Nanometric glycoclusters designed to fighting bacterial pathogens

Résumé **Glycoclusters supramoléculaires conçus pour lutter contre les agents pathogènes bactériens**
Une multitude de processus naturels tirent profit de la présentation sous forme de multimères d'entités biochimiques afin d'exacerber l'efficacité de leurs interactions. Ce phénomène, appelé « multivalence » ou « effet multivalent », joue un rôle majeur en biologie. Ceci est particulièrement vrai pour les interactions sucres-protéines qui sont individuellement faibles mais qui peuvent être fortement exacerbées lorsque le ligand (un mono- ou oligosaccharide) est présenté d'une manière multivalente. Ce phénomène a inspiré un grand nombre de scientifiques qui ont dès lors consacré beaucoup d'efforts à créer de nouveaux systèmes multivalents artificiels et à comprendre les mécanismes sous-jacents aux effets multivalents. Une des applications importantes est l'inhibition de l'adhésion de bactéries pathogènes à leur tissu hôte afin d'empêcher le processus d'infection. Un autre champ de recherche émergeant est l'inhibition multivalente d'enzymes bactériennes.
Mots-clés **Multivalence, glycocluster, infection bactérienne, sucres, lectine, fullerène.**

Abstract Many natural processes take advantage of the multimeric presentation of biological entities to enhance the efficiency of binding events. Because of its critical role in major biological phenomena, multivalency has received much attention in biomedicine in the last few years. This is particularly true for carbohydrate-protein interactions, which are notoriously weak at the monomer level, but can be dramatically strengthened if the ligand is presented in a multivalent manner (supramolecular glycoside cluster effect). Inspired by these natural phenomena, scientists have dedicated tremendous effort both to understand the underlying mechanisms of multivalency and to create artificial multivalent systems for diverse applications, such as the inhibition of the adhesion of pathogenic bacteria to their host tissues to prevent infections. Another emerging field of application is the multivalent inhibition of biologically relevant bacterial enzymes.
Keywords **Multivalency, glycocluster, bacterial infections carbohydrate, lectin, fullerene.**

Biorecognition, tools and glycoclusters

Nature benefits from supramolecular interactions (*e.g.* hydrophobic, electrostatic, H-bonding, π-π, ion-π, metal coordination and van der Waals forces) to fulfil innumerable biological processes. For instance, enzymes recognize their substrates *via* combination of supramolecular interactions, the double-helix DNA exists thanks to H-bonding and π-π interactions, etc. The global strength of these multiple interactions is enhanced more than it should be expected by simply taking into account the monovalent interactions. This well-known phenomenon, often called "multivalent effect" or "multivalency", can thus be exploited to control biorecognition and binding events. Many examples of multivalent processes can be found in Nature. For instance, cell-cell communication, fertilization, immune response, and cell proliferation often benefit from the power of multivalency.

Hence, multivalency is a fundamental issue for attaining both strong and reversible interactions. Innumerable biological entities, ranging from small molecules, macromolecules, organelles, and membranes to whole cells, virus and bacteria exploit the multiple interactions of complementary binding units to enhance their selectivity and global affinity. A significant number of these multivalent interactions take place between proteins and carbohydrates. In 1995, the enhancement of the affinity of multivalent carbohydrates toward lectins (carbohydrate binding proteins) was described as the "glycoside cluster effect" [1]. Inspired by this effect, during the last decades researchers have developed a plethora of multivalent chemical entities functionalized with carbohydrates (glycoclusters) to study relevant biorecognition processes. In this article, we will focus on the synthesis of glycoclusters designed to target two bacterial pathogens, *Escherichia coli* and *Pseudomonas aeruginosa*, as well as a bacterial glycosyltransferase of therapeutic relevance in the development of antibacterial agents.

Glycoclusters are constituted by a central scaffold that can distribute at least two saccharidic ligands (mono- or oligosaccharides). Most often, the ligands are the same (homovalent glycoclusters) but heterovalent structures displaying more than one type of ligand have recently emerged as efficient tools in glycobiology. An immense collection of synthetic glycoconjugates displaying various valences, geometries and topologies have been prepared to study carbohydrate-protein interactions during the last two decades. For instance, such diverse architectures as oligonucleotide and PNA, cyclopeptides, carbosilane dendrimers, calixarenes, liposome and micelles, nanoparticles (gold, CdSe, FeO, etc.), cyclodextrines, carbon nanotubes and graphene, and aromatic scaffolds have been developed [2].

Lectins (carbohydrate binding proteins) have been the primary focus of glycoclusters' design, especially plant lectins. Then, bacterial and viral carbohydrate binding receptors have emerged as relevant targets because of their potential biomedical applications. Indeed, if the targeted receptor plays an essential role in the infection process or the virulence of the microbe, glycoclusters could become antibacterial agents if pathogens have more affinity for them than for the host cells. Other applications such as the development of diagnostic tools can also be envisioned. Prominent examples are the synthesis of pentavalent saccharidic ligands of the cholera toxin and the Shiga toxin (from *Shigella dysenteriae*) whose affinities were enhanced by several orders of magnitude through multivalency [2a-3]. Therapeutically relevant

applications of glycoclusters are not limited to prokaryotes: indeed, galectins are a class of eukaryotic lectins that can be targeted through a multivalent strategy with potential applications in cancer treatment [4].

Preventing pathogenic bacteria to adhere to their host: a new approach to develop antibacterial agents

Glycofullerenes and uropathogenic *Escherichia coli*

E. coli is a Gram-negative bacteria that owes its name both to Theodor Escherich, a German pediatrician who discovered the bacteria in the feces of healthy individuals in 1885, and to its localization in the colon. Although usually harmless, some strains are pathogenic and may cause a wide variety of illnesses. For instance, Shiga-toxin producing *E. coli* (STEC) is the major source of foodborne outbreaks. Apart from intestinal diseases, extra-intestinal diseases can also be caused by diverse strains of *E. coli*, such as urinary tract infections (UTI) mainly caused by uropathogenic *E. coli* strains (UPEC) [5]. In industrialized countries, UTIs represent one of the most common bacterial infectious diseases. It is known that women are considerably more likely to suffer from UTI than men. Statistically, 60% of all women will have at least one episode of acute UTI during their lives, and a 25 to 44% of probability of developing a second episode within six months of the initial UTI, which results in enormous inconveniences and economical expenses.

The first step for successful bacterial colonization and infection is adhesion to the host tissue, which is generally mediated by the microorganism's pili, also known as *fimbriae*. These pili not only enable the adhesion to the bladder and kidney, but are also involved in crucial functions as invasion and biofilm formation. Type 1 *fimbriae*, which are widely expressed by UPEC, specifically bind α-mannosides displayed on the surface of the bladder epithelium, through FimH, a lectin (in this case an adhesin) that selectively binds D-mannose. Without the strong binding of these multivalently exposed type 1 pili, UPEC would not be able to resist the fluid forces and would easily be cleared from the bladder by the urine. Many experiments have attempted to prevent the UPEC colonization of the urinary tract by blocking the adhesion with inhibitors able to bind FimH.

The two opposite strategies for designing multivalent ligands consist in generating flexible or rigid architectures. If the scaffold displays flexible spacers, which give conformational freedom to the ligands, there are more possibilities for random interactions, although the multivalent interaction results in an increased conformational entropy. On the contrary, the entropy penalty decreases if the scaffold and spacer are rigid, but this demands an optimal design of geometry (and consequently a high knowledge of the lectin structure) to prevent a loss of binding enthalpy. As such accuracy is highly challenging to reach, a compromise between the two approaches by combining design with flexibility seems to be the most promising strategy.

In collaboration with the team of Jean-François Nierengarten (University of Strasbourg), we identified that Buckminsterfullerene (C_{60}) could be an ideal central scaffold to generate globular glycofullerenes (C_{60} as a central core surrounded by carbohydrates thanks to a linker), especially for an anti-adhesive strategy of bacterial pathogens. It can be functionalized

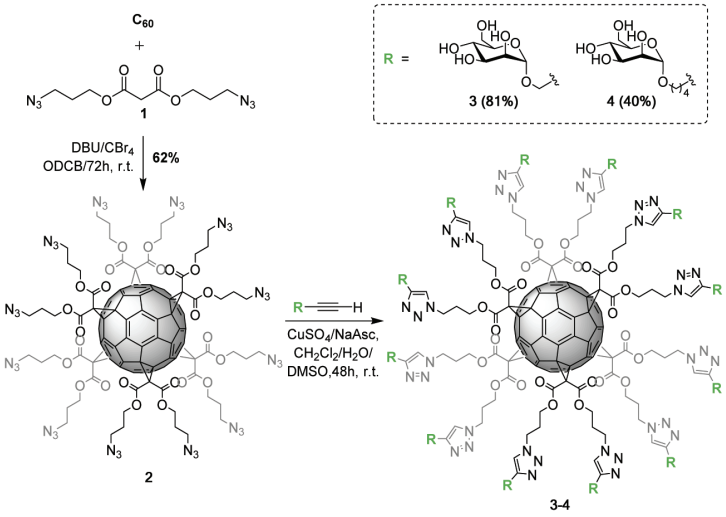

Figure 1 - Preparation of glycofullerenes bearing twelve carbohydrates.

to display a controlled functionalization pattern and displays very interesting electrochemical, photochemical and physical properties that could be exploited in biology. Noteworthy, Nierengarten *et al.* produced a polyazide **2** containing twelve azide groups by simultaneous Bingel-Hirsch cyclopropanations onto C_{60} with six azido-malonates. In collaboration with this group, we could "click" to this multivalent scaffold diverse deprotected sugar derivatives bearing a terminal alkyne group (*figure 1*) [6]. After optimization, the final glycofullerenes were obtained in good to excellent yields, taking into account that twelve reactions took place. The products were isolated by precipitation and size-exclusion chromatography.

These glycofullerenes, presenting a unique globular structure, were fully soluble in aqueous media and did not form aggregates. Their chemical structures were confirmed by ^{1}H and ^{13}C NMR, IR and MS. The ^{13}C NMR spectra were especially useful to prove the T_h-symmetrical structure. Mass spectrometry was the definitive proof of the structure of the glycofullerenes [6].

Using both isothermal titration calorimetry (ITC) and surface plasmon resonance (SPR), we could show that the generated glycofullerenes are very potent, low nanomolar ligands of purified FimH. Rewardingly, we could also show their efficiency in a whole cell competition assay using uropathogenic bacteria and erythrocytes [7].

In the particular case of FimH, which is monomeric and whose binding site can only accommodate one ligand, the multivalent effects observed can be explained on the basis of statistical effects derived from:

- a high local concentration of mannoside ligands close to the binding site;
- the existence of additional carbohydrate binding modules on the FimH surface;
- the occurrence of natural multivalent binding processes between the multivalent inhibitor and the multiple pili expressed on the bacterial surface.

In the next section, we will detail our efforts to generate novel supramolecular glycoclusters designed to bind two lectins of *Pseudomonas aeruginosa*, another important bacterial pathogen.

Pillar-arenes and rotaxanes targeting *Pseudomonas aeruginosa*

Mechanically-interlocked molecules (MIMs) are molecules connected not by means of covalent or non-covalent bonds

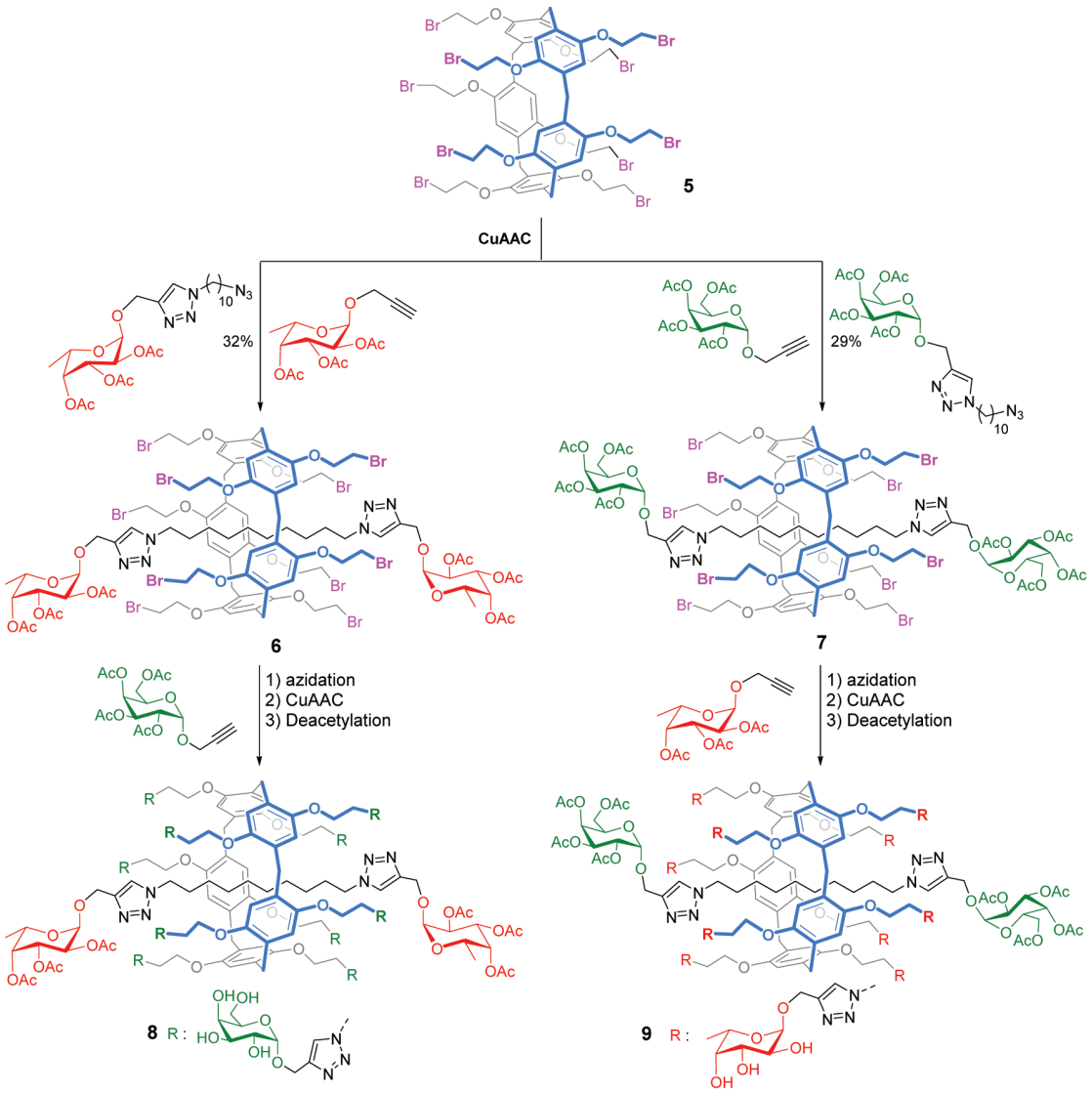

Figure 2 - Host-guest chemistry exploited to generate rotaxane heteroglycoclusters **8** and **9** as simultaneous ligands of the two bacterial lectins LecA and LecB.

but as a consequence of their topology ("mechanical bonds"). They cannot be separated without breaking down the whole system. The very first attempts for the production of catenanes and rotaxanes relied on statistical approaches, covalent templates and most often low-yielding multi-step syntheses. A milestone for these MIMs preparation was the introduction of metal templating by Sauvage and co-workers [8]. Rotaxane synthesis has nowadays reached a level of maturity to allow their exploitation in various fields such as chemical biology. In our continuous efforts to develop new molecular tools as bacterial anti-adhesives, we recently disclosed the synthesis of rotaxanes bearing two different lectin ligands, namely L-fucoseand D-galactose, in collaboration with the Nierengarten group as well (*figure 2*) [9]. These two carbohydrates were selected because the bacterial pathogen *Pseudomonas aeruginosa* express two lectins (LecA and LecB) that selectively bind L-fucose and D-galactose. These two lectins are virulent factors responsible for cell adhesion, internalization, and biofilm formation [10].

In fact, we exploited the unique features of the rotaxane scaffold to achieve the synthesis of heteroglycoclusters in a controlled manner. Indeed, the selected central platform, a pillar[5]arene can be functionalized by ten identical carbohydrates. The central cavity of the pillar[5]arene can accommodate an alkyl chain that bears two other ligands that play the role of stoppers, thus generating the mechanical bond. This way, we could obtain a heterovalent glycocluster that could inhibit, simultaneously, two distinct receptors of the same bacterial pathogen. Biophysical and biochemical investigations, realized in the laboratory of Anne Imberty (CERMAV, Grenoble), showed that, indeed, a multivalent effect was observed both for LecA and LecB with the same molecules **8** and **9** [9].

Multivalent enzyme inhibition

Genesis of a novel enzyme inhibition mode

In spite of the success in the affinity enhancement of synthetic glycoconjugates toward lectins, these achievements had remained mainly restricted to the field of carbohydrate-binding proteins until a few years ago [11]. Traditionally, the inhibition of enzymes has been attempted either by designing transition state mimics or by screening small molecules (natural or synthetic) that bind either the catalytic site or allosteric binding pockets. Enzymes being generally monomeric and/or displaying only one catalytic site, a cluster or multivalent effect is not expected to be effective. Nevertheless, impressive enhancements of several orders of magnitude of iminosugar (sugar analogue where the O atom has been substituted by a N atom) clusters toward glycosidases (enzymes that catalyse

the hydrolysis of glycosidic bonds) have been recently reported [12].
These results reinforced the proof of concept that multivalent phenomena can be extended from carbohydrate-recognition proteins to carbohydrate-processing enzymes and may reach similar levels of affinity enhancement. Furthermore, these pioneering studies illustrated how multivalent clusters can modulate not only the inhibitory potency but also the selectivity by modifying structural parameters.

Application of glycoclusters to other enzymes of therapeutic interest

One of the first examples of multivalent inhibition of enzymes was given for influenza neuraminidase (NA) before the discovery (and characterization) of multivalent effects in the inhibition of glycosidases. NA is a glycosidase responsible for the spread of virus infection and thus an important target for antiviral therapies. Zanamivir (Relenza®) is a nanomolar inhibitor of NA used as anti-influenza drug. Di-, tri-, tetra-, and polymeric inhibitors have been prepared and their affinity compared to Zanamivir *in vitro* and *in vivo* [13]. Interestingly, the dimeric inhibitor showed a ten-fold decrease in activity *in vitro*, but 100-fold more potency *in vivo* in mice model. The apparent divergence between the results *in vitro* and *in vivo* was explained by means of two arguments: the clusters can form aggregates of high molecular weight with the virus, and there is longer *in vivo* retention of the derivatives in comparison with the monovalent Zanamivir. Another representative example of multivalent enzyme inhibition is a very recent study on bacterial heptosyltransferase WaaC inhibition performed in our group.

Heptosyltransferase WaaC: a bacterial therapeutic target with an unusual antibacterial mechanism

In Gram-negative bacteria, heptosyltransferase WaaC catalyzes the incorporation of L-*glycero*-α-D-*manno*-heptopyranose (L-heptose) into lipopolysaccharide (LPS) present in the outer membrane. This enzyme transfers a L-heptose moiety form an activated donor substrate (ADP-heptose **11**, *figure 3*) onto a growing glycolipid acceptor (lipid A-Kdo2 **10**). LPS is not only an essential component of the bacterial cell wall, but is also involved in the virulence of pathogenic bacteria. If the heptose biosynthesis is inhibited (by means of WaaC inhibition for instance), the phenotype of the bacterium will change and it will become susceptible to many antibiotics, and more importantly, to the innate immune system. Therefore, WaaC has become an appealing target to generate novel anti-bacterial agents with an unusual mechanism of action: instead of being bactericidal, WaaC inhibitors would target the virulence of a bacterial pathogen, not its survival. In a therapeutic intervention, those molecules would not be the killers of the bacteria, but would create the conditions to provoke the bacterial death or stop the disease by preventing the virulence mechanism.
Inspired by the elegant work performed on glycosidases [11a-b], our group first generated glycofullerenes bearing twelve copies of the bacterial L-heptose: the mannoside **4**, the heptoside **13**, an octoside **14**, all sharing the D-mannopyranose core present in the natural donor substrate of WaaC (see *figure 3*) [14]. Biochemical assays against WaaC showed that these glycofullerenes inhibited the enzyme in the low micromolar range (7 to 47 µM), where the best inhibitor was the octose derivative (61-fold lower than the monovalent counterpart).

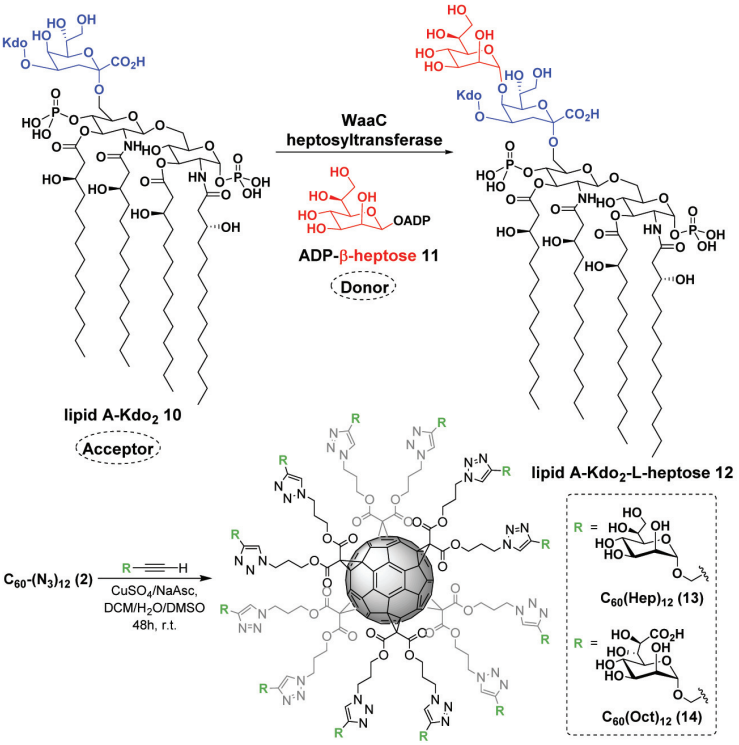

Figure 3 - The WaaC catalysed reaction (top) and synthesis of glycofullerenes **13** and **14** as WaaC inhibitors.

These results were extremely encouraging because glycosyltransferases are notoriously challenging to inhibit, even at the low micromolar level, but also because a significant, although not dramatic, multivalent effect was observed. We thus pursued this study by the synthesis of a novel series of multivalent molecules bearing this time the Kdo sugar present in the acceptor glycolipid of WaaC [15]. As illustrated in *figure 4*, we generated not only glycofullerenes, but also derivatives of porphyrins, calix- and pillar-arenes.
Important conclusions could be drawn from this study. First, we could demonstrate that all these molecules exclusively bind the WaaC acceptor pocket and not the heptose donor pocket, as initially anticipated. The observed multivalent effects arose from the enhancement of non-specific weak interactions, a result that we could also extrapolate to some glycosidases [16]. We could also show, by dynamic light scattering, that a mechanism of WaaC aggregation could also contribute to the global enzyme inhibition.

Perspectives

In order to fine-tune molecules designed to resolve specific biological problems, continuous efforts are dedicated to the generation of novel multivalent entities that can push forward our knowledge related to this striking field. For instance, in collaboration with the team of Prof. Yves Dufrênes (Université Catholique de Louvain, Belgium), we developed an AFM platform for quantifying the activity of anti-adhesion compounds directly on living bacteria thanks to fullerene-based manno-conjugates bearing ten carbohydrate ligands and a thiol generated *in situ* [17]. Beyond the applications linked to the chemical biology of multivalent effects, research efforts are also produced to generate, chemically, novel glycoclusters in the hope to optimize or fine-tune the biological activities *in vitro* or *in vivo*.

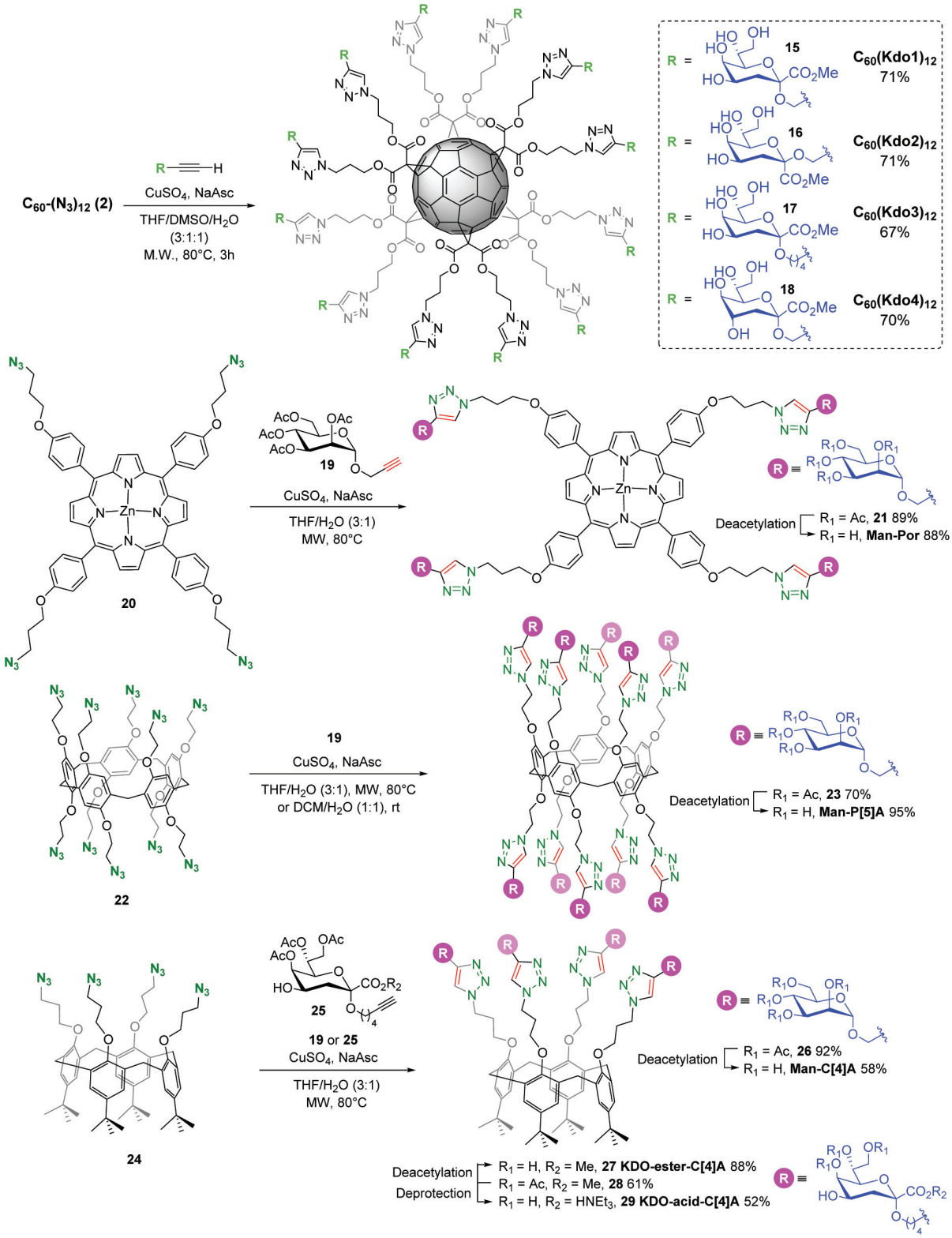

Figure 4 - Representative examples of novel generation of WaaC multivalent inhibitors.

Borromean rings as new multivalent scaffold

We showed above that supramolecular chemistry could be exploited to generate in a controlled manner complex heterovalent glycoclusters. The regioselectivity of the synthesis originated from the central mechanical bond of the glycorotaxanes. We were also inspired by the recent developments of constitutional dynamic chemistry (CDC) [18] and especially its impact in the synthesis of Solomon Knots and Borromean Rings [8]. Indeed, the synthesis of mechanically-interlocked molecules deeply benefited from the reversibility of templating in dynamic systems and the robustness of covalent bonds. In these systems, the template molecule is a part of the system, a property that can be exploited to create topological bonds.

Borromean Rings' name is related to an aristocratic family (the Borromeos), established in Northern Italy in the Renaissance period, who used the three interlocked rings in their family coat of arms. Stoddart *et al*. exploited metal-templating to provide geometrical precision thanks to its dynamic coordinative nature, along with the proper organic ligands [19]. As a result of the powerful combination of intuition, computer modelling, CDC and metal-templating, covalent and non-covalent

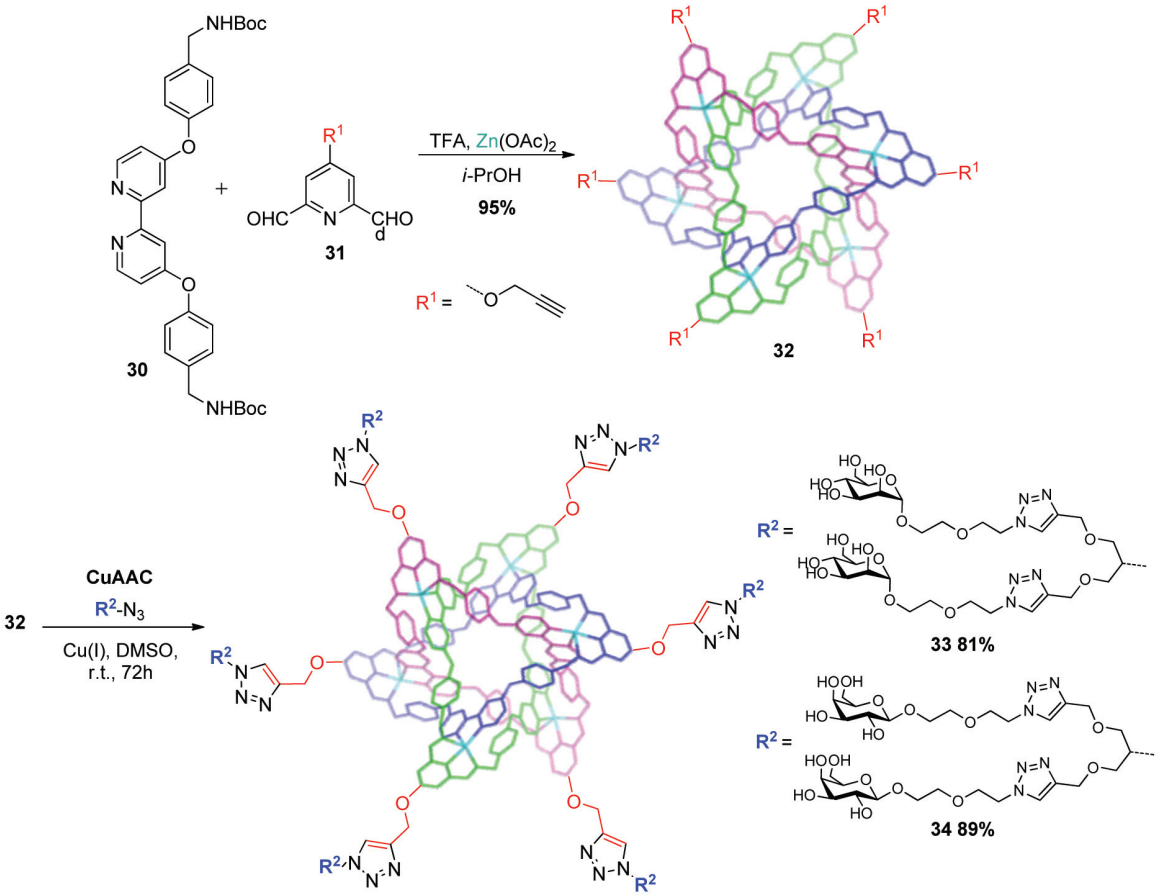

Figure 5 - Final glycoborromeates synthesized by CuAAC, manno-borromeate **33** and galacto-borromeate **34**.

bonding interactions under both kinetic and thermodynamic control could afford the designed BR in nearly quantitative yield. In collaboration with the laboratory of Prof. Olof Ramström (KTH Stockholm, Sweden), we managed to prepare a multivalent glycosylated version of Stoddart's Borromean rings [20]. Dimeric glycosides were clicked onto a Borromean scaffold bearing six terminal alkynes (see *figure 5*). The resulting dodecameric glycoclusters could be directly compared to the glycofullerenes previously prepared in our group because the latter are also dodecameric [20].

The results of hemmagglutination inhibition assay (HIA) showed that the affinity of the mannoborromeate **33** for uropathogenic *E. coli* was excellent (MIC = 7.8 µM) and in the same range than the mannofullerenes initially described in our laboratory.

In conclusion, supramolecular chemistry can be exploited as a mean to generate, in a few steps, complex molecular architectures that can efficiently interact with biological receptors or even living bacteria. We deeply believe that supramolecular chemistry will nurture even further the field of chemical biology and biomedical sciences. These supramolecules will provide new tools or new chemical entities designed to tackle major therapeutic problems such as the need to resolve the impact of antibiotic resistance on human health.

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