Synthesis and RNA Binding Properties of Novel Azaspirocycles

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Spirocycles, found in natural and synthetic products,[1] have recently gained attention in medicinal chemistry due to their unique 3D structure and favorable physicochemical properties, such as enhanced solubility, reduced lipophilicity, and improved metabolic stability.[2] Their rigidity also facilitates better binding element orientation, boosting efficacy and selectivity, making them valuable compounds for drug development.[3]

In this study, we present diverse synthetic pathways for the preparation of novel azaspirocycles, starting from bicyclic hydrazines functionalized at their bridgehead carbon atoms. Key reactions leading to the desired spirocyclic cores include double reductive amination, intramolecular cyclization, and N−N bond cleavage.[4]

As stated above, the resulting molecules show promise in medicinal chemistry. With increasing interest in nucleic acid targeting as a complementary strategy to protein-directed approaches for developing new bioactive compounds, we explored the applicability of the different azaspirocycles as RNA binders. As a proof of concept, select compounds demonstrated strong affinity for HIV-1 TAR RNA and effectively inhibited Tat/TAR interactions, suggesting their potential relevance for therapeutic development.[5]

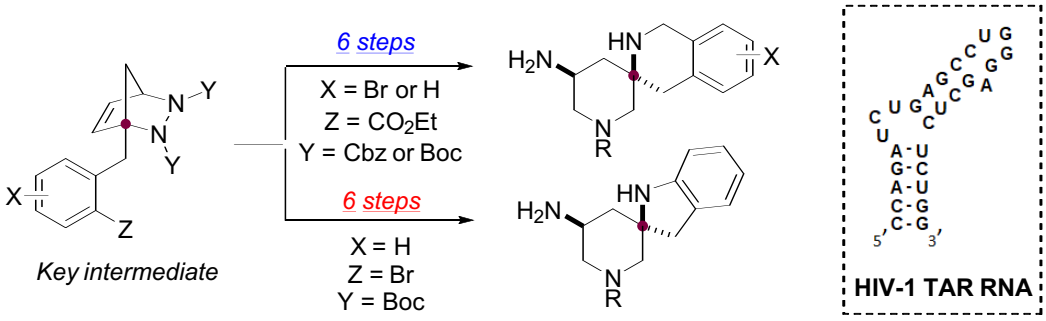

Figure 1: Access to novel azaspirocycles

References

[0] Moss, G. P. *Pure Appl. Chem.* **1999**, *71*, 531.
[2] Benedetti, E. Micouin, L. *Expert Opin. Drug Discov.* **2024**.
[3] Talele, T. T. *J. Med. Chem.* **2020**, *63*, 13291.
[4] Fleurisson, C. Graidia, N. Foricher, Y. Benedetti, E. Micouin, L. *Org. Biomol. Chem.* **2023**, *21*, 3542.
[5] Fleurisson, C. Graidia, N. Azzouz, J. Di Giorgio, A. Gaysinski, M. Foricher, Y. Duca, M. Benedetti, E. Micouin, L. *Chem. Eur. J.* **2024**, e202403518.