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Efficient and tunable synthesis of new polydentate bifunctional chelating agents using click chemistry

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Abstract

Two novel bifunctional chelating agents, which are bistriazole-based polyaminocarboxylic acids, have been designed and synthesised in high yields. An elegant synthetic approach using the Cu-catalysed azide–alkyne cycloaddition has been developed. This convenient route could be employed for the synthesis of a variety of polydentate bifunctional chelators.

Keywords: Polydentate chelating agents; Bifunctional chelator; Click chemistry; Triazole

Interest in the development of new polydentate bifunctional chelating agents (BCAs) continues to be stimulated by the ability of such ligands to be used as molecular sensors or diagnostic/therapeutic tools in biomedical applications. They are particularly suitable for bioanalytical applications[1] (luminescent sensors), MRI contrast agents[2] and target-specific radiopharmaceuticals[3] for scintigraphy and radioimmunotherapy (RIT) in nuclear medicine.

An ideal BCA should coordinate a metal ion with a high yield to form a metal-chelate with high thermodynamic stability as well as high in vivo kinetic inertness, to allow localisation of the metal at the target site (tumours or organs) and to minimise intoxication arising from the loss of the metal. Among these chelating ligands, polyaminocarboxylic acids represent the most common and studied class of chelators for biomedical applications as they form very stable complexes with a variety of di- and trivalent metal ions.[4] Commonly, the preparation of such chelators requires multiple-step syntheses, the most employed procedure being the synthesis of a functionalised polyamine, alkylation of the amino groups by an excess of alkyl bromoacetate then hydrolysis of the ester functions.[5] Although effective, this procedure generally suffers from low overall yields. Therefore, alternative, versatile and easier strategies are desirable.

Click chemistry is an increasingly common method for rapid synthesis of organic and bioorganic compounds. This term, coined by Sharpless, refers to a Cu(I) catalysed Huisgen 1,3-dipolar cycloaddition of azides and alkynes, providing 1,4-disubstituted 1,2,3-triazole ring in high yield without the need for further purification, without generating side reactions and proceeding under friendly conditions, in aqueous media at room temperature.[6] Recently, Schibli et al. reported the use of 1,4-disubstituted 1,2,3-triazole as an efficient chelator system for $Tc(CO)_3^+$ or $Re(CO)_3^+$ organometallic cores ('click-to-chelate' approach). They showed that click chemistry simplifies the synthesis of efficient chelators in which 1,4-disubstituted 1,2,3-triazoles form an integral part of the metal chelating system.[7]

These considerations have drawn our attention to the possibility of applying click chemistry to the synthesis of a new generation of polydentate BCAs whose design features, illustrated in Scheme 1, may be summarised as follows: (i) a multi-ligating site, formed by the two triazole units bearing an iminodiacetic (IDA) moiety, for the

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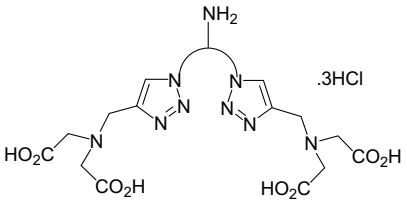
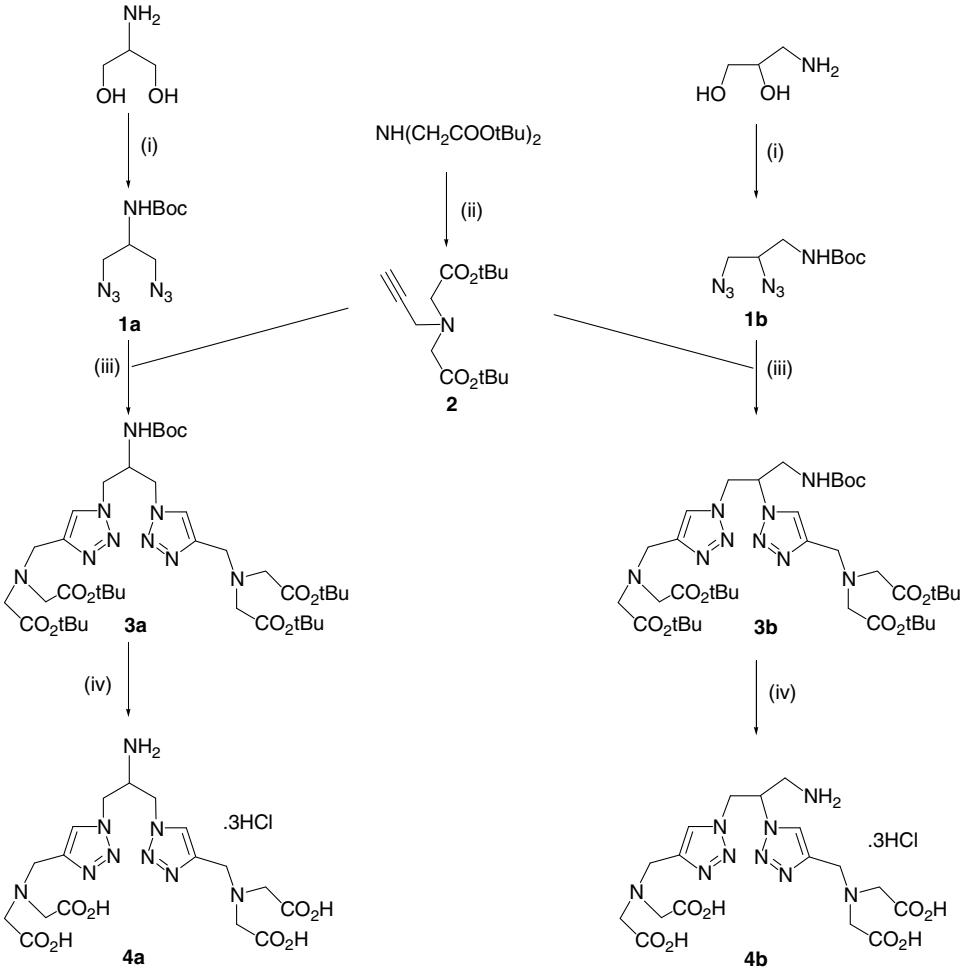


Scheme 1. Bistriazole-based polyaminocarboxylic acid derivatives.

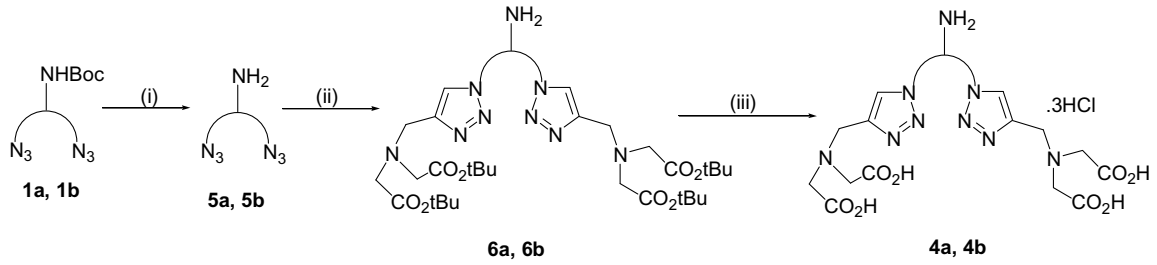
complexation of lanthanide and 'pseudo-lanthanide' or transition metal cations (ii) a linking site to a biomolecule via the amino functionality (iii) a tethering moiety (an ethylene or propylene bridge) between the linking and coordinating sites. In this contribution, we present an elegant and facile synthetic approach leading to two novel bistriazole-based polyaminocarboxylic acids in good yield. In addition, we validated that this convenient and highly tunable route could be employed for the synthesis of a variety of polydentate bifunctional chelators.

Two convergent synthetic routes were envisaged to prepare the desired compounds **4a**, **4b** (Schemes 2 and 3). Both of them involve amino-functionalised azide derivatives and an acetylenic compound bearing a *tert*-butyl iminodiacetate moiety. As previously described, the intermediates **1a**, **1b** were prepared in three steps from commercially available aminodiols.[8] Briefly, *N*-Boc protection of the amino function followed by the mesylation of the hydroxy groups gave the corresponding bismesylates, which were converted into bisazides **1a**, **1b** in 62% and 74% overall yields, respectively (Scheme 2). It is noteworthy that this kind of intermediates could be interesting dendrons to synthesise unsymmetrical peptide-dendrimers based on click chemistry, as reported recently.[9] Compound **2** was prepared in 90% yield by reacting *tert*-butyl iminodiacetate with propargyl bromide in the presence of potassium carbonate in acetonitrile.

With these two starting materials in hands, it was easy to produce the 1,4-disubstituted bistriazole scaffolds by coupling 1 equiv of **1a** or **1b** with 2 equiv of **2** under classical click reaction conditions as shown in Scheme 2 (copper(I) catalyst, room temperature, *t*BuOH/water mixture...). According to the literature, the copper(I) species can be used directly or generated by the reduction of Cu(II) species.[10] In our case, the copper(II) salt/reducing agent system



Scheme 2. General synthetic routes to target compounds **4a**, **4b**. Reagents and conditions: (i) Ref. 8, three steps, 62% (**1a**), 74% (**1b**); (ii) Propargyl bromide, K_2CO_3, ACN, 70°, one night, 90%; (iii) **2** (2 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv), sodium ascorbate (0.4 equiv), H_2O/*t*BuOH: 1/1, rt, one night, 74% (**3a**), 86% (**3b**); (iv) TFA then HCl 1 M, 91%.



Scheme 3. Alternative route for the synthesis of **4a**, **4b**. Reagents and conditions: (i) TFA/CH_2Cl_2 then NaOH, 89% (**5a**), 91% (**5b**); (ii) **2** (2 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv), sodium ascorbate (0.4 equiv), H_2O/*t*BuOH: 1/1, rt, one night, 60% (**6a**), 66% (**6b**); (iii) TFA then HCl 1 M, 90%.

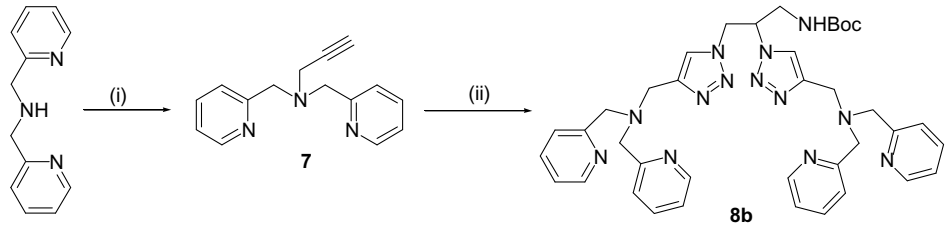
($Cu(OAc)_2{\cdot}H_2O$, 20 mol %/sodium ascorbate, 40 mol %) revealed to be a better efficient catalyst than copper(I) species used directly (CuI, 20% mol, diisopropylamine). Under these optimal conditions, the two cyclo-additions proceeded very well and the corresponding bistriazole products **3a**, **3b** were isolated in fair yields (74% and 86%, respectively) after the treatment with a saturated Na_2EDTA solution (to remove copper species) and purification by column chromatography on silica gel.[11] However, under these conditions, we always observed the minor formation of a less-polar by-product (yield < 5%), which corresponds to the monoazide monotriazole species, as identified by IR and positive DCI mass spectra ($\nu(N_3) = 2162\ cm^{-1}$; $m/z =$ 525, $[M+H^+]$; 542, $[M + NH_4^+]$). This result was consistent with a recent work on the reactivity of 1,3-diazides under click chemistry conditions.[12]

Final tetraacids **4a**, **4b** were isolated as trichlorhydrate salts, in excellent yield, after hydrolysis of the esters in neat trifluoroacetic acid at ambient temperature followed by a treatment with 1 M HCl. These hydroscopic compounds were unambiguously characterised by the common analytical techniques.[13] In summary, this six-step way led to two novel bistriazole-based BCAs **4a**, **4b** in 37% and 52% overall yields, respectively. Such ligands could be used for target-specific radiopharmaceuticals. The octadentate coordinating site could complex one trivalent cation like ^{111}In, ^{90}Y or two transition metal cations by both IDA moieties, which are powerful chelating systems for $M(CO_3)^+$ core (M = ^{99m}Tc or $^{186/188}Re$).[14]

The second route (Scheme 3) envisaged was analogous to the precedent synthetic way. In this approach, the removal of the *N*-Boc protecting group of **1a**, **1b** with TFA afforded the aminodiazides **5a**, **5b**, and click chemistry reaction of these materials with **2** gave the bistriazole tetra-*tert*-butyl esters **6a**, **6b** in 53% and 60% overall yields from **1a**, **1b**, respectively. Then, the final compounds were obtained using the acidic hydrolysis conditions depicted in the first route. This procedure has the advantage of producing BCA precursors **5a**, **5b** with full orthogonal protection of the metal-chelating site, thereby allowing a conjugation step with a biomolecule like peptide or biotin derivatives.[15]

Our methodology offers numerous advantages: good overall yield, mild reaction conditions, high functional group tolerance and gram-scale preparation. So, this method has the flexibility to allow the generation of various polydentate bifunctional chelators using other functionalised azide and/or acetylenic compounds. As an extension, and to prove the versatility of this general approach, we synthesised a bistriazole-based polyaminomethylpyridine derivative (Scheme 4).

The reaction of commercial di-(2-picolyl)amine with propargyl bromide in the presence of potassium carbonate in acetonitrile gave the corresponding propargyl di-(2-picolyl)amine **7** in 87% yield.[16] The bistriazole compound **8b** was then obtained from **1b** and **7** using the click chemistry protocol described above, in moderate yield (44%). The yield of the 1,3-dipolar cycloaddition is deeply affected by the nature of the used functionalised alkyne (86% for **3b** vs 44% for **8b**). In this latter case, the modest yield could be explained considering compound **7** as a copper chelating ligand.[17] So, we achieved the 1,3-cycloaddition reaction using the copper acetate in excess quantities (2.2 equiv) to compensate for copper being sequestered by **7**. Under these conditions, the desired bistriazole compound **8b** was obtained in 61% yield.[18]



Scheme 4. Synthesis of bistriazole-based polyaminomethylpyridine derivative **8b**. Reagents and conditions: (i) Propargyl bromide, K_2CO_3, ACN, 70°, one night, 87%; (ii) $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv), sodium ascorbate (0.4 equiv), H_2O/*t*BuOH: 1/1, rt, one night, 61%.

This novel BCA possesses two *N*,*N*′-bis(2-pyridylmethyl)-*N*″-(4-triazolylmethyl)amino units which could be effective transition metals and lanthanides tripodal chelating systems for radiopharmaceutical[19] or luminescent[20] applications, respectively.

Preliminary complexation study has been realised with ligand **8b** and a Re(I) precursor with a metal-to-ligand ratio of 2:1. As expected, the bis-rhenium tricarbonyl derivative $[(Re(CO)_3)_2(\mathbf{8b})]Cl_2$ **9** was obtained in 65% yield from the reaction of $Re(CO)_5Cl$ and **8b** in refluxing methanol. The dinuclear complex was unambiguously characterised by NMR (^1H–^1H and ^1H–^{13}C experiments), IR and mass spectra.[21] Briefly, NMR analysis was indicative of the mode of ligand binding (tridentate coordination via the N-atoms of the tertiary amine and the two pyridines) and illustrated the lower symmetry of the ligand once bound to the $Re(CO)_3^+$ cores.[22] The pattern of the C–O stretching frequencies in the IR spectra of one sharp and intense absorption at 2030 cm^{-1} and a second broad, intense band in the 1900–1920 cm^{-1} region confirms the facial arrangement of the CO ligands in the complex.[19a] In the mass spectra, the prominent peak observed at *m*/*z* 628 is assigned to $[\mathbf{9}-2Cl^-]^{2+}$ on the basis of the isotopic distribution of $^{185/187}$Re. In addition, two higher mass peaks at *m*/*z* 1254 and 1290 correspond to $[\mathbf{9}-H^+-2Cl^-]^+$ and $[\mathbf{9}-Cl^-]^+$, respectively. This complex is stable to aerial oxidation.

In conclusion, we have developed a convenient and elegant synthetic protocol to obtain original bifunctional polyaminocarboxylic acids based on click chemistry with good overall yields. Extension of this general approach to the preparation of structurally diverse bifunctional ligand systems has been demonstrated. These products may find application as luminescent or radiopharmaceutical probes. Further work on the complexation of these novel bifunctional chelating agents with lanthanide, 'pseudo-lanthanide' and transition metal cations is in progress and will be reported in due course.

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11. **CAUTION**: Because of their potentially explosive character, all reactions involving azido or bis(azido) compounds were carried out with the appropriate protection under a well-ventilated hood.
Typical procedure for the double Huisgen 1,3-dipolar cycloaddition step: Diazide (2.08 mmol), N-functionalised acetylenic compound (4.16 mmol), copper(II) acetate monohydrate (80 mg, 0.40 mmol) and sodium ascorbate (160 mg, 0.83 mmol) were mixed in an equivolumic mixture of water/*tert*-butanol (30 mL) and stirred at rt overnight. The resulting green solution was diluted with ethyl acetate (30 mL) and washed successively with water (2 × 30 mL) and saturated with Na_2EDTA solution (2 × 30 mL). The aqueous solutions were extracted with ethyl acetate (15 mL). The organic extracts were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography on a silica gel (eluent: CH_2Cl_2/MeOH: 99/1 then 96/4) to afford the desired product as a white solid. Selected analytical data. *Compound* **3a**: Yield: 74%, ^1H NMR (300 MHz, $CDCl_3$) 1.41 (s, 9H, CH_3), 1.45 (s, 36H, CH_3), 3.41 (s, 8H, CH_2), 3.99 (s, 4H, CH_2), 4.32–4.38 (m, 5H, CH+CH_2), 5.24 (m, 1H, NH), 7.73 (s, 2H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.2 (CH_3), 48.8, 49.8 (CH_2), 51.0 (CH), 55.4 (CH_2), 81.2 ($C(CH_3)_3$), 124.8 (=C–H), 145.8 (=C–N), 170.3 (C=O); DCI-MS 808 [M+H^+], 825 [M+NH_4^+]. *Compound* **3b**: Yield: 86%, ^1H NMRN (300 MHz, $CDCl_3$) 1.45 (m, 45H, CH_3), 3.38–3.42 (2s, 8H, CH_2), 3.66 (m, 2H, CH_2), 3.87–3.93 (m, 4H, CH_2), 4.81–4.84 (m, 2H, CH_2), 5.06–5.11 (m, 2H, NH+CH), 7.30 (s, 1H, =CH), 7.38 (s, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3 (CH_3), 42.4, 48.7, 51.0, 55.4 (CH_2), 60.7 (CH), 81.1 ($C(CH_3)_3$), 124.1, 124.3 (=C–H), 145.5, 145.6 (=C–N), 170.3 (C=O); DCI-MS 808 [M+H^+], 825 [M+NH_4^+].
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13. Selected analytical data for polyaminocarboxylic acids. *Compound* **4a**: ^1H NMR (500 MHz, DMSO-d_6) 3.41 (s, 8H, CH_2COOH), 3.99 (m, 5H, CH+CH_2), 4.47 (dd, 2H, CH_2, $^3J_{1H} = 6.7$ Hz, $^2J_{1H} = 14.5$ Hz), 4.59 (dd, 2H, CH_2, $^3J_{1H} = 4.8$ Hz, $^2J_{1H} = 14.5$ Hz), 8.02 (s, 2H, =CH); ^{13}C NMR (125 MHz, MeOD) 48.8, 49.0 (CH_2), 50.4 (CH), 53.2 (CH_2), 129.2 (=C–H), 136.2 (=C–N), 167.0 (C=O); IR (KBr, cm^{-1}) $\nu_{NH} = 3425$, $\nu_{C=O} = 1673$, 1661; ESI$^-$-MS 482 [M−H^+], 504 [M+Na^+−2H^+]; ESI$^-$-HMRS *m*/*z* calcd for $C_{17}H_{24}N_9O_8$: 482.1748; found, 482.1764 [M−H^+]. *Compound* **4b**: ^1H NMR (500 MHz, DMSO-d_6) 3.31 (s, 4H, CH_2COOH), 3.37 (s, 4H, CH_2COOH), 3.48 (m, 2H, CH_2), 3.86 (s, 2H, CH_2), 3.93 (s, 2H, CH_2), 4.91–4.99 (m, 2H, CH_2), 5.32 (m, 1H, CH), 7.67 (s, 1H, =CH), 8.01 (s, 1H, =CH); ^{13}C NMR (125 MHz, DMSO-d_6) 48.5, 48.7, 51.2, 54.9, 55.0 (CH_2), 59.5 (CH), 124.4, 124.9 (=C–H), 144.1; 144.5 (=C–N), 172.8, 173.0 (C=O); IR (KBr, cm^{-1}) $\nu_{NH} = 3425$; $\nu_{C=O} = 1673$, 1631; ESI$^-$-MS 482 [M−H^+], 504 [M+Na^+−2H^+]; ESI$^-$-HMRS *m*/*z* calcd for $C_{17}H_{24}N_9O_8$: 482.1748; found, 482.1751 [M−H^+].
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18. *Compound* **8b**: Yield: 61%, ^{1}H NMR (300 MHz, $CDCl_3$) 1.35 (m, 9H, CH_3), 3.59–3.68 (m, 14H, CH_2), 4.85 (m, 2H, CH_2), 5.23 (m, 1H, CH), 5.26 (m, 1H, NH), 7.01 (m, 4H, CH_{pyr}), 7.21 (s, 1H, =CH), 7.40 (m, 5H, =CH+CH_{pyr}), 7.52 (m, 4H, CH_{pyr}), 8.04 (m, 4H, CH_{pyr}); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3 (CH_3), 42.4, 48.1, 51.1, 59.4 (CH_2), 60.6 (CH), 80.2 ($C(CH_3)_3$), 122.0, 123.2, 136.1, 149.0 (CH_{pyr}), 124.2, 124.4 (=C–H), 144.3, 144.4 (=C–N), 156 (C=O), 158.9 (C_{pyr}); DCI-MS 716 [M+H^+], 733 [M + NH_4^+].
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21. *Compound* **9**: Yield: 65%, ^{1}H NMR (500 MHz, $CDCl_3$) 1.43 (m, 9H, CH_3), 3.95 (m, 2H, CH_2), 4.09 (d, $J = 17$ Hz, 2H, CH_2), 4.96–5.30 (m, 10H, CH_2), 5.49 (d, $J = 17$ Hz, 2H, CH_2), 5.73 (m, 1H, CH), 6.08 (m, 1H, NH), 7.20 (m, 4H, CH_{pyr}), 7.76–8.00 (m, 8H, CH_{pyr}), 8.65 (m, 4H, CH_{pyr}), 9.30 (s, 2H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) 28.4 (CH_3), 42.0, 51.8, 64.4, 64.6, 67.7–68.1 (CH_2), 61.6 (CH), 79.3 ($C(CH_3)_3$), 124.8–125.4, 140.2, 140.3, 150.5–150.8 (CH_{pyr}), 127.7, 128.4 (=C–H), 139.0, 138.9 (=C–N), 156.6 (C=O), 160.7–161.2 (C_{pyr}), 195.5–195.8 (CO); IR (KBr, cm^{-1}) $\nu_{NH} = 3411$; $\nu_{CO} = 2030$, 1908; $\nu_{C=O} = 1697$; ES^+-MS 628 [**9**−2Cl^-]$^{2+}$, 1254 [**9**−H^+−2Cl^-]$^+$, 1290 [**9**−Cl^-]$^+$.
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