Covalent inhibitors library

Covalent inhibitors have many desirable features, including increased biochemical efficiency of target disruption, less sensitivity toward pharmacokinetic parameters and increased duration of action that outlasts the pharmacokinetics of the compound. Safety concerns that must be mitigated include lack of specificity and the potential immunogenicity of protein-inhibitor adduct(s).

Compounds from Life Chemicals Covalent Inhibitors Library were selected by presence of specific structural fragments (functional groups) that are known to form covalent bonds with amino acid residues in binding sites of target proteins: Lys, Cys, Ser, Asp, Glu and Tyr.

Following chemical classes and structural fragments were used for selection of possible covalent inhibitors:

- β-lactams
- Alkyl halides
- Epoxides, aziridines
- Michael acceptors: α,β-unsaturated ketones, -nitriles, -esters; maleimide-like compounds; activated vinyl derivatives
- Cyanoacrylamides
- Sulfonate esters
- Sulfonyl fluoride
- Thioles
- Rodanides
- Thiourea and thioketone
- o-quinones
- p-quinones
- Ketales
- Acetales
- Disulfides
- Terminal acetylenes
- Sulfoalkenes

Compound set passed these filters were narrowed down according to expanded “Rule of Five”:

1) MW from 120 to 500
2) clogP from -0.4 to 5
3) Hb donor 0 – 5
4) Hb acceptor 0 – 10
5) rotatable bonds no more than 10
6) PSA no greater than 140Å^2

Finally a Library of 6,400 compounds was obtained.

References:

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To download a file with compound structures for this library, please follow this link:
http://www.lifechemicals.com/downloads/Screening_Libs/13062/Covalent_inhibitors