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Synthesis and antimicrobial activity of novel amphiphilic aromatic amino alcohols

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ABSTRACT

We report in this work the preparation and in vitro antimicrobial evaluation of novel amphiphilic aromatic amino alcohols synthesized by reductive amination of 4-alkyloxybenzaldehyde with 2-amino-2-hydroxymethyl-propane-1,3-diol. The antibacterial activity was determined against four standard strains (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*) and 21 clinical isolates of methicillin-resistant *Staphylococcus aureus*. The antifungal activity was evaluated against four yeast (*Candida albicans*, *Candida tropicalis*, *Candida glabrata* and *Candida parapsilosis*). The results obtained showed a strong positive correlation between the lipophilicity and the antibiotic activity of the tested compounds. The best activities were obtained against the Gram-positive bacteria (MIC = 2–16 μg ml^{-1}) for the five compounds bearing longer alkyl chains (**4c–g**; 8–14 carbons), which were also the most active against *Candida* (MIC = 2–64 μg ml^{-1}). Compound **4e** exhibited the highest levels of inhibitory activity (MIC = 2–16 μg ml^{-1}) against clinical isolates of MRSA. A concentration of twice the MIC resulted in bactericidal activity of **4d** against 19 of the 21 clinical isolates.

The evolutionary adaptation of microorganisms has led to the development of drug-resistant strains of bacteria and fungi. The emergence of multidrug resistant organisms has become a major public health problem, as they turn the management of infectious diseases more precarious,[1–3] and there is an urgent need for new active compounds. Amino alcohols are important as building blocks in organic synthesis, and their presence in chemical structures is often associated with biological activities, as in ethambutol and other antimicrobial compounds.[4–7] Our group showed in previous works the antimicrobial and immunological activities of series of aliphatic and aromatic amino alcohols derivatives are related to their lipophilicity.[8–11] The present paper describes the synthesis of new amphiphilic aromatic amino alcohols derived from 4-hydroxybenzaldehyde and their evaluation as antibacterial and antifungal compounds, as well as the study of the relationship between activity and lipophilicity.

Compounds **2a–g** were obtained using described procedures.[12,13] 4-hydroxy-benzaldehyde **1** was first alkylated using the Williamson ether synthesis and then submitted to direct reductive amination reaction[9] in the presence of 2-amino-2-hydroxymethyl-propane-1,3-diol (Tris) to give the targeted amino alcohols **4a–f** in 62–87% yield (Scheme 1). All the synthesized compounds were characterized by FTIR, ^{1}H and ^{13}C NMR, and high resolution mass spectrometry.

The antibacterial activity of the prepared compounds was assessed in vitro against two Gram-positive bacterial strains (*Staphylococcus aureus* ATCC 29213 and *Staphylococcus epidermidis* ATCC 12228), two Gram-negative bacteria (*Escherichia coli* ATCC 11229 and *Pseudomonas aeruginosa* ATCC 27853) and 21 clinical isolates of MRSA obtained from the culture collection at the Laboratory of Bacterial Physiology and Molecular Genetics, Federal University of Juiz de Fora. The minimal inhibitory concentration (MIC) of the selected compounds was determined by the broth dilution method in Mueller Hinton medium (DIFCO Laboratories, Detroit, MI, USA), according to the CLSI guidelines.[14,15]

The MIC values of the compounds, as well as of chloramphenicol and vancomycin, used as positive controls, are reported in Table 1. The datas show that the series of amino alcohols was more active against Gram-positive bacteria (MIC = 2–1024 μg ml^{-1}) than against Gram-negative strains (16–1024 μg ml^{-1}). Compounds **4a** and **4b**, bearing the shortest alkyl chains (respectively 4 and 6 carbon atoms) were the less active substances. Compounds **4c–g** displayed a higher antibacterial activity than chloramphenicol, but they were less active than the reference drug vancomycin. These compounds were highly active against *S. aureus*, with MIC ranging

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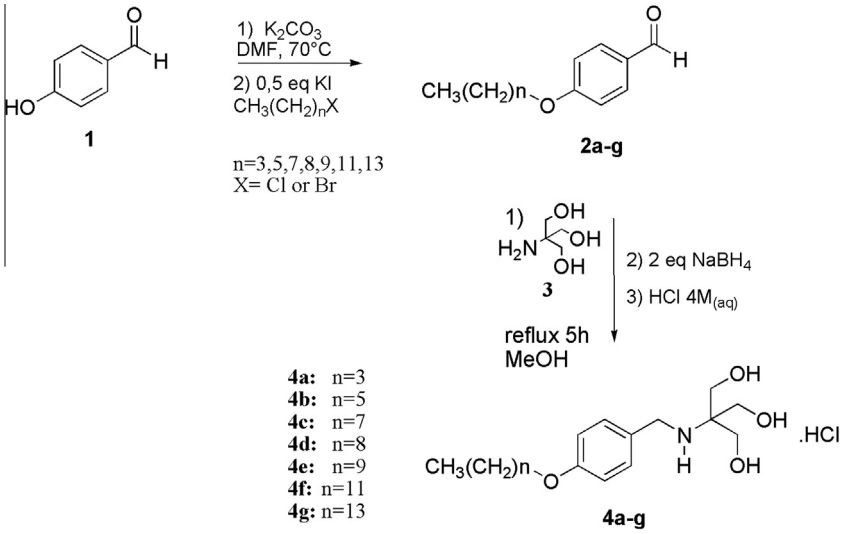

Scheme 1. Synthesis of amino alcohols **4a**–**f**.

Table 1
Inhibitory activity of compounds **4a**–**g** expressed as MIC (μg ml^{-1})

	MIC (μg/ml)								
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	Chloramphenicol	Vancomycin
Reference strains									
Staphylococcus aureus ATCC 29213	1024	128	8	8	8	8	2	16	0.5
Staphylococcus epidermidis ATCC 12228	512	128	16	8	4	8	2	32	—
Escherichia coli ATCC 11229	1024	256	32	16	32	>256	>256	16	—
Pseudomonas aeruginosa ATCC 27853	512	512	>256	>256	16	>256	>256	32	—
MRSA clinical isolates									
176	—	—	32	8	8	8	16	64	1
178	—	—	128	16	8	8	8	4	1
195	—	—	32	8	8	8	16	4	0.5
205	—	—	16	8	8	8	16	8	1
207	—	—	64	16	8	4	>1024	4	1
212	—	—	32	32	8	8	>1024	8	1
215	—	—	16	16	4	8	>1024	64	1
218	—	—	16	8	4	4	8	64	0.5
225	—	—	128	8	8	8	>1024	8	1
227	—	—	32	16	4	4	>1024	64	1
231	—	—	16	8	8	4	2	64	1
232	—	—	16	16	16	8	8	64	1
235	—	—	16	8	4	4	4	64	1
236	—	—	16	8	4	4	8	64	1
237	—	—	16	16	16	4	4	32	1
238	—	—	16	32	8	4	4	32	1
255	—	—	8	16	4	4	8	4	0.5
257	—	—	8	8	4	16	2	8	1
259	—	—	8	8	4	4	2	128	0.5
260	—	—	16	16	8	4	2	4	0.5
264	—	—	8	8	2	4	16	8	0.5

from 2 to 8 μg ml^{-1}. The highest inhibitory activity was found for **4g** (carrying an alkyl chain with 14 carbon atoms), showing MIC = 2 μg ml^{-1} against both *S. aureus* and *S. epidermidis*.

The inhibitory potencies, MIC_{50} and MIC_{90}, corresponding to 50% and 90% inhibition, were determined against 21 MRSA clinical strains for lipophilic amino alcohols **4c**–**g**. The results, depicted in Tables 1 and 2, show that compounds **4c**–**f** were active against all the MRSA isolates (MIC = 2–128 μg ml^{-1}). Compounds **4e** and **4f**

Table 2
Inhibitory activity of compounds **4c**–**g** against MRSA, expressed as MIC_{50} and MIC_{90}

	4c	**4d**	**4e**	**4f**	**4g**	Chloramphenicol[a]
MIC_{50}	16	8	8	4	8	16
MIC_{90}	64	16	8	8	>1024	32
Range	8–128	8–32	2–16	4–16	2 >1024	8–128

[a] Sensibility: 43.7%; resistence: 56.3%.