RNA-targeting Small Molecules

ASINEX

Modulation of the functional roles of RNAs in prokaryotic and eukaryotic cells with small molecules is becoming increasingly important in drug discovery [1]. Unfortunately, to this point, there has been little clinical success involving RNA-binding small molecules [2]. We, therefore, believe that a critical component for future RNA-directed drug discovery is access to the appropriate screening collection containing small molecules with an increased probability of engaging the target in an advantageous way. The choice of such a library could be based on structural knowledge of the binding cavity, the physicochemical properties complementary to RNA, along with other pharmacological properties such as cellular permeability. In order to understand the scope of potentially druggable RNA targets and applicable screening libraries we analyzed RNA structures in the PDB database (www.rcsb.org) extracting 30 of the most promising macromolecule-ligand complexes based on the following criteria (Figure 1):

- Sufficient complexity of RNA
- Uniqueness
- Presence of high-quality pockets
- Small-molecule ligand bound to RNA with high affinity

Figure 1

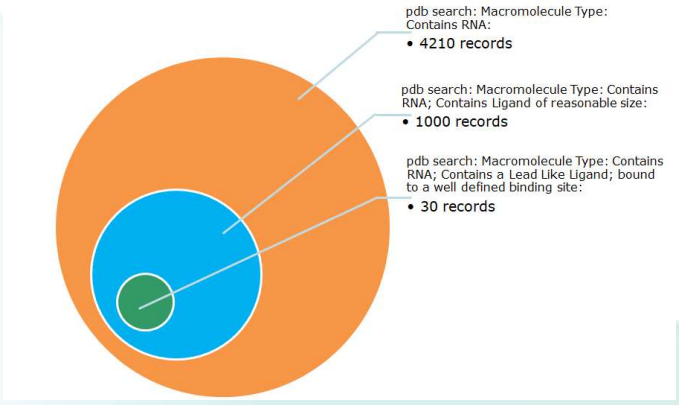
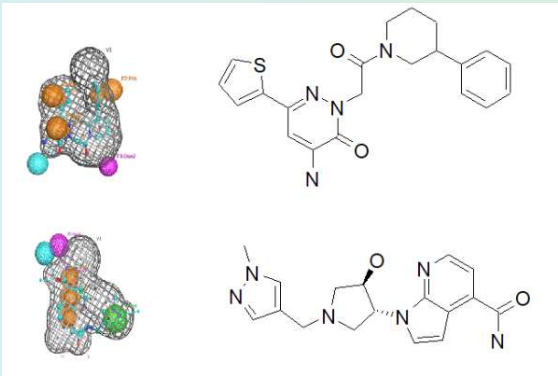


Table 1

"1F1T"	"MALACHITE GREEN APTAMER RNA"
"1LVJ"	"HIV-1 Trans Activating Region RNA"
"1YKV"	"Diels-Alder ribozyme"
"2HOO"	"Thi-Box Riboswitch"
"2KGP"	"tau pre-mRNA splicing regulatory element"
"2KTZ"	"HCV IRES Domain IIa RNA"
"3F4G"	"Flavin Mononucleotide Riboswitch"
"3GCA"	"PreQ1 riboswitch"
"3SD3"	"Tetrahydrofolate riboswitch"
"4NYB"	"thiM TPP riboswitch"
"4NYG"	"thiM TPP riboswitch"
"5C45"	"Flavin Mononucleotide Riboswitch"
"5OB3"	"iSpinach aptamer"
"6DN1"	"Flavin Mononucleotide Riboswitch"

Based on these 30 RNA structures we have created 16 pharmacophore queries that capture the characteristic features of a small molecule ligand bound to RNA (Figure 2). We then applied the resulting queries in searching through ASINEX BioDesign and Elite collections. These searches resulted in several hundred molecules that could be tagged with a particular pharmacophore. The matching RNA targets are summarized in Table 1.

Figure 2



1. K. Warner, C. Hajdin, K. Weeks. Nature Reviews Drug Discovery volume 17, pages 547–558 (2018)
2. F. Aboul-ela, Future Med Chem. 2010 Jan;2(1):93-119.