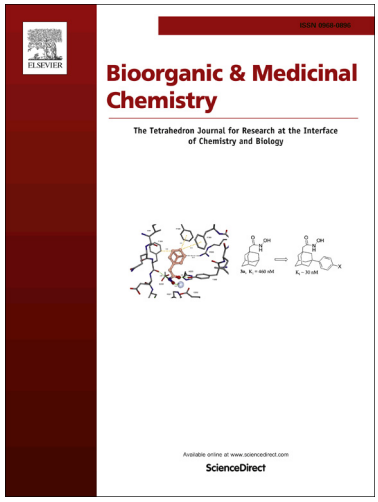

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Synthesis and antimicrobial activity of chloramphenicol-polyamine conjugates

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ABSTRACT

A series of chloramphenicol (CAM) amides with polyamines (PAs), suitable for structure-activity relationship studies, were synthesized either by direct attachment of the PA chain on the 2-aminopropane-1,3-diol backbone of CAM, previously oxidized selectively at its primary hydroxyl group, or from chloramphenicol base (CLB) through acylation with succinic or phthalic anhydride and finally coupling with a PA. Conjugates **4** and **5**, in which the CLB moiety was attached on N4 and N1 positions, respectively, of the N^8,N^8-dibenzylated spermidine through the succinate linker, were the most potent antibacterial agents. Both conjugates were internalized into *E. coli* cells by using the spermidine-preferential uptake system and caused decrease in protein and polyamine content of the cells. Noteworthy, conjugate **4** displayed comparable activity to CAM in MRSA or wild-type strains of *Staphylococcus aureus* and *Escherichia coli*, but superior activity in *E. coli* strains possessing ribosomal mutations or expressing the CAM acetyltransferase (*cat*) gene. Lead compounds, and in particular conjugate **4**, have been therefore discovered during the course of the present work with clinical potential.