New Covalent Probes: parallel synthesis of covalent binders and their application in early discovery

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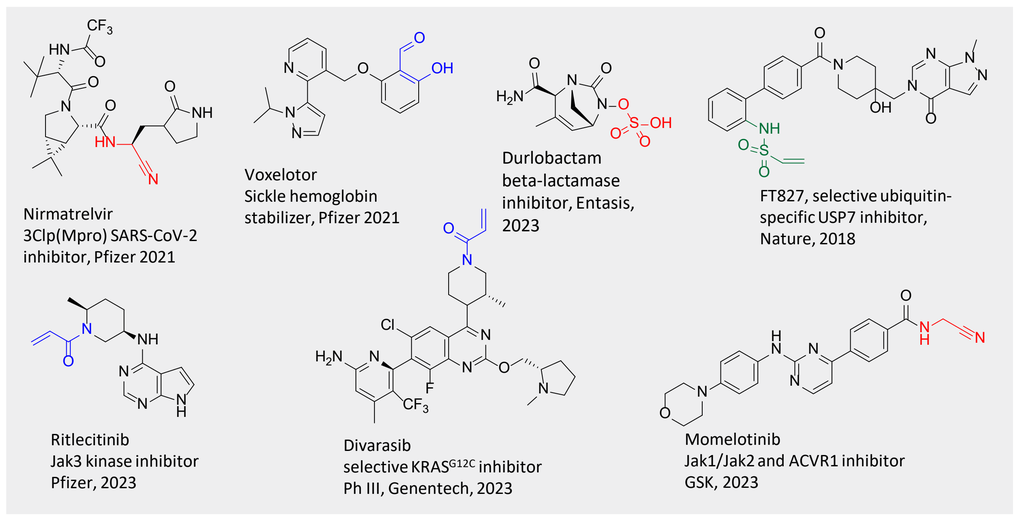
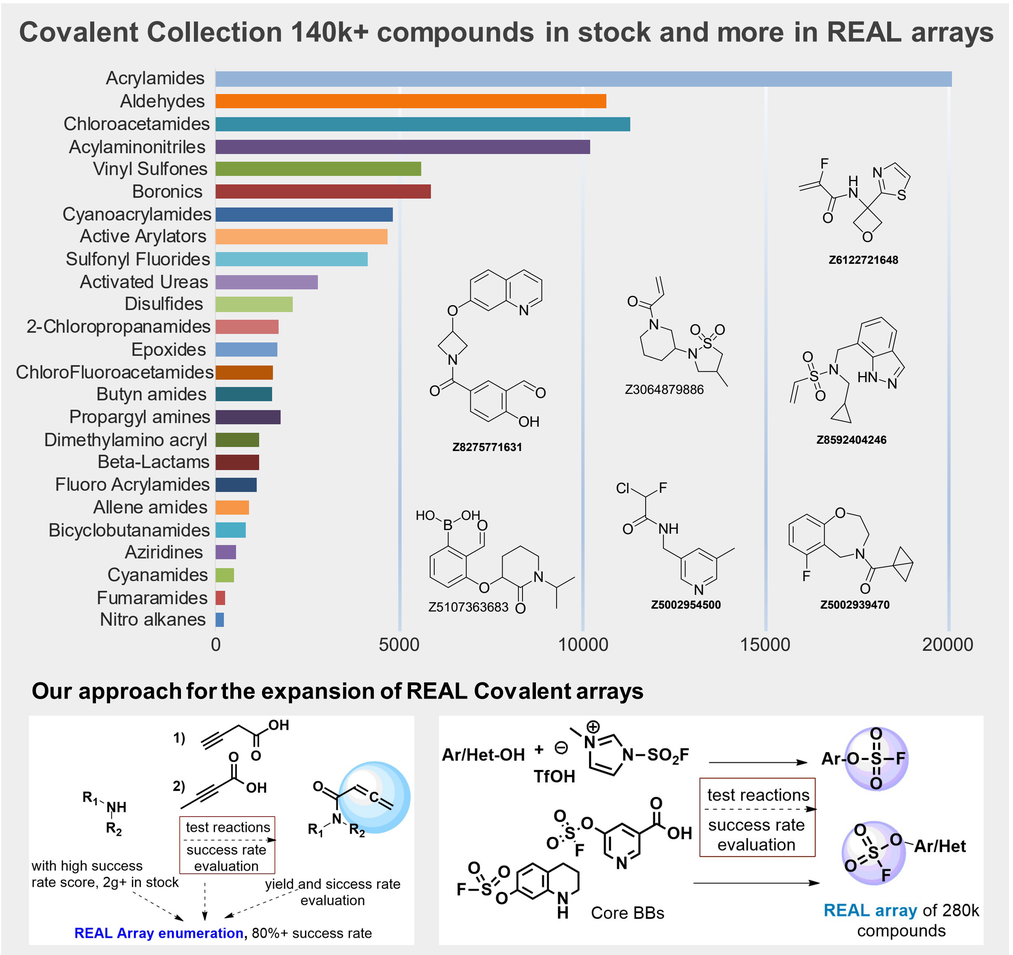
Introduction and Aim

Covalent binders become an integral part of the current discovery process. To be efficient for early-stage drug discovery, covalent compounds should represent novel MedChem attractive scaffolds and reliable synthesis for optimization. To address growing interest in this field and bring a new level of novelty we are continuously working on the elaboration of parallel chemistry approaches to synthesize a series of new covalent binders. Herein, we describe our approach to parallel synthesis of various covalent modifiers, enumeration of REAL covalent arrays, and two case studies of optimization of covalent fragment hits. The increased number of approved drugs with covalent modes of action within the past two years reflects the high importance of the discovery of new covalent probes.

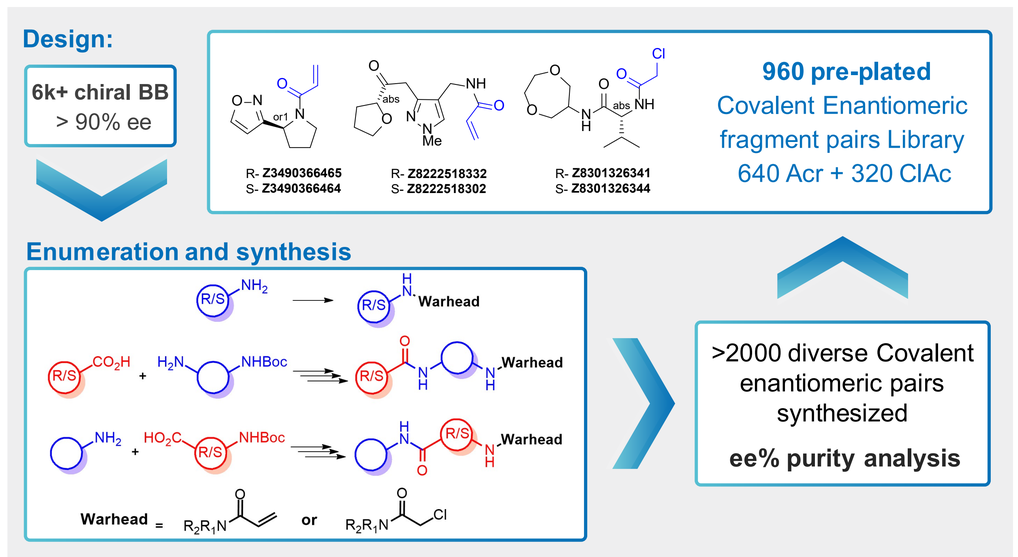


Covalent Compound Collection



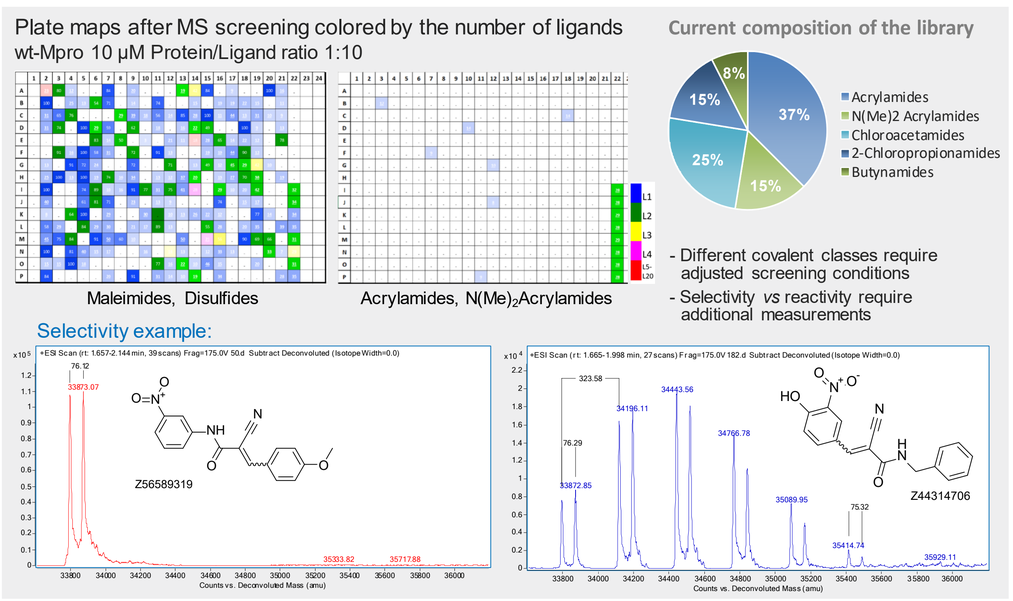
Covalent Enantiomeric Pairs Library

The most attractive and diverse chiral building blocks were selected and progressed into Covalent Enantiomeric Pairs. We utilize parallel chemistry approach to synthesize enantiomers of the most robust covalent binders, acrylamide and chloroacetamides. All compounds were analyzed with chiral chromatography to ensure 90%+ ee purity.



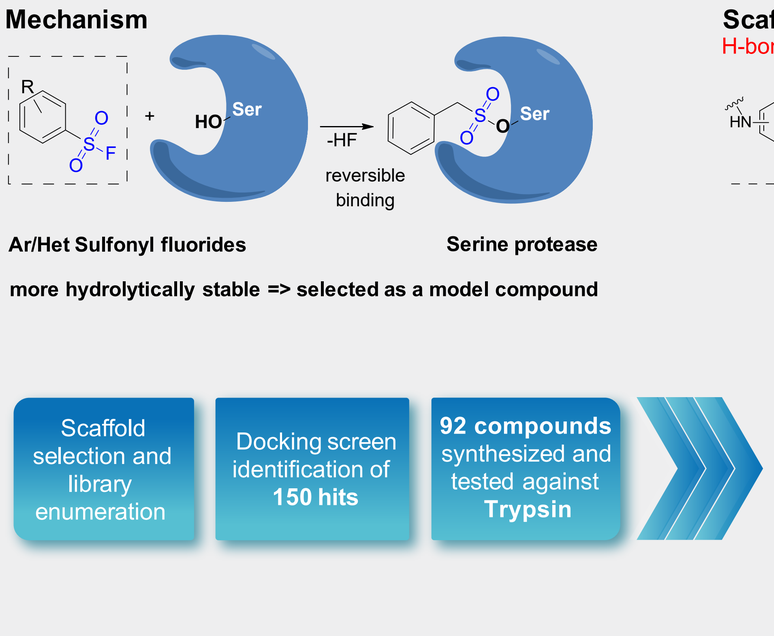
Screening against SARS-CoV-2 Mpro

Cysteine-focused fragment library of 3200 compounds was screened against coronavirus Main protease using MS-based screening. Analysis of results revealed interesting findings in the selectivity and reactivity of some covalent classes.



Case Study: N-arylsulfonyl fluorides as inhibitors of serine proteases

Entry No.	Compound	ΔT_m, °C	IC_{50} (μM)	cLogP[32]	LLE
1	Z1672278953 8{3,74}	–9.5	338	2.23	1.24
2	Z1672278926 8{3,56}	–10.6	224	2.60	1.05
3	Z1672278918 8{3,98}	–7.8	648	2.09	1.10
6	Z2216296226 8{1,122}	–3.6	84	0.80	3.28



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References

K. Tolmachova *et. al. ACS Comb. Sci.* **2018**, *20*, 11, 672–680: 10.1021/acscombsci.8b00130