Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Cyclopropane in Medicinal Chemistry

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Cyclopropyl ring has been playing versatile roles in drug discovery, as can be seen from approved drug and clinical candidate molecules (**Figure 128**). Important features of the cyclopropyl ring are: 1) coplanarity of the three carbon atoms, 2) relatively shorter C-C bonds, 3) enhanced pi-character of C-C bonds, and 4) C-H bonds are shorter and stronger than those in alkanes. These distinct features confer cyclopropyl ring with great value in molecule design and ability to address multiple critical issues that can occur during drug discovery such as: a) enhancing potency, b) increasing selectivity, c) increasing metabolic stability, d) increasing permeability and BBB-penetration, e) increasing solubility, f) contributing to an entropically more favorable binding to target and g) improve PK profile. Cyclopropyl ring can be exploited either as a substituent, as a chiral bridge, and as a spiro or fused ring (discussed in previous sections) in solving multiple challenges that occurs during the course of drug discovery program. [1]

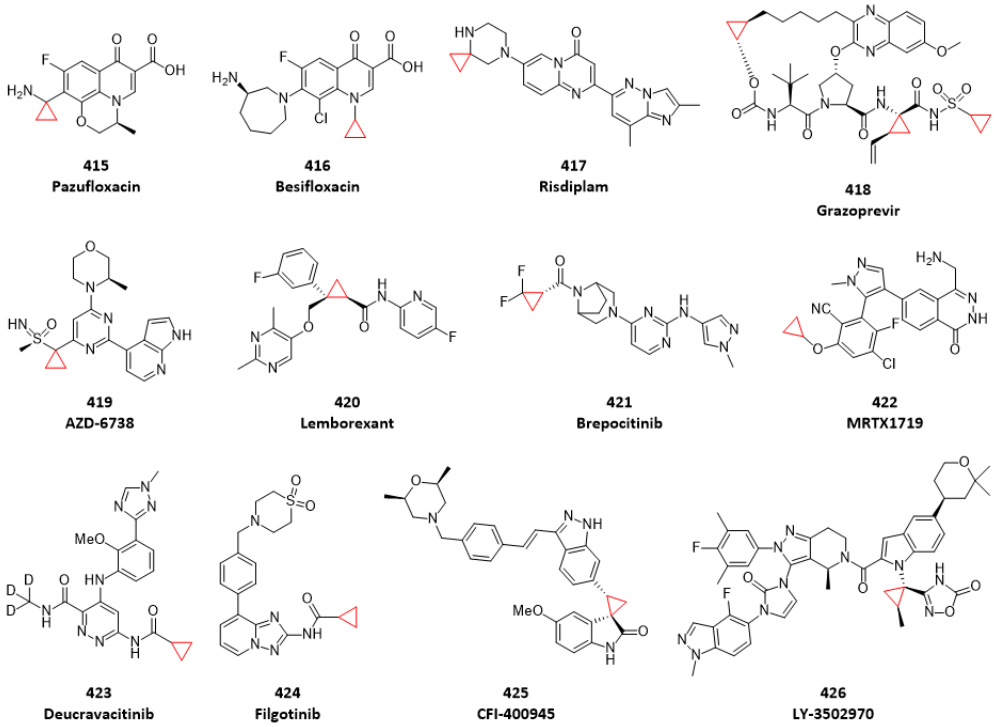


Figure 128. Approved drug and clinical candidate molecules containing cyclopropyl rings

Cyclopropanes and other hydrocarbons containing three-membered rings have a certain sp2 character and gain substantial H-bond acidity which can serve as a hydrogen bond donor. In the course of discovery of **Filgotinib** (compound **424**) as a selective JAK1 inhibitor, compound **429** was identified as a primary hit with modest JAK1 inhibition. Replacement of the cyclopropyl amide moiety showed the importance of this position on the activity. Surprisingly, close amide analogues, such as isopropylamide **428** or acetamide **427** displayed much reduced potency against JAK1. Addition of a methyl group on cyclopropane in compound **429** was also detrimental to JAK1 inhibition. Only the crystal structure of **Filgotinib** (compound **424**) obtained later gave a possible explanation for this SAR observations. It was hypothesized that the superior ability of the cyclopropane ring to donate an H-bond could explain the SAR observations. The crystal structure demonstrates a putative hydrogen bond between the C-H of the cyclopropylamide and the carbonyl

oxygen of Leu932 and of Pro933 (**Figure 129**). This type of interaction has been previously described in the literature. [2-3]

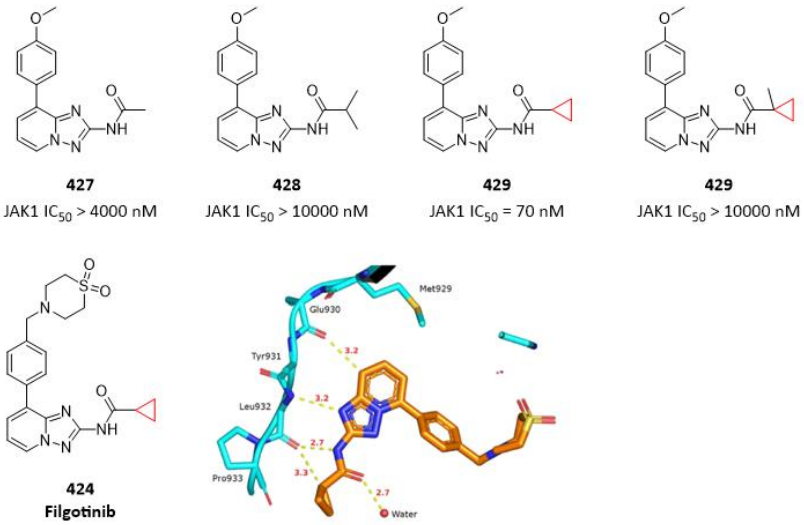


Figure 129. C-H of cyclopropylamide serves as a hydrogen bond donor. (PDB code: 4P7E)

The special ability to serve as a hydrogen bond donor makes cyclopropane-1-carboxylic acid building blocks of great value for molecule design (**Figure 130**).

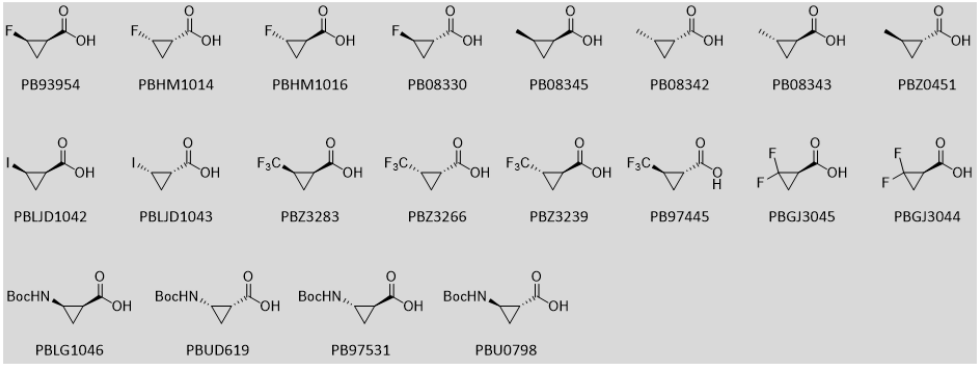


Figure 130. Cyclopropane-1-carboxylic acid building blocks

In the course of discovery of **MRTX1719** (compound **422**) as a synthetic lethal inhibitor of the PRMT5 MTA complex for the treatment of MTAP-deleted cancers, compound **430** was identified from a fragment-based campaign which displayed a modest cellular potency. In order to further increase cellular potency, X-ray crystal structure indicated that there was a small lipophilic pocket sandwiched between Phe300 and Tyr304 around methoxyl group of compound **430**. With this in mind, a variety of small, lipophilic substituents on oxygen were examined. Among of them, cyclopropane ring in compound **431** demonstrated increased cellular potency by 7-fold. Further optimization based on compound **431** aiming to increase cellular potency and improve ADMET profile led to identification of **MRTX1719** (compound **422**). The X-ray crystal structure of **MRTX1719** (compound **422**) bound to PRMT5 MTA demonstrated that cyclopropane ring occupied the small lipophilic pocket sandwiched between Phe300 and Tyr304 (**Figure 131**). [4]

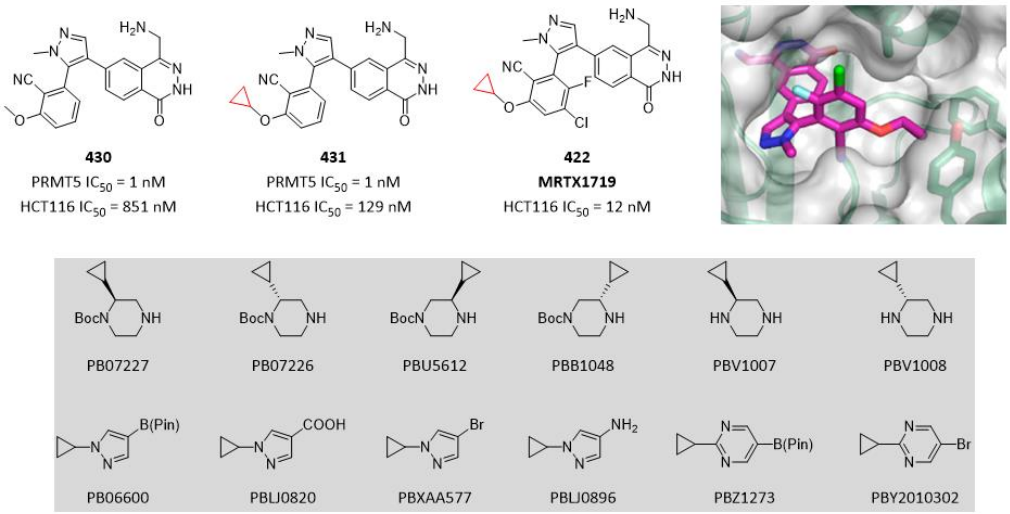


Figure 131. Cyclopropane ring increased potency by occupying a small lipophilic pocket. (PDB code: 7S1S)

Compound **432** was discovery by a fragment-based drug discovery (FBDD) campaign, which was a potent PDE10 inhibitor. The team sought to functionalize selected positions in the aliphatic chain with the goal of blocking possible sites of metabolism. It was soon realized that significant improvements by incorporation of cyclopropane constraint in compound **433** and compound **434**. While the potency of *cis*-cyclopropane linker in compound **433** was compromised relative to compounds with more flexible linkers, the corresponding *trans*-cyclopropane linker in compound **434** provided a dramatic improvement in potency (> 10-fold). Further optimization of compound **434** led to discovery of compound **435** with more promising ADMET and PK profiles which was advanced to *in vivo* study (**Figure 132**). [5]

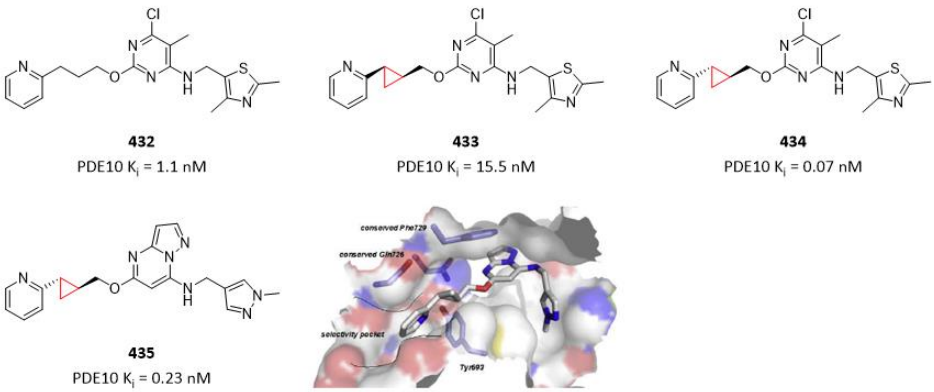


Figure 132. Cyclopropane linker increased potency by locking conformation. (PDE code: 5DH5)

In the course of discovery of clinical candidate **CFI-400945** (compound **425**) as a PLK4 selective inhibitor, compound **436** was identified as a promising hit. In order to lock the molecule into a stable configuration, it was computationally to predict whether compound activity would be retained upon replacing the *E*-alkene in compound **436** with the *trans*-cyclopropane in compound **437**. PLK4 docking predicted retention of activity for this bioisostere replacement. It can be seen that the *E*-form of compound **436** and *1R,2S* stereoisomer **437** have nearly identical topology and similar binding poses. It was equally pleasing to see that compound **437** was active against PLK4 and performed favorably with respect to compound **436** in terms of selectivity toward FLT3 and KDR. Furthermore, it was found that the cyclopropane modification imparts improved aqueous solubility. This improvement is attributed to the nature of the cyclopropane ring, being orthogonal to the

plane of the indolinone, it serves to counter crystal packing forces. Compound **437** also demonstrated desirable ADMET properties, which included an improved profile for CYP isomers, and better microsome stability. More significantly, compound **437** achieved up to 100-fold higher level of exposure in mouse plasma. Further optimization led to discovery of compound **438** and clinical candidate **CFI-400945** (compound **425**) (**Figure 133**). [6]

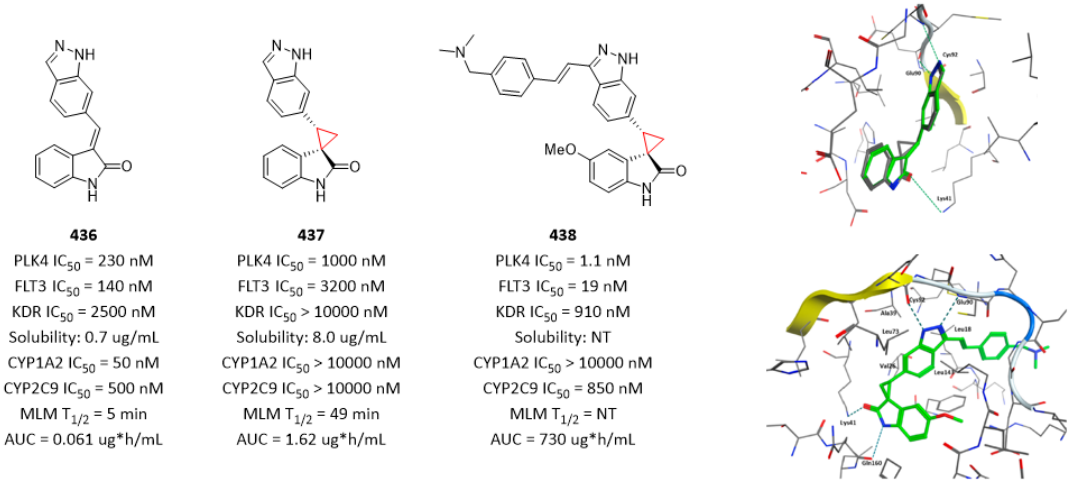


Figure 133. Cyclopropane addressed selectivity and ADMET profile issues. (PDB code: 4JXF)

From above two case stories, 2-phenylcyclopropane building blocks are of great value as bioisosteres of styrene, potentially addressing critical issues associated with styrene (**Figure 134**).

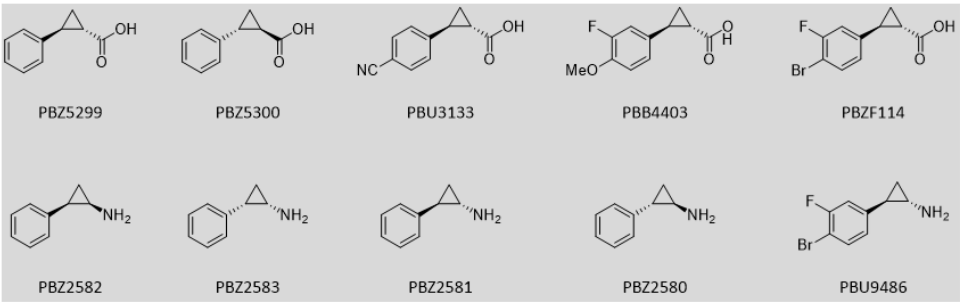


Figure 134. 2-Phenylcyclopropane building blocks as bioisosteres of styrene

Guided by the model, the prime side SAR was further explored by introducing structural features designed to more effectively complement the uniquely defined S1' subsite. Most immediately, the cyclopropylacylsulfonamide compound **441** was evaluated and this compound inhibited HCV NS3/4A activity with IC_{50} of 1 nM, which is 30-fold potent than compound **439**. Close analogues were significantly less active, with ethylacylsulfonamide compound **440** showing 6-fold reduced activity, isopropylacylsulfonamide compound **442** showing 19-fold reduced activity, and cyclobutylacylsulfonamide compound **443** showing 7-fold reduced activity. It can be concluded that this specific aliphatic binding element was critical to activity while also sensitive to small structural modification. These prime side SAR were rationalized using a plot of the van der Waals surface of the protein which highlights the shallow cavity within the S1' site that is defined by Gln41, Phe43, Val55 and Gly58. An assessment of the optimized geometries of the sulfonamide caps suggested that the cyclopropane exhibited a shape most complementary with the S1' pocket, thus maximizing van der Waals surface contact and explaining the potency of compound **441** (**Figure 135**). [7]

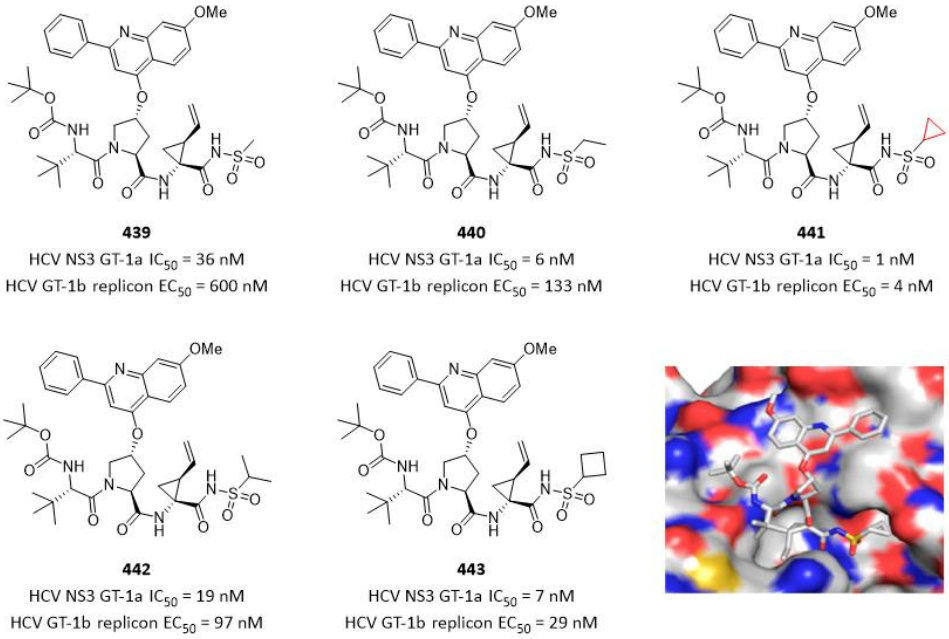


Figure 135. Cyclopropane increased anti-HCV potency by occupying a small hydrophobic pocket.

In the lead optimization course of small-molecule IL-17 inhibitors, although compound **444** gave the best potency, it came with significant metabolic instability in human live microsome. In contrast, biscyclopropylalanine compound **445** was stable in human liver microsome even with the increased lipophilicity. The X-ray crystal structure of compound **445** bound to IL-17 revealed that the biscyclopropyl moiety makes hydrophobic contacts with Tyr85, Leu120, Leu122, and Leu135 of subunit B (**Figure 136**). [8]

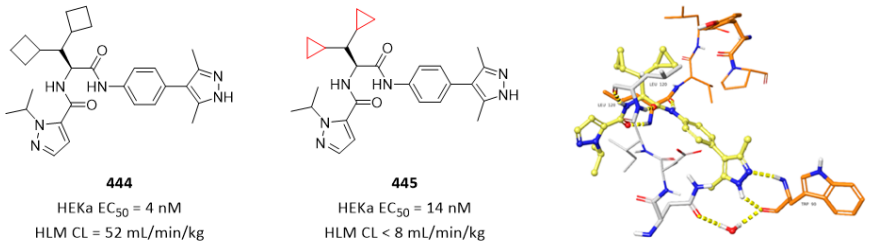
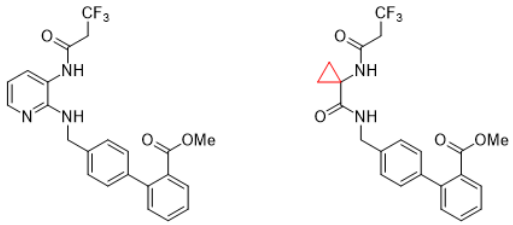


Figure 136. Cyclopropane increased metabolic stability in human liver microsome. (PDB code: 7AMA)

Further development of compound **446** was hampered by realization that this scaffold formed reactive metabolites. To overcome this metabolic liability, the team discovered that the problematic diaminopyridine scaffold could be efficiently replaced with a cyclopropylamino acid moiety. The design concept yielded compound **447** with an improved PK profile (**Figure 137**). [9]



446
hBK1 K_i = 12 nM
$T_{1/2}$ = 0.2 h
CL = 35 mL/min/kg
F: 9%

447
hBK1 K_i = 63 nM
$T_{1/2}$ = 9.5 h
CL = 9.3 mL/min/kg
F: 26%

Figure 137. Cyclopropylamino acid amide as a bioisostere of 2,3-diaminopyridine

References

[1] Tanaji T. Talele. The “cyclopropyl fragment” is a versatile player that frequently appears in preclinical/clinical drug molecules. *J. Med. Chem.* **2016**, *59*, 8712-8756.
[2] Ibon Alkorta; *et al.* Ring strain and hydrogen bond acidity. *J. Org. Chem.* **1998**, *63*, 7759-7763.
[3] Christel J. Menet; *et al.* Triazolopyridines as selective JAK1 inhibitors: from hit identification to GLP0634. *J. Med. Chem.* **2014**, *57*, 9323-9342.
[4] Christopher R. Smith; *et al.* Fragment-based discovery of MRTX1719, a synthetic lethal inhibitor of the PRMT5 MTA complex for the treatment of MTAP-deleted cancers. *J. Med. Chem.* **2022**, *65*, 1749-1766.
[5] Izzat T. Raheem; *et al.* Discovery of pyrazolopyrimidine phosphodiesterase 10A inhibitors for the treatment of schizophrenia. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 126-132.
[6] Peter B. Sampson; *et al.* The discovery of Polo-like kinase 4 inhibitors: design and optimization of spiro[cyclopropane-1,3’[3H]indol]-2’(1’H)-ones as orally bioavailable antitumor agents. *J. Med. Chem.* **2015**, *58*, 130-146.
[7] Paul M. Scola; *et al.* Discovery and early clinical evaluation of BMS-605339, a potent and orally efficacious tripeptidic acylsulfonamide NS3 protease inhibitor for the treatment of hepatitis C virus infection. *J. Med. Chem.* **2014**, *57*, 1708-1729.
[8] Mark D. Andrews; *et al.* Discovery of an oral, rule of 5 compliant, interleukin 17A protein-protein interaction modulator for the potential treatment of psoriasis and other inflammatory diseases. *J. Med. Chem.* **2022**, *65*, 8828-8842.
[9] Michael R. Wood; *et al.* Cyclopropylamino acid amide as a pharmacophoric replacement for 2,3-diaminopyridine. Application to the design of novel bradykinin B1 receptor antagonists. *J. Med. Chem.* **2006**, *49*, 1231-1234.

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