

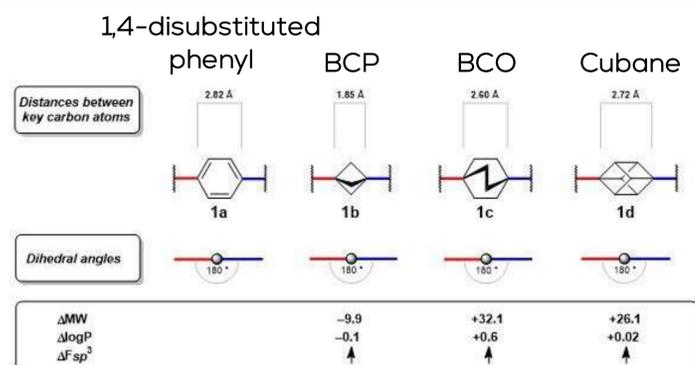
# Bioisosteres Replacement of 1,4-Disubstituted Phenyl Rings

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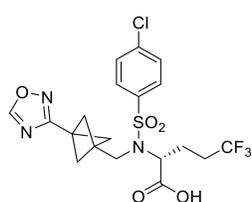
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## Overview

A 2017 paper by Auberson and co-workers reported a comprehensive comparison of the effects of replacing a *para*-substituted benzene with a bicyclo[1.1.1]pentane (BCP), a bicyclo[2.2.2]octane (BCO) and a cubane.<sup>[1]</sup> All three of these groups share similar spatial features to a 1,4-disubstituted phenyl ring, with identical dihedral angles making them interesting bioisosteres. The effects of these groups on the solubility and non-specific binding characteristics of the compounds into which they were incorporated as replacements for a phenyl ring were evaluated and compared. An improvement in both parameters was observed for BCP and cubane but not for the BCO-containing derivative. Incorporation of these moieties can provide potential benefits in drug discovery programs and form part of the toolbox for medicinal chemists.

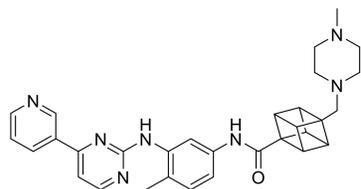


## Examples



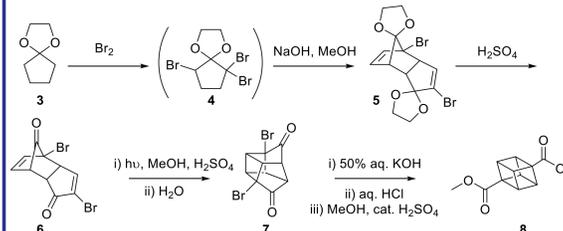
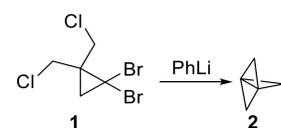
Stepan and co-workers showed that replacement of the central *para*-substituted fluorophenyl ring in a  $\gamma$ -secretase inhibitor with the BCP moiety resulted in significant improvements in aqueous solubility and passive permeability, with little change in the potency.<sup>[2]</sup>

Nicolaou and co-workers synthesized a range of structural analogues of Imatinib, in which the *para*-substituted phenyl group was replaced with various non-aromatic structural motifs.<sup>[3]</sup> It was found that the cubane-containing derivative possessed the joint highest thermodynamic solubility as well as the highest potency against both cancer cell lines tested.



## Synthesis

The most commonly used intermediate in the synthesis of BCP derivatives is [1.1.1]propellane **2**.<sup>[4]</sup> The current, optimized method involves the treatment of compound **1** with two equivalents of phenyl lithium. This is then followed by co-distillation of **2** with diethyl ether.<sup>[5]</sup>

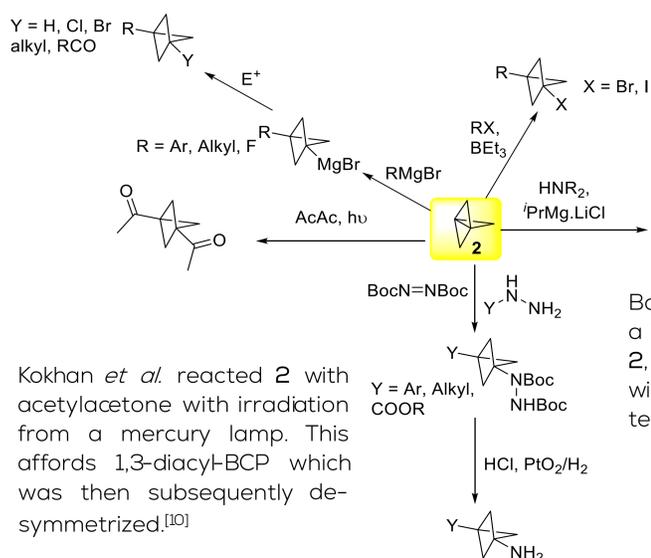


The majority of cubane-containing compounds are derived from compound **3**.<sup>[6]</sup> Falkiner and co-workers published a pilot-scale synthesis (560 g) of building block **8** in 2003.<sup>[7]</sup> Affording an approximate yield of 22% over 8 process steps.

## Functionalization of BCP

Published by Messner *et al.* in 2000 – **2** can be reacted with a variety of Grignard's followed by subsequent quenching with an electrophile to give 1,3-unsymmetrically substituted BCP derivatives.<sup>[8]</sup>

Caputo *et al.*<sup>8</sup> used a 'triethylborane initiated atom transfer radical addition ring opening reaction' of **2**. The resultant iodo-BCP compounds were then further functionalized.<sup>[9]</sup>



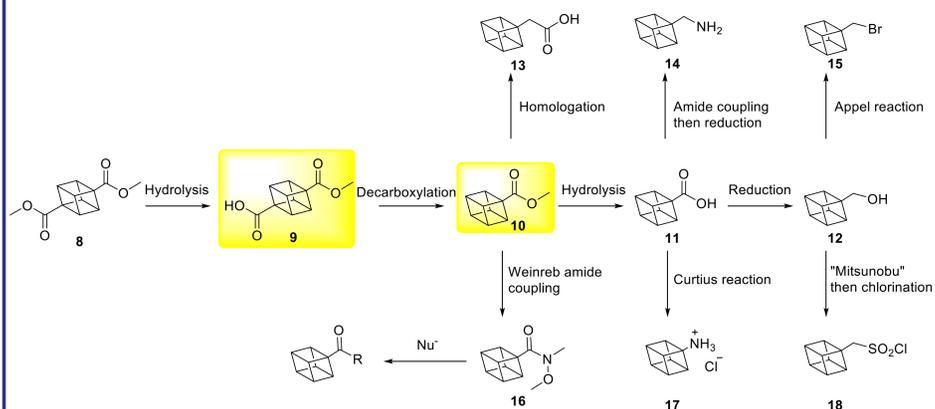
Kokhan *et al.* reacted **2** with acetylacetone with irradiation from a mercury lamp. This affords 1,3-diacetyl-BCP which was then subsequently de-symmetrized.<sup>[10]</sup>

Kanazawa *et al.* demonstrated that the multi-component reaction between **2**, di-*tert*-butyl-diazodicarboxylate and a variety of acyl-hydrazide derivatives affording BCP-hydrazides which could be converted to amino-BCP via deprotection and hydrogenation.<sup>[12]</sup>

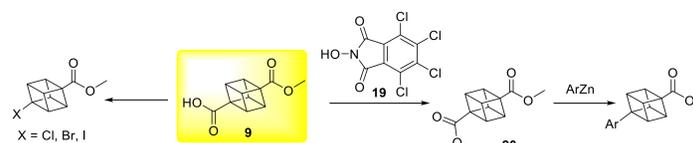
Baran *et al.* reacted a 'turbo-amide' with **2**, to generate a wide range of tertiary amines.<sup>[11]</sup>

## Functionalization of Cubane

Compound **8** can be mono-functionalized by selective hydrolysis to give **9** followed by decarboxylation to **10**. The remaining ester can be further functionalized as summarised below.<sup>[13]</sup>



Compound **9** can also be used to synthesis a range of 1,4-disubstituted cubanes exploiting chemistry analogous to that shown above. Coupling between **9** and **19** followed by reaction with aryl zinc reagents in the presence of a nickel catalyst gave aryl substituted cubanes. The acid of compound **9** can also be converted to Cl, Br or I through radical chemistry, providing another useful handle for further functionalization



## Summary

BCP and cubane can be used as replacements for 1,4-disubstituted phenyl rings. These structures offer improvements in properties such as enhancements in solubility, permeability and stability. Multiple reaction have been investigated to derivatize BCP and cubane cores to provide a set of building blocks to allow these moieties to be incorporated into molecules.

References: [1] - *ChemMedChem* 2017, 12, 590-598, [2] - *J. Med. Chem.* 2012, 55, 3414-3424, [3] - *ChemMedChem* 2016, 11, 31-37, [4] - *SynLett* 2018, 29, A-K, [5] *Chem. Sci.* 2018, 9, 5295-5300, [6] - *J. Med. Chem.* 2019, 62, 1078-1095, [7] - *Org. Process Res. Dev.* 2013, 17, 1503-1509, [8] - *Eur. J. Org. Chem.* 2000, 1137-1155, [9] - *Chem. Sci.* 2018, 9, 5295-5300, [10] - *Eur. J. Org. Chem.* 2017, 6450-6456, [11] - *Science*, 2016, 351, 241-246, [12] - *J. Am. Chem. Soc.* 2017, 139, 17791-17794, [13] - *J. Med. Chem.* 2019, 62, 1078-1095.

