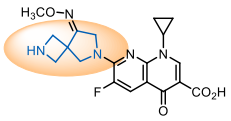
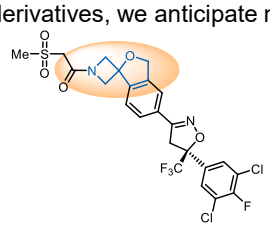
Magic Methyl for Spirocyclic Scaffolds

Introduction

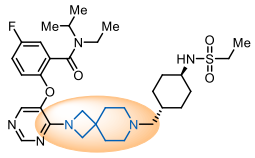
Recent medicinal chemistry projects frequently use spirocyclic linkers to enhance molecular three-dimensionality and reduce metabolic susceptibility. A notable example is the family of spirocyclic azetidines, found in 5 approved drugs and 19 clinical trial candidates. However, crystal structure analyses often reveal crystallographic water in binding sites, suggesting a room for small substituents like methyl groups.[1,2] To date, Deglocitinib, a Janus kinase inhibitor FDA-approved in 2025 for chronic hand eczema,[3] is the only drug exemplifying the "magic methyl" concept[4] in spiroazetidines. With *Enamine* now supplying a battery of methylated and other substituted derivatives, we anticipate more structures adopting this design.



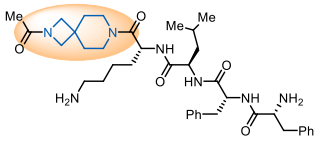
Zabofloxacin (**DW-224a**)
inhibitor of DNA gyrase
South Korea approved 2015
Dong Wha Pharm



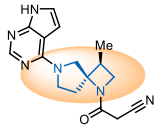
Sarolaner (**PF-6450567**)
blocker of ligand-gated chloride channels
FDA approved 2016 (for dogs!)
Zoetis/Pfizer



Revumenib (**SNDX-5613**)
inhibitor of menin - KMT2A (MLL1) interaction
FDA approved 2024
Syndax Pharm

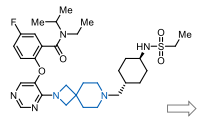


Anrikefon (**HSK-21542**)
agonist of the kappa-type opioid receptor
China approved 2025
Haisco Pharm Group

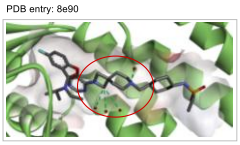


Delgocitinib (**LEO-124249**, **JTE-052**)
inhibitor of Janus kinase isoforms
FDA approved 2025
LEO/Japan Tobacco

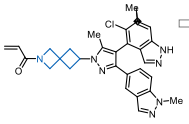
Crystal structures



Revumenib (**SNDX-5613**)
FDA approved 2024
Syndax Pharm

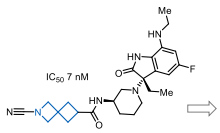


PDB entry: 8e90
human menin isoform 2
Nature **2023**, *615*, 913

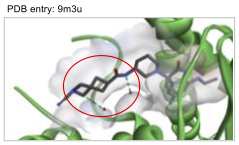


Opnurasib (**JDQ-443**)
Phase 3 trials for cancer
Novartis

PDB entry: 7r0m
human GTPase KRAS Gly12Cys
Cancer Discov. **2022**, *12*, 1500



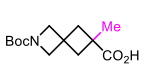
inhibitor of pyruvate dehydrogenase kinase 1/2
Hoffmann-La Roche



PDB entry: 9m3u
human mitochondrial pyruvate dehydrogenase kinase 2
Bioorg. Med. Chem. Lett. **2025**, *122*, 130190

We offer: over 50 methyl spiroazetidines from stock on 5-10 gram scale.

linkers



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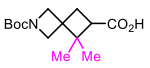

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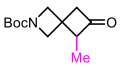

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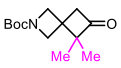

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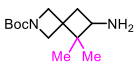

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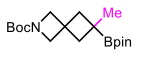

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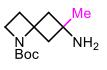

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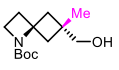

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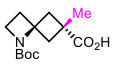

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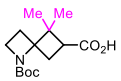

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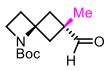

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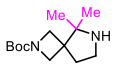

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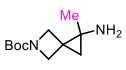

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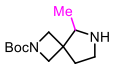

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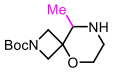

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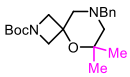

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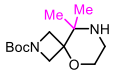

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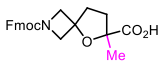

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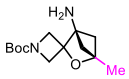

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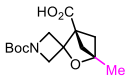

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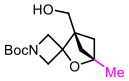

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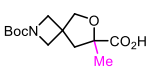

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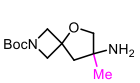

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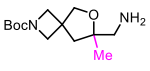

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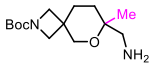

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References

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2. H. Xu et al. *Bioorg. Med. Chem. Lett.* **2025**, *122*, 130190.
3. S. Noji et al. *J. Med. Chem.* **2020**, *63*, 7163.
4. P. Pinheiro et al. *Pharmaceuticals* **2023**, *16*, 1157.