3-D NATURAL PRODUCT-LIKE COMPOUNDS

Spirocycle Library

Highlights

- High quality, small molecule compounds with spirocycles conferring natural product-like 3-D character
- More than 30,000 compounds with 90% having Fsp3 of 0.4 or higher and 68% having Fsp3 of 0.5 or higher
- Custom select compounds to meet your specific requirements

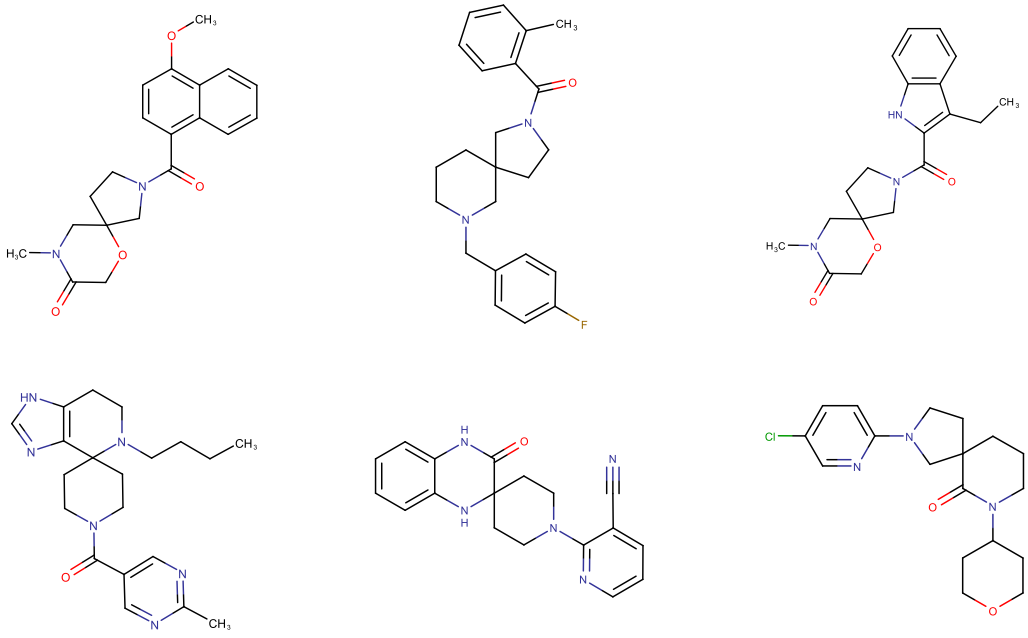
Introduction

Spirocycles (two rings fused through a single atom) are well represented in natural products, which have evolved mainly to interact with proteins. The most significant characteristic of spirocycles is their inherent ability to project functionality in three dimensions. For example, in a binding site equally projected in all three dimensions spirocycles occupy the binding site in a more atom efficient manner than planar (hetero)aromatic systems. By the nature of the quaternary spiro atom, spirocycles always contain some sp3 character. Lovering et al[1] in their 2009 article demonstrate that both molecular complexity, as measured by fraction sp3 (Fsp3), and the presence of chiral centers correlate with success through the drug discovery process. The authors also showed that saturation correlated with increased solubility, an experimental physical property important to success.

In the drug discovery literature spirocyclic compounds have demonstrated broad utility across a range of target classes including enzymes, GPCRs and protein-protein interactions. For example, AMG-8718 is a secretase inhibitor for Alzheimers disease; Compound 4, an inhibitor of acetyl CoA carboxylase, a target for treatment of metabolic syndrome; ETX0914, a DNA gyrase inhibitor which entered clinical trials for the treatment of gonorrhea; MK-1602, a calcitonin gene-related peptide antagonist, reported to have completed Phase 2 clinical trials for the treatment of migraine; Rolapitant, a neurokinin 1 receptor antagonist approved in 2015 for the treatment of delayed-phase chemotherapy-induced nausea and vomiting; Ledipasvir, which binds to the HCV NS5A protein, approved in 2014 for the treatment of hepatitis C; and MI-77301, a spirooxindole p53/MDM2 protein-protein interaction inhibitor that progressed into Phase 1 clinical trials in 2012.

The increased synthetic complexity of spirocyclic compounds has resulted in spirocyclic compounds being less well represented in the drug discovery patent literature and in small molecule screening offerings compared to non-spirocyclic compounds. Thus, where synthesis allows, designing spirocyclic systems into screening molecules is an attractive approach to achieve novelty and more 3D character. In addition, spirocycles composed of six-membered or smaller rings are either rigid or have a limited number of well-defined conformations; this attribute makes spirocyclic compounds well suited to structure-based drug design where spirocyclic scaffolds can be used to accurately position functional groups within a binding site targeting specific protein-ligand interactions.

Example Structures



Properties

Spirocycle Library compounds are lead-like and drug-like and have the following physiochemical and calculated property averages and ranges:

	Average	Range
Molecular Weight	353	240 – 500
Fsp3	0.53	0.1 – 0.9
H-bond Donors	1	0 – 3
H-bond Acceptors	4	1 – 7
clogP	1.61	1.8 – 5.4
TPSA	59	20 – 110

Format

- Download structures and custom select compounds from the Spirocycle Library SDfile
- Compounds can be provided in 96-well or 384-well format
- Compounds available dry or as DMSO solutions

[1]Lovering F et al. Escape from flatland: increasing saturation as an approach to improving clinical success. J Med Chem. 2009 Nov 12;52(21):6752-6.

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Rev. 11072018