Pikromycin Derivative of Solithromycin: Discussion of Activity

Abstract F-1505

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Background:

In an effort to decrease cost of fluoroketolide synthesis, pikromycin, a naturally occurring ketolide, which can be thought of as an advanced intermediate, was selected as the starting material for the synthesis of a solithromycin (Soli, CEM-101) analog. The key distinguishing feature of the pikromycin is the lack of 6-OMe and C-10 methyl groups found in clarithromycin class macrolides. A pikromycin based analog of Soli (pikro-CEM-101) was prepared and tested in vitro.

Methods:

Pikro-CEM-101 was synthesized in 5 steps from pikromycin. MICs were determined by broth microdilution. Modeling and simulation studies were performed. Soli and pikro-CEM-101 structures were minimized using CHARMm force field to achieve 0.0001 gradient tolerance followed by an exhaustive conformational search to identify the Boltzmann distribution of conformers. Different conformers were identified for each molecule and were analyzed for their energy differences. Unique conformers of each molecule were used as starting structures for 1 nano second molecular dynamics studies to identify the barriers in attaining previously unidentified low or high energy conformers.

Results:

Although structurally similar to Soli, pikro-CEM-101 was less active in vitro against a panel of organisms. Molecular modeling studies including a study of Boltzmann distribution of conformers, indicate that the conformations of pikro-CEM-101 and Soli are fundamentally different. Differences between Soli and pikro-CEM-101 were observed in the core macrolide ring shape, desosamine's angle of connectivity with the macrolide ring and the aryl alkyl side chain orientation.

Conclusions:

Molecular modeling studies of the structurally similar Soli and pikro-CEM-101 have identified preferred conformations for ribosome binding and can be correlated with MIC results. The modeling results indicate that only specific conformers can interact and bind with the *E. coli* ribosome, which in turn influences the biological activity of structurally similar fluoroketolides.

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