Serine Focused Covalent Inhibitors Library

An effective strategy for enhancing the potency and selectivity of initial active molecules is *via* cova-lent bond formation with a nucleophilic residue that is specific to a target of interest and ideal-ly absent from off-targets. Such covalent-acting chemical probes have increasingly been used in prote-ome-wide target identification and imaging and for finding inhibitors with high specificity among re-lated enzymes and enzyme isoforms. Covalent drugs and natural products are also well known. Serine hydrolases are one of the largest and most diverse classes of enzymes found in nature[1]. These en-zymes, which include lipases, esterases, thioesterases, amidases, peptidases and proteases, all utilize a base-activated serine nucleophile to cleave amide or ester (or thioester) bonds in substrates via a cova-lent acyl-enzyme intermediate.

Life Chemicals' Team has designed Serine Focused Covalent Library on the basis of combination of specific structural fragments (functional groups) that were reported to form covalent bonds with serine residue in binding sites of proteins[2-6] and drug-like filters ("Lipinski's Ro5", "Veber rules", reactive groups and selected PAINS filters). Compounds with following structure fragments were included into the library:

- Carbamates
- Activated aliphatic nitriles (retro Michael acceptors)
- Epoxides
- *β*-propiolactones; *γ*-butyrolactones
- *β*-lactams
- Boronic acids
- Aryl ureas (no isolated benzene ring)
- Trifluoroacetamides
- *α*-hydroxy ketones
- *α*-ketoalkyl oxazoles
- *N*-carbamoyl azoles
- *1,2*-diazetidones

Total number of compounds in the libarary: **1,700**

References

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2. Bachovchin D. A., Cravatt B. F. The pharmacological landscape and therapeutic potential of serine hydrolases. *Nat. Rev. Drug Discov*., **2012**, *11*, 52–68.
3. Cognetta A. B., Niphakis M. J., Lee H. C., Martini M. L., Hulce J. J., Cravatt B. F. Selective N-Hydroxyhydantoin Carbamate Inhibitors of Mammalian Serine Hydrolases. *Chem. Biol*., **2015** Jun 25.
4. Hoover H. S., Blankman J. L., Niessen S. Cravatt B. F. Selectivity of inhibitors of endocannabinoid biosynthesis evaluated by activity-based protein profiling. *Bioorg. Med. Chem. Lett*., **2008**, 18, 5838–5841.
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6. Singh J., Petter R. C., Baillie T. A., Whitty, A. The resurgence of covalent drugs. *Nature Rev. Drug Discov*., **2011**, 10, 307–317.

To download a file with compound structures for this library, please follow this link:

http://www.lifechemicals.com/downloads/Screening_Libs/13062/Covalent_inhibitors