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Structure-guided design, synthesis, and evaluation of guanine-derived inhibitors of the eIF4E mRNA-cap interaction

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Abstract

The eukaryotic initiation factor 4E (eIF4E) plays a central role in the initiation of gene translation and subsequent protein synthesis by binding the 5' terminal mRNA cap structure. We designed and synthesized a series of novel compounds display potent binding affinity against eIF4E despite their lack of a ribose moiety, phosphate, and positive charge as present in m7-GMP. The biochemical activity of compound **33** is 95 nM for eIF4E in an SPA binding assay. More importantly, the compound has an IC_{50} of 2.5 □M for inhibiting cap-dependent mRNA translation in a rabbit reticular cell extract assay (RRL-IVT). This series of potent, truncated analogues could serve as a promising new starting point towards the design of neutral eIF4E inhibitors with physicochemical properties suitable for cellular activity assessment.

