An "Ideal" Bioisoster of the *para*-substituted Phenyl Ring

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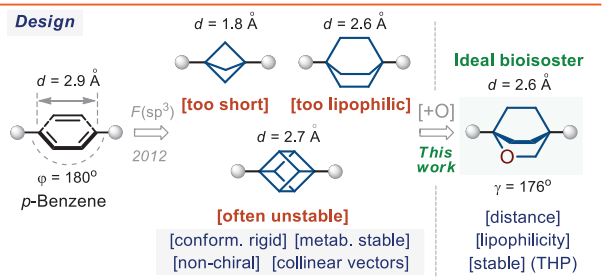
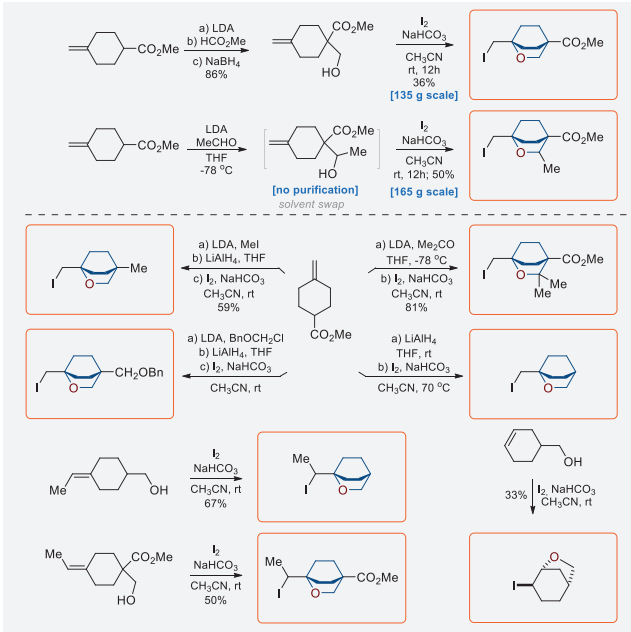
Introduction and Aim

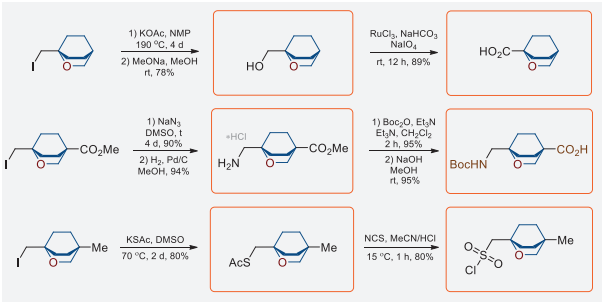
More than five hundred drugs contain a fragment of *para*-disubstituted benzene. However, organic compounds with more than two phenyl rings often suffer from poor solubility and low metabolic stability.[1-3] We have developed an *"ideal"* saturated bioisoster of the *para*-substituted phenyl ring, - 2 oxabicyclo[2.2.2]octane. Its incorporation into *Imatinib* drug led to dramatic improvement of all physicochemical properties. This study opens new horizons in science, given the commonplace of the phenyl ring everywhere. In this work, we have rationally designed, synthesized, and characterized the ideal bioisoster of the *para*-substituted phenyl ring – 2-oxabicyclo[2.2.2]octane.[4]



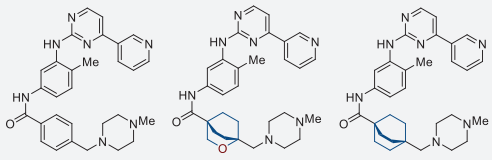
Synthesis



Modifications

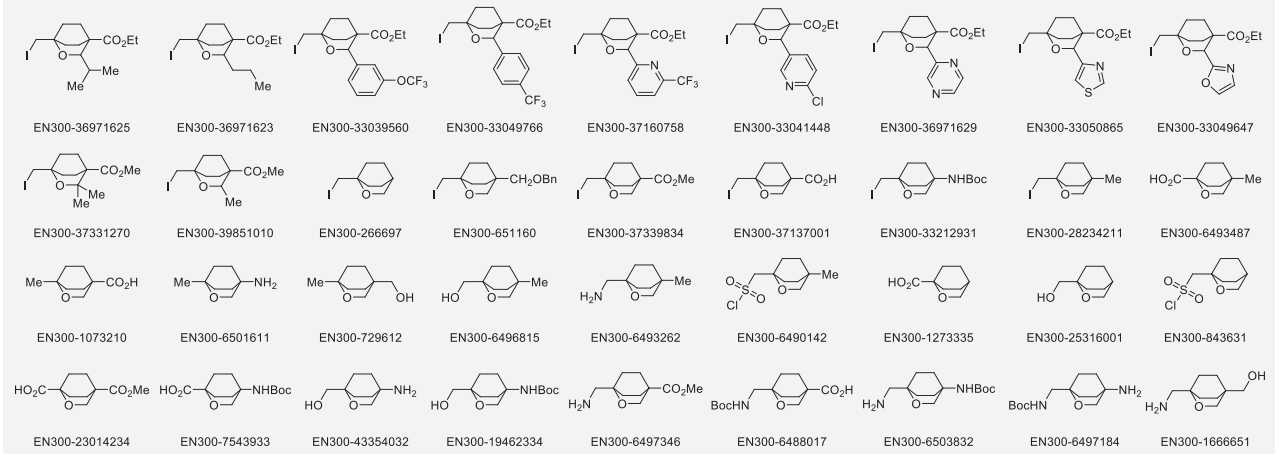


Physicochemical properties



Compound	Sol.	clogP	logD (7.4)	CL_{int}	$t_{1/2}$
Imatinib	351±2	4.5	2.6±0.1	28	60
S-1 [2.2.2]	113±1	3.6	2.7±0.1	16	107
S-2 O-[2.2.2]	389±1	2.6	1.8±0.1	19	87

Results



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References

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4. V. V. Levterov *et al. Nat Commun,* **2023**, *14*, 5608.