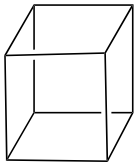
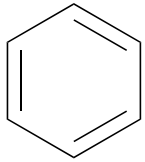
Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere

Chalmers, B. A.; Xing, H.; Houston, S.; Clark, C.; Ghassabian, S.; Kuo, A.; Cao, B.; Reitsma, A.; Murray, C. E.; Stok, J. E.; Boyle, G. M.; Pierce, C. J.; Littler, S. W.; Winkler, D. A.; Bernhardt, P. V.; Pasay, C.; De Voss, J. J.; McCarthy, J.; Parsons, P. G.; Walter, G. H.; Smith, M. T.; Cooper, H. M.; Nilsson, S. K.; Tsanaktsidis, J.; Savage, G. P.; Williams, C. M., Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere. *Angew Chem Int Ed Engl* **2016,** *55* (11), 3580-5.





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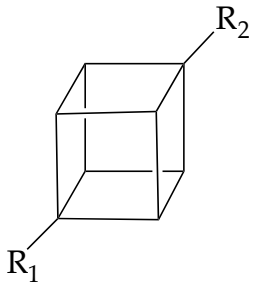
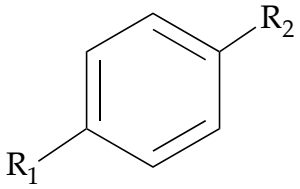
Wipf Group
07/09/16

Bioisosteres and Eaton's Hypothesis

Eaton's Hypothesis: Cubane may be a suitable bioisostere of Phenyl due to it having a similar size and shape

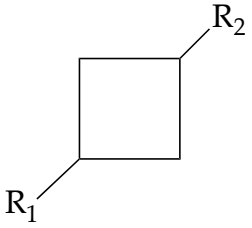


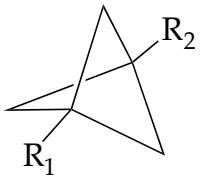


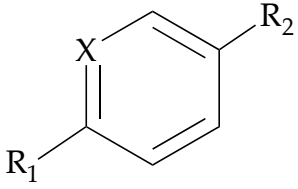
C_{R1}–C_{R2} = 2.72 Å

C_{R1}–C_{R2} = 2.79 Å

Other phenyl bioisosteres







C_{R1}–C_{R2} = 2.2 Å

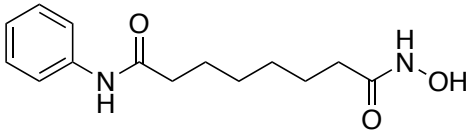
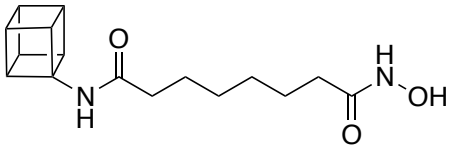
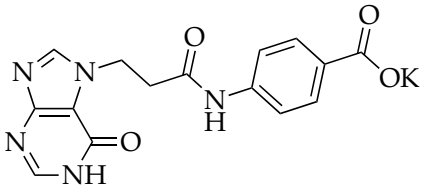
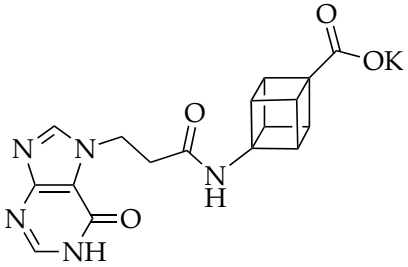
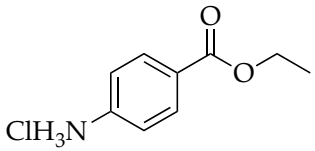
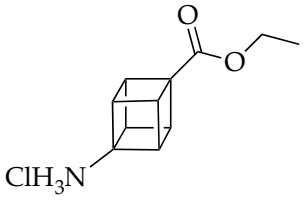
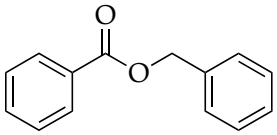
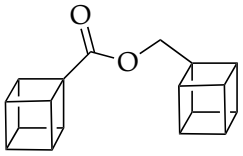
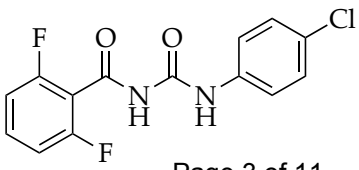
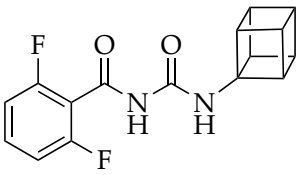
C_{R1}–C_{R2} = 1.7 Å

X=heteroatom substitution

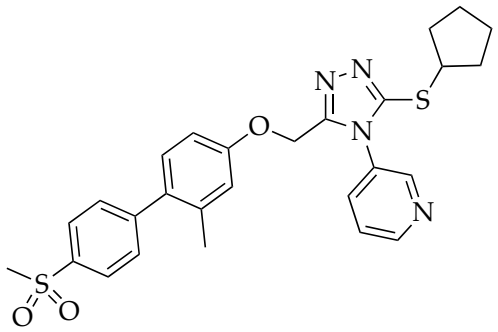
C_{R1}–C_{R2} = varies on heterocycle

1. Wager, T. T.;. *et el. J Med Chem* **2011,** *54* (21), 7602-20.
2. Stepan, A. F.; *et el. J Med Chem* **2012,** *55* (7), 3414-24.

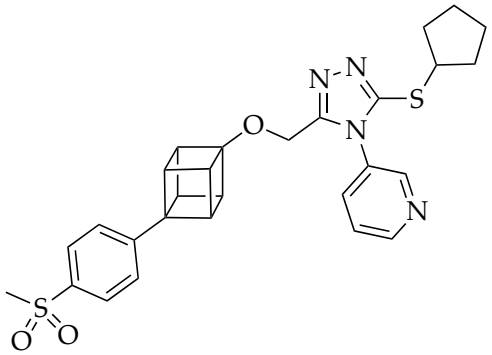
Highlight of Work Presented

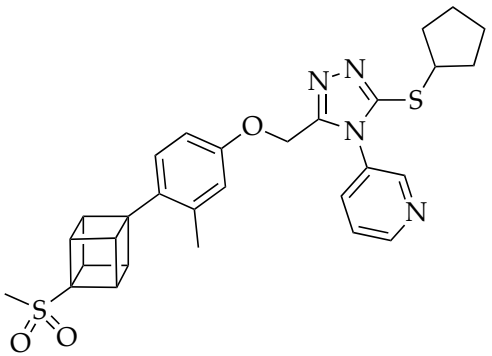
Activity		pharmaceutical or agrochemical compound	corresponding cubane derivative
Same	(IC_{50})	 suberanilohydroxamic acid (SAHA)	
Increase	(neuronal differentiation capacity)	 Leteprinim	
Same	(paw thermal threshold)	 Benzocaine	
Decrease	(efficacy)	 Benzyl benzoate	
Increase	(efficacy)	 Diflubenzuron	

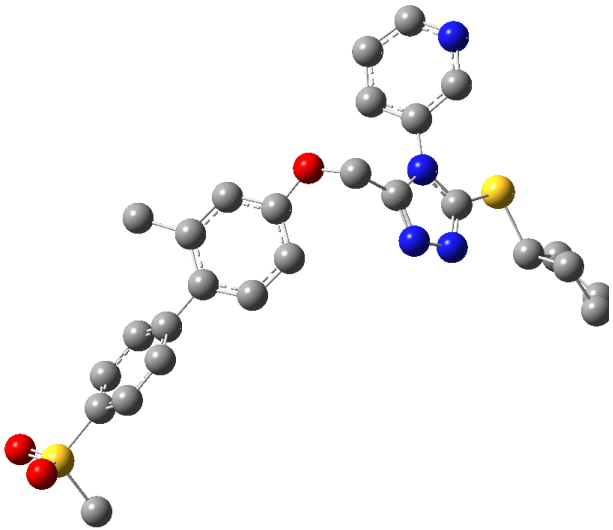
DFT Computations are Compelling

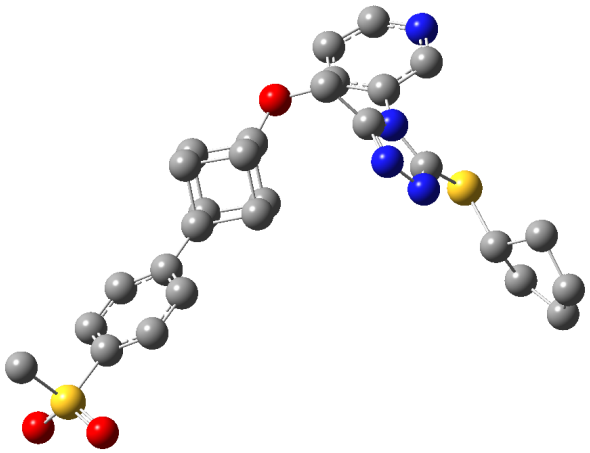


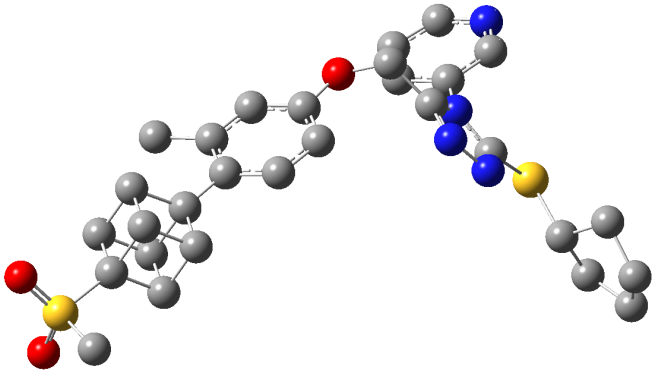
NMS-873



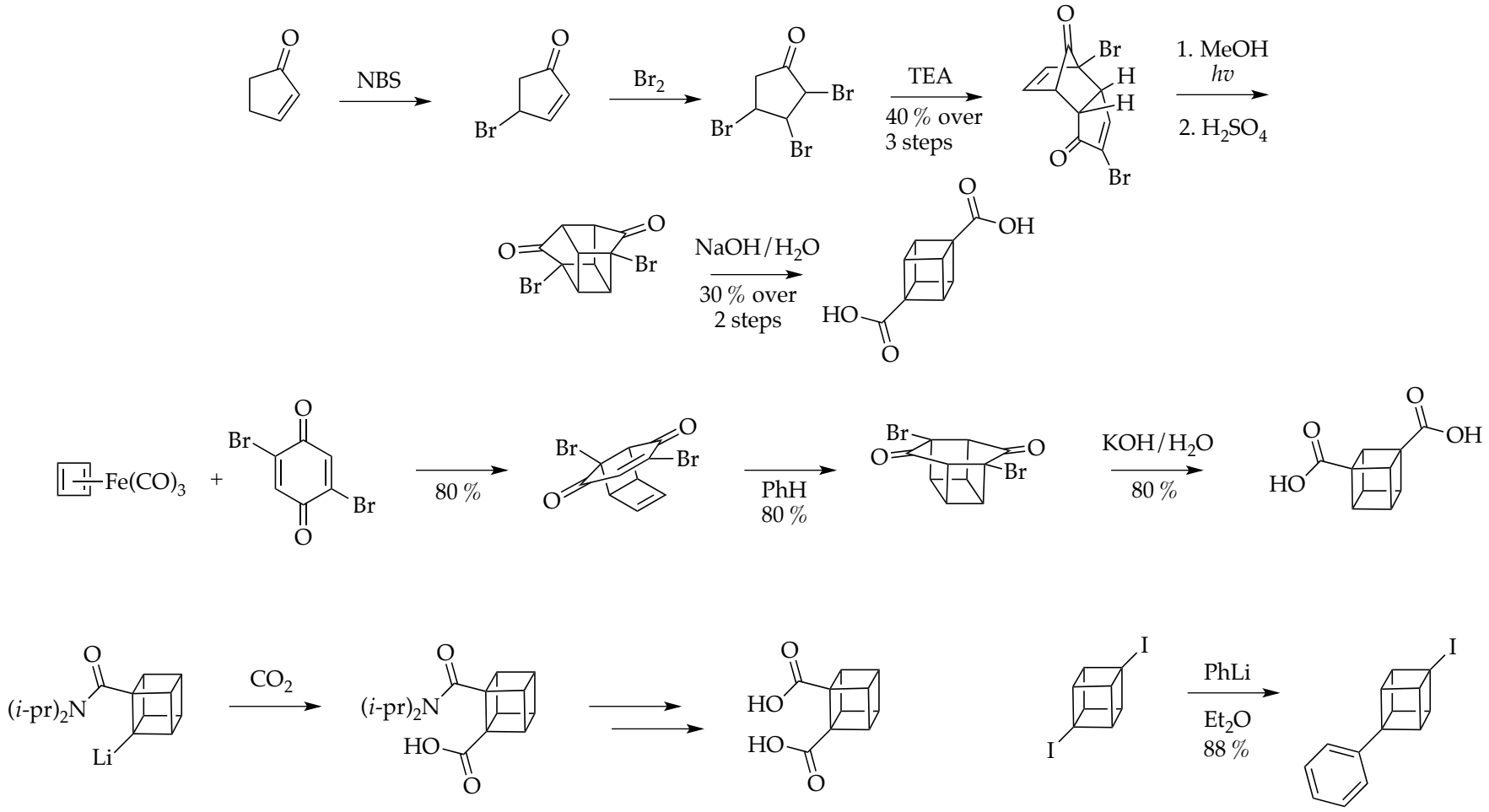






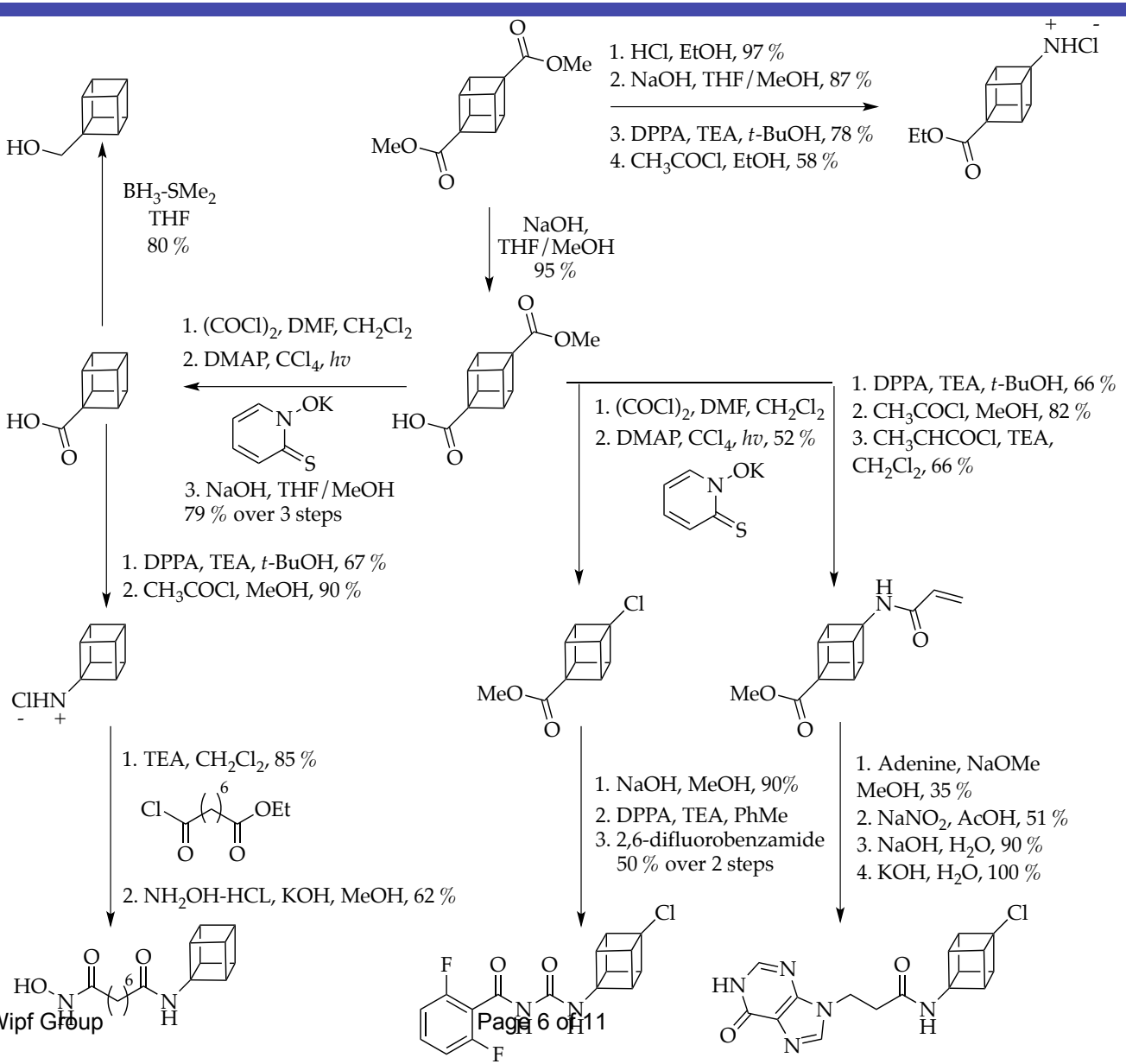


Cubane Synthesis

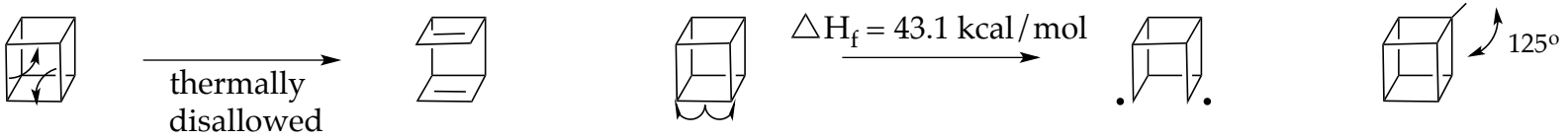


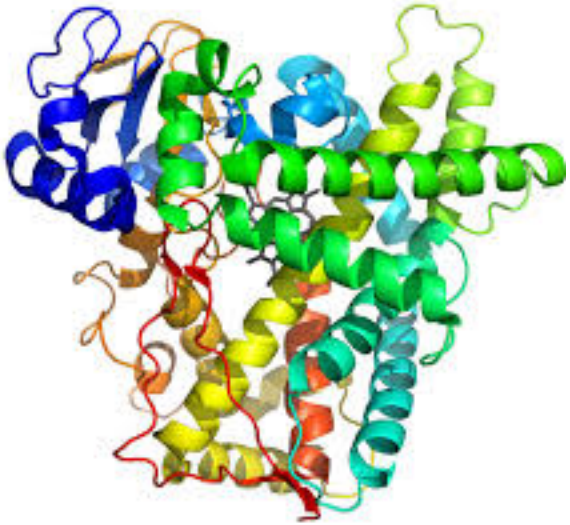
1. P. E. Eaton, T. W. Cole, Jr., *J. Am. Chem. Soc.* **1964**, *86*, 3157 – 3158.
2. P. E. Eaton, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1447–1462.
3. Statton, G. L.; Ramey, K. C. *J. Am. Chem. Soc.* **1966**, *86*, 1328 – 1329.
4. 4. Wlochal, J.; Davies, R. D.; Burton, J. *Org Lett.* **2014,** *16* (16), 4094-7.

Cubane Transformations in This Paper

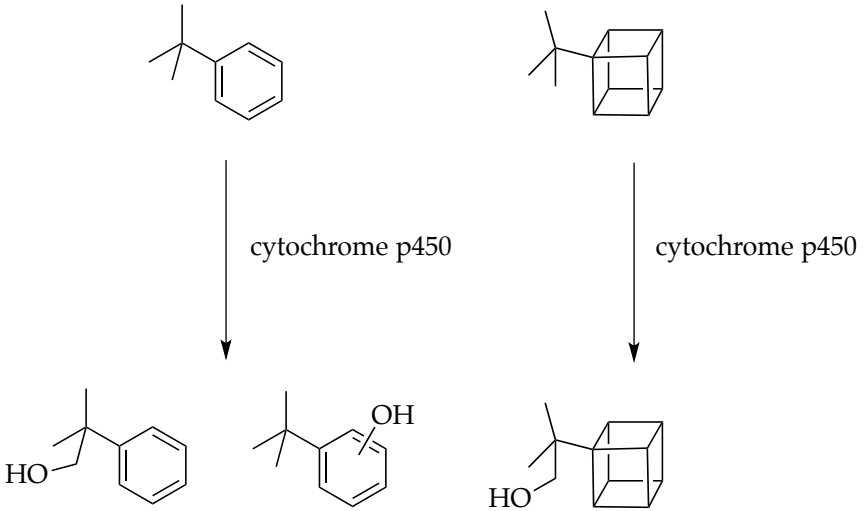


High Stability and Metabolic Stability of Cubane



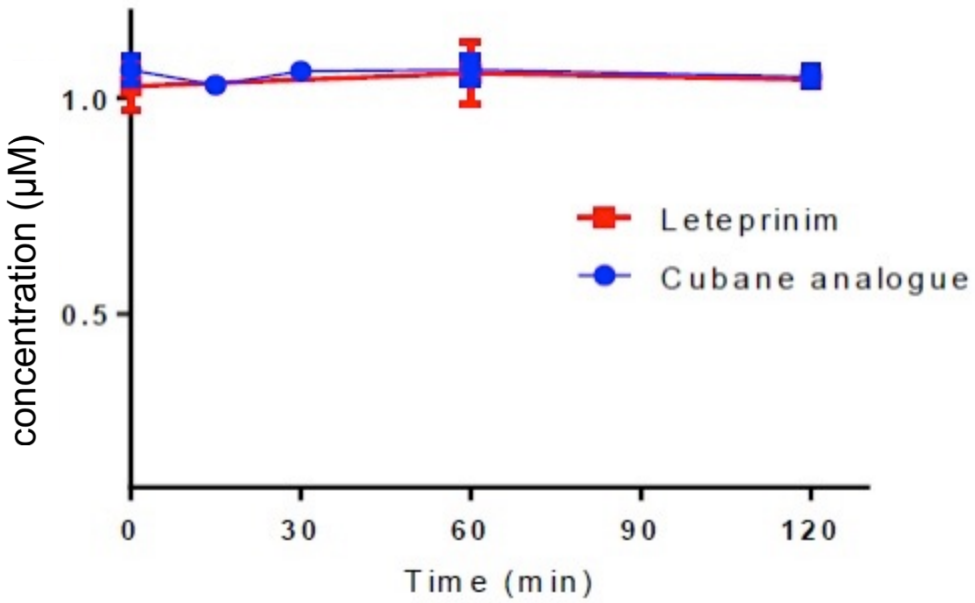


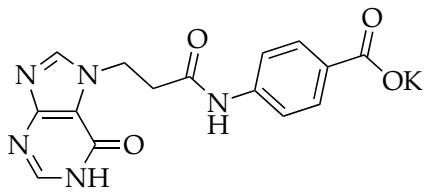
cytochrome p450



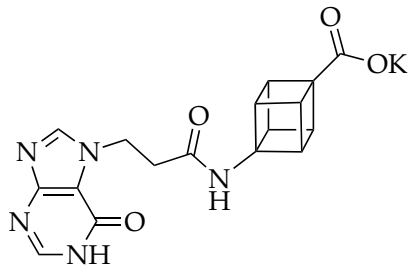
High Stability and Metabolic Stability of Cubane

In vitro human liver microsomes showed no metabolism of either the phenyl or cubane derivative



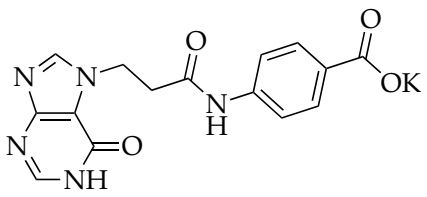


Leteprinim

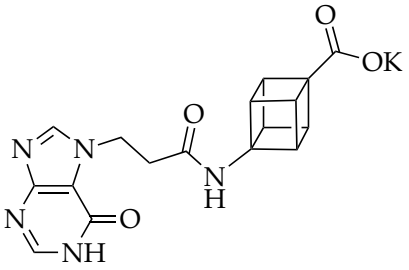


Letepricube

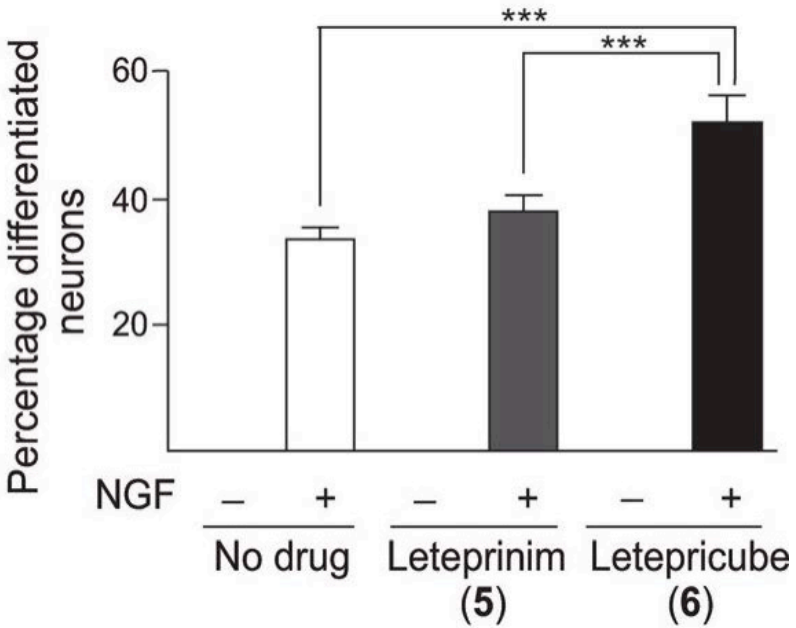
Advantages and Disadvantages of Cubane



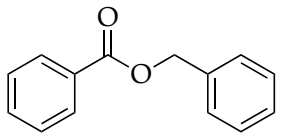
Leteprinim



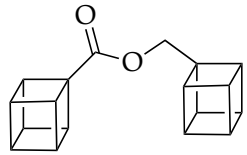
Letepricube



-The increased activity of Letepricube could be attributed to its increased lipophilicity complimenting the CNS target's hydrophobic environment.



Benzyl benzoate
Log*P* = 3.86



Cubyl cubates
Log*P* = 5.43

- The decrease in efficacy with the cubane derivative is traced to a lower solubility. This result suggests solubility matching must be taken into account.

Conclusions

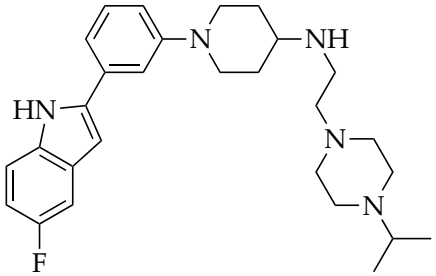
- Successfully showed cubane is a competent bioisostere for a phenyl group, thus validating Eaton's hypothesis

- Synthesized cubane derivatives of molecules with a wide range of applications

- Identified practical considerations when designing this isostere replacement

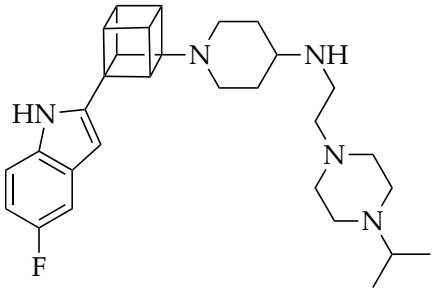
- Although convincing, the examples in the paper focused exclusively on *para* substituents

Possible Future Directions



UPCDC30245

C_{Ph1}–C_{Ph3} = 2.45 Å



C_{C1}–C_{C3} = 2.22Å