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Medicinal Chemistry of RNA Therapeutics: Balancing Potency, Selectivity and ADMET

Stang Torres*

Department of Pharmaceutical Chemistry, University of Debrecen, Debrecen, Hungary

Introduction

RNA therapeutics have emerged as a disruptive modality capable of directly modulating gene expression, offering new treatment possibilities for genetic disorders, cancers and infectious diseases. From Antisense Oligonucleotides (ASOs) to siRNAs, mRNA vaccines and RNA-editing tools, these molecules bring unprecedented precision to therapeutic design. However, realizing their full potential requires overcoming critical challenges related to chemical stability, delivery, selectivity and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity). Medicinal chemistry plays a central role in optimizing these properties, thereby transforming fragile nucleotide strands into robust, safe and efficacious drugs. To enhance potency, medicinal chemists apply sugar, backbone and base modifications that improve target affinity and resistance to nuclease degradation. Common strategies include the use of 2′-O-methyl, 2′-fluoro and phosphorothioate substitutions, as well as Locked Nucleic Acids (LNAs), which stabilize RNA conformation. These modifications extend half-life and maintain high sequence-specific binding, ensuring efficient gene silencing or protein translation. Selectivity is engineered through precise sequence design, avoiding off-target base pairing and immunostimulatory motifs. Targeted delivery is achieved using chemical conjugation methods such as GalNAc (N-acetylgalactosamine) for liver-directed delivery or encapsulation in Lipid Nanoparticles (LNPs), which enable uptake by specific cell types [1].

Description

These systems reduce systemic exposure and maximize functional outcomes while minimizing immune activation. ADMET optimization remains one of the most active areas of RNA therapeutic development. Strategies include modulating molecular charge, size and hydrophilicity to control biodistribution and renal clearance. Moreover, delivery systems must ensure endosomal escape for cytoplasmic or nuclear action. LNPs used in mRNA vaccines have demonstrated the clinical viability of this approach, inspiring further design improvements for therapeutic RNA payloads. Ongoing research into circular RNA, self-amplifying RNA and site-directed RNA editing is rapidly expanding the complexity and reach of RNA therapeutics. These emerging modalities will require equally advanced medicinal chemistry frameworks to balance their potency, selectivity and ADMET properties. Circular RNAs offer increased stability and longer duration of expression due to their resistance to exonuclease degradation, making them attractive for protein replacement therapies. Self-amplifying RNA can produce sustained protein output at lower doses, but its larger size poses formulation and delivery challenges that must be addressed through innovative chemical strategies. Site-directed RNA editing tools, such as those leveraging ADAR enzymes, allow for transient correction of genetic mutations without permanent changes to the genome, offering a safer alternative to DNA editing. Medicinal chemistry must now evolve to accommodate these platforms by designing delivery vectors, structural modifications and conjugation methods that preserve activity while enhancing pharmacological performance [2-3].

RNA therapeutics have rapidly evolved into a transformative drug class, encompassing modalities such as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), microRNA modulators, aptamers and messenger RNA (mRNA)-based therapies. These agents hold tremendous promise for addressing diseases that are difficult to target with traditional small molecules or biologics. However, their successful translation into the clinic depends on overcoming fundamental challenges in potency, selectivity and ADMET (absorption, distribution, metabolism, excretion and toxicity) areas where medicinal chemistry plays a decisive role. Potency in RNA therapeutics is governed by sequence design, chemical backbone modifications and conjugation strategies that enhance binding affinity to target RNA and ensure efficient gene silencing or expression modulation. Selectivity is equally critical, as unintended interactions with non-target transcripts can lead to off-target effects and toxicity. Medicinal chemistry solutions such as locked nucleic acids (LNAs), phosphorothioate linkages, ribose modifications and stereochemical optimization are employed to improve hybridization fidelity and minimize cross-reactivity. These design principles help maximize therapeutic windows while preserving RNA's inherent biological function [4].

ADMET considerations present unique challenges in RNA drug discovery. Naked RNA molecules are highly susceptible to nuclease degradation, have poor cellular uptake and face hurdles in endosomal escape. To address these barriers, chemists employ lipid nanoparticles (LNPs), peptide conjugates, GalNAc conjugation for liver targeting and biodegradable polymer carriers. Additionally, modification of the sugar-phosphate backbone enhances plasma stability, while careful chemical tuning minimizes immunogenicity and systemic toxicity. These strategies exemplify the delicate balance between maintaining biological activity and ensuring safe pharmacokinetics. The medicinal chemistry of RNA therapeutics is thus a dynamic interplay between molecular design, delivery engineering and safety optimization. As RNA drugs expand into areas such as oncology, rare genetic disorders, infectious diseases and vaccines, the ability to fine-tune their chemical properties will be central to their long-term success. Balancing potency, selectivity and ADMET not only enhances clinical outcomes but also establishes RNA therapeutics as a sustainable and versatile drug class in modern precision medicine [5].

Conclusion

The rapid rise of RNA therapeutics underscores their transformative potential in modern medicine, yet their success depends heavily on the precise application of medicinal chemistry principles. By carefully balancing potency, selectivity and ADMET properties, researchers can overcome the inherent challenges of instability, delivery barriers and off-target effects. Chemical modifications to the backbone and nucleobases, innovative

***Address for Correspondence:** Stang Torres, IISER Pune, Department of Pharmaceutical Chemistry, University of Debrecen, Debrecen, Hungary, E-mail: torres.stang@debrecen.hg*

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conjugation strategies and advanced delivery platforms have already reshaped the therapeutic landscape, enabling RNA drugs to progress from experimental concepts to approved medicines. Medicinal chemistry lies at the heart of RNA therapeutic development, enabling these fragile biomolecules to become powerful and targeted drugs. Through chemical modification, delivery innovation and pharmacokinetic tuning, RNA-based treatments are now overcoming previous limitations to address unmet medical needs. The next generation of RNA medicines will benefit from continued multidisciplinary collaboration and advanced molecular design that ensures safety, stability and precision.

Acknowledgment

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Conflict of Interest

None.

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