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POSTER

Targeting the production of oncogenic miRNAs using synthetic small molecules

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Abstract

MicroRNAs (miRNAs or miRs) are a class of evolutionary conserved small non-coding RNAs that act as post-transcriptional regulators of gene expression. A wide number of studies has shown that the aberrant expression of miRNAs could be responsible for initiation and development of human cancers. Most of these deregulated miRNAs are overexpressed, thus being oncogenic. For these reasons, the inhibition of oncogenic miRNAs function or production would be a very promising approach for the development of new anticancer therapies [1].

The purpose of this work is the discovery of small-molecule drugs targeting the precursors of specific oncogenic miRNAs thus modulating their production. We have focused our attention on miRNA-372 and miRNA- 373 that are implicated in various cancers. For example, these two oncogenics (pre-miRNAs 372 and pre-miRNAs 373): two stem-loop structured RNAs that lead to mature miRNAs after cleavage by the enzyme Dicer. In the aim of inhibiting this biogenesis step and based on our previous works [2], we synthesized a novel series of RNA ligands composed of two different domains: (i) 2-deoxystreptamine (2-DOS) known as RNA-interacting group due to its role as a central scaffold of any known aminoglycosides [3] and (ii) aromatic or heteroaromatic groups that should improve affinity and selectivity of these ligands for the targeted RNAs. These two domains have been conjugated through carbamate, triazole and ether bonds in order to develop a simple and straightforward synthetic methodology and obtain a large number of diversified compounds.

We obtained a library of 16 compounds which will be evaluated in vitro in order to identify the strongest RNA ligands that could be able to inhibit the production of the targeted oncogenic miRNAs and eventually lead to the inhibition of cancer cells proliferation.

Keywords

Inhibition, miRNA, small molecule ligands

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