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Библиотеки РНК-изостерических тринуклеотидомиметиков

RNA Isosteric Trinucleotide Mimetics (rITM)
RNA Expansion Repeats Targeted Small Molecule Library

RNA Expansion Repeats – New Druggable Targets

Expansions of short nucleotide repeats produce several neurological and neuromuscular disorders, including

- Amyotrophic Lateral Sclerosis (ALS)
- Frontotemporal lobar degeneration (FTLD)
- Huntington disease (HD)
- Muscular dystrophy (MD)
- Spinal and bulbar muscular atrophy (SBMA)
- Spinocerebellar ataxia (SCA)
- Fragile XE mental retardation (FRAXE)

Connelly, C.M. et al. (2017) The Emerging Role of RNA as a Therapeutic Target for Small Molecules. Cell Chem. Biol. 23 (9) 1077-1090.

Angelbello, A.J. et al. (2018). Using Genome Sequence to Enable the Design of Medicines and Chemical Probes. Chem. Rev. 118 (4), 1599–1663.

Berry-Kravis, E.M. (2018) Drug development for neurodevelopmental disorders: lessons learned from fragile X syndrome. Nat. Rev. Drug. Discov. 17 (4), 280-299.

Challenges for Selective Targeting of Folded 3D RNA Structures

- Different weights of the contributing physico-chemical interactions in the total score of ligand-target ensemble in RNA chemical space vs protein chemical space
- Need to identify physiochemical properties and desirability thresholds for the corresponding descriptors that can distinguish RNA binders from protein binders
- Various RNAs have been validated as therapeutic targets through the use of antisense oligonucleotides, however, the latter have non-druglike properties and therefore have limitations as pharmaceutical agents.

Rizvi, N.F. et al. (2017) RNA as a small molecule druggable target. Bioorg. & Med. Chem. Lett. 27 (23), 5083–5088.

Liang, X. et al. (2016) Translation efficiency of mRNAs is increased by antisense oligonucleotides targeting upstream open reading frames. Nature Biotechnology 34, 875–880.

Expansion nucleotide repeats linked to neurogenerative disorders

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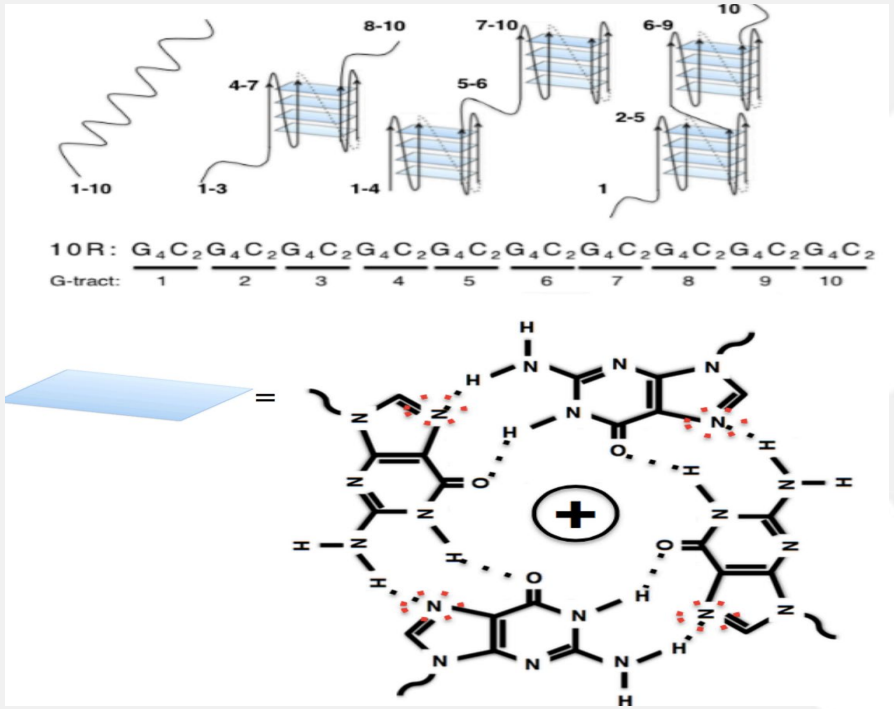
Disease Type	Gene	RNA Repeat	Normal/wild type	Pathogenic
DRPLA (Dentatorubropallidoluysian atrophy)	ATN1 / DRPLA	CAG	6 - 35	49 - 88
HD (Huntington's disease)	HTT	CAG	6 - 35	36 - 250
SBMA (Spinal and bulbar muscular atrophy)	AR	CAG	9 - 36	38 - 62
SCA1 (Spinocerebellar ataxia Type 1)	ATXN1	CAG	6 - 35	49 - 88
SCA2 (Spinocerebellar ataxia Type 2)	ATXN2	CAG	14 - 32	33 - 77
SCA3 (Machado-Joseph disease)	ATXN3	CAG	12 - 40	55 - 86
FRAXA (Fragile X syndrome)	FMR1	CGG	6 - 53	230+
FXTAS (Fragile X-associated tremor/ataxia syndrome)	FMR1	CGG	6 - 53	55-200
FRAXE (Fragile XE mental retardation)	AFF2 / FMR2	CCG	6 - 35	200+
FRDA (Friedreich's ataxia)	FXN or X25	GAA	7 - 34	100+
DM1 (Myotonic dystrophy Type 1)	DMPK	CUG	5 - 34	50+
ALS (Amyotrophic lateral sclerosis) and FTLD (Frontotemporal lobar degeneration)	C9orf72	GGGGCC	2 - 30	250+

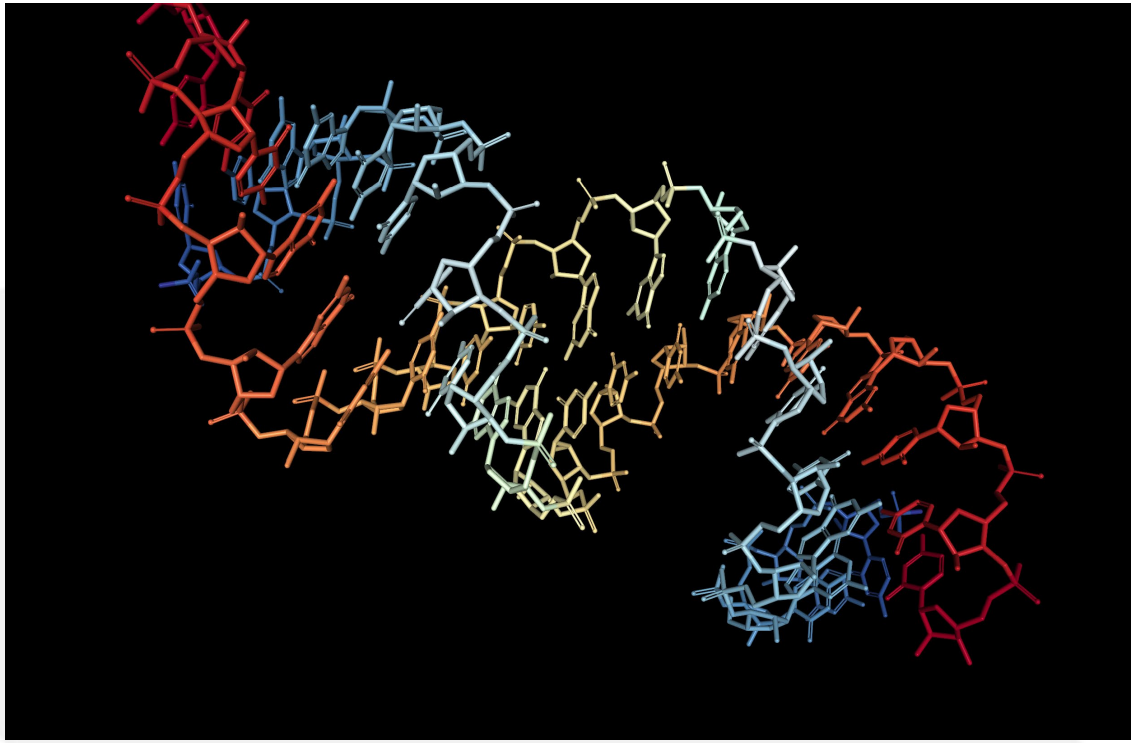
Disease Type	RNA Repeat	Complementary RNA Trinucleotide Repeats
DRPLA (Dentatorubropallidoluysian atrophy)	CAG	GUC
HD (Huntington's disease)	CAG	GUC
SBMA (Spinal and bulbar muscular atrophy)	CAG	GUC
SCA1 (Spinocerebellar ataxia Type 1)	CAG	GUC
SCA2 (Spinocerebellar ataxia Type 2)	CAG	GUC
SCA3 (Machado-Joseph disease)	CAG	GUC
FRAXA (Fragile X syndrome)	CGG	GCC
FXTAS (Fragile X-associated tremor/ataxia syndrome)	CGG	GCC
FRAXE (Fragile XE mental retardation)	CCG	GGC
FRDA (Friedreich's ataxia)	GAA	CUU
DM1 (Myotonic dystrophy Type 1)	CUG	GAC
ALS (Amyotrophic lateral sclerosis) and FTLD (Frontotemporal lobar degeneration)	GGGGCC	CCC, CCG, CGG

Complementary RNA trinucleotide repeats used as templates for the 3D shape similarity virtual screening

Knowledge Progression & Selection - Example

Amyotrophic lateral sclerosis C9orf72 => r(GGGGCC)n | Antisense r(CCCCGG)n





Conlon, E.G. et al. (2016) The C9ORF72 GGGGCC expansion forms RNA G-quadruplex inclusions and sequesters hnRNP H to disrupt splicing in ALS brains.
Elife. 5. pii: e17820. doi: 10.7554/eLife.17820.

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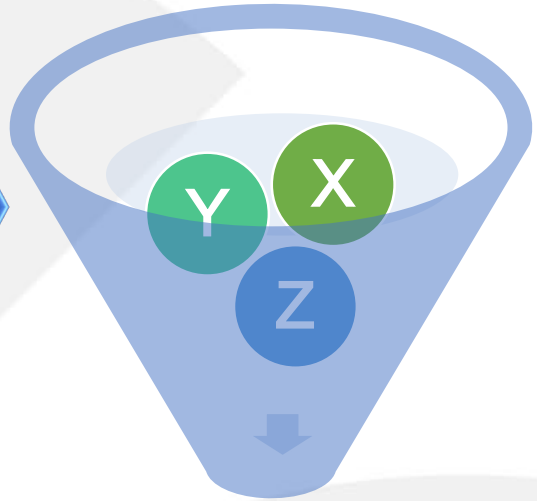
1.5M Stock Compounds



Search in PDB for 3D structures containing GUC, GCC, GGC, CUU, GAC, CCC, CCG, CGG

Learning → Analysis → Virtual Screening and CADD → Selection → Screening

Reference Compounds FASTA search for 3D structures in PDB

► Extracting 3D coordinates of trinucleotide sequences
► Calculating molecular surfaces
► Detaching the backbone

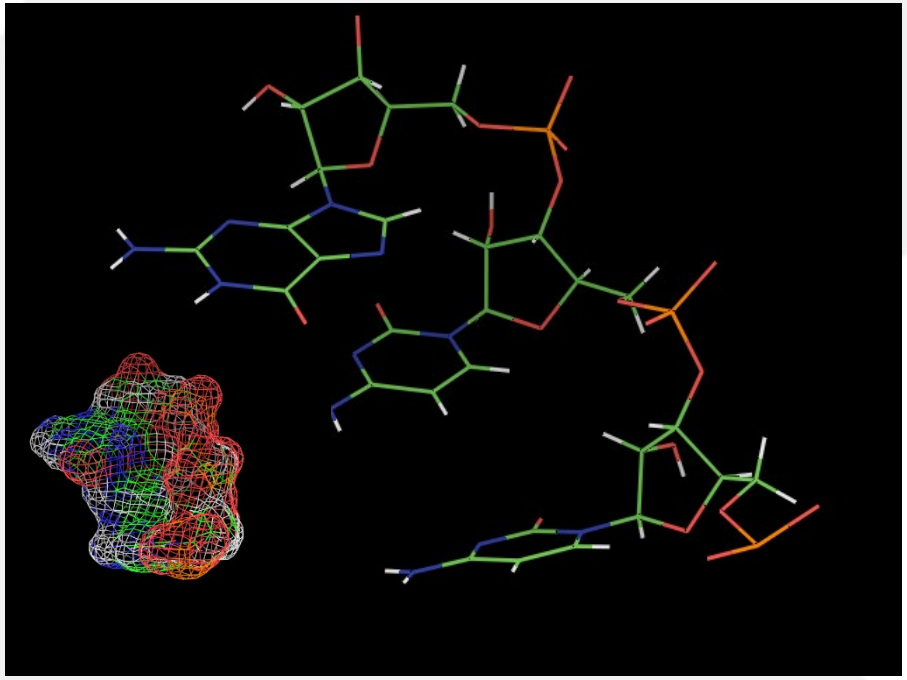
► 3D Shape similarity
► van der Waals surfaces alignment
► Electrostatic potential surfaces alignment
► 3D Pharmacophore modeling
► Integral scoring function
► Expert opinion

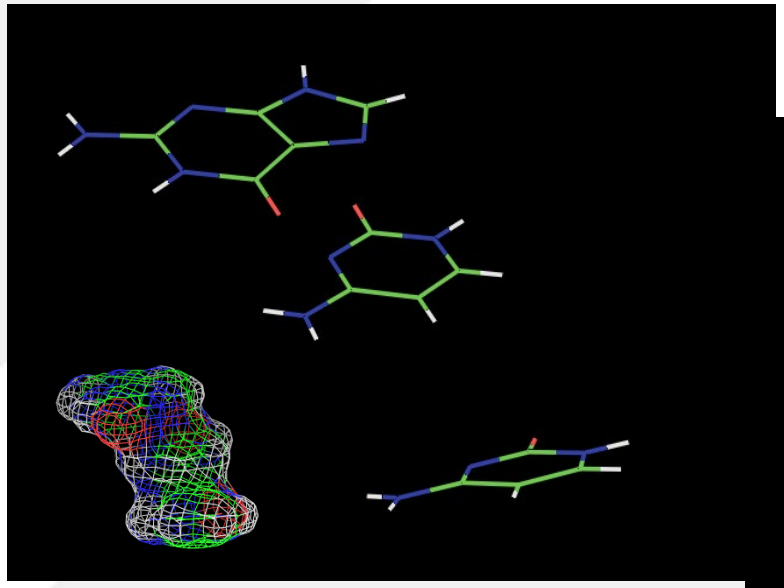
► Combining each trinucleotide mimetics hit series
► Focus on novel chemistry
► Scaffold prioritization
► MedChem Filters

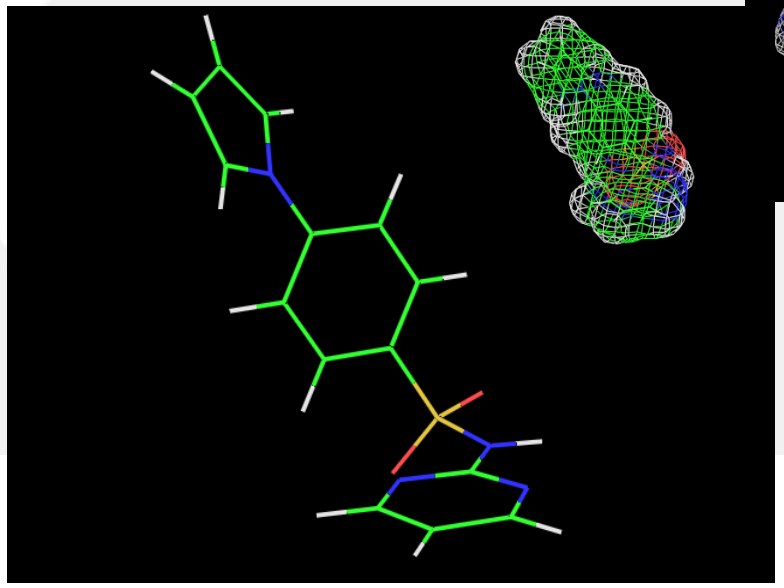
RNA Isosteric Trinucleotide Mimetics Library 26,000 compounds

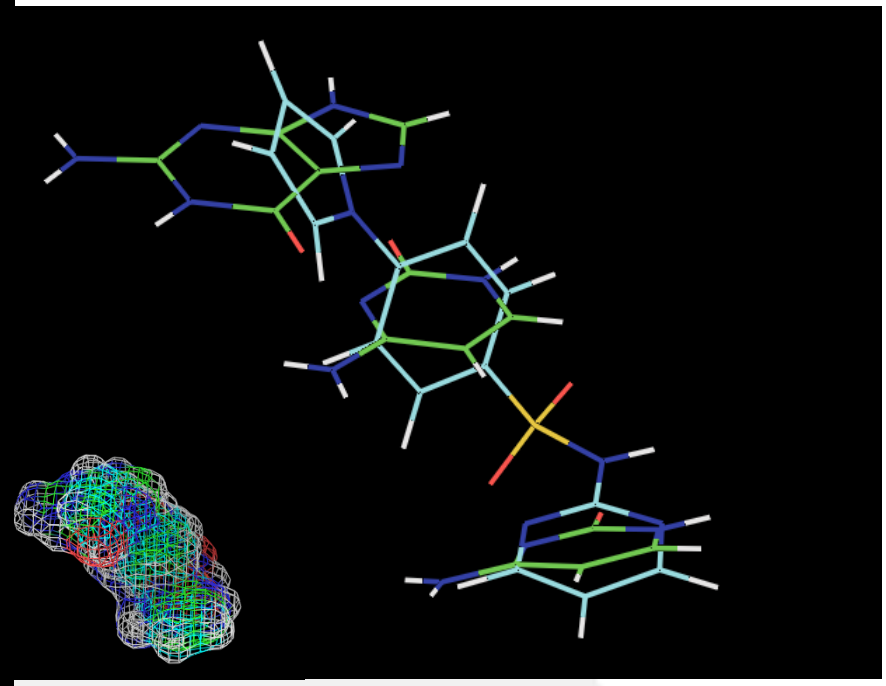
We improve the quality of life by creating new medicines

Search in PDB for 3D structures containing GUC, GCC, GGC, CUU, GAC, CCC, CCG, CGG

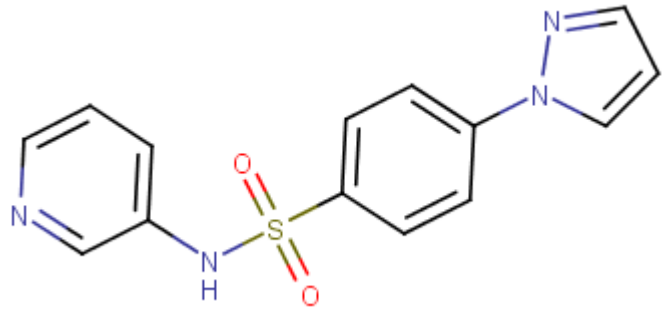




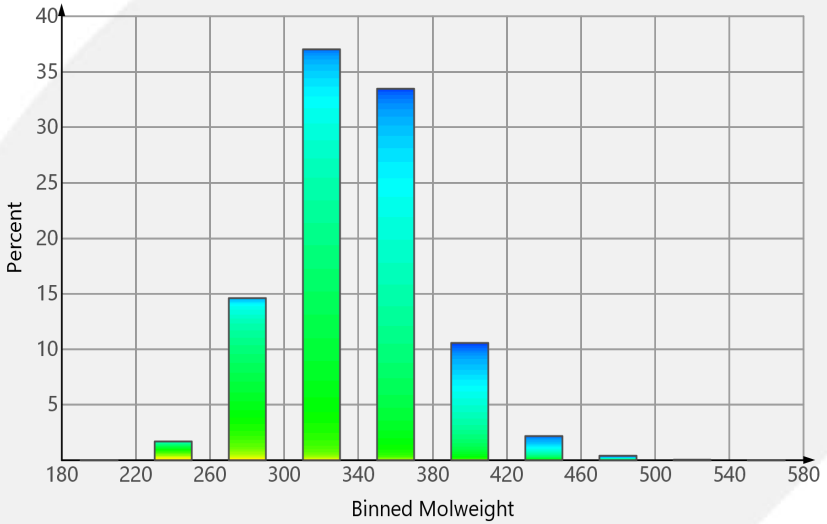


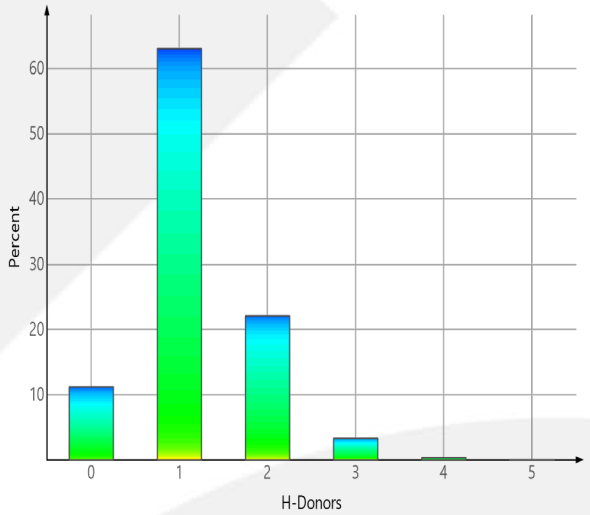


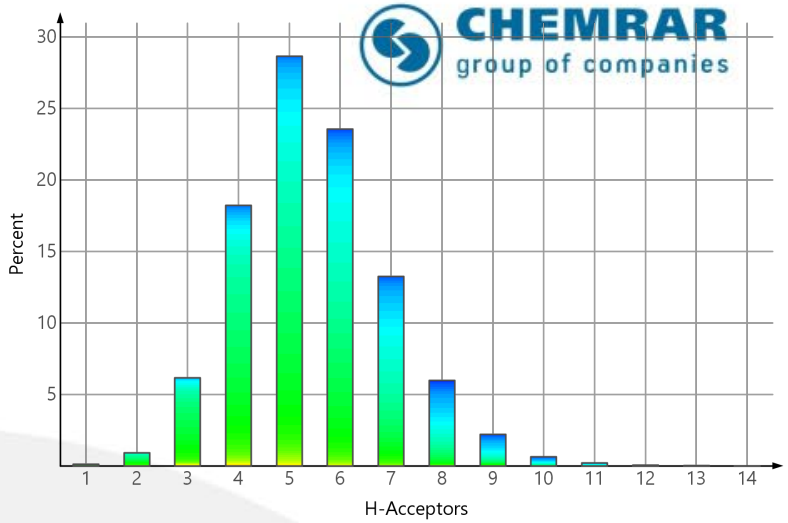
1.5M Stock Compounds
3D optimization and an ensemble of conformers

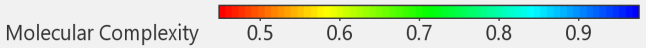


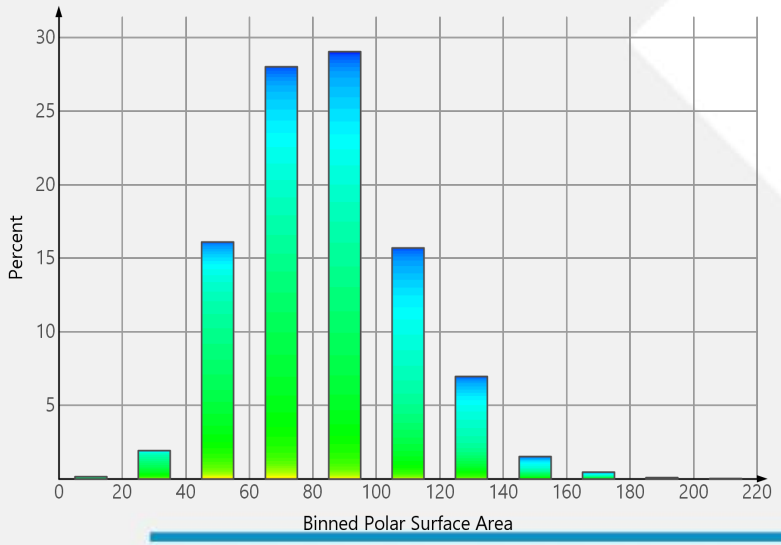
Distribution of Descriptors

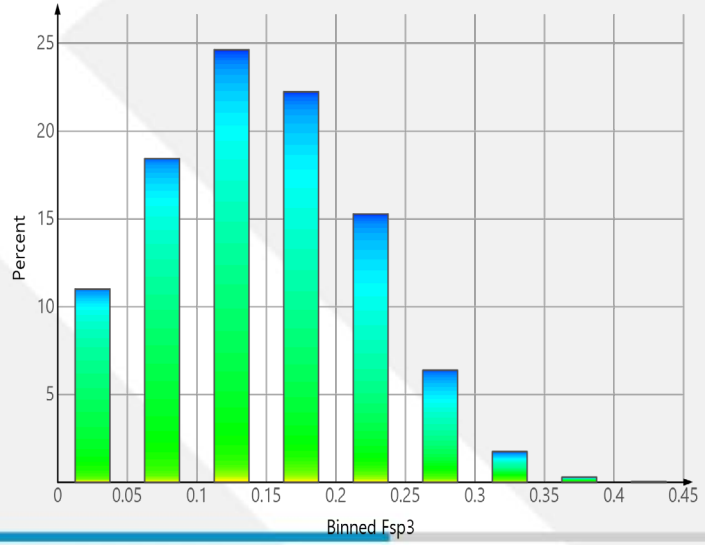


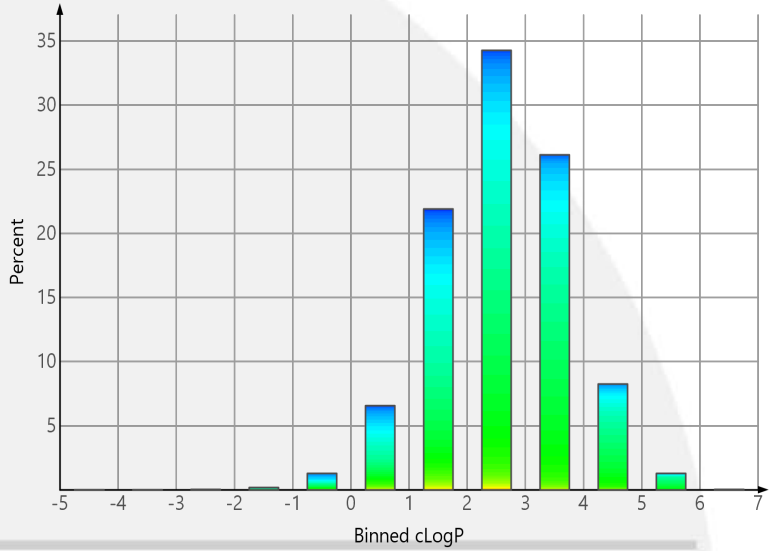












We improve the quality of life by creating new medicines

The 3D shape of the library molecules is resembling predominantly elongated ellipses – an important structural feature of known RNA binders

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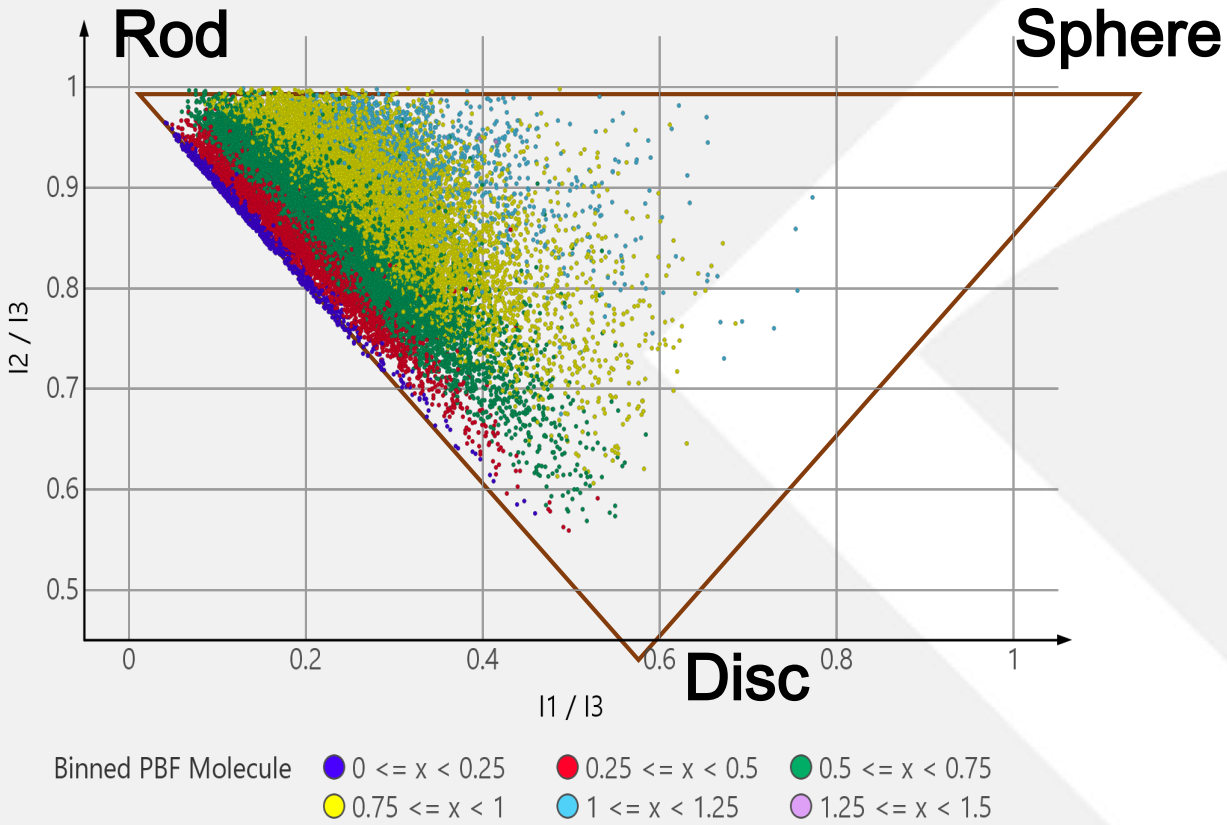
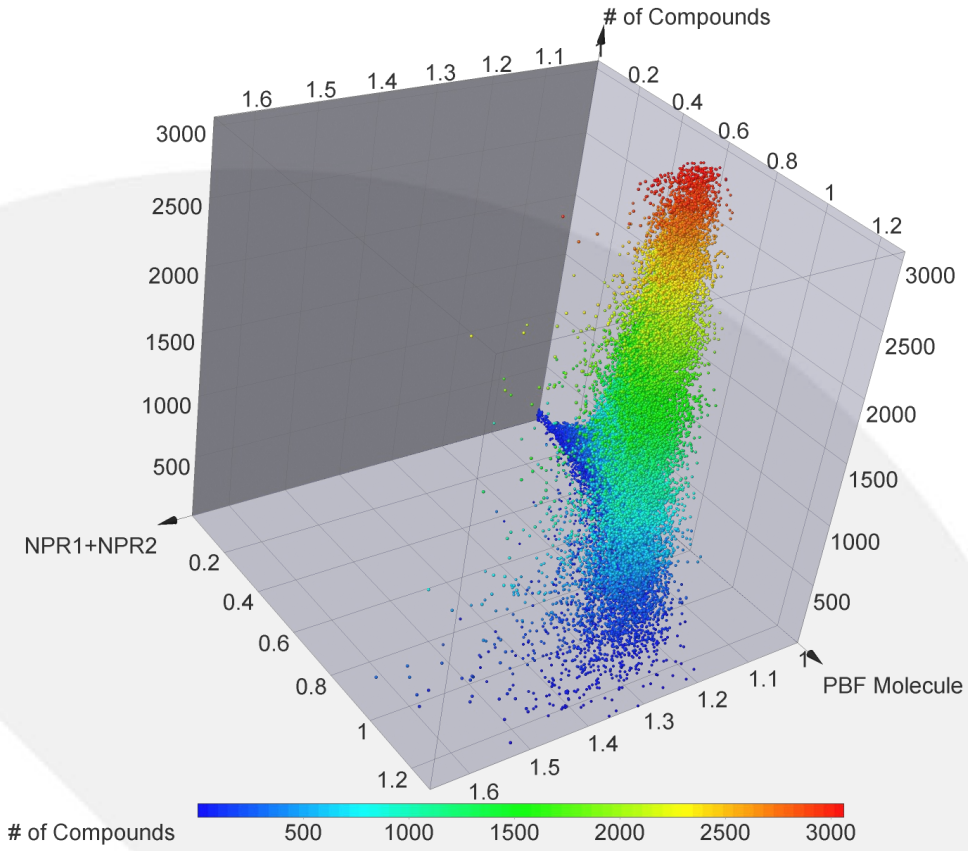
Normalized Principal Moments of Inertia



Plane of Best Fit vs Sum of I1/I3+I2/I3



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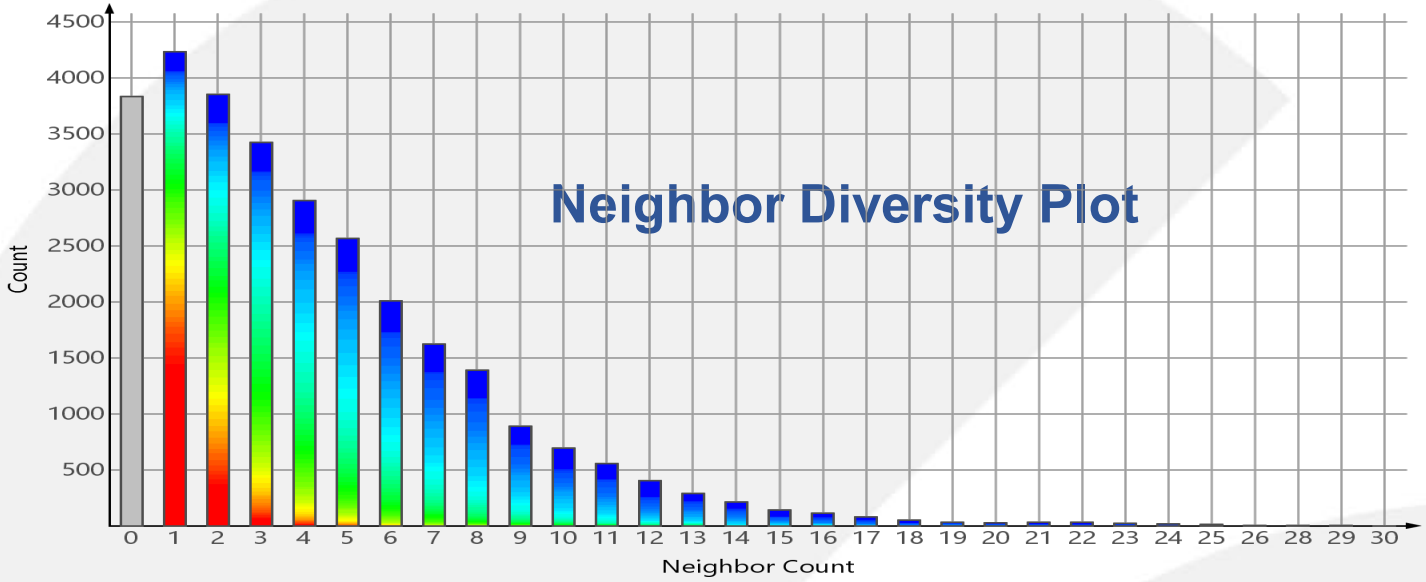

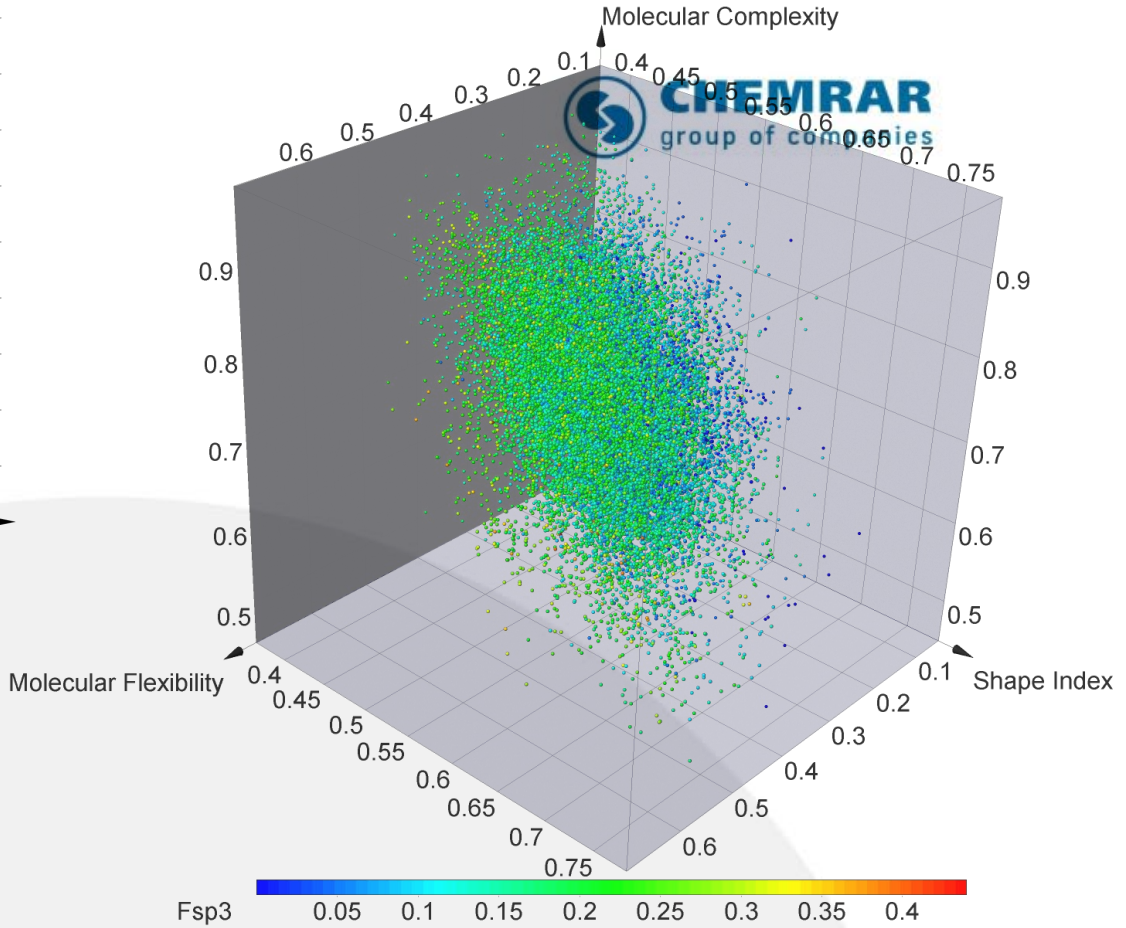

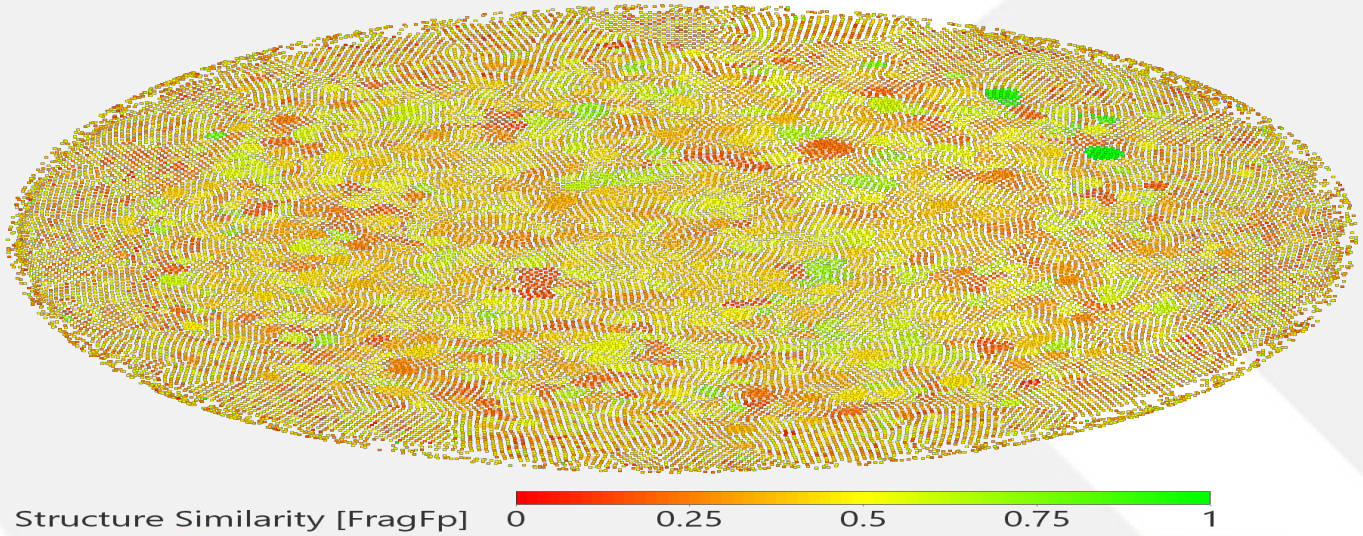

Diversity Distribution in Compounds by Structural Motifs

We improve the quality of life by creating new medicines

RNA Expansion Repeats Targeted Library

- Largest commercially available the first principle small molecules library specifically designed for targeting RNA expansion repeats
- Unique chemistry – strong IP potential
- Customizable to your specific needs
  - ✓ Size
  - ✓ Cherry-picking
  - ✓ Lead-likeness profiling
  - ✓ Format options
  - ✓ Delivery options
- Expandable from stock and synthesis
- Attractively priced

Examples of Scaffolds

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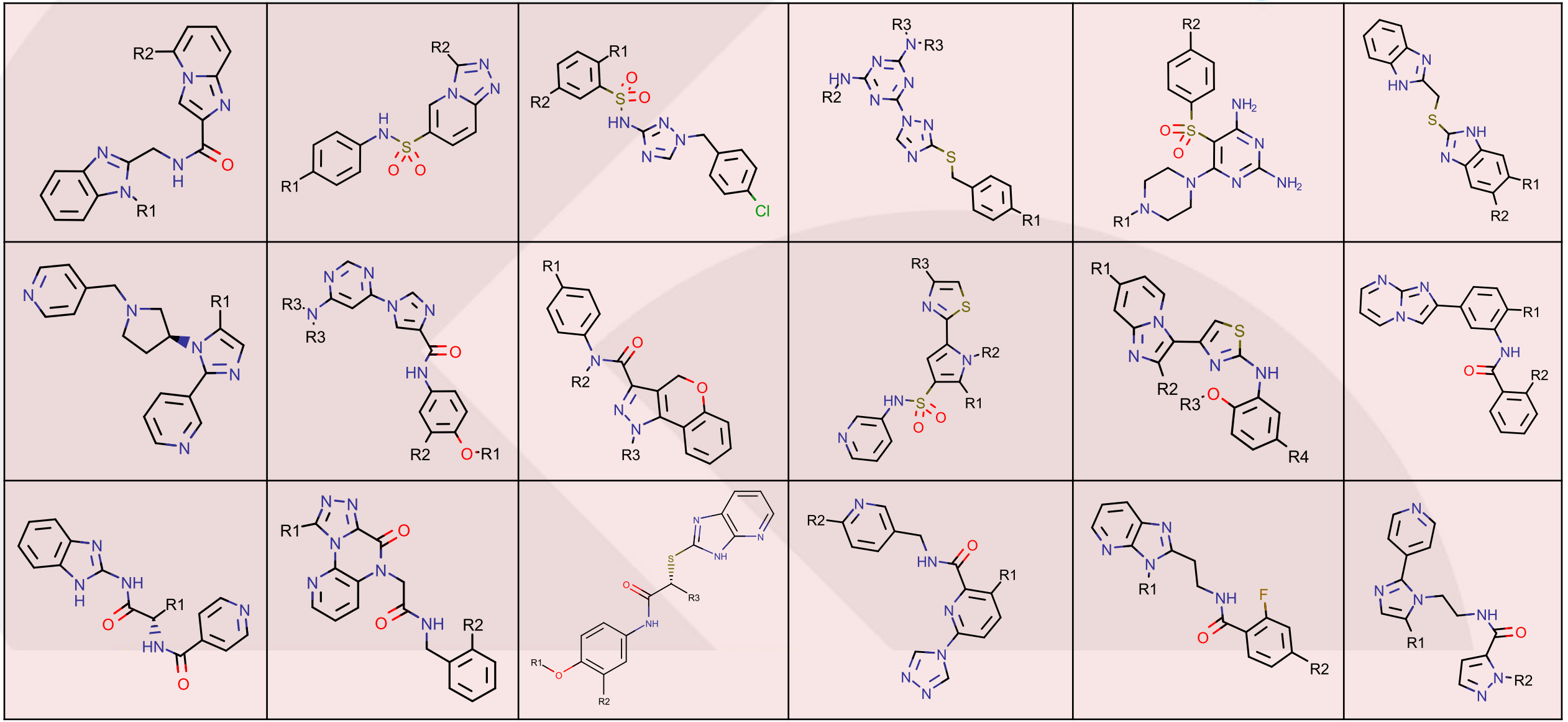

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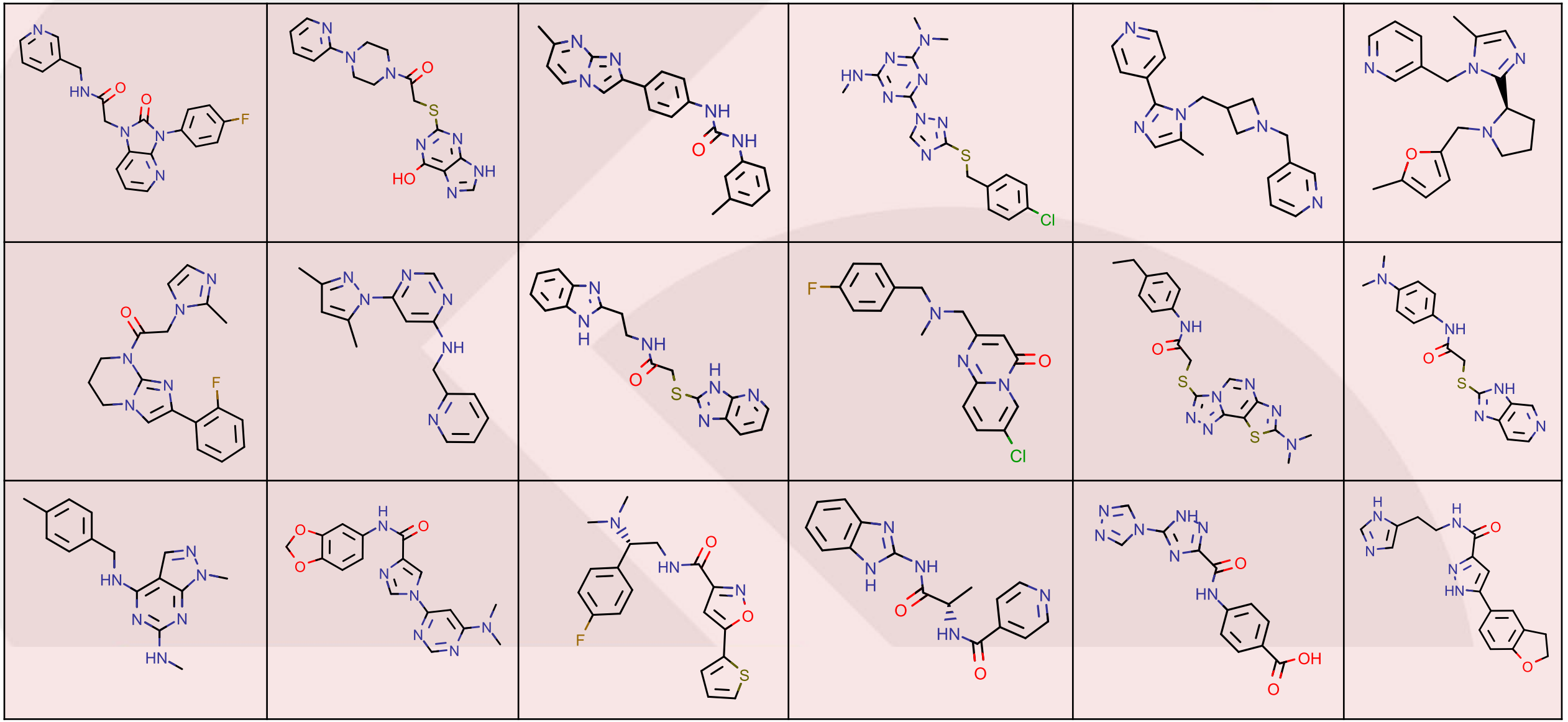

Methodology Sources

- Connelly, C.M. et al. (2017) The Emerging Role of RNA as a Therapeutic Target for Small Molecules. Cell Chem. Biol. 23 (9) 1077-1090.
- Angelbello, A.J. et al. (2018). Using Genome Sequence to Enable the Design of Medicines and Chemical Probes. Chem. Rev. 118 (4), 1599–1663.
- Jain, A. et al. (2017) RNA phase transitions in repeat expansion disorders. Nature 546 (7657) 243-247.
- Rossi, S. et al. (2015) Nuclear accumulation of mRNAs underlies G4C2-repeat-induced translational repression in a cellular model of C9orf72 ALS. J. Cell Sci. 128, 1787-1799.
- Berry-Kravis, E.M. (2018) Drug development for neurodevelopmental disorders: lessons learned from fragile X syndrome. Nat. Rev. Drug Discov. 17 (4), 280-299.
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- Liang, X. et al. (2016) Translation efficiency of mRNAs is increased by antisense oligonucleotides targeting upstream open reading frames. Nature Biotechnology 34, 875–880.
- Eddy, S.R. (2014) Computational Analysis of Conserved RNA Secondary Structure in Transcriptomes and Genomes. Annual Review of Biophysics 43, 433-456.

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Благодарим за внимание

Инструкция по заказу соединений из библиотеки «ХимРар»:

Наш сайт: https://chemrar.ru/library-full-list/

Направьте список интересующих соединений на email: vvk@chemrar.ru

В соответствии с вашим запросом менеджер выполнит подборку соединений и направит информацию о наличии. Имеется возможность сделать поиск по структуре/буквенному идентификатору (ID, CAS, MFCD), а также импортировать файл в различных форматах: SMILE, sdf, txt.