

**W0574**

**Molecular Recognition of RNA by Neomycin and a Restricted Neomycin Derivative.** Qiang Zhao, Fang Zhao\*, Kenneth F. Blount\*, Qing Han, Yitzhak Tor\*, Thomas Hermann\*, Anadys Pharmaceuticals, Inc. 3115 Merryfield Row, San Diego, CA 92121, \*Dept of Chem & Biochem, UCSD, La Jolla, CA 92093.

Aminoglycoside antibiotics bind to ribosomal RNA at the decoding site and interfere with the accuracy of protein synthesis, ultimately leading to bacterial cell death. We have determined the three-dimensional structure of decoding-site RNA (19 residues) complexes of the aminoglycoside antibiotic neomycin and a conformationally restricted analogue. Both complexes crystallized in space group P212121 with cell dimensions of  $a=b=50\text{\AA}$ , and  $c=145\text{\AA}$ . The structures were solved by molecular replacement at  $3\text{\AA}$  resolution.

The intramolecular 2,-5,, cross-link introduced into the restricted natural product is compatible with binding. Comparison of the structures reveals the sensitivity of aminoglycoside target recognition toward even slight modifications to the architecture of the ligand. While most key interactions are undisturbed by the modification, two hydrogen bonding contacts are abolished. Neomycin binds to the decoding-site RNA in the same conformation and at the same site as the structurally similar paromomycin. Unexpectedly, a secondary binding site was discovered for both neomycin and the restricted derivative.

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