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"Click" synthesis of amphiphilic carbohydrate-alkyl triazole derivatives

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ABSTRACT

1,4-disubstituted 1*H*-1,2,3-triazole with a hydrophobic and hydrophilic moiety were synthesized by using Cu(I) catalyzed alkyne-azide 1,3-dipolar cycloaddition reaction. The hydrophilic moiety was D-galactopiranosyl or L-galactitoyl while an alkyl chain of eight to sixteen carbons corresponds to the hydrophobic portion. All compounds were characterized by NMR and mass spectrometry. Partition coefficient was experimentally determinate by HPLC ranging from 0.7 to 4.5. Compounds with the lowest partition coefficient showed self-aggregation in water leading to supramolecular structure, with size ranging from 108 to 588 nm.

1. Introduction

Cu(I) catalyzed alkyne-azide 1,3-dipolar cycloaddition reaction (CuAAC) is an example of "click reaction" and was quickly introduced in organic chemistry since it was first described by Sharpless and Meldal in 2002 [1].

The main advantages of CuAAC are to process at middle temperature, the use of a widely type of solvent, different pH, the high efficiency and atom economy [2].

In addition, CuAAC was employed for the assembly of hydrophilic and hydrophobic polymeric moieties leading to amphiphilic supramolecular structures [3,4]. Synthetic glycolipids as non-ionic detergents were also obtained by CuAAC [5,6].

In this context, the purpose of this study is the synthesis of small amphiphilic molecules based on 1,4-disubstituted 1*H*-1,2,3-triazole with a hydrophilic moiety (D-galactopiranosyl or L-galactitoyl) and a hydrophobic moiety (alkyloxy methylen) as well as to perform a preliminary physical characterization that might help to figure up future applications for the proposed compounds.

All compounds were synthesized by CuAAC reactions performed under microwave irradiation at 80C during 40 min and the products were obtained with generally satisfactory yields.

Fig. 1 depicts the synthesis of the final compounds.

The synthesis of precursors was performed using methodologies previously reported in literature. Briefly, on one hand alkyl alcohol (octanol, decanol, dodecanol, tetradecanol and cetyl alcohol) was treated with NaOH and propargyl bromide to yield the different alkyl-propargylether [7]. On the other hand, 6-deoxy-6-azido-D-galactose was synthesized from 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose treated with NaN_3 and later deprotected in acidic media [8,9]. The reduction of 6-deoxy-6-azido-D-galactose with $NaBH_4$ yielded the 1-deoxy-1-azido-L-galactitol [10,11]. The synthesis of precursors is detailed in the supplementary information section.

2. Results and discussion

CuAAC reactions were easily confirmed by NMR due to the appearance of diagnostic signal corresponding to the resonance of triazole produced (^{1}H NMR $\delta = 7.95$ ppm; ^{13}C NMR $\delta = 125.0$ ppm and 148.5 ppm, expressed as an average for all compounds). ^{1}H and ^{13}C NMR spectra as well as their assignations of all compounds are shown in the supplementary information section.

The full mass spectrum (ESI-MS) of each compound revealed that the principal adduct correspond to $[M + Na]^+$, but $[M + H]^+$ intensity is increased by adding formic acid. Fragmentation pattern was studied for each compound by selecting the $[M + H]^+$ or $[M + Na]^+$ ion and applying different collision energy to get the product ions. Sodium adducts resulted more stable than proton adducts as higher energies are required to get products ions. Fragmentation pathways of each compound were different depending on both the carbohydrate moiety

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present and the selected adduct as it is summarized in Fig. 2. In the case of sodium adducts from compounds with galactopiranosyl moiety fragmentation leads to fragments that keep the alkyl chain (pathway a). On the other hand, compounds with galactitoyl moiety leads to one common fragment (pathway c). Fragmentation of proton adducts is produced by pathway b, which lead to a common fragment, for both type of carbohydrate moiety and by pathway c which is remarkable in compounds with the galactitoyl moiety (Fig. 2). Mass spectra and proposed fragmentation mechanism are shown in the supplementary information section.

Logarithms of octanol/water partition coefficient (Log *P*) were estimated by HPLC according to previous procedure as a measure of lipophilicity. Experimental logarithms of capacity factor (log *K*) and calculated Log *P* from known compounds were employed as a calibration model and Log *P* from synthesized compounds were estimated by comparison of their experimental log *K* in the calibration model (see supplementary information).

As depicted in Fig. 3 a linear correlation between estimated Log *P* and the number of methylene groups present in the alkyl chain was found. A similar correlation is found when the theoretical values from a computational approach (ChemDraw, PerkinElmer, Waltham, Massachusetts, United Estates) are used. For compounds **6**–**10**, individual Log *P* values from experimental and computational approaches show a difference, the later one reports the lowest values. It is worth noting that the computational approach also predicts higher Log *P* values for compounds with D-galactopiranosyl moiety than compounds with galactitoyl residue with the same alkyl chain. However, the experimental approach predicts similar Log *P* values for both compounds with D-galactopiranosyl or galactitoyl moiety with the same alkyl chain.

The aggregation structures assembled in water for compounds **1**, **6** and **7** were studied by dynamic light scattering (DLS) by means of dispersions in water as solvent at 25° C. The resulted suspensions showed a slight turbidity due to Tyndall effect which might point to self-assembled nanoparticles. Conversely the other compounds resulted highly water insoluble or not dispersible.

Hydrodynamic diameter (Dh) for self-assembled structures derived from compound **1** showed a bimodal distribution of Dh of 108 nm and 588 nm (Fig. 57S). On the contrary for compounds **6** and **7** Dh was 201 and 246 nm respectively and the corresponding size distribution curve exhibit a unimodal distribution, polydispesity index were lower than 0.3 (Fig. 58S, 59S). This last observed size difference can partially be attributed to the difference in the molecular weight. Those experimental hydrodynamic diameters suggest that the architecture of the formed supramolecular structures for compound **1**, **6** and **7** correspond to self-assembled nanoparticles and not classical micelles [12].

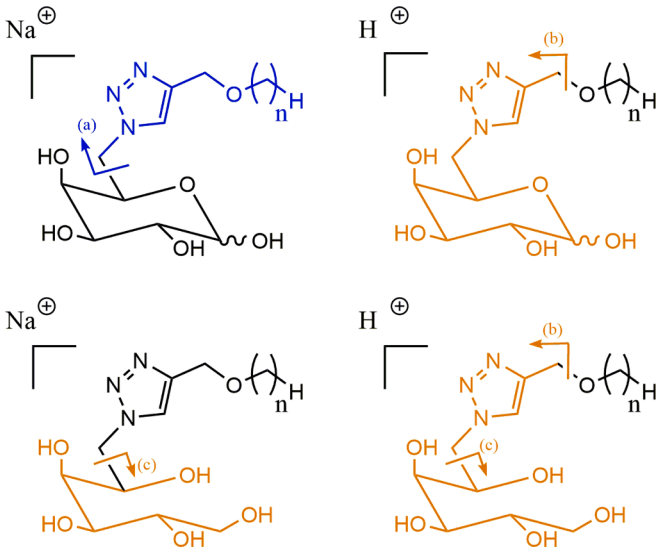

Fig. 2. Principal mass spectra fragmentation pathway proposed.

3. Conclusion

The synthetic pathway by CuAAC provided a simply and versatile approach to connect the hydrophobic and hydrophilic moieties, both coming from renewable biomass. Experiments conducted by DLS showed that compound **1**, **6** and **7** has the capacity to self- aggregate into nanoparticles when dispersed in water. This information will be useful in forthcoming proposed applications for the synthesized compounds.

CRediT authorship contribution statement

Mario Daniel Contin: Conceptualization, Data curation, Formal analysis, Writing – review & editing. **M. Leticia Bravi Costantino:** Data

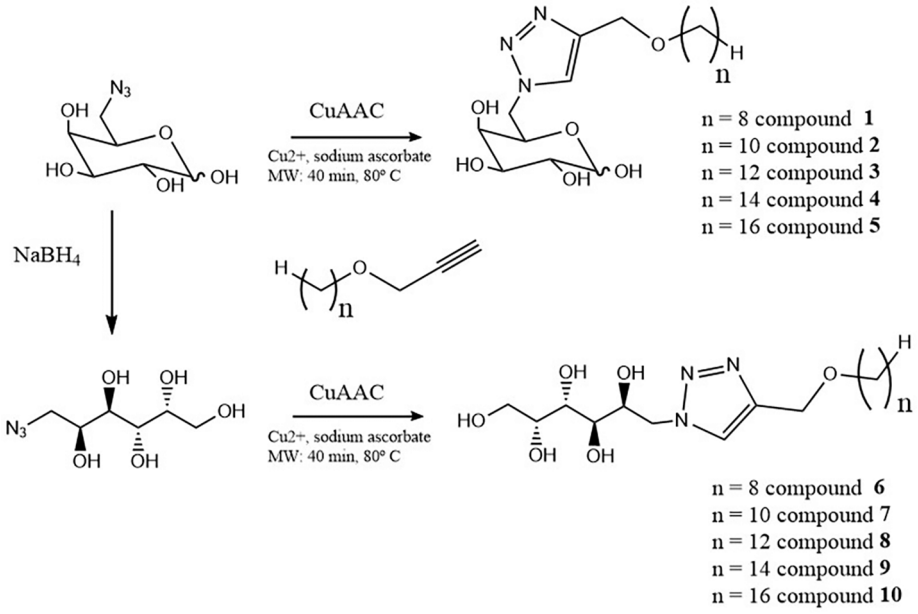

Fig. 1. Schematic synthesis of proposed compounds. CuAAC: Cu(I) catalyzed alkyne-azide 1,3-dipolar cycloaddition reaction. MW: microwave.

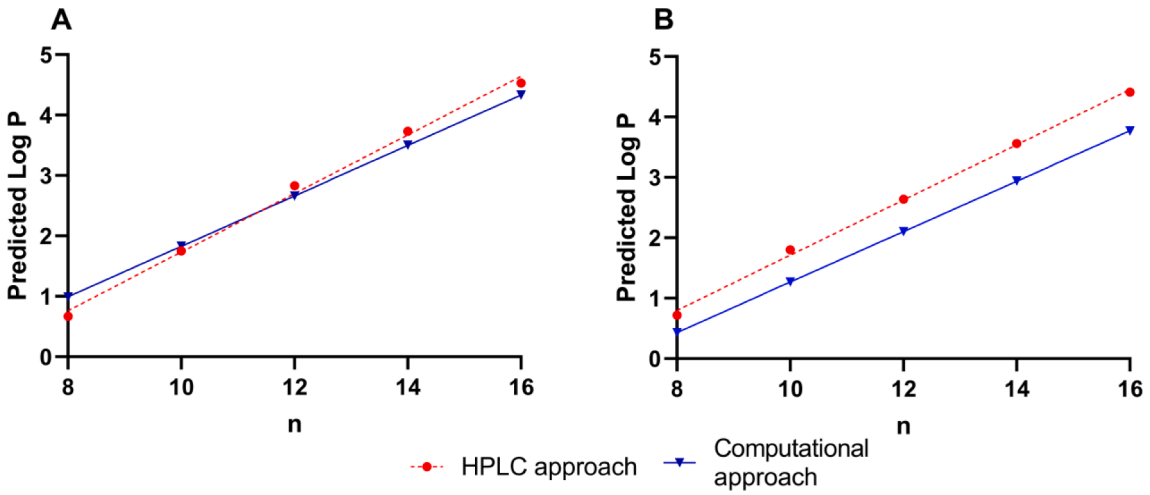

Fig. 3. Estimated Log *P* for synthesized compounds by experimental and computational approach. The dependence of Log P and the number of methylene in the alkyl chain (n) is shown. A) compounds **1**–**5**. B) compounds **6**–**10**.

curation, Formal analysis, Writing – review & editing. **Norma B. D'Accorso:** Conceptualization, Funding acquisition, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100558.

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