New Covalent Fragment Libraries by parallel synthesis

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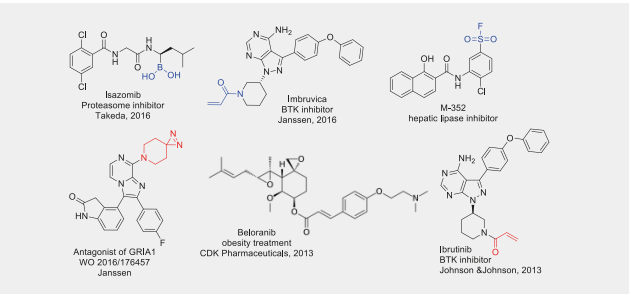
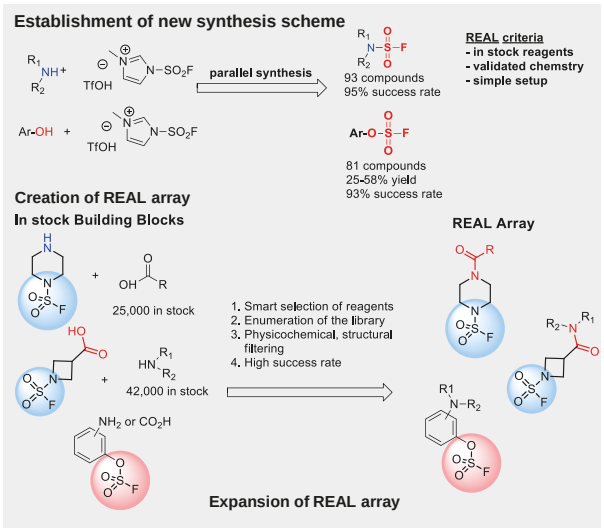
Introduction and Aim

Covalent chemical probes have become a hot topic in drug discovery within last few years. To be efficient for early stage drug discovery, covalent modifiers have to integrate novel scaffolds and easy, potentially enumerated setups. To address continuously growing interest in this field and bring new high level of novelty we elaborated parallel chemistry approaches to synthesize series of new covalent binders. Herein, we describe our approach to parallel synthesis of various covalent modifiers, that resulted in enumeration of arrays of REAL compounds – covalent fragments available for cherry-picking and reliable supply within only 3 weeks, and high success rate.

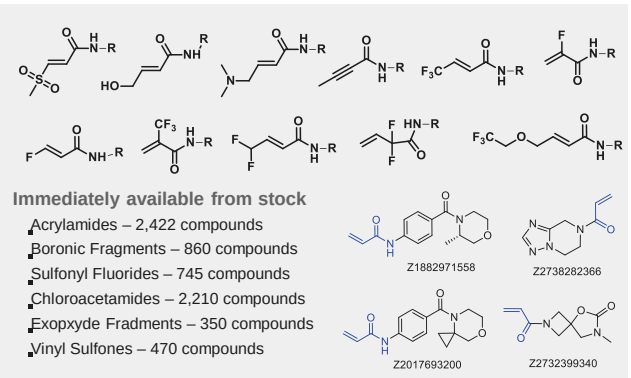


REAL concept



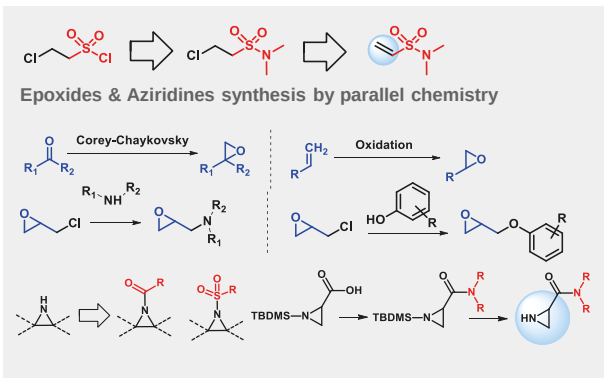
Advanced acrylamides

Enamine specially synthesized series of acrylic-like building blocks for synthesis of new covalent libraries. Fluorinated acrylamides can also be used for F19 NMR contrscreen. Synthesis of corresponding amides was validated by parallel chemistry



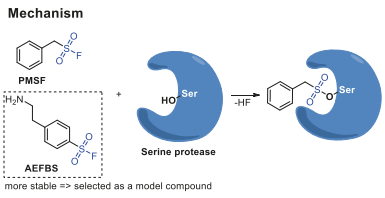
Synthesis of new covalent probes

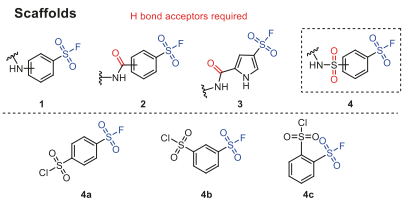
Careful choice of the building blocks and elaboration of specific reaction conditions and purification procedures has allowed synthesis of different novel covalent fragments, not yet represented by commercial proposal.

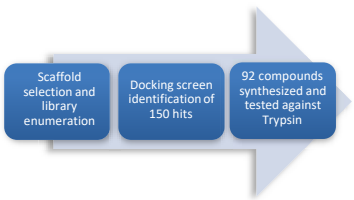


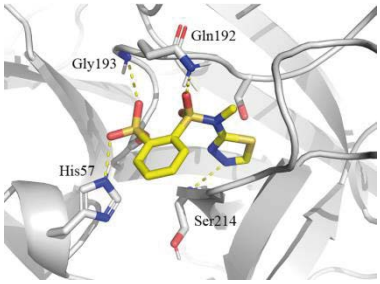
Case Study: N-arylsulfonyl fluorides as inhibitors of serine proteases

Entry No.	Compound	ΔTm, °C	IC50 (μM)	cLogP[32]	LLE
1	Z1672278953	-9.5	338	2.23	1.24
2	Z1672278926	-10.6	224	2.60	1.05
3	Z1672278918	-7.8	648	2.09	1.10
6	Z2216296226	-3.6	84	0.80	3.28









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