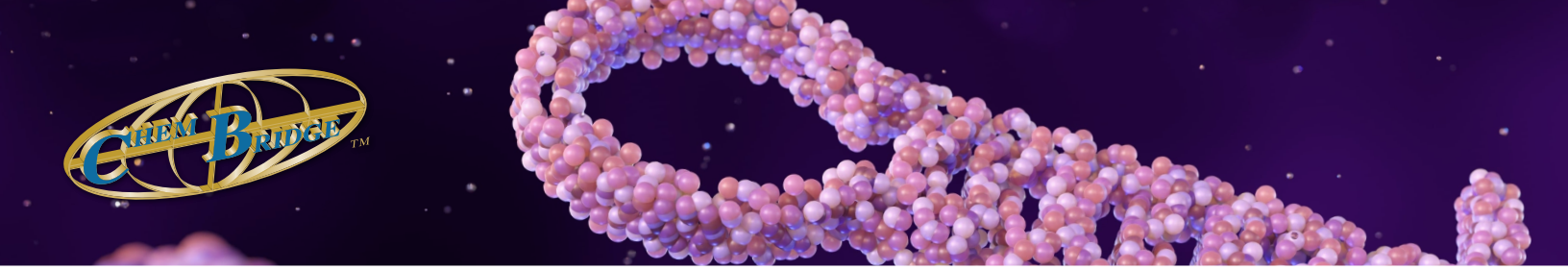


HIGH-QUALITY COMPOUNDS FOR SCREENING AGAINST RNA TARGETS

RNA Focused Libraries

- **ROBIN RNA Binders:** In-stock, structural matches to small molecule binders of non-ribosomal RNA targets reported in the ROBIN database.
- **RNA Focused Library:** Structures selected from ChemBridge's stock using a machine learning approach to identify compounds with a higher probability of binding non-ribosomal RNA targets.

Small molecules that target nucleic acids, in particular non-ribosomal RNA targets, offer an attractive option to the use of siRNAs, shRNAs and other nucleic acid silencing/antisense approaches for targeting nucleic acids, based on the limitations of such approaches. Non-ribosomal RNA targets have been implicated in a range of different disease areas, including cancer, cardiovascular, and neurodegenerative diseases, which has led to an increased interest in identifying small molecule chemical probes and hits for use as starting points in drug discovery programs targeting RNA.

Resources

The ROBIN RNA Binders set and RNA Focused Library are based on the following primary resources.

ROBIN Database

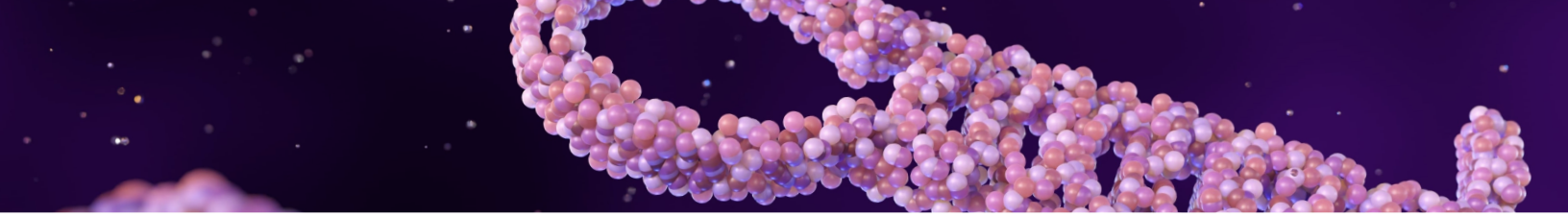
The ROBIN database[1], curated by the Chemical Biology Laboratory of the Center for Cancer Research at the NCI, Frederick, MD, provides a source of 2,003 non-ribosomal RNA-binding small molecule compounds[2,3]. These structures were identified through small molecule microarray screening and are based on the result of 27 individual screens performed using compounds from a library of 24,572 small molecules. The RNA targets screened represented G-quadruplex, hairpin, pseudoknot, three-way junction, and triple helix RNA structure types.

R-BIND Database

The R-BIND database[4,5], curated by the Hargrove Lab (University of Toronto) provides a source of 153 structures for bioactive small molecule chemical probes active against non-ribosomal RNA targets. It contains non-covalent, small molecule chemical probes with reported biological activity that target non-ribosomal RNA targets. The chemical probes were found to be active in cell-based and/or animal models. The probes have been classified by the following RNA structural target classes: Bulges, G-quadruplexes, double-stranded RNA, internal loops, and stem loops.

ROBIN RNA Binders Set

All compounds in this set represent structural matches to compounds included in the file "ROBIN_RNA_Binders_3D.sdf" made available by the authors of the ROBIN database article as part of supplementary material.[2] ChemBridge compounds included in this set are available to order from our stock (availability can change over time).



RNA Focused Library

Highlights

- Machine learning approach used to identify compounds with higher probability of binding to RNA targets
- Offers both diverse final compound structures and Murcko scaffold diversity
- Custom-select from more than 70,000 compounds according to your requirements

Method

To identify compounds with a higher probability of occupying RNA-binding chemical space, a machine-learning classifier trained entirely on publicly available experimental data was developed. The positive training set combined 2,003 validated RNA binders from the ROBIN dataset with 153 curated bioactive RNA ligands from the R-BIND database. The negative set comprised 2,000 compounds from the same ROBIN small-molecule microarray campaigns that showed no measurable binding to the RNA targets assessed.

Each compound was characterized by 208 calculated 2D physicochemical and topological descriptors. Feature selection reduced this to the 25 most informative descriptors, and a Random Forest classifier was trained on these descriptors under 5-fold cross-validation. The most influential descriptors describe molecular complexity, saturation and polar-atom character: BertzCT (topological complexity), FractionCSP3 (fraction of sp3-hybridized carbon), HallKierAlpha (branching and flexibility), and a set of BCUT2D terms encoding atomic contributions to molecular refractivity, lipophilicity and mass. This profile is consistent with the higher three-dimensionality and distinct polarity reported for RNA-targeted bioactives relative to conventional protein-directed screening libraries.

The trained model returns a continuous RNA Space Probability (RSP) score between 0 and 1 for any input structure. The model was applied to a lead-like and drug-like subset of ChemBridge's stock, with compounds scoring RSP greater than or equal to 0.84 retained. These compounds comprise the RNA-Focused Library, enriched for structures resembling experimentally validated RNA binders.

Characteristics

The set of more than 70,000 compounds offers diverse structures, and more than 42,000 unique Murcko scaffolds are represented. The RNA Focused Library compounds are lead-like and drug-like and have the following physiochemical and calculated property averages:

- Molecular Weight: 364
- Fsp3: 0.44
- clogP: 1.45
- TPSA: 79
- H-bond Donor Count = 1.75
- H-bond Acceptor Count = 4.57
- Rotatable Bond Count = 4.9

References

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