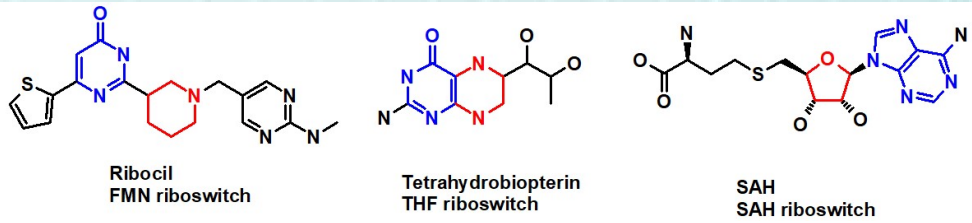
Small Molecule Libraries for RNA Drug Discovery
Cell Permeable Dinucleoside Mimetics

ASINEX

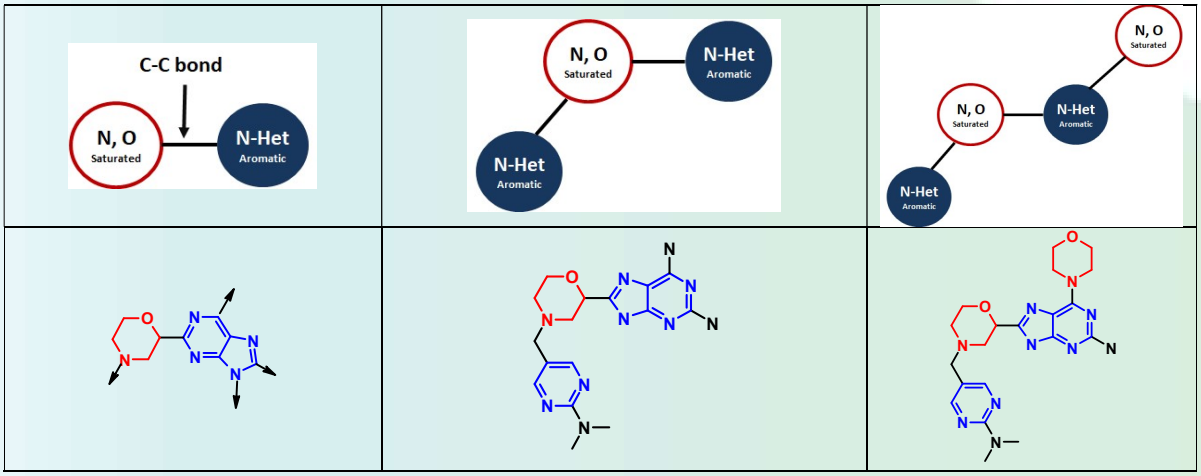
Small molecule modulation of the functional role(s) of RNAs in prokaryotic and eukaryotic cells is becoming increasingly important in drug discovery [1,2]. We believe that a critical component for an efficient RNA-directed drug discovery campaign is access to the appropriate screening collection of drug-like molecules with an increased probability of RNA binding. Ideally, the choice of such a library is guided by structural knowledge of the binding cavity, the optimal physicochemical properties of molecules complementary to RNA, and favorable bioavailability such as cellular permeability. Compared to small molecules designed to target protein targets, the diversity of chemotypes known to bind to RNA is rather limited. There are, however, recent examples of molecules such as Ribocil which support the fact that RNA is a druggable target. Some natural cofactors known to recognize RNA binding grooves such as SAH or tetrahydrobiopterin may also work as structural templates for the design of novel chemical entities attractive for RNA drug discovery (Figure 1).

Figure 1



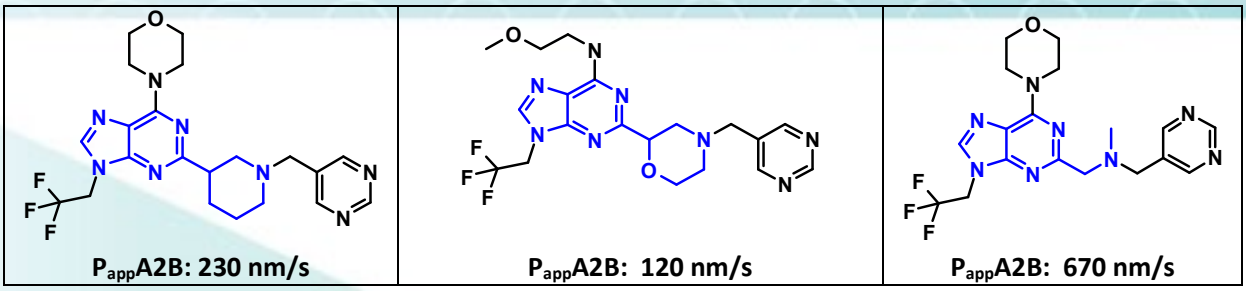
Systematic analysis of published small molecules with declared RNA activity has revealed several prominent structural elements that can be used as design templates for the creation of novel chemical libraries for RNA drug discovery. In particular, a combination of aromatic heterocyclic rings such as nucleobases or bioisosteric analogs with a saturated linear or ring component connected via a carbon-carbon bond are very common motifs among RNA-bound ligands with favorable drug-like properties. This observation confirms earlier published data suggesting that molecules having a favorable carbon bond saturation (defined by Fsp3) represent “biologically relevant chemical space” [3]. In the case of RNA ligands, the right balance of aromaticity and saturation embedded in the RNA-compatible molecular framework may enhance binding probability. We have identified several such advantageous combinations as shown in Figure 2.

Figure 2



Among multiple feasible ring system combinations, we selected those that can be achieved in a relatively low number of synthetic steps using robust synthetic methods. Additional criteria included structural novelty verified by substructure and similarity searches in the Reaxys database (www.reaxys.com). The resulting nucleoside-like cores were further functionalized using established parallel chemistry methods. A secondary amine moiety presented in a saturated ring is the most convenient point of diversity which was exploited for array synthesis. We deliberately focused on reductive amination reactions which provided final molecules with improved solubility and permeability [4].

Cellular permeability is an essential property of small molecule drugs required for activity against intracellular targets such as RNA. Therefore, it is very important to verify that the proposed design would enable reasonable cellular bioavailability. The Caco-2 assay with experimentally measured apparent permeability (Papp) is considered the gold standard for assessing the uptake efficiency of drugs correlated to their cell permeability. Several molecules were experimentally tested for solubility PAMPA and Caco-2 permeability to provide valuable input for designing compounds with improved properties.



P_{app}A2B: 230 nm/s	**P_{app}A2B: 120 nm/s**	**P_{app}A2B: 670 nm/s**

Compounds are available in several formats including dry stock and DMSO solutions. A much large complementary virtual space of 4 million molecules biased toward RNA targets is available for virtual screening and follow-up chemistry support.

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Literature:

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2. F. Aboul-ela, Future Med Chem. 2010 Jan;2(1):93-119.
3. Kombarov, R., Altieri, A., Genis, D. et al. Mol Divers (2010) 14: 193.
4. Rishton, G.M. Curr. Opin. Chem. Biol.(2008) 12, 340–351