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Research paper

Synthesis and evaluation of antibacterial and antitumor activities of new galactopyranosylated amino alcohols

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ABSTRACT

Three series of D-galactose derivatives linked to a lipophilic aminoalcohol moiety were synthesized and their antibacterial activity was evaluated against *Mycobacterium tuberculosis* and representative species of Gram positive and Gram negative bacteria. Five out of the thirteen tested compounds displayed activity against *M. tuberculosis*, with a minimal inhibitory concentration (MIC) of 12.5 μg/mL and seven compounds were active against the four bacterial strains tested. The best results were obtained for amino alcohols **10** and **11** against *Staphylococcus epidermidis* (MIC = 2 μg/mL). The antitumor activity was evaluated against three tumor cell lines (MCF-7, HeLa and MO59J) and compared to the normal cell line GM07492A. The results showed that the lowest IC_{50} values were observed for the amino alcohol **16** against MCF-7 (11.9 μM) and MO59J (10.0 μM).

1. Introduction

Due to their chemical and biological applications amino alcohols are an important class of organic molecules. These compounds have been shown to display activity in Alzheimer's disease [1], inflammatory processes [2], or against protozoal diseases [3]. Furthermore, another important biological activity related to this class of compounds is their antibacterial effect [4]. Lipophilic aromatic and heteroaromatic amino alcohols carrying an octyl chain in their structure (**I**, Fig. 1) showed activity against *Staphylococcus epidermidis* and *Staphylococcus aureus* [5]. Salmi and co-workers reported the synthesis of hydroxyalkylaminosteroid derivatives (**II**, Fig. 1) having moderate to excellent activities against *S. aureus* and *Staphylococcus faecalis* [6].

Mycobacterium tuberculosis is an important pathogenic bacteria highly resistant to several available antimicrobials. Its cell wall is made of complex lipids and polysaccharides, in which the galactose and the arabinose units are predominant. As a consequence, glycosylated amino alcohols are good candidates as antitubercular drugs, and previous works have shown that bis-xylofuranosylated, glycofuranosylated, arabinofuranosylated and galactopyranosylated amino alcohols display good *in vitro* antitubercular and immunosuppressive activities [7–13]. A structure activity relationship between the lipophilicity and the antibacterial activity of *N*-glycosylated aminoalcohols can be established [10] and there could be a synergistic effect between lipophilicity and the presence of an amino alcohol group. Our research group has described in a previous work the synthesis of amino alcohol derivatives of galactopyranose (**III** and **IV**, Fig. 1), with good anti-tubercular (anti-TB) activity (MIC below 12.5 μg/mL) [8,10]. The glycosylation of the *N*-alkylated amino alcohols increased their activity, suggesting that the carbohydrate moiety is important for the anti-TB activity (**V**, Fig. 1) [10]. In continuation of our efforts towards the development of new bioactive compounds, we report here the preparation and the evaluation of the antibacterial and antitumoral activities of new *N*-alkylated amino alcohols derivd from D-galactopyranose.

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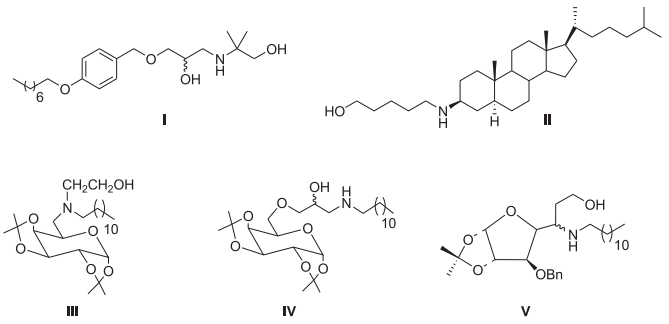

Fig. 1. Chemical structures of antibacterial amino alcohols.

2. Experimental

2.1. General methods

2.1.1. Chemistry

IR spectra were recorded using a BOMEM-FTIR MB102 spectrometer (AABB Bomem Inc., Quebec, Canada). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DRX300 spectrometer (Bruker Corporation, Billerica, MA, USA). Thin-layer chromatography (TLC) was performed on silica gel sheets (Silica Gel F254; Merck, Whitehouse Station, NK, USA), visualized with iodine vapor, and/or ethanolic H_2SO_4 solution. Column chromatography was carried out on silica gel 60 (E. Merck 70–230 mesh). Solvents were purchased from Vetec Química (Vetec, Xerem, RJ, Brazil) and were distilled prior to use. Reagents were purchased from Aldrich (Sigma Aldrich, Saint Louis, MI, USA) and used without further purification. LogP was calculated using Chemdraw Ultra 12 software (trial version).

2.1.1.1. Preparation of 6-O-[(2R,S)-2,3-epoxypropyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***7***. To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (18.4 mmol) in THF (25 mL) were added tetrabutylammonium bromide (5.3 mmol) and 40% w/w aqueous sodium hydroxide (40 mL). The mixture was magnetically stirred at 0 °C for 40 min. Racemic epichlorohydrin (32.3 mmol) was slowly added to this mixture and stirring was continued at 0 °C for 1 h, then at room temperature (30 °C) for 23 h. The progress of the reaction was monitored by thin layer chromatography (1:1 EtOAc/hexane). After completion of the reaction, the mixture was extracted twice with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulphate, filtered and evaporated to dryness furnishing the compound **3** as a brown oil (27.08 mmol, 94% yield) which was used without further purification.

2.1.1.2. General procedure for the preparation of the glycosylated derivatives ***8***–***14***. To a solution of compound **7** (1.0 mmol) in EtOH (5 mL) were added tetrabutylammonium bromide (0.01 mmol) and an ethanolic solution of *N*-alkyl amino alcohol (1.2 mmol/5 mL). The reaction mixture was stirred at room temperature (30 °C) for 24 h and concentrated under reduced pressure. The crude product was chromatographed on silica gel (CH_2Cl_2/MeOH) to furnish the desired compounds **8**–**14**.

2.1.1.3. General procedure for the preparation of the glycosylated derivatives ***15***–***20***. To a solution of compound **7** (1.0 mmol) in EtOH (5 mL) were added ammonium chloride (0.01 mmol) and an ethanolic solution of *N*-alkyl diamine (1.2 mmol/5 mL). The mixture was stirred under reflux for 24 h and concentrated under reduced pressure. The crude product was chromatographed on silica gel (CH_2Cl_2/MeOH) to furnish the desired compounds **15**–**20**.

2.1.2. Spectral data

2.1.2.1. 6-O-[(2R,S)-2,3-epoxypropyl]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **7**. Oil, Yield 96%, R_f: 0.69 (EtOAc/hexane 1:1); IR (ν, cm^{-1}, KBr): 2995, 2938, 1383, 1045; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 5.51 (d, $J = 3.7$ Hz, H1, *R*-,*S*-), 4.58 (d, $J = 5.7$ Hz, H3, *R*-,*S*-), 4.24–4.28 (m, H2 and H4, *R*-,*S*-), 3.96 (s, H5, *R*-,*S*-), 3.40–3.71 (m, H6, H1′, *R*-,*S*-), 3.14 (s, H2′, *R*-,*S*-), 2.59–2.76 (s, H3′, *R*-,*S*-), 1.52 and 1.42 (s, $C(CH_3)_2$), 1.31 (s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 24.6–26.2 ($C(CH_3)_2$, *R*-,*S*-), 44.5 and 2x50.9 (C3′ and 2xC2′, *R*-,*S*-), 59.3, 66.9, 67.2, 70.2, 70.4, 70.7, 70.8, 71.3, 72.0, 72.3 (C2, 2xC3, 2xC4, 2xC5, C6 and 2xC1′, *R*-,*S*-), 96.5 (C1, *R*-,*S*-), 108.7 and 109.4 ($C(CH_3)_2$, *R*-,*S*-).

2.1.2.2. 6-O-[(2R,S)-N-(2-hydroxyethyl-N-octylamino)propan-2-ol]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***8***. Oil; Yield, 51%; R_f: 0.42 (CH_2Cl_2/MeOH 9:1); IR (ν, cm^{-1}, KBr): 3426, 2938, 2854, 1373, 1186; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 5.52 (d, $J = 5.0$ Hz, H1, *R*-,*S*-), 4.60 (d, $J = 6.8$ Hz, H3, *R*-,*S*-), 4.22–4.31 (m, H2 and H4, *R*-,*S*-), 3.84–3.97 (m, H5 and H2′, *R*-,*S*-), 3.40–3.66 (m, H6, H1′ and H5′, *R*-,*S*-), 2.89 (s, OH, *R*-,*S*-), 2.49–2.67 (m, H3′, H4′ and NCH_2, *R*-,*S*-), 1.53, 1.43 (s, $C(CH_3)_2$, *R*-,*S*-), 1.32 (s, $C(CH_3)_2$, *R*-,*S*-), 1.25 (s, CH_2 aliph, *R*-,*S*-), 0.87 (t, $J = 6.9$ Hz, 3H, CH_3, *R*-,*S*-); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 14.2 (CH_3, *R*-,*S*-), 22.7, 24.6, 25.0, 2x26.1, 27.1, 27.5, 29.4, 29.6, 29.8, 31.9 (CH_2 aliph and $C(CH_3)_2$, *R*-,*S*-), 55.6, 56.7, 57.1, 57.2, 59.7, 66.8, 67.1, 68.0, 68.4, 70.1, 70.6, 70.7, 70.8, 71.3, 73.9, 74.2 (NCH_2, C3′ C4′, C5′, C1′, C2′, C6, C5, C4, C3, C2, *R*-,*S*-), 96.5 (C1, *R*-,*S*-), 108.8 and 109.5 ($C(CH_3)_2$, *R*-,*S*-).

2.1.2.3. 6-O-[(2R,S)-N-(2-hydroxyethyl-N-decylamino)propan-2-ol]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***9***. Oil; Yield, 61%; R_f: 0.68 (CH_2Cl_2/MeOH 9:1); IR (ν, cm^{-1}, KBr): 3356, 2911, 2872, 1448, 1051; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 5.52 (d, $J = 4.8$ Hz, H1, *R*-,*S*-), 4.60 (d, $J = 7.4$ Hz, H3, *R*-,*S*-), 4.23–4.30 (m, H2 and H4, *R*-,*S*-), 3.87–3.98 (m, H2′ and H5, *R*-,*S*-), 3.40–3.65 (m, H6, H1′ and H5′, *R*-,*S*-), 3.06 (s, OH, *R*-,*S*-), 2.50–2.68 (m, H3′, H4′ and NCH_2, *R*-,*S*-), 1.52, 1.42 (s, $C(CH_3)_2$, *R*-,*S*-), 1.31 (s, $C(CH_3)_2$, *R*-,*S*-), 1.24 (s, CH_2 aliph, *R*-,*S*-), 0.86 (t, $J = 5.9$ Hz, CH_3, *R*-,*S*-); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 14.2 (CH_3, *R*-,*S*-), 22.8, 24.6, 25.1, 26.1, 26.2, 27.1, 27.5, 29.4, 29.7, 29.8, 32.0 (CH_2 aliph and $C(CH_3)_2$, *R*-,*S*-), 55.6, 56.8, 57.2, 57.3, 59.7, 66.8, 67.1, 68.0, 68.3, 70.1, 70.6, 70.7, 70.8, 71.4, 73.9, 74.1 (NCH_2, C3′ C4′, C5′, C1′, C2′, C6, C5, C4, C3, C2, *R*-,*S*-), 96.5 (C1, *R*-,*S*-), 108.8 and 109.5 ($C(CH_3)_2$, *R*-,*S*-).

2.1.2.4. 6-O-[(2R,S)-N-(2-hydroxyethyl-N-dodecylamino)propan-2-ol]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***10***. Oil; Yield, 61%; R_f: 0.55 (CH_2Cl_2/MeOH 9:1); IR (ν, cm^{-1}, KBr): 3343, 3356, 2930, 2842, 1399, 1263; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 5.52 (d, $J = 4.8$ Hz, H1, *R*-,*S*-), 4.60 (d, $J = 7.5$ Hz, H3, *R*-,*S*-), 4.24–4.29 (m, H2 and H4, *R*-,*S*-), 3.87–3.97 (m, H5 and H2′, *R*-,*S*-), 3.40–3.66 (m, H6, H1′ and H5′, *R*-,*S*-), 3.03 (s, OH, *R*-,*S*-), 2.51–2.69 (m, H3′, H4′ and NCH_2, *R*-,*S*-), 1.52, 1.43 (s, $C(CH_3)_2$, *R*-,*S*-), 1.31 (s, $C(CH_3)_2$, *R*-,*S*-), 1.24 (s, CH_2 aliph, *R*-,*S*-), 0.86 (t, $J = 5.3$ Hz, 3H, CH_3 aliph, *R*-,*S*-); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 14.2 (CH_3, *R*-,*S*-), 22.8, 24.6, 25.0, 2x26.1, 27.0, 27.5, 29.4, 2x29.7, 32.0 (CH_2 aliph and $C(CH_3)_2$, *R*-,*S*-), 55.6, 56.8, 57.1, 57.2, 2x59.6, 66.8, 67.1, 67.9, 68.3, 70.1, 2x70.6, 70.8, 71.3, 73.9, 74.1 (NCH_2, C3′ C4′, C5′, C1′, C2′, C6, C5, C4, C3, C2, *R*-,*S*-), 96.4 (C1, *R*-,*S*-), 108.8 and 109.5 ($C(CH_3)_2$, *R*-,*S*-).

2.1.2.5. 6-O-[(2,S)-N-(2-hydroxyethyl-N-dodecylamino)propan-2-ol]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose ***10a***. Oil; Yield, 69%; R_f: 0.55 (CH_2Cl_2/MeOH 9:1); IR (ν, cm^{-1}, KBr): 3343, 3356, 2930, 2842, 1399, 1263; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 5.54 (d, $J = 4.8$ Hz, H1), 4.61 (d, $J = 6.2$ Hz, H3), 4.22–4.31 (m, H2 and H4),