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(54) Title: MODIFIED RNA AGENTS WITH REDUCED OFF-TARGET EFFECT

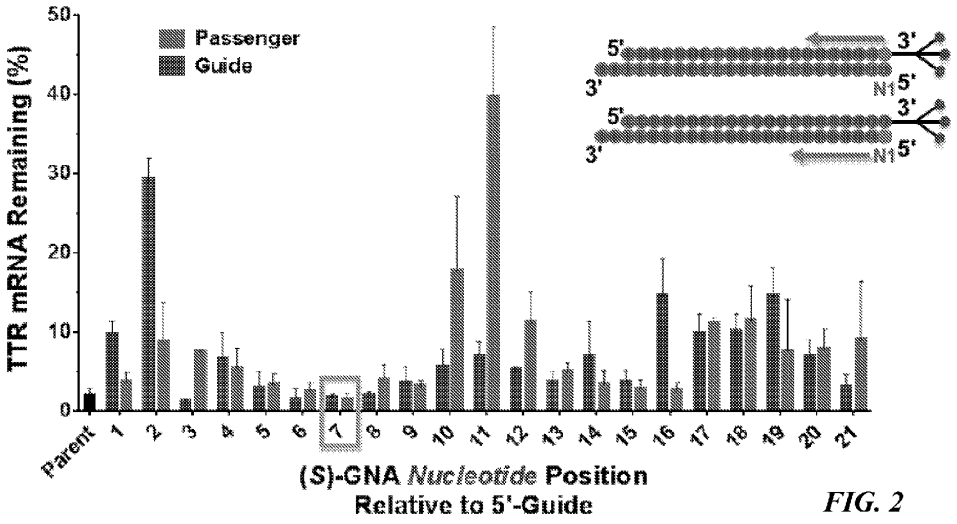


FIG. 2

(57) Abstract: One aspect of the present invention relates to double-stranded RNA (dsRNA) agent capable of inhibiting the expression of a target gene. The antisense strand of the dsRNA molecule comprises at least one thermally destabilizing nucleotide occurring at a seed region; the dsRNA comprises at least four 2'-fluoro modifications, and the sense strand of the dsRNA molecule comprises ligand, wherein the ligand is an ASGPR ligand. Other aspects of the invention relates to pharmaceutical compositions comprising these dsRNA molecules suitable for therapeutic use, and methods of inhibiting the expression of a target gene by administering these dsRNA molecules, *e.g.*, for the treatment of various disease conditions.

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