Covalent Screening Library

Specially designed for covalent target modification

15,600 compounds

Covalent modifiers have attracted much attention in recent years; over 30% marketed drugs have this mode of action. The increased biochemical potency associated with an irreversible mechanism can actually lead to increased therapeutic profitability, as lower drug concentrations are required for effectiveness. Nevertheless, design of selective covalent modifiers is a difficult task since it is difficult to find the right balance between reactivity and selectivity.

Library design

Enamine Covalent Screening Library has been extracted from the "Rule of Five" compliant subset of the Screening Collection using substructure searches of specified structural features (Figure 1). Active functionalities able to form covalent bonds with protein residues have been analyzed, and the "warheads" listed below were selected as optimal in terms of reactivity and essential stability. Additionally, the chemical environment of each reactive group was checked to be suitable for moderate reactivity of the compound. Molecules with non-druglike cores and structural features were removed from the library using internal structure filters and in-house elaborated rules. The final set of selected compounds has been evaluated manually to avoid too reactive entities and eliminate structural shortcomings of the substructure searches (Figure 2).

MW	230…500
clogP	–2.0…4.0
TPSA	<150 Å^2
H-Donors	≤4
H-Acceptors	≤9
RotBonds	0…5
Rings count	1…4

Structural fragments used for compounds selection:

- Acrylamides, acrylonitriles
- Activated terminal acetylenes
- Alkyl halides
- Epoxides, aziridines
- Alkyl thioles, disulfides
- *β*-lactams, -lactones
- Sulfonyl fluorides/esters
- Carbamates
- 2-cyano/-Cl nitrogen heterocycles
- Vinylsulfones, -sulfonamides
- Boronic acids

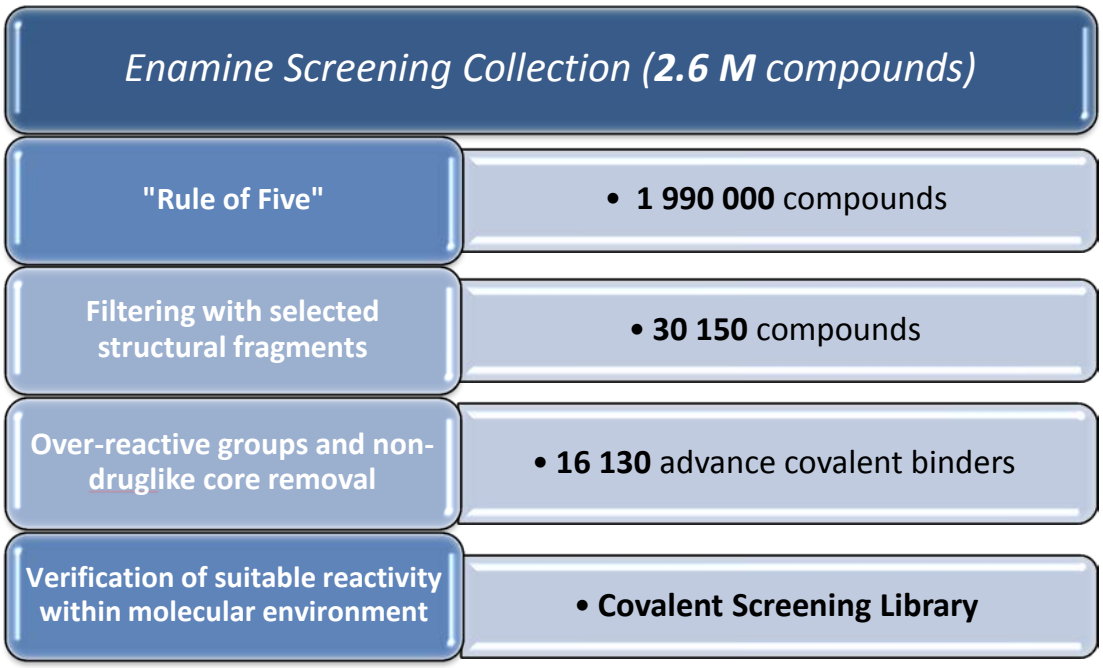

Figure 1. Design of the Covalent Screening Library

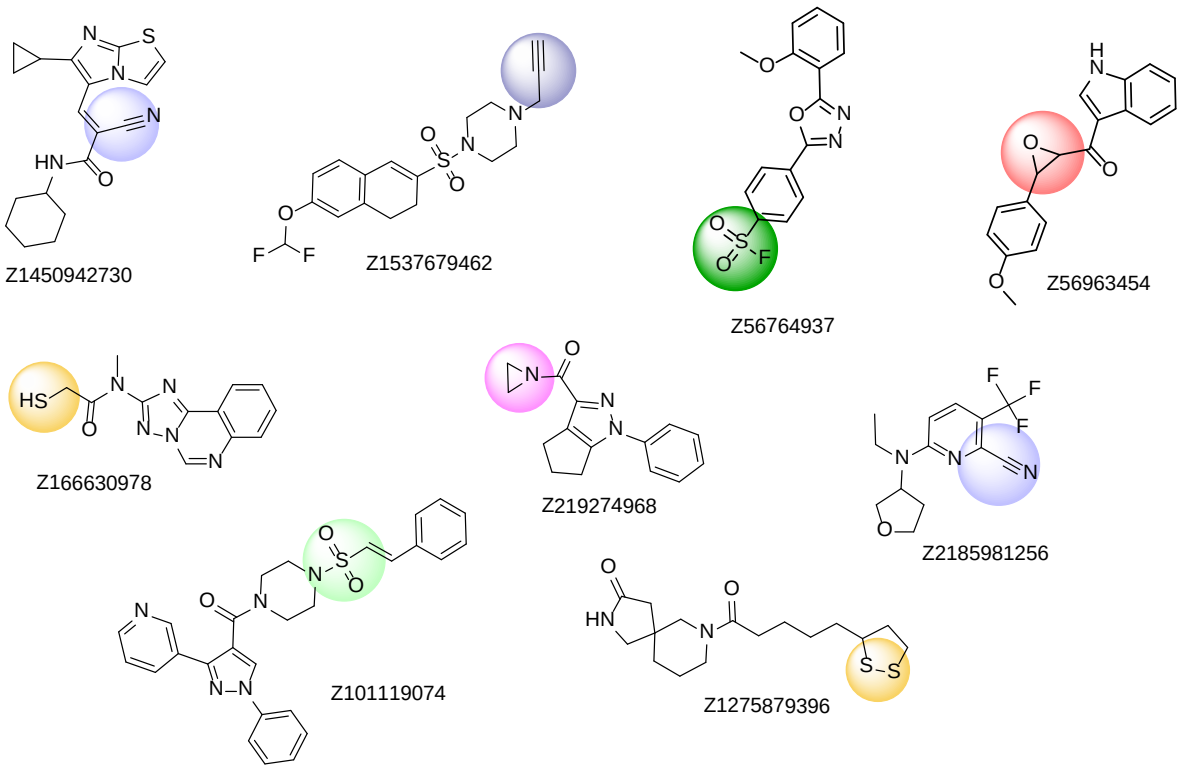

Figure 2. Examples of molecules in the Library