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Article

Synthesis, Antibacterial and Antitubercular Evaluation of Cardanol and Glycerol-Based β-Amino Alcohol Derivatives

Bhaskar R. Manda,[a] Avvari N. Prasad,[a] Narendar R. Thatikonda,[a] Valdemar Lacerda Jr.,[b] Layla R. Barbosa,[b] Heloa Santos,[b] Wanderson Romão,[b] Fernando R. Pavan,[c] Camila M. Ribeiro,[c] Edson A. dos Santos,[d] Maria R. Marques,[d] Dênis P. de Lima,[a] Ana C. Micheletti*[,a] and Adilson Beatriz*[,a]

[a]*Instituto de Química (INQUI), Universidade Federal do Mato Grosso do Sul, Av. Senador Felinto Müller, 1555, 79074-460 Campo Grande-MS, Brazil*

[b]*Departamento de Química, Universidade Federal do Espírito Santo (UFES), 29075-910 Vitória-ES, Brazil*

[c]*Faculdade de Ciências Farmacêuticas, Universidade Estadual Paulista, 14801-902 Araraquara-SP, Brazil*

[d]*Instituto de Biociências (INBIO), Universidade Federal de Mato Grosso do Sul, Cidade Universitária, s/n, CP 549, 79070-900 Campo Grande-MS, Brazil*

The synthesis of novel amino alcohol derivatives based on cardanol and glycerol were achieved in good yields and characterized by ^{1}H and ^{13}C NMR (nuclear magnetic resonance) and MS (mass spectrometry). In addition, we evaluated the *in vitro* antimicrobial activity against Gram-positive (*Staphylococcus aureus*, standard and clinical strains), Gram-negative (*Escherichia coli*) and *M. tuberculosis* bacterial strains. The bioassay results indicated that four compounds showed activity against *S. aureus*, including the clinical resistant strain, with MIC (minimum inhibitory concentration) ranging from 3.90 to 15.60 μg mL^{-1} and *M. tuberculosis*, with MIC_{90} (minimum inhibitory concentration required to inhibit the growth of 90% of organisms) ranging from 3.18 to 7.36 μg mL^{-1}.

Keywords: CNSL, cardanol, amino alcohols, epoxide ring opening, antimicrobial activity

Introduction

The synthesis of fine chemicals from natural renewable resources has received great interest in synthetic community and is becoming a significant and challenging theme for researchers of both the academic and industrial sectors. Among the renewable materials, cardanol has attracted considerable attention due to its unique nature.[1] Cardanol is a low cost, naturally occurring renewable non-isoprenoic phenolic lipid-mixture of cashew nut shell liquid (CNSL). The structural benefits of cardanol are carrying reactive phenolic group and hydrophobic alkyl/alkenyl side chain at *meta*-position of phenolic group. With these unique structural features, cardanol and its derivatives are renowned amphiphilic building blocks and precursors of high-value fine chemicals and supramolecular structures. Its derivatives present many biological activities such as: fungicidal, bactericidal, molluscicidal, larvicidal, anti-inflammatory, antioxidant and, towards serious disorders like cancer and obesity.[2-9] It is also described in the literature in recent years, that cardanol frameworks are involved to build phenolic resins,[10-12] bio-based polymers,[13] epoxy curing resins,[14-16] reactive diluents,[17,18] and fluorescent compounds.[19,20] Similarly, glycerol is another important renewable material used in the synthesis of higher value-added fine chemicals through green chemistry procedures in the last years. It may be applied, for instance, to generate hydrogen gas,[21] potential fuel additive,[22] ethanol,[23] acrolein and,[24,25] epichlorohydrin.[26] Accordingly, studies aiming to new industrial applications for glycerol are of great industrial, social, economic, and environmental interest.[27,28]

*e-mail: anamicheletti@gmail.com; adilson.beatriz@ufms.br

Cardanol and glycerol can be starting materials to prepare β-amino alcohols which is a vital interesting class of organic intermediates due to their abundant existence in nature and they are useful in the preparation of wide range of biologically active natural and synthetic frameworks, pharmaceuticals (e.g. β-blockers), unnatural β-amino acids, pesticides and chiral auxiliaries.[29-32] Additionally, β-amino alcohols have many applications as antibiotics, anti-bacterial drugs and, steroids.[33] One of the most classical approaches toward the synthesis of β-amino alcohols is the direct ring opening by amines of epoxides. The existing protocols of β-amino alcohols have been achieved by ring opening of epoxides with simple amines (aromatic/aliphatic) in the presence of various catalysts including metals such as Cu,[34,35] Fe,[30,36,37] Zn,[38] metal tiflates,[39,40] metal amides,[41] metal alkoxides,[42,43] and other metal salts,[44-48] microwave assisted montmorillonite clay,[49] amberlist-15,[50] zirconia-based materials,[33,51] ionic liquids,[52] and few organic reagents have also been explored for β-amino alcohols namely, DABCO (1,4-diazabicyclo[2.2.2]octane),[53] β-cyclodextrin,[54] and Bu_3P.[55] These protocols were significant, however, some of them have some drawbacks including the use of expensive chemicals, air and moisture sensitive reagents or catalysts, high pressures, inert atmospheric conditions, the requirement for protracted work-up procedures and so on. Therefore, there is a demand to develop new and efficient methods for the preparation of β-amino alcohols under mild conditions.

Considering these significant characteristics of renewable materials such as cardanol and glycerol as well as ample biological activities of lipophilic β-amino alcohols, our research group aims to combine their properties into single compounds with their unique qualities. Lipophilic character of some antibiotic has a significant influence on the antibacterial activity,[56-58] which prompted us to the design of new biologically active molecules. Herein we report a new strategy for the synthesis of β-amino alcohols by reacting cardanol epoxide with diverse amines (aliphatic/aromatic) under catalyst-free and mild conditions in which ethanol is used as the reaction medium. Subsequently, these synthesized amino alcohols were subjected to antimicrobial evaluation.

Experimental

General methods

All the starting materials employed were obtained from commercial sources and used as received. Catalytic hydrogenation was carried out in a Parr Hydrogenation apparatus, according to our previously reported method.[19] Thin layer chromatography (TLC) analyses were performed on glass plates coated with silica gel 60 F_{254}. The plates were visualized using UV light (254 nm) and/or iodine. Column chromatography was performed on silica gel (60 × 120 mesh) into a glass column. ^1H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a Bruker Avance DPX-300 spectrometer using TMS (tetramethylsilane) as an internal standard. Chemical shifts (δ) were recorded in ppm with respect to TMS and coupling constants (J) were given in hertz (Hz). High-resolution mass spectrometry (HRMS) coupled to positive-ion electrospray ionization (ESI) mode, ESI(+), were performed on a Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR MS, model 9.4 T Solarix, Bruker Daltonics Bremen, Germany).

Experimental procedure

To the solution of cardanol epoxide[19] (1 mmol) in ethanol, amine (1.5 mmol) was added at room temperature and stirred under reflux for 8-12 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature and ethanol was removed under vacuum. Then the reaction mixture was partitioned between water (30 mL) and ethyl acetate (40 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 40 mL) and dried over Na_2SO_4. Solvent was removed in vacuum and the crude compound was purified by column chromatography using 20-50% of EtOAc in hexane as eluent to afford the desired amino alcohol derivative of cardanol. To prepare compound **2d**, 2.1 equivalents of cardanol epoxide (**1**) were used.

^1H NMR, ^{13}C NMR, and MS data of isolated compounds

1-Morpholino-3-(3-pentadecylphenoxy)propan-2-ol (**2a**)

Yield: 87%; light yellow solid; mp 45-47 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J 7.74 Hz, 1H), 6.81-6.70 (m, 3H), 4.11 (sextet, J 4.97 Hz, 1H), 3.98 (d, J 4.97 Hz, 2H), 3.77-3.67 (m, 4H), 3.22 (bs, 1H), 2.72-2.42 (m, 8H), 1.60 (quintet, J 7.31 Hz, 2H), 1.37-1.19 (m, 24H), 0.88 (t, J 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 144.6, 129.1, 121.2, 114.8, 111.3, 70.0, 66.9, 65.5, 61.1, 53.7, 36.0, 31.9, 31.3, 29.6, 29.5, 29.4, 29.3, 22.6, 14.1. HRMS (ESI): $C_{28}H_{49}NO_3$ calcd. 448.37803; m/z $[M + H]^+$ found 448.37852.

1-(3-Pentadecylphenoxy)-3-(piperidin-1-yl)propan-2-ol (**2b**)

Yield: 83%; light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J 7.89 Hz, 1H), 6.80-6.70 (m, 3H),

4.13-3.91 (m, 3H), 3.60 (bs, 1H), 2.67-2.32 (m, 8H), 1.66-1.41 (m, 8H), 1.35-1.17 (m, 24H), 0.89 (t, *J* 7.02 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 144.5, 129.0, 121.0, 114.8, 111.4, 70.3, 65.3, 61.2, 54.7, 36.0, 31.9, 31.3, 29.6, 29.5, 29.4, 29.4, 29.3, 26.0, 24.2, 22.6, 14.1. HRMS (ESI): $C_{29}H_{51}NO_2$, calcd. 446.39900; *m/z* $[M + H]^+$ found 446.39926.

1-(3-Pentadecylphenoxy)-3-(pyrrolidin-1-yl)propan-2-ol (**2c**)

Yield: 85%; light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, *J* 7.75 Hz, 1H), 6.80-6.68 (m, 3H), 4.17-4.06 (m, 1H), 4.02-3.90 (m, 2H), 3.80 (bs, 1H), 2.90-2.49 (m, 8H), 1.95-1.74 (m, 4H), 1.67-1.51 (m, 2H), 1.39-1.16 (m, 24H), 0.87 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 144.5, 129.0, 121.0, 114.7, 111.3, 70.2, 67.2, 58.7, 54.2, 35.9, 31.8, 31.3, 29.6, 29.6, 29.6, 29.6, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 23.5, 22.6, 14.0. HRMS (ESI): $C_{28}H_{49}NO_2$ calcd. 432.38332; *m/z* $[M + H]^+$ found 432.38361.

3,3'-(Piperazine-1,4-diyl)bis(1-(3-pentadecylphenoxy) propan-2-ol) (**2d**)

Yield: 64%; white solid; mp 54-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* 7.80 Hz, 2H), 6.81-6.68 (m, 6H), 4.09 (dd, *J* 4.82 and 4.68 Hz, 2H), 3.98 (d, *J* 4.82 Hz, 4H), 2.81-2.45 (m, 16H), 1.59 (quintet, *J* 7.45 Hz, 4H), 1.39-1.15 (m, 48H), 0.88 (t, *J* 6.87 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 144.7, 129.1, 121.2, 114.9, 111.4, 70.1, 65.6, 60.5, 53.4, 53.3, 36.0, 31.9, 31.4, 29.7, 29.5, 29.4, 22.7, 14.1.

1-(4-(4-Nitrophenyl)piperazin-1-yl)-3-(3-pentadecyl-phenoxy)propan-2-ol (**2e**)

Yield: 53%; yellow solid; mp 49-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* 9.35 Hz, 2H), 7.20 (t, *J* 7.45 Hz, 1H), 6.86-6.66 (m, 5H), 4.15 (quintet, *J* 4.09 Hz, 1H), 4.04-3.99 (d, *J* 4.97 Hz, 2H), 3.51-3.41 (m, 4H), 3.24 (bs, 1H), 2.88-2.78 (m, 2H), 2.73-2.53 (m, 6H), 1.60 (quintet, *J* 7.02 Hz, 2H), 1.40-1.21 (m, 24H), 0.88 (t, *J* 6.72 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 154.7, 144.7, 138.7, 129.2, 125.9, 121.3, 114.8, 112.8, 111.4, 70.0, 66.0, 60.6, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1.

1-(Diisopropylamino)-3-(3-pentadecylphenoxy)propan-2-ol (**2f**)

Yield: 91%; light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* 7.89 Hz, 1H), 6.80-6.70 (m, 3H), 4.05-3.88 (m, 3H), 3.09 (sept, *J* 6.58 Hz, 2H), 2.74 (d, *J* 3.51 Hz, 1H), 2.60-2.42 (m, 3H), 1.59 (quintet, *J* 6.56 Hz, 2H), 1.35-1.17 (m, 24H), 1.09 (d, *J* 6.58 Hz, 6H), 1.03 (d, *J* 6.43 Hz, 6H), 0.87 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 144.4, 129.0, 120.9, 114.7, 111.3, 70.5, 65.4, 48.5, 47.3, 35.9, 31.8, 31.3, 31.8, 31.3, 29.6, 29.5, 29.4, 29.2, 22.6, 22.0, 19.4, 14.0. HRMS (ESI): $C_{30}H_{55}NO_2$ calcd. 462.43056; *m/z* $[M + H]^+$ found 462.43011.

1-((4-Methoxyphenyl)amino)-3-(3-pentadecylphenoxy) propan-2-ol (**2g**)

Yield: 64%; light yellow solid; mp 50-51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* 7.89 Hz, 1H), 6.84-6.71 (m, 5H), 6.66 (d, *J* 8.92 Hz, 2H), 4.28-4.21 (m, 1H), 4.09-3.98 (m, 2H), 3.75 (s, 3H), 3.39 (dd, *J* 12.79 and 4.20 Hz, 1H), 3.25 (dd, *J* 12.79 and 7.24 Hz, 1H), 2.57 (t, *J* 7. 89 Hz, 2H), 2.26 (s, 3H), 1.60 (quintet, *J* 6.43 Hz, 2H), 1.37-1.20 (m, 24H), 0.88 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 144.8, 129.2, 121.4, 117.6, 115.2, 115.0, 114.8, 111.4, 69.6, 69.5, 68.5, 58.4, 55.7, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1.

1-(3-Pentadecylphenoxy)-3-(*p*-tolylamino)propan-2-ol (**2h**)

Yield: 76%; light yellow solid; mp 49-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* 7.75 Hz, 1H), 7.01 (d, *J* 8.04 Hz, 2H), 6.84-6.71 (m, 3H), 6.62 (d, *J* 8.33 Hz, 2H), 4.27-4.21 (m, 1H), 4.09-4.01 (m, 2H), 3.42 (dd, *J* 12.94 and 4.24 Hz, 1H), 3.28 (dd, *J* 12.94 and 7.16 Hz, 1H), 3.01-2.85 (bs, 1H), 2.58 (t, *J* 7.60 Hz, 2H), 2.26 (s, 3H), 1.61 (quintet, *J* 6.28 Hz, 2H), 1.37-1.23 (m, 24H), 0.89 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 145.7, 144.8, 129.8, 129.2, 127.3, 121.5, 114.7, 113.5, 111.5, 70.0, 68.8, 47.0, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 20.4, 14.1. HRMS (ESI): $C_{31}H_{49}NO_2$ calcd. 468.3853; *m/z* $[M + H]^+$ found 468.3836.

1-(3-Pentadecylphenoxy)-3-(*o*-tolylamino)propan-2-ol (**2i**)

Yield: 67%; light yellow solid; mp 42-43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.07 (m, 3H), 6.92-6.68 (m, 5H), 4.75-4.27 (m, 3H), 3.55-3.30 (m, 2H), 2.59 (t, *J* 7.60 Hz, 2H), 2.25 (s, 3H), 1.62 (quintet, *J* 7.16 Hz, 2H), 1.41-1.22 (m, 24H), 0.91 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 144.79, 143.8, 130.5, 129.2, 127.2, 121.4, 119.8, 114.7, 111.4, 70.0, 68.0, 48.5, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 17.4, 14.1. HRMS (ESI): $C_{31}H_{49}NO_2$ calcd. 468.3833; *m/z* $[M + H]^+$ found 468.3836.

1-((4-Bromophenyl)amino)-3-(3-pentadecylphenoxy) propan-2-ol (**2j**)

Yield: 69%; light yellow solid; mp 66-68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 3H), 6.82-6.68 (m, 3H), 6.53 (d, *J* 8.77 Hz, 2H), 4.26-4.17 (m, 1H), 4.09-3.96 (m, 2H), 3.37 (dd, *J* 12.72 and 4.02 Hz, 1H), 3.24 (dd, *J* 12.72 and 7.16 Hz, 1H), 2.55 (t, *J* 7.60 Hz, 2H), 1.58 (quintet,

J 6.72 Hz, 2H), 1.34-1.14 (m, 24H), 0.86 (t, *J* 7.31 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 147.1, 144.9, 131.9, 129.3, 121.6, 114.8, 111.5, 109.6, 69.9, 68.7, 46.5, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1. HRMS (ESI): $C_{30}H_{46}BrNO_2$ calcd. 532.2785; *m/z* $[M + H]^+$ found 532.2613.

1-((2-Bromophenyl)amino)-3-(3-pentadecylphenoxy) propan-2-ol (**2k**)

Yield: 70%; light yellow solid; mp 39-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* 7.9 and 1.30 Hz, 1H), 7.25-7.15 (m, 2H), 6.86-6.69 (m, 4H), 6.61 (td, *J* 7.85 and 1.30 Hz, 1H), 4.77 (bs, 1H), 4.32-4.25 (m, 1H), 4.13-4.04 (m, 2H), 3.54-3.32 (m, 2H), 2.64 (bs, 1H), 2.59 (t, *J* 7.60 Hz, 2H), 1.62 (quintet, *J* 7.02 Hz, 2H), 1.40-1.22 (m, 24H), 0.90 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 144.8, 132.5, 129.2, 128.5, 121.5, 118.3, 114.7, 111.5, 111.4, 110.2, 69.8, 68.6, 46.4, 35.9, 31.8, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1. HRMS (ESI): $C_{30}H_{46}BrNO_2$ calcd. 532.27870; *m/z* $[M + H]^+$ found 532.27847.

1-((4-Chlorophenyl)amino)-3-(3-pentadecylphenoxy) propan-2-ol (**2l**)

Yield: 78%; light yellow solid; mp 69-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* 7.75 Hz, 1H), 7.13 (d, *J* 8.48 Hz, 2H), 6.84-6.70 (m, 3H), 6.59 (d, *J* 8.62 Hz, 2H), 4.29-3.99 (m, 3H), 3.40 (dd, *J* 12.79 and 4.20 Hz, 1H), 3.26 (dd, *J* 12.79 and 7.02 Hz, 1H), 2.58 (t, *J* 7.75 Hz, 2H), 1.60 (quintet, *J* 7.02 Hz, 2H), 1.38-1.21 (m, 24H), 0.88 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 146.7, 144.9, 129.3, 129.1, 121.6, 114.7, 114.3, 111.5, 69.9, 68.8, 46.7, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1. HRMS (ESI): $C_{30}H_{46}ClNO_2$ calcd. 488.3289; *m/z* $[M + H]^+$ found 488.3293.

1-((2-Chlorophenyl)amino)-3-(3-pentadecylphenoxy) propan-2-ol (**2m**)

Yield: 66%; light yellow solid; 40-41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.11 (m, 3H), 6.86-6.64 (m, 5H), 4.33-4.17 (m, 1H), 4.14-4.04 (m, 2H), 3.83-3.70 (m, 1H), 3.48 (dd, *J* 13.0 and 4.60 Hz, 1H), 3.36 (dd, *J* 13.0 and 6.75 Hz, 1H), 2.71 (bs, 1H), 2.60 (t, *J* 7.89 Hz, 2H), 1.63 (quintet, *J* 7.75 Hz, 2H), 1.42-1.21 (m, 24H), 0.91 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 158.2, 144.8, 143.9, 129.2, 127.8, 121.6, 121.5, 119.6, 117.7, 114.8, 111.4, 69.9, 68.6, 68.4, 46.3, 45.9, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1. HRMS (ESI): $C_{30}H_{46}ClNO_2$ calcd. 488.32921; *m/z* $[M + H]^+$ found 488.32898.

1-(3-Pentadecylphenoxy)-3-(phenylamino)propan-2-ol (**2n**)

Yield: 73%; light yellow solid; mp 44-45 °C; ^{1}H NMR (75 MHz, $CDCl_3$) δ 7.20 (t, *J* 7.60 Hz, 3H), 6.84-6.66 (m, 6H), 4.31-4.22 (m, 1H), 4.11-4.02 (m, 2H), 3.45 (dd, *J* 12.0 and 4.39 Hz, 1H), 3.30 (dd, *J* 12.0 and 7.02 Hz, 1H), 3.04 (bs, 1H), 2.58 (t, *J* 7.75 Hz, 2H), 1.61 (quintet, *J* 7.02 Hz, 2H), 1.38-1.22 (m, 24H), 0.89 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 148.0, 144.8, 129.3, 129.2, 121.5, 118.0, 114.7, 113.3, 111.5, 70.0, 68.8, 46.6, 36.0, 31.9, 31.4, 29.7, 29.6, 29.5, 29.3, 22.7, 14.1. HRMS (ESI): $C_{30}H_{47}NO_2$ calcd. 454.36818; *m/z* $[M + H]^+$ found 454.36818.

1-(3-Pentadecylphenoxy)-3-(pyridin-2-ylamino)propan-2-ol (**2o**)

Yield: 82%; light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90-8.80 (m, 1H), 7.62-7.49 (m, 3H), 7.10 (t, *J* 7.45 Hz, 1H), 6.77-6.57 (m, 3H), 4.62-4.02 (m, 7H), 2.51 (t, *J* 7.31 Hz, 2H), 1.61-1.49 (m, 2H), 1.35-1.17 (m, 24H), 0.86 (t, *J* 6.87 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 155.3, 144.7, 141.2, 139.5, 129.2, 121.4, 116.6, 114.7, 112.7, 111.4, 67.8, 66.8, 56.5, 35.9, 31.8, 31.3, 29.6, 29.5, 29.4, 29.3, 29.2, 22.6, 14.0. HRMS (ESI): $C_{29}H_{46}N_2O_2$ calcd. 455.36330; *m/z* $[M + H]^+$ found 455.36312.

Antimicrobial assays

S. aureus and *E. coli*

The 96-well plates were prepared by dispensing 100 μL Mueller-Hinton broth (Sigma-Aldrich) into each well. A stock solution was prepared at a concentration of 2 mg mL^{-1} and serial dilutions were performed to reach a final concentration within 1 to 1000 μg mL^{-1} range, with a 100 μL final volume in each well. For gentamicin, final concentration ranged from 64 to 0.5 μg mL^{-1}. The test organisms used in this study were *S. aureus* (ATCC 25923 and clinical isolates of oxacillin and penicillin G resistant *S. aureus*) and *E. coli* (ATCC 25922). Clinical strain was donated by the Laboratory of Bacteriology of the Center for Clinical Analysis of the UFMS Teaching Hospital, in Campo Grande, Brazil, and assays were performed at Sintmol (Biotechnology Lab of Institute of Chemistry, UFMS). The inoculum was an overnight culture of each bacterial species in Mueller-Hinton agar (Sigma-Aldrich) diluted in saline sterile solution (0.45%) to a concentration of approximately 10^8 CFU mL^{-1}. This solution was diluted 1/10 in saline solution (0.45%) and 5 μL (10^4 CFU mL^{-1}) were added to each well containing the test samples. All experiments were performed in triplicate and the microdilution trays were incubated at 36 °C for 18 h. Then, 20 μL of an aqueous solution (0.5%) of triphenyl tetrazolium chloride (TTC) were added to each well and the trays were again incubated at 36 °C for 2 h. Afterwards, in those wells where bacterial growth did occur, TTC

changed from colorless to red. MIC was defined as the lowest concentration of each substance at which no color change occurred, and was expressed in μg mL^{-1}.

Mycobacterium tuberculosis

The antitubercular activity of all compounds was determined through the resazurin microtiter assay (REMA) methodology according to the procedures described by Palomino *et al*.[59] Stock solutions of the tested compounds were prepared in dimethyl sulfoxide (DMSO) and diluted in Middlebrook 7H9 broth (Difco) supplemented with 10% OADC enrichment (oleic acid, albumin, dextrose and catalase) and using a Precision XS™ (BioTek®), to obtain final drug concentration ranging from 0.09 to 25 μg mL^{-1}. Rifampicin was used as a control drugs. A suspension of the MTB H37Rv ATCC 27294 was cultured in Middlebrook 7H9 broth supplemented with 10% OADC and 0.05% Tween 80. The culture was frozen at –80 °C in aliquots. The concentration was adjusted to 2×10^5 CFU mL^{-1} and 100 μL of the inoculum was added to each well of a 96-well microtiter plate together with 100 μL of the compounds. Samples were set up in three independent assays. The plate was incubated for 7 days at 37 °C. After 24 h, 30 μL of 0.01% resazurin in distilled water was added. The fluorescence of the wells was read using a Cytation™ 3 (BioTek®) in which excitations and emissions filters were used at wavelengths of 530 and 590 nm, respectively. The MIC_{90} value was defined as the lowest drug concentration at which 90% of the cells are infeasible relative to the control.

Results and Discussion

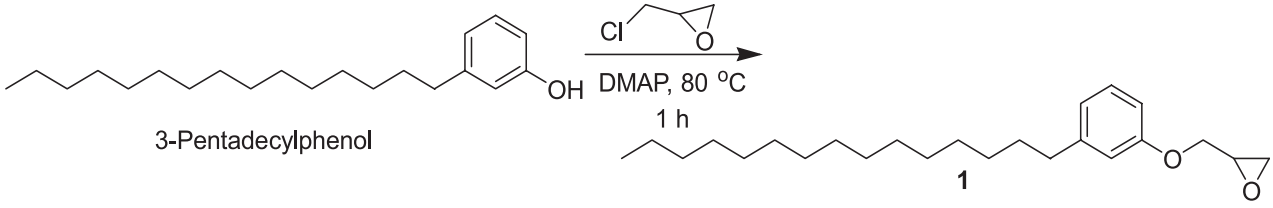
The cardanol-ene mixture was isolated from technical CNSL by vacuum distillation, and subsequently, it was subjected to catalytic hydrogenation with Pd/C (5%), according to our previously reported method.[19] The key starting material cardanol epoxide **1** was attained in excellent yield (85%) by the reaction of cardanol (3-pentadecylphenol) with epichlorohydrin (obtained from glycerol)[60] in the presence of 4-dimethylaminopyridine (DMAP) under reflux conditions (Scheme 1).[9,19]

After having the crucial precursor in hand, reactions with various amines with cardanol-epoxide **1** were carried out. To check our hypothesis, initially, we attempted the amination of cardanol epoxide **1** (1 mmol) with morpholine (1.5 mmol) in ethanol (1.5 mL) at room temperature as a model reaction. As anticipated, the reaction did not proceed well and the starting materials were fully recovered. Subsequently, the same reaction was performed at 80 °C and it was observed that a new spot appeared on the TLC. The work-up followed by purification of the product and analysis by ^1H, ^{13}C NMR and ESI mass revealed that the product is amino alcohol derivative of cardanol. To our delight, we observed a clean formation of the desired product towards amino alcohol, which was attained in excellent yield (87%, Table 1, entry 1) after simple work up. This method did not require any additives or catalysts to promote the reaction. The reaction was quite general and efficient.

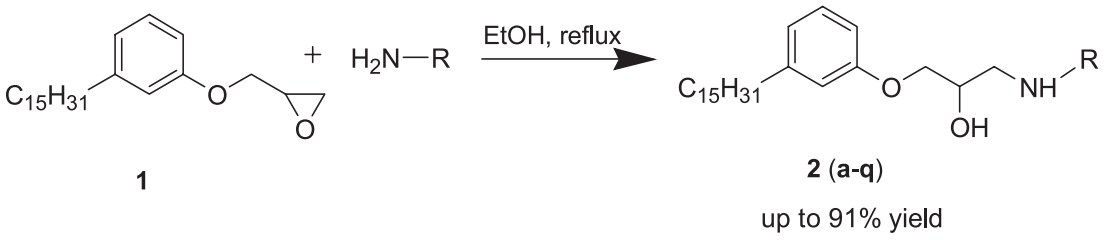
Having successfully identified the desired product, the generality of the method was investigated by elaborating the same reaction protocol for the construction of various other aminated cardanol-glycerol analogues. The reaction of cardanol-epoxide **1** with aliphatic and aromatic amines such as piperidine, pyrrolidine, piperazine, 1-(4-nitrophenyl) piperazine, di-isopropylamine, 4-methoxyaniline, 4-methylaniline, 2-methylaniline, 4-bromoaniline, 2-bromoaniline, 4-chloroaniline, 2-chloroaniline, aniline and 2-aminopyridine were carried out (Scheme 2). Interestingly, reactions of most of the substrates with amines having electron-neutral, -donating and -withdrawing groups were executed smoothly and the corresponding aminated cardano-glycerols were obtained in good to excellent yields and are illustrated in Table 1. However, the reactions of cardanol-epoxide **1** with deactivated 4-nitroaniline and 2-nitroaniline were not successful (Table 1, entries 16, 17). Usually, it is necessary a catalyst to perform epoxide aminolysis with poor nucleophiles.[61] The new compounds synthesized were completely characterized by their spectral data before proceeding for antimicrobial evaluation.

The β-amino alcohols **2a**-**2o** were examined for antibacterial and antitubercular activities using methods previously reported.[59] The results are shown in Table 2.

From the results, it was observed that compounds **2b**, **2c** and **2f** showed good to moderate activity[63] for both standard and clinical strains of *S. aureus*; the amino alcohol **2o** was



Scheme 1. Synthesis of cardanol epoxide **1**.



Scheme 2. Synthesis of cardanol based amino alcohols by using various amines.

Table 1. Synthesis of amino alcohol derivatives based on cardanol and glycerol[a]

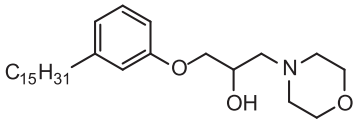
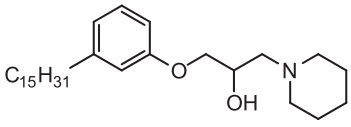
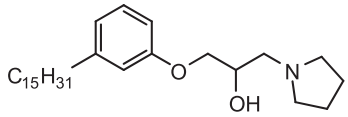
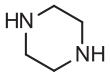
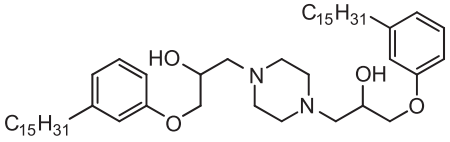
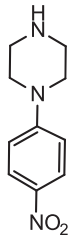
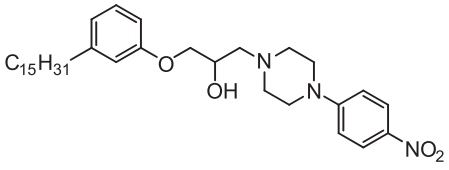
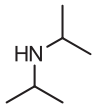
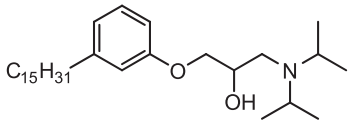
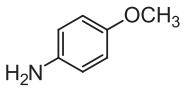
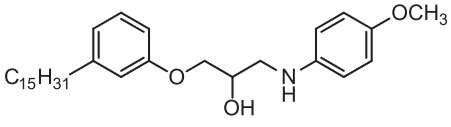
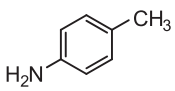
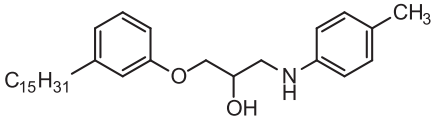
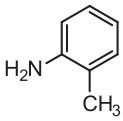
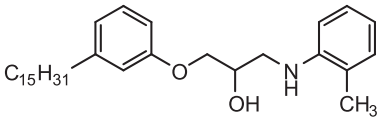
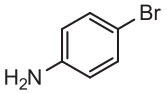
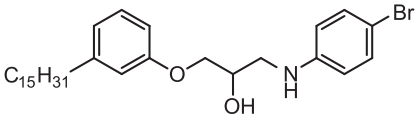
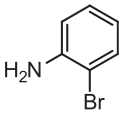
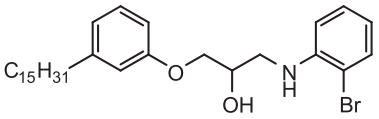
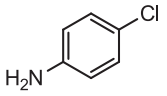
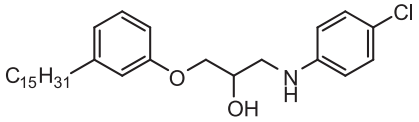
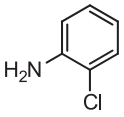
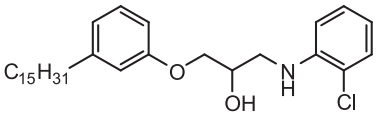
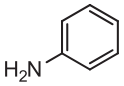
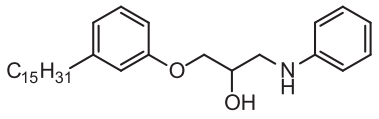
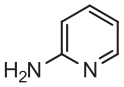
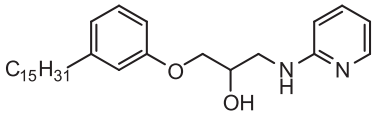
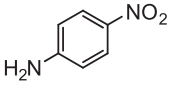
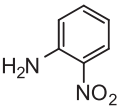
entry	Compound	Amine	Product	time / h	Yield[b] / %
1	**2a**			8	87
2	**2b**			8.5	83
3	**2c**			8.5	85
4	**2d**			9	64
5	**2e**			10	54
6	**2f**			8	91
7	**2g**			8.5	64
8	**2h**			8.5	76
9	**2i**			9	67

Table 1. Synthesis of amino alcohol derivatives based on cardanol and glycerol[a] (cont.)

entry	Compound	Amine	Product	time / h	Yield[b] / %
10	**2j**			8	69
11	**2k**			8.5	70
12	**2l**			8.5	78
13	**2m**			9.5	66
14	**2n**			8	73
15	**2o**			8	82
16	**2p**		–	12	–
17	**2q**		–	12	3

[a]Reaction conditions: cardanol epoxide (1 mmol), amine (1.5 mmol) and solvent (1.5 mL), unless otherwise mentioned, stirred at 80 °C for an appropriate time; [b]isolated yields.

active only against the standard strain. The lipophilicity (reported as log P) of the amino alcohols **2a**-**2o** is shown in Table 2. Interestingly, except for the compound **2f**, the log P values of the most active compounds **2a**, **2b**, **2c** and **2o** are lower than 9, whereas for the other compounds (with low or no activity) the log P value is higher than 9. None of the compounds had any effect on *E. coli*, which is in accordance with the fact that the outer membrane of Gram-negative bacteria seems to act as a barrier to lipophilic compounds. Also, this membrane protects enteric bacterial cells from the action of detergents, amphiphilic compounds like the derivatives presented here.[64,65]

For antitubercular activity a similar profile was observed, and compounds **2a**-**2c**, **2e**, **2f** and **2o** showed good to moderate activity, with MIC_{90} ranging from 3.18 to 16.54 μg mL^{-1}. Previous studies have reported that the outer layer functions as an exclusion barrier for hydrophilic compounds,[66] and highly hydrophobic drugs are the most active antitubercular compounds because they could easily dissolve in the lipids of the outer cell wall layer and interact with bacterial amphiphilic surface. Therefore, it is assumed that the lipophilic compounds could cross the cell wall through the lipophilic periplasmic space of the mycobacterial cell wall leading to antimycobacterial efficacy.[66,67]

The more active compounds against *S. aureus* and *M. tuberculosis* were heterocyclic aliphatic amines (**2a**, **2b**, and **2c**) or those possessing a pyridine moiety (**2o**) or aliphatic chains bonded to the nitrogen atom in their structures (**2f**). This set of structural features could be responsible for the antibacterial activity of these amino alcohols. In addition, the presence of separate hydrophilic and hydrophobic regions indicates a potentially strong amphiphilic character of the synthesized amino alcohols. The ability of these type of compounds to inhibit bacterial growth appears to depend on their interaction with proteins and/or

Table 2. MIC and MIC_{90} values for synthesized compounds against bacterial strains and log P

Compound	log P[a]	*S. aureus* (ATCC 25923)		*S. aureus* (clinical)		*E. coli* (ATCC 25922)		*M. tuberculosis* H37Rv (ATCC 27294)	
		MIC / (μg mL^{-1})	MIC_{90} / μM	MIC / (μg mL^{-1})	MIC_{90} / μM	MIC / (μg mL^{-1})	MIC_{90} / μM	MIC / (μg mL^{-1})	MIC_{90} / μM
2a	8.48	na		125.0	279.41	na		3.18	7.12
2b	8.99	7.81	17.53	7.80	17.51	na		3.27	7.34
2c	8.78	15.63	36.23	15.60	36.16	na		7.36	17.07
2d	10.31	na		na		na		> 25	> 30.97
2e	9.20	na		na		na		16.54	39.15
2f	9.14	3.90	8.45	7.80	16.90	na		4.37	9.46
2g	9.19	na		na		na		nd	
2h	9.30	na		na		na		> 25	> 53.59
2i	9.29	na		na		na		> 25	> 53.49
2j	9.40	na		na		na		> 25	> 47.06
2k	9.38	na		na		na		> 25	> 47.06
2l	9.36	na		na		na		> 25	> 51.30
2m	9.35	na		na		na		> 25	> 51.30
2n	9.17	na		na		na		> 25	> 55.14
2o	8.85	3.90	8.45	na		na		5.22	11.51
Gentamicin		1.86	3.89	> 64		3.75	7.84	–	
Rifampicin		–		–		–		0.08	0.01

clinical: clinical isolates of oxacillin and penicillin G resistant *S. aureus*; na: not active at the tested concentrations; nd: not determined. [a]The theoretical log P was calculated using the MolInspiration algorithm.[62]

their membrane disrupting properties.[64,68] It is important to highlight that phenolic lipids, for example, are highly active for Gram-positive bacteria, *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, as well as for phytopathogenic bacteria,[68,69] matching the results obtained in this work.

Conclusions

In conclusion, we have demonstrated that a simple and efficient protocol for synthesis of cardanol-based amino alcohols by using cardanol and glycerol frameworks with diverse amines in good to excellent yields. The advantages of this procedure involved readily available starting materials, good substrate generality and catalyst-free under mild conditions. The goal of this investigation was to transform renewable materials into a new class of amphiphilic compounds and to evaluate their antibacterial activities. Our results show that this strategy can be an effective way for the discovery of new antimicrobial agents.

Supplementary Information

Supplementary data (NMR and HRMS spectra) are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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