P06

Automated Synthesis Provides Rapid Hit Validation of Virtual Screening Hits

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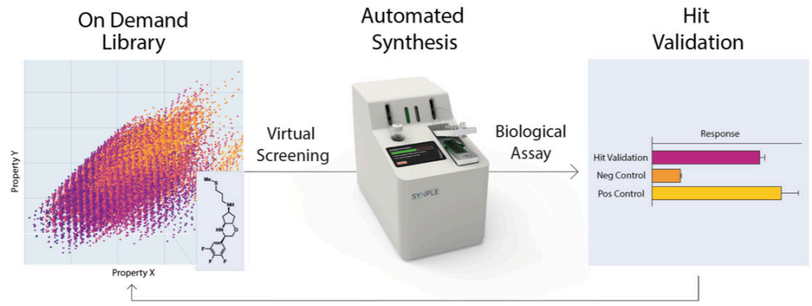
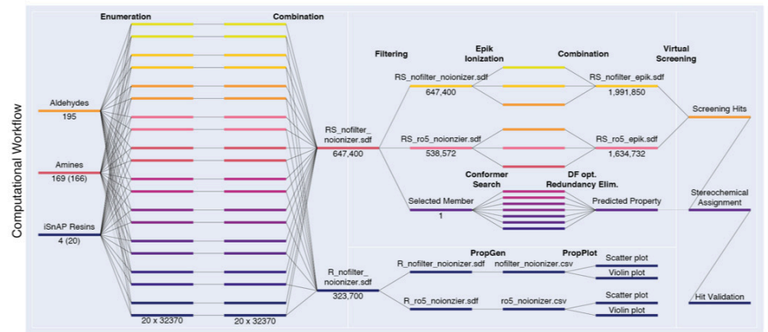
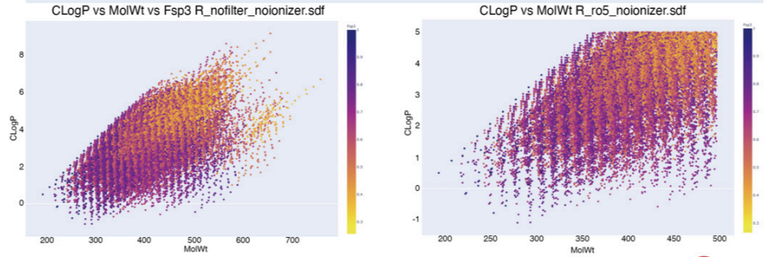
- Synthesis is the rate determining step in the Design, Make, Test discovery cycle
- A computational workflow was used to construct and screen an attractive virtual library whose members can be rapidly prepared by an automated synthesis console
- Hits against several targets, including SARS-CoV-2 (MPro), were expeditiously prepared in an automated manner and validated in a biological assay

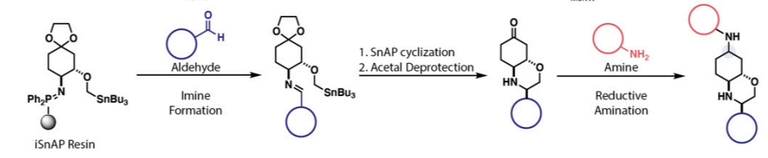


1 Construction and Analysis of Virtual Library

- Commercial aldehydes and amines were combined with iSnAP resins to give 650k molecules
- Library was filtered (Lipinski's rule of 5, 83% retention) and ionized (EPIK) prior to virtual screening
- The R enantiomers were analysed (RDkit, python) and showed coverage of drug-like chemical space with a high fraction of sp^3 carbons

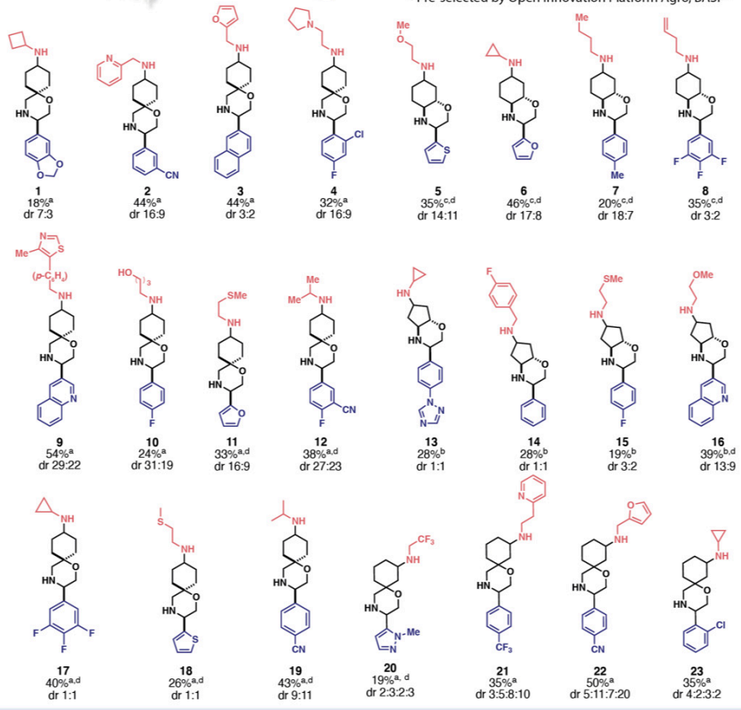






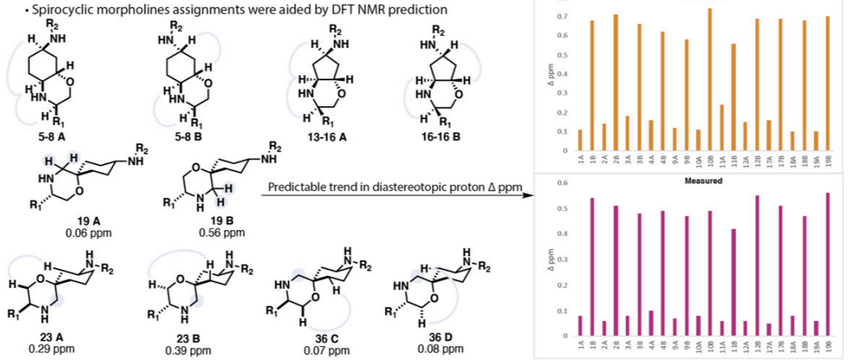
2 Automated Synthesis of Library Members

- Selected aldehydes were transformed with an iSnAP capsule, concentrated and run with the selected amine and reductive amination capsule using the Synple Chem system
- Resolution was achieved using preparative HPLC in all cases except 13-16 which were isolated as diastereomeric mixtures
- Deprotection times 5 h[a], 24 h[b], 12 h[c]
- Pre-selected by Open Innovation Platform Agro, BASF[d]



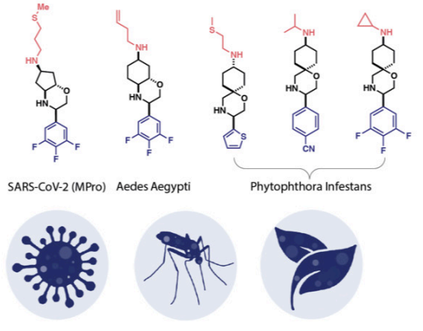
3 Assignment of Relative Stereochemistry

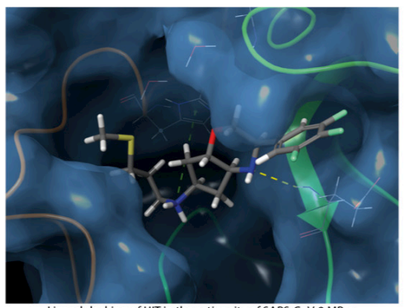
- Fused morpholines can be assigned from 2D ^{1}H NOESY experiment
- Spirocyclic morpholines assignments were aided by DFT NMR prediction



4 Hit Validation

1. SARS-CoV-2 MPro inhibitors identified using ligand and structure based virtual screening then validated in a cellular assay
2. Anti-fungal and insecticidal molecules selected and screened by Open Innovation Platform Agro, data supplied by courtesy of BASF SE





Ligand docking of HIT in the active site of SARS-CoV-2 MPro