Azetidines in Drug Discovery

Key Points

- A privileged scaffold in drug discovery
- Providing an efficient tuning of pharmacological properties

Overview

Azetidines are good compromise between a satisfactory stability and a strong molecular rigidity, allowing an efficient tuning of pharmacological properties displayed by molecules bearing this moiety. Therefore, azetidine is considered a privileged scaffold in drug discovery.

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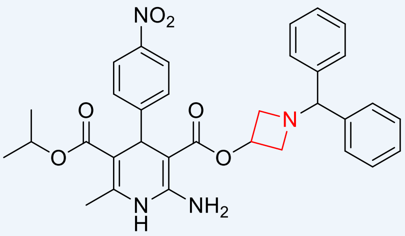
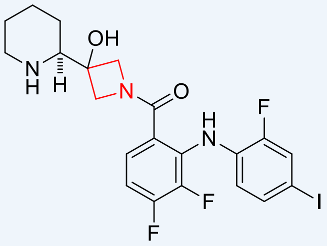
Azetidine-containing Drugs

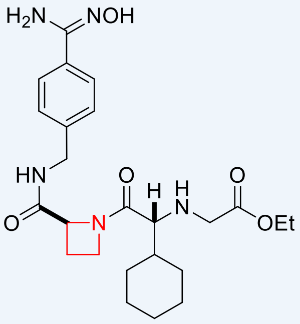
Azetidines are a good compromise between a satisfactory stability and a strong molecular rigidity, allowing an efficient tuning of pharmacological properties displayed by molecules bearing this moiety.[1] Two azetidine-containing drugs are currently on the market. Dihydropyridine azelnipidine (Calblock, **1**) is Sankyo's calcium channel blocker.[2] Exelixis' cobimetinib (Cotellic, **2**), as a targeted cancer therapy, is a mitogen-activated protein kinase-1/2 (MEK1/2) inhibitor.[3] Another azetidine-containing drug ximelagatran (Exanta, **3**) as a direct thrombin inhibitor was discovered by AstraZeneca. Initially sold as an anticoagulant, it was pulled off the market in 2006 due to hepatoxicity.[4]



azelnidipine (CalBlock, **1**)
Daiichi-Sankyo, 1989
calcium channel blocker



cobimetinib (Cotellic, **2**)
Exelixis/Genentech, 2015
MEK1/2 inhibitor

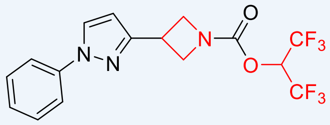


ximelagatran (Exanta, **3**)
AstraZeneca
direct thrombin inhibitor

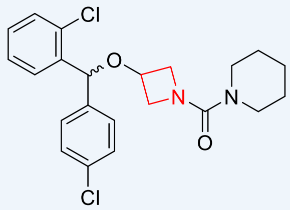
Azetidines in Drug Discovery

Azetidine carbamate **4** is an efficient, covalent inhibitor of monoacylglycerol lipase (MAGL) discovered by Pfizer.[5] The hexafluoroisopropanol (HFIP) group here serves as the leaving group when attacked by the key serine residue (Ser122) at the enzyme's active site. Covalent inhibition is attractive in that it offers the potential for extended duration of pharmacodynamic modulation relative to pharmacokinetic profile of the inhibitor.

Fatty acid amide hydrolase (FAAH) inhibitors are potential treatment for pain. Vernalis discovered a mixture of chiral azetidine-ureas VER-24052 (**5**) as a FAAH inhibitor (rat FAAH, IC$_{50}$ = 188 nM, t = 3 h). Interestingly, while the isomer with a positive optical rotation was active (rat FAAH, IC$_{50}$ = 78 nM, t = 3 h), its corresponding enantiomer was completely inactive in the same assay.[6]

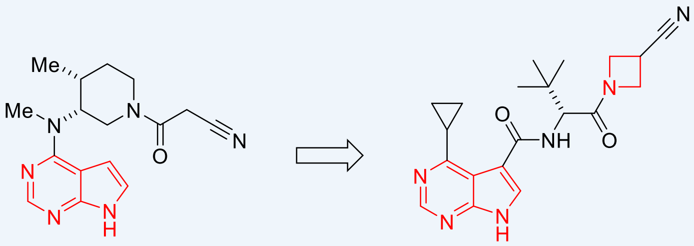


4
MAGL, IC$_{50}$ = 0.18 nM
LipE = 5.5



VER-24052 (**5**)
rat FAAH, IC$_{50}$ = 1205 nM

Marketed since 2012, Pfizer's tofacitinib (Xeljanz, **6**) is the first-in-class Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). In 2013, Roche reported an azetidine-containing bis-amide **7** as a selective JAK3 inhibitor (IC$_{50}$ = 0.26 nM) with a 10-fold selectivity over JAK1 (IC$_{50}$ = 3.2 nM). In addition, the combination of its selectivity over the kinome, good solubility and reasonable exposure was translated to *in vivo* potency and selectivity in an acute

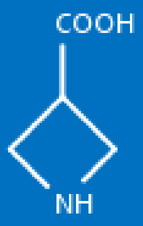


tofacitinib (Xeljanz, **6**)
Pfizer, 2012
JAK Inhibitor for RA

bis-amide **7**
JAK3, IC$_{50}$ = 0.26 nM
JAK1, IC$_{50}$ = 3.2 nM

Spirocyclic azetidines, like all spirocyclic scaffolds, are inherently three dimensional and offer structural novelty. For example, 3,3′-spiro[azetidine]-2-oxo-indoline derivative **8** was discovered as a fusion inhibitor for the treatment of respiratory syncytial virus (RSV).[8] On the other hand, spirocyclic piperidine-azetidine **9** is an inverse agonist of the ghrelin receptor (GR), a GPCR target that plays a role in obesity and glucose homeostasis.[9]

PharmaBlock Products



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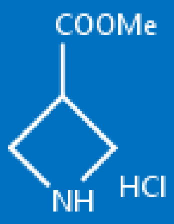

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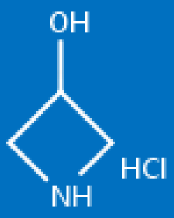

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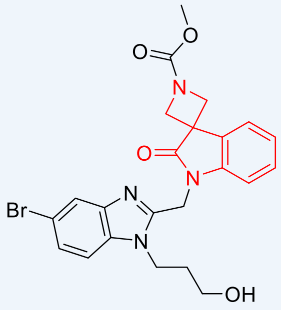
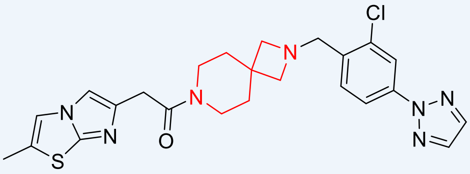


8

RSV EC_{50} = 0.8 nM
CC_{50} > 100 μM
%F = 71%

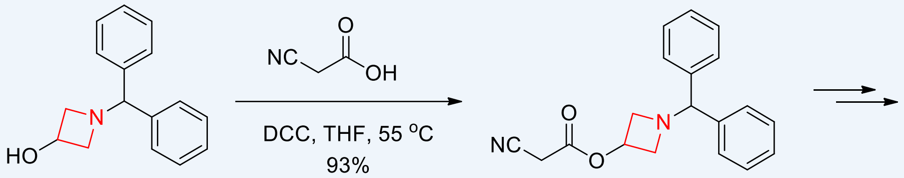


9

HGR IC_{50} = 4.6 nM
HGR K_i = 7.0 nM
LE = 0.33

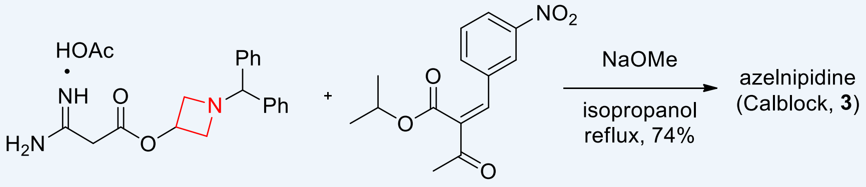
Synthesis of Some Azetidine-containing Drugs

Sankyo's synthesis of azelnipidine (Calblock, **3**) began with 1-benzhydryl-3-hydroxyazetidine (**10**), readily assembled from condensation of benzhydrylamine with epichlorohydrin. Subsequent 1,3-dicyclohexylcarbodiimide (DCC)-mediated esterification of **10** with cyanoacetic acid produced ester **11**, which was converted to amidine **12** in two additional steps. A Hantzsch dihydropyridine synthesis between amidine **12** and enone **13** then delivered azelnipidine (**3**).[10]



hydroxy-azetidine **10**

ester **11**



amidine **12**

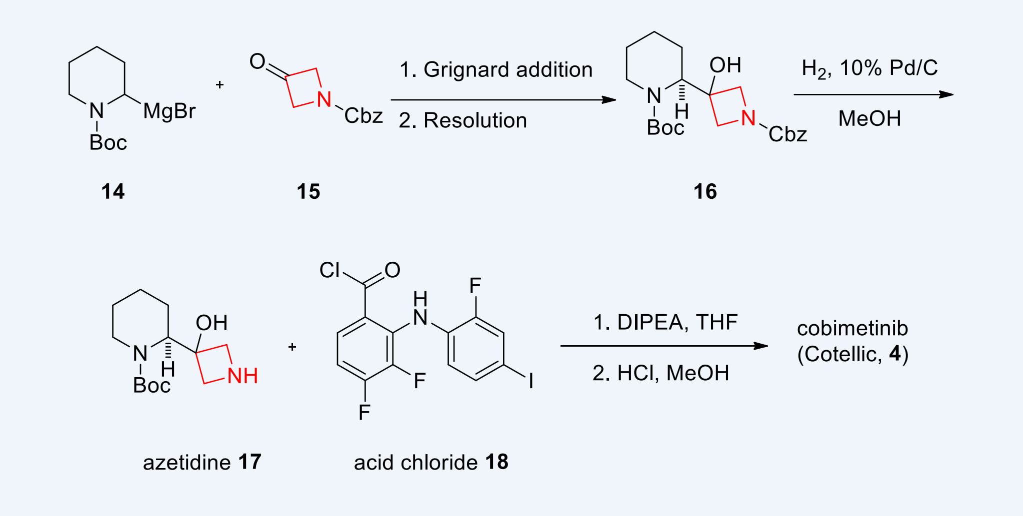
enone **13**

Exelixis' synthesis of cobimetinib (Cotellic, **4**) commenced with addition of piperidine-Grignard reagent **14** to azetidinone **15**. The (*S*)-adduct **16** was secured after chiral resolution employing the Mosher's ester technique. Palladium-catalyzed hydrogenation of **16** removed the Cbz protection to afford the exposed azetidine **17**. Ester formation from the coupling between **17** and acid chloride **18** in the presence of diisopropylethylamine (DIPEA) produced cobimetinib (**4**) after deprotection of the Boc group.[3]

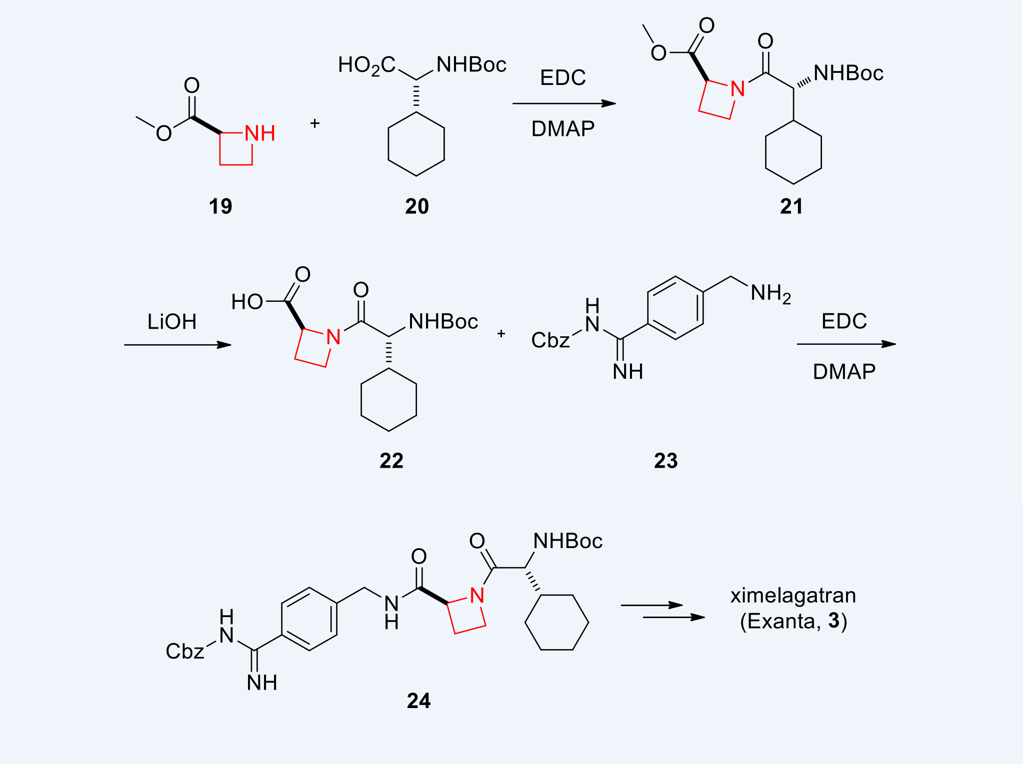
Contact Us

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



AstraZeneca's synthesis of ximelagatran (Exanta, **3**) started with formation of amide **21** from azetidine ester **19** and chiral amino acid **20**. Subsequently, LiOH-promoted saponification of **21** afforded azetidine acid **22**. An additional amide formation between azetidine acid **22** and benzylamine **23** prepared bis-amide **24**, which was converted to the desired ximelagatran (**3**) after several additional steps.[11]



In summary, azetidines are good compromise between a satisfactory stability and a strong molecular rigidity, allowing an efficient tuning of pharmacological properties displayed by molecules bearing this moiety. Therefore, azetidine is considered a privileged scaffold in drug discovery.

References

1. Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008,** *108*, 3988–4035.
2. Yagil, Y.; Miyamoto, M.; Frasier, L.; Oizumi, K.; Koike, H. *Am. J. Hypertens.* **1994,** *7,* 637–646.
3. Rice, K. D.; Aay, N.; Anand, N. K.; Blazey, C. M.; Bowles, O. J.; Bussenius, J.; Costanzo, S.; Curtis, J. K.; Defina, S. C.; Dubenko, L.; Engst, S.; Joshi, A. A.; Kennedy, A. R.; Kim, A. I.; Koltun, E. S.; Lougheed, J. C.; Manalo, J.-C. L.; Martini, J.-F.; Nuss, J. M.; Peto, C. J.; Tsang, T. H.; Yu, P.; Johnston, S. *ACS Med. Chem. Lett.* **2012,** *3,* 416–421.
4. Ericksson, B. I.; Carlsson, S.; Halvarsson, M.; Risberg, B.; Mattsson, C. *Thromb. Haemostasis* **1997,** *78*, 1404–1407.
5. Butler, C. R.; Beck, E. M.; Harris, A.; Huang, Z.; McAllister, L. A.; am Ende, C. W.; Fennell, K.; Foley, T. L.; Fonseca, K.; Hawrylik, S. J.; et al. *J. Med. Chem*. **2017,** *60*, 9860–9873.
6. Hart. T.; Macias, A. T.; Benwell, K.; Brooks, T.; D'Alessandro, J.; Dokurno, P.; Francis, G.; Gibbons, B.; Haymes, T.; Kennett, G.; Lightowler, S.; Mansell, H.; Matassova, N.; Misra, A.; Padfield, A.; Parsons, R.; Pratt, R.; Robertson, A.; Walls, S.; Wong, M.; Roughley, S. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 4241–4244.
7. Soth, M.; Hermann, J. C.; Yee, C.; Alam, M.; Barnett, J. W.; Berry, P.; Browner, M. F.; Frank, K.; Frauchiger, S.; Harris, S.; et al. *J. Med. Chem*. **2013,** *56*, 345–356.
8. Shi, W.; Jiang, Z.; He, H.; Xiao, F.; Lin, F.; Sun, Y.; Hou, L.; Shen, L.; Han, L.; Zeng, M.; et al. *ACS Med. Chem. Lett.* **2018,** *9,* 94–97.
9. Kung, D. W.; Coffey, S. B.; Jones, R. M.; Cabral, S.; Jiao, W.; Fichtner, M.; Carpino, P. A.; Rose, C. R.; Hank, R. F.; Lopaze, M. G.; Swartz, R.; Chen, H. T.; Hendsch, Z.; Posner, B.; Wielis, C. F.; Manning, B.; Dubins, J.; Stock, I. A.; Varma, S.; Campbell, M.; DeBartola, D.; Kosa-Maines, R.; Steyn, S. J.; McClure, K. F. *Bioorg. Med. Chem. Lett.* **2016,** *24*, 2146–2157.
10. Koike, H.; Nishino, H.; Yoshimoto, M. *Dihydropyridine derivatives, their preparation and their use*. US 4,772,596 (1988).
11. Lila, C.; Gloanec, P.; Cadet, L.; Hervé, Y.; Fournier, J.; Leborgne, F.; Verbeuren, T. J.; De Nanteuil, G. *Synth. Commun.* **1998,** *28*, 4419–4429.