1,4-disubstituted 1,2,3-triazole 5, which was catalytically hydrogenated under a hydrogen pressure to remove the carbamate protection. Thus, the aminoalkyl-1,2,3-triazole 6 with two potential coordination sites (N2 atom of triazole and NH2) was formed in a 5-step synthesis and isolated in an overall yield of 49% (Scheme 1).

![Fig. 1 Retro-synthesis of potential tridentate 1,2,3-triazole-based ligands.](image-url)
In order to extend the above-mentioned methodology, the synthesis of the potential heteroleptic $N,N,O$-donor ligand 13 was also derived from aminoalkyl-1,2,3-triazole 6. The pendant hydroxyl group with geometry suitable for tridentate ligation, together with two nitrogen donors, was installed by the reaction of 6 with 2-chloroethyl chloroformate. A basic hydrolysis of the resulting carbamate 12 gave the desired product 13 in a good isolated yield (70% from 6) (Scheme 4).

**Metal complexes**

The reaction of ligand 9 with 1 equivalent of ZnCl$_2$ in the mixture of methanol and dichloromethane at room temperature over 24 hours, followed by the recrystallization of the crude residue from the EtOH/MeOH 1:1 mixture led to the formation of white crystals of product 14 (Scheme 5). The elemental analysis indicated that ligand 9 formed a zinc(II) complex with a 1:1 metal:ligand stoichiometry, and the formation of the complex was additionally confirmed by the Maldi-Tof HRMS study ($m/z = 406.1$). In the $^1$H NMR spectrum of 14 in DMSO-$d_6$ all three amino protons appear as one broad singlet at approximately 4 ppm, strongly (for about 2 ppm) shifted downfield compared to the free ligand 9, indicating that both the primary and secondary amino groups undergo an interaction with the metal atom. In addition, recognizable downfield shifts in the $^1$H NMR resonances of all the methylenic protons and of the proton at the chiral centre were observed. However, the resonance of the proton of the triazole unit of the complex 14 remained virtually unchanged, suggesting that the triazole ring is not involved in the zinc coordination. Indeed, a single-crystal X-ray diffraction study of 14 revealed that the zinc ion is embedded in a tetrahedral coordination sphere formed by two nitrogen donors from the ligand side chain and two chlorine anions (Fig. 2). The overall conformation of the potentially tridentate ligand molecule is defined by a strong intramolecular hydrogen bond N20–H20 $\cdot$ N2 [2.32 Å, 2.951 (5) Å, 126°] forming a hydrogen-bonded six-membered ring. In addition to this intramolecular H-bond, there is the intermolecular hydrogen bond N23–H23B $\cdot$ N3 [2.29 Å, 3.109 (4) Å, 151°] observed in the structure of 14, connecting two molecules related by a crystallographic inversion centre, and thus forming the molecular dimers as the basic molecular building blocks of the crystal structure. This means that both available triazole nitrogens (N2 and N3) act as hydrogen-bond acceptors rather than being involved in the Zn(II) coordination.

We assumed that the dipyrindyl compound 10 could act as a scorpionate-like tridentate ligand involving a triazole N2 atom and two pyridine nitrogens as the donors. Ligand 10 was mixed with 1 equivalent of ZnCl$_2$ in methanol and after cooling, colourless crystals of 15 were formed (Scheme 5). While the HRMS of the product gave only the signal for dissociated ligand 10, its coordination to the zinc centre was well supported by the
NMR analysis. The $^1$H NMR spectrum in DMSO-$d_6$ of 15 shows a single set of resonances for all pyridine hydrogen atoms appearing as broadened signals (without a fine structure) and are all shifted downfield relative to the free ligand 10. Moreover, methylenic protons of the 2-picoly group appear as two very broad singlets, also slightly shifted at 3.87 and 4.08 ppm, respectively. These results indicate that the two picoly groups are equivalent and thus both bind to the metal in a symmetric fashion. Similarly, the $^{13}$C NMR signals of pyridyl carbons (except $^{13}$C and the methylenic carbon of the picoly group are broadened. The broadening of the $^1$H and $^{13}$C picoly signals suggests a fluxional structure, probably due to the weak interaction between the pyridyl nitrogens and the zinc ion. Interestingly, the signal of a proton at the chiral centre in ligand 10 changed its fine structure from a doublet of doublets to a not-well-resolved doublet once 10 coordinated to zinc and is also remarkably shifted downfield ($\Delta \delta \approx 0.3$ ppm) in comparison to the free ligand. On the other hand, the resonance of the triazole proton in complex 15 is practically the same as that for the proton in the free ligand 10 (8.72 and 8.71 ppm), indicating the absence of triazole coordination to the metal atom. A detailed insight into the geometry and the binding mode of the zinc atom to ligand 10 was obtained by single crystal X-ray analysis.

The complex 15 is monomeric and features a five coordinated zinc centre in a distorted trigonal bipyramidal geometry (Fig. 3). The distortion of a trigonal bipyramid can be best described by the structural parameter $\tau$ (0 for an ideal square pyramid and 1 for an ideal trigonal bipyramid),$^{28}$ which in our case adopts the value of 0.72. The ligand 10 is tridentately coordinated to the Zn metal centre in fac-geometry with Zn-N bonding distances with N1 and N2 pyridyl atoms of 2.068(3) and 2.074(4) Å, respectively, and one longer distance with the amino N3 atom [2.418(3) Å]. The Zn–Cl bonding distances are 2.2630(11) and 2.3110(12) Å. The N-Zn-N angles are 117.56(14)$^\circ$, 75.90(11)$^\circ$ and 74.78(12)$^\circ$ and these deviate from the values expected for an ideal trigonal bipyramid. The lattice structure is stabilized by weak CH$\cdots$Cl and CH$\cdots$π interactions. Although the compound 15 has five aromatic rings, no significant π–π interactions can be observed in the crystal structure.

The nickel complex with ligand 11 was formed by reacting the ligand with 1 equivalent of NiCl$_2$·6H$_2$O (Scheme 5). Blue crystals, separated from the mother liquor by filtration, revealed a broad and ill-defined $^1$H NMR spectrum, which is in agreement with the paramagnetic nature of the 3d$^8$ species. The evidence for the formation of a nickel complex with the ligand 11 was provided by the IR spectrum, significantly altered with respect to the one obtained for the free ligand. The metal coordination was further supported by mass spectrometry (ESI$^+$), which showed a signal corresponding to a [[NiCl][+ ion. The coordination of ligand 11 to Ni was finally confirmed by the single crystal X-ray analysis. The asymmetric unit consists of two crystallographically independent complexes (molecule A and B) and two methanol solvate molecules (Fig. 4). The octahedral geometry in both molecules (A, B) is slightly distorted, with maximum deviations from the ideal angles of 90 and 180° ranging from 0.08(5)$^\circ$ to 10.71(6)$^\circ$ and from 2.94(3)$^\circ$ to 9.60(6)$^\circ$, respectively. Ligand 11 is tridentately coordinated to the Ni metal centre in the mer-geometry with Ni-N bonding.

**Fig. 3** Crystal structure of 15. Selected bond lengths [Å] and angles [°]: Zn1–N1 2.068(3), Zn1–N2 2.074(4), Zn1–N3 2.418(3), Zn1–Cl1 2.2630(11), Zn1–Cl2 2.3110(12), N1–Zn1–N2 117.56(14), N1–Zn1–N3 75.90(11), N2–Zn1–N3 74.78(12), N1–Zn1–Cl1 109.38(10), N1–Zn1–Cl2 101.94(9), N2–Zn1–Cl2 96.45(10), N2–Zn1–Cl1 124.94(10), C1–Zn1–N1 91.10(8), C1–Zn1–N3 168.12(8), C1–Zn1–Cl2 100.58(5).

**Fig. 4** Crystal structure of [16(MeOH)]·MeOH, only molecule A is presented. Selected bond lengths [Å] and angles [°] for molecule A: Ni(1)–N(2) 2.0733(15), Ni(1)–N(4) 2.0488(15), Ni(1)–N(5) 2.0718(15), Ni(1)–O(1) 2.0902(13), Ni(1)–Cl(1) 2.4311(5), Ni(1)–Cl(2) 2.4289(5), Ni(2)–Ni(1)–O(1) 92.92(5), Ni(2)–Ni(1)–Cl(1) 89.92(5), Ni(2)–Ni(1)–Cl(2) 88.22(5), N(4)–Ni(1)–N(2) 91.11(6), N(4)–Ni(1)–N(5) 79.29(6), N(4)–Ni(1)–O(1) 174.97(6), N(4)–Ni(1)–Cl(1) 122.36(5), N(4)–Ni(1)–Cl(2) 89.94(5), N(5)–Ni(1)–N(2) 170.40(6), N(5)–Ni(1)–Cl(1) 96.66(6), N(5)–Ni(1)–Cl(2) 90.49(5), N(5)–Ni(1)–Cl(2) 91.73(5), O(1)–Ni(1)–Cl(1) 84.65(4), O(1)–Ni(1)–Cl(2) 93.18(4), C(1)–Ni(1)–Cl(1) 177.06(18), selected bond lengths [Å] and angles [°] for molecule B: Ni(2)–N(7) 2.0465(15), Ni(2)–N(9) 2.0492(15), Ni(2)–N(10) 2.0457(15), Ni(2)–O(2) 2.0858(13), Ni(2)–Cl(3) 2.4533(5), Ni(2)–Cl(4) 2.4698(5), N(7)–Ni(2)–N(9) 91.77(6), N(7)–Ni(2)–O(2) 93.04(6), N(7)–Ni(2)–Cl(3) 89.67(5), N(7)–Ni(2)–Cl(4) 86.60(5), N(9)–Ni(2)–O(2) 173.74(6), N(9)–Ni(2)–Cl(3) 89.30(5), N(9)–Ni(2)–Cl(4) 91.57(5), N(10)–Ni(2)–N(7) 171.60(6), N(10)–Ni(2)–N(9) 81.42(6), N(10)–Ni(2)–O(2) 93.42(6), N(10)–Ni(2)–Cl(3) 95.13(4), O(2)–Ni(2)–Cl(3) 94.72(4), N(10)–Ni(2)–Cl(4) 88.66(5), O(2)–Ni(2)–Cl(4) 84.73(4), Cl(3)–Ni(2)–Cl(4) 176.19(19).
metal complexes is currently ongoing and will be the subject of our forthcoming report.

Conclusions

The synthesis of potential tridentate ligands containing a 1,2,3-triazole moiety with either nitrogen or mixed nitrogen and oxygen donor sites was achieved by employing the convergent protocol starting from 2-amino-1-phenylethanol. Their coordination ability was tested with two biorelevant metals to mimic a histidine-carboxylate active site of metallopeptidases. An all-nitrogen-donor ligand containing a terminal amino functionality was coordinated to the Zn \textsuperscript{II} ion in a bidentate fashion, not including a triazole N2 atom. A 1,2,3-triazole-based ligand containing two 2-picolyl groups was coordinated to the Zn \textsuperscript{II} ion through tertiary and two pyridine nitrogens, while the N,N,N ligand with one 2-picolyl arm acted as an inverse-click chelator for the Ni \textsuperscript{II} ion, since an N2 atom of the triazole ring together with the amino and pyridyl nitrogens was successfully coordinated to the metal. However, the coordination of the N,N,O ligand with a terminal hydroxyl group was not achieved under neutral or under basic conditions. The synthesized complexes may have potential as bioinspired catalysts and due to the possibility of introducing a chiral centre they may also be used in asymmetric transformations.

Experimental section

General considerations

The reagents and solvents were used as received from commercial suppliers. The reagent 7 was prepared according to the reported procedure.\textsuperscript{29} Melting points were determined on a Kofler micro hot stage. The NMR spectra were recorded at 302 K either on a Bruker Avance DPX 300 or Avance III 500 MHz spectrometer operating at 300 MHz (or 500 MHz) and 75.5 MHz (or 125 MHz) for \textsuperscript{1}H and \textsuperscript{13}C. The \textsuperscript{1}H NMR spectra are referenced with respect to TMS as the internal standard. The \textsuperscript{13}C NMR spectra are referenced against the central line of the solvent signal (DMSO-\textit{d}_6, septet at \( \delta = 39.5 \) ppm, CDCl\textsubscript{3} triplet at \( \delta = 77.0 \) ppm). The coupling constants \( (J) \) are given in Hz. The multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broadened).

IR spectra were obtained with a Bruker ALPHA FT-IR spectrophotometer or Bio-Rad FTS 3000MX. MS spectra were recorded with an Agilent 6224 Accurate Mass TOF LC/MS instrument, VG-Analytical AutoSpec Q instrument or 4800 MALDI TOF/TOF Analyzer, Applied Biosystems. Elemental analyses (C, H, N) were performed using a Perkin-Elmer 2400 Series II CHNS/O Analyzer. TLC was carried out on Fluka silica gel TLC-cards. Merck silica gel 60 PF254 containing gypsum was used to prepare chromatotron plates. Radial chromatography was performed using a Harrison Research, model 7924T chromatotron.

X-ray diffraction analysis

Single-crystal X-ray diffraction data were collected using an Agilent Technologies SuperNova Dual diffractometer with an
Atlas detector and Mo-Kα radiation (λ = 0.71073 Å) at room temperature (14 and 15) and 150 K ([16(MeOH)] MeOH). The data were processed using CrysAlis Pro. The structures were solved by direct methods using the program SHELXS-97 (ref. 31) (15) or SIR97 (ref. 32) (14 and [16(MeOH)] MeOH) and refined on F² using full-matrix least-square procedures (SHELXL-97). Single crystals of 14 were of an extremely poor quality and the data collection was difficult. Hence the somewhat ill-refined structure. However, the main goal was to establish the zinc binding mode which is undoubtedly and fully achieved. All our later efforts to produce the better quality single crystals were unsuccessful. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were treated as riding atoms in geometrically idealized positions, except the hydrogen atoms attached to O1 and O2 atoms in [16(MeOH)] MeOH that were refined fixing the bond lengths and isotropic temperature factors. Crystallographic data are listed in Table 2.

**Syntheses**

**Benzyl (2-hydroxy-2-phenylethyl)carbamate** (2). To the cooled (0 °C) mixture of 2-amino-1-phenylethanol (7.36 g, 53.65 mmol), triethylamine (10 mL, 80.24 mmol) and CH₂Cl₂ (80 mL), solution of benzyl chloroformate (9.2 mL, 64.45 mmol) in CH₂Cl₂ (20 mL) was slowly added. The resulting mixture was allowed to warm to r.t. and stirred overnight. Then water (100 mL) was added and after separation, the aqueous phase was extracted with CH₂Cl₂ (50 mL). Combined organic layers were washed with water (100 mL) and dried (Na₂SO₄). After removal of the solvent, 3.674 g (92%) of orange oil was obtained. 1H NMR (500 MHz, CDCl₃): δ = 1.26 (br, 1H, OH), 2.66 (dd, J = 10.6 Hz, 1H, CH₂), 3.56 (m, 1H, CH₂Ph), 3.84 (dd, J = 3.1, 7.5 Hz, 1H, CH), 5.11 (s, 2H, CH₂Ph), 5.13 (br, 1H, NH), 7.28–7.41 (m, 10H, Ar) ppm.

**Benzyl (2-azido-2-phenylethyl)carbamate** (4). The mixture of 3 (4.695 g, 13.44 mmol) used directly from the previous reaction, NaN₃ (4.369 g, 67.21 mmol) and DMF (15 mL) was stirred at r.t. for 3 h. Then water (100 mL) was added and extracted with Et₂O (3 × 80 mL). The combined organic layers were washed with brine (2 × 80 mL) and dried (Na₂SO₄). After removal of volatiles, 3.674 g (92%) of orange oil was obtained. 1H NMR (300 MHz, CDCl₃): δ = 3.32 (m, 1H, CH a-CH), 3.56 (m, 1H, CH a-CH), 4.84 (dd, J = 10.6 Hz, 1H, CH₂), 5.13 (br, 1H, NH), 7.28–7.41 (m, 10H, Ar) ppm.

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</table>

a \( R = \sum ||F_{o}|| - |F_{c}| ||/\sum |F_{o}| \), b \( wR₂ = \sum [w(F₀² - F_c²)]²/\sum [w(F₀²)]² \) 0.12. c \( S = \left( \sum [(F₀² - F_c²)]^2/ [(n/p)]^0.5 \right) \) where n is the number of reflections and p is the total number of parameters refined.
65.5, 66.9, 126.9, 128.0, 128.1, 128.5, 128.7, 128.9, 136.2, 136.8, 156.2 ppm. IR (NaCl) ν = 3149, 3334, 3063, 3033, 2939, 2103, 1708, 1522, 1455, 1250, 1147, 1067, 989, 755, 699 cm⁻¹. HRMS (ESI) calcd for C₁₂H₁₃N₂O₂ [M + H⁺]: 297.1352; found 297.1346.

Benzy l [2-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl]carbamate (5). To the mixture of 4 (1.689 g, 5.77 mmol), phenylacetylene (0.873 g, 8.55 mmol), and t-BuOH/H₂O (20 mL, 1 : 1), freshly prepared aqueous solutions of sodium ascorbate (570 μL, 1 M) and CuSO₄·5H₂O (37 μL, 1 M) were added and extracted with EtOAc (3 × 50 mL). Combined organic layers were dried (Na₂SO₄). After removal of volatiles, the oily residue was subjected to radial chromatography (silica gel, CH₂Cl₂/EtOAc) and column chromatography (silica gel with MeOH as the eluent). After the removal of the solvent, 1.59 g (70%) of the product.

To the mixture of 5 (2.22 g, 5.57 mmol), MeOH (250 mL), and Pd/C (0.18 g, 1.11 mmol; 10 wt%) was hydrogenated under H₂ (60 psi) at r.t. for 8 h. Then the catalyst was filtered off, the filtrate was concentrated and the residue was passed through a short column of silicagel with MeOH as the eluent. After the removal of the solvent, 1.41 g (96%) of a white solid was obtained. Rf = 0.35 (1 : 10 MeOH/CH₂Cl₂); m.p. 152–154 °C. ¹H NMR (300 MHz, CDCl₃): δ = 4.09 (m, 1H, CH₂H₂-CH), 4.22 (m, 1H, CH₂H₂-CH), 5.05 (d, J = 12.3 Hz, 1H, CH₂H₂-Ph), 5.45 (br, 1H, NH), 5.76 (dd, J = 4.2, 9.0 Hz, 1H, CH), 7.26–7.44 (m, 13H, Ar), 7.68 (s, 1H, CH triazole) ppm. ¹³C NMR (125.7 MHz, DMSO-d₆): 44.4, 63.5, 65.3, 120.8, 125.1, 127.0, 127.5, 127.7, 127.8, 128.2, 128.5, 128.6, 128.9, 130.7, 136.3, 137.4, 143.6, 156.2 ppm. IR (KBr): ν = 3451, 3366, 3283, 1607, 1456, 1218, 1075, 834, 760, 723 cm⁻¹.

After removal of volatiles, the solid residue was suspended in Et₂O (50 mL) and filtered off to give 1.59 g (70%) of the product. Rf = 0.41 (1 : 1 petroleum ether/EtOAc); m.p. 152–154 °C. ¹H NMR (300 MHz, CDCl₃): δ = 4.09 (m, 1H, CH₂H₂-CH), 4.22 (m, 1H, CH₂H₂-CH), 5.05 (d, J = 12.3 Hz, 1H, CH₂H₂-Ph), 5.45 (br, 1H, NH), 5.76 (dd, J = 4.2, 9.0 Hz, 1H, CH), 7.26–7.44 (m, 13H, Ar), 7.68 (s, 1H, CH triazole) ppm. ¹³C NMR (125.7 MHz, DMSO-d₆): 44.4, 63.5, 65.3, 120.8, 125.1, 127.0, 127.5, 127.7, 127.8, 128.2, 128.5, 128.6, 128.9, 130.7, 136.3, 137.4, 143.6, 156.2 ppm. IR (KBr): ν = 3395, 3078, 2934, 1699, 1523, 1458, 1425, 1261, 1104, 1157, 1076, 998, 932, 909, 854, 745, 693, 544, 515 cm⁻¹. HRMS (ESI) calcd for C₂₄H₂₃N₄O₂ [M + H⁺]: 399.1821; found 399.1835.

After removal of volatiles, the oily residue was subjected to radial chromatography (silica gel, CH₂Cl₂/EtOAc) and column chromatography (silica gel with MeOH as the eluent). After the removal of the solvent, 1.59 g (70%) of the product.

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After removal of volatiles, the oily residue was subjected to radial chromatography (silica gel, CH₂Cl₂/EtOAc) and column chromatography (silica gel with MeOH as the eluent). After the removal of the solvent, 1.59 g (70%) of the product.

After removal of volatiles, the oily residue was subjected to radial chromatography (silica gel, CH₂Cl₂/EtOAc) and column chromatography (silica gel with MeOH as the eluent). After the removal of the solvent, 1.59 g (70%) of the product.
period of 1 h and afterwards stirred for additional 0.5 h. The reaction mixture was evaporated and the mixture of NaOH (2 mL, 35%) and water (10 mL) was added, and extracted with DCM (4 × 10 mL). Combined organic layers were dried (Na2SO4) and evaporated. The residue was purified by radial chromatography (SiO2: MeOH/CH2Cl2 50:1) giving 32 mg (22%) of a yellowish product. Rf = 0.63 (1:10 MeOH/CH2Cl2); m.p. 116–119 °C (petroleum ether/EtOAc).

1H NMR (500 MHz, DMSO-d6): δ = 2.53 (br, 1H, NH), 3.28 (dd, J = 5, 13 Hz, 1H, CH2-NH-CH), 3.61 (dd, J = 9.5, 13 Hz, 1H, CH2-NH-CH), 3.87 (AB, 2H, Py-CH2), 5.96 (dd, J = 5, 9.5 Hz, 1H, CH), 7.22 (dd, J = 1, 4.5, 7.5 Hz, 1H, Py), 7.31–7.47 (m, 9H, Py and Ar), 7.70 (dd, J = 2, 7.5, 7.5 Hz, 1H, Py), 7.86 (m, 2H, Ar), 8.47 (dd, J = 1, 2, 5 Hz, 1H, Py), 8.82 (s, 1H, CH triazole) ppm. 13C NMR (125.7 MHz, DMSO-d6): δ = 52.6, 53.9, 64.3, 120.9, 121.8, 121.9, 125.1, 126.9, 127.8, 128.2, 128.7, 128.9, 130.8, 136.5, 138.6, 146.2, 148.8, 159.9 ppm. IR (neat): /C0 841, 759, 688 cm⁻¹ (m, 8H, Ar), 7.86 (m, 2H, Ar), 8.79 (s, 1H, CH triazole) ppm. 1H NMR (75.5 MHz, DMSO-d6): δ = 5.58 (t, J = 127.8, 128.2, 128.7, 128.9, 130.8, 136.5, 138.6, 146.2, 148.8, 159.9 ppm. IR (KBr): /C0 841, 759, 688 cm⁻¹ (m, 8H, Ar), 7.86 (m, 2H, Ar), 8.79 (s, 1H, CH triazole) ppm. 1H NMR (300 MHz, CDCl3): δ = 3.61 (t, J = 5.7 Hz, 2H, CH2), 4.09 (m, 1H, CH2-NH-CH), 4.21 (m, 1H, CH2-NH-CH), 4.28 (m, 2H, CH2), 5.58 (s, J = 4.7 Hz, 1H, NH), 7.55 (dd, J = 4.7, 9.3 Hz, 1H, CH), 7.23–7.45 (m, 8H, Ar), 8.77 (s, 1H, CH triazole), 7.79 (m, 2H, Ar) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 41.8, 45.2, 64.7, 64.9, 120.5, 125.7, 126.7, 128.3, 128.9, 129.0, 132.0, 136.8, 148.1, 156.0 ppm. IR (KBr): ν = 2696, 2650, 2363, 1608, 1481, 1456, 1441, 1432, 1333, 1219, 1164, 833, 769, 724, 696 cm⁻¹. HRMS (ESI⁺) calc for C19H21N5O (M + H)⁺: 356.1870; found 356.1870. C22H21N5 (355.44): calcd C 74.34, H 5.96, 9.56, N 19.70; found C 74.23, H 6.11, N 19.49.

2-Chloroethyl-2-phenyl-2-(4-phenyl-1,2,3-triazol-1-yl)ethylcarbamate (12). To a solution of 6 (368 mg, 1.392 mmol) and pyridine (156 µL, 1.94 mmol) in CH2Cl2 (10 mL), 2-chloroethyl chlorofomate (157 µL, 1.52 mmol) was added. The resulting mixture was stirred at r.t. for 2.5 h, afterwards water (15 mL) was added. Layers were separated and the water phase was extracted with CH2Cl2 (3 × 10 mL). Combined organic layers were dried (Na2SO4) and evaporated to give 467 mg (90%) of a white solid. Rf = 0.59 (1:20 MeOH/CH2Cl2); m.p. 138–140 °C. 1H NMR (300 MHz, CDCl3): δ = 3.61 (t, J = 5.7 Hz, 2H, CH2), 4.09 (m, 1H, CH2-NH-CH), 4.21 (m, 1H, CH2-NH-CH), 4.28 (m, 2H, CH2), 5.58 (s, J = 4.7 Hz, 1H, NH), 7.55 (dd, J = 4.7, 9.3 Hz, 1H, CH), 7.23–7.45 (m, 8H, Ar), 8.77 (s, 1H, CH triazole), 7.79 (m, 2H, Ar) ppm. 13C NMR (75.5 MHz, CDCl3): δ = 41.8, 45.2, 64.7, 64.9, 120.5, 125.7, 126.7, 128.3, 128.9, 129.0, 132.0, 136.8, 148.1, 156.0 ppm. IR (KBr): ν = 2696, 2650, 2363, 1608, 1481, 1456, 1441, 1432, 1333, 1219, 1164, 833, 769, 724, 696 cm⁻¹. HRMS (ESI⁺) calc for C19H21Cl2N5 (M + Cl)⁺: 384.1270; found 384.1270. C19H21Cl2N5O (443.81): calcd 443.79; found 443.78. C19H21Cl2N5 (443.81): calcd 443.79; found 443.78.

**Acknowledgements**

We thank the Ministry of Higher Education, Science and Technology of the Republic of Slovenia and the Slovenian
Thank S. Marković, N. Dragoš and J. Bobnar for their laboratory assistance.

Notes and references


30 *CrysAlis PRO*, Agilent Technologies, Yarnton, 2011.

