*J. Braz. Chem. Soc.*, Vol. 19, No. 6, 1065-1072, 2008.
Printed in Brazil - ©2008 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

# Synthesis and Antimicrobial Activity of Amphiphilic Carbohydrate Derivatives

***Roberta C. N. Reis,[a] Simone C. Oda,[a] Mauro V. De Almeida,[a] Maria C. S. Lourenço,[b] Felipe R. C. Vicente,[b] Nadia R. Barbosa,[c] Rafael Trevizani,[c] Priscila L. C. Santos[c] and Mireille Le Hyaric*[,a]***

[a]*Departamento de Química, Universidade Federal de Juiz de Fora, 36036-330 Juiz de Fora-MG, Brazil*

[b]*Instituto de Pesquisa Clínica Evandro Chagas, IPEC, Fundação Oswaldo Cruz, 21041-250 Rio de Janeiro-RJ, Brazil*

[c]*Faculdade de Farmácia e Bioquímica, Universidade Federal de Juiz de Fora, 36036-330 Juiz de Fora-MG, Brazil*

Diaminas *N*-monoalquiladas foram sintetizadas e tratadas com D-ribonolactona ou D-gliconolactona. As aldonamidas resultantes foram avaliadas para atividade antimicrobiana contra *S. aureus*, *E. coli*, *M. tuberculosis* and *C. albicans*. Duas hidrazidas foram também preparadas a partir da ribonoidrazida e suas atividades biológicas comparadas com aquelas de análogos amida. Todos os derivados da ribonolactona mostraram ter atividade antitubercular moderada, alguns foram ativos também contra *S. aureus.*

*N*-monoalkylated diamines were synthesised and treated with D-ribonolactone or D-gluconolactone. The resulting aldonamides were evaluated for their antimicrobial activity against *S. aureus*, *E. coli*, *M. tuberculosis and C. albicans*. Two hydrazides were also prepared from ribonohydrazide and their biological activity was compared to their amide analogues. All the ribono-derivatives displayed moderated antitubercular activity, and some of them were also active against *S. aureus.*

**Keywords**: antimicrobial, *M. tuberculosis*, amphiphilic, aldonamide

## Introduction

Surfactants are amphiphilic molecules which are widely used in many industries. Although conventional nonionic surfactants can be produced in large scale from petrochemical raw materials, the increasing need for biodegradable and less toxic products has led to numerous studies of new sugar-based surfactants, which can be prepared from natural raw materials.[1-11] These compounds possess a carbohydrate hydrophilic head (mono- or oligosaccharide), and a hydrophobic tail, usually derived from a fatty acid. The two moieties can be directly linked *via* a functional group (ester, ether, hydrazine, amine, etc) or separated by a spacer (gemini surfactants). Carbohydrate surfactants are of great interest because they are not noxious for the environment.[12,13] Due to their functional properties they can be used in several areas, such as food industry (emulsion stabilization, foaming),[14,15] biology (extraction membrane proteins),[16] glycobiology,[17,18] immunology,[19] detergents, and cosmetology (non-alergic compounds).

*e-mail: mireille.hyaric@ufjf.edu.br

Carbohydrate-derivated amphiphilic compounds have also been studied for their antimicrobial action.[20-24] These compounds can display two mechanisms of action. They can act as nonionic surfactants: the hydrophilic moiety of surface active compounds binds to the hydrophilic portion of the membrane *via* hydrogen bonds. The hydrophobic moiety is then able to penetrate the lipid bilayer structure, provocating a disorder in the permeability and fluidity of the membrane.[25] They can also act as inhibitors of enzymes involved in the biosynthesis of the bacterial cell wall. Galactofuranosyl **1**[26] and galactopyranosyl derivatives **2**[27] and **3**[28] (Figure 1) bearing long alkyl chains displayed antitubercular activity.

In the last years the intensive use of antibiotic has lead to an increase of the emergence of resistant bacteria.[29,30] There is a growing need for new class of antibacterial compounds having different mechanism of action compared to existing drugs. The antibiotic action of several of these drugs involves binding to specific receptors or enzyme inhibition, against which bacteria developed strategies, like mutation or gene acquisition, leading to resistance.[31] The mechanism by which nonionic surfactants cause cell death involves an unspecific interaction with the bacterial membrane, difficulting the generation of resistance.

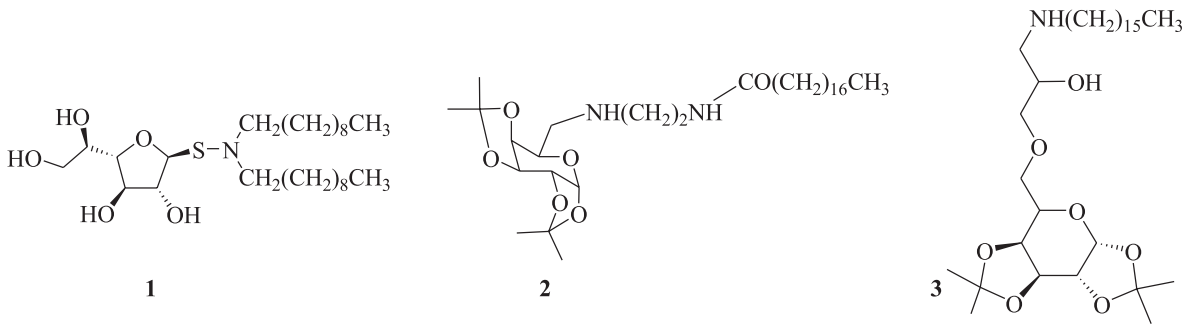


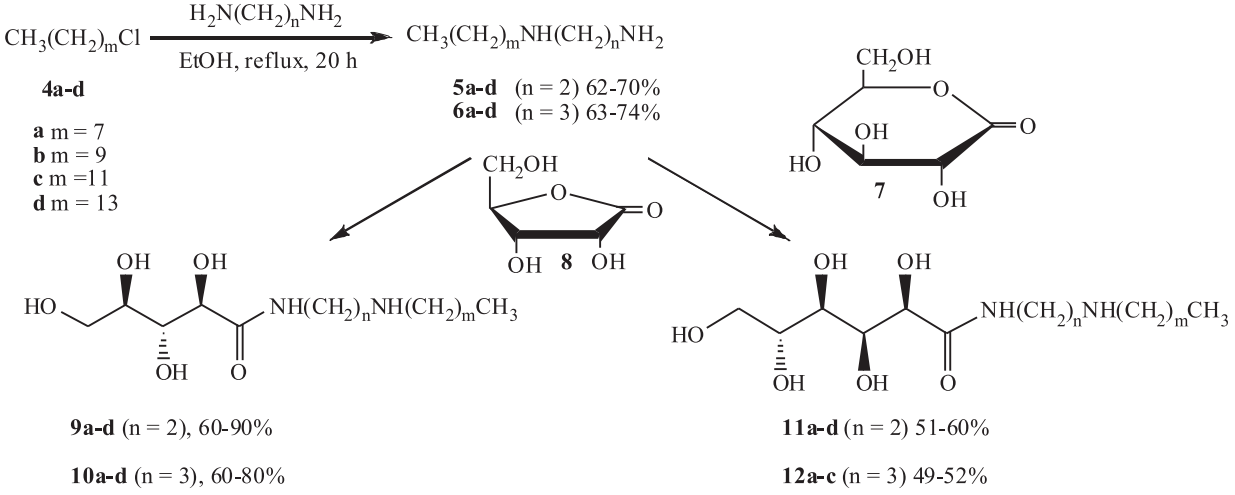
**Figure 1.**

We report in this work the synthesis and biological evaluation of *N*-alkyl-amino aldonamides from D-glucono-1,5-lactone and D-ribono-1,4-lactone, as well as two hydrazones prepared from D-ribono-1,5-lactone. The influence of the hydrophilic portion of the molecule and the length of the spacer and of the alkyl chain on antimicrobial activity will be discussed.

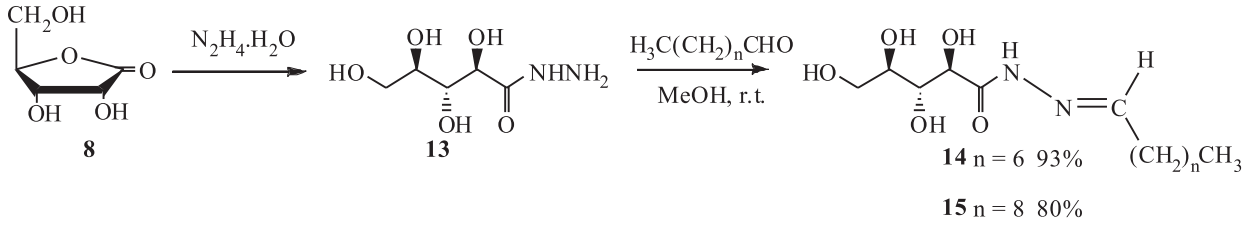
## Results and Discussion

Synthesis of *N*-alkyl amines were performed according to literature procedure,[32,33] by treatment of alkyl chlorides **4a-d** with an excess of 1,2-ethanediamine or 1,3-propanediamine in ethanol under reflux, leading to diamine **5a-d** and **6a-d** in 62-70% and 63-74% yield, respectively (Scheme 1).

Preparation of aldonamides **9a-d**, **10a-d**, **11a-d**,[34] and **12a-c**[35] was achieved by the nucleophilic addition of alkylamines **5a-d** and **6a-d** to D-glucono-1,5-lactone **7** or D-ribono-1,4-lactone **8** (1 equiv/mol) in ethanol for 20 h. After purification by crystallization or chromatographic column, all compounds were obtained in good to moderate yields (Table 1) and were characterized by IR and NMR spectroscopy. Spectroscopic data were in full agreement with those expected. $^1$H NMR spectra of compounds **9a-d** and **10a-d** showed signals referring to the hydrophobic portion of the molecule between 0.8 and 3.0 ppm. Characteristic resonances corresponding to the carbohydrate moiety were observed between 4.0 and 5.3 ppm, while the diamine portion displayed signals in the 3-4 ppm region of the spectra. $^{13}$C NMR spectra showed signals at *ca.* 174 (CO amide), 76-61 ppm (carbohydrate moiety), 14-50 ppm (alkyl chain and methylene carbons of the diamine). Hydrazones **14** and **15** were obtained by treatment of ribonohydrazide **13**[36] with octanaldehyde and decanaldehyde in 93 and 80% yield respectively (Scheme 2). $^1$H NMR spectra of both compounds showed signals corresponding to the alkyl chain (0.8-2.2 ppm) and to the carbohydrate protons (4.4-5.3 ppm). The fact that only one signal was observed at 7.7 ppm (CH=N) suggested that only the *E* isomer of the hydrazone was formed. $^{13}$C NMR spectra showed signals at *ca.* 170 ppm (CO), 152 (CH=N), 74-67 ppm (carbohydrate mioety), 33-16 ppm (alkyl chain).



**Scheme 1.**




**Scheme 2.**

*Biological activity*

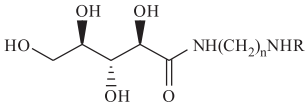
The *in vitro* antibacterial activity of compounds **9a-d**, **10a-d**, **14**, and **15** was evaluated by minimal inhibition concentration (MIC) method against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25723. Antifungal activity was tested against *Candida albicans* ATCC 10231. Compounds **9a-d**, **10a-d**, **14, 15**, **11b-d**, and **12a-c** were also tested against *Mycobacterium tuberculosis* virulent strain H37Rv, using the Microplate Alamar Blue Assay (MABA method).

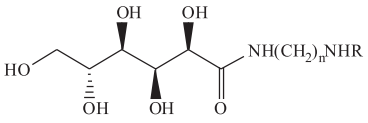
The minimum inhibitory concentration (MIC), concentration that inhibits the colony forming ability, was determined by incorporating decreasing concentrations of the tested compound to a culture of the bacteria and incubated at 37 ºC for 24 h (*M. tuberculosis, E. coli*) or 48 h (*C. albicans*). Rifampicin, penicillin-G (400000 UI $mg^{-1}$), nystatin (5914 UI $mg^{-1}$), and chloramphenicol were used as controls. The results are reported in Table 2.

Compounds **9b**, **9c**, **10a**, and **10d**, derived from D-ribono-1,4-lactone were active against the Gram-positive bacteria *S. aureus*. The most potent compounds were **9c** and **10d** (MIC = 25 μg $mL^{-1}$). Compounds **9c**, **9d** and **10d** were also the most active against *M. tuberculosis* (MIC = 25 μg $mL^{-1}$). Compounds derived from D-glucono-1,5-lactone have previously been tested against *E. coli*, *S. aureus* and *C. albicans*[35] and were not tested against these organisms in this study. The referenced work showed that they were active against *S. aureus* (MIC = 10-50 ppm), compound **12c** being the most active one. Due to their low solubility only a few derivatives could be tested against *M. tuberculosis.* The most active was **12b** (MIC = 50 μg $mL^{-1}$). Hydrazides **14** and **15** displayed low antitubercular activity (MIC = 100 μg $mL^{-1}$) and were inactive against *S. aureus* in the tested concentrations. Compound **10a** was the only compound with antifungal activity.

These results showed that Gram-positive bacteria *S. aureus* and *M. tuberculosis* were more sensitive to these amphiphilic compounds than Gram-negative *E. coli.* The sensitivity increased with the elongation of hydrocarbon chain, and the best results were obtained for compounds having an alkyl chain with more than 10 carbons. Gram-positive bacteria are characterized by having as part of their cell wall structure peptidoglycan as well as polysaccharides. The hydrogen bonding between the cell wall and the hydrophilic moiety is therefore stronger than in Gram-

**Table 1.** Unoptimized yields for ribonamides and gluconamides




| R | *n* | | Yield/(%) | *n* | | Yield/(%) |
|---|---|---|---|---|---|---|
| $CH_2(CH_2)_6CH_3$ | 2 | **9a** | 81 | 2 | **11a** | 51 |
| $CH_2(CH_2)_8CH_3$ | 2 | **9b** | 74 | 2 | **11b** | 60 |
| $CH_2(CH_2)_{10}CH_3$ | 2 | **9c** | 70 | 2 | **11c** | 60 |
| $CH_2(CH_2)_{12}CH_3$ | 2 | **9d** | 90 | 2 | **11d** | 55 |
| $CH_2(CH_2)_6CH_3$ | 3 | **10a** | 80 | 3 | **12a** | 50 |
| $CH_2(CH_2)_8CH_3$ | 3 | **10b** | 60 | 3 | **12b** | 50 |
| $CH_2(CH_2)_{10}CH_3$ | 3 | **10c** | 60 | 3 | **12c** | 52 |
| $CH_2(CH_2)_{12}CH_3$ | 3 | **10d** | 70 | | | |

negative bacteria. Having its polar head anchored in the membrane, the hydrophobic tail can interact with the lipid membrane, causing distortions leading to cell death. This mechanism would explain the similar antitubercular activity of ribonamide derivatives **9b** and **10b** and their analogues **11b** and **12b** (100 μg $mL^{-1}$ and 50 μg $mL^{-1}$, respectively). In the same way, the length of the spacer does not interfere with the antibacterial activity, and similar results were obtained using 1,2-ethanediamine, 1,3-propanediamine or an hydrazide linker.

**Table 2.** Antimicrobial and antifungal activity

| MIC/ (μg $mL^{-1}$) | *M. tuberculosis* | *S. aureus* | *E. coli* | *C. albicans* |
|---|---|---|---|---|
| **9a** | 100 | > 50 | > 50 | > 50 |
| **9b** | 100 | 50 | > 50 | > 50 |
| **9c** | 25 | 25 | > 50 | > 50 |
| **9d** | 25 | > 50 | > 50 | > 50 |
| **10a** | 100 | 50 | > 50 | 50 |
| **10b** | 50 | > 50 | > 50 | > 50 |
| **10c** | 50 | > 50 | > 50 | > 50 |
| **10d** | 25 | 25 | > 50 | > 50 |
| **11a** | res | n.t. | n.t. | n.t. |
| **11b** | 100 | n.t. | n.t. | n.t. |
| **11c** | n.s. | n.t. | n.t. | n.t. |
| **11d** | n.s. | n.t. | n.t. | n.t. |
| **12a** | res | n.t. | n.t. | n.t. |
| **12b** | 50 | n.t. | n.t. | n.t. |
| **12c** | n.s. | n.t. | n.t. | n.t. |
| **14** | 100 | > 50 | > 50 | > 50 |
| **15** | 100 | > 50 | > 50 | > 50 |
| Control | 1[a] | 0.5[b] | 5[c] | 20[d] |

(n.s.: not soluble, n.t.: not tested, res.: resistant); [a]rifampicin; [b]penicillin-G UI $mL^{-1}$; [c]chloramphenicol UI $mL^{-1}$; [d]nystatin UI $mL^{-1}$.

## Conclusion

A series of amphiphilic carbohydrate derivatives were synthesized and evaluated as antimicrobial and antifungal agents. Almost all of them displayed a moderated activity against *M. tuberculosis*, and some of them were also active against *S. aureus*. Nonionic amphiphilic compounds having low antibacterial activity and emulsification potential ($8 < HLB < 18$)[36] are suitable compounds for cosmetic formulations, as they are less aggressive to skin and cause least disturbance in skin flora.[37]

## Experimental

*General methods*

TLC were performed on glass plates coated with silica gel 60G (Merck). Detection was accomplished with iodine vapor, by spraying the plates with a solution of sulphuric acid in ethanol (20% v/v) or with a ninhydrin solution in ethanol (0.5% m/v), followed by heating at 120 °C. Column chromatography was carried out on silica gel (E. Merck 230-400 mesh). Solvents were purchased from Vetec Química and were distilled before use. Reagents were purchased from Aldrich and used without further purification. Melting points were determined on a Microquímica MQAPF apparatus and are uncorrected. IR spectra were recorded using a BOMEM-FTIR MB102 spectrometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter, using a sodium lamp ($\lambda$ = 589 nm) at 20 ºC. $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker Advance DRX300 and DRX400 spectrometer. Elementary analyses were performed by the Central Analítica of Instituto de Química of Universidade de São Paulo, Brazil.

*Synthesis*

*General procedure for the obtention of aldonamides*

A solution of the lactone (4 mmol) in ethanol (20 mL) or in a mixture ethanol/water 1:1 (10 mL) was added to a solution of the alkylamine (4 mmol) in ethanol (20 mL). The mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The residue was chromatographed on silica gel when oily or crystallized from water.

*N*-[2-(*N*-octyl)-2-aminoethyl]-D-ribonamide **9a**: 1.03 g, 81%; mp 58-60 ºC; $[\alpha]_D$ +2.55 (*c* 1.0; $C_5H_5N$); IR (KBr), $\nu_{max}/cm^{-1}$: 3390-3340, 2930-2855, 1659, 1540, 1070; $^{1}H$ NMR (300 MHz, $C_5D_5N$): δ 8.67 (s, 1H, CONH,); 5.68 (m, 4H, OH); 5.12 (m, 1H, $H_2$); 4.92 (m, 1H, H3); 4.81-4.47 (m, 2H, H4, H5'); 4.39 (m, 1H, H5'); 3.80 (m, 2H, CONHC$\underline{H}_2$); 2.90 (m, 2H, CONHC$H_2$C$\underline{H}_2$NH); 2.67 (m, 2H, H6); 1.53 (m, 2H, H7); 1.18 (m, 10H, $CH_2$ aliph.); 0.85 (t, 3H, *J* 7.1Hz, $CH_3$); $^{13}C$ NMR (75 MHz, $C_5D_5N$): δ 174.7 (C1); 75.8; 74.2; 73.2 (C2, C3, C4); 65.1 (C5); 49.7 and 49.3 ($\underline{C}H_2$-NH-$\underline{C}H_2$); 39.2 (CONH$\underline{C}H_2$); 32.1-23.0 ($CH_2$ aliph); 14.3 ($CH_3$); Elemental Anal. Calcd. for $C_{15}H_{32}N_2O_5.H_2O$: C, 53.23; H, 10.13; N, 8.28. Found: C, 54.21; H, 10.80; N, 7.90%.

*N*-[2-(*N*-decyl)-2-aminoethyl]-D-ribonamide **9b**: 1.03 g, 74%; mp 78-81 ºC; $[\alpha]_D$ +6.83 (*c* 1.5; $C_5H_5N$);

IR (KBr), $\nu_{max}$/cm$^{-1}$: 3412-3355, 2922-2850, 1655, 1537, 1073; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 8.69 (s, 1H, CONH); 5.50 (m, 4H, OH); 5.16 (m, 1H, H2); 4.84 (m, 1H, H3); 4.75-4.41 (m, 2H, H4, H5'); 4.39 (m, 1H, H5); 3.62 (m, 2H, CONHC$\underline{H}_2$); 2.94 (m, 2H, CONHCH$_2$C$\underline{H}_2$NH); 2.63 (m, 2H, H6); 1.52 (m, 2H, H7); 1.33 (m, 14H, $CH_2$ aliph); 0.86 (t, 3H, *J* 6.9Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 175.3 (C1); 76.5; 75.1; 74.7 (C2, C3, C4); 65.8 (C5); 50.8 and 50.4 ($\underline{C}H_2NH\underline{C}H_2$); 40.1 (CONH$\underline{C}H_2$); 32.9-23.8 ($CH_2$ aliph.); 15.1 ($CH_3$); Elemental Anal. Calcd. for $C_{17}H_{36}N_2O_5.2H_2O$: C, 53.10; H, 10.49; N, 7.29. Found C 53.97; H, 11.07; N, 6.99%.

*N*-[2-(*N*-dodecyl)-2-aminoethyl]-D-ribonamide **9c**: 1.02 g, 70%; mp 92-95 ºC; $[\alpha]_D$ +9.9 (*c* 1.5; DMSO); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3450-3330, 2919-2851, 1650, 1542, 1054; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 8.59 (s, 1H, CONH); 5.13 (m, 1H, H2); 4.81 (m, 1H, H3); 4.72-4.38 (m, 2H, H4, H5'); 4.36 (m, 1H, H5); 3.64 (m, 2H, CONHC$\underline{H}_2$); 2.8 (t, 2H, *J* 5.6 Hz, CONHCH$_2$C$\underline{H}_2$NH); 2.59 (t, 2H, *J* 6.9 Hz, H6); 1.48 (m, 2H, H7); 1.24 (m, 14H, $CH_2$ aliph.); 0.88 (t, 3H, *J* 6.9Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 174.5 (C1); 75.8; 74.5; 73.9 (C2, C3, C4); 65.1 (C5); 50.1 and 49.6 ($\underline{C}H_2NH\underline{C}H_2$); 39.4 (CONH$\underline{C}H_2$); 32.2-23.0 ($CH_2$ aliph.); 14.4 ($CH_3$); Anal. Calcd. for $C_{19}H_{40}N_2O_5$: C, 60.61; H, 10.71; N, 7.44. Found: C, 60.57; H 10.72; N 7.40%.

*N*-[2-(*N*-tetradecyl)-2-aminoethyl]-D-ribonamide **9d**: 1.44 g, 90%; mp 94.5-97.2 ºC; $[\alpha]_D$ +4.4 (*c* 1.25; $C_5H_5N$); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3430-3332, 2920-2856, 1652, 1540, 1055; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 8.59 (s, 1H, NH); 5.13 (m, 4H, OH); 5.11 (m, 1H, H2); 4.82. (m, 1H, H3); 4.80-4.39 (m, 2H, H4, H5'); 4.38 (m, 1H, H5); 3.67 (m, 2H, CONHC$\underline{H}_2$); 2.89 (m, 2H, CONHCH$_2$C$\underline{H}_2$NH); 2.62 (t, 2H, *J* 6.8 Hz, H6); 1.51 (m, 2H, H7); 1.27 (m, 22H, $CH_2$ aliph.); 0.89 (t, 3H, *J* 6.6 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$); $\delta$ 174.8 (C1); 75.9; 74.8; 73.8 (C2, C3, C4); 65.1 (C5); 50.1 and 49.6 ($\underline{C}H_2NH\underline{C}H_2$); 39.3 (CONH$\underline{C}H_2$); 32.3-23.1 ($CH_2$ aliph.); 14.5 ($CH_3$); Elemental Anal. Calcd. for $C_{21}H_{44}N_2O_5$: C, 62.34; H, 10.96; N, 6.92. Found: C, 62.11; H, 11.07; N, 6.91%.

*N*-[3-(*N*-octyl)-3-aminopropyl]-D-ribonamide **10a**: Oil, 1.06 g, 80%; $[\alpha]_D$ +8.33 (*c* 1.5; $C_5H_5N$); IR (CsI) $\nu_{max}$/cm$^{-1}$: 3450-3398, 2925-2856, 1650, 1541, 1060; $^1$H NMR (300 MHz, $D_2O$); $\delta$ 4.25 (d, 1H, *J* 3.0 Hz, H2); 3.85 (m, 1H, H3); 3.71-3.76 (m, 2H, H4, H5'); 3.58 (m, 1H, H5); 3.21 (m, 2H, CONHC$\underline{H}_2$ ); 2.60 (m, 4H, C$\underline{H}_2$NHC$\underline{H}_2$); 1.69 (m, 2H, NHCH$_2$C$\underline{H}_2$CH$_2$NH); 1.46 (m, 2H, $CH_2$); 1.23 (m, 10H, $CH_2$ aliph.); 0.81 (t, 3H, *J* 6.8 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ 175.8 (C1); 75.5; 74.7; 72.9; (C2, C3, C4); 64.8 (C5); 50.9 and 48.1 ($\underline{C}H_2NH\underline{C}H_2$); 38.7 (CONH$\underline{C}H_2$); 33.7 (NHCH$_2\underline{C}H_2$CH$_2$NH); 31.2-24.5 ($CH_2$ aliph.); 15.6 ($CH_3$); Elemental Anal. Calcd. for $C_{16}H_{34}N_2O_5.3H_2O$: C, 49.47; H, 10.38; N, 7.21. Found: C, 49.80; H, 9.90; N, 6.88%.

*N*-[3-(*N*-decyl)-3-aminopropyl]-D-ribonamide **10b**: 0.87 g, 60%; mp 72-75.5 ºC; $[\alpha]_D$ +6.15 (*c* 1,0; $C_5H_5N$); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3430-3395, 2930-2860, 1652, 1540, 1060; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 5.11 (m, 4H, O$\underline{H}$); 5.10 (m, 1H, H2); 4.81 (m, 1H, H3); 4.72-4.41 (m, 2H, H4, H5'); 4.31 (m, 1H, H5); 3.64 (m, 2H, CONHC$\underline{H}_2$); 2.83 (m, 2H, CONHCH$_2$CH$_2\underline{C}H_2$NH); 2.62 (m, 2H, NHC$H_2$); 1.87 (m, 2H, NHCH$_2\underline{C}H_2$CH$_2$NH); 1.57 (m, 2H, $CH_2$); 1.20 (m, 14H, $CH_2$ aliph.); 0.87 (t, 3H, *J* 7.1 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 175.0 (C1); 76.1-73.5 (C2, C3, C4); 65.8 (C5); 50.6 and 48.2 ($\underline{C}H_2NH\underline{C}H_2$); 38.2 (CONH$\underline{C}H_2$); 32.5 (NHCH$_2\underline{C}H_2$CH$_2$NH); 32.6-23.4 ($CH_2$ aliph.); 14.7 ($CH_3$); Elemental Anal. Calcd. for $C_{18}H_{38}N_2O_5.2H_2O$: C, 54.25; H, 10.62; N, 7.03. Found: C 54.35; H, 10.57; N, 6.95%.

*N*-[3-(*N*-dodecyl)-3-aminopropyl]-D-ribonamide **10c**: 0.95 g, 60%; mp 72-76.5 ºC; $[\alpha]_D$ +7.3 (*c* 1.5; DMSO); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3374-3290, 2923-2852, 1650, 1545, 1048; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 5.08 (d, 1H, *J* 4.4Hz, H2); 4.78 (m, 1H, H3); 4.70-4.47 (m, 2H, H4, H5'); 4.36 (m, 1H, H5); 3.64 (t, 2H, *J* 6.6 Hz, NHCH$_2$CH$_2\underline{C}H_2$NH); 2.73 (t, 2H, *J* 6.3 Hz, CONHC$\underline{H}_2$); 2.55 (t, 2H, *J* 7.1 Hz, NHC$H_2$); 1.81 (m, 2H, NHCH$_2\underline{C}H_2$CH$_2$NH); 1.51 (m, 2H, $CH_2$); 1.23 (m, 18H, $CH_2$ aliph.); 0.86 (t, 3H, *J* 7.1 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 175.0 (C1); 76.2–74.7 (C2, C3, C4); 65.5 (C5); 51.0 and 48.7 ($CH_2NH\underline{C}H_2$; 38.6 (CONH$\underline{C}H_2$); 32.7 (NHCH$_2\underline{C}H_2$CH$_2$NH); 31.2-23.6 ($CH_2$ aliph.); 14.9 ($CH_3$); Elemental Anal. Calcd. for $C_{20}H_{42}N_2O_5.H_2O$: C, 58.79; H, 10.85; N, 6.86. Found: C, 57.92; H, 10.96; N, 6.79.

*N*-[3-(*N*-tetradecyl)-3-aminopropyl]-D-ribonamide **10d**: 1.16 g, 70%; mp 81-85.5 ºC; $[\alpha]_D$ +8.66 (*c* 0.6; $C_5H_5N$); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3390-3298, 2919-2851, 1650, 1550, 1057; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 5.07 (m, 4H, O$\underline{H}$); 5.06 (m, 1H, H2); 4.68 (m, 1H, H3); 4.48-4.34 (m, 2H, H4, H5'); 4.33 (m, 1H, H5); 3.60 (m, 2H, NHCH$_2$CH$_2\underline{C}H_2$NH); 2.71 (t, 2H, *J* 6.0 Hz, CONHC$\underline{H}_2$); 2.54 (t, 2H, *J* 7.0 Hz, NHC$H_2$); 1.81 (m, 2H, NHCH$_2\underline{C}H_2$CH$_2$NH); 1.50 (m, 2H, $CH_2$); 1.25 (m, 22H, $CH_2$ aliph.); 0.84 (t, 3H, *J* 7.0 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 174.9 (C1); 76.1-74.5 (C2, C3, C4); 65.4 (C5); 50.9 and 48.5 (CONH$\underline{C}H_2$ and $CH_2NH\underline{C}H_2$); 38.4 (NHCH$_2\underline{C}H_2$CH$_2$NH); 32.6 (NH$\underline{C}H_2$CH$_2$CH$_2$NH); 31.0 (C17); 23.5-14.8 ($CH_2$ aliph.); Elemental Anal. Calcd. for $C_{22}H_{46}N_2O_5.H_2O$: C, 60.52; H, 11.08; N, 6.42. Found: C, 60.02; H, 11.08; N, 6.32%.

*N*-[2-(*N*-octyl)-2-aminoethyl]-D-gluconamide **11a**: 0.72 g, 51%; mp 181.7-186.0 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3533, 3394, 3350, 2954, 2736, 1662, 1533 and 1097; $^1$H NMR (300 MHz, $D_2O$): $\delta$ 4.35 (d, 1H, *J* 3.0 Hz, H2); 4.10 (t, 1H, *J* 3.0 Hz, H3); 3.83-3.76 (m, 1H, H4); 3.75-3.71 (m, 2H, H6); 3.67-3.64 (m, 1H, H5); 3.63-3.55 (m, 2H, CONHC$\underline{H_2}$); 3.21 (t, 2H, *J* 6.2 Hz, COCH$_2$C$\underline{H_2}$NH); 3.04 (t, 2H, *J* 7.7 Hz, H7); 1.72-1.60 (m, 2H, H8); 1.40-1.21 (m, 10H, $CH_2$ aliph.); 0.82 (t, 3H, *J* 7.0 Hz, $CH_3$); $^{13}$C NMR ($D_2O$, 75 MHz): $\delta$ 176.3 (C1); 73.7; 72.5; 71.7; 70.9 (C2, C3, C4, C5); 63.2 (C6); 48.6 and 47.5 (C$\underline{H_2}$NHC$\underline{H_2}$); 36.3 (CONHC$\underline{H_2}$); 31.7-22.6 ($CH_2$aliph.); 14.0 ($CH_3$); Elemental Anal. Calcd. for $C_{16}H_{34}N_2O_6$: C, 54.84; H, 9.78; N, 7.99; Found: C, 55.04 ; H, 9.64 ; N, 8.01.

*N*-[2-(*N*-decyl)-2-aminoethyl]-D-gluconamide **11b**: 0.92 g, 60%; mp 139.3-142 °C (decomposition); IR (KBr) $\nu_{max}$/cm$^{-1}$: 3532, 3390, 3351, 2953, 2792, 1661, 1534 and 1098; $^1$H NMR (300 MHz, $D_2O$): $\delta$ 4.41 (d, 1H, *J* 3.0 Hz, H2); 4.20 (m, 1H, H3); 3.86-3.79 (m, 2H, H4, H6); 3.75-3.71 (m, 1H, H5); 3.70-3.62 (m, 2H, CONHC$\underline{H_2}$); 3.28 (t, 2H, *J* 6.0 Hz, COCH$_2$C$\underline{H_2}$NH); 3.11 (t, 2H, *J* 7.3 Hz, H7); 1.78-1.66 (m, 2H, H8); 1.47-1.26 (m, 14H, $CH_2$ aliph.); 0.90 (t, 3H, *J* 6.6 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ 176.3 (C1); 74.6; 73.8; 72.5; 71.1 (C2, C3, C4, C5); 63.2 (C6); 48.6 and 47.5 (C$\underline{H_2}$NHC$\underline{H_2}$); 36.3 (CONHC$\underline{H_2}$); 31.8-26.1 ($CH_2$ aliph.); 14.2 ($CH_3$);

*N*-[2-(*N*-dodecyl)-2-aminoethyl]-D-gluconamide **11c**: 1,08 g, 60%; mp 177.2-183.8 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3532, 3391, 3353, 2953, 2792, 1661, 1534 and 1098; $^1$H NMR (300 MHz, $CF_3CO_2D$): $\delta$ 7.83 (ls, 1H, CON$\underline{H}$); 5.37-5.30 (m, 2H, H2, H3); 5.08-4.95 (m, 1H, H4); 4.76 (m, 3H, H6, H5); 4.43 (m, 2H, CONHC$\underline{H_2}$); 4.06 (m, 2H, COCH$_2$C$\underline{H_2}$NH); 3.81 (m, 2H, H7); 2.37 (m, 2H, H8); 1.88 (ls, 18H, $CH_2$ aliph.); 1.43 (t, 3H, *J* 6.6 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CF_3CO_2D$): $\delta$ 179.0 (C1); 76.4; 75.1; 74.5; 72.9 (C2, C3, C4, C5); 65.3 (C6); 52.8 and 51.6 (C$\underline{H_2}$NHC$\underline{H_2}$); 39.6 (CONHC$\underline{H_2}$); 34.4-25.1 ($CH_2$ aliph.); 15.3 ($CH_3$).

*N*-[2-(*N*-tetradecyl)-2-aminoethyl]-D-gluconamide **11d**: 0.96 g, 55%; mp 177.2-183.8 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3505, 3385, 3276, 2954, 2815, 1655, 1538 and 1099; $^1$H NMR (300 MHz, $CF_3CO_2D$): $\delta$ 7.75 (ls, 1H, CON$\underline{H}$); 5.40-4.57 (m, 5H, H2, H3, H5, H6); 3.95-3.81 (m, 3H, H4, CONHC$\underline{H_2}$); 3.43-3.09 (m, 2H, COCH$_2$C$\underline{H_2}$NH); 1.81 (m, 2H, H8); 1.47(m, 24H, $CH_2$ aliph.); 1.03 (m, 3H, $CH_3$); $^{13}$C NMR (75 MHz, $CF_3CO_2D$): $\delta$ 178.9 (C-1); 76.2; 74.7; 74.1; 72.8 (C2, C3, C4, C5); 65.1 (C6); 52.6 and 51.7 (C$\underline{H_2}$NHC$\underline{H_2}$); 39.5 (CONHC$\underline{H_2}$); 34.3-24.9 ($CH_2$ aliph.); 14.0 ($CH_3$).

*N*-[3-(*N*-octyl)-3-aminopropyl]-D-gluconamide **12a**: 0.74 g, 50%; mp 186.7-188 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3541, 3406, 3294, 2954, 2787, 1658, 1534 and 1095; $^1$H NMR (300MHz, $D_2O$): $\delta$ 4.32 (d, 1H, *J* 3.2 Hz, H2); 4.07 (ls, 1H, H3); 3.82-3.77 (m, 1H, H4); 3.74 (ls, 2H, H6); 3.67-3.59 (m, 1H, H5); 3.46-3.26 (m, 2H, CONHC$\underline{H_2}$); 3.03 (m, 5H, COCH$_2$C$\underline{H_2}$NHC$\underline{H_2}$); 1.90 (qui, 2H, *J* 7.5 Hz, NHCH$_2$C$\underline{H_2}$CH$_2$NH); 1.71-1.58 (m, 2H, H8); 1.40-1.22 (m, 10H, $CH_2$ aliph.); 0.84 (t, 3H, *J* 7.1 Hz, $CH_3$); $^{13}$C NMR (75MHz, $D_2O$): $\delta$ 175.5 (C1); 73.9; 72.7; 71.6; 70.9 (C2, C3, C4, C5); 63.1 (C6); 48.3 and 45.4 (C$\underline{H_2}$NHC$\underline{H_2}$); 36.3 (CONHC$\underline{H_2}$); 31.6 (C12); 28.7-22.5 (NHCH$_2$C$\underline{H_2}$CH$_2$NH, $CH_2$ aliph.); 14.0 ($CH_3$).

*N*-[3-(*N*-decyl)-3-aminopropyl]-D-gluconamide **12b**: 0.82 g, 52%; mp 167.0-176.6 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3530, 3391, 3358, 2954, 2741, 1656, 1536 and 1098; $^1$H NMR (300 MHz, $D_2O$): $\delta$ 4.35 (d, 1H, *J* 4.0 Hz, H2); 4.10 (ls, 1H, H3); 3.86-3.80 (m, 1H, H4); 3.79-3.74 (m, 2H, H6); 3.71-3.64 (m, 1H, H5); 3.48-3.31 (m, 2H, CONHC$\underline{H_2}$); 3.11-3.00 (m, 4H, C$\underline{H_2}$NHC$\underline{H_2}$); 2.90 (qui, 2H, NHCH$_2$C$\underline{H_2}$CH$_2$NH); 1.74-1.62 (m, 2H, H8); 1.42-1.23 (m, 14H, $CH_2$ aliph.); 0.86 (t, 3H, *J* 6.8 Hz, $CH_3$); $^{13}$C NMR (75MHz, $D_2O$): $\delta$ 176.9 (C1); 75.3; 74.1; 72.9; 72.3 (C2, C3, C4, C5); 64.5 (C6); 49.7 and 46.8 (C$\underline{H_2}$NHC$\underline{H_2}$); 37.7 (CONHC$\underline{H_2}$); 33.1 (C12); 30.5-24.0 (NHCH$_2$C$\underline{H_2}$CH$_2$NH, $CH_2$ aliph.); 14.0 ($CH_3$).

*N*-[3-(*N*-dodecyl)-3-aminopropyl]-D-gluconamide **12c**: 0.82 g, 49%; mp 156.8-177.9 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3529, 3391, 3359, 2953, 2782, 1656, 1536 and 1098; $^1$H NMR (300 MHz, $CF_3CO_2D$): $\delta$ 7.15 (ls, CONH); 4.90 (ls, 1H, H2); 4.79 (ls, 1H, H3); 4.43 (ls, 1H, H4); 4.24 (ls, 3H, H5, H6); 3.66 (ls, 2H, CONHC$\underline{H_2}$); 3.40-3.12 (m, 4H, C$\underline{H_2}$NHC$\underline{H_2}$); 2.20 (ls, 2H, NHCH$_2$C$\underline{H_2}$CH$_2$NH); 1.83 (ls, 2H, H8); 1.54-1.22 (m, 18H, $CH_2$ aliph.); 0.90 (t, 3H, *J* 7 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CF_3CO_2D$): $\delta$ 178.6 (C1); 76.2; 75.1; 74.3; 72.9 (C2, C3, C4, C5); 65.2 (C6); 52.3 and 48.6 (C$\underline{H_2}$NHC$\underline{H_2}$); 38.8 (CONHC$\underline{H_2}$); 34.3-24.8 (NHCH$_2$C$\underline{H_2}$CH$_2$NH, $CH_2$ aliph.); 15.2 ($CH_3$).

Ribonic acid [(*n*-heptyl)methylene] hydrazide **14**: To a solution of hidrazide **13** (0.4 g, 2.2 mmmol) in methanol (10 mL) was added a solution of octanal (0.35 mL, 2.2 mmol). The reaction was stirred at room temperature for 24 h and concentrated under reduced pressure. The resulting hydrazide was recrystallized from acetone, and diethyl ether. 0.6 g; 93%; mp140.9-143 ºC; $[\alpha]_D$ +14,75 (*c* 1.0; DMSO); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3414-3273, 2917-2850, 1656, 1087, 1627; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 11.40 (m, 1H, CONH); 7.75 (m, 1H, N=CH); 5.26 (m, 1H, H2); 4.91 (m, 1H, H3);

4.80-4.44 (m, 2H, H4, H5'); 4.42 (m, 1H, H5); 2.24 (m, 2H, N=CH-C<u>H</u>$_2$); 1.39 (m, 2H, N=CH-CH$_2$C<u>H</u>$_2$); 1.14 (m, 8H, CH$_2$ aliph.); 0.82 (t, 3H, *J* 7.1Hz, CH$_3$), $^{13}$C NMR (75MHz, $C_5D_5N$): $\delta$ 170.4 (C1); 152.4 (N=CH); 76.1-73,8 (C2, C3, C4); 65.2 (C5); 33,1 (N=CH-<u>C</u>H$_2$); 32.1–23.1 (CH$_2$ aliph.); 14.4 (CH$_3$); Elemental Anal. Calcd. for $C_{13}H_{26}N_2O_5$: C, 53.78; H, 9.03; N, 9.65. Found: C, 53.57; H, 9.01; N, 9.68.

Ribonic acid [(*n*-nonyl)methylene] hydrazide **15**: The same experimental procedure described to prepare compound **14** was followed. 0.28 g; 79%; mp: 142-144 ºC; $[\alpha]_D$ +1.15 (*c* 1.0; DMSO); IR (KBr), $\nu_{max}$/cm$^{-1}$: 3368-3196, 2918-2848, 1664, 1049, 1627; $^1$H NMR (300 MHz, $C_5D_5N$): $\delta$ 11.40 (m, 1H, CONH); 7.82 (m, 1H, N=CH); 7.75 (m, 1H, OH); 7.08 (s, 1H, OH); 6.64 (s, 1H, OH); 6.34 (s, 1H, OH); 5.25 (m, 1H, H2); 5.08 (m, 1H, H3); 4.90-4.80 (m, 2H, H4, H5'); 4.49 (m, 1H, H5); 2.26 (m, 2H, N=CH-C<u>H</u>$_2$); 1.42 (m, 2H, N=CH-CH$_2$CH$_9$); 1.16 (m, 12H, CH$_2$ aliph.); 0.86 (t, 3H, *J* 7.1Hz, CH$_3$); $^{13}$C NMR (75 MHz, $C_5D_5N$): $\delta$ 170.5 (C1); 152.6 (N=CH); 76.3-74.0 (C2, C3, C4); 65.4 (C5); 33.3 (N=CH-<u>C</u>); 32.5-23.4 (CH$_2$ aliph.); 14.7 (CH$_3$); Elemental Anal. Calcd. for $C_{15}H_{30}N_2O_5$: C, 56.58; H, 9.50; N, 8.80. Found: C, 56.31; H, 9.29; N, 8.53.

*Biological activity*

Tested substances were initially diluted in 100 µL of sterilized dimethyl sulfoxide (DMSO)/Tween (1:2, v/v) and completed up to 10 mL with sterilized saline. A serial dilution was prepared to yield the following concentrations: 250, 125, 62.5, 31.25 and 15.62 µg mL$^{-1}$. A screening was held to confirm the activity of microorganisms and to select strains for the determination of the Minimum Inhibitory Concentration (MIC) of new compounds. The strains selected were from American Type Culture Collection (ATCC): *S. aureus* ATCC 29213*, E.coli* ATCC 25723 and *C. albicans* ATCC 10231.

A microbiologic suspension from cultures previously incubated for 24 h (bacteria) and 48 h (fungi) was prepared in sterilized saline until a 25% transmittance reading was reached at $\lambda$ = 580 nm (UV-Vis mini1240, Shimadzu®, Japan). The standardized microbiological solution was prepared by serial dilution in sterilized saline, and the colonies counted in Tryptic Soy Agar (Acumedia®, Canada), by plating technique. The dilution which presented $10^3$-$10^4$ CFU mL$^{-1}$ was selected for further inoculation in Tryptone Soy Broth (Merck, Germany) (adapted from The United States Pharmacopoeia, 1985).

Four mL of the seeded broth were added to 1 mL of the previously diluted solutions. Positive control consisted of 4 mL of the seeded broth, 10 µL of sterilized DMSO/Tween (1:2, v/v) and 990 µL of sterilized saline. To ensure the material remained sterile for the whole assay, a negative control was prepared with 4 mL of non-inoculated broth, 10 µL of sterilized DMSO/Tween (1:2, v/v) and 990 µL of sterilized saline. The MIC was evaluated by the turbidity of the broth after 24 h (bacteria) and 48 h (fungi) incubation. Tests were performed in triplicate.

The antitubercular activity against *M. tuberculosis* virulent strain H37Rv was determined in vitro. Stock solutions of tested compounds were prepared in DMSO. The mycobacteria was subcultured on Lowenstein-Jensen medium at 37 ºC for 3 weeks, followed by subculture in Middlebrook 7H9 broth medium at 37 ºC for at least 10 days, until bacterial density corresponding to a 1.0 McFarland turbidity standard was reached. The tests were performed through the microplate Alamar Blue assay.[39-41] The mycobacteria suspension were diluted 1:25 in Middlebrook 7H9 broth medium (4 $\times$ 10$^5$ mycobacteria/mL) and 100 µL of serial dilutions of compounds in the same medium. After incubation at 37 ºC for 6 days, 25 µL of a 1:1 (v/v) mixture of Alamar Blue reagent and 10% Tween 80 was added and the plates were re-incubated at 37 ºC for 24 h. A change in the colour from blue to pink was observed in the wells where the mycobacteria grew. The visual MICs were defined as the lowest drug concentration that prevented the colour change.

## Acknowledgments

R. C. N. R., S. C. O. and M. V. A. gratefully acknowledge CAPES and CNPq for fellowships. This work was supported by FAPEMIG.

## References

1. Milius, A.; Greiner, J.; Riess, J. G.; *New J. Chem.* **1992**, *16* , 771.
2. Hill, K.; Von Rybinski, W.; Stoll, G.; *Alkyl Polyglycosides: Technology, Properties and Applications*, VCH: Weinheim, 1997.
3. Prata, C.; Mora, N.; Polidori, A.; Lacombe, J. -M.; Pucci, B.; *Carbohydr. Res.* **1999**, *321*, 15.
4. Riess, J. G.; Greiner, J.; *Carbohydr. Res.* **2000**, *327*, 147.
5. Polat, T.; Linhardt, R. J. ; *J. Surfact. Deterg.* **2001**, *4*, 415.
6. Abert, M.; Mora, N.; Lacombe, J. -M.; *Carbohydr. Res*. **2002**, *337*, 997.
7. Pilakowska-Pietra, D.; Lunkenheimer, K.; Piasecki, A.; *J. Coll. Interf. Sci.* **2004**, *271*, 192.
8. Satgé, C.; Granet, R.; Verneuil, B.; Champavier, Y.; Krausz, P.; *Carbohydr. Res*. **2004**, *339*, 1243.
9. Chaveriat, L.; Stasik, I.; Demailly, G.; Beaupère. D.; *Carbohydr. Res.* **2004**, *339,* 1817.

10. De Almeida, M. V.; Le Hyaric, M.; *Mini-Rev. Org. Chem.* **2005**, *2*, 546.
11. Aich, U.; Loganathan, D.; *Carbohydr. Res.* **2007***, 342, 704.*
12. Warwel, S.; Bruse, F.; Demes, C.; Kunz, M.; Klass, M.; *Chemosphere* **2001**, *43*, 39.
13. García, M. T.; Ribosa, I.; Campos, E.; Sanchez Leal, J.; *Chemosphere* **1997**, *3,* 545.
14. Franco, J. M.; Berjano, M.; Munoz, J.; Gallegos, C.; *Food Hydrocoll.* **1995**, *9*, 111.
15. Akoh, C. C.; *J. Am. Oil Chem. Soc*. **1992**, *69*, 9
16. Uchegbu, I. F.; Vyas, S. P.; *Int. J. Pharm.* **1998**, *172*, 33
17. Varki, A.; *Glycobiol.* **1993**, *3*, 97.
18. Rigaud, J. L.; Chami, M.; Lambert, O.; Levy, D.; Ranck, J. L.; *Biochem. Biophys. Acta* **2000**, *1508*, 112.
19. Lockhoff, O.; *Angew. Chem. Int. Ed.* **1991**, *30*, 1611.
20. Rosevear, P.; VanAken, T.; Baxter, J.; Ferguson-Miller, S.; *Biochemistry* **1980**, *19***,** 4108.
21. Devulapalle, K. S.; de Segura, A. G.; Ferrere, M.; Alcalde, M.; Mooser, G.; Plou, F. J.; *Carbohydr. Res.* **2004**, *339*, 1029.
22. Marshall, D. L.; Bullerman, L. B. In *Carbohydrates Polyesters as Fat Substitutes*; Akoh, C.C.; Swanson, B. G., eds.; Marcel Dekker: New York, 1994, p. 149.
23. Kabara, J. J. In *Antimicrobials in Food*; Branem, A. L.; Davidson, P. M., eds; Marcel Dekker: New York, 1983, p. 149.
24. Rauter, A. P.; Lucas, S.; Almeida, T.; Sacoto, D.; Ribeiro,V.; Justino, J.; Neves, A.; Silva F. V. M.; Oliveira, M. C.; Ferreira, M. J.; Santos, M. -S.; Barbosa, E.; *Carbohydr. Res.* **2005**, *340*, 191.
25. Kubo, I.; Fujita, K.; Nihei, K.; Masuoka, N.; *Bioorg. Med. Chem.* **2003**, *11*, 573.
26. Owen, D. J.; Davis, C. B.; Hartnell, R. D.; Madge, P. D.; Thomson, R. J.; Chong, A.; K. J.; Coppel, R. L.; von Itzein. M.; *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2274.
27. De Almeida, M. V.; Le Hyaric, M.; Amarante, G. W.; Lourenço, M. C. S.; Brandão, M. L. L.; *Eur. J. Med. Chem.* **2007**, *42*, 1076.
28. Tewari, N.; Tiwari, V. K.; Tripathi, R. P.; Chaturvedi, V.; Srivastava, A.; Srivastava, R.; Shukla, P. K.; Chaturvedi, A. K.; Gaikwad, A.; Sinha, S.; Srivastava, B. S.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 329.
29. Neu, H.C.; *Science* **1992**, *257*, 1064
30. Travis, J.; *Science* **1994**, *264*, 360.
31. Linsker, F.; Evans, R. L.; *J. Am. Chem. Soc.* **1945**, *67*, 1581.
32. Alekshun, N.; Levy S. B.; *Cell* **2007**, *128*, 1037.
33. De Almeida, M. V.; Saraiva, M. F.; De Souza, M. V. N.; Costa, C. F.; Vicente, F. R. C.; Lourenço, M. C. S.; *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5661; Lu, X.; Zhang, Z.; Liang, Y.; *Langmuir* **1997**, *13*, 533.
34. Okahara, M.; Nishino, K.; Komori, S.; *Yukagaku* **1966**, *15*, 155.
35. Maak, N.; Lehmann, R.; *Ger. Offen*. **1983**, DE 3148047 A1.
36. Van Marle, T. W. J.; *Rec. Trav. Chim. Pays-Bas* **1920**, *39*, 549.
37. Griffin, W. C.; *J. Soc. Cosmetic Chem*. **1954**, *5*, 259
38. Hill, K.; Rhode, O.; *Fett Lipid* **1999**, *1*, 25.
39. Collins, L. A.; Franzblau, S. G.; *J. Antimicrob. Chemother.* **1997**, *41*, 1004.
40. De Souza, A. O.; Hemerly, F. P.; Busollo, A. C.; Melo, P. S.; Machado, G. M. C.; Miranda, C. C.; Santa-Rita, R. M.; Haun, M.; Leon, L. L.; Sato, D. N.; Castro, S. L.; Duran, N.; *J. Antimicrob. Chemother.* **2002**, *50*, 629.

*Received: October 16, 2007*
*Web Release Date: June 23, 2008*