Exploring bicyclic diamines as drug scaffolds

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Drug discovery is in constant need of new molecules to develop drugs addressing unmet medical needs. To assess the chemical space available for drug design our group developed tools to enumerate, visualize and search chemical space. The Generated DataBases (GDBs) list billions of possible organic small molecules following simple rules of chemical stability and synthetic accessibility. [1a-1d]

Following the synthesis of triquinazine as a novel piperazine analog for drug design from our GDBs, we asked the question whether even simpler diamine scaffolds might still be unexplored. [2] Therefore, we enumerated all 1323 bicyclic ring systems containing only 5, 6 or 7-membered rings and decorated them with two nitrogen atoms. Such diamines are interesting as drug scaffolds due to their favorable solubility and pharmacokinetic profile compared to aromatic scaffolds, as recently demonstrated for the γ-secretase modulator RO7185876. [3] To our surprise, more than half of our GDB diamine cores are not found as molecular cores when considering any possible substituents on the nitrogen atoms in public databases.

Here we present the synthesis of fused bicyclic diamines, all of which represent yet unknown scaffolds. Furthermore, we have used our polypharmacology browser PPB2 to predict possible targets for the GDB-inspired bicyclic diamines and their *N*-monobenzylated analogs. [4] Activity screening showed that one of the *N*-benzylated diamines is a micromolar inhibitor of neurotransmitter transporters. To progress in the synthesis, we have implemented AIZynthfinder and have found that about half of the diamines can be solved by the tool. [5] In particular, AIZynthfinder proposed a retrosynthesis for the bicyclic diamine discussed above, from the same precursor but giving access to the previously unexplored *syn*-diastereoisomer due to inverted reaction sequence and milder conditions.

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