Comparative analysis of the mechanism of action of Furvina and GE81112, two inhibitors of translation initiation

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Approximately half of all known antibiotics interfere with the bacterial translation apparatus but the translation initiation pathway represents an underexploited target for anti-infectives; Furvina®, (or G1) and GE81112 are among the few antibiotics which selectively inhibit this step of protein synthesis. Both molecules are effective against a wide range of gram-positive and gram-negative bacteria and inhibit protein synthesis both in vivo and in vitro. Both antibiotics target the small ribosomal subunit at or near the P-decoding site and inhibit fMet-tRNA binding during 30S initiation complex formation. Aside from these similarities, the mechanism of inhibition is different for the two antibiotics. G1 interferes with the formation of the 30S pre-initiation complex while GE81112 inhibits the first order isomerization of the 30S pre-initiation complex which yields the 30S initiation complex. Furthermore, inhibition by G1 displays a bias for the nature (purine vs. pyrimidine) of the 3' base of the codon, being effective only when the mRNA directing 30S initiation complex formation and translation contains the canonical AUG initiation triplet or the rarely found AUA triplet, but hardly occurs when the mRNA start codon is either one of the non-canonical triplets AUU or AUC. The codon discrimination by G1 depends upon the presence of IF3 and is reminiscent, though of opposite type, of that displayed by IF3 in its fidelity function. The results of in situ hydroxyl radical probing of the 16S rRNA in the presence and absence of G1 allow the rationalization of the codon bias by G1. On the other hand, inhibition by GE81112 is due to a severe structural modifications of h33 and h44 in the P-site region of the 30S subunit which causes a faulty positioning of both fMet-tRNA and mRNA and prevents canonical codon-anticodon base-pairing between these two ligands which is characteristic of a locked 30S initiation complex. Therefore, the 30S complex formed in the presence of GE81112 has an altered structure, unfit for optimal docking by the 50S subunit so that the 30S initiation complex → 70S initiation complex transition and dissociation of the initiation factors IF1, IF2 and IF3, which accompanies this process, are slowed.

Key words Translation initiation; P-site inhibition; fMet-tRNA binding; initiation triplet bias; initiation factors