Bicyclo[1.1.1]pentane (BCP) as an sp^3 Carbon-rich Bioisostere for *para*-Phenyl and *tert*-Butyl Groups

Key Points

- A non-classical *p*-phenyl isostere as well as a *t*-butyl isostere
- An especially useful isostere providing superior biopharmaceutical properties such as solubility, permeability, and *in vitro* stability.

Overview

Bicyclo[1.1.1]pentane (BCP) is unique as a non-classical *p*-phenyl isostere as well as a *t*-butyl isostere. In comparison to CUB and BCO, it is the shortest in terms of diagonal distance and the smallest in size. Since it has the least number of carbons vs. BCO and CUB, BCP is the least lipophilic. BCP is an especially useful isostere for phenyl fragment when it serves largely as a spacer rather than engaging π-stacking interactions with the target protein. While maintaining the biological activities as the *p*-phenyl analogue, BCP isosteres provide superior biopharmaceutical properties such as solubility, permeability, and *in vitro* stability. BCP's utility in medicinal chemistry is expected to grow in the future.

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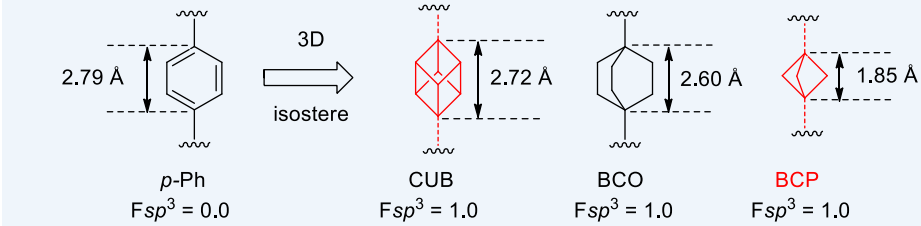
There Is Something about BCP

Bicyclo[1.1.1]pentyl (BCP) may serve as an sp^3 carbon-rich bioisostere for both *para*-phenyl[1] and *tert*-butyl[2] groups in the form of either bicyclo[1.1.1]-pentane-1,4-diyl or bicyclo[1.1.1]pentane-1-yl.

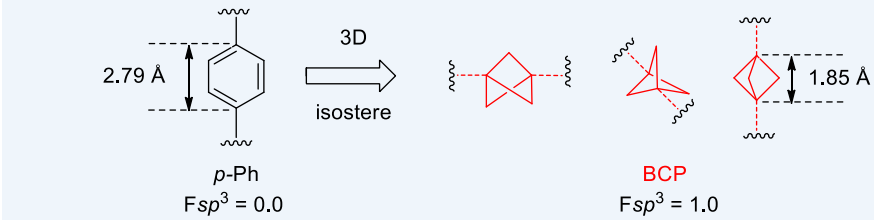
Bicyclo[1.1.1]pentane-1,4-diyl (BCP) is one of the three common non-classical *para*-phenyl (*p*-Ph) isosteres. The other two are cubane-1,4-diyl (CUB), and bicyclo[2.2.2]octane-1,4-diyl (BCO). The bridgehead lengths decrease in the following order:[1]

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

Bicyclo[1.1.1]pentane-1,4-diyl (BCP) stands out in comparison to CUB and BCO. It is the shortest in terms of diagonal distances and the smallest in size, in fact, 35% smaller than *p*-Ph. Since it has the least number of carbons (5) compared to those of BCO (6) and CUB (8), BCP is the least lipophilic. This information is helpful in deciding which particular 3-D isostere to use to replace the 2-D *p*-phenyl moiety for structure-based drug design (SBDD).



Fsp^3 = (number of sp^3-hybridized carbon)/(total carbon count) (1)[2]



Due to *t*-butyl substituent's lipophilicity thus metabolic instability, many *t*-butyl bioisosteres have been explored to mitigate its liabilities. They include pentafluorosulfanyl (SF_5), bicyclo[1.1.1]pentane-1-yl (BCP), and cyclopropyltrifluoromethyl (cyclopropyl–CF_3).[3] As early as in 1993,

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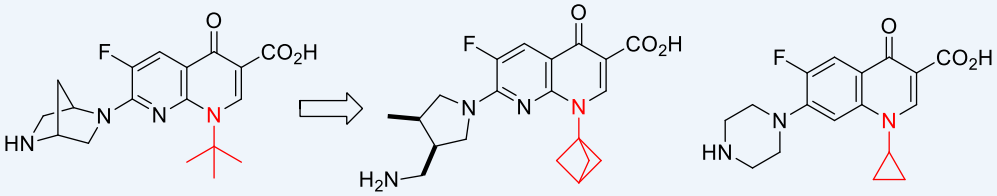
Barbachyn et al. employed BCP as a *t*-butyl bioisostere.[4] By installing a BCP group at the *N*-1 position of fluoroquinolone antibacterial agents, they arrived at U-87947E (**2**) in an effort to improve upon BMY-40062 (**1**). The BCP group was expected to exert a unique electronic effect in light of the increased electronegativity of its bridged carbon atom. U-87947E (**2**) exhibited enhanced activity relative to that of ciprofloxacin (Cipro, **3**, the gold standard for the second generation fluoroquinolones) against both gram-positive aerobic bacteria and anaerobic organisms. Time-kill kinetic studies revealed that U-87947E (**2**) was exquisitely bactericidal against (greater than 32-fold more active) ciprofloxacin (**3**)-resistant *Staphylococcus aureus*.[4]



BMY-40062 (**1**) U-87947E (**2**) ciprofloxacin (Cipro, **3**)

Metabotropic glutamate receptors (mGluRs) have been known for over thirty years. mGluR modulators, both agonists and antagonists hold great promise in treating central nervous system (CNS) disorders such as psychosis and Parkinson's disease. After decades of intense research, regrettably, no drug targeting an mGluR has yet received marketing approval. An mGluR antagonist, (*S*)-(4-carboxyphenyl)glycine (**4**), may be considered as an isostere of L-glutamate. Pellicciari and colleagues sought to replace the 2-D *p*-phenyl ring on **4** with its 3-D brethren as isosteres. Three (*S*)-BCP-glycine **5** were prepared.[5] When R = CO_2H, the BCP–glutamate **5a** was tested as a selective mGluR1a antagonist.[5a] Once the carboxylic acid was replaced with a tetrazole, a known carboxylic acid isostere, the resulting BCP–glutamate **5b** was a weaker mGluR1a antagonist than **5a**.[5b] If the carboxylic acid was replaced by a phosphate, the BCP-glutamate **5c** became an mGluR4 and mGluR8 selective ligand.[5c] Interestingly, one-carbon homologation of **5a** gave rise to (*S*)-ω-acidic-BCP-glycine **6** and (*R*)-ω-acidic-BCP-glycine **6′**, respectively. Although both of them were tested inactive for mGluRs, they were found to be *N*-methyl-D-aspartic acid (NMDA) receptor ligands.[5d]

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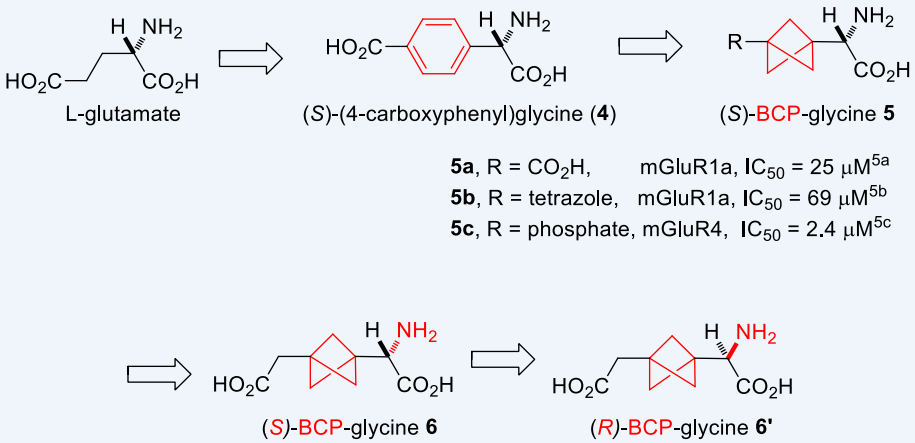
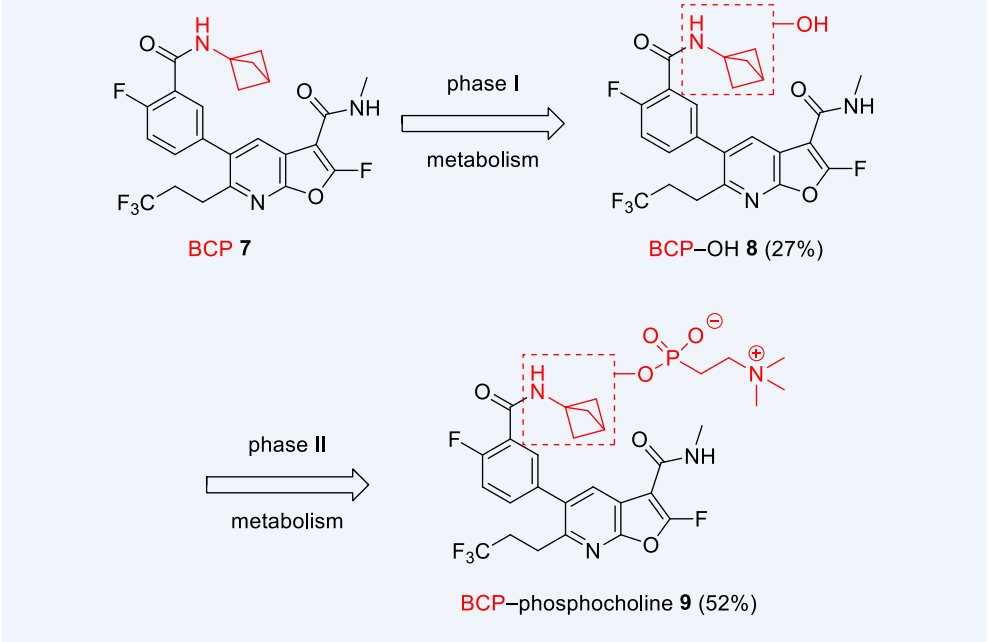


Hepatitis C virus non-structural protein 5B (HCV NS5B, a RNA-dependent RNA polymerase) inhibitors are successful treatments for HCV infection. In an effort to improve the *t*-butyl group's metabolic stability, a bicyclo[1.1.1]-pentane-1-yl (BCP) was introduced into the molecular scaffold as an isostere to afford BCP **7**. Compared to NS5B inhibitors featuring *t*-butyl groups in the same position, the bicyclo[1.1.1]pentane-1-yl analogues such as BCP **7** evaluated in the study retained comparable antiviral activity against genotype (gt) 1a, 1b, and 2a proteins (< 10 nM).[6] The absorption, distribution, metabolism, and excretion (ADME) properties were subsequently investigated. Although BCP **7**'s *in vitro* metabolite was BCP–OH **8**, just as expected, its *in vivo* metabolism was unique. The two major metabolites were BCP–OH **8** (27%) and BCP–phosphocholine conjugate **9** (52%). The BCP–phosphocholine conjugate **9** is rare. The other better known drug to form phosphocholine conjugate with a hydroxyl group is everlimus, a hydroxyethyl prodrug of rapamycin.[6]



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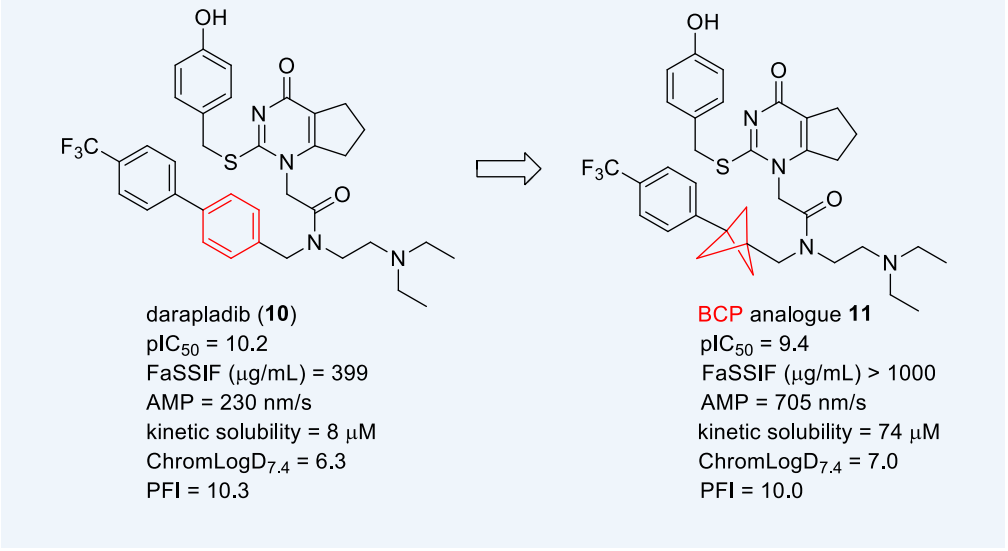
Bicyclo[1.1.1]pentanes in Drug Discovery

It has been shown that for some drug candidates, replacing a *p*-phenyl or a *t*-butyl group with BCP could maintain pharmacological efficacy while improving solubility and oral bioavailability.

Darapladib (**10**), a lipoprotein-associated phospholipase A_2 ($LpPLA_2$) inhibitor, was in phase III clinical trials as a treatment of atherosclerosis. But it had a suboptimal physicochemical properties including high molecular weight, low solubility, and high property forecast index (PFI) and failed to meet phase III endpoints in 2013 in a trial of 16,000 patients with acute coronary syndrome (ACS). Substituting one phenyl ring with the fully saturated bicyclo[1.1.1]pentane-1,4-diyl (BCP) gave rise to BCP-analogue **11**. Although it is slightly less potent than the parent darapladib (**10**), BCP-analogue **11** is bestowed with superior physicochemical properties with an improved permeability of 705 nm/s from 203 nm/s for darapladib (**10**, AMP, artificial membrane permeability). It has gained a 3-fold increase of thermodynamic fasted state simulated intestinal fluid (FaSSIF) solubility and a 9-fold increase in kinetic solubility. As a consequence, analogue **11** has a slightly lower PFI value.[7]



Resveratrol (**12**) has garnered much attention in medical research for the last two decades. But the progress has been hampered since its bioavailability is too low: with three phenol group, resveratrol (**12**) goes through rapid first-pass metabolism to its glucuronide and sulfate conjugates. Replacing one of the *p*-phenyl ring with bicyclo[1.1.1]pentane-1,4-diyl (BCP) resulted in BCP–resveratrol (**13**). The alcohol on **13** is nearly neutral in comparison to acidic phenol on **12**. In addition to being more lipophilic, the BCP portion has all sp^3

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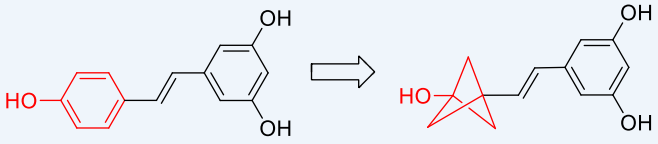
carbons. BCP–resveratrol (**13**) gained a 32-fold boost of aqueous solubility, a 3-fold increase of C_{max}, and is 10-fold more bioavailable as measured by the AUC values than resveratrol (**12**). Experimental data indicated that formation of glucuronide and sulfate conjugates in human hepatocytes for BCP–resveratrol (**13**) was significantly reduced since its steric hindrance retards secondary metabolism. More importantly, BCP–resveratrol (**13**) exerted similar biological activities in selected cancer cell lines.[8]



resveratrol (**12**)
Log $D_{7.4}$ = 1.9
solubility at pH7.4 = 19 μg/mL
$t_{1/2}$ = 0.19 h
C_{max} = 273 ng/mL
AUC = 47.5 ng•h/kg
T_{max} (h) = 0.083
Cl/F (L/h/kg) = 409

BCP–resveratrol (**13**)
Log $D_{7.4}$ = 2.9
solubility at pH7.4 = 619 μg/mL
$t_{1/2}$ = 2.6 h
C_{max} = 942 ng/mL
AUC = 587 ng•h/kg
T_{max} (h) = 0.067
Cl/F (L/h/kg) = 21.8

Sulfonamides **14** (BMS-708,163) and **15** are γ-secretase inhibitors with similar potencies, indicating that the main role of the fluorophenyl fragment is that of a *spacer*.[6] Employing bicyclo[1.1.1]pentane-1,4-diyl (BCP) on **15** as a bioisostere for the fluorophenyl moiety on **14**, the Fsp^3 carbon atom count doubled to 0.52 for **15** from 0.25 for **14**. As shown in equation 1, Fsp^3 is the fraction of saturated carbons within a molecule, a descriptor of complexity and an alternative to the number of aromatic rings (#Ar).[2] Disruption of aromaticity translated to a higher LipE value of 5.95 for **15** from 4.95 for **14**. More important, this maneuver also translated to practical advantages of improved kinetic and thermodynamic aqueous solubility and increased membrane permeability, probably brought about by a reduction in lipophilicity since the ElogD is reduced by 0.9.[9]

Imatinib (Gleevec, **17**) was revolutionary in medicine because it was the first kinase inhibitor on the market as the target cancer treatment. It is a Bcr–Abl kinase inhibitor approved to treat a variety of leukemia such as chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). But with an Fsp^3 value of 0.24, imatinib (**17**) is woefully deficient of sp^3 carbons. As a consequence, it has a high clog *P* of 4.53, high melting point of 204 °C, and a low aqueous solubility at pH7.4 of 30.7 μM. Nicolaou et al. prepared several

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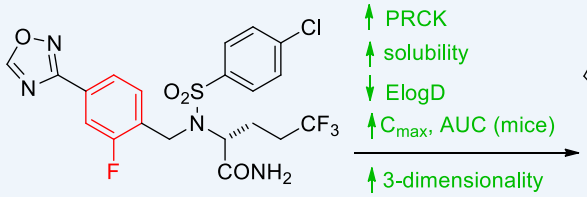
non-classical *p*-phenyl isosteres including cubane, cyclopropane, and cyclobutane to replace the *para*-phenyl ring sandwiched between the amide bond and the piperazine appendage. BCP–imatinib (**18**) was also prepared and investigated for its biopharmaceutical properties. While it had similar biological activities, BCP–imatinib (**18**)'s Fsp^3 value almost doubled that of the prototype imatinib (**17**). The thermodynamic solubility increased by > 80-fold from this maneuver, making BCP–imatinib (**18**) more "drug-like".[10]

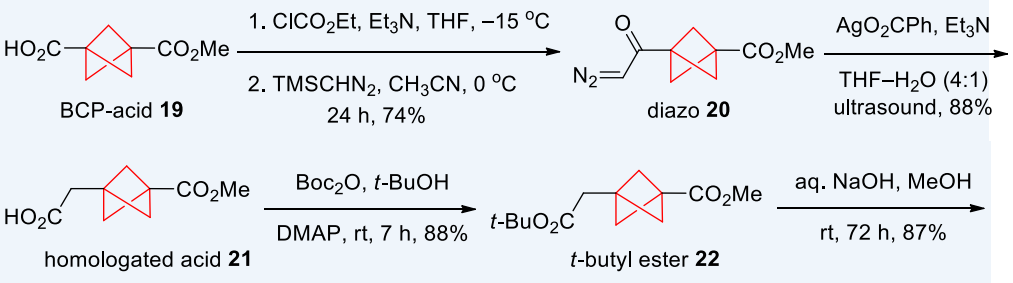


14, IC_{50} ($A\beta_{42}$) = 0.225 nM
ElogD = 4.7
sol pH7.4 = 0.9 μM
PRCK P_{app} (A to B) (10^{-6} cm/s) = 5.52
Fsp^3 = 0.25
LE = 0.40
LipE = 4.95
LELP = 11.75

15, IC_{50} ($A\beta_{42}$) = 0.178 nM
ElogD = 3.8
sol pH7.4 = 29.4 μM
PRCK = 19.3
Fsp^3 = 0.52
LE = 0.43
LipE = 5.95
LELP = 8.83

Synthesis of Some Bicyclo[1.1.1]pentane-containing Drugs

Pellicciari's synthesis of (*S*)-ω-acidic-BCP-glycine **6** commenced with commercially available ester-BCP-acid **19**. One-carbon homologation of **19** was carried out by a modified Arndt–Eistert reaction via the intermediacy of diazo compound **20**, followed by a Wolff rearrangement to afford homologated acid **21**. Acid **21** was converted to mixed diester **22**, which was readily hydrolyzed to acid **23**. Borane reduction of acid **23** was followed by a Dess–Martin oxidation to produce aldehyde **24**. A Strecker reaction between **24** and *R*-(–)-α-phenylglycinol gave rise to nitrile **25** after chiral separation. Finally, after cleavage of the chiral auxiliary, hydrolysis delivered (*S*)-ω-acidic-BCP-glycine 6.[5d]



BCP-acid **19**
diazo **20**
homologated acid **21**
t-butyl ester **22**

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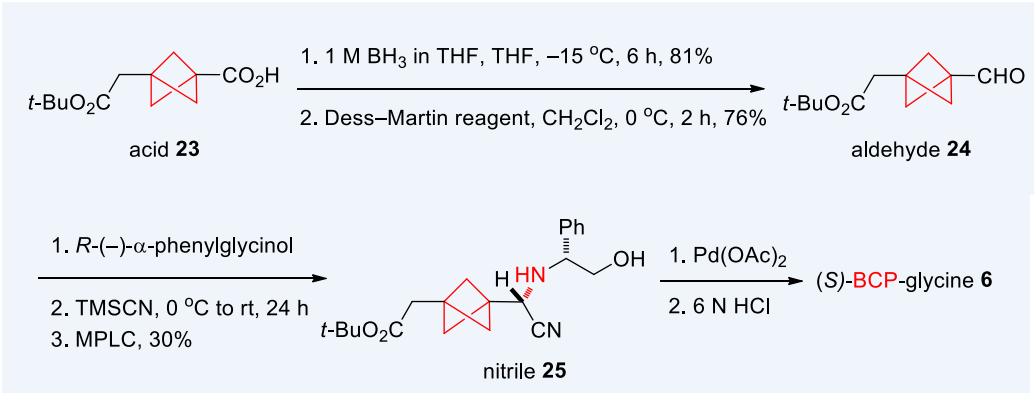
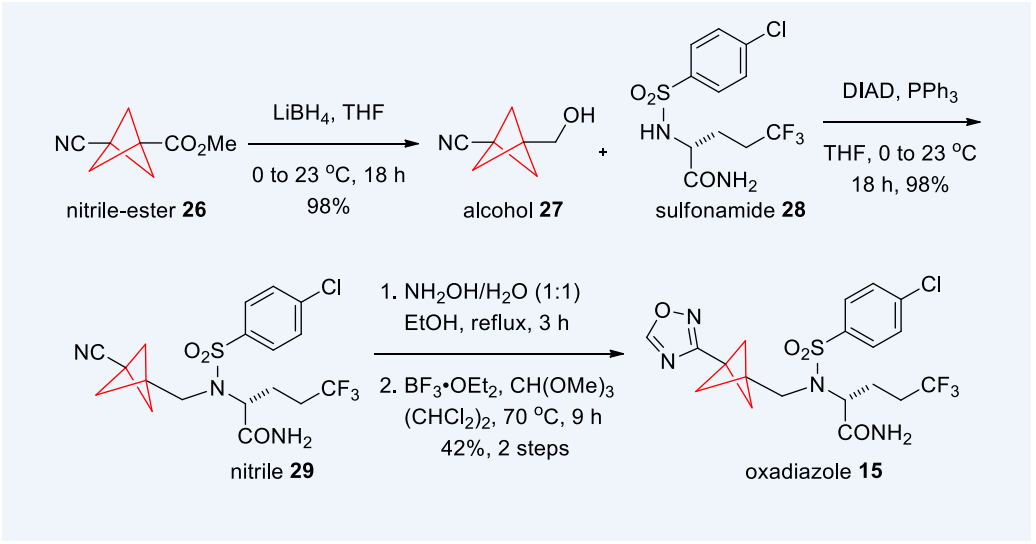
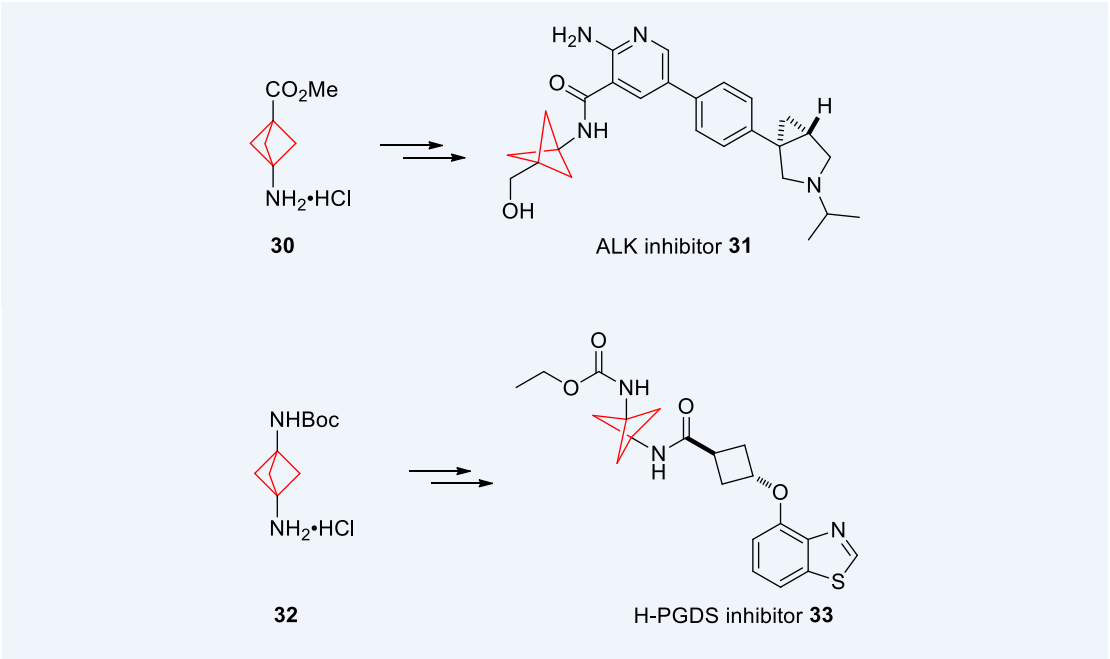


Preparation of Pfizer's γ-secretase inhibitor **15** began with known nitrile-BCP-ester **26**. Simple reduction of **26** gave alcohol **27**, which underwent a Mitsunobu reaction with amide-sulfonamide **28** selectively to afford nitrile **29**. Nitrile **29** was converted to the title oxadiazole **15** via a two-step sequence involving treatment with hydroxylamine to generate an intermediate amide-oxime, which was then transformed to **15** in the presence of triethyl orthoformate and a catalytic amount of boron trifluoride etherate.[9]



Amino-BCP and di-amino-BCP have been employed as building blocks in the preparation of potential medicines. Aminopyridine **31**, a selective anaplastic lymphoma kinase-2 (ALK-2) inhibitor, was synthesized using amino-BCP **30** as the starting material. It has a potential in the treatment of heterotopic ossification and fibrodysplasia ossificans progressiva.[11] On the other hand, hematopoietic prostaglandin D synthase (H-PGDS) inhibitor **33** was prepared employing diamino-BCP **32** as the starting material.[12]



References

1. Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; La Vecchia, L.; Briard, E. *ChemMedChem* **2017**, *12*, 590–598.
2. (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756. (b) Lovering, F. *MedChemComm* **2013**, *4*, 515–519.
3. Westphal, M. V.; Wolfstaedter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. *ChemMedChem* **2015**, *10*, 461–469.
4. Barbachyn, M. R.; Hutchinson, D. K.; Toops, D. S.; Reid, R. J.; Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 671–676.
5. (a) Pellicciari, R.; Raimondo, M.; Marinozzi, M.; Natalini, B.; Costantino, G.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2874–2976. (b) Costantino, G.; Maltoni, K.; Marinozzi, M.; Camaioni, E.; Prezeau, L.; Pin, J.-P.; Pellicciari, R. *Bioorg. Med. Chem.* **2001**, *9*, 221–227. (c) Filosa, R.; Marinozzi, M.; Costantino, G.; Hermit, M. B.; Thomsen, C.; Pellicciari, R. *Bioorg. Med. Chem.* **2006**, *14*, 3811–3817. (d) Filosa, R.; Fulco, M. C.; Marinozzi, M.; Giacche, N.; Macchiarulo, A.; Peduto, A.; Massa, A.; de Caprariis, P.; Thomsen, C.; Christoffersen, C. T.; et al. *Bioorg. Med. Chem*. **2009**, *17*, 242–250.
6. Zhuo, X.; Cantone, J. L.; Wang, Y.; Leet, J. E.; Drexler, D. M.; Yeung, K.-S.; Huang, X. S.; Eastman, K. J.; Parcella, K. E.; Mosure, K. W.; et al. *Drug Metab. Dispos.* **2016**, *44*, 1332–1340.
7. Measom, N. D.; Down, K. D.; Hirst, D. J.; Jamieson, C.; Manas, E. S.; Patel, V. K.; Somers, D. O. *ACS Med. Chem. Lett.* **2017**, *8*, 43–48.
8. Goh, Y. L.; Cui, Y. T.; Pendharkar, V.; Adsool, V. A. *ACS Med. Chem. Lett*. **2017**, *8*, 516–520.
9. Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; et al. *J. Med. Chem*. **2012**, *55*, 3414–3424.

10. Nicolaou, K. C.; Vourloumis, D.; Totokotsopoulos, S.; Papakyriakou, A.; Karsunky, H.; Fernando, H.; Gavrilyuk, J.; Webb, D.; Stepan, A. F. *ChemMedChem* **2016**, *11*, 31–37.
11. Li, J.; Arista, L.; Babu, S.; Bian, J.; Cui, K.; Dillon, M. P.; Lattmann, R.; Liao, L.; Lizos, D.; Ramos, R.; et al. (Novartis) WO2018014829 (2018).
12. Deaton, D. N.; Guo, Y.; Hancock, A. P.; Schulte, C.; Shearer, B. G.; Smith, E. D.; Stewart, E. L.; Thomson, S. A. (GSK) WO2018069863 (2018).

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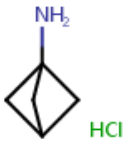

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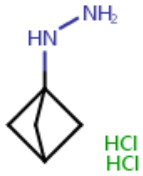

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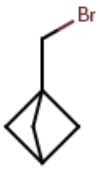

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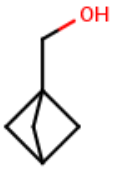

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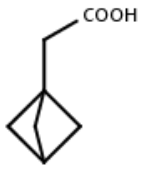

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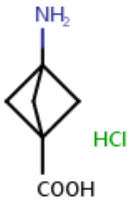

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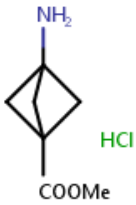

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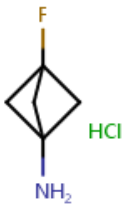

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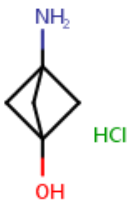

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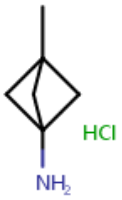

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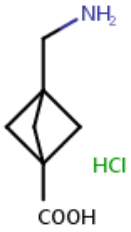

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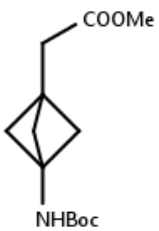

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For product and service inquiries, please contact:

China & India
Tel: +86-400 025 5188
Fax: +86-25 8691 8232
E-mail: sales_china@pharmablock.com

US & Europe
PA Tel: +1-877 878 5226 / 267 649 7271
CA Tel: +1-408 735 7571 / 408 921 9969
E-mail: salesusa@pharmablock.com

Other Countries
Tel: +86-25 8691 8086 / 8691 8288
Fax: +86-25 8691 8232
E-mail: sales@pharmablock.com