Structure-activity relationship for natural tetracenomycin X congeners

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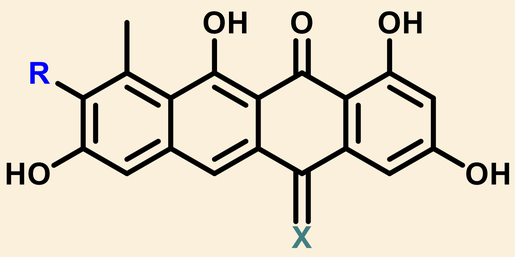
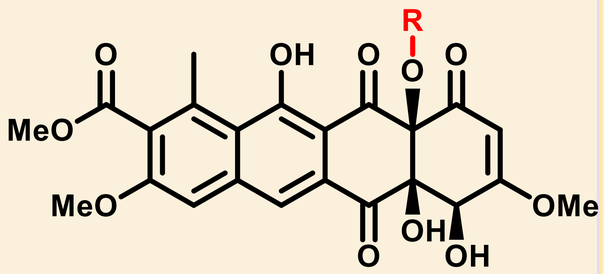
Tetracenomycin antibiotic family





R = CO_2Me, X = O, tetracenomycin A2
R = H, X = O, tetracenomycin D
R = CO_2H, X = H_2, tetracenomycin F1

R = H, tetracenomycin C
R = Me, tetracenomycin X

Tetracenomycins (Tcm) are aromatic polyketides with four fused rings.

Despite structural similarity, only TcmX and TcmC have distinctive 4a,12a-deoxygenation dramatically distrupting the planar structure.

Recently TcmX was shown to have the **unique binding site in the large ribosomal subunit.**

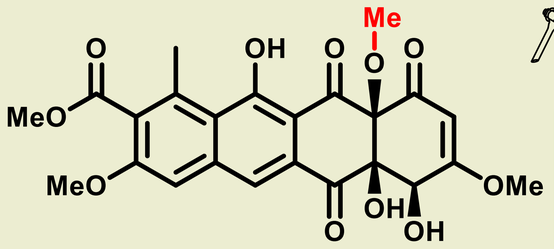
STATE OF ART

Isolation of the novel natural teracenomycins

Amycolatopsis sp. strain A23

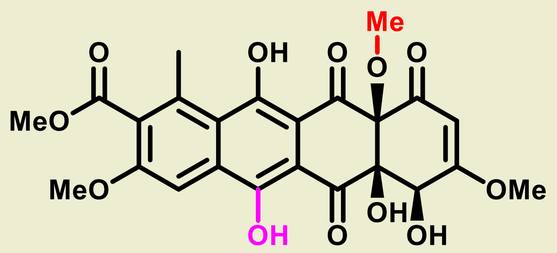
Cultivation → **Extraction** → **Chromatography**

2 novel Tcm congeners

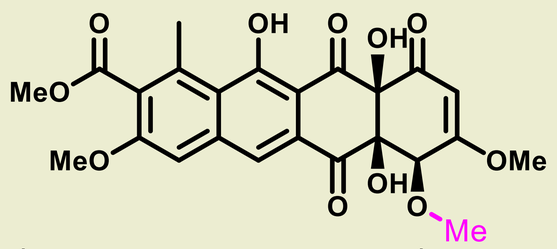


Tetracenomycin X (TcmX)

this work



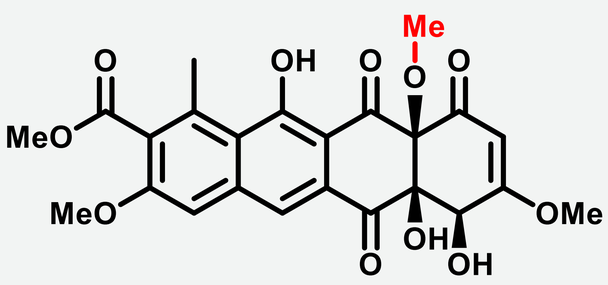
6-OH-Tetracenomycin X (6-OH-TcmX)



O^4-Me-Tetracenomycin C (O^4-Me-TcmC)

STRUCTURE ELUCIDATION

Antibacterial properties Translation inhibition



TcmX

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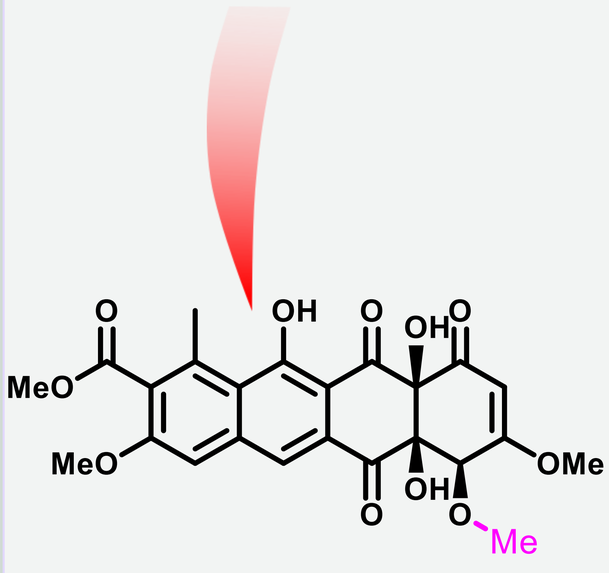
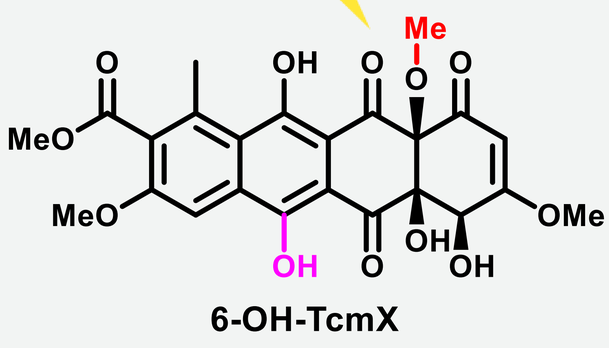
BIOLOGICAL EVALUATION

High antibacterial activity
Potent translation inhibition



O^4-Me-TcmC

Inactive
No translation inhibition



6-OH-TcmX

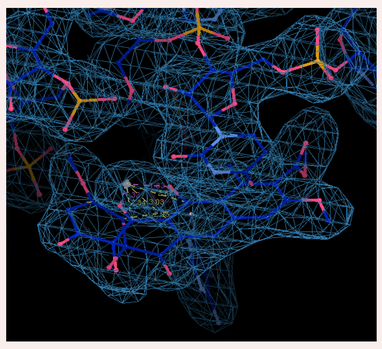
Reduced antibacteral activity
Potent translation inhibition

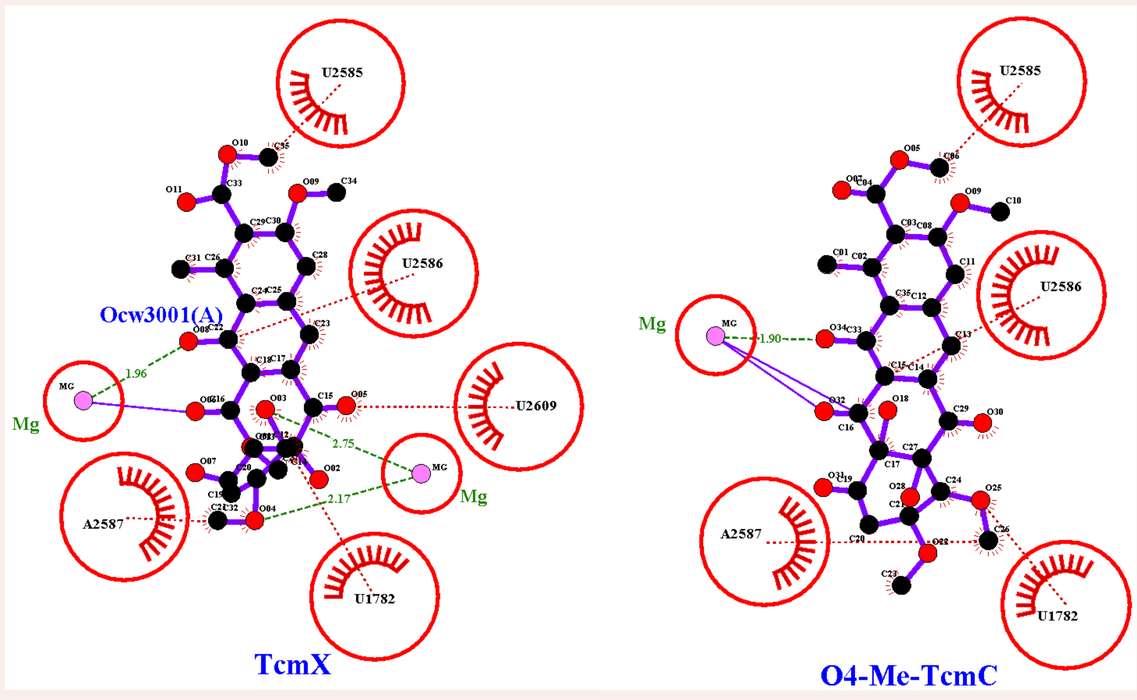
6-hydroxylation impairs activity of 6-OH-TcmX, but **does not interfere with key target interaction sites**

RIBOSOME BINDING

Schematic map on the ribosome

O^4-Me-TcmC fit to cryo-EM TcmX-70S ribosome (PDB 6Y69)





O^4-Me-TcmC exhibits only a single coordination with magnesium.

Methylation in O^4 position prevents hydrogen bonding, further supporting the idea, that this site is **essential for the ribosome binding**

Alferova, V. A.; Maviza, T. P.; Biryukov, M. V.; Zakalyukina, Y. V.; Lukianov, D. A.; Skvortsov, D. A.; Vasilyeva, L. A.; Tashlitsky, V. N.; Polshakov, V. I.; Sergiev, P. V.; Korshun, V. A.; Osterman, I. A. Biological Evaluation and Spectral Characterization of a Novel Tetracenomycin X Congener. *Biochimie* **2022**, *192*, 63–71. https://doi.org/10.1016/j.biochi.2021.09.014.