R-SIM: A Database of Binding Affinities for RNA-small Molecule Interactions

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Abstract

Ribonucleic acids (RNAs) are involved in a multitude of crucial cellular functions by acting as a central conduit for information transfer. Due to their essential and versatile functional roles in the cell, RNAs have also been implicated in multiple disease conditions of therapeutic relevance including cancers, bacterial and viral infections and neurodegenerative disorders. Recently, several approaches have emerged to tap into the potentially unexplored regions of the druggable genome, which refers to the genes and gene products that are focused during drug development. For example, considering RNAs as viable alternative therapeutic targets for drug development can potentially expand the range of therapeutic targets. Consequently, the availability of adequate binding affinity measurements for RNA-small molecule interactions is essential to understand target selectivity and design more potent RNA-targeting drug-like molecules. To facilitate this growing need, we have curated a database of experimentally validated RNA-small molecule interactions, called RNA-Small molecule Interaction Miner (R-SIM). Each entry in R-SIM provides comprehensive information on sequence, structure and classification of the RNA target, various physicochemical properties of the small molecule, binding affinity value and corresponding experimental conditions, three-dimensional structure (experimental or modelled) of the RNA-small molecule complex, and the literature source for the data. It also provides a user-friendly web interface with several options for search, display, sorting, visualization, download and upload of the data. R-SIM is freely available at: https://web.iitm.ac.in/bioinfo2/R_SIM/index.html. We envisage that R-SIM has several potential applications in understanding and accelerating the development of novel RNA-targeted small molecule therapeutics.

Introduction

Ribonucleic acids (RNAs) are involved in several essential functions of the cell including regulation of gene expression (miRNA, siRNA), splicing (snRNPs), transfer of genetic information during protein synthesis (mRNA), enzymatic activity (ribozymes), metabolite sensing (riboswitches), and storage of genetic information (RNA viruses).[1] It has been estimated that, approximately 70% of the human genome codes for the diverse types of RNA present in a cell.[2] With RNAs dominating a major proportion of the druggable human genome and their association in several disease conditions,[3] there is a growing interest in understanding the interaction of RNAs with small molecules, which

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can become potential therapeutics upon optimization.[4–6] Consequently, multiple RNA targets of therapeutic interest have been identified, which include SMN2 pre-mRNA in Spinal Muscular Atrophy (SMA), the ribosomal frameshifting stimulation element (FSE) of SARS-CoV-2 (COVID-19), HIV-1 transactivation response element (TAR) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) long non-coding RNA in cancers.[3] The structure-activity relationship of the interaction between an RNA and a small molecule can be quantified by its binding affinity value. Consequently, availability of data on binding affinity of experimentally validated RNA-small molecule complexes in a large scale, can lead to development of computational approaches to design novel small molecules for targeting RNAs, and curate datasets of small molecules for virtual screening and drug repurposing.[4] It can also help leverage the power of machine learning algorithms to accelerate RNA-targeted small molecule design,[7] similar to the AI-driven drug discovery approaches in the space of druggable proteins.[8,9]

With advancements in high-throughput biochemical and biophysical experiments, there is an increase in experimentally validated RNA-small molecule interaction data available in literature. The existing databases containing binding affinity data for RNA-small molecule interactions including, SMMRNA,[10] R-BIND[11] and NALDB,[12] have limitations in terms of their scope, features, update and availability. The SMMRNA database is currently not accessible and contains binding affinity data for only coding RNAs. The R-BIND database contains data on both coding and non-coding RNAs, but includes only a very limited number of RNA-small molecule interactions, which is insufficient to develop and validate computational methods. The NALDB database contains binding affinity data on both coding and synthetic RNAs (aptamers), but covers only three classes of RNA structures namely, G-quadruplex, double-stranded RNA and special structure RNAs. Further, additional databases on RNA-small molecule complexes without binding affinity information such as NoncoRNA[13] are also available, but cannot be used to quantitatively study and potentially score novel RNA-small molecule interactions. It is also notable that the existing databases do not include information on the RNA sequence, three-dimensional structure of RNA-small molecule complexes and RNA-disease associations, which are necessary to elucidate the mechanism of action of small molecules at the RNA binding site. To address these limitations with existing databases and to accommodate the growing body of information available in literature, we have developed a manually curated database of binding affinities for RNA-small molecule interactions, called R-SIM (RNA-Small molecule Interaction Miner).

R-SIM is a comprehensive database for RNA-small molecule binding affinity data, which includes association constant (K_a), dissociation constant (K_d), inhibitory constant (K_i), half-maximal inhibitory concentration (IC_{50}) and half-maximal effective concentration (EC_{50}). Each entry in R-SIM contains information on five categories such as (i) RNA, (ii) small molecule, (iii) RNA-small molecule interaction, (iv) experimental condition, and (v) literature. The experimentally determined three-dimensional structures of RNA-small molecule complexes are obtained from PDB,[14] but the structures are modelled when experimental structural data is not available. Each entry in R-SIM is linked to other public databases including PubChem,[15] Protein Data Bank (PDB)[16] and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), which provide detailed information on small molecules, three-dimensional structures of RNA-ligand complexes and literature, respectively. The R-SIM search page provides a wide array of search and sorting options through which users can filter their search. Further, multiple display options and visualizations are also given for each entry. R-SIM is freely available at https://web.iitm.ac.in/bioinfo2/R_SIM/index.html.

Results and Discussion

Contents of the database

Each RNA-small molecule interaction in R-SIM has been supplemented with additional information (Table 1), which can be divided into the following categories.

a) RNA target information: RNA name, a unique identifier for the RNA target, source organism, disease involved, RNA sequence, RNA type, RNA subclass, target region within the RNA, secondary structure, length. RNA type and RNA subclass were assigned based on the conventions followed in R-BIND database, and the RNA sequence was collected either from the respective reference articles or public databases such as NCBI RefSeq and Rfam.[17]

b) Small molecule information: Molecule name, a unique identifier for the molecule, Simplified molecular input line entry system (SMILES) string, IUPAC name, link to the PubChem chemical identifier (CID) for the molecule, two-dimensional structure (molecular graph), physicochemical properties of the molecule (hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), octanol-water partition coefficient (LogP), molecular weight (MW), number of rotatable bonds (NRB), number of benzene rings, quantitative estimate of drug-likeness (QED), synthetic accessibility score (SAS) and topological polar surface area (TPSA)). QED quantifies the drug-likeness of a molecule as a weighted aggregate of eight major physicochemical properties namely, molecular weight (MW),

Table 1 Description of an entry from the R-SIM database containing information related to S-adenosyl methionine (SAM) riboswitch aptamer – SAM interaction.

Description	Example
Entry ID	415
RNA name	S-adenosyl methionine aptamer
RNA target ID	Target_71
Source organism	*Thermoanaerobacter tengcongensis*
Disease involved	Bacterial growth and infection
RNA sequence	GGCUUAUCAAGAGAGGUGGAG GGACUGGCCCGAUGAAACCCGGCAACCAGAAAUGGUGCCAAUUCCU GCAGCGGAAACGUUGAAAGAUGAGCCA
RNA type	Riboswitch
RNA subclass	Riboswitch
Target region	-
Small molecule name	S-adenosyl methionine (SAM)
Molecule ID	Target_lig_314
Canonical SMILES	C[S +](CCC(C(=O)[O-])N)CC1C(C(C(O1)N2C = NC3 = C(N = CN = C32)N)O)O
IUPAC name	2-amino-4-[[5-(6-aminopurin-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl-methylsulfonio] butanoate
PubChem CID	5136
Hydrogen bond acceptors (HBA)	11
Hydrogen bond donors (HBD)	4
Octanol-water partition coefficient (LogP)	-3.2569
Molecular weight (MW)	398.13 Da
Number of rotatable bonds (NRB)	7
Number of benzene rings	2
Quantitative estimate of drug-likeness (QED)	0.34
Synthetic accessibility score (SAS)	4.75
Topological polar surface area (TPSA)	185.46 $Å^2$
K_a (M^{-1})	-
K_i (M)	-
K_d (M)	0.00000135
IC_{50} (M)	-
EC_{50} (M)	-
PDB code	2GIS
Experimental method	Isothermal Titration Calorimetry (ITC)
RNA concentration	200 μM
Small molecule concentration	20 μM
pH	8
Temperature	37 °C
Ion concentration	1 mM Mg^{2+}
PubMed ID	20106958
DOI	10.1261/rna.1852310
Title	Idiosyncratically tuned switching behavior of riboswitch aptamer domains revealed by comparative small-angle X-ray scattering analysis
Author(s) involved	Baird NJ, Ferré-D'Amaré AR

octanol-water partition coefficient (ALogP), number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), polar surface area (PSA), number of rotatable bonds (ROTB), number of aromatic rings (AROM) and number of toxic subgroups present based on the PAINS filters (ALERTS). QED values range between 0 and 1 wherein, values closer to 1 indicate highly drug-like small molecules and vice-versa.33 The physicochemical properties for each small molecule were computed using the RDKit python package (https://www.rdkit.org). A radar plot comparing the properties of the compound with the FDA-approved RNA drug,[18] Risdiplam, is also generated.

c) RNA-small molecule interaction information: Experimentally calculated binding affinity value in molar units (K_a, K_i, K_d, IC_{50} or EC_{50}), PDB code for the experimental RNA-small molecule complex (wherever available) or modelled structure of the complex using RxDock[19] (for 530 entries). Model structures were generated only for entries where at least one experimental RNA-small molecule complex involving the RNA target of interest was available in PDB. Further, JSmol web applet[20] was integrated with R-SIM to visualize both experimental and modelled structures in the database.

d) Experimental conditions: Experimental method, temperature (in celcius), pH, buffer, ion

concentrations, RNA and small molecule concentrations.

e) Literature information: PubMed identifier, Digital Object Identifier (DOI), title of the reference article, author(s) involved, journal of publication, volume, year and page number.

Database statistics

R-SIM includes 2,501 RNA-small molecule interactions covering 461 unique RNA targets and 1,288 unique small molecules. The binding affinity information present in the database was collected from 216 research articles and reviews, published between 1977-2022. The database contains structural information from 68 unique PDB structures and 530 modelled structures of RNA-small molecule complexes. The RNA targets in R-SIM can be mapped to 27 different organisms including several bacteria and viruses of therapeutic relevance. It is notable that R-SIM spans all three major categories of RNA targets: coding RNAs (56.26%), non-coding RNAs (9.40%) and synthetic RNA aptamers (34.4%). The sub-categorization of RNA targets present in R-SIM, based on RNA type and secondary structure are provided along with statistics on the distribution of activity type, experimental methods involved and the disease attribution of RNA targets in Supplemental Figure S1.

The average physicochemical property distributions of the unique small molecules present in R-SIM are comparable with that of SMMRNA and R-BIND databases (see Supplemental Table S1). Majority of the molecules exhibit non-conformity to the Lipinski rules as observed previously in literature[21,22] and also discernible from the lower QED scores (below 0.5). The complete list of molecules available in R-SIM along with their physicochemical properties and molecular structures are also provided as part of Supplemental Tables S2 and S3, respectively.

Data retrieval from R-SIM

In this section, the data retrieval options available in R-SIM search page are illustrated with an example query: *find all RNA-small molecule interactions involved in acquired immunodeficiency syndrome (AIDS) published between 2010 and 2015, where the small molecules have HBA in the range of 1 to 3*. The above query can be split into three sub-queries corresponding to the search options available in R-SIM (Q1-Q3 in Figure 1), along with the required display options. The result includes 25 entries from R-SIM which match all of the above three search parameters provided (Figure 1).

As shown in Figure 1, the search options are displayed in a tabulated form with the contents, which are decided dynamically based on the display options chosen by the user. Each entry is represented by a unique entry ID selecting which, the detailed information corresponding to the entry (Table 1) will be fetched and rendered from the database. The search results can also be downloaded in CSV format for further analysis.

Comparison with existing databases

A detailed comparison of the features of R-SIM database with three existing RNA-small molecule interaction databases has been provided below (Table 2). R-SIM has an increase in RNA-small molecule interaction data with binding affinity by, 57%, 89%, 51%, and 23% in comparison with SMMRNA, R-BIND, NALDB, and Inforna 2.0[34] databases, respectively. Further, R-SIM has the highest number of sequence and structural information on RNA-small molecule complexes in comparison with all four existing databases. RNA targets in R-SIM have also been clearly classified into RNA type and RNA subclass following the conventions introduced by the R-BIND database. In comparison with all four existing databases, R-SIM includes data on maximum number of unique small molecules, thereby increasing the diversity in the repertoire of experimentally verified small molecules which can interact with RNA targets.

Applications

The data from R-SIM can be used for research on different directions:

- **Structure-activity relationship (SAR) studies**: Understand the sequence- and structure-level features of RNA targets and small molecules, that govern their interaction. With the increase in structural information provided by R-SIM, the extracted features can be used to establish a relationship between the binding affinity of specific small molecules to the observed interactions an RNA target.[23,24]
- **Design of novel RNA-specific small molecules**: Generative chemistry has gained significant focus in recent years, with the application of machine learning and deep learning techniques to expand the explored chemical space of inhibitors against protein targets. R-SIM can aid in the development of such generative models for *de novo* RNA-specific small molecule design.[23,25,26]
- **Curation of small molecule datasets for virtual screening**: R-SIM can potentially serve as a resource for virtual screening studies, wherein the small molecules with the desirable property profile can be filtered out and utilized in drug-repurposing studies for RNA targets of interest.[27,28]
- **Identification of novel RNA targets of therapeutic potential**: Based on sequence and structure similarity to existing RNA targets available in R-SIM, novel

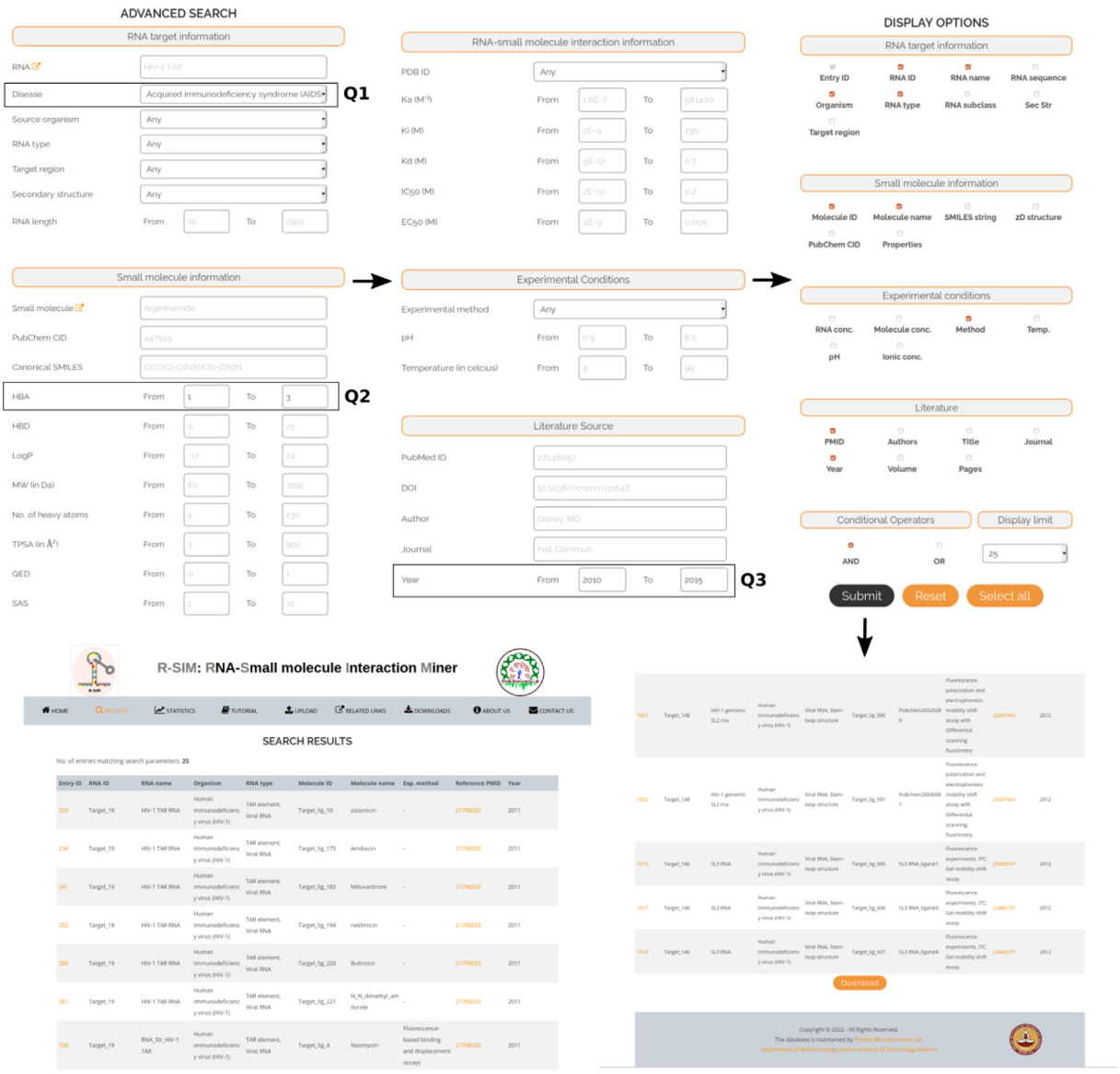

Figure 1. An illustration of data retrieval from R-SIM where a complex search query is split into three sub-queries (Q1-Q3) based on the search options available. The results from the search are also provided for reference.

RNA targets of therapeutic potential can be identified and known RNA-specific small molecules can be repurposed and tested against such novel RNA targets.[29,30]

Materials and Methods

Data curation strategy

R-SIM contains experimentally validated binding affinity information for RNA-small molecule complexes collected from a detailed survey of existing literature and related databases. The data collation was performed in two phases: literature mining and integration of existing databases.

- **Literature mining**: The set of research articles and reviews related to experimental characterization of RNA-small molecule complexes was retrieved through PubMed keyword search with logical operators (AND and OR). The keywords utilized include combinations of: RNA, small molecule, binding affinity, target, experiment, inhibition, validation etc. Through a careful survey of the collected articles, the following information were manually curated: RNA target involved, small molecule involved, availability of experimental structure for the RNA-small molecule interaction, binding affinity value in molar units (K_a, K_i, K_d, IC_{50} or EC_{50}), experimental conditions such as temperature, pH, buffer, ion concentrations, RNA and small molecule concentrations and

Table 2 A comparison of various features of R-SIM database with four existing databases of RNA-small molecule interactions.

Feature	SMMRNA	R-BIND	NALDB	Inforna 2.0	R-SIM
Availability of webpage	No	Yes	Yes	No	Yes
Number of entries	1,086	279	1,235	1,936	2,501
Number of unique RNA targets	160	114	511	-	461
Number of unique small molecules	625	111	776	437	1,288
Number of unique PDB structures	0	5	0	0	68
Number of unique modelled structures	0	0	0	0	530
Structure visualization	No	No	No	No	Yes
RNA types covered	Coding	Coding, Non-coding	Coding, Synthetic	Coding, Non-coding, Synthetic	Coding, Non-coding, Synthetic
Availability of RNA sequence	No	No	Partial	Yes	Yes
Availability of RNA classification	No	Yes	No	No	Yes
Availability of small molecule properties	No	Yes	Yes	No	Yes
Availability of binding affinity	Yes	Yes	Yes	Yes	Yes
Availability of experimental conditions	No	Yes	No	No	Yes
Availability of upload options	No	No	No	No	Yes
Number of publications covered	116	68	217	-	216
Literature coverage	1977-2015	1998-2018	1982-2015	-	1977-2022

the choice of experimental method for the study. Based on literature mining, 1,172 additional experimentally characterized RNA-small molecule interactions were obtained.

- **Integration of existing databases**: SMMRNA[10] and R-BIND[11] databases were considered for integration with R-SIM due to the availability of experimentally validated binding affinity values and the respective published source for the same, from these databases. While integrating the data from SMMRNA and R-BIND, redundancies in the data were resolved, references provided for the binding affinity values were verified, and missing information was manually compiled. Post-integration, a total of 1,329 RNA-small molecule interactions were obtained from existing databases.

The curated data was further supplemented with additional information specific to RNA, small molecules, RNA-small molecule interactions, experimental conditions involved and the literature source for the data.

Modelling of RNA-small molecule complexes

The structures of RNA-small molecule complexes were modelled using RxDock[31] for which no experimentally determined RNA-ligand complex structure is available. To ensure that the ligand binds at the correct binding site in the modelled RNA-ligand complex structure, the modelling was done for those cases, where the binding site of the corresponding RNA is known experimentally, albeit with another small molecule. The initial 3D conformation of small molecules with hydrogens were generated using RDKit (https://www.rdkit.org) or OpenBabel,[32] and optimized with the MMFF94 force field using steepest descent method before docking. The automatic grid identification program "rbcavity" was used to obtain the docking grid coordinates for the RNA target, based on the bound ligand coordinates. This was used as input to the "rbdock" program to sample 10 binding poses per small molecule. Both the "rbcavity" and "rbdock" programs are part of the RxDock package.[31] The binding pose with the best docking score was chosen for visualization in the R-SIM database entry.

Data Availability

R-SIM database is available at: https://web.iitm.ac.in/bioinfo2/R_SIM/index.html. The database was developed using HTML5, CSS, JavaScript, PHP and MySQL. It supports the latest version of both Firefox and Chrome browsers. The database will be maintained and updated regularly. The updated information will be reflected in the homepage of the database.

Data Download and Upload

A copy of the latest version of data in R-SIM can be obtained by submitting a download request from

the Downloads page of R-SIM. R-SIM includes options to allow users to upload their own experimentally validated RNA-small molecule interactions with binding affinity, other appropriate experimental information and published references, to the database. Prior to integration, the uploaded data will be subject to redundancy check and sanity checks to fill missing information.

Conflict of Interest Statement

Sowmya Ramaswamy Krishnan and Arijit Roy are employed by Tata Consultancy Services Limited.

CRediT authorship contribution statement

Sowmya Ramaswamy Krishnan: Data curation, Validation, Formal analysis, Software, Writing – original draft, Writing – review & editing, Visualization. **Arijit Roy:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision. **M. Michael Gromiha:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmb.2022.167914.

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References

1. Chen, Y., Varani, G., (2010). RNA Structure. *Encyclopedia of Life Sciences (ELS)*. John Wiley & Sons Ltd:, Chichester.
2. Warner, K.D., Hajdin, C.E., Weeks, K.M., (2018). Principles for targeting RNA with drug-like small molecules. *Nature Rev. Drug. Discov.* **17**, 547–558.
3. Connelly, C.M., Moon, M.H., Schneekloth Jr, J.S., (2016). The Emerging Role of RNA as a Therapeutic Target for Small Molecules. *Cell Chem. Biol.* **23**, 1077–1090.
4. Manigrasso, J., Marcia, M., De Vivo, M., (2021). Computer-aided design of RNA-targeted small molecules: A growing need in drug discovery. *Chem.* **7**, 2965–2988.
5. Nakatani, K., (2022). Possibilities and challenges of small molecule organic compounds for the treatment of repeat diseases. *Proc. Jpn. Acad. Ser. B. Phys. Biol. Sci.* **98**, 30–48.
6. Lan, T.C.T., Allan, M.F., Malsick, L.E., Woo, J.Z., Zhu, C., Zhang, F., (2022). Secondary structural ensembles of the SARS-CoV-2 RNA genome in infected cells. *Nature Commun.* **13**, 1128.
7. Grimberg, H., Tiwari, V.S., Tam, B., Gur-Arie, L., Gingold, D., Polachek, L., (2022). Machine learning approaches to optimize small-molecule inhibitors for RNA targeting. *J. Cheminform.* **14**, 4.
8. Krishnan, S.R., Bung, N., Bulusu, G., Roy, A., (2021). Accelerating De Novo Drug Design against Novel Proteins Using Deep Learning. *J. Chem. Inf. Model.* **61**, 621–630.
9. Krishnan, S.R., Bung, N., Vangala, S.R., Srinivasan, R., Bulusu, G., Roy, A., (2021). *De Novo* Structure-Based Drug Design Using Deep Learning. *J. Chem. Inf. Model.*
10. Mehta, A., Sonam, S., Gouri, I., Loharch, S., Sharma, D.K., Parkesh, R., (2014). SMMRNA: a database of small molecule modulators of RNA. *Nucleic Acids Res.* **42**, D132–D141.
11. Morgan, B.S., Sanaba, B.G., Donlic, A., Karloff, D.B., Forte, J.E., Zhang, Y., (2019). E. R-BIND: An Interactive Database for Exploring and Developing RNA-Targeted Chemical Probes. *ACS Chem. Biol.* **14**, 2691–2700.
12. Mishra, S.K., Kumar, A., (2016). NALDB: nucleic acid ligand database for small molecules targeting nucleic acid. *Database (Oxford).*, 1–11.
13. Li, L., Wu, P., Wang, Z., Meng, X., Zha, C., Li, Z., (2020). NoncoRNA: a database of experimentally supported non-coding RNAs and drug targets in cancer. *J. Hematol. Oncol.* **13**, 15.
14. Rose, Y., Duarte, J.M., Lowe, R., Segura, J., Bi, C., Bhikadiya, C., (2021). RCSB Protein Data Bank: architectural advances towards integrated searching and efficient access to macromolecular structure data from the PDB archive. *J. Mol. Biol.* **433**, 166704
15. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., et al., (2021). PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Res.* **49**, D1388–D1395.
16. Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., (2000). The Protein Data Bank. *Nucleic Acids Res.* **28**, 235–242.
17. Kalvari, I., Nawrocki, E.P., Ontiveros-Palacios, N., Argasinska, J., Lamkiewicz, K., Marz, M., (2021). Rfam 14: expanded coverage of metagenomic, viral and microRNA families. *Nucleic Acids Res.* **49**, D192–D200.
18. Mullard, A., (2020). FDA approves RNA-targeting small molecule. *Nature Rev. Drug. Discov.* **19**, 659.
19. Ruiz-Carmona, S., Alvarez-Garcia, D., Foloppe, N., Garmendia-Doval, A.B., Juhos, S., Schmidtke, P., (2014). rDock: a fast, versatile and open source program for docking ligands to proteins and nucleic acids. *PLoS Comput. Biol.* **10**, e1003571.

20. Hanson, R.M., Prilusky, J., Renjian, Z., Nakane, T., Sussman, J.L., (2013). JSmol and the Next-Generation Web-Based Representation of 3D Molecular Structure as Applied to Proteopedia. *Isr. J. Chem.* **53**, 3–4.
21. Yu, A., Choi, Y.H., Tu, M., (2020). RNA Drugs and RNA Targets for Small Molecules: Principles, Progress, and Challenges. *Pharmacol. Rev.* **72**, 862–898.
22. Childs-Disney, J.L., Yang, X., Gibaut, Q.M.R., Tong, Y., Batey, R.T., Disney, M.D., (2022). Targeting RNA structures with small molecules. *Nature Rev. Drug Discov.*, 1–27.
23. Kognole, A.A., Hazel, A., MacKerell Jr, A.D., (2022). SILCS-RNA: Toward a Structure-Based Drug Design Approach for Targeting RNAs with Small Molecules. *J. Chem. Theory. Comput.* **18**, 5672–5691.
24. Mattox, D.E., Bailey-Kellogg, C., (2021). Comprehensive analysis of lectin-glycan interactions reveals determinants of lectin specificity. *PLoS Comput. Biol.* **17**, e1009470.
25. Grimberg, H., Tiwari, V.S., Tam, B., Gur-Arie, L., Gingold, D., Polachek, L., Akabayov, B., (2022). Machine learning approaches to optimize small-molecule inhibitors for RNA targeting. *J. Cheminform.* **14**, 4.
26. Yazdani, K., Jordan, D., Yang, M., Fullenkamp, C.R., Allen, T.E.H., Khan, R.T., Schneekloth Jr., J.S., (2022). Machine Learning Informs RNA-Binding Chemical Space. *BioRxiv.*.
27. Haniff, H.S., Knerr, L., Chen, J.L., Disney, M.D., Lightfoot, H.L., (2020). Target-Directed Approaches for Screening Small Molecules against RNA Targets. *SLAS Discov.* **25**, 869–894.
28. Kallert, E., Fischer, T.R., Schneider, S., Grimm, M., Helm, M., Kersten, C., (2022). Protein-Based Virtual Screening Tools Applied for RNA-Ligand Docking Identify New Binders of the preQ1-Riboswitch. *J. Chem. Inf. Model.* **62**, 4134–4148.
29. Li, Q., Lai, L., (2007). Prediction of potential drug targets based on simple sequence properties. *BMC Bioinformatics.* **8**, 353.
30. Wang, J.T., Liu, W., Tang, H., Xie, H., (2014). Screening drug target proteins based on sequence information. *J. Biomed. Inform.* **49**, 269–274.
31. Ruiz-Carmona, S., Alvarez-Garcia, D., Foloppe, N., Garmendia-Doval, A.B., Juhos, S., Schmidtke, P., Barril, X., Hubbard, R.E., et al., (2014). rDock: a fast, versatile and open source program for docking ligands to proteins and nucleic acids. *PLoS Comput. Biol.* **10**, e1003571.
32. O'Boyle, N.M., Banck, M., James, C.A., Morley, C., Vandermeersch, T., Hutchison, G.R., (2011). Open Babel: An open chemical toolbox. *J. Cheminform.* **3**, 33.
33. Bickerton, G.R., Paolini, G.V., Besnard, J., Muresan, S., Hopkins, A.L., (2012). Quantifying the chemical beauty of drugs. *Nature Chem.* **4**, 90–98.
34. Disney, M.D., Winkelsas, A.M., Velagapudi, S.P., Southern, M., Fallahi, M., Childs-Disney, J.L., (2016). Inforna 2.0: A Platform for the Sequence-Based Design of Small Molecules Targeting Structured RNAs. *ACS Chem. Biol.* **11**, 1720–1728.