Piperidine, The Enchanted Ring

Key Points

- Offering additional binding to the targets
- More easily crossing the cell membrane
- Addressing drug-resistance issues
- Improving aqueous solubility of drugs

Overview

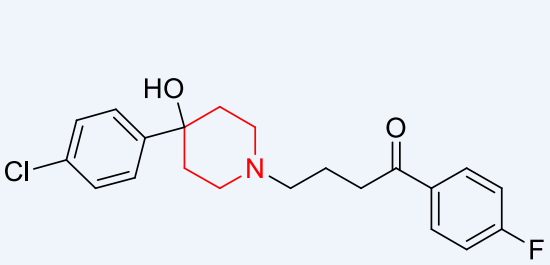
Thanks to its ubiquitous presence in drugs, piperidine is a truly “enchanted” ring. Like many nitrogen-containing drugs, when charged, piperidine may enhance solubility and offer additional binding to the targets. Meanwhile, when neutral, piperidine-containing drugs may cross the cell membrane more readily.

PharmaBlock

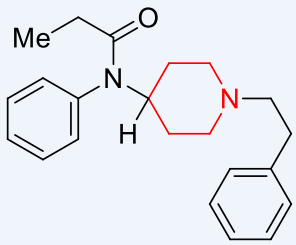
PharmaBlock designs and synthesizes over 3896 Piperidines, and 901 Piperidine products are in stock. A list of featured Piperidine derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

Piperidine-containing drugs

Paul Janssen bestowed us with two powerful piperidine-containing drugs. One is haloperidol (Haldol, **1**), a typical antipsychotic. The other is fentanyl (Duragesic, **2**), which is 100-fold more potent than morphine. Fentanyl (**2**) has contributed much to today's opioid epidemic.

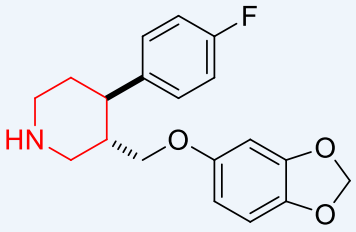


haloperidol (Haldol, **1**)
Janssen, 1959
typical anti-psychotic

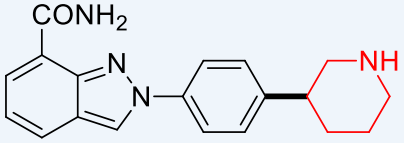


fentanyl (Duragesic, **2**)
Janssen, 1959
100X more potent than morphine

Piperidine is one of the "privileged scaffolds", present in drugs encompassing all therapeutic areas. In addition to alkylated forms such as in haloperidol (**1**) and fentanyl (**2**), some piperidines exist in the "naked" form, i.e., the NH form. Paroxetine (Paxil, **3**) is a selective serotonin reuptake inhibitor (SSRI) for treating depression and niraparib (Zejula, **4**) is a poly(ADP-ribosyl) polymerase (PARP) inhibitor for treating ovarian cancer. Furthermore, two kinase inhibitors also have the "naked" form of the piperidine ring. Pfizer's crizotinib (Xalkori, **5**) is an anaplastic lymphoma kinase (ALK) inhibitor and Exelixis' cobimetinib (Cotellic, **6**) is a mitogen-activated protein kinase-1/2 (MEK1/2) inhibitor. Both crizotinib (**5**) and cobimetinib (**6**) are targeted cancer therapies.



paroxetine (Paxil, **3**)
GSK, 1992
SSRI



niraparib (Zejula, **4**)
Tesaro, 2017
PARP inhibitor

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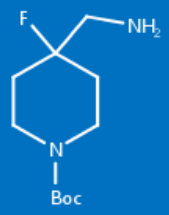

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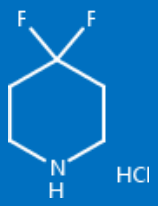

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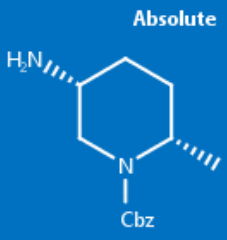

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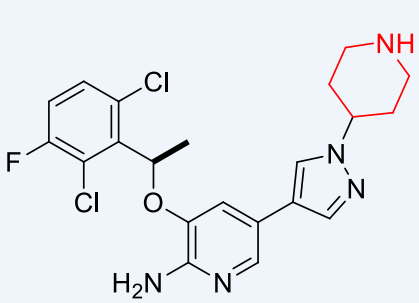
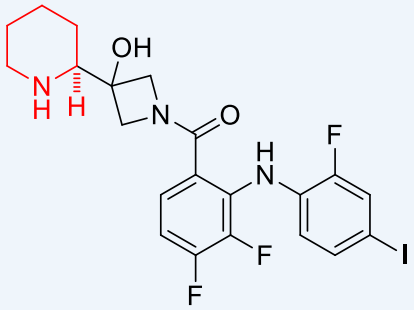
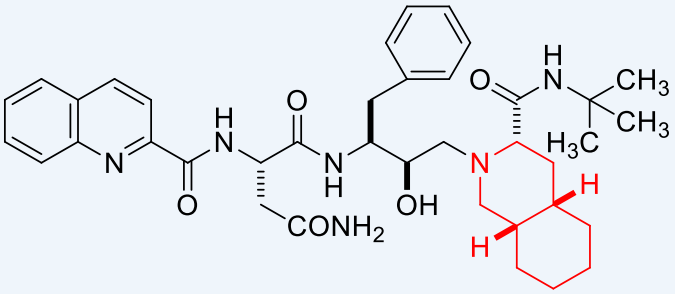


crizotinib (Xalkori, **5**)
Pfizer, 2011
ALK/ROS Inhibitor



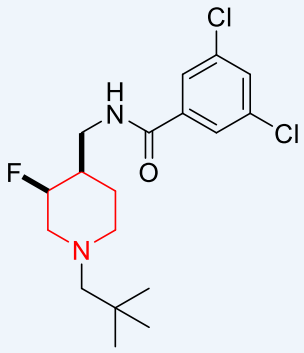
cobimetinib (Cotellic, **6**)
Exelixis/Genentech, 2015
MEK1/2 inhibitor

Many more complicated, substituted piperidine rings also exist in drugs and potential drugs. Merck's HIV protease inhibitor saquinavir (Invirase, **7**) contains a piperidine as part of a bicyclic architecture.

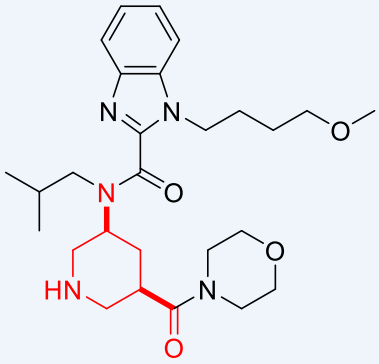


saquinavir (Invirase, **7**)
Merck, 1995
HIV protease inhibitor

While drugs **1**–**7** are marketed drugs, many piperidine-containing drugs are in the discovery or development stages. For example, 3-fluoro-1,4-substituted piperidine **8** is a selective T-type calcium channel inhibitor[1] and 3,5-disubstituted piperidine **9** is an orally active renin inhibitor with an improved pharmacokinetic profile over older ones.[2]



3-fluoro-1,4-substituted piperidine **8**
selective T-type
calcium channel inibitor



3,5-disubstituted piperidine **9**
renin inhibitor

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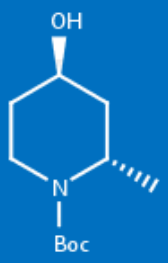

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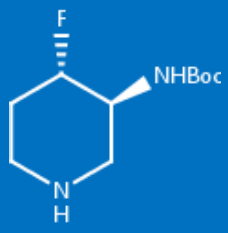

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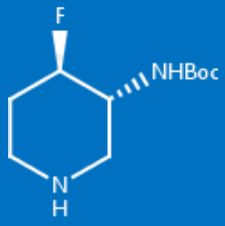

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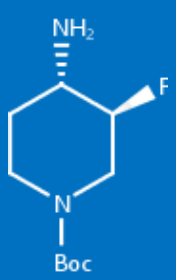

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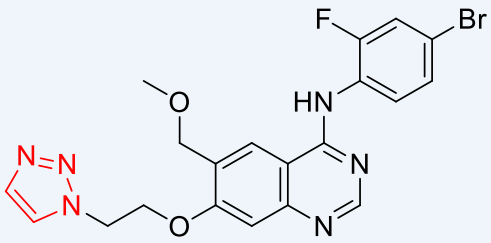
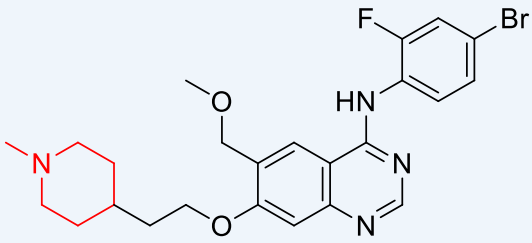
Piperidine improves aqueous solubility of drugs

In addition to being a part of a drug's pharmacophore, piperidines have been used to improve drug's aqueous solubility.

With a p*K*a of 11.22 for piperidine *per se*, *N*-alkylated piperidines have a p*K*a of approximately 9.5. Installation of piperidine rings has been routinely employed to boost drug's aqueous solubility. For instance, 4-aminoquinazoline **10** was a potent kinase insert domain receptor (KDR) inhibitor with a poor solubility. A basic piperidine ring was installed on the side chain to replace the triazole, which resulted in **11** with up to a 500-fold improvement of solubility at pH7.4, the physiological acidity.[3]



10, p*K*a = 5.3
sol, 0.7 μM



11, p*K*a = 9.4, 5.3
sol, 330 μM

Piperidine addresses drug-resistance issues

Pgp (permeability glycoprotein), the most prevalent drug efflux transporter, is often overexpressed in tumor cells and is implicated as a cause of multidrug resistance. Half of the marketed drugs are Pgp substrates. One of the tactics of addressing the Pgp issue is modifying log *P* to reduce penetration into the lipid bilayer where binding to Pgp occurs.

Tetracyclic compound **12** is a chemotherapy plagued with cytotoxic drug resistance as a consequence of being a Pgp substrate.[4] A Mannich reaction of **12** offered the corresponding 3-aminomethyl-piperidine derivative **13**. The maneuver conferred a salient feature to the resulting piperidine compound, namely, the potency for tumor cells otherwise resistant to a variety of anticancer drugs. It is likely that the steric hindrance of bicyclic piperidine **13** minimized the hydrogen bond-donating potential of the adjacent phenol group.

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.

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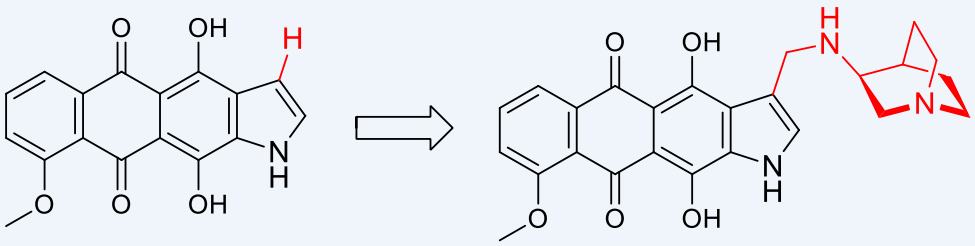
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination,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

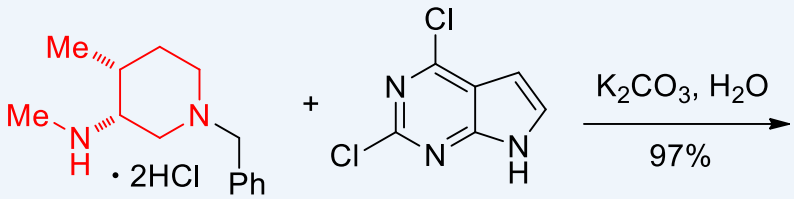


12, Pgp substrate

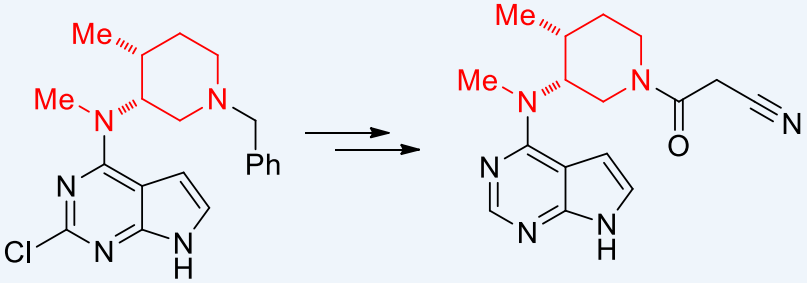
13, **NOT** a Pgp substrate

Synthesis of some piperidine-containing drugs

Pfizer's tofacitinib (Xeljanz, **17**) is the first-in-class Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). One of its syntheses began with tri-substituted piperidine **14**.[5] An S_NAr coupling between **14** and 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **15** produced adduct **16**. Debenzylation and concurrent dechlorination of **16** was followed by amidation using ethyl cyanoacetate to deliver tofacitinib (**17**).[6]



14 **15**



16

tofacitinib (Xeljanz, **17**)
Pfizer, 2012
JAK Inhibitor for RA

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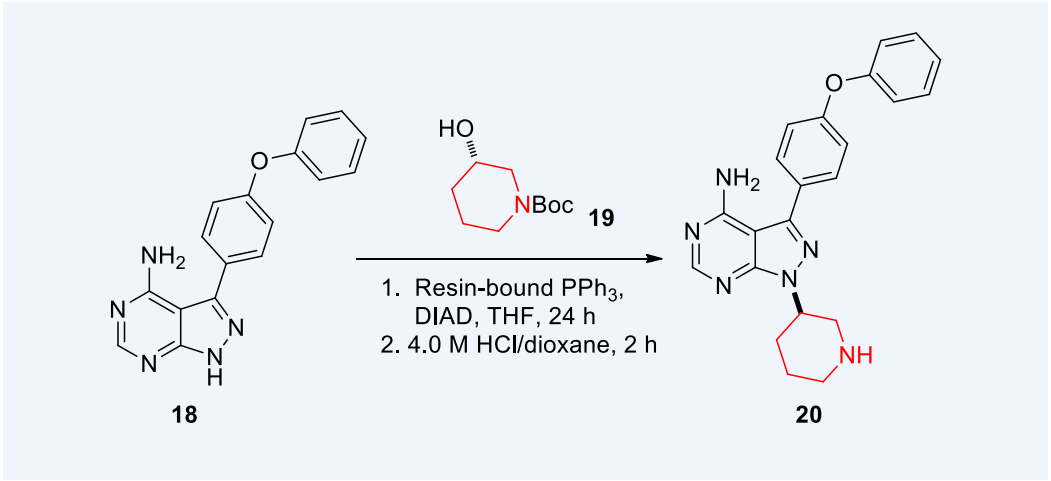
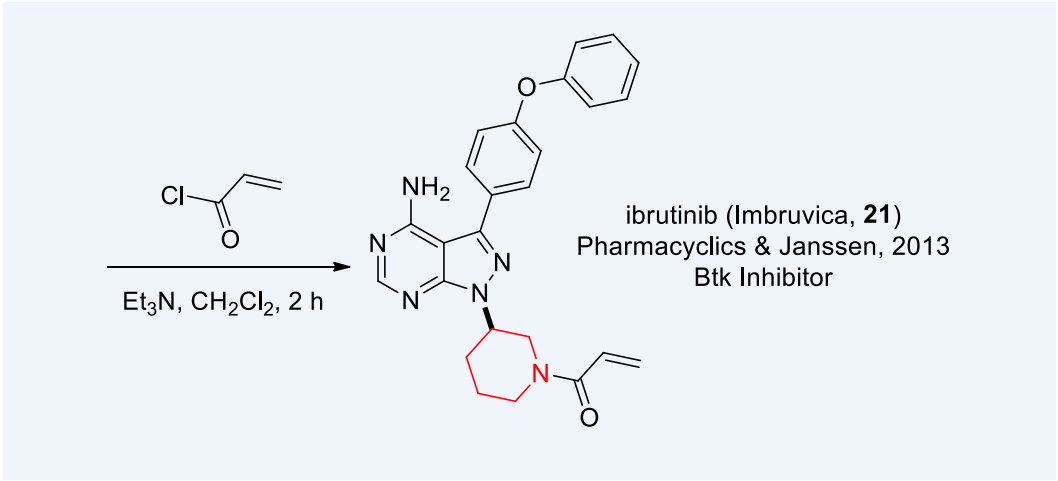
Pharmacyclics' ibrutinib (Imbruvica, **21**) is the first-in-class Bruton's tyrosine kinase (Btk) inhibitor for treating mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom's macroglobulinemia. Inhibition of Btk activity prevents downstream activation of the B-cell receptor (BCR) pathway and subsequently blocks cell growth, proliferation, and survival of malignant B cells. Therefore, Btk inhibitors are good targeted cancer therapies.

One of the syntheses of ibrutinib (**21**) involves a Mitsunobu reaction between 1*H*-pyrazolo[3,4-*d*]pyrimidine **18** and 3-hydroxyl-piperidine **19** to afford adduct **20** after removal of the Boc protection. Reaction between piperidine **20** and acryloyl chloride then assembled ibrutinib (**21**).[7]





Summary

In summary, piperidine is a privileged scaffold. It contributes to pharmacology via tighter binding to the enzymes or the receptors. Its nitrogen atom is responsible to elevate the drug's aqueous solubility. With many exquisitely decorated piperidine-containing building blocks now commercially available, they will find more and more utility in medicinal chemistry.

References

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