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A FAST NMR-ASSISTED COMBINATORIAL METHOD FOR OPTIMIZING NUCLEIC ACID BINDERS

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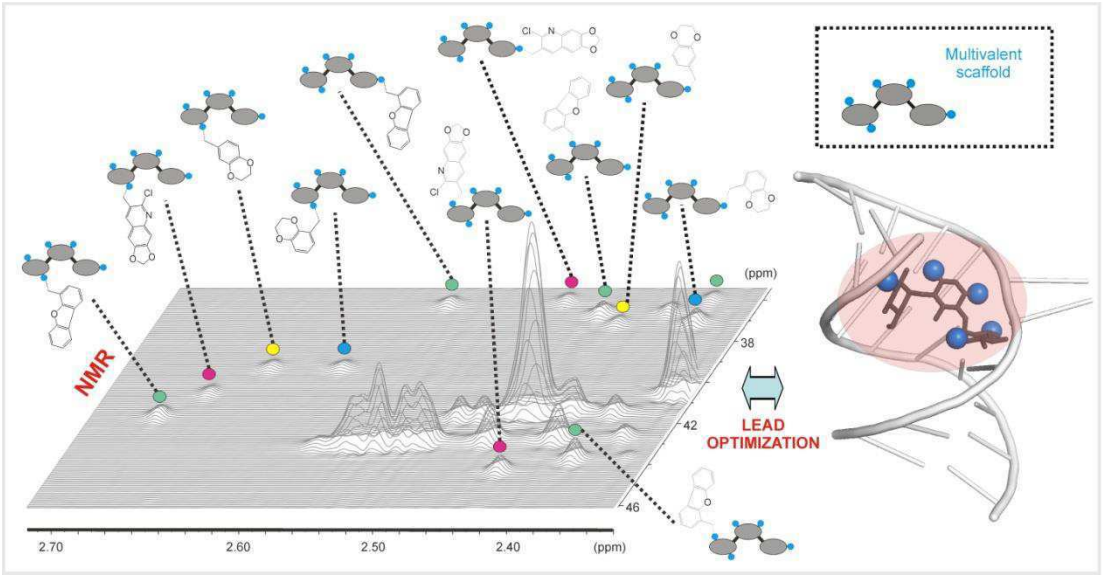
Development of strong and selective binders from promiscuous lead compounds represents one of the most expensive and time-consuming tasks in drug discovery. Herein we present a novel fragment-based combinatorial strategy for the optimization of multivalent polyamine scaffolds as DNA/RNA ligands. Our protocol provides a quick access to a large variety of regioisomer libraries that can be tested for selective recognition by combining microdialysis assays with simple isotope labeling and NMR experiments. To illustrate our approach, 20 small libraries comprising 100 novel kanamycin-B derivatives have been prepared and evaluated for selective binding to the ribosomal decoding A-Site sequence. Contrary to the common view of NMR as a low-throughput technique, we demonstrate that our NMR methodology represents a valuable alternative for the detection and quantification of complex mixtures, even when integrated by highly similar or structurally related derivatives, a common situation in the context of a lead optimization process. Furthermore, this study provides valuable clues about the structural requirements for selective A-site recognition [1].



[1] E. Jiménez-Moreno, L. Montalvillo-Jiménez, A.G. Santana, A.M. Gómez, G. Jiménez-Osés, F. Corzana, A. Bastida, J. Jiménez-Barbero, F.J. Cañada, I. Gómez-Pinto, C. González, J.L. Asensio, *J. Am. Chem. Soc.* **2016**, *138,* 6463-6474.