Docket #: S23-476

Molecules and methods for modifying RNA with aryl groups

Researchers at Stanford have identified a novel class of ribonucleic acid (RNA)-reactive groups that effectively modify the RNA by placing heteroaryl and aryl groups at the 2'-hydroxyl (OH) positions.

RNA plays a pivotal role in many crucial cellular processes, and the reactivity and interactions of its functional groups are central to its dynamic and versatile nature. Because the 2'-OH functional group is found in almost every RNA nucleotide regardless of sequence, 2'-OH targeting molecules can be used to manipulate the RNA for various experimental or therapeutic purposes. However, previous studies have identified only a limited number of chemical structures that react with 2'-OH groups, all of them in acyl (carbonyl) or sulfonyl groups. These structures have not been ideal for RNA modification, because most of them hydrolyze in water and require a potentially toxic cosolvent for solubility.

Stanford researchers have recently demonstrated that tertiary amine-activated aryl groups can react in high yields with 2'-OH groups in RNA. Because these aryl groups are chemically stable and water soluble, they could easily maintain the effective concentration for reactions. Combined with next-generation sequencing and biophysical studies, such reactions could provide a better understanding of RNA biology and enable a wide range of applications.

Stage of Development
In vitro research

Applications

- Labeling RNAs (e.g., with biotin, fluorescent labels) for detection and analysis
- Stabilizing RNA from hydrolysis
- Enhancing protein expression

- Mapping RNA folded structure
- Profiling RNA interactions
- Probing RNA structure and function
- Modulating RNA immunogenicity

Advantages

- Selective reactions at 2'-OH
- High reactivity
- Easily synthesized, conjugated, and purified
- Water soluble (can function without organic solvent)
- Chemically stable
- Distinct chemical structure (aromatic) that may confer new properties to RNA

Publications

- Xiao, L., Fang, L., Chatterjee, S., & Kool, E. T. (2023). Diverse Reagent Scaffolds Provide Differential Selectivity of 2'-OH Acylation in RNA. *Journal of the American Chemical Society, 145*(1), 143–151.

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