Bicyclo[2.2.2]octane as A 3-D-rich Bioisostere for A Phenyl Ring

Key Points

- One of the three prominent 3-D isosteres for the 2-D phenyl ring
- Maintain pharmacological efficacy
- Improve solubility and oral bioavailability

Merits of sp^3-rich Carbon Bioisosteres—Escape from Flatland

The perils of high aromatic ring count are well known with regard to aqueous solubility, lipophilicity, serum albumin binding, CYP450 inhibition, and hERG inhibition.[1] Fully aliphatic bicyclo[2.2.2]octane-1,4-diyl (BCO) is a 3-dimensional bioisostere for the 2-dimensional *para*-phenyl group (*p*-Ph). The fraction of saturated carbon (Fsp^3, defined as equation 1)[2a] for BCO is 1.0 at one extreme of the spectrum, but it is 0 for the aromatic *p*-phenyl ring, at another extreme. From a geometrical point of view, the distance between connecting atoms in the BCO scaffold (2.60 Å) is very similar to the *p*-Ph group (2.82 Å).

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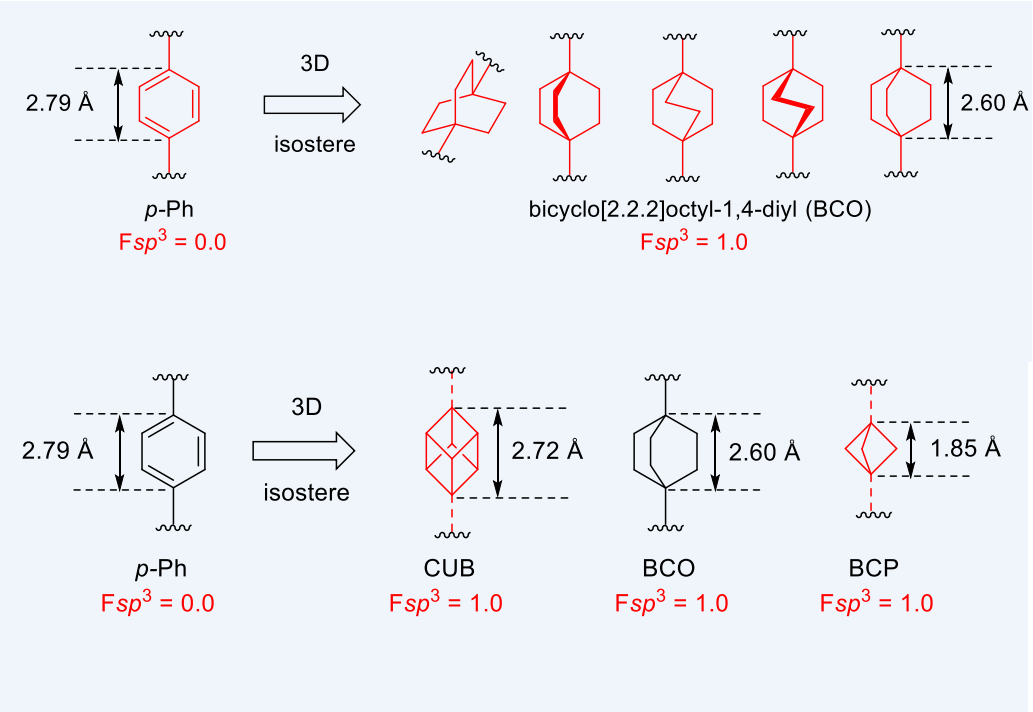
PharmaBlock designs and synthesizes over 193 Bicyclo[2.2.2]octane, and 32 Bicyclo[2.2.2]octane products are in stock. A list of featured Bicyclo[2.2.2]octane derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

Fsp^3 = (number of sp^3-hybridized carbon)/(total carbon count) (1)



In addition to BCO, there are two closely related non-classical *p*-phenyl isosteres: bicyclo[1.1.1]pentane-1,4-diyl (BCP) and cubane-1,4-diyl (CUB). The distances between their bridgeheads are 2.72 Å and 1.85 Å, respectively. The bridgehead lengths decrease in the following order:

p-Ph (2.79 Å, 100%) > CUB (2.72 Å, 96%) > BCO (2.60 Å, 94%) > BCP (1.85 Å, 65%).

This information is useful in deciding which particular 3-D isostere to use to replace the 2-D *p*-phenyl moiety for structure-based drug design (SBDD).

There is a myriad of advantages for a drug with a higher Fsp^3 value to escape from flatland.

a A higher degree of saturation for a molecule provides increased opportunity to design in out-of-plane substituents and to adjust molecular shape that could increase receptor–ligand complementarity. The molecular complexity might allow the engineering

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of additional protein–ligand interactions not accessible to a flat aromatic ring, and thus improve potency and selectivity to a given target, which should mitigate off-target effects.[1] Compounds with greater specificity and selectivity are expected to show less toxicity due to off-target effects.[2b]

b. Compounds containing ionizable amines are more promiscuous than neutral ones. But both amine-containing drugs and neutral drugs tend to have higher promiscuity against drug targets when they have lower Fsp^3 values. In other words, saturation mitigates a drug's promiscuity.[2b]

c. Compounds with higher Fsp^3 values tend to have lower cytochrome P450 (CYP450) inhibitions. Therefore, saturation reduces a drug's tendency to have drug–drug interactions (DDIs).[2b]

d. Disruption of aromaticity reduces the ease with which to form crystalline lattices. Empirically, π stacking enhances crystallinity of compounds containing aromatic rings. Therefore, disruption of planarity hence aromaticity results in improvement of melting point and solubility.

The last few decades have seen clog*P* getting higher and Fsp^3 lower when proper attention was not paid to a drug's physiochemical properties. In order to increase our success rate in drug discovery, it is essential that we get clog*P* down and Fsp^3 up. Employing BCO to replace *para*-phenyl fragment is one-step closer to the right direction.[3] Overall, complexity, as measured by both Fsp^3 and the presence of chiral centers, impacts the probability of success in the clinic.

Bicyclo[2.2.2]octanes in Drug Discovery

It has been shown that for some drug candidates, replacing a phenyl group with BCO could maintain pharmacological efficacy while improving solubility and oral bioavailability.

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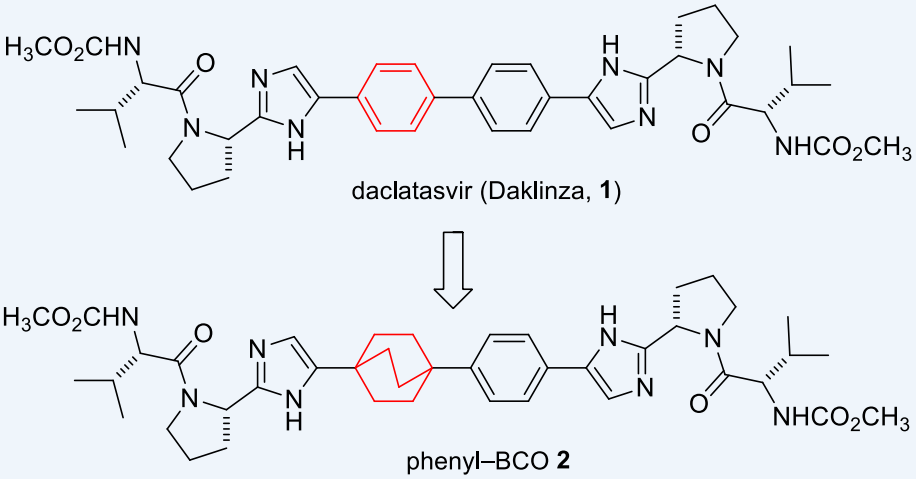

	HCV gt-1a EC_{50} (nM)	HCV gt-1a EC_{50} (nM)	Solubility at pH7.4 (μg/mL)
daclatasvir (Daklinza, **1**)	0.14	0.023	6.8
phenyl–BCO **2**	1.4	0.060	45.0

BMS's daclatasvir (Daklinza, **1**) is the first-in-class hepatitis C virus non-structural protein 5A (HCV NS5A) inhibitor approved by the FDA in 2014 for the treatment of hepatitis C. In an effort to improve its physiochemical properties, constraint cycloalkane–phenyl motifs were employed to replace the flat biphenyl core structure.[4] One of the analogues was phenyl–BCO **2**, which is 10-fold less potent than daclatasvir (**1**) in genotype-1a (gt-1a) replicon, indicating that the biphenyl residue not only serves as a conformationally restrained spacer, but also contributes to certain interaction with the NS5A protein. As expected, phenyl–BCO **2** is 6-fold more soluble than daclatasvir (**1**) in aqueous solution at pH7.4, the physiological acidity.[4]

Pyrimidinooxazinyl *trans*-cyclohexane-acetic acid **3** is a potent, selective, and orally efficacious diacylglycerol acyltransferase-1 (DAT-1) Inhibitor. But it undergoes phase II metabolism via conjugation of acid group to from the acyl glucuronide, Since the reactivity of such metabolites can lead to covalent protein adducts, which may give rise to idiosyncratic toxicity, it is logical to introduce greater degree of steric crowding around the acid group by replacing the cyclohexane ring with various bi- and tri-cyclic systems.

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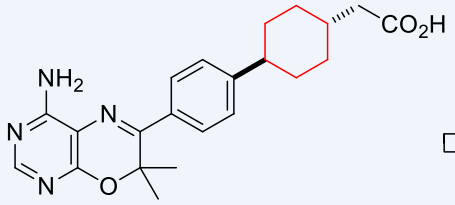
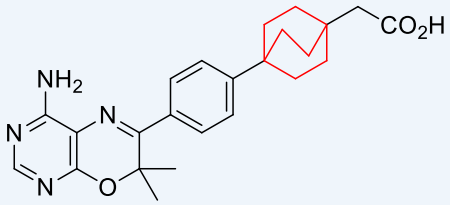
Certain sterically hindered carboxylic acid acyl glucuronide have been shown to be inherently more stable both to hydrolysis and to rearrangement to more reactive isomers, making them less likely to react with proteins *in vivo*. One of the bicyclic derivatives, BCO-acetic acid **4** was tested as potent as the prototype **3**, yet had superior pharmacokinetic (PK) properties with smaller clearance (Cl_p) and volume of distribution (V_{dss}), as well as a longer half-life.[5] One added advantage of using BCO to replace the *trans*-cyclohexane is that there is no *cis/trans*-stereochemistry to be of concern.



cyclohexane-acetic acid **3**
human DGAT-1 IC_{50} (μM), 0.015
PK parameters in dogs:
Cl_p (mL/min/kg), 12
V_{dss} (L/kg), 2.0
iv half-life (h), 3.9
oral half-life (h), 2.8
bioavailability (%), > 100



BCO-acetic acid **4**
human DGAT-1 IC_{50} (μM), 0.015
PK parameters in dogs:
Cl_p (mL/min/kg), 3.3
V_{dss} (L/kg), 1.0
iv half-life (h), 8.6
oral half-life (h), 9.9
bioavailability (%), > 100

Adenosine is the A on ATP, *a*denosine *tri*phosphate. As a metabolite of ATP, adenosine exerts a plethora of pharmacologic effects via four G-protein-coupled receptors (GPCRs): A_1, A_{2A}, A_{2B}, and A_3. One of the early adenosine A_1 receptor antagonists was 8-aryl-substituted xanthine amine congener (XAC, **5**). While potent, XAC (**5**) has only a moderate aqueous solubility: 90 μM in 0.1 M sodium phosphate at pH7.2. In an effort to improve its solubility by disrupting aromaticity, hence crystalline lattices, Biogen–Idec employed BCO to replace the phenyl ring on XAC (**5**). One of the BCO analogues, BG9928 (**6**), was tested to be highly potent against human adenosine A_1 receptor, and selective: 915-fold vs. hA_{2A} receptor and 90-fold vs. hA_{2B} receptor. With a solubility of 25.4 mg/mL, BG9928 (**6**) showed excellent bioavailability and was tested orally efficacious with an ED_{50} of 0.01 mg/mg in animal diuresis models. BG9928 (**6**) was moved to clinical trials in 2006.[6]

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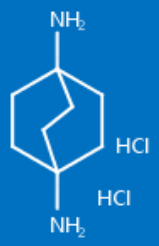

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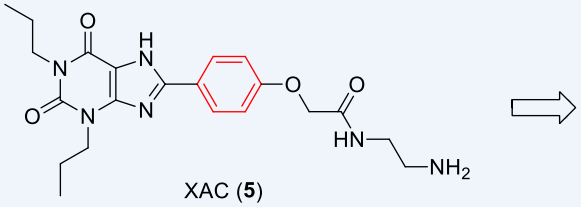
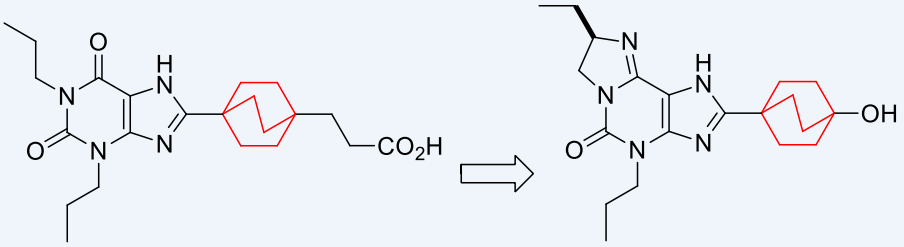
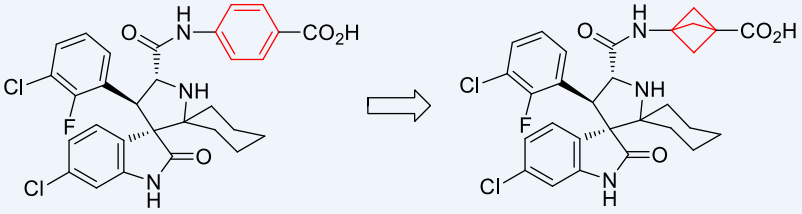




Inspired by Fujisawa's FK838, a pyrazolopyridine, Biogen–Idec came up with their backup candidate tricyclic imidazoline **7**, which has a similar biological profile as to the prototype BG9928 (**6**). Different from compounds **1**–**6**, compound **7**'s BCO fragment is sandwiched by a carbon and an oxygen atom, whereas **1**–**6**'s BCOs are all sandwiched by two carbon atoms.

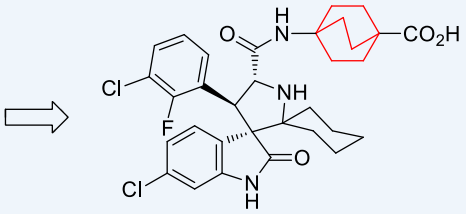
One recent drug candidates in clinical trials is AA-115/APG-115 (**10**), which is a potent, selective, non-peptide-2 (MDM-2) inhibitor containing a BCO moiety.[2] MDM2 inhibitors blocking the MDM2–p53 interaction [a protein–protein interaction (PPI)] can liberate the tumor suppressor function of p53 and may have potentials as cancer therapies. In the process of improving chemical stability of a previous clinical development MDM2 inhibitor, Wang's group prepared spirooxindole–phenyl analogue **8**. Compound **8** was stable, potent in both enzymatic and cellular (in the SJSA-1 cell line) assays, and capable of achieving partial tumor regression in the SJSA-1 xenograft model. But it had lower C_{max} and AUC than the original MDM2 inhibitor in clinics. In order to improve **8**'s PK properties while retaining its high binding affinity to MDM2 and cellular potency, replacements of the benzoic acid with

non-classical benzoic acid mimetics bicycle[1.1.1]pentyl (BCP) analogue **9** and BCO analogue **10** were carried out. The BCO analogue **10** proved to have high affinity to MDM and is as potent as **8** in inhibiting cell growth in the SJSA-1 cell line. With an excellent oral pharmacokinetic profile, BCO analogue **10** is capable of achieving complete and long-lasting tumor regression *in vivo* and is currently in phase I clinical trials for cancer treatment.[8]



phenyl analogue **8**
MDM2 IC_{50} = 4.4 nM
MDM2 K_i < 1 nM
SJSA-1 IC_{50} = 100 nM

BCP analogue **9**
MDM2 IC_{50} = 6.4 nM
MDM2 K_i < 1 nM
SJSA-1 IC_{50} = 542 nM



BCO analogue **10**
MDM2 IC_{50} = 3.7 nM
MDM2 K_i < 1 nM
SJSA-1 IC_{50} = 89 nM

Synthesis of Some Bicyclo[2.2.2]octane-containing Drugs

The synthesis of HCV HS5A inhibitor phenyl–BCO **2** began with dimethyl cyclohexane-1,4-dicarboxylate (**11**) to prepare bromide **12** in four steps, 47% overall yield. The bromide **12** is now commercially available. An $AlCl_3$-catalyzed Friedel–Crafts alkylation of bromide **12** with benzene prepared phenyl **13**, which underwent an $AlCl_3$-catalyzed Friedel–Crafts acylation with AcCl to produce ketone **14**. Six additional steps converted ketone **14** to keto-ester **15**. After transforming keto ester **15** to bis-imidazole **16**, an additional four steps delivered phenyl–BCO **2**.[4]

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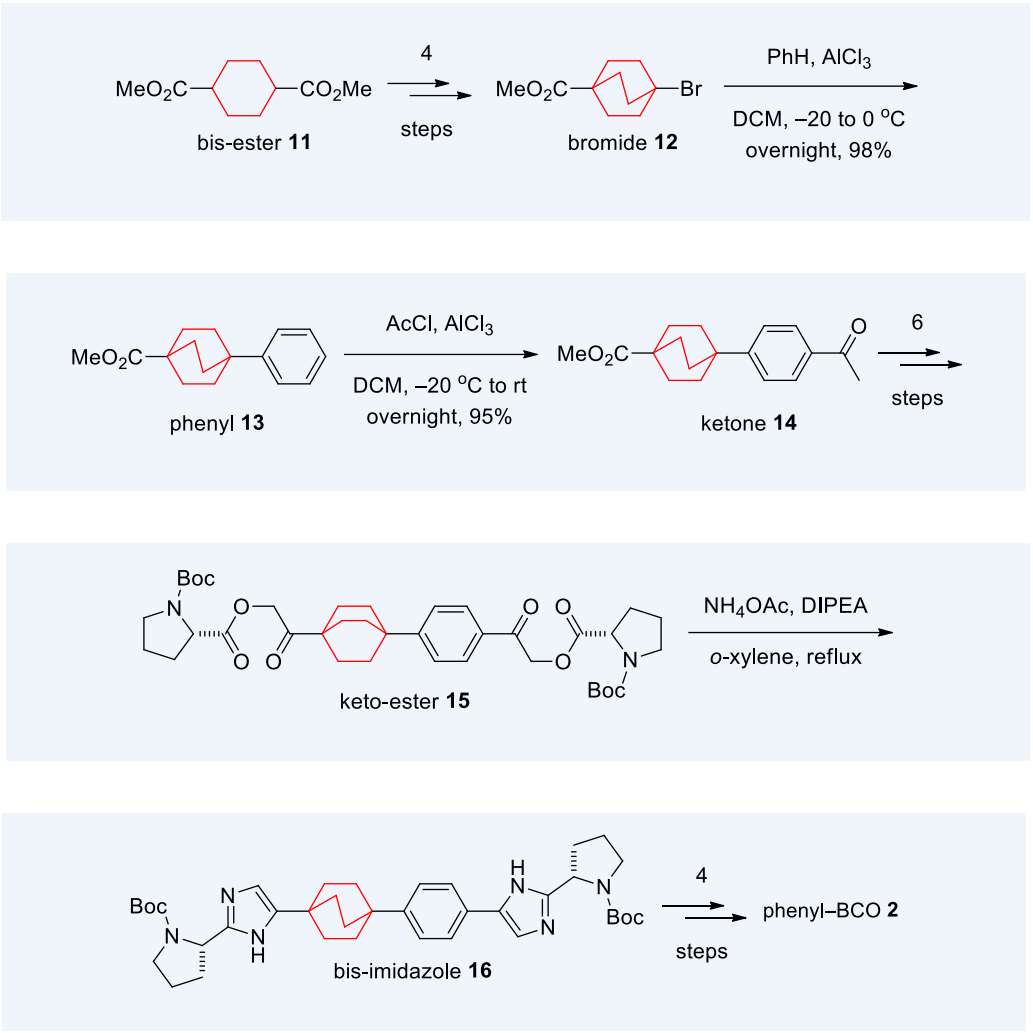
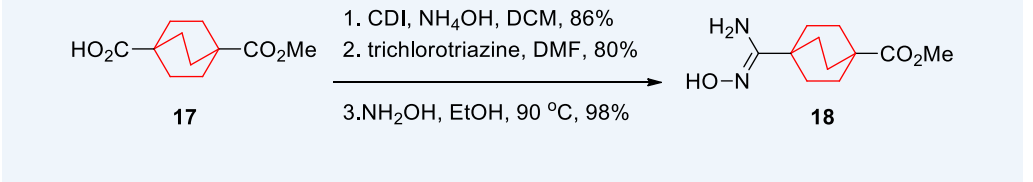


Preparation of Merck's 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor BCO–triazole **20** commenced with BCO–ester–acid **17**. Intermediate amide-oxime **18** was produced in three steps from the starting material **17**. Additional three steps transformed **18** to oxadiazole **19** with its ester converted to amide. Conversion of **19** to BCO–triazole **20** was accomplished in two additional steps.[9]



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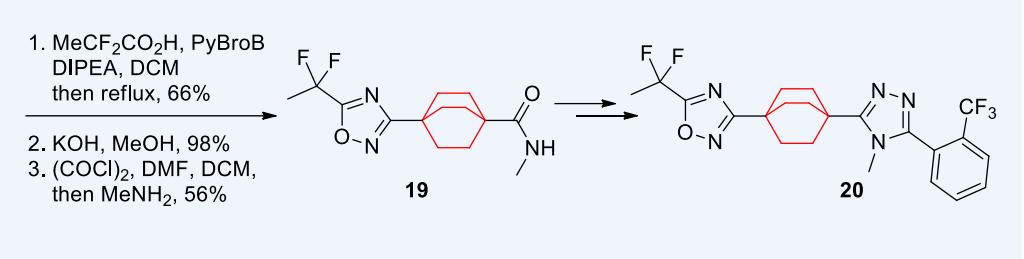
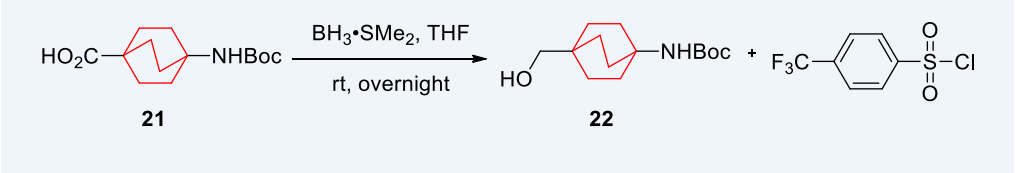
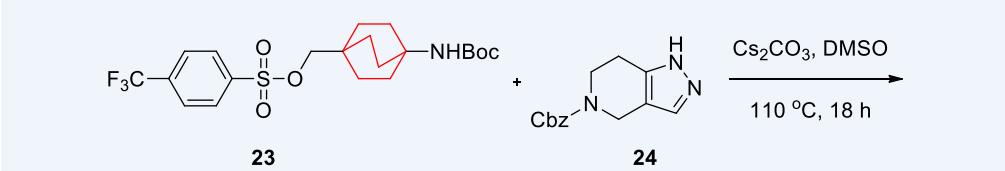
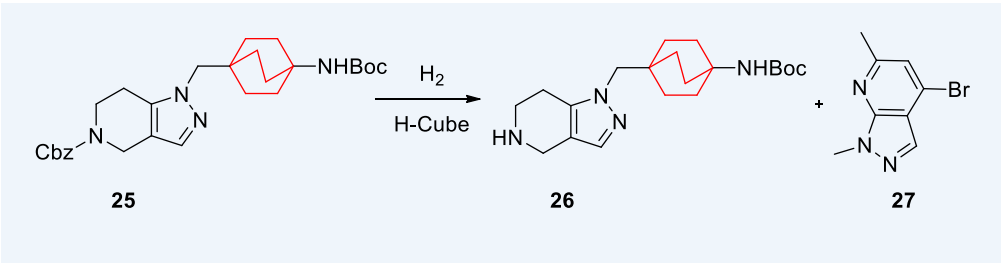


Novartis' synthesis of pyrazolopyridine **27** as an inhibitor of endosomal toll-like receptors (TLRs) for the treatment of autoimmune diseases began with commercially available BCO derivative **21**. After reducing the acid on **21** to the corresponding alcohol **22**, subsequent sulfonylation with 4-(trifluoromethyl)benzene-1-sulfonyl chloride then afforded tosylate **23**. An S_N2 displacement of tosylate **23** with bicyclic **24** gave rise to adduct **25**. Palladium-catalyzed hydrogenation of **25** removed its Cbz protection to provide secondary amine **26**. A Buchwald–Hartwig coupling between **26** and bromide **27** assembled the core structure, which was readily converted to pyrazolopyridine **27** after acidic removal of the Boc protection.[10]







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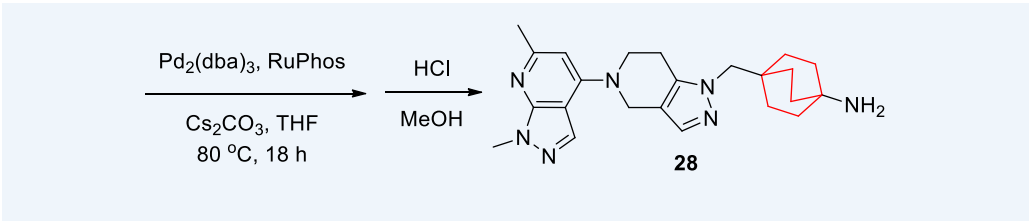

Summary

To conclude, along with bicyclo[2.2.2]pentane (BCP) and cubane (CUB), bicyclo[2.2.2]octane (BCO) is one of the three prominent 3-D isosteres for the 2-D phenyl ring. Since BCO has all sp^3 carbons, it could potentially offer several advantages over the flat phenyl group, including possible better binding with the targets thus higher potency, better selectivity thus lower promiscuity and lower toxicity, and potentially improved solubility as a consequence of disrupting aromaticity. However, BCO is 3-carbon larger and more lipophilic than the bicyclo[2.2.2]pentyl group (BCP). It is sometimes beneficial to consider using BCP in place of BCO as the bioisostere of a phenyl group.

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