

Design of an RNA-Targeting Compound Collection: A Methodological Journey Through Chemical Space

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RNA splicing modulation is a promising therapeutic strategy applicable to a broad range of diseases with high unmet medical need, including myotrophies, Alzheimer's disease, and cancers, with up to 70.5% of the human genome potentially druggable at the RNA level. However, biological evaluation of splicing modulators is costly and resource-intensive, making rational collection design essential. We developed a multi-step cheminformatics strategy to build a focused RNA-targeting chemical space. Starting from experimentally validated RNA binders, we used several tools to navigate chemical space and assess complementarity with Sanofi's compound patrimony, leading to the acquisition of commercial RNA-focused collections. Systematic mining of patents revealed a chemical space largely orthogonal to known RNA binders, along with a common structural pattern. These findings and methods were then combined to guide de novo compound design and cherry-picking from commercial catalogs, filling remaining gaps in the targeted chemical space. This integrated approach—combining chemical space analysis, patent intelligence, and expert curation—produced a diverse, curated RNA-targeting collection now undergoing biological evaluation. The methodology enables rational compound prioritization for costly splicing assays and is generalizable to other emerging target classes.