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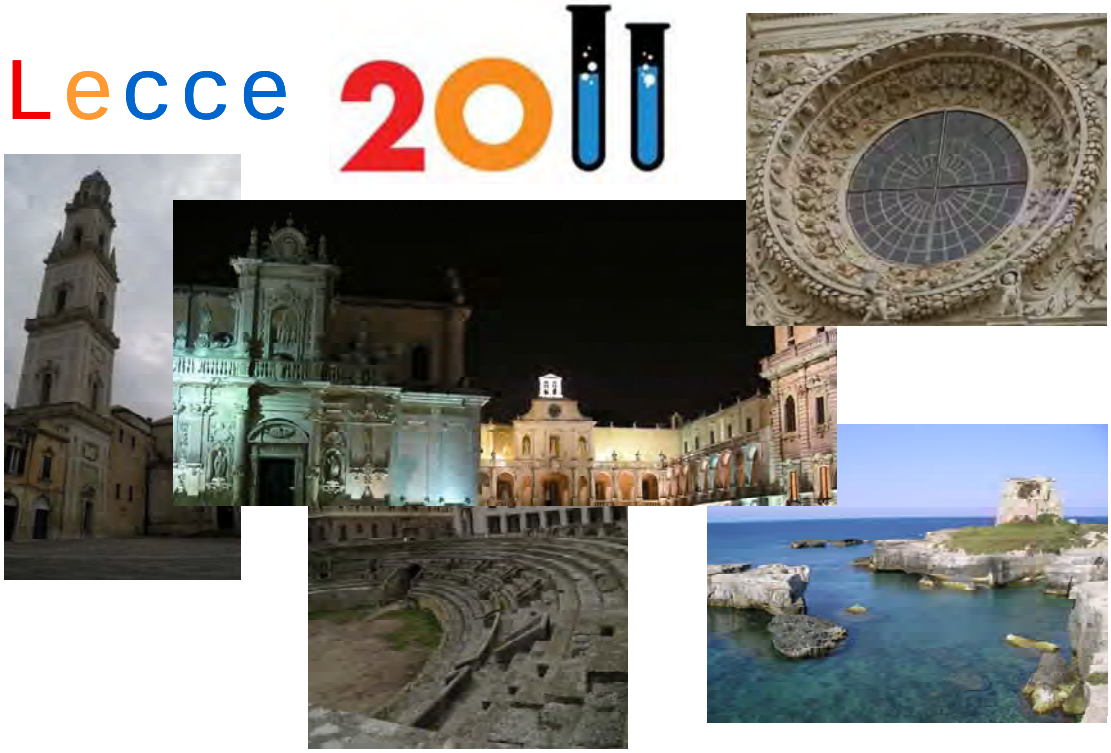

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ATTI DEL CONGRESSO

CSB-OR-17 siRNAs bearing aromatic residues in the 3'-overhang region

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RNA interference (RNAi) is a biological process whereby small interfering RNA (siRNA) and microRNA (miRNA) silence gene expression in a sequence-specific manner [1]. These effectors regulate gene expression through the RNA-induced silencing complex (RISC). It has been suggested that RISC preferentially selects and incorporates one of two strands of the siRNA duplex depending on its thermodynamic features and that the off-target effects of siRNAs can be correlated to the T_m of the duplex [2]. The problem of unwanted incorporation of the passenger strand into RISC could be address altering the thermodynamic asymmetry of the duplex by using specific chemical modifications [3, 4]. Structural studies have revealed that the 3'-overhang region of the guide strand of siRNA is recognized by the PAZ domain and is accommodated into its hydrophobic binding pocket. We expected that aromatic-based modifications in 3'-overhang would enhance RISC selection of antisense strands of siRNA duplexes, reducing off-target effects induced by sense strands.
In this study, we report the synthesis of siRNAs bearing diphenylpropylamine, tyramine and tryptamine units at the 3'-end of sense and antisense strands. We found thermodynamic stability of the conjugates was increased by these modifications. Furthermore, but not surprisingly, the modified duplexes were found to retain RNA-like A-type conformation. We also assessed the nuclease resistance of the modified siRNAs and found it was similar to those of unmodified siRNAs. These results prompted us to investigate the silencing activity of the siRNAs possessing the aromatic moiety in the 3'-end by *in vitro* experiments in mammalian cells.

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