Towards an HTS library of RNA targeting small-molecules

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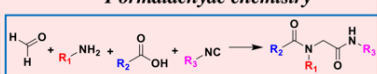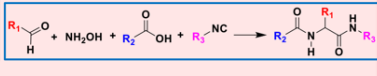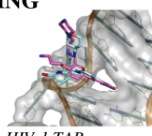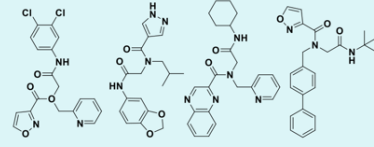m.hadian@rug.nl, a.reyes.romero@rug.nl, a.s.s.domling@rug.nl

Different classes of RNA are involved in regulating aspects of life, thus their dysregulation is linked to a plethora of diseases. RNA has recently emerged as a promising drug target modality [1-3]. Besides classical antibiotics, two RNA modifier drugs have recently received market approval (Branaplam, Ataluren). However, the field of small molecule RNA modifiers is *in status nascendi*, therefore, their accelerated synthesis deserves special attention.

Aims
Here we describe the design and synthesis strategy to access a library of small molecules targeting RNA via multicomponent reaction (MCR) for high-throughput screening.

Methods
For the fast and efficient construction of RNA-directed small molecule libraries we choose two types of MCRs. Among the advantages of MCR, a large number of compounds can be prepared due to the combinatorial potential of the different starting material classes. Next, we were utilizing previously in our group validated MCRs, allowing easy experimental access to the target compounds in high purity and yields [4-5]. Based on chemoinformatics analysis of the scaffolds and building blocks, a RNA directed library enriched with three pharmacophores, (aromatic) heterocycles, hydrogen bond acceptor (HBA) and donor (HBD) and positively charge moieties was constructed. After docking, potential applications have been explored with nearest neighbors search [6].

Results / Conclusions
In summary, we describe a design and HTS for the construction of RNA-directed libraries of small molecules. Next, we plan to screen the libraries against several RNA targets using NMR. We hope our strategy accelerate compounds synthesis for RNA drug discovery.

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