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Abstract

Structure–Activity Relationship for Natural Tetracenomycin X Congeners †

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Abstract: The aromatic polyketide tetracenomycin X (TcmX) was recently found to be a potent inhibitor of protein synthesis; its binding site is located in a unique locus within the tunnel of the large ribosomal subunit. The distinct mode of action makes this relatively narrow class of aromatic polyketides promising for drug development in the quest to prevent the spread of drug-resistant pathogens. We isolated two novel tetracenomycin congeners: 6-hydroxytetracenomycin X (6-OH-TcmX) and O^4-Me-Tcm C (TcmX isomer). Spectral properties of the compounds were studied. 6-OH-TcmX exhibited lower antimicrobial and cytotoxic activity, whereas the TcmX isomer was found to be completely inactive. Interestingly, the *in vitro* protein synthesis inhibition ability of TcmX and 6-OH-TcmX were found to be comparable, suggesting a significant influence of 6-hydroxylation on the tetracenomycin X cell penetration ability. The complete absence of both antimicrobial activity and the *in vitro* protein synthesis inhibition ability of the TcmX isomer corroborates the crucial role of the 4-OH group in ribosome binding.

Keywords: aromatic polyketides; protein synthesis inhibitors; structure–activity relationship; antibiotics

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