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Synthesis of Novel Benzocaine and Procaine Glycodrugs †

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Abstract: In this manuscript, we present the synthesis and structural identification of two novel glycodrugs derived from benzocaine and procaine. D-galactose was converted into a substrate suitable for the introduction of amino derivatives at the C6 position. The glycodrugs were obtained in good yields through a two-step process involving the formation of an imine followed by subsequent reduction.

Keywords: glycoside synthesis; p-aminobenzoate derivatives; 6-deoxy-6-*N*-aryl-galactosides

1. Introduction

The need for new bioactive compounds warrants research in the field of organic synthesis to discover novel chemotherapeutics. The p-aminobenzoate moiety has been demonstrated as a potent substructure in medicinal chemistry. Several derivatives have been synthesized and their antibacterial and anticancer activities have been analyzed, yielding promising results [1].

In glycodrugs, the specific biological activity cannot be exclusively attributed to the aglycone moiety. It has been well demonstrated that the sugar residue may play a crucial role in therapeutic efficiency by modifying transport through various biological barriers or interacting with receptors or lectins on the cell surface [2].

As part of our ongoing efforts to synthesize novel glycosides [3], in the present work, we investigate the synthesis and structural analysis of novel benzocaine and procaine D-galactose derivatives. The molecule design incorporates two principles: the attachment of the bioactive aglycone at a non-anomeric position and, through a nitrogen atom; these structural features generate novel compounds that differ from classical O-glycosides, thereby creating molecular diversity to achieve more accurate structure-activity relationships [4].

2. Material and Methods

2.1. General

Unless otherwise noted, commercially available reagents were used without further purification. All reactions were performed in oven-dried glassware and monitored by thin layer chromatography (TLC) on silica gel (Merck 60 F254 plates), using either UV light (254 nm) or sulfuric acid stain for compound detection. Flash chromatography was developed using silica gel (230–400 mesh).

^{1}H and ^{13}C NMR spectra were obtained at 25 °C using a Bruker UltraShield 14.1 T with shim Boss II (Probe multinuclear Bruker Smart Probe BBFO 5 mm) at 600.13 MHz and 150.91 MHz, respectively. HSQC and COSY spectra were unambiguously used to aid peak assignments in ^{1}H and ^{13}C NMR.

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2.2. Synthesis of 1,2:3,4-Di-O-isopropylidene-α-D-galactohexodialdo-1,5-pyranose (1)

Compound **1** was prepared from 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose in dimethyl sulfoxide and toluene with pyridine, phosphoric acid, and *N*,*N*′-dicyclohexylcarbodiimide according to already known procedures [5].

2.3. Synthesis of Glycodrugs

To a solution of **1** (1.2 mmol) in anhydrous DCM (14 mL) were added the arylamine (1 eq.) and molecular sieves (4 Å MS). The reaction mixture was stirred for 24 h at reflux. The mixture was filtered and concentrated under reduced pressure.

The residue (**2**) was dissolved in 7 mL of anhydrous isopropanol and $NaBH_4$ was added (1 eq.) this suspension was stirred at room temperature for 24 h. After adding DCM (35 mL), the reaction mixture was filtered and washed with water (3 × 12 mL), the resulting organic phase was dried over $NaSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using solvent mixtures yielding products **3a** and **3b**.

3. Results and Discussion

We synthesized 6-*N*-galactosyl derivatives of p-aminobenzoate using a two-step methodology in good yields (Figure 1).

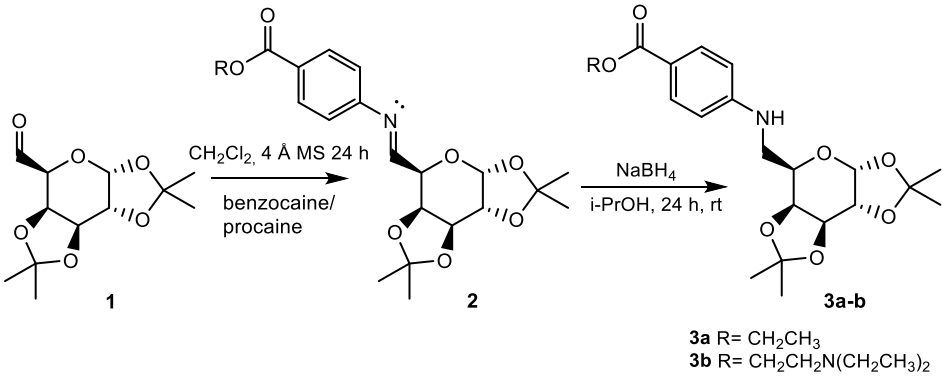

Figure 1. Synthetic route developed for the synthesis of novel p-aminobenzoate glycodrugs.

The oxidation of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose with DMSO/DCC yielded the corresponding galactosyl aldehyde. This aldehyde subsequently reacted with arylamines (benzocaine or procaine) in dichloromethane, forming the Schiff bases. The imine functional group was then reduced with $NaBH_4$ in isopropanol. The resulting galactosyl derivatives of benzocaine (**3a**) and procaine (**3b**) were carefully purified (overall yields: 54 and 52% respectively) and subsequently fully characterized using NMR spectroscopy (Figure 2).

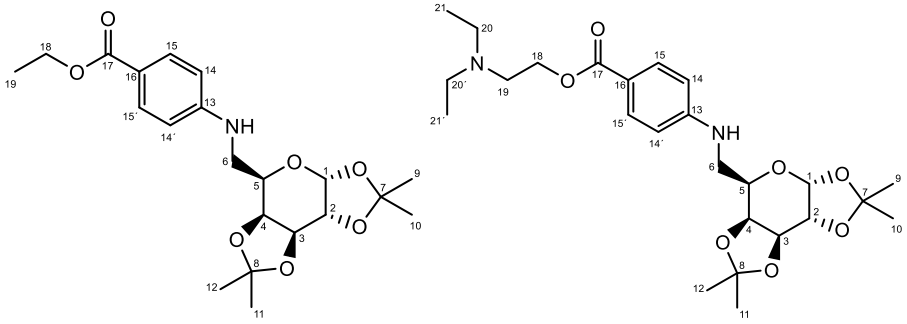

Figure 2. Description and numbering of the novel products obtained: **3a** and **3b**.

At first, the gHSQC NMR spectra enable the rapid identification of the obtained products. The characteristic signals of the molecule were easily identified (Figure 3).

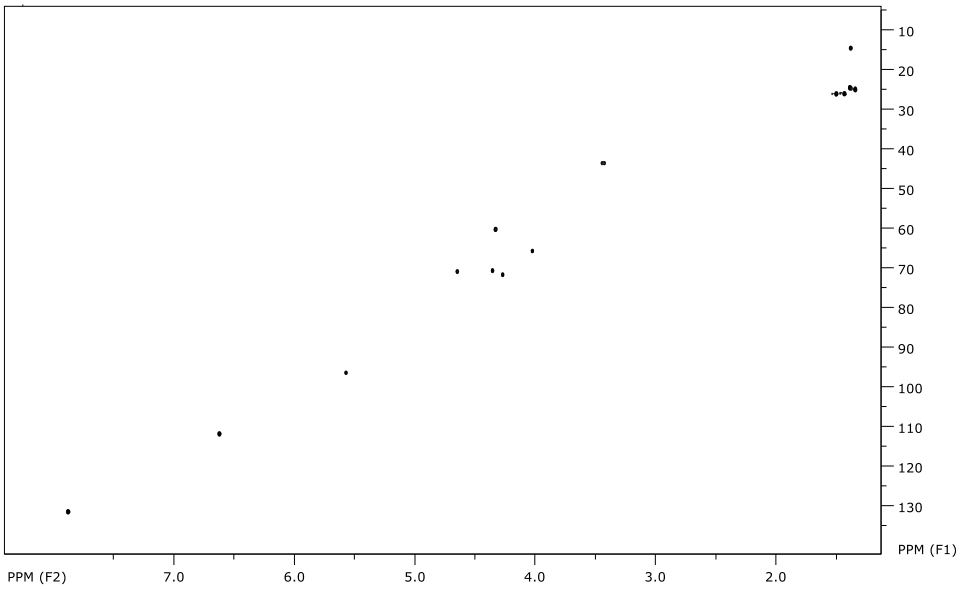

Figure 3. gHSQC spectra of the benzocaine derived glycodrug (**3a**).

The signals of the sugar moiety were as expected, comprising four CH_3 signals corresponding to the acetal protecting groups, four CH signals from the carbohydrate ring, one signal from the anomeric center, and one CH_2-N methylene signal. Additionally, the presence of p-aminobenzoate derivatives in the glycodrug structure was confirmed by the aromatic and ethyl signals. A comprehensive description of the analytical data extracted from the ^1H and ^{13}C NMR spectra is provided herein.

3a. Rf: 0.55 (Hexane/ethyl acetate 7:3); ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.7 Hz, 2H, H15 and 15′), 6.62 (d, J = 8.7 Hz, 2H, H14 and 14′), 5.57 (d, J = 5.0 Hz, 1H, H1), 4.65 (dd, J = 8.0, 2.4 Hz, 1H, H3), 4.37–4.31 (m, 3H, H2 and H18), 4.27 (dd, J = 7.9, 1.6 Hz, 1H, H4), 4.04–4.00 (m, 1H, H5), 3.43 (qdd, J = 13.2, 7.8, 4.6 Hz, 2H, H6), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.38 (d, J = 3.3 Hz, 6H CH_3 and H19), 1.34 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$); δ 166.86 (C17), 151.81 (C13), 131.48 (C15 and C15′), 119.03 (C16), 111.83 (C14 and C14′), 109.57, 108.80 (C7, C8), 96.42 (C1), 71.63 (C4), 70.83 (C3), 70.59 (C2), 65.65 (C5), 60.21(C18), 43.48 (C6), 26.01, 25.96, 24.94, 24.43 (C9, C10, C11, C12) 14.46 (C19).

3b. Rf: 0.46 (Dichloromethane/methanol 10:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H, H15 and 15′), 6.62 (d, J = 8.7 Hz, 2H, H14 and 14′), 5.57 (d, J = 5.0 Hz, 1H, H1), 4.65 (dd, J = 8.0, 2.2 Hz, 1H, H3), 4.42 (t, J = 5.7 Hz, 2H, H18), 4.35 (dd, J = 5.0, 2.4 Hz, 1H, H2), 4.29–4.25 (m, 1H, H4), 4.02 (m, 1H, H5), 3.43 (ddd, J = 12.6, 7.9, 4.9 Hz, 2H, H6), 2.96–2.92 (m, 2H, H19), 2.75–2.71 (m, 4H, H20 and H20′), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.14 (t, J = 7.3 Hz, 6H, H21 and H21′); ^{13}C NMR (126 MHz, $CDCl_3$); δ 166.68 (C17), 151.99 (C13), 131.59 (C15 and C15′), 118.49 (C16), 111.86 (C14 and C14′), 109.58, 108.80 (C7, C8), 96.42 (C1), 71.62 (C4), 70.82 (C3), 70.58 (C2), 65.61 (C5), 62.03 (C18), 50.88 (C19), 47.75 (C20 and C20′), 43.45 (C6), 26.01, 25.94, 24.93, 24.43, (C9, C10, C11, C12), 11.64 (C21 and C21′).

4. Conclusions

We developed a synthetic methodology to prepare glycodrugs derived from benzocaine and procaine. D-galactose substituted at the C6 position with p-aminobenzoate derivatives were obtained in good yields following a two-step process. The products were identified and characterized by NMR spectroscopy. In the future, we plan to remove the acetal protective groups and conduct preliminary biological assays.

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Conflicts of Interest: The authors declare no conflicts of interest.

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