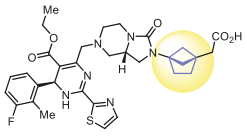
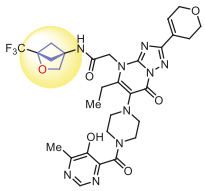
Aliphatic *para-/meta*-Surrogates

Introduction

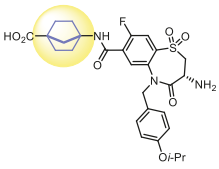
To date, over 700 FDA-approved drug structures have been based on the simple and reliable geometry of the benzene ring.[1] However, this geometry only provides discrete parameters, such as 180° and 120° exit angles for *para*- and *meta*-phenylene scaffolds, respectively. Meanwhile, several promising saturated skeletons produce angles of approximately 150°, serving as hybrid surrogates that enable exploration of the otherwise inaccessible intermediate angle between *para*- and *meta*-substitution. The bicyclic skeletons maintain a molecular volume similar to that of the benzene ring, while high three-dimensionality helps reduce susceptibility to metabolic clearance.[2,3] Inclusion of oxygen atoms reduces lipophilicity and markedly improves solubility of the structures.[4]



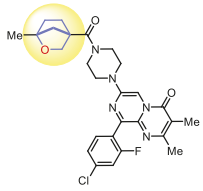
selective agonist of toll-like receptor 7/8
WO 2025/061095
Suzhou Shentuo



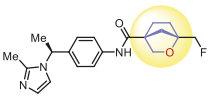
inhibitor of Werner syndrome helicase
WO 2025/049746
Eikon



inhibitor of cytochrome P450 3A4
WO 2025/181251
Sanofi

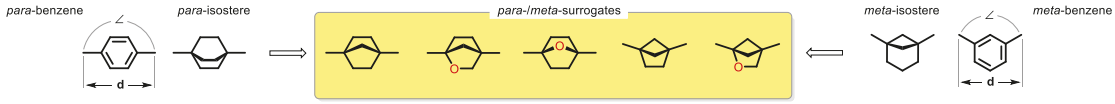


agonist of triggering receptor expressed on myeloid cells 2
WO 2025/136936
Merck



inhibitor of sterile alpha and TIR motif containing 1
WO 2024/126777
AstraZeneca

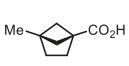
Case study



	∠ 180°	∠ 180°	∠ 151°	∠ 152°	∠ 151°	∠ 147°	∠ 150°	∠ 122°	∠ 120°
distance **d**, Å	5.78	5.69	5.15	5.10	5.11	4.81	4.83	4.71	5.00
mol. volume, Å^3	117.2	157.9	141.1	133.3	133.3	124.3	116.5	141.1	117.2
clogD_7	3.00	3.38	2.93	1.58	1.62	2.49	1.14	2.93	3.00

parameters calculated for dimethyl substitutions, geometry calculated by semi-empirical geometry optimization, volume calculated by https://www.molinspiration.com/ , clogD_7 calculated by ChemAxon

We offer: over 250 *para-/meta*- aliphatic surrogates from stock on 5-10 gram scale.



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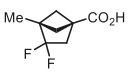

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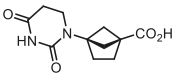

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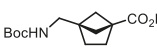

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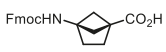

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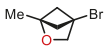

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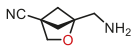

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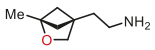

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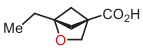

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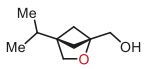

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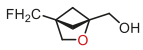

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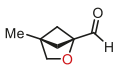

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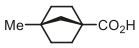

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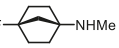

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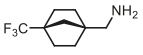

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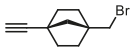

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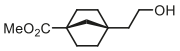

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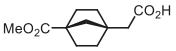

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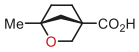

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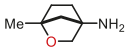

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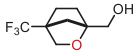

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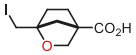

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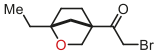

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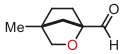

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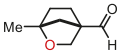

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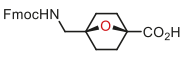

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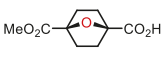

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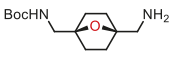

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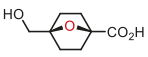

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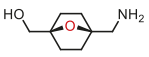

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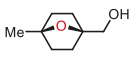

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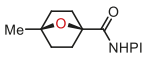

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References

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3. M. Himmelbauer et al. *J. Med. Chem.* **2024**, *67*, 8122.
4. A. Denisenko et al. *Nat. Chem.* **2023**, *15*, 1155.