Aminoglycosides inhibit bacterial growth by binding to the A-site decoding region of the bacterial 16s ribosomal RNA (rRNA) within the 30S ribosomal subunit. Previous work has shown that there is approximately a five-fold difference in the affinity of neomycin for the human A-site model and the E. coli model. We have developed a screening assay that rapidly identifies compounds that discriminate between the two model rRNA structures. This approach, coupled with a rapid solid phase synthesis method, has identified active aminoglycosides that show large differences in binding affinity for the E. coli A-site and the human A-site than that of neomycin (~30 fold). The methodology for synthesizing, screening for both ribosomal binding/selectivity and bacterial growth inhibition, and rapid analysis of the data provides a systematic method for identification of bacterial ribosome specific antibacterial that can evade bacterial resistance pathways.


3. Jiang, Li; Watkins, D; jin, y; Gong, C; King, Ada; Washington, A; Green, K; Garneau-Tsodikova, S; Oyelere, A; Arya, D. "Rapid Synthesis and Screening of a Peptidic-aminosugar (PA) library targeting rRNA". ACS Chemical Biology 2015, May 15;10(5):1278-89. doi: 10.1021/cb5010367.
