

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 O⁴-Me-Tcm C (TcmX isomer). Spectral properties of the compounds were studied. 6-OH-TcmX exhibited lower antimicrobial and cytotoxic activity, whereas TcmX isomer was found to be completely inactive. Interestingly, *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. Complete absence of both antimicrobial activity and *in vitro* protein synthesis inhibition ability of TcmX isomer corroborates crucial role of 4-OH group in ribosome binding. This work was supported in part by Ministry of Science and Higher Education of the Russian Federation (Agreement No 075–15-2021-1085). V.A. Alferova was supported by a RF President's Scholarship (project SP-4094.2022.4).

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