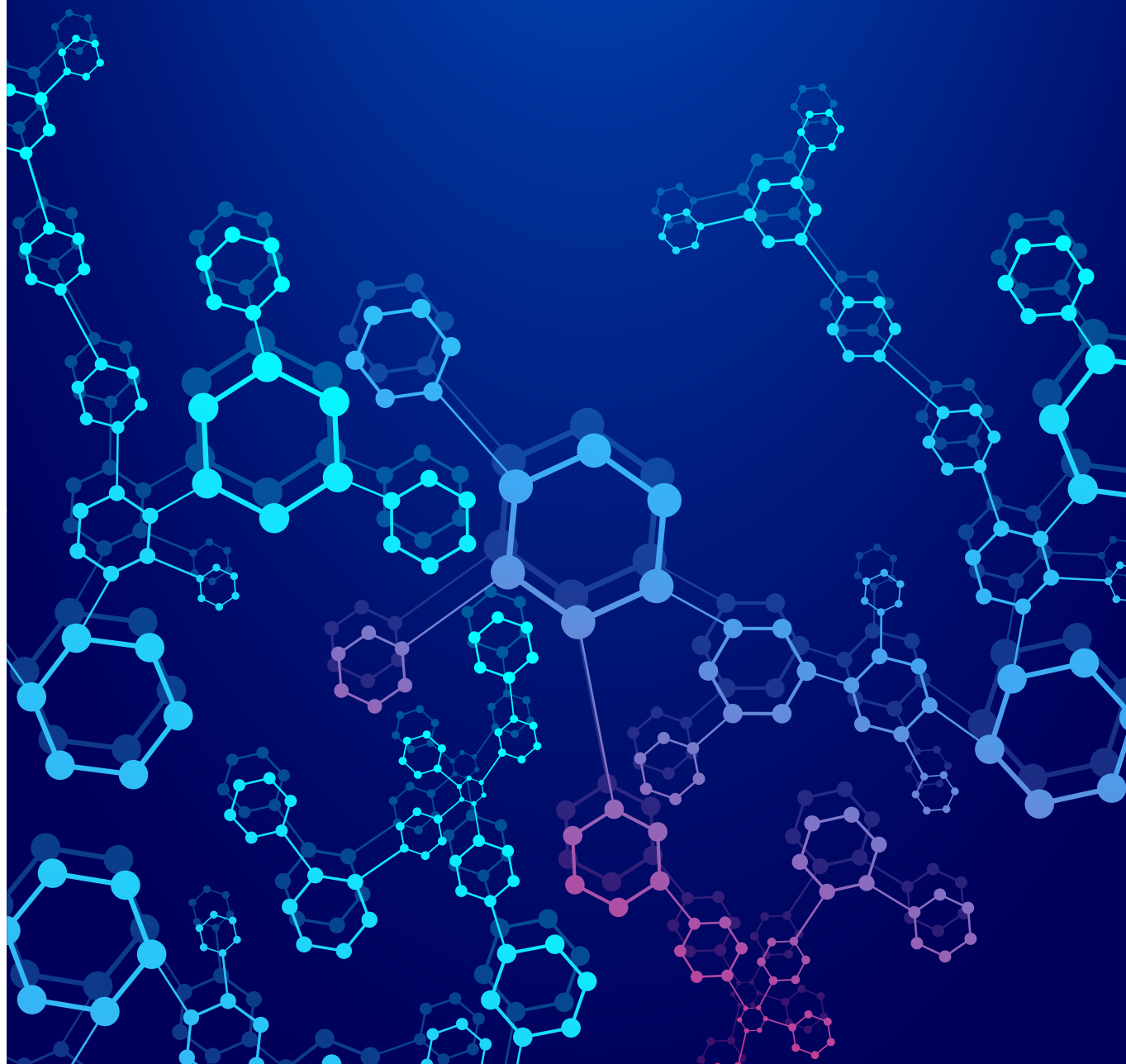


Application of Cyclopropane in Drug Discovery

Jan 2023



Introduction

Cyclopropane is a highly strained three-membered carbocyclic ring which has unique physio-chemical properties and structural characteristics, such as (1) coplanarity of the three carbon atoms, (2) relatively shorter (1.51 Å) C–C bonds, (3) enhanced π -character of C–C bonds, and (4) C–H bonds are shorter and stronger than those in alkanes.^[1] Because of those attractive characteristics, cyclopropane is widely used in small-molecule drugs (**Figure 1**) to enhance the potency (**Figure 2**), to improve the metabolic stability (**Figure 3**), to reduce the efflux ratio (**Figure 4**), to increase the solubility (**Figure 5**), and to increase the oral bioavailability (**Figure 6**).^[1] In recent years, cyclopropane has been routinely used in the discovery of small molecule drug candidates, partly due to advances in synthetic cyclopropane chemistry that allow facile and practical introduction of cyclopropane in target molecules.

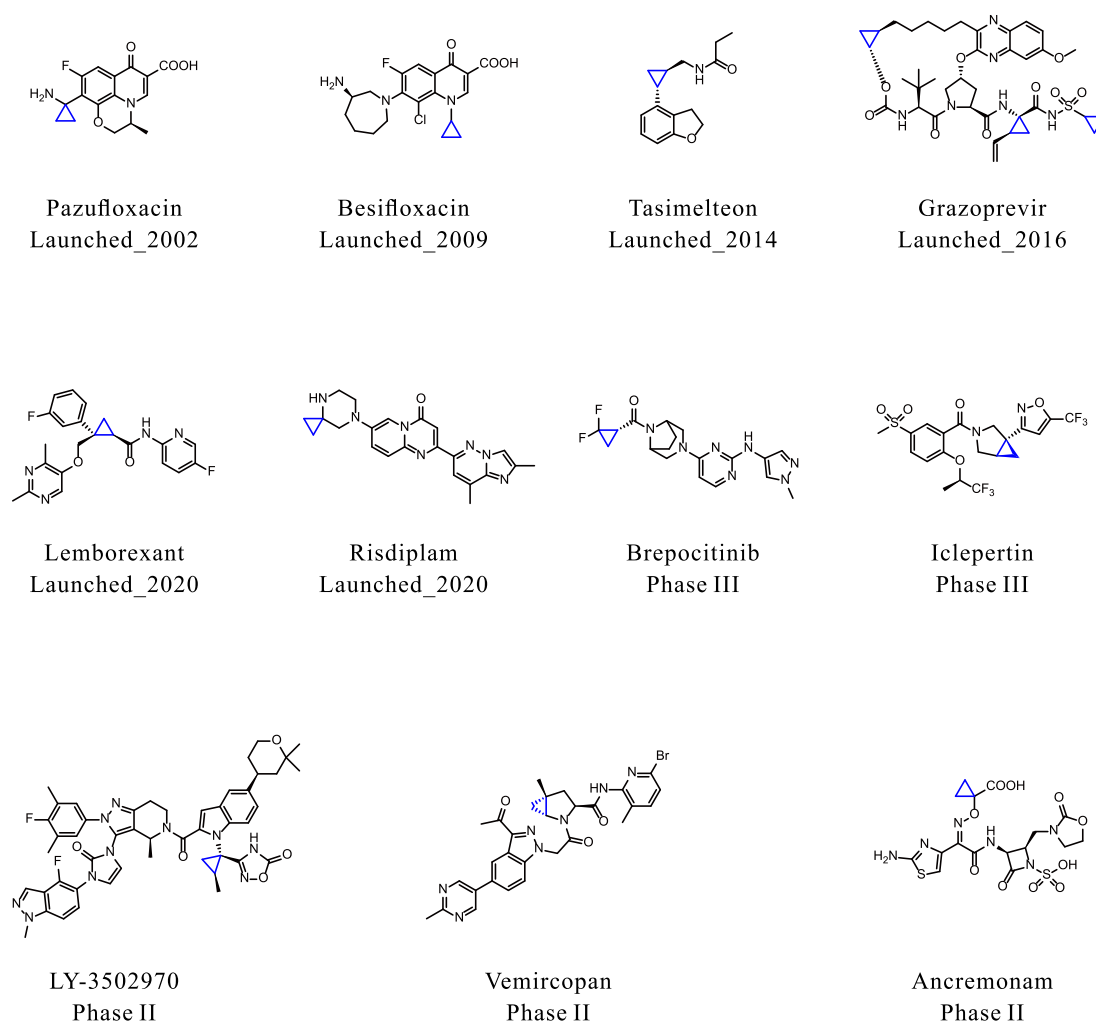


Figure 1. Approved drugs and (pre-) clinical candidates containing cyclopropyl group



Figure 2. Cyclopropane can enhance the potency



Figure 3. Cyclopropane can improve the Metabolic Stability

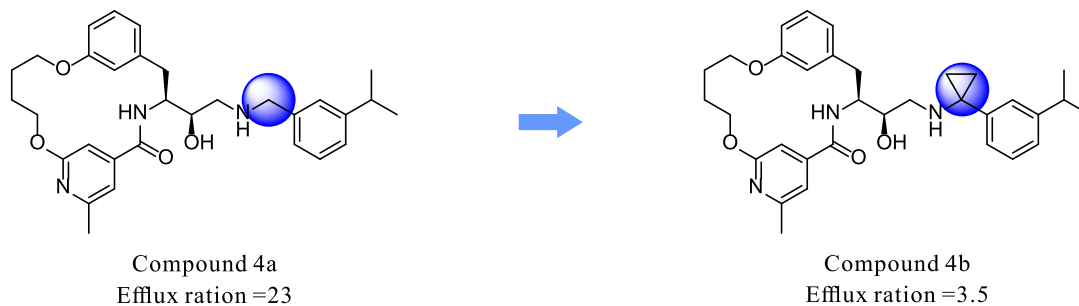


Figure 4. Cyclopropane can reduce the efflux ratio

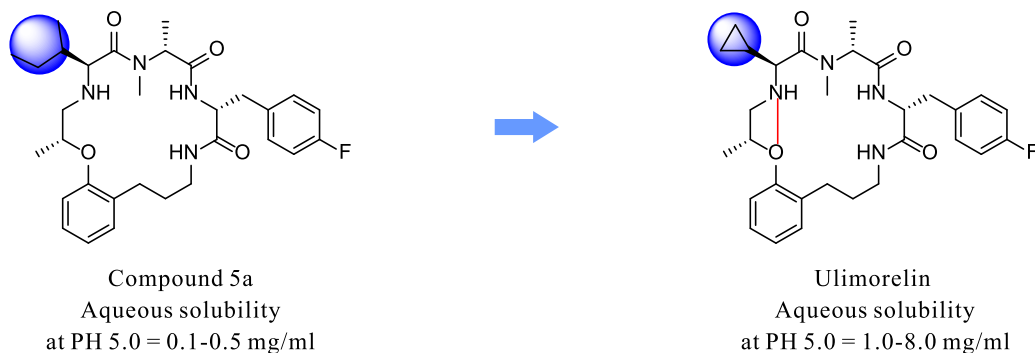


Figure 5. Cyclopropane can increase the solubility

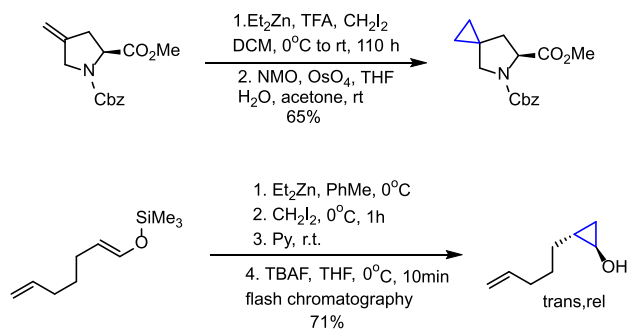


Figure 6. Cyclopropane can increase the oral bioavailability

Cyclopropane Chemistry Developed at PharmaBlock

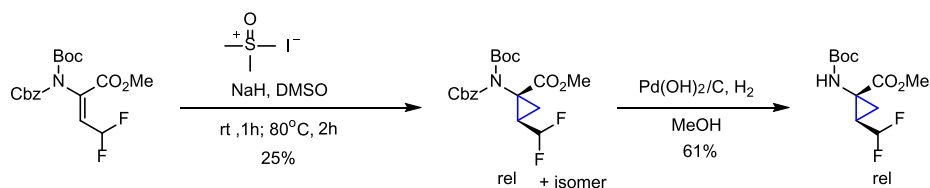
Chemists at PharmaBlock have been applying versatile cyclopropane chemistry to synthesize novel building blocks containing cyclopropane and keep optimizing the process for large scale manufacturing of cyclopropane-containing products.

1) Cyclopropanation via Simmons-Smith reaction^[2]

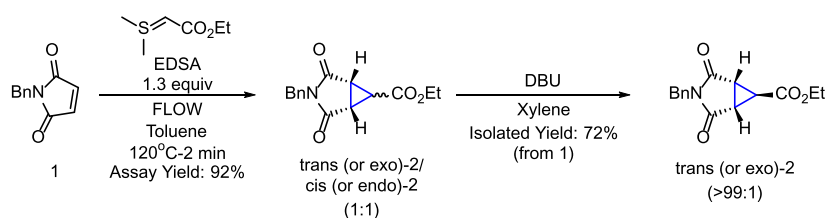


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2) Cyclopropanation via Johnson-Corey-Chaykovsky Reaction^{[3][4]}

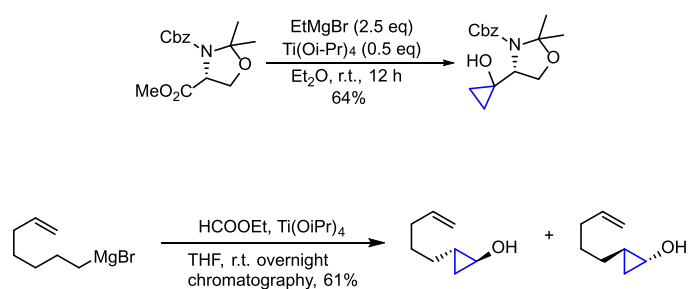


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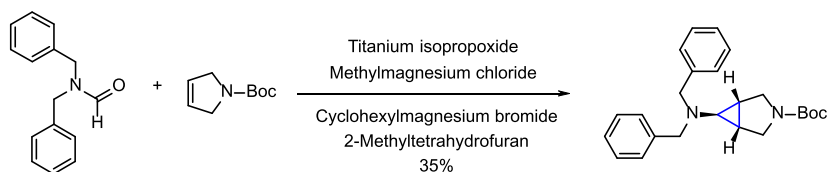


Organic Process Research & Development, 2014, 18(11), 1527-1534

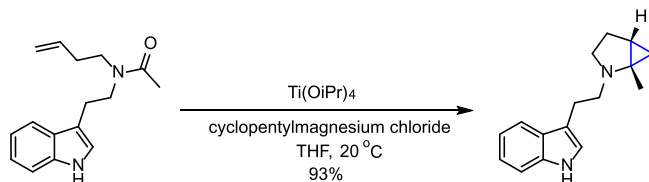
3) Cyclopropanation via Kulinkovich Reaction^[5]



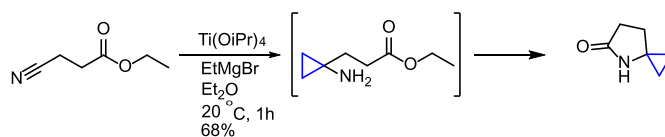
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4) Cyclopropanation via Kulinkovich-De Meijere reaction^{[6][7][8]}


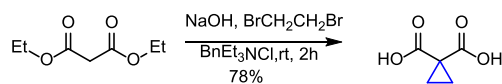
Organic Process Research & Development, **2018**, 22(6), 728-735



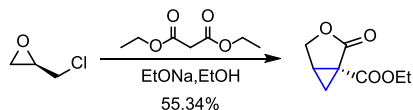
European Journal of Organic Chemistry, **2004**, #16, p. 3517 - 3525



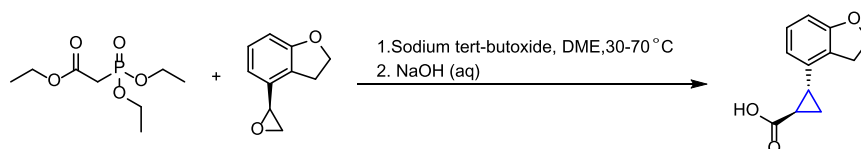
Synlett, **2003**, # 2, p. 265 - 267

 5) Cyclopropanation via Nucleophilic disubstitution^{[9][10][11]}


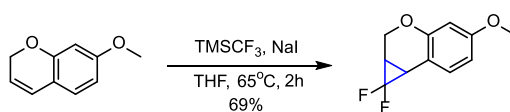
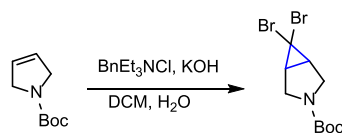
Organic Letters, **2019**, 21(4), 890-894



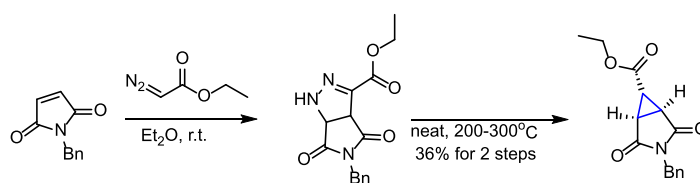
Organic Letters **2022**, 24(23), 4151-4154

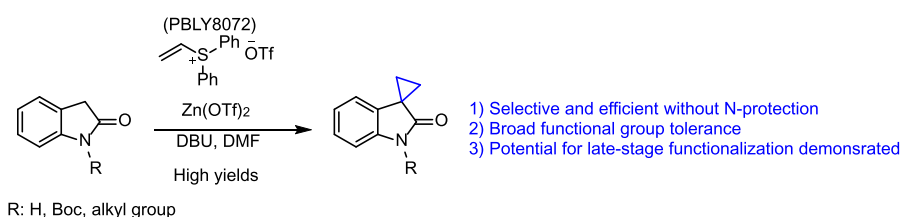


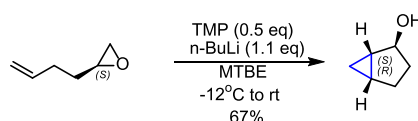
Organic Process Research & Development **2002**, 6, 618-620

6) Cyclopropanation of Olefins with Dihalocarbene^{[12][13][14]}

 Organic Letters **2020**, 22(21), 8681-8686

 Organic Letters **2018**, 20(10), 2867-2871

 Chemistry - A European Journal **2018**, 24(6), 1455-1458

 7) Cyclopropanation of Diazane and Olefins^[15]

 Bioorganic & Medicinal Chemistry Letters, **2008**, 18(20), 5493-5496

 8) Zinc triflate-mediated cyclopropanation of oxindoles with vinyl diphenyl sulfonium triflate: a mild reaction with broad functional group compatibility^[16]

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 9) Intramolecular cyclopropanation of alkene and epoxy functional groups^[17]

 ACS Medicinal Chemistry Letters, **2017**, 8(12), 1309-1313

Building Blocks Containing Cyclopropane

PharmaBlock has conducted a systematic study on marketed, clinical and preclinical drug structures containing cyclopropane, our chemists constantly monitor the latest researches to design and synthesize new building blocks containing cyclopropane that can be used to explore structure-activity relationship (SAR) and structure-property relationship (SPR). We offer >5,000 unique building blocks containing cyclopropane from gram to kilogram scale with most of them in stock (**Figure 7**).

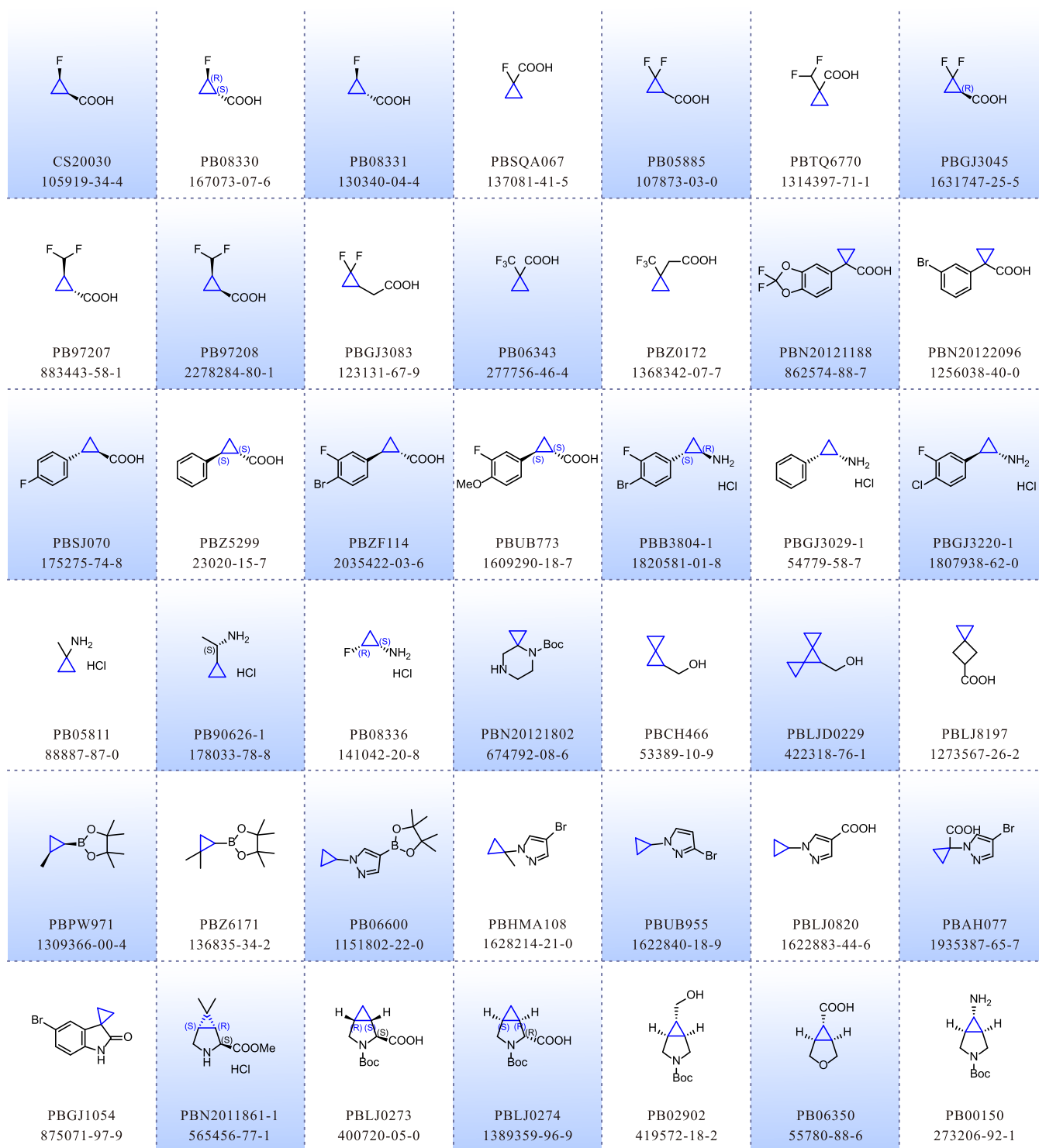
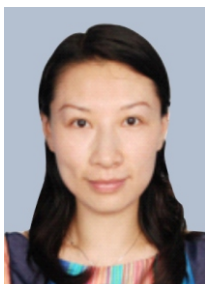


Figure 7. Representative building blocks containing cyclopropyl group at PharmaBlock

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