Automated Synthesis Provides Rapid Hit Validation of Virtual Screening Hits


1. Construction and Analysis of Virtual Library
- Commercial alkylamines and amines were combined with 6×1000 rotors to give 6500 molecules
- The library was filtered by cLogP and cLogW, and 5000 molecules were selected before virtual screening
- The 5000 molecules were analyzed (RDKit, python) and showed coverage of drug-like chemical space with a high fraction of sp² carbons.

2. Automated Synthesis of Library Members
- Selected molecules were transformed with an Fmoc resin, concentrated and purified with the selected apolar and reducing amination reagent.
- Reactions were achieved using preparative HPLC in all cases except 15-36 which were isolated as diastereomeric mixtures.
- Deprotection times 3 h, 24 h, 12 h.
- Pre-selected by Open Innovation Platform Agos, BASF

3. Assignment of Relative Stereochemistry
- Substituted molecules can be assigned from 2D 1H NMR and experiment.
- Stereocentric molecules assignments were aided by DFT NMR prediction.

4. Hit Validation
- SARS-CoV-2 3CLpro exhibit identified using ligand and structure-based virtual screening and validated in a cellular assay.
- Anti-fungal and insecticidal molecules selected and screened by Open Innovation Platform Agos, data supplied by courtesy of BASF SE