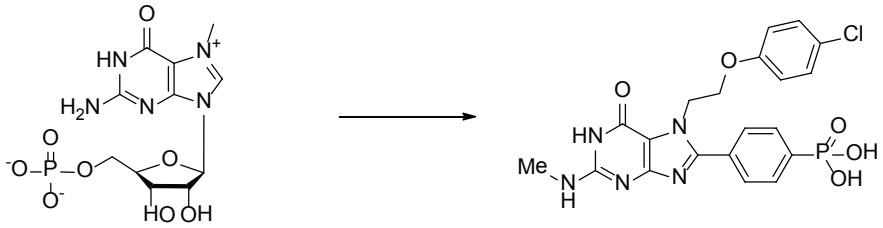
OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

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

Xiaoqi Chen
Amgen, USA

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 displaying 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 IC50 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.



m7-GMP, eIF4E SPA IC_{50}=14∝M

33, eIF4E SPA IC_{50}=95nM

xiaoqic@amgen.com