Validating Eaton’s Hypothesis: Cubane as a Benzene Bioisostere


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

$$C_{R1}-C_{R2} = 2.72 \text{ Å}$$  $$C_{R1}-C_{R2} = 2.79 \text{ Å}$$

Other phenyl bioisosteres

$$C_{R1}-C_{R2} = 2.2 \text{ Å}$$  $$C_{R1}-C_{R2} = 1.7 \text{ Å}$$  $$C_{R1}-C_{R2} = \text{varies on heterocycle}$$

### Highlight of Work Presented

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pharmaceutical or Agrochemical Compound</th>
<th>Corresponding Cubane Derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same (IC₅₀)</td>
<td>![suberanilohydroxamic acid (SAHA)]</td>
<td>![suberanilohydroxamic acid (SAHA)]</td>
</tr>
<tr>
<td>Increase (neuronal differentiation capacity)</td>
<td><img src="#" alt="Leteprinim" /></td>
<td><img src="#" alt="Leteprinim" /></td>
</tr>
<tr>
<td>Same (paw thermal threshold)</td>
<td><img src="#" alt="Benzocaine" /></td>
<td><img src="#" alt="Benzocaine" /></td>
</tr>
<tr>
<td>Decrease (efficacy)</td>
<td><img src="#" alt="Benzyl benzoate" /></td>
<td><img src="#" alt="Benzyl benzoate" /></td>
</tr>
<tr>
<td>Increase (efficacy)</td>
<td><img src="#" alt="Diflubenzuron" /></td>
<td><img src="#" alt="Diflubenzuron" /></td>
</tr>
</tbody>
</table>

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DFT Computations are Compelling
Cubane Synthesis

1. MeOH
2. H₂SO₄

Br₂

TEA

NaOH/H₂O

KOH/H₂O

PhH

(i-pr)₂N

CO₂

(i-pr)₂N

PhLi

Et₂O

Cubane Transformations in This Paper

1. HCl, EtOH, 97%
2. NaOH, THF/MeOH, 87%
3. DPPA, TEA, t-BuOH, 78%
4. CH₃COCl, EtOH, 58%

1. DPPA, TEA, t-BuOH, 66%
2. CH₃COCl, MeOH, 82%
3. CH₃CHCOCI, TEA, CH₂Cl₂, 66%
4. (COCl)₂, DMF, CH₂Cl₂
5. DMAP, CCl₄, hv, 52%
6. NaOH, THF/MeOH, 79% over 3 steps
7. DPPA, TEA, t-BuOH, 67%
8. CH₃COCl, MeOH, 90%
9. (COCl)₂, DMF, CH₂Cl₂
10. DMAP, CCl₄, hv, 52%

1. TEA, CH₂Cl₂, 85%
2. NH₂OH-HCl, KOH, MeOH, 62%

1. NaOH, MeOH, 90%
2. DPPA, TEA, PhMe
3. 2,6-difluorobenzamide
4. KOH, H₂O, 100%
5. Adenine, NaOMe
6. MeOH, 35%
7. NaNO₂, AcOH, 51%
8. NaOH, H₂O, 90%
9. KOH, H₂O, 100%

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High Stability and Metabolic Stability of Cubane

thermally disallowed

$\Delta H_f = 43.1$ kcal/mol

Hf 125°

cytochrome p450

High Stability and Metabolic Stability of Cubane

*In vitro* human liver microsomes showed no metabolism of either the phenyl or cubane derivative.
Advantages and Disadvantages of Cubane

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

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

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

$C_{\text{Ph}1} - C_{\text{Ph}3} = 2.45$ Å

$C_{\text{C}1} - C_{\text{C}3} = 2.22$ Å