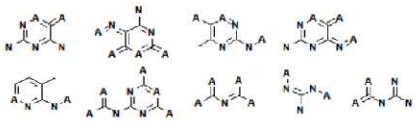
Macrocycles for RNA Drug Discovery

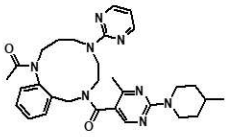
RNA is an emerging class of therapeutic targets that require identification and development of potent small molecule drugs. RNA-relevant chemical matter is deemed to be somewhat different from existing protein-targeting modalities and this area of research requires the integration of new ideas, design concepts, and efficiency in the production of new molecules. Comparative analyses of binding sites and ligands of RNAs and proteins have revealed that RNA pockets are less buried and more polar, and often adopt ligands that have elongated "rod"-like molecular shapes [1]. The incorporation of known RNA recognition pharmacophores [2-4] into the design of novel RNA-binding molecules is beneficial as this increases the corresponding success rate in finding new RNA-targeted hits. In addition to promising target recognition features, an RNA-binding molecule should also demonstrate reasonable intracellular bioavailability. There is a growing scientific record that properly functionalized macrocyclic scaffolds could generate very ligand-efficient molecules with advantageous cell permeability properties. These and other factors make macrocycles promising scaffolds for the design of novel RNA-targeting molecules.

Our collection of macrocycles for RNA consists of very diverse, drug-like molecules which incorporate certain known RNA-recognition elements (e.g. nucleobase ring systems and analogs) distributed withing macrocyclic rings or peripheral fragments. As macrocyclic molecules tend to be larger than traditional screening molecules, it is vital to carefully assess and control their physicochemical properties. All our macrocycles have been tested for **aqueous and DMSO solubility** with cut-offs applied at 10 mM in DMSO and 50 µM in PBS (pH 7.4); **PAMPA** permeability has also been tested for representative set of macrocycles.

Figure 1

Ring size: 10-18
MW: av. 510
RNA-recognition features[1] inbuilt into a macrocyclic core
Final Compounds: 5-15 mg (LCMS and 10% ^{1}HNMR)
Experimental Solubility & PAMPA 10%





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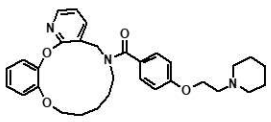

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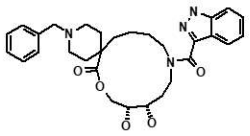

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Feature of Binders	RNA	Protein
Number of positive atoms	2	1-3
Number of negative atoms	0	1
HBD	1-5	0-3
HBA	6-10	7-9

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Literature:

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2. JRizvi NF, Santa Maria JP Jr, Nahvi A, et al. Targeting RNA with Small Molecules: Identification of Selective, RNA-Binding Small Molecules Occupying Drug-Like Chemical Space. SLAS Discov.
3. KD Warner, CE Hajdin, KM Weeks Principles for targeting RNA with drug-like small molecules Nat Rev Drug Discov 2018 Aug;17(8):547-5
4. Sanjukta Mukherjee, Leszek Błaszczyk, Wojciech Rypniewski, Christoph Falschlunger, Ronald Micura, Asako Murata, Chikara Dohno, Kazuhiko Nakatani, Agnieszka Kiliszek, Structural insights into synthetic ligands targeting A–A pairs in disease-related CAG RNA repeats, Nucleic Acids Research, Volume 47, Issue 20, 2019, p 10906–10913