Tetrahedron 66 (2010) 9475–9492

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 926

Application of copper(I)-catalysed azide/alkyne cycloaddition (CuAAC) 'click chemistry' in carbohydrate drug and neoglycopolymer synthesis

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ARTICLE INFO

Article history:
Received 17 September 2010
Available online 8 October 2010

Keywords:
Copper(I)-catalysed azide/alkyne cycloaddition
Click chemistry
Huisgen 1,3-dipolar cycloaddition
Carbohydrate bioactive compounds
Neoglycopolymers

Contents

1. Introduction

'Click chemistry' is a synthetic approach that uses the most practical and reliable chemical transformations, connecting two readily available reagents or building blocks to give products selectively in high yield. Its application has been explored in all aspects of drug discovery, ranging from lead finding through combinatorial chemistry and target-template in situ chemistry, to proteomics and DNA research using bioconjugation reactions.[1,2] The use of click chemistry in the discovery of new bioactive molecules provides a means for the fast exploration of chemical space, facilitating lead optimisation by structure–activity relationship (SAR) through the generation of analog libraries.[1,3] The application of click chemistry has also been extended to materials science and chemical biology including, respectively, the construction of polymeric structures[4] and biological probes for selective labelling of biomolecules either in cells or within living organisms.[5]

Click reactions can be divided into four different categories (Scheme 1): (i) cycloaddition of unsaturated species, such as 1,3-dipolar cycloaddition reactions and Diels–Alder transformations; (ii) nucleophilic substitution chemistry, involving ring-opening reactions of strained heterocyclic electrophiles, such as epoxides, aziridines and aziridinium and episulfonium ions; (iii) reactions involving non-aldol carbonyl group, such as formation of ureas, thioureas, oxime ethers, hydrazones, etc.; (iv) addition reactions to carbon–carbon multiple bonds, such as epoxidation, dihydroxylation, aziridination, sulfenyl halide addition and Michael additions

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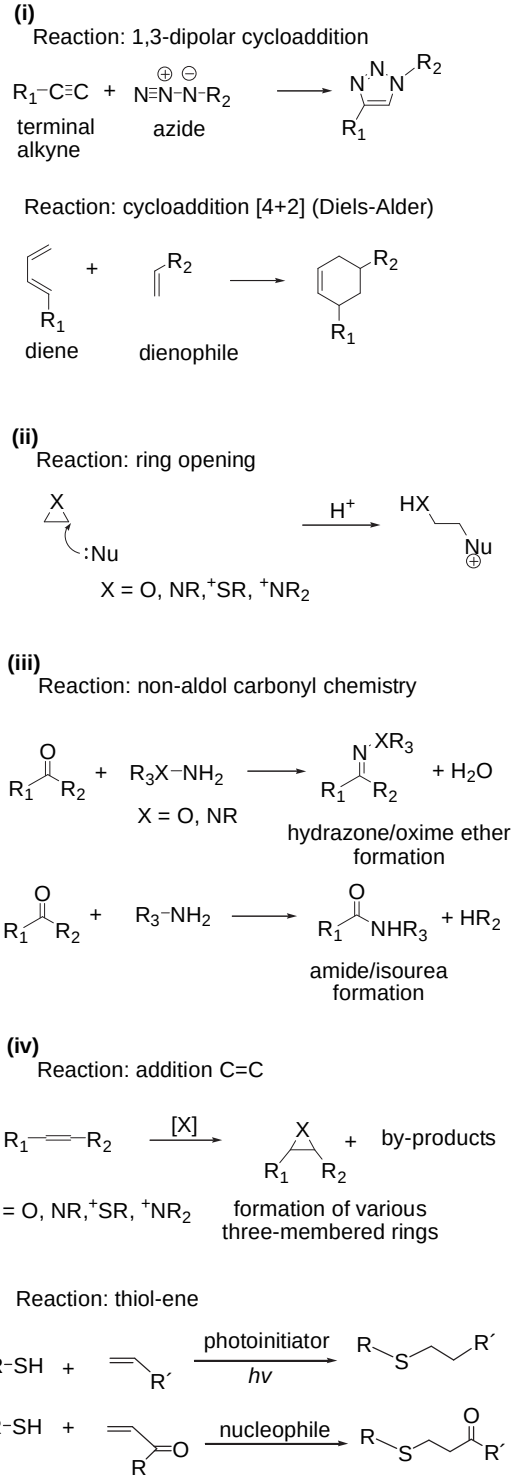
0040-4020/$ – see front matter
doi:10.1016/j.tet.2010.10.001

of Nu–H reactants, such as thiol-ene reactions (radical- or nucleophile-mediated), which have been useful for polymer synthesis under mild conditions.[1,6–8]

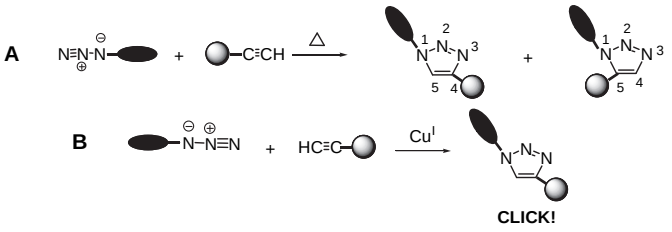


Scheme 1. Categories of click reactions. Nu: nucleophile.[7]

Reactions that utilise click chemistry are easily performed, fast, highly selective, insensitive to oxygen and water and can lead to great structural diversity in high yields. Moreover, the workup of these reactions is very simple and does not require excessive chromatographic purifications.[9] Among these reactions, the cycloadditions, particularly the Huisgen 1,3-dipolar cycloaddition[10,11] catalysed by Cu(I) involving carbon–heteroatom bond-forming processes, are the most extensively utilised.[12–17] The purpose of this review is to provide a general illustrative overview of the potential application of Cu(I)-catalysed 1,3-dipolar cycloaddition reactions in the synthesis of bioactive carbohydrates and neoglycopolymers.

2. 1,3-Dipolar cycloaddition reactions—'click chemistry'

The classical Huisgen pericyclic reaction, described over a period of 40 years, gives 1,2,3-triazoles as a mixture of 1,4- and 1,5-substituted regioisomers (Scheme 2).[10,11] Meldal and Sharpless have described, independently, however, the use of Cu(I) salts as catalysts for 1,3-dipolar cycloaddition reactions, which gave a new impetus to its use by several research groups, considering that it generates only the 1,4-triazolic isomer, being designated as 'copper-catalysed azide/alkyne cycloaddition' (CuAAC) (Scheme 2).[12,13] According to Sharpless et al.,[2] the CuAAC couplings of terminal alkynes and azides are characterized by a high thermodynamic force (>20 kcal/mol), which gives rise to highly modular and stereospecific reactions.



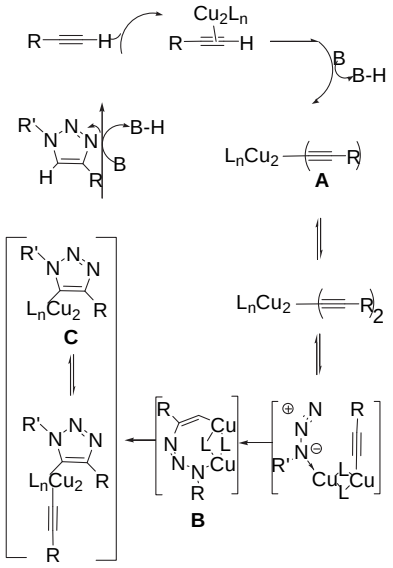
Scheme 2. (A) Generation of 1,4- and 1,5-disubstitued regioisomers using high-temperature reactions.[12] (B) Schematic representation of click chemistry reaction.[17]

Azides and alkynes are relatively straightforward to introduce into organic molecules and, in spite of their potential chemistries, they are also among the least reactive functional groups in organic chemistry.[13] This stability, being kinetic in origin, is responsible for the slow nature of the CuAAC reaction and the inertness of these functional groups towards biological systems. The Cu(I)-catalysed reaction is, however, dramatically accelerated (10^6-fold) and the advantages of the use of water as a solvent makes this reaction very attractive, since it is highly exothermic and can be controlled when performed on a large scale.[1,12] Furthermore, the use of protecting groups is not necessary and the quantitative and selective conversion into the 1,4-disubstituted 1,2,3-triazole product often eliminates the necessity for purification, allowing the direct utilisation of products in biological assays. Microwave irradiation considerably accelerates the CuAAC reaction, with completion achieved in minutes rather than hours required at room temperature.[13] The high tolerances towards several functional groups and reaction conditions are also relevant properties of CuAAC reactions. Recent studies have demonstrated the versatility of using a mixture of dichloromethane as solvent and water as co-solvent, due to the increased speed and yield.[9] Moreover, the use of dimethylformamide has also proved satisfactory in reactions involving azide or alkyne derivatives with different solubilities, e.g., linked to sugars.[18]

CuAAC-mediated synthesis of 1,2,3-triazoles has proved to be attractive in medicinal chemistry.[7,19] The physicochemical properties of the triazole group are particularly favourable in studies involving the discovery of new drugs, since the triazole unit acts as a rigid link, which places the carbon atoms linked to the 1,4 positions of the triazole at a distance of 5.0 Å (compared to the corresponding linkage in amides at 3.8 Å). In contrast to amides, the triazole group cannot be hydrolytically cleaved, oxidised or reduced. 1,4-Linked triazoles possess a high dipole moment and the nitrogen atoms at the 2 and 3 positions can act as weak hydrogen-bond acceptors.[20]

The source of Cu(I) salts commonly used involves the reduction of copper (II) sulfate by sodium ascorbate, although other conditions have been described, such as Cu(I) salts,[12] Cu(I) complexes,[21] stabilised derivatives of Cu(I)[22] and also copper wire.[23] The catalysis carried out by copper nanoclusters proved to be more effective than the corresponding reaction catalysed by copper powder or Cu(II) sulfate/sodium ascorbate, owing to the larger surface area. Recently, Sharpless et al.[24] demonstrated that Huisgen 1,3-dipolar cycloaddition reactions can be catalysed by ruthenium complexes, such as $Cp^*RuCl(PPh_3)_2$, but with opposite regioselectivity to that observed for Cu(I) salts—,i.e., 1,5-substituted triazoles are formed.

The mechanism of the azide/alkyne [3+2] dipolar cycloaddition reaction has been revised and includes bimolecular species, as illustrated in Scheme 3.[6,25] In this proposal, at least two copper atoms are involved in the reaction and, in particular, it is difficult to predict the structure of the Cu-acetylide **A**, because of the large number of possible interactions and also the several known Cu-acetylide structures.[26] Metallacycle **B** is rapidly formed from the complex **A** by the entry of an azide group into the cycle, followed by ring contraction to form a more stable intermediate, the copper triazolide **C**. Finally, the catalytic species is regenerated and the product 1,2,3-triazole is formed. The increase in the rate of the Cu (I)-catalysed reaction and the use of various co-solvents is mainly related to the formation of the Cu-acetylide complex, decrease of oxidation of the Cu(I) species and also to the prevention of side reactions of the acetylenes or dimerisation of the finally formed 1,4-triazole product.[26–28]

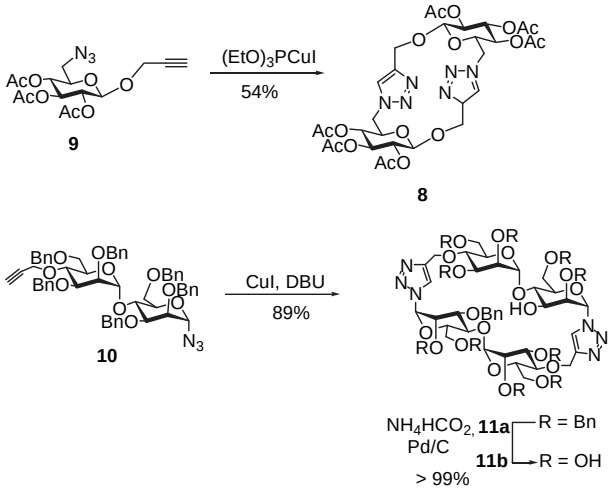


Scheme 3. Mechanism of bimolecular CuAAC reaction proposed by van Maarseveen et al.[25,28]

3. 'Click chemistry' and synthesis of carbohydrate derivatives

The CuAAC reaction finds extensive application in the preparation of carbohydrate derivatives and many examples can be found in the recent literature,[14,15] including the generation of *N*-glycosyl triazoles from simple acetylenes or derivatives containing the acetylenic function linked to sugars or amino acids, such as triazoles **1**,[29] **2**,[30] **3**,[31] **4**,[31] **5**,[32] **6**[33] and **7**[34] (Fig. 1).

In addition to glycosides, click reactions have been applied to the preparation of oligosaccharides, glyco-polycycles and macrocycles, glycopeptides, glyco-clusters and carbohydrates immobilised on plastic microtitre plates.[14] Moreover, multi-cyclic structures can be formed by Huisgen cyclisation reactions of monosaccharides or disaccharides containing azide/alkyne functions by intermolecular coupling, as illustrated for the synthesis of the cyclic dimer **8** from building block **9**,[35] and by the use of compound **10** in the development of novel cyclodextrin mimics **11a** and **11b** (Scheme 4).[36,37]



Scheme 4. Synthesis of cyclic carbohydrates, obtained by sequential cycloaddition reactions.

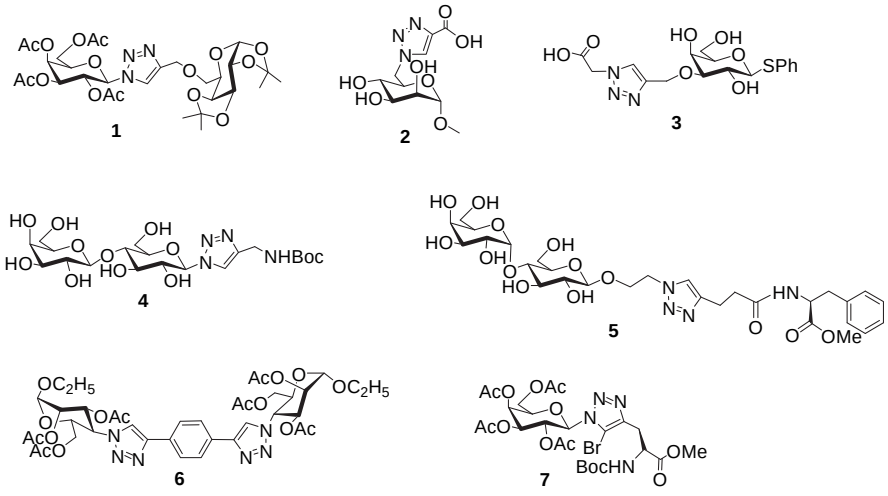


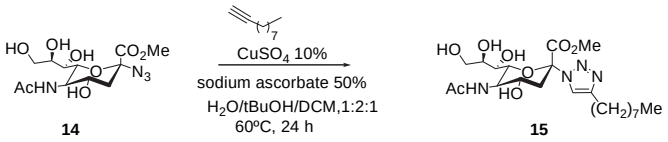
Fig. 1. Mimetic glycosides obtained by cycloaddition reaction between azide and alkyne derivatives.

This type of reaction has also been exploited in complexation with antibodies,[38] DNA conjugation[39] and sugar functionalisation for biological probes.[40] Therefore, it is possible to assert that CuAAC reactions do not replace existing synthetic methods as such, but open up new possibilities for the preparation of novel building blocks and polymeric materials that are capable of mimicking or representing pharmacophores.

4. 'Click chemistry' and carbohydrate drug discovery

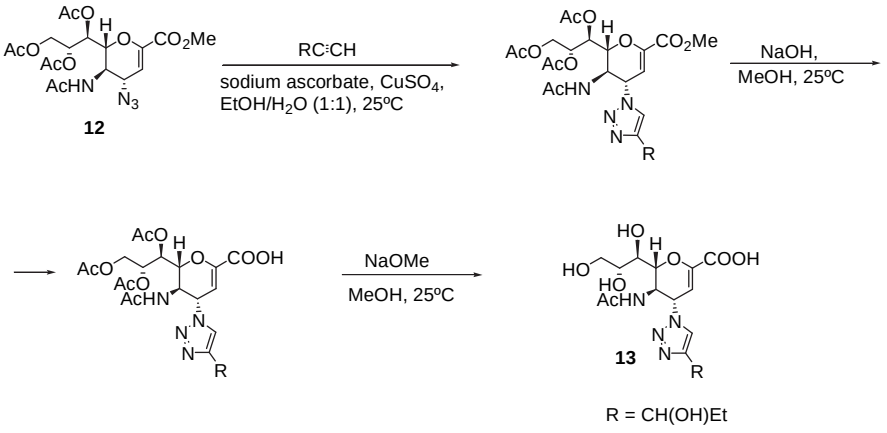
Click chemistry is finding wide application in the discovery and optimisation of lead compounds, as well as in the development of new drugs against various therapeutic targets. In one example, click chemistry reactions have been applied to the design of new neuraminidase inhibitors with the aim of obtaining more effective drugs for the treatment of avian influenza virus (AIV) infection.[41] Neuraminidase promotes the cleavage of the glycosidic bond of glycoproteins and glycolipids, with the release of terminal Neu5Ac (sialic acid) residues, facilitating the release of virion progeny and general mobility of the virus in the respiratory tract. Jiang et al.[42] synthesised a series of zanamivir analogues with different substituted triazoles, as shown in Scheme 5. Starting from a key intermediate containing an azide group **12**, it was possible to obtain a library of neuraminidase inhibitors; the highest antiviral activity was verified for compound **13** (IC_{50}=6.4 μM), which had comparable activity to zanamivir (IC_{50}=2.8 μM).

azide **14** and different terminal alkyne-containing molecules, as exemplified for compound **15** (IC_{50}=28 μM) (Scheme 6). In order to obtain inhibitors with increased affinity for neuraminidase, multivalent derivatives were prepared. A sialic acid disaccharide mimic **16** (IC_{50}=17 μM) was then first synthesised using the [3+2] dipolar azide/alkyne cycloaddition, followed by the synthesis of a model dendrimer of sialic acid **17** (IC_{50}=20 μM) (Fig. 2).



Scheme 6. Synthesis of the 1,2,3-triazole-linked sialic acid **15**.

Leishmania β-1,2-mannosyltransferase enzymes display a relevant role in the biosynthesis of β-1,2-mannan and/or mannose-containing surface glycoconjugates that are essential for intracellular survival of *Leishmania* amastigotes in macrophages.[30] Therefore, to explore the substrate specificity of *Leishmania* β-1,2-mannosyltransferases for further design of potential inhibitors, Williams et al.[30] prepared a library of modified substrates using the highly selective CuAAC reactions. Thus, it was possible to couple mannose derivatives containing either an alkyne **18** or azide **19** moiety to an



Scheme 5. Synthesis of zanamivir analogues by click chemistry.

More recently, non-hydrolysable 1,2,3-triazole-linked sialic acid derivatives were synthesised by Linhardt et al.[43] as potential neuraminidase inhibitors. Initially, a small library of 1,2,3-triazole-linked sialic acid was prepared by click reaction of α-sialic acid azide- or alkyne-based diversity set, respectively, to form 1,4-disubstituted 1,2,3-triazoles (Scheme 7).

The application of CuAAC-catalysed reactions for the synthesis of fucosyltransferase inhibitors was described by Wong et al.[44]

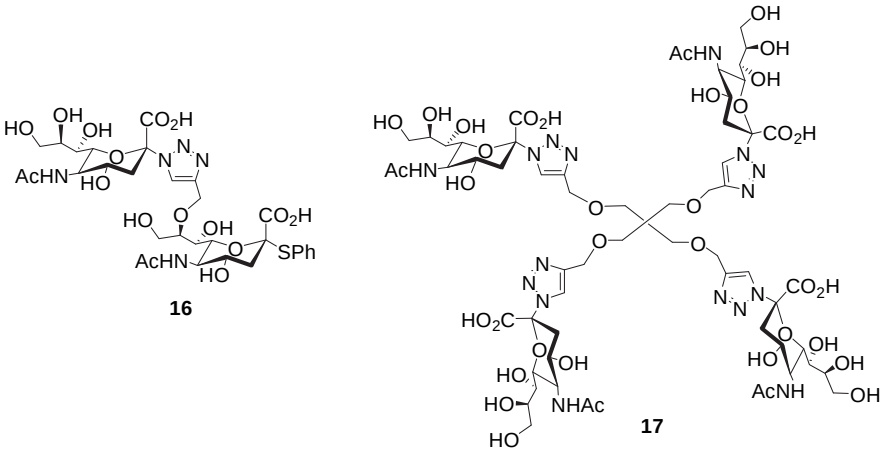
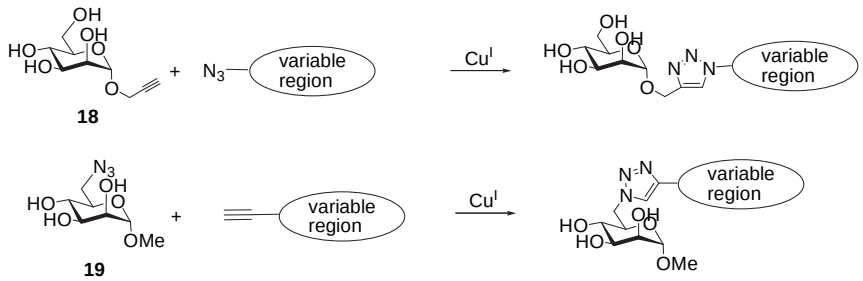
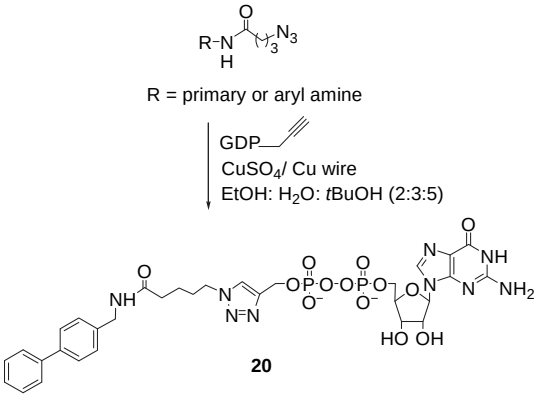


Fig. 2. Sialic acid disaccharide mimic **16** and dendrimer of sialic acid **17** as neuraminidase inhibitors.



Scheme 7. Synthesis of mannose derivatives by click chemistry reactions.

Fucosyltransferases (FucT) catalyse the transfer of L-fucose from guanosine diphosphate β-L-fucose (GDP-fucose) to the corresponding glycoconjugate acceptor and are essential for the biosynthesis of important fucosylated oligosaccharides involved in various physiological and pathological processes. Thus, 85 triazole compounds were synthesised using Cu(I)-catalysed reaction conditions; each azide molecule was linked to the GDP-alkyne core, as exemplified for compound **20**, which showed the highest affinity for α-1,3-fucosyltransferase VI (IC_{50}=0.15 μM) (Scheme 8).[44]



Scheme 8. Synthesis of α-1,3-fucosyltransferase VI inhibitor **20** by Cu(I) conditions.

1,2,3-Triazole glycosides prepared by 'click chemistry' have been tested as glucosidase inhibitors. As an example, derivatives of acarbose, a current anti-glucosidase drug to treat diabetes, have been prepared (Fig. 3).[45] Although the triazole derivatives **21** and **22** showed weak inhibition towards a series of glucosidases, this methodology is being explored for the preparation of more active derivatives. Similar results were observed for 1-glycosyl-4-phenyl

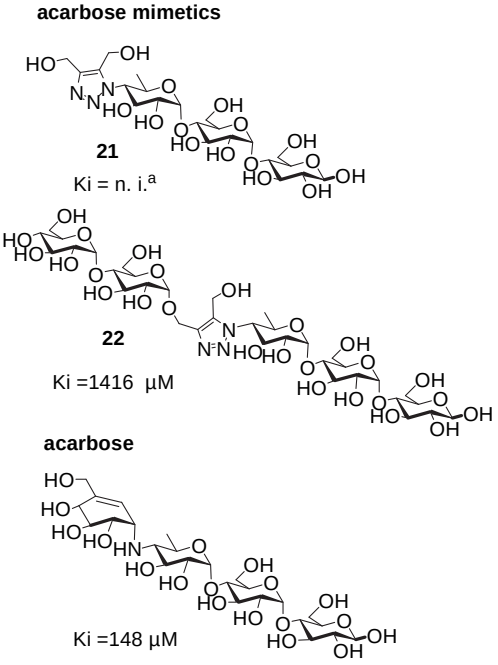
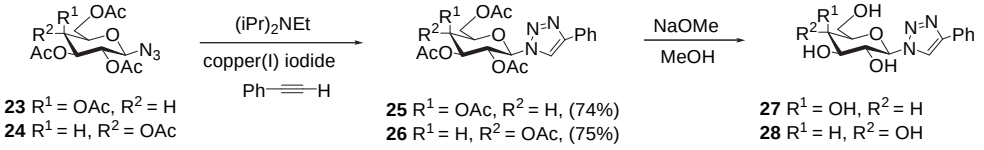


Fig. 3. Oligosaccharide triazole mimetics, designed from acarbose, and their inhibitory activity against α-glucosidase. [a]No inhibition detected.

CuAAC reactions were recently applied by Field et al.[47] to assemble a library of 21 α-D- and β-D-glucopyranosyl triazoles, which were evaluated as potential glycosidase inhibitors. Click reactions between β-D-glucopyranosyl azide **29** and the corresponding α isomer **30** with selected alkynes, under reaction conditions involving



Scheme 9. Synthesis of glycosyl triazoles via copper-catalysed [3+2] cycloaddition, as glucosidase inhibitors.

triazoles **25** and **26**, obtained by CuAAC of glycosyl-azides **23** and **24** with phenylacetylene (Scheme 9), when tested against sweet almond glucosidase (SAG).[46] These compounds were then deacetylated and the products **27** and **28** were tested against β-glycosidases, such as *Escherichia coli* galactosidase (ECG) and bovine liver galactosidase (BLG). The results were compared with the known glycosidase inhibitors, deoxygalactonojirimycin (DNJGal) and deoxynojirimycin (DNJGluco), but only weak inhibition was observed for compounds **27** (30%) and **28** (48%) against, respectively, ECG and BLG glycosidases (Table 1).[46]

Table 1
Inhibition of glycosidases by triazoles[46]

Compound[a]	Enzyme		
	SAG (%)	ECG (%)	BLG (%)
27	<20	30±11	<20
28	<20	<20	48±11
DNJGal	<20	91±1	<20
DNJGluco	50±8	<20	<20

[a] All compounds were screened at the concentration of 0.24 mM.

the use of the catalytic system $CuSO_4$/NaAsc (normal heating or microwave irradiation at 70 °C), afforded the compounds **31a**–**37a**/**31b**–**37b** in very high yields (88–99%), as shown in Fig. 4. In addition, the catalytic system $CuSO_4$/Cu turnings (room temperature) was applied to click reactions between β-D-glucopyranosyl azide **29** and other alkynes, with the resultant compounds **38**–**44** obtained in reasonable-to-high yields (28–92%).[47] Different reactivities of α- and β-glucopyranosyl azides under CuAAC conditions were observed in this study, emphasising the impact of glycosyl azide anomeric configuration on the rate of CuAAC reactions. While reactions with β-glucopyranosyl azide were typically complete in 10–45 min, similar reactions with α-glucopyranosyl azide often required 45–120 min. This difference was further investigated using competition reactions and rationalised on the basis of X-ray crystallographic data,[48] which revealed significant differences in bond lengths within the azido groups of the α- and β-anomers.

The synthesis of novel glucosidase inhibitors containing a 1-deoxynojirimycin (DNJ) core has been achieved by *N*-alkylation of DNJ followed by a Huisgen cycloaddition reaction (Fig. 5). The glycosidases inhibitors were efficiently prepared (Fig. 6). These compounds were submitted to inhibition assays against several glycosidases. The results indicate that, in some cases, it is possible to modulate the potency and the selectivity towards different glycosidases (Table 2).

A small library of non-hydrolysable 1,4-disubstituted 1,2,3-triazole galactosides was also recently synthesised by Carvalho et al.[51] as potential inhibitors of *Trypanosoma cruzi trans*-sialidase (TcTS), which plays a key role in the recognition and invasion of

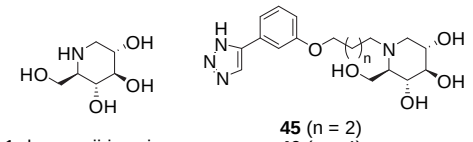


Fig. 5. Structures of DNJ and hybrids **45**, **46** and **47**.

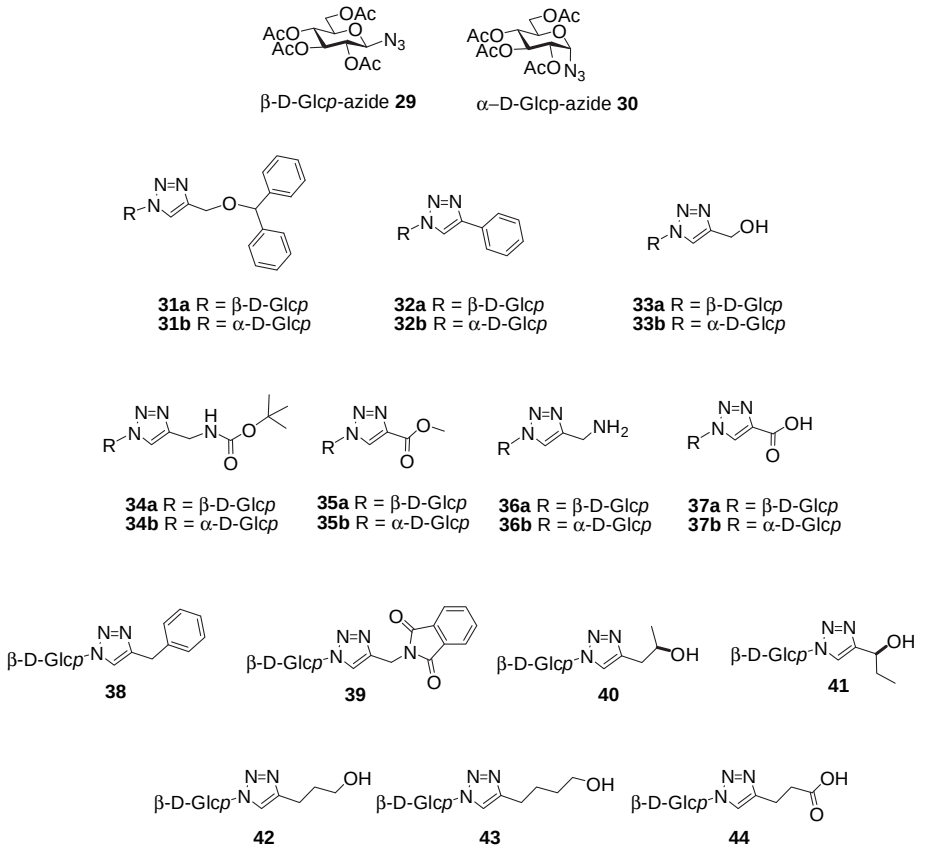


Fig. 4. Structures of glucopyranosyl triazoles as potential glycosidase inhibitors.

resulting novel compounds were evaluated for their α-glucosidase inhibitory activity, with compound **47** (IC_{50}=1.15 μM) being more active than DNJ (IC_{50}=1.67 μM), in spite of compounds **45** (IC_{50}=6.07 μM) and **46** (IC_{50}=2.41 μM) being less potent than DNJ. The activity shown by compound **47** indicates that the *N*-substituent may make favourable interactions in the active site of the glucosidase enzyme.[49]

Recently, Diot et al.[50] reported the synthesis of multivalent iminosugars from a click chemistry reaction between oligoethylene scaffolds and *N*-substituted DNJ derivatives. Thus, mono-(**48**, **49**), di-(**50**, **51**) and tri-valent derivatives **52** of the DNJ-based host cells and in enabling the parasite to escape from the human immune response. Galactose derivatives containing an azide group at the C-6 (**53**) or C-1 (**54**) positions were coupled to a panel of 23 structurally diverse terminal alkynes (**55**–**77**) using the copper(I)-catalysed alkyne-azide cycloaddition (CuAAC) reaction under microwave irradiation,[1,15,16,52] thus generating 46 disubstituted triazoles represented by **78**–**100c**/**d** in good-to-excellent yield and with complete regioselectivity (Scheme 10). The obtained triazole-galactosides were subsequently submitted to inhibition assays of TcTS and to in vitro trypanocidal activity against trypomastigote forms of *T. cruzi* Y strain. The strongest

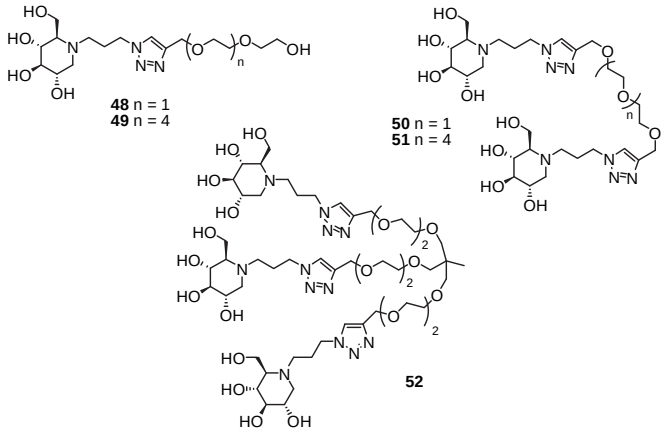


Fig. 6. Structures of synthetic iminosugars.

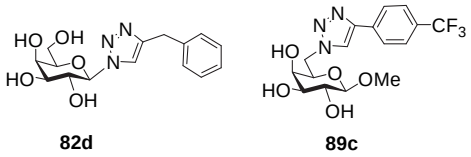


Fig. 7. Galactose derivatives that showed highest TcTS inhibition and trypanocidal activity.

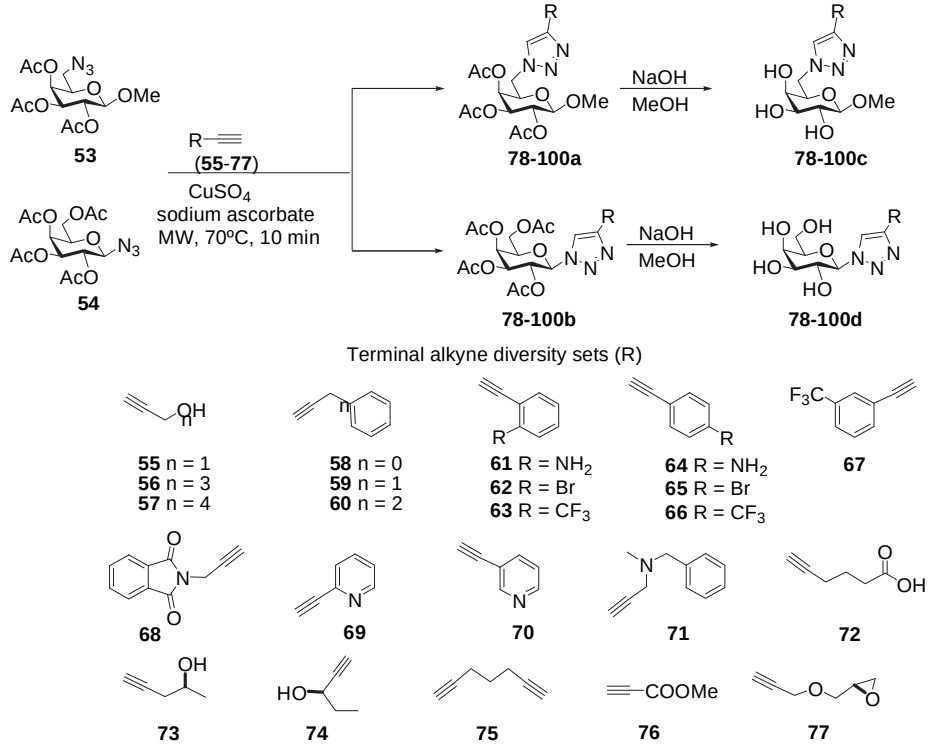
In the search for effective antagonists of selectins, a family of cell adhesion molecules that play a key role in the early inflammatory response, Ernst et al.[53] developed a series of E-selectin antagonists derived from Huisgen 1,3-dipolar cycloadditions. The antagonist synthesis was conducted based on the terminal tetrasaccharide epitope, sialyl Lewis^x (1, sLe^x),[54,55] present in physiological selectin ligands and thus considered as a lead structure. Therefore, an sLe^x derivative **101**, containing a residue of (*S*)-isoserine in place of the Neu5Ac sugar, was first prepared, followed by conversion of amine group of **101** into azide **102**, which was then reacted with different commercially available alkynes by click reactions (Scheme 11). Unexpectedly, azide **102** and the unsubstituted triazole **103** showed the best

Table 2
Glycosidase inhibitory activities (K_i, μM) for DNJ and synthetic iminosugars **48**–**52** obtained by 'click chemistry'[a]

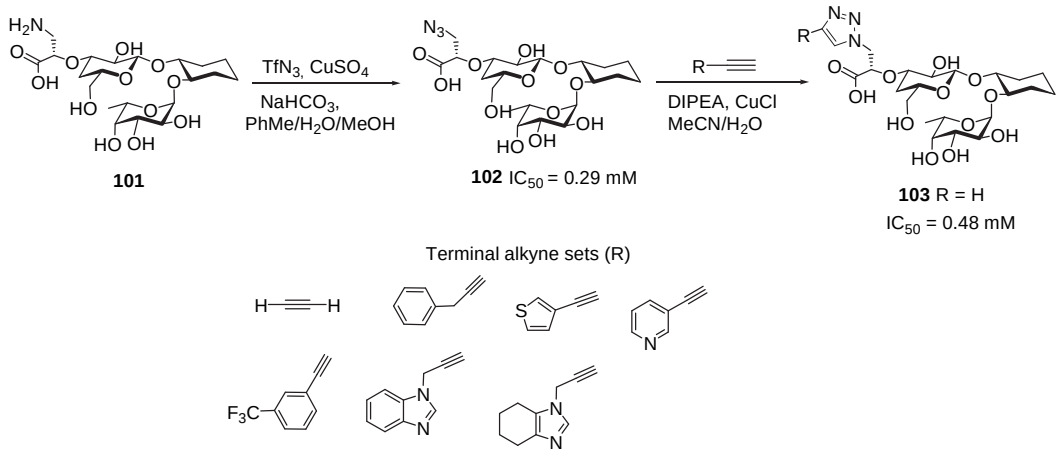
Enzyme	DNJ	**48**	**49**	**50**	**51**	**52**
β-galactosidase (bovine liver)	42	950±20	n.i.	n.i.	760±10	790±10
α-galactosidase (green coffee beans)	—	120±5	95±5	215±5	105±5	225±5
β-glucosidase (almonds, pH 7.3)	47	47±2	100±5	70±2	70±2	400±10
α-glucosidase (bakers' yeast)	25	n.i.	n.i.	n.i.	n.i.	n.i.
β-mannosidase (*Helix pomatia*)	—	n.i.	n.i.	n.i.	772±10	n.i.
α-mannosidase (Jack bean)	270	230±10	265±10	120±5	90±3	35±2
isomaltase	11	1050±20	480±15	n.i.	770±15	1440±20
naringinase (*Penicillium decumbens*)	—	80±3	95±5	60±3	55±2	75±3
amyloglucosidase (Aspergillus niger)	2.1	28±1	30±2	17±1	20±2	11±1

[a] n.i.=no inhibition at 2 mM.

TcTS inhibition (37%), at 1 mM concentration, was verified for compound **82d**, while compound **89c** showed the best trypanocidal activity at four different concentrations (0.1–1.0 mM), with an IC_{50} of 0.18 mM (Fig. 7).



Scheme 10. Synthesis of library of 1,2,3-triazole-galactosides obtained from 1,3-dipolar cycloaddition reactions as potential TcTS inhibitors.



Scheme 11. Synthesis of E-selectin antagonists derived from Huisgen 1,3-dipolar cycloadditions.

affinities for E-selectin among the obtained triazoles, with IC_{50}s of 0.29 and 0.48 mM, respectively.

5. 'Click chemistry' and the development of neoglycopolymers

The preparation of polyfunctional macromolecules requires the use of highly efficient and selective reactions in order to obtain specific products in high yield. Although the synthesis of macromolecules can be performed by conventional organic chemistry, the fully functionalised products are isolated in low yields from laborious purification procedures. The reasons depend on the type of polymer, but typically are related to steric hindrance, 'random coil' conformation and large solubility changes.[6] On the other hand, 'click chemistry' reactions have been widely applied to the synthesis of biopolymers of great structural diversity by a combination of polymeric and biological materials through a triazole bridge, involving the coupling of azide and alkyne-containing molecules, such as nucleic acids, peptides, sugars, proteins or viruses and cells (Fig. 8).[56] Therefore, this is a robust synthetic approach with wide application in industry of polymeric materials and in the identification of biological systems, such as proteins and nucleotides.[6]

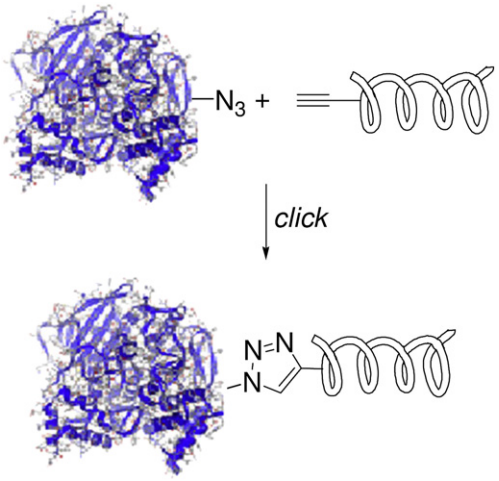
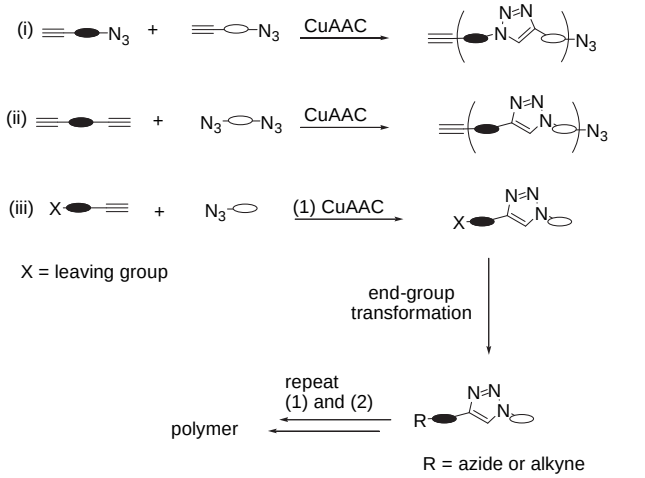


Fig. 8. Synthesis of biomolecular structures by click chemistry.[56]

The application of CuAAC reactions can produce polymeric materials with different formats and macromolecular architectures, the integrity of which depends upon the triazole group. These materials can be represented by linear polymers, dendrimers, polymer networks or polymeric nanoparticles, amongst others.[57] In fact, the development of this synthetic strategy has been explored by several researchers to accelerate and increase the efficiency and versatility of the synthesis of traditional and novel polymers, since it does not compromise the environment, e.g., using routes with fewer reactions and purification steps that provide satisfactorily the desired products.[6]

Basically, there are two fundamental approaches in the synthesis of polymeric materials comprising the *construction*, involving the coupling of building blocks, or *modification* of polymeric materials by the addition or removal of existing functional groups in polymers in order to modify and introduce new properties (Scheme 12). Thus, most CuAAC reactions used in the synthesis of materials involve the modification of polymers, dendrimers, nanoparticles, viruses, among others. On the other hand, the construction of polymers with large chemical diversity depends on the availability of polyfunctionalised building blocks, so that the formation of these blocks needs to include azide and terminal alkyne groups into simpler molecules. It is worth noting that some reactions can be classified as both construction and modification, since the addition of a polymer containing a terminal alkyne group to another polymer derivatised with an azide group in a side chain, obtained by the modification reaction, can generate or lead to the construction of more complex copolymers.[57]

Finn et al.[58] have described the construction of linear polymers and oligomers by 'click chemistry', coupling a bis-azide with a bis-



Scheme 12. Schematic representation of linear polymer construction using CuAAC: (i) addition-type polymerisation of AB; (ii) AA or BB and (iii) iterative CuAAC/end-group transformation reactions.

alkyne in the presence of Cu(I), for the generation of soluble polymers with adhesive properties.[57] As an example, compound **104** (Fig. 9) has copper adhesion properties due to the formation of networked triazoles.[58] Based on the correlation between thermoreversible organogelling properties with the partial permanence of Cu ions from the catalyst in the polymer matrix, Ravelo et al.[59] described the polymer **105** (Fig. 9), which has selective gelation properties (i.e., forms organogels) in DMSO or DMSO/organic solvent (e.g., toluene, chlorobenzene, ethyl acetate, *N*,*N*-dimethylformamide) mixtures containing at least 80% v/v DMSO.

110, which was obtained from multiple fluorinated alkyne building blocks (Fig. 9). They presented small polydispersity, good solubility and thermal stability, which can make them attractive candidates for linear polymers.[64]

Aucagne and Leigh[65] explored the use of 'click–click chemistry' in the synthesis of peptide analogues; this methodology involves one-pot CuAAC combined with Ag(I)-catalysed TMS-alkyne deprotection (Scheme 13). Thus, after the first coupling of a free terminal acetylene group with the free azide in the presence of Cu(I), the product was treated with silver(I) salts for deprotection of the TMS-alkyne func-

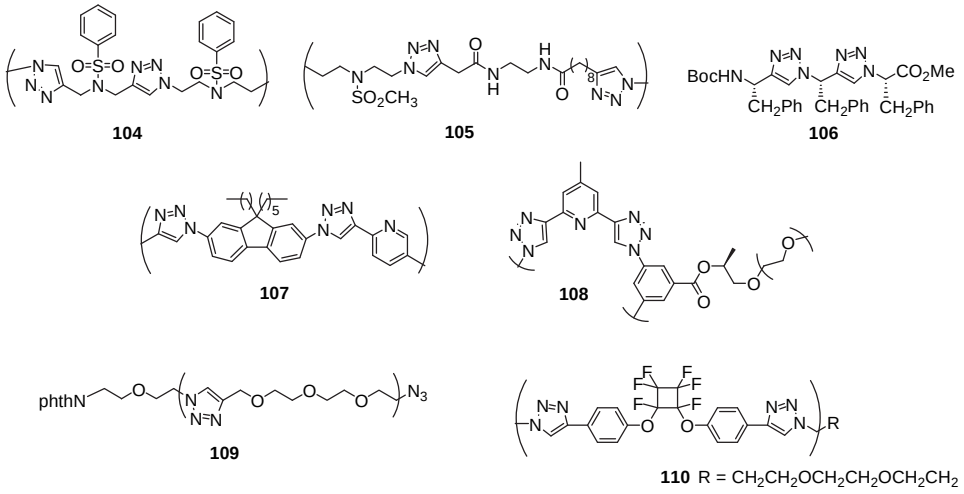
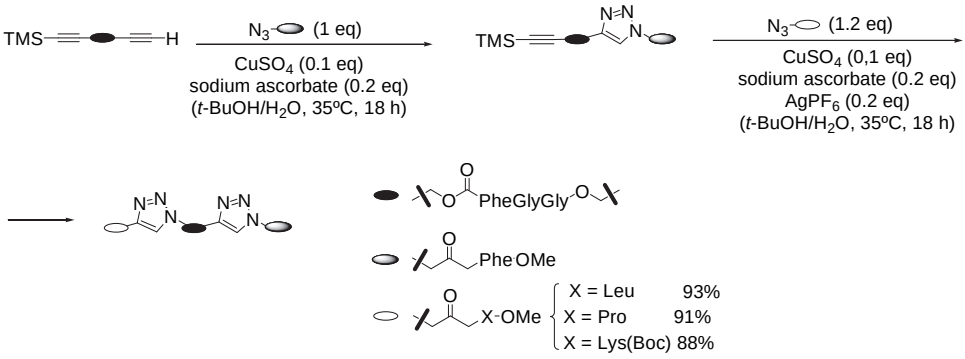


Fig. 9. Representative structures of linear polymers constructed by CuAAC connection of small- molecule building blocks.

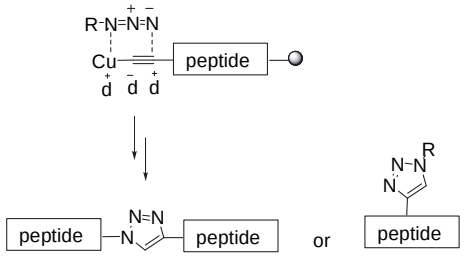


Scheme 13. Construction of trifunctional oligomers via CuAAC and Ag(I)-catalysed deprotection of terminal alkyne.

Arora and Angelo[60] described the synthesis of peptidomimetics, such as compound **106**, in which the amide bond is replaced by triazole rings, from a click reaction between functionalised amino acids. NMR studies suggest that these oligomers adopt zigzag conformations, obtained from dipole–dipole interactions between adjacent triazole rings. The polymer **107** has interesting luminescent properties; in addition, bipyridine type ligands are incorporated into the polymer, allowing the preparation of transition–metal complexes.[61] Meudtner and Hecht[62] reported the preparation of the polymer **108**, a 2,6-bis(1,2,3-triazol-4-yl)pyridine scaffold, which was able to adopt a helical conformation in several solvents, as confirmed by circular dichroism (CD) spectroscopy. The solution of this polymer in the presence of several transition-metal ions, such as Zn^{2+}, Fe^{2+}, or Eu^{3+}, resulted in coordinative crosslinking and formation of gels. Additionally, the use of functionalised triethylene glycol (TEG) blocks as a linker with defined chain length containing functionalised azide and alkyne end groups, in a CuAAC reaction, gave compound **109**.[63] Another interesting example of CuAAC is the synthesis of a fluoro-polymer

tion and a new azide derivative was added for a new coupling, generating copolymers from three different building blocks.

The potential application of peptidotriazoles in studies of cellular recognition to mimic natural peptides was also investigated by the coupling of peptides containing terminal alkyne or azide groups with different amino acid sequences via copper(I)-catalysed 1,3-dipolar cycloadditions, as exemplified in Scheme 14.[12]



Scheme 14. CuAAC reaction generating triazole-peptide or *N*-substituted histidine analogues.

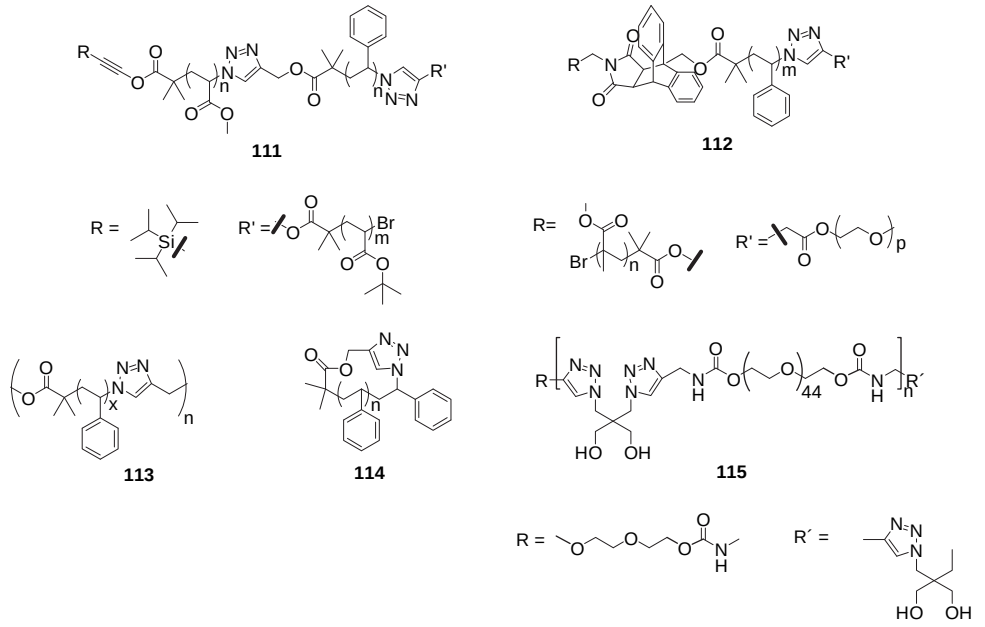


Fig. 10. Linear polymeric structures prepared by CuAAC connection of polymeric building blocks.

'Click chemistry' can be extended to the preparation of linear macromolecules of high molecular weight. In this way, polymeric building blocks containing terminal acetylene or azide functional groups have been prepared via atom transfer radical polymerisation (ATRP) and employed in the modular synthesis of block copolymers via 1,3-dipolar cycloaddition reactions. The work described by Opsteen and van Hest[66] illustrates this approach, using a variety of polystyrene (PS), poly(methyl methacrylate) (PMMA) and poly (ethylene glycol) (PEG) copolymer blocks in CuAAC reactions. Recently, these authors have reported the use of triisopropylsilyl (TIPS)-protected acetylene end groups to prepare heterobifunctional polymers by ATRP reactions (compound **111**, Fig. 10).[67] Thus, the extensive application of this reaction[68] is shown by the synthesis of the copolymer **112**, PEG-PS-PMMA (ABC triblock), which was obtained in a one-pot reaction combining in situ 1,3-dipolar cycloaddition [3+2] and Diels–Alder [4+2] reactions.[57] Other examples of PS copolymers prepared via ATRP are presented in Fig. 10, such as telechelic polymers **113**[69] and cyclic styrenic polymer **114**.[70]Moreover, Wang et al.[71] reported an interesting synthesis of a linear multifunctional polymer PEG **115** by CuAAC.

Fig. 11. Triazole-linked glycopeptide vaccines derived from click chemistry reactions between alkyne and azide groups.

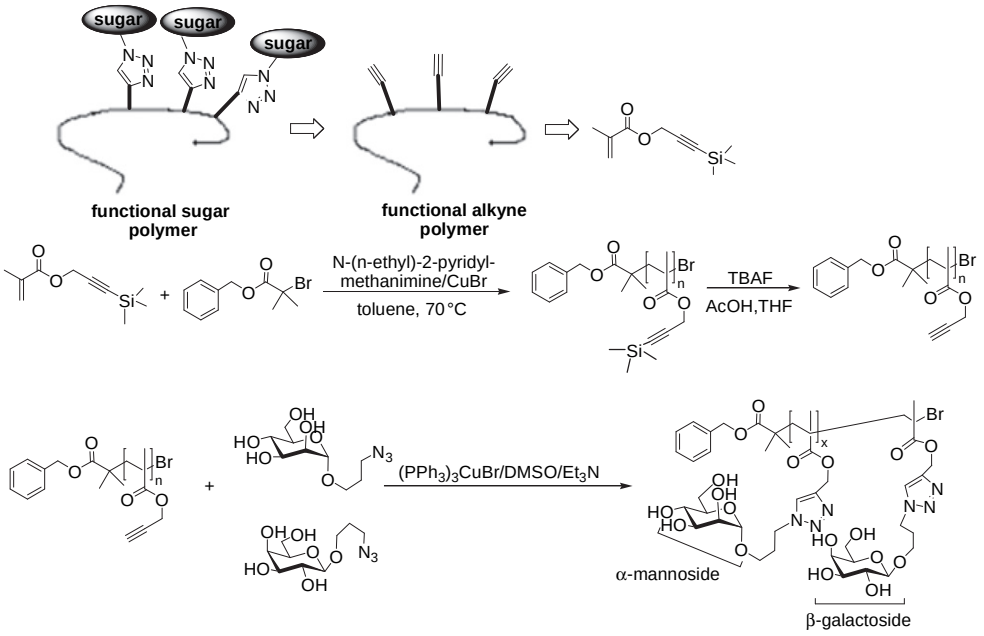


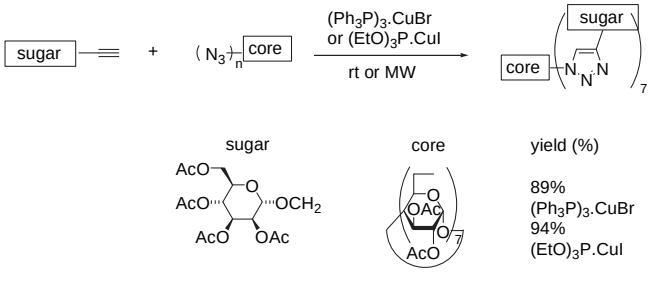
Fig. 12. Retrosynthetic approach to side chain carbohydrate functional polymers and synthesis of glycopolymers.

With regard to triazole-linked glycopeptides and glycosyl amino acids, several examples are described in the literature and their preparations generally involve the coupling of glycosyl-azides or glycosyl-alkynes to the corresponding alkyne- or azide-amino acids, respectively. The synthesis of potential anti-cancer vaccines, such as compounds **116**–**118**, exemplifies this approach, which employs the coupling of pentynoic acid amides of peptide-based lysine side chains with glycosyl amino acids containing an azide function (Fig. 11).[72]

Several glycopolymers with a well-defined macromolecular structure, such as chain length and branching, have been prepared by 'click chemistry' with the inclusion of sugars in a multivalent arrangement to mimic or increase the binding efficiency of natural carbohydrate interactions to biological targets.[73–79] Considering that glycoconjugates are information-rich molecules, an increasing number of known lectins are able to recognise slight variations of oligosaccharide structures and act as decoders for carbohydrate-encoded information. The synthesis of glycopolymers can be justified by the fact that monomers often have weak interactions with protein receptors and thus only produce a weak response to in vivo events mediated by carbohydrate–protein binding. The higher-order oligomeric structures of proteins and carbohydrates in nature, presenting multiple binding sites, act as polydentate donors, which help to circumvent the intrinsically weak binding limitations related to the use of monovalent ligands.[80] The enhancement in activity that can be achieved with appropriate synthetic multivalent polymers, as compared to the corresponding monovalent ligands, is known as the 'glycoside-cluster effect'.[81]

Although the use of controlled radical polymerisation reactions of monomers is often exploited to obtain glycopolymers, there are some difficulties inherent to this method, such as the synthesis of the necessary monosaccharides, the compatibility of these highly functionalised monomers with the radical polymerisation conditions and, in some cases, the subsequent deprotection reaction of the carbohydrate functional groups.[82–85] Therefore, the Cu(I)-catalysed Huisgen 1,3-dipolar cycloaddition reaction is an attractive alternative method for the synthesis of new glycopolymers, as the reaction conditions are compatible with unprotected sugars containing an azide and alkyne function.[86] Owing to its high specificity, this reaction can be performed under biological conditions where both organic azides and alkynes are essentially inert. A simple and efficient synthetic route to glycopolymers, containing different protected and unprotected carbohydrates, was described by Haddleton et al.,[73] through coupling of the azide present in the C-6 or anomeric (α and β) positions with the functional alkyne polymer by a Cu(I)-catalysed reaction, and transition-metal-mediated ATRP.[87,88] Applying these strategies, it was possible to prepare a library of glycopolymers with the same size and structural architecture, but with differences in the nature of the sugars added to the polymer framework (Fig. 12).[73] A recent review describing the enormous interest in the combination of reactions involving click chemistry with radical-polymerisation processes was published by Binder and Sachsenhofer.[26]

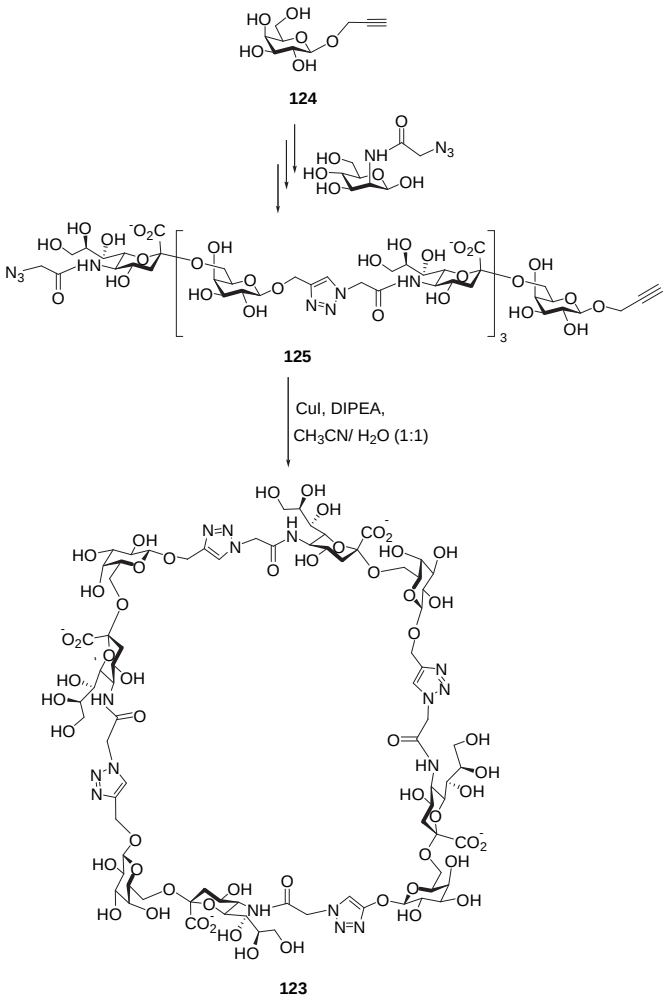
An interesting application of 'click chemistry' in the preparation of potentially active neoglycoconjugates in events involving cellular recognition was described by Santoyo-González et al.[21] From the coupling of carbohydrate derivatives containing azide or acetylene functions, in the presence of a Cu(I) catalyst, it was possible to generate carbohydrate mimics in high yield and with regiochemical control. As an example, a CuAAC reaction, under microwave irradiation, of propargyl mannose (sugar) and per-(C-6)-azide β-cyclodextrin (core) in the presence of $(Ph_3P)_3{\cdot}CuBr$ or $(EtO)_3P.CuI$ afforded the corresponding branched β-cyclodextrin in high yields. (Scheme 15).[21]



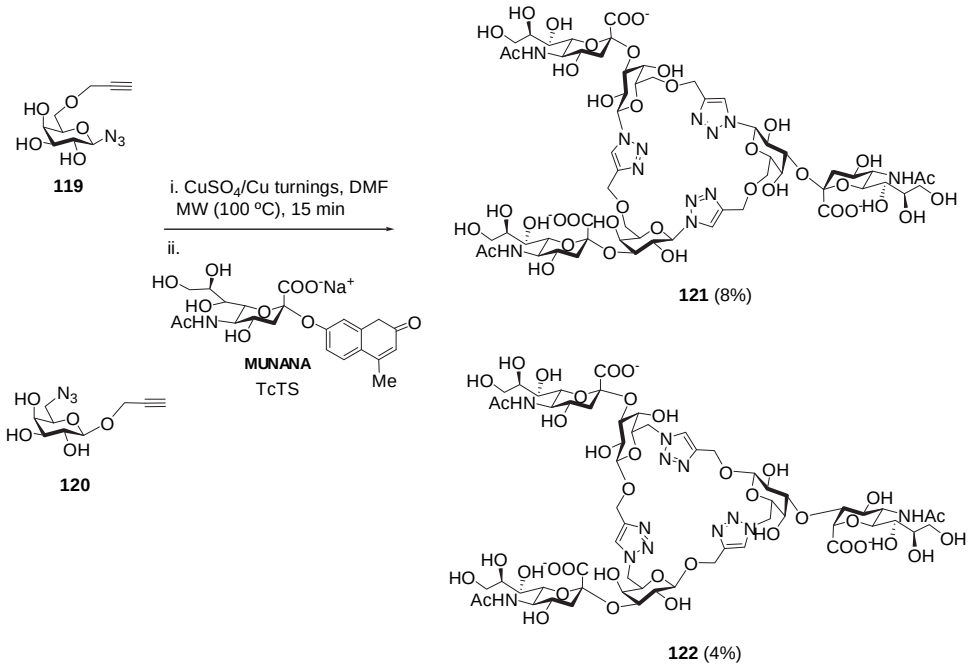
Scheme 15. Synthesis of multivalent neoglycoconjugates.

The cyclooligomerisation reactions of bifunctional galactose monomers bearing azido and propargyl groups, using Cu(I)-assisted azido/alkyne 1,3-dipolar cycloaddition, were recently investigated by Campo et al.[89] with the aim of obtaining new cyclic *pseudo*-oligosaccharides that can be used for the study of *T. cruzi trans*-sialidase activity and in the search for potential inhibitors of this enzyme. CuAAC reactions from building blocks **119** and **120** in DMF, utilising $CuSO_4$/Cu turnings as a catalytic system, afforded a series of macrocycles with two to five repeating units (Scheme 16). The obtained glycomacrocycles were subsequently submitted to enzymatic assays with TcTS, in the presence of MUNANA as a sialic acid-donor substrate, to give the corresponding sialylated products, as illustrated for compounds **121** and **122** in Scheme 16. A different approach involving the synthesis of size-defined sialic acid-containing macrocycles, such as **123** (Scheme 17), was described by Chen et al.[90] In this case, starting from 2-propynyl-β-D-galactopyranose **124**, it was possible to obtain the intermediate **125**, a sialic acid-containing acyclic oligosaccharide comprising azide and alkyne groups at two termini, through chemoenzymatic synthesis. Subsequently, the coupling of **125** under Cu(I)-catalysed 1,3-dipolar cycloaddition condition afforded the macrocycle **123**.

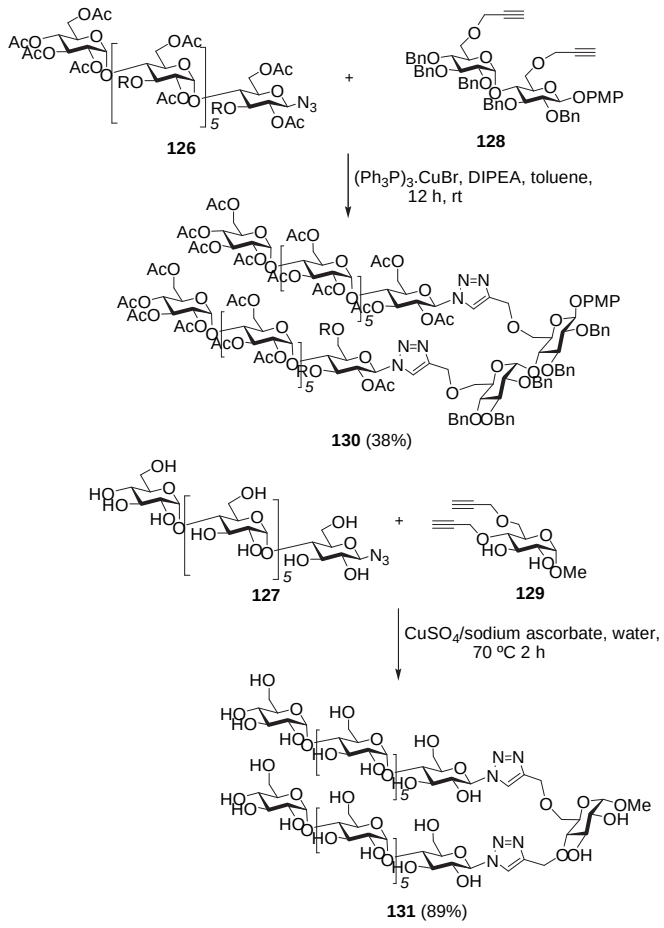
The synthesis of starch fragment analogues using click chemistry was performed by Field et al.,[91,92] taking into consideration that the knowledge of structural features of starch fragments is crucial for understanding the biosynthesis of starch components and their assembly into the starch granules. Synthetic α-(1→4)-glucans incorporating α-(1→6)-branch points have been suggested as models of starch, which are useful tools for physicochemical and biochemical studies. Thus, hexadecasaccharide mimics containing two parallel maltoheptaosyl chains linked via 1,2,3-triazoles to a maltose or glucose core were synthesised using Cu(I)-catalysed [3+2] dipolar cycloaddition of azido saccharides **126** or **127** with the corresponding 6,6′-dipropargylated *p*-methoxyphenyl maltoside **128** or 4,6-di-*O*-propargylated methyl α-D-glucopyranoside **129**, affording compounds **130** (38%) and **131** (89%), respectively (Scheme 18).[91,92] According to the obtained results, the click reaction for the synthesis of **131**, carried out from *O*-deprotected **127** and **129** using the catalytic system $CuSO_4$/sodium ascorbate (70 °C),



Scheme 17. Chemoenzymatic synthesis of sialic acid-containing macrocyclic oligosaccharides.



Scheme 16. Synthesis of glycomacrocycles by click chemistry from building blocks **119** and **120**.



Scheme 18. Synthesis of bis-maltoheptaosides **130** and **131** as starch fragment mimics.

proved to be more effective than the synthesis of **130**, which was performed from *O*-protected **126** and **128** utilising $(Ph_3P)_3{\cdot}CuBr$ (room temperature) as catalyst.

For several years, click chemistry has been employed in the synthesis of dendrimers. Such syntheses require extremely efficient reactions for each interactive step of the coupling process to ensure quantitative conversion of precursors, which have a number of functionalisations that increases geometrically as the dendrimer is constructed. Hawker et al.[93] explored CuAAC in a chemoselective approach to prepare multivalent bifunctional dendrimers that would be virtually inaccessible by the use of conventional methods. Thus, the compound **132**, containing 16 mannose residues and two fluorescent coumarin units, connected by triazole rings, showed extremely potent activity in hemagglutination tests when compared with the monomeric structure of mannose (Fig. 13).

An interesting application of CuAAC recently described by Sumerlin and Vogt[8] involves the functionalisation of biological substrates, such as virus particles or enzymes, with small molecules. This approach was also extended to the attachment of polymers to several biological macromolecules. It is exemplified by the coupling of an alkyne-terminated polymer to an azido-functionalised protein and by the conjugation of azide-terminated polystyrene to alkyne-functionalised proteins to form vast amphiphiles that self-assemble in water (Scheme 19).

Recently, the monitoring of biomolecules in a physiological environment, such as time-lapse imaging of cell-surface glycans in live cells, has been achieved by bioorthogonal 'click chemistry' strategies. In contrast to proteins, which normally require a genetically GFP (green fluorescent protein) encoded tag, the labelling of glycans is much more challenging, considering their specificity, structural diversity and post-translational modification. Thus, to label glycans in cells or living organisms for dynamic in vivo imaging, Bertozzi et al.[94] have demonstrated the use of the metabolic pathway to include a bioorthogonal azide group in an unnatural substrate, such as the azide-bearing ManNAc analogue (ManNAz), into a target glycoconjugate on the cell-surface, to detect the modified sialic acid

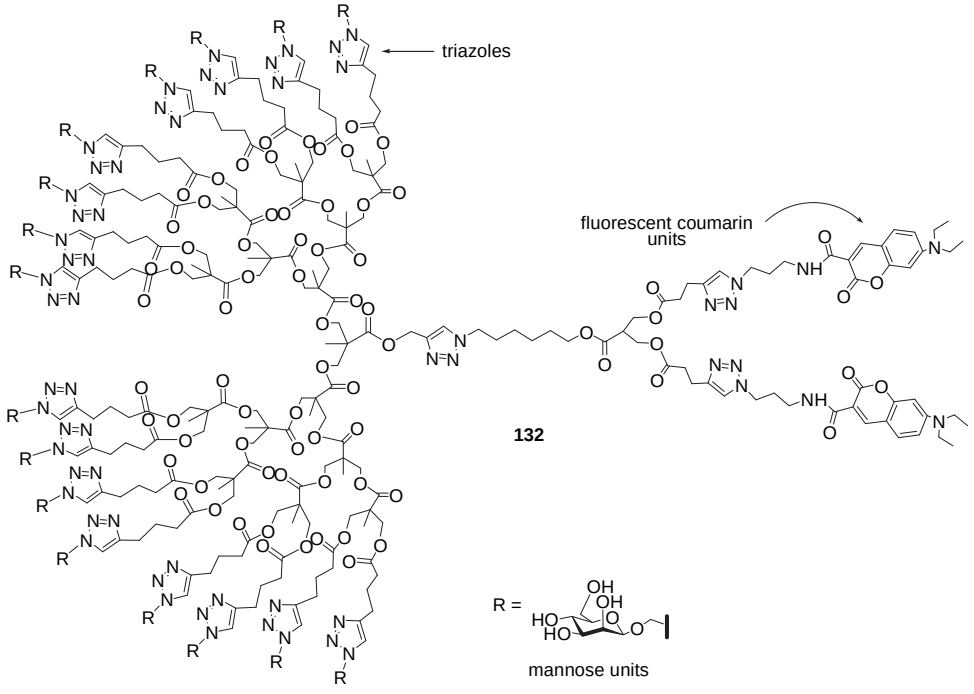
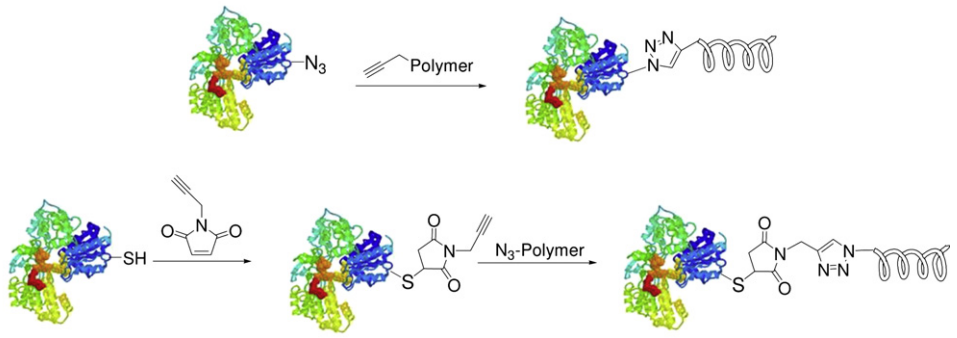
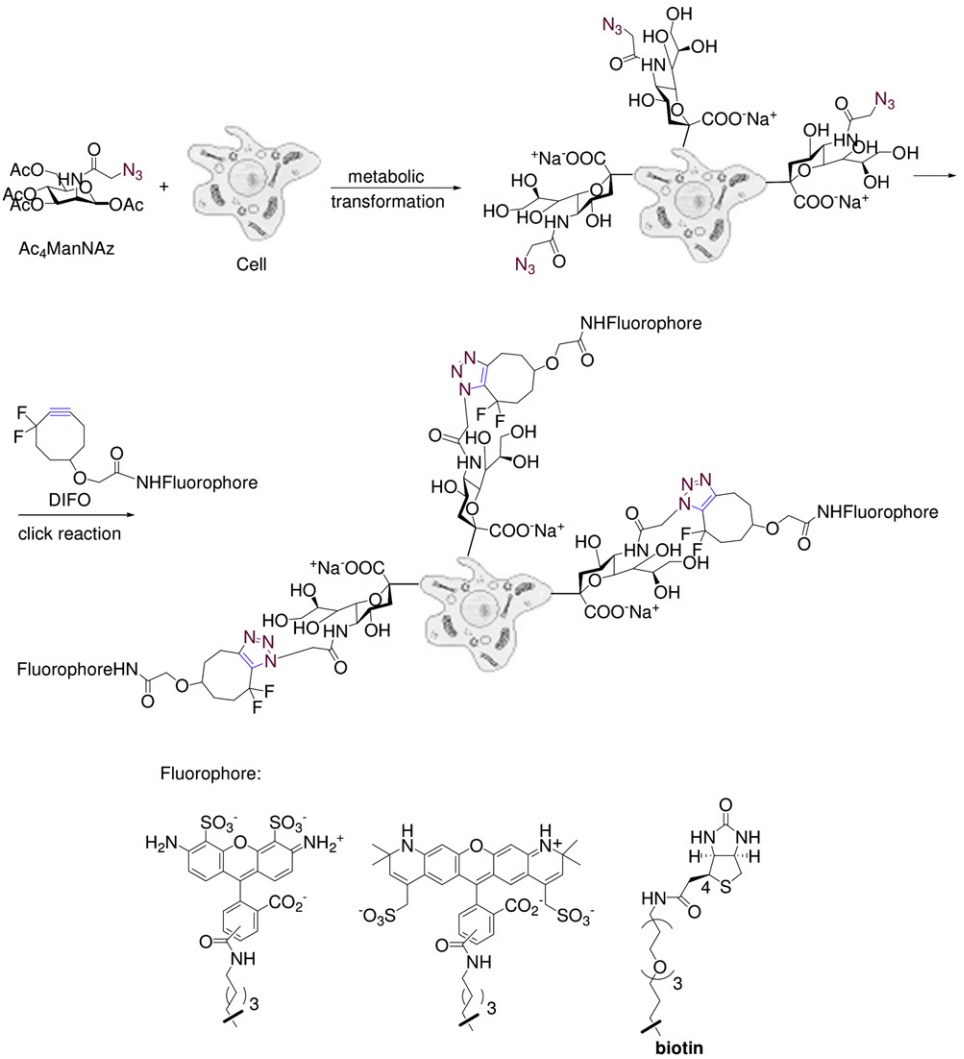


Fig. 13. Synthesis of multivalent, asymmetrical dendrimer **132** containing 16 mannose units and 2 coumarin chromophores.

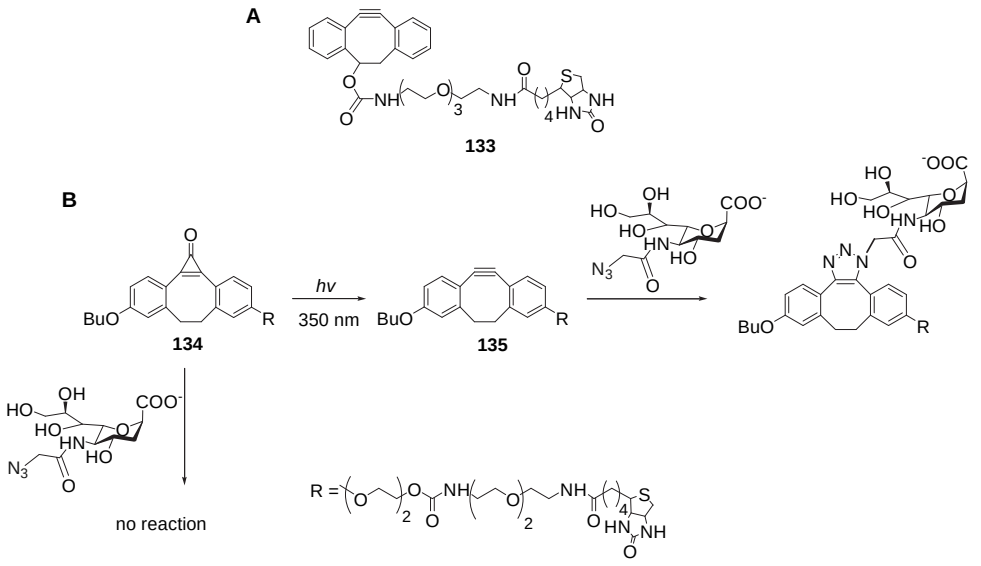


Scheme 19. Polymer-protein conjugates prepared by CuAAC reactions of azide- or alkyne-labelled proteins with polymers bearing complementary functionality.

metabolite, which further reacts covalently with an alkyne-modified functional probe by [3+2] dipolar cycloaddition to form triazole conjugates with minimal physiological perturbation. Therefore, the fast click reaction to visualise biological processes was accomplished using hydrophilic cyclooctynes, activated by a difluoromethylene moiety as an electron-withdrawing substituent in the ring and a chemical tag, such as a small fluorophore, for the consolidated detection (named DIFO),[95] compatible with the aqueous biological environment, neutral pH and room temperature conditions.[5] By combining the kinetic stability and the high thermodynamic energy of azide, as an interesting bioorthogonal species, which does not interact with the functionality presented in biological systems and exploring the high reactivity of DIFO-based reagents for azide detection, it was possible to perform a non-hazardous copper-free click reaction, for covalent labelling of the cell-surface[96] (Scheme 20) and intracellular glycans.[97]



Scheme 20. Bioorthogonal cupper-free click chemistry for dynamic monitoring of cell-surface glycans by in vivo imaging.

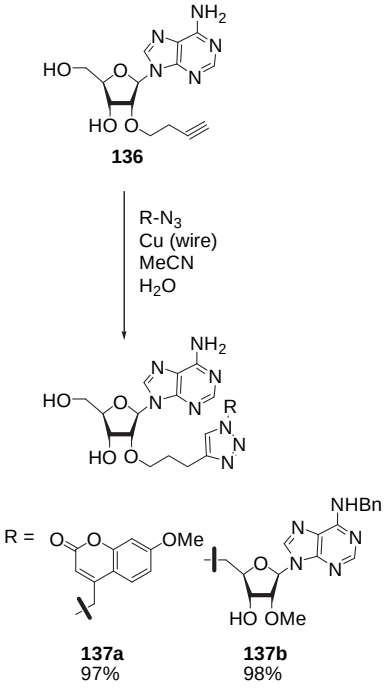


Scheme 21. (A) Structure of 4-dibenzocyclooctynol **133** linked to biotin. (B) Photo-triggered click reaction of cyclopropenone **134** with *N*-azidoacetylsialic acid.

With the aim of developing a versatile and selective method for the labelling of biomolecules, Boons et al.[98] investigated the use of 4-dibenzocyclooctynols, such as compound **133** modified with biotin (Scheme 21), which was employed in an experiment involving the labelling of *N*-azidoacetylsialic acid (SiaNAz) moieties in glycoproteins of Jurkat cells, these being verified with high fluorescent intensities after treatment with avidin-fluorescein isothiocyanate (FITC).[98] More recently, the selective labelling of living cells by a photo-triggered click reaction was described by Popik et al.[99] This approach was based on the in situ light activation of a cyclopropenone, such as **134**, linked to biotin, with the resultant formation of the corresponding dibenzocyclooctyne **135** (Scheme 21), which makes possible the labelling of living cells expressing glycoproteins containing *N*-azidoacetylsialic acid in a temporally and/or spatially controlled manner.

The bioorthogonal click reaction was also employed in a class of enzymes, such as serine hydrolases[100,101] and glycosidases,[102] with active-based probes bearing unnatural amino acids installed by a site-specific process.

Antisense derivatives can also be prepared by CuAAC, enabling the conjugation of nucleotides to carbohydrates, steroids and peptides in order to facilitate their recognition by membrane surface receptors and to increase the efficiency of internalisation of these polymers by cells. Recently, adenosine derivatives containing 2′-azide or 2′-acetylene groups have been described as versatile building blocks for application in the synthesis of hetero- and homo-conjugated oligonucleotides. Thus, adenosyl acetylene **136** was conjugated to different azide derivatives, e.g., containing a fluorescent coumarin label and an azidonucleoside, which provides triazoles **137a** and **137b**, respectively, in almost quantitative yields (Scheme 22).[103]



Scheme 22. Azide/alkyne cycloaddition in synthesis of adenosine dimers and derivatives.

6. Conclusions

The potential of the modified Huisgen 1,3-dipolar cycloaddition reaction between a terminal alkyne and an azide is highlighted by its high efficiency (high yield and rate), practicality and selectivity (several functional groups). This method has gained wide-ranging applications in several scientific areas, such as drug development, identification of biological systems by cell labelling and preparation of polymeric materials (including biopolymers and their mimetics), with applications extending to the major industrial sectors. Although it does not replace the conventional synthetic methods, this synthetic approach allows new and efficient approaches to the preparation of novel biologically or medicinally active agents. In particular, click chemistry is of great relevance in carbohydrate chemistry, where it is finding wide-ranging use in the preparation of drug-like molecules, neoglycoconjugates and neoglycopolymers. In summary, the potential for utilising this contemporary synthetic tool is enormous in several research fields, and is likely to continue to lead to

compounds and materials with unique chemical properties, physical structures and biological activities.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.001.

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Biographical sketch

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Vanessa Leiria Campo graduated in Biochemistry-Pharmacy at the Federal University of Mato Grosso do Sul in 2001. She received her Ph.D. degrees from University of São Paulo (USP) in 2007, concluding her doctoral thesis on the chemical and enzymatic synthesis of glycopeptides related to mucins found in *T. cruzi* under the supervision of Professor Ivone Carvalho and Professor Rob Field (2005–2006, University of East Anglia-UK). From 2008 to 2010, she did her post-doctoral work at USP (Professor Ivone Carvalho) and at John Innes Centre (April–September/2009, Professor Rob Field), working on the synthesis of glycoamino acids and glycopolymers as inhibitors of *T. cruzi trans*-sialidase enzyme. She is currently working as a research fellow at USP on the development of glycoconjugates with therapeutic and diagnostic applications to tumoral and infeccious processes.

Rob Field is a University of East Anglia graduate (1986) and Ph.D. (1989; Dr. A.H. Haines). Following post-doctoral work in Oxford (1989–1991; Professor Sir J.E. Baldwin), Dundee (1992–1994; Professor M.A.J. Ferguson and Professor S.W. Homans) and Alberta (1994; Professor O. Hindsgaul), he was appointed to the faculty at the University of St Andrews in 1994, where he was promoted through the ranks to Professor (1999). He returned to Norwich in 2001, initially at UEA and latterly at the John Innes Centre. His research programme focuses on plant and microbial carbohydrate chemistry, in particular cell wall biosynthesis, starch metabolism and the enzymology of antibiotic biosynthesis. He is also involved in the development of analytical tools (glyco-arrays, nanoparticles and quantum dots) and chemical genetics approaches to study the role of glycosylation in biological systems.

Ivone Carvalho received her B.Sc., Master and Ph.D. degrees from the University of São Paulo (USP), completing her doctoral thesis on synthesis of natural products in 1991 under the guidance of Professor Maurőcio Gomes Constantino. In 1995, she joined Professor A. H. Haines's group at University of East Anglia as a post-doctoral researcher to work on the synthesis of pseudodisacharides as potential alpha-glucosidase inhibitors. She then returned to Great Britain in 2000 to complete another post-doctoral period in Professor R.A. Field's group at the University of St Andrews in Scotland, where she worked on the synthesis of glycopeptides to study the mechanism and function of parasite enzymes. She is currently working as a Professor of Medicinal Chemistry at Faculty of Pharmaceutical Sciences of Ribeirão Preto/USP and her research interests concentrate on the design and synthesis of potential bioactive compounds.