Cyclopentane Derivatives in Drug Discovery

Key Points

- Improve drugs' pharmacokinetic profiles
- Serve as either the core scaffold or an appendage to occupy a hydrophobic pocket on the target

Overview

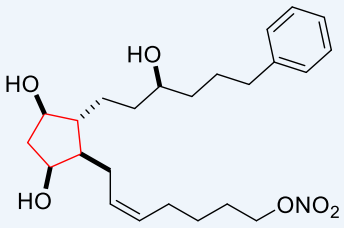
To minimize torsional strain, cyclopentane puckers to adopt an "envelope" conformation. Cyclopentanes on drugs may serve as either the core scaffold or an appendage to occupy a hydrophobic pocket of the target such as an enzyme or a receptor.

PharmaBlock

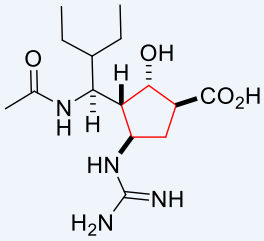
PharmaBlock designs and synthesizes over 921 Cyclopentanes, and 172 Cyclopentane products are in stock. A list of featured Cyclopentane derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

Cyclopentane-containing drugs

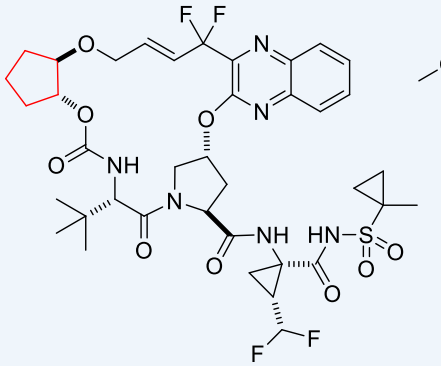
All steroid-based drugs have a fused cyclopentane ring as an integral part of the steroidal architecture. The majority of prostaglandins have a cyclopentane core structure as the consequence of oxidation of arachidonic acid by cyclooxygenases (COXs). The latest example of prostaglandin analogues is Bausch and Lomb's latanoprostene (Vyzulta, **1**) for treating open-angle glaucoma or ocular hypertension. It is a nitric oxide (NO)-donating prostaglandin F-2α analogue. BioCryst's peramivir (Rapivab, **2**) is a neuraminidase inhibitor to treat influenza. Abbvie/Enanta's glecaprevir (**3**, with pibrentasvir, Mavyret), with a di-substituted cycplopentane motif, is a hepatitis C virus nonstructural protein (HCV NS)-3/4A protease inhibitor. Similarly, simeprevir (Olysio, **4**), Janssen/Medivir's HCV NS3/4A protease inhibitor, has a tri-substituted cyclopentane scaffold.



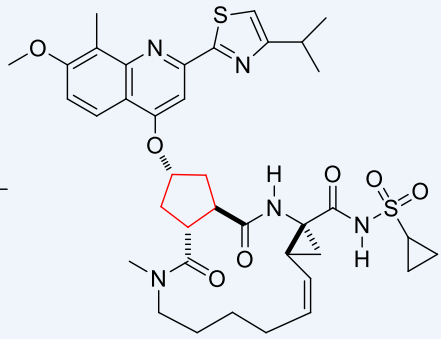
latanoprostene (Vyzulta, **1**)
Bausch and Lomb, 2017
a nitric oxide (NO)-donating
prostaglandin $F_{2\alpha}$ analogue



peramivir (Rapivab, **2**)
BioCryst, 2014
neuraminidase inhibitor

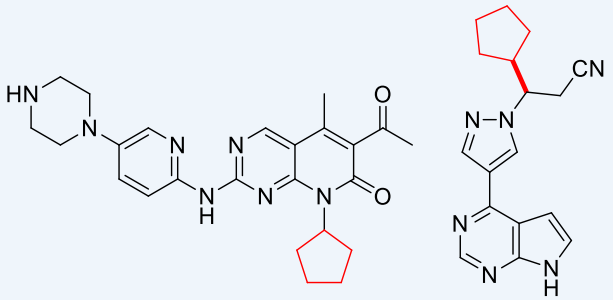


glecaprevir (and pibrentasvir, Mavyret, **3**)
Abbvie/Enanta, 2017
HCV NS 3/4A protease inhibitor



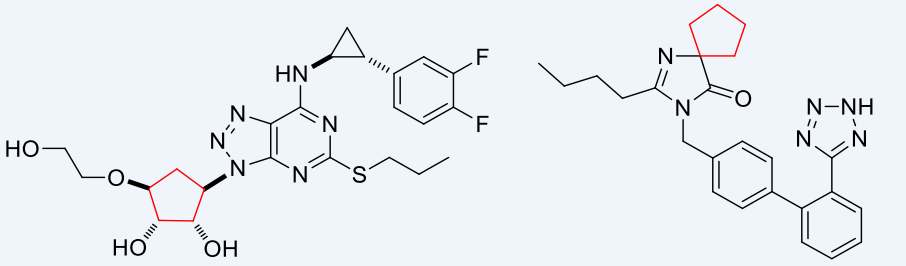
simeprevir (Olysio, **4**)
Janssen/Medivir, 2013
HCV NS3/4A protease inhibitor

Pfizer's palbociclib (Ibrance, **5**) is a cyclin-dependent kinase (CDK) 4/6 inhibitor approved by the FDA in 2015 for treating ER-positive and HER2-negative breast cancer. On the other hand, Incyte's ruxolitinib (Jakafi, **6**), a Janus kinase (JAK) 1/2 inhibitor, was approved in 2011 for the treatment of bone marrow cancer. AstraZeneca's ticagrelor (Brilinta, **7**), a synthetically challenging $P2Y_{12}$ platelet inhibitor as an anticoagulant, has a tetra-substituted cyclopentane as its sidechain. Cyclopentanes occasionally show up on drugs in the form of spirocyclic bicycles. In addition to BMS' buspirone (Buspar, not shown), Sanofi/BMS' irbesartan (Avapro, **8**), an angiotensin II receptor blocker (ARB) for treating hypertension, also has a spirocyclic cyclopentane.



palbociclib (Ibrance, **5**)
Pfizer, 2015
CDK4/6 inhibitor

ruxolitinib (Jakafi, **6**)
Incyte, 2011
JAK1/2 inhibior



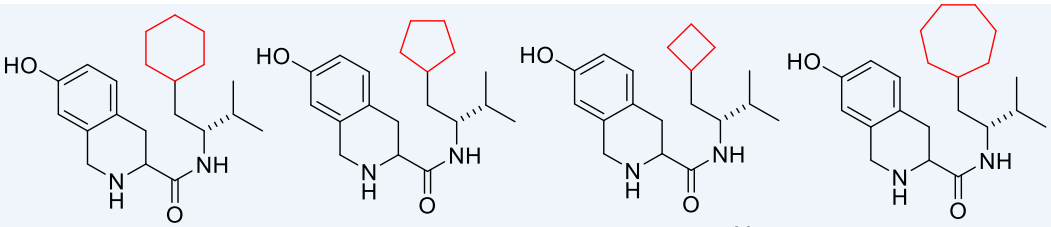
ticagrelor (Brilinta, **7**)
AstraZeneca, 2010
$P2Y_{12}$ platelet inhibitor

irbesartan (Avapro, **8**)
Sanofi/BMS, 2001
angiotensin II receptor antagonist

Cyclopentanes in Drug Discovery

In comparison to the ubiquitous cyclohexanes, there are fewer examples of cyclopentanes in medicines. But nothing succeeds like success. When it works, cyclopentane may be the optimal fragment on a drug.

In drug discovery, sizes matter. In pursuit of kappa (κ) opioid receptor antagonists as potential pharmacotherapies for treating depression, anxiety, and substance abuse, cyclopentane proved to be the right size. The lead compound cyclohexane **9** was a potent κ opioid receptor antagonist (*K*e = 0.14 nM)and selective against mu (μ) and delta (δ) subtypes. Changing the six-membered ring on **9** to cyclopentane **10**, cyclobutane **11**, and cycloheptane **12** revealed that cyclopentane **10** had the optimal profile. Not only was cyclopentane **10** the most potent (*K*e = 0.048 nM), it was more selective against mu (μ) and delta (δ) subtypes as well.[1]



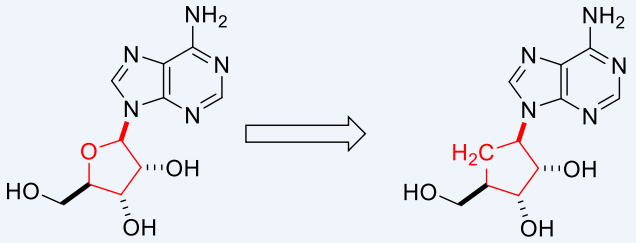
cyclohexane **9**
*K*e(κ) = 0.14 nM
μ/κ = 1,730
δ/κ = 24,570

cyclopentane **10**
*K*e(κ) = 0.058 nM
μ/κ = 5,900
δ/κ = 27,000

cyclobutane **11**
*K*e(κ) = 2.61 nM
μ/κ = 102
δ/κ = 1,245

cycloheptane **12**
*K*e(κ) = 0.20 nM
μ/κ = 292
δ/κ = 3,760

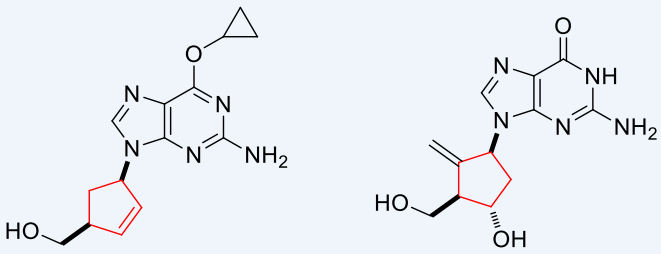
In the field of nucleosides, *carbocyclic nucleosides* (*carbanucleosides*) are important. The substitution of the endocyclic oxygen atom by a CH_2 moiety increases not only the chemical stability of the *N*-glycosidic bond but also makes these derivatives metabolically resistant to the action of several enzymes such as pyrimidine and purine nucleoside phosphorylases.[2] For instance, aristeromycin (**14**) is a direct carbon analogue of adenosine (**13**). The *N*-glycosidic bond between ribose and adenine (A) on adenosine (**13**) is subjected to metabolism and cleavage by both phosphorylases and hydrolases. In contrast, the carbocyclic isostere aristeromycin (**14**) is unaffected by metabolism and cleavage by those two classes of enzymes but still maintains similar biological activities.[3]



adenosine (**13**)
$t_{1/2}$ < 2 min (iv)
%F = 0%

aristeromycin (**14**)
$t_{1/2}$ = 23 min
CL = 7.9 ml/min
V_{ss} = 260 mL

Building upon aristeromycin (**14**)'s improved pharmacokinetic profile, two cyclopentane-containing carbanucleosides gained FDA's approvals. Abacavir (Ziagen, **15**) as an HIV reverse-transcriptase inhibitor, initially discovered by Vince and later developed by GSK, has been on the market since 1998 to treat AIDS.[4] BMS' entecavir (Baraclude, **16**) for the treatment of hepatitis B, has a remarkably improved bioavailability in comparison to the furanose counterparts.[5]

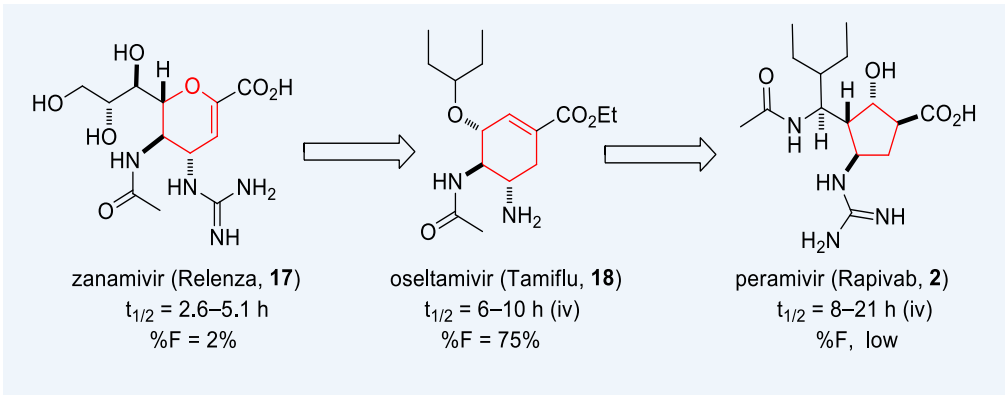


abacavir (Ziagen, **15**)
GSK, 1998
carbocyclic nucleoside
$t_{1/2}$ = 1.5 h
%F = 83%
PPB = 50%

entecavir (Baraclude, **16**)
BMS, 2005
carbocyclic nucleoside
$t_{1/2}$ = 4–9 h
%F = 70%
PPB = 13%

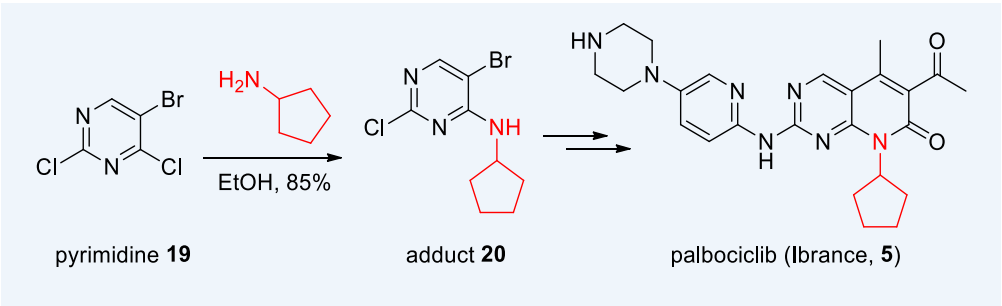
Influenza neuraminidase inhibitor zanamivir (Relenza, **17**) is not bioavailable and has to be given as an oral inhalation. Switching its pyranose scaffold to cyclohexene, among other optimizations, gave rise to oseltamivir (Tamiflu, **18**), which is orally bioavailable. As an ester prodrug, it has a bioavailability of 75% for the corresponding carboxylic

acid. X-Ray crystal structures of complexes of the neuraminidase enzyme and its inhibitors indicated that potent inhibition of the enzyme is determined by the relative positions of the interacting inhibitor substituents (carboxylate, glycerol, acetamido, and hydroxyl) rather than by the absolute position of the central ring. To that end, BioCryst designed peramivir (**2**) with a cyclopentane core scaffold. It has several common functionalities as both zanamivir (**17**) and oseltamivir (**18**) including carboxylate, glycerol, acetamido, and hydroxyl groups.[6]



Synthesis of Some Cyclopentane-containing Drugs

Pfizer's process route for preparing palbociclib (**5**) commenced with an S_NAr displacement of 5-bromo-2,4-dichloropyrimidine (**19**) with cyclopentylamine. The resultant adduct **20** was then converted to palbociclib (**5**) in additional three steps.[7]



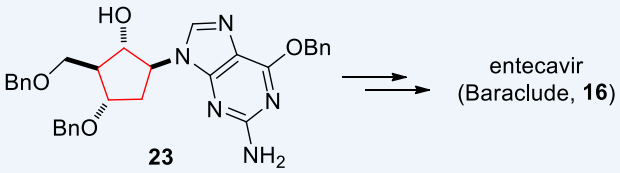
Synthesis of tetra-substituted cyclopentane with four contiguous chiral centers on BMS' entecavir (**16**) is not trivial. Advanced intermediate cyclopentyl epoxide **21** was prepared in five steps from sodium cyclo-

PharmaBlock is recognized for its outstanding capability in the design, synthesis, production and commercialization of novel building blocks for use throughout the drug R&D process.

- 80000+ building blocks
- 10000+ in stock in both USA and China
- 20000+ supplied within two weeks
- 1000+ SAR tool kits
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance

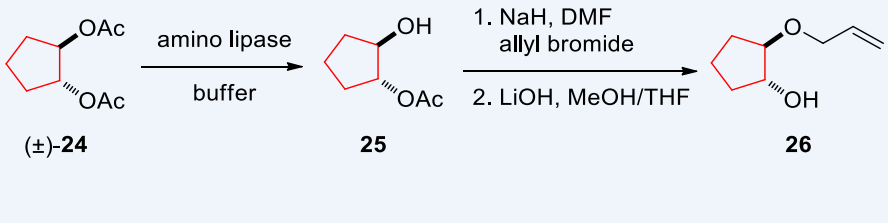
pentadienide. An S_N2 displacement of **21** with purine-amine **22** assembled adduct **23**, which was transformed to entecavir (**16**) in three additional steps.[5]

21 **22**

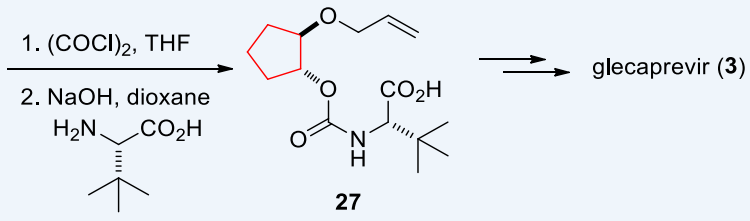


23

HCV NS3/4A protease inhibitor glecaprevir (**3**) has a di-substituted cyclopentane moiety. Its synthesis started with racemic cyclopentane-1,2-diyl diacetate [(±)-**24**], simply prepared from the corresponding diol. Chiral resolution using amino lipase provided (1*R*,2*R*)-2-hydroxy-cyclopentyl acetate (**25**). The cyclopentane fragment **26** was obtained from allylation of **25** and hydrolysis of the acetate. Coupling between alcohol **26** and L-*tert*-butyl-leucine led to carbamate **27**, which was converted to glecaprevir (**3**) after 5 additional steps.[8]



(±)-**24** **25** **26**



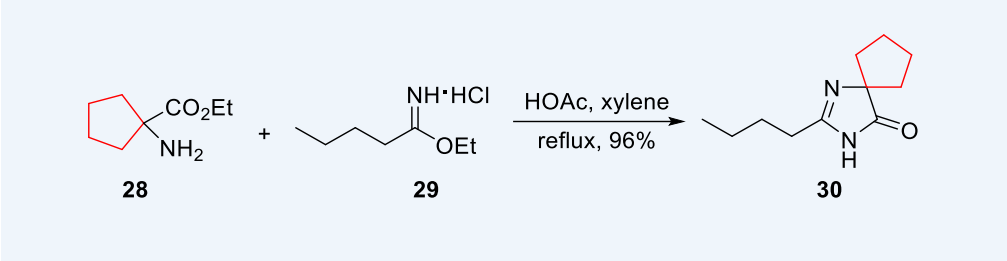
27

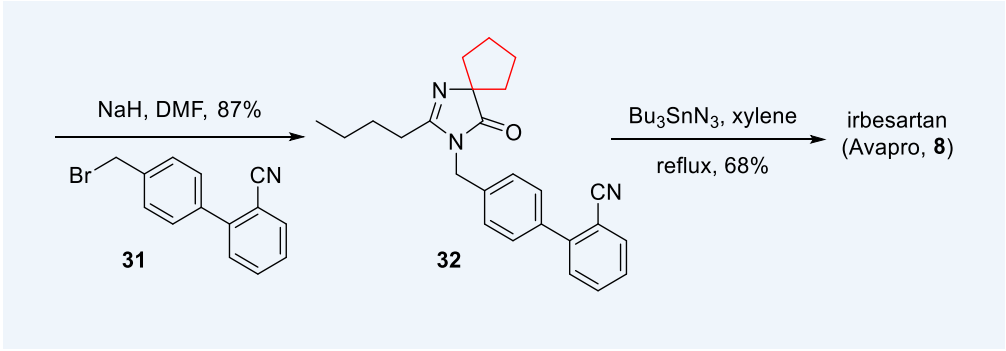
Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel (PA): 1-877 878 5226
Tel (CA): 1-267 649 7271
Email: salesusa@pharmablock.com

BMS' short process route to irbesartan (**8**) began with the reaction of 1-amino-cyclopentane-carboxylic acid ester **28** with ethyl pentanimidate (**29**) in the presence of acetic acid in refluxing xylene to assemble dihydroimidazolone **30**. An S_N2 alkylation of **30** with phenylbenzyl bromide **31** in the presence of sodium hydride in DMF gave **32**. Finally, the synthesis of irbesartan (**8**) was completed by the tetrazole formation from reaction of the nitrile group of **32** with tributyltin azide in refluxing xylene.[9]





Summary

In summary, cyclopentanes may serve as either the core scaffold or an appendage on drugs to occupy the target's hydrophobic pocket. One of its more important utility is serving as a bioisostere of furanose to prepare carbanucleosides to improve the drugs' pharmacokinetic profiles.

References

1. Kormos, C. M.; Ondachi, P. W.; Runyon, S. P.; Thomas, J. B.; Mascarella, S. W.; Decker, A. M.; Navarro, H. A.; Fennell, T. R.; Snyder, R. W.; Carroll, F. I. *J. Med. Chem.* **2018**, *61*, 7546–7559.
2. Boutureira, O.; Matheu, M. I.; Diaz, Y.; Castillón, S. *Chem. Soc. Rev.* **2013**, *42*, 5056–5072.
3. Schaddelee, M. P; Dejongh, J.; Collins, S. D.; de Boer, A. G; Ijzerman, A. P.; Danhof, M. *Eur. J. Pharmacol.* **2004**, 504, 7–15.
4. Vince, R. *Chemtracts* **2008**, *21*, 127–134.
5. Ruediger, E.; Martel, A.; Meanwell, N.; Solomon, C.; Turmel, B. *Tetrahedron Lett.* **2004**, *45*, 739–742.
6. Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Babu, Y. S.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379–4392.
7. Duan, S.; Place, D.; Perfect, H. H.; Ide, N. D.; Maloney, M.; Sutherland, K.; Price Wiglesworth, K. E.; Wang, K.; Olivier, M.; Kong, F.; et al. *Org. Proc. Res. Dev.* **2016**, *20*, 1191–1202.
8. Or, Y. S.; Ma, J.; Wang, G.; Wang, B. (Enanta), WO2012040167 (2012).
9. Miranda, E. I.; Vlaar, Co.; Zhu, J. (BMS) US7211676 (2007)