

Spiro[3.3]heptane as a Benzene Bioisostere for Drug Discovery

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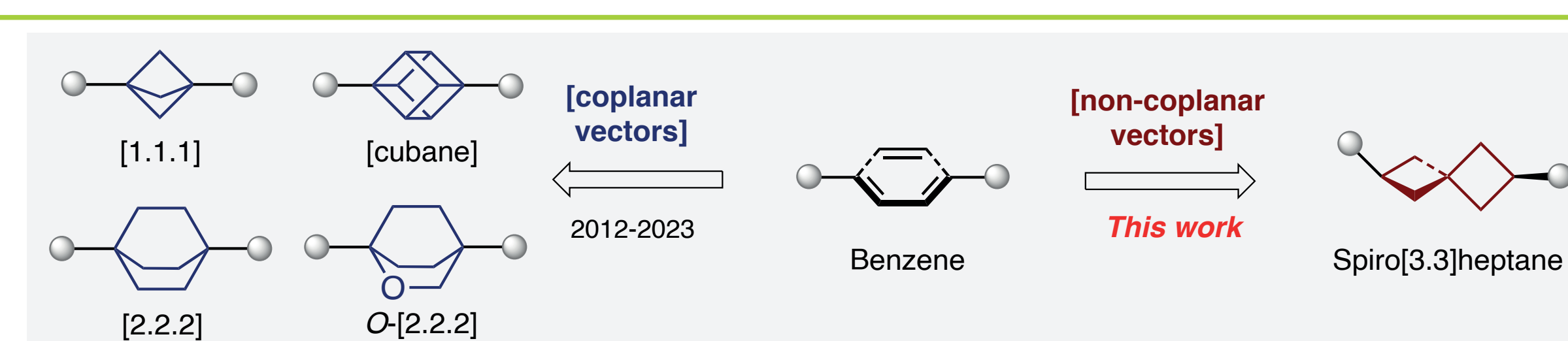
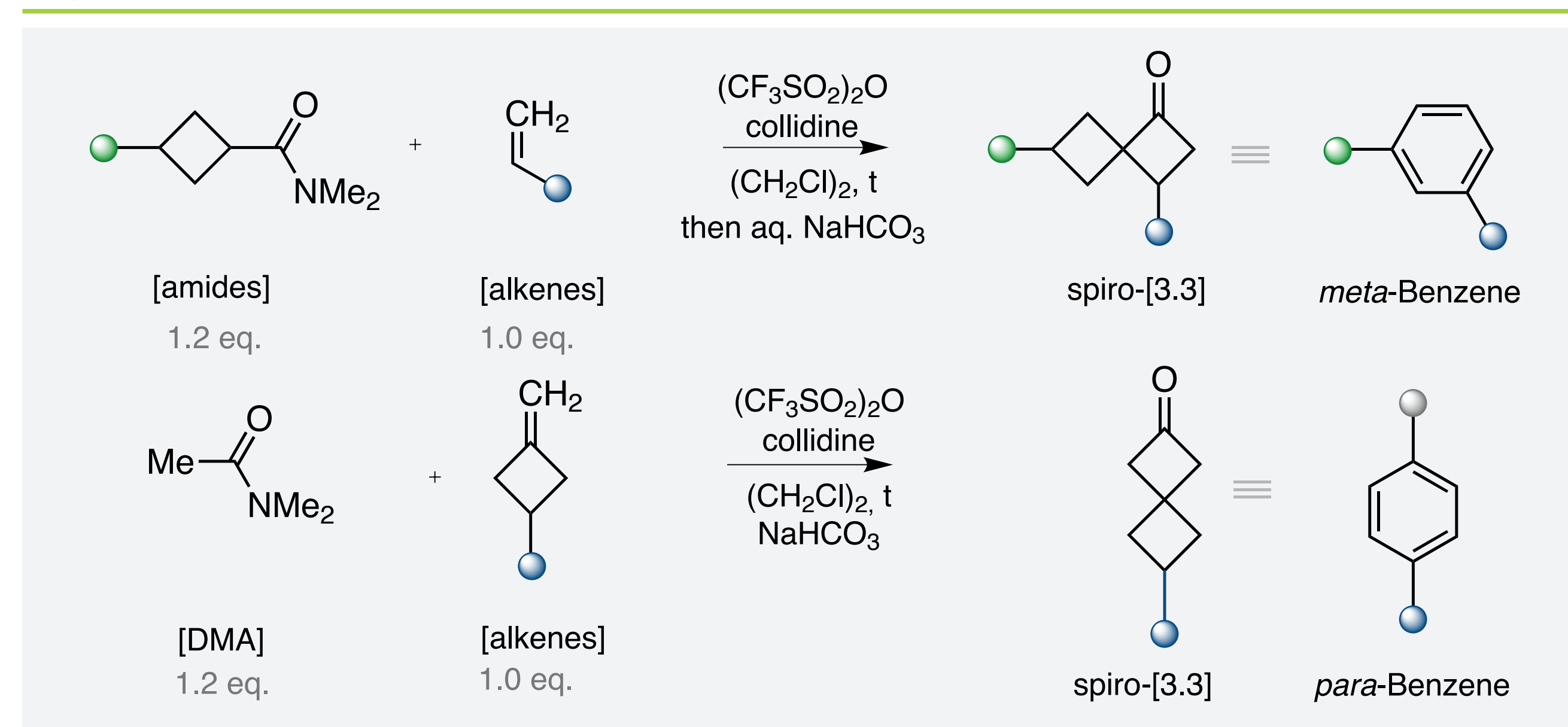
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Introduction and Aim

The benzene ring is a key structural element in chemistry. It is the most popular ring in natural products,¹ bioactive compounds, and drugs.² During the past decade, researchers actively used the saturated cores with the coplanar exit vectors to mimic the parasubstituted benzene ring.

In this work, we show that spiro[3.3]heptane with the non-coplanar exit vectors can mimic the mono-, meta- and para-substituted benzene rings in drugs.³ This scaffold was incorporated into the anticancer drug Sonidegib (instead of the meta-benzene), the anticancer drug Vorinostat (instead of the phenyl ring), and the anesthetic drug Benzocaine (instead of the para-benzene).

Synthesis



Results

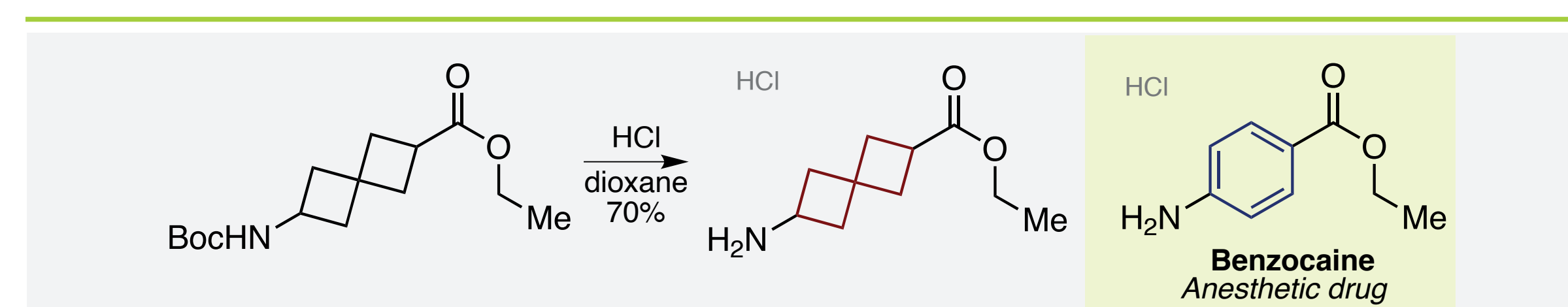
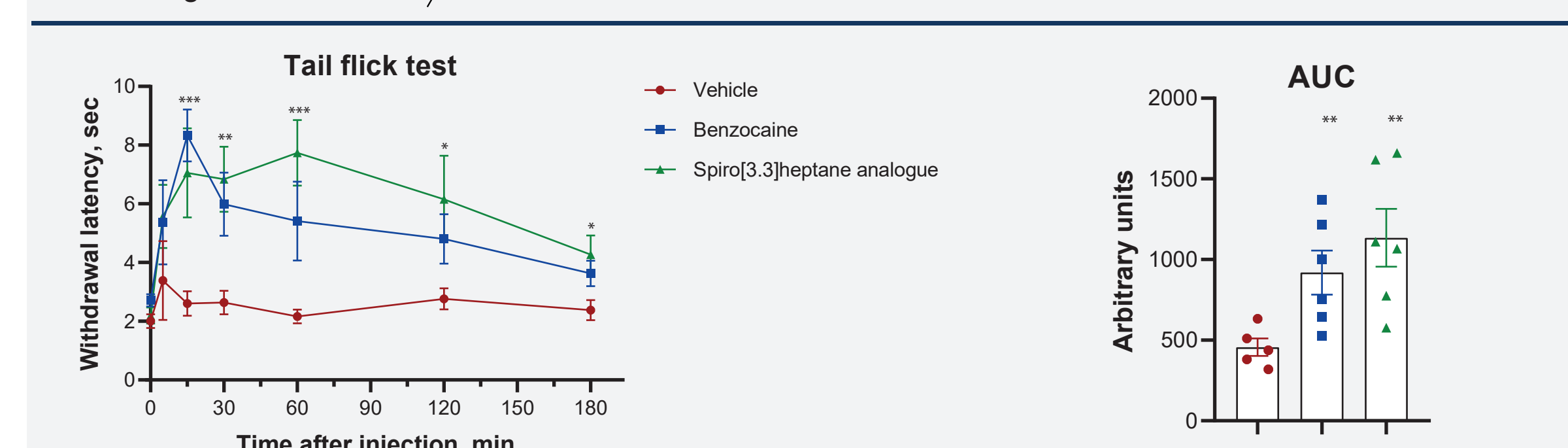
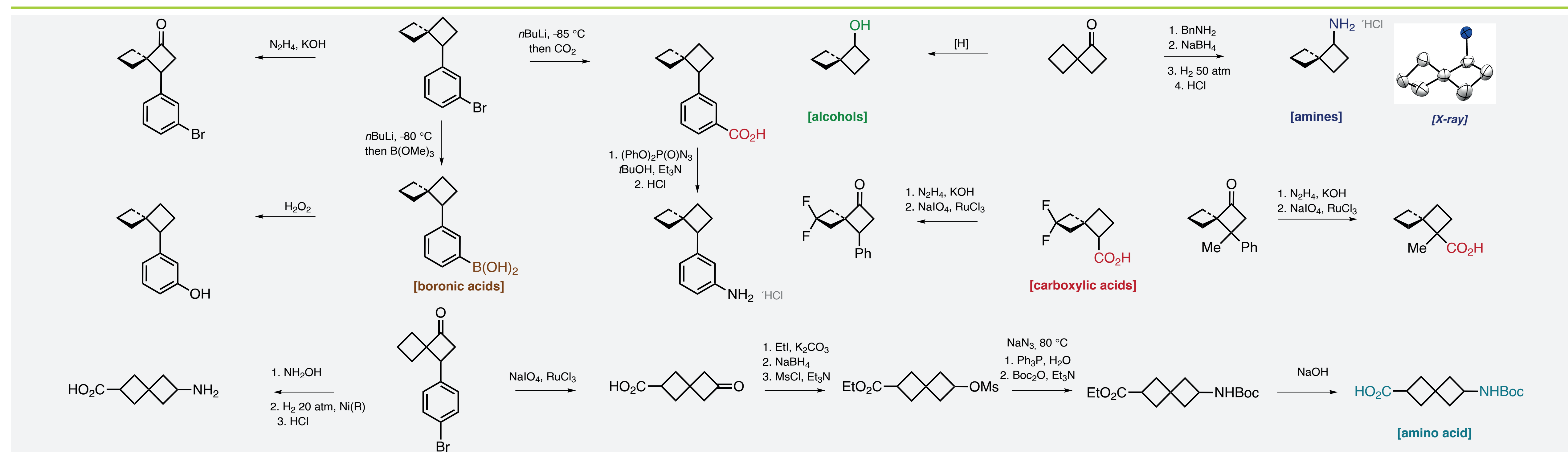


Table 1. ADME properties of Benzocaine and analogs

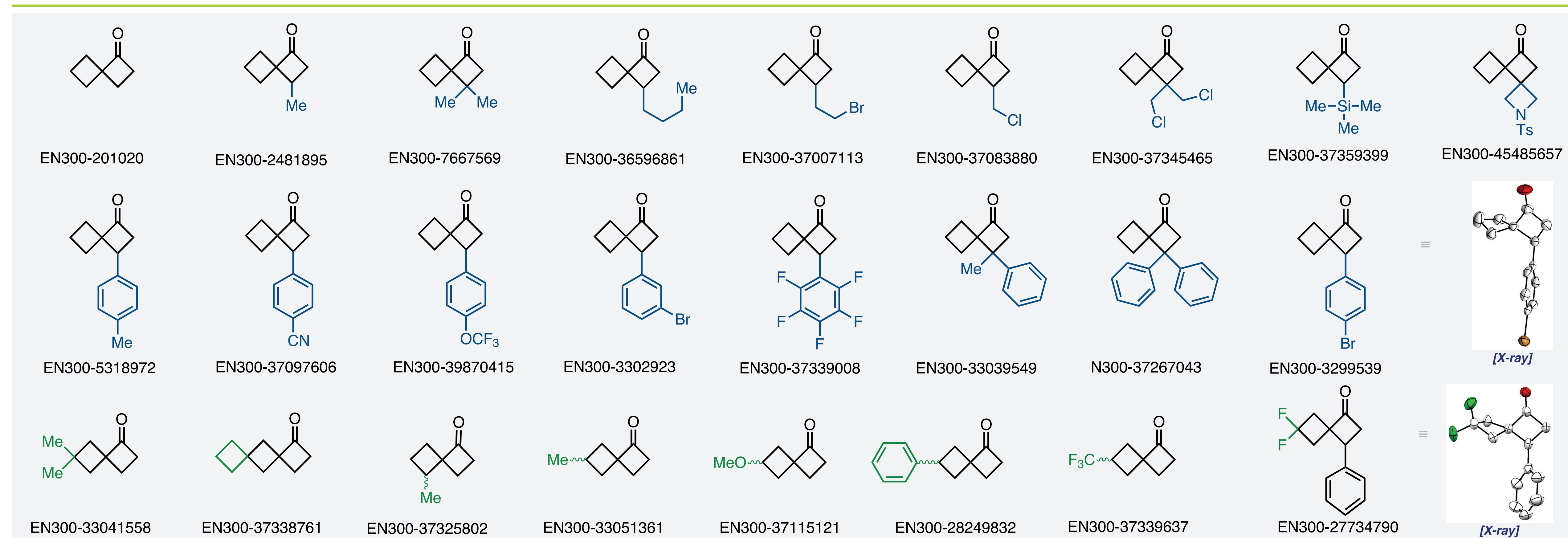
Compound	Structure	Solubility*, PBS pH 7.4, μM	LogD, pH 7.4	CLint, ul/min/mg, HLM	t _{1/2} , min, HLM	k _{el} , min ⁻¹ , HLM
Benzocaine hydrochloride		385±1.4	1.8±0.02	83 [#]	20.1	0.034
Spiro[3.3]heptane analogue		332±2.5	-0.4±0.06	29 [#]	56.7	0.012



Modifications



Representative examples



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References

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- R. D. Taylor *et al.*, *J. Med. Chem.* **2014**, 57, 5845-5859
- Prysiazniuk, K. *et al.* *Angew. Chem. Int. Ed.* **2024**.