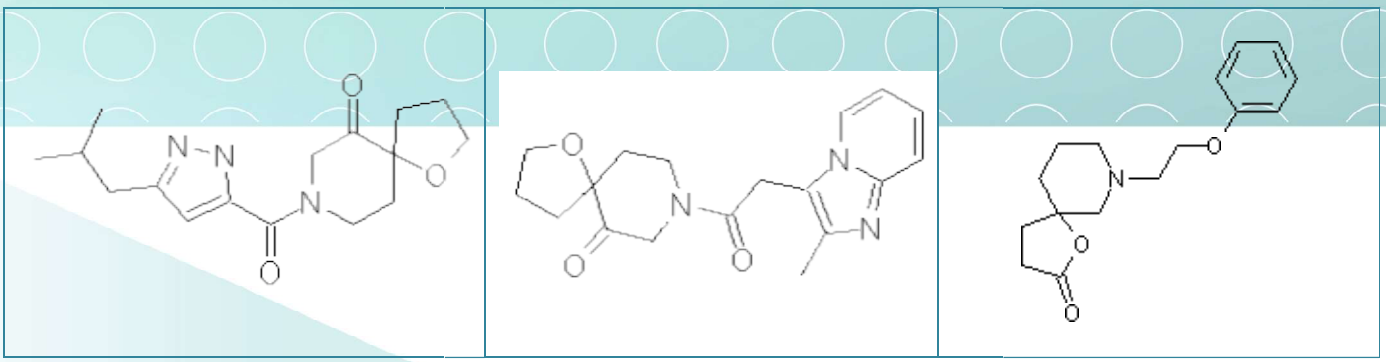
SL-27. Soft Electrophiles-4. Covalent Inhibitors

ASINEX
Signature Libraries

Historically, in screening libraries, reactive molecules have been disregarded due to selectivity and safety concerns. However, many successful drugs act as covalent inhibitors based on a specific reactive group or moiety [1]. Covalent drugs typically have higher affinity and specific kinetics which, in turn, lead to dose reduction and minimal side effects in therapeutics. Covalent inhibitors often possess an electrophilic "warhead" which interacts with a nucleophilic residue at the binding site under certain physiological conditions; examples of such electrophilic groups include acrylamides, epoxides, nitriles, and electron-deficient ketones.

At ASINEX, we have created a library of α-oxyketone and spiro-lactone derivatives that contain mild electrophilic functional groups. Both lactones and oxyketones provide interesting small molecule probes for covalent drug discovery across multiple disease areas [2] as they interact with nucleophilic residues (e.g. Ser, Thr, Lys and Cys) of target proteins.

Structurally, a combination of saturated and aromatic rings in the final compounds provides a favorable physicochemical profile resulting in improved ADME properties.



Signature Library 27

Formats	Supplementary Information
80 compounds per plate 0.1 mg; 1 mg; 2 mg dry film/powder 0.1 µmol; 1 µmol DMSO solutions	SL#27_Soft Electrophile-4_06-16.sdf

References:

1. *Drug Discov Today.* 2015 Sep;20(9):1061-73. doi: 10.1016/j.drudis.2015.05.005
2. *Current Opinion in Chemical Biology* 2010, 14:421–427 doi:10.1016/j.cbpa.2010.03.035

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