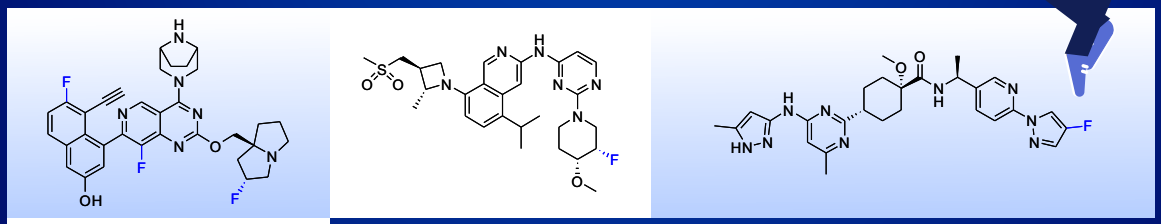
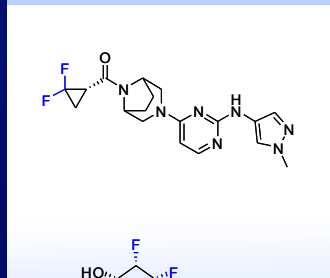
PharmaBlock

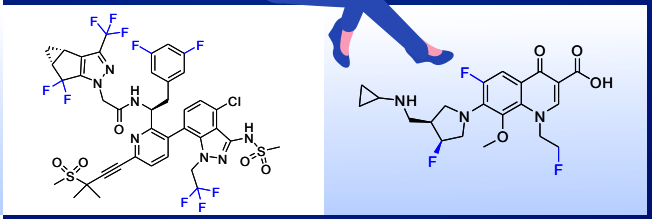
SCIENTIFIC INSIGHTS

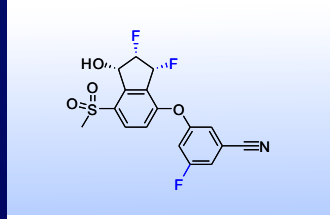
Application of Fluorine in Drug Discovery

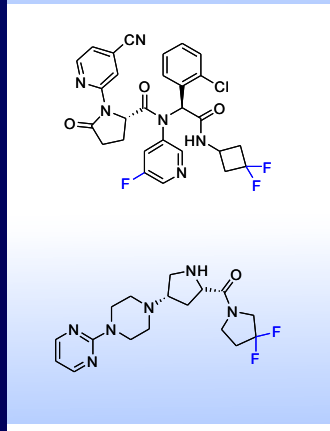
Sept 2022











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Introduction

Fluorine atom is widely present in approved small-molecule drugs (**Figure 1**). In recent years, fluorine substitution has been routinely used in the discovery of small molecule drug candidates, partly due to advances in synthetic fluorine chemistry that allow facile and practical introduction of fluorine atoms in target molecules. Moreover, the simple substitution of a hydrogen atom with a fluorine atom can result in tremendous improvements on potency and pharmacokinetic properties[1-10].

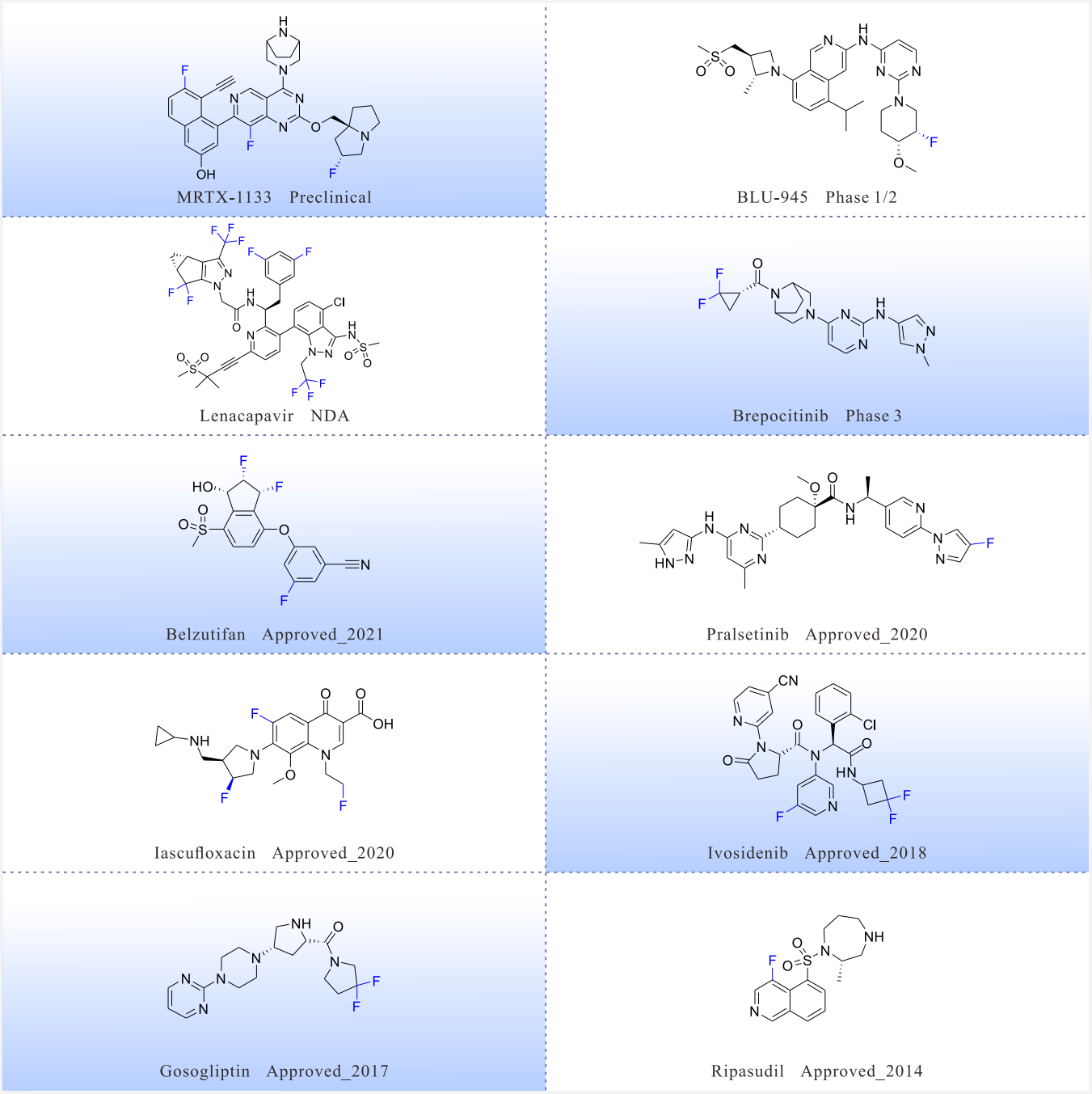
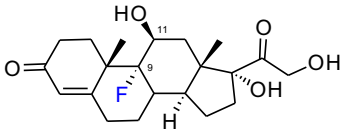
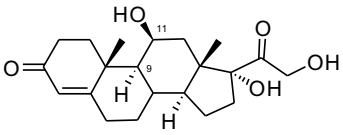


Figure 1. Approved drugs and (pre-) clinical candidates containing fluorine

Fluorine-containing drugs were erroneously conceived as being toxic in the past. Since FDA in 1955 approved the first fluorine-containing drug, Florinef (**Figure 2a**), a fluorinated cortisol (**Figure 2b**), more and more approved drugs and (pre-) clinical candidates involve fluorine atoms in their structures[11].



2a Florinef

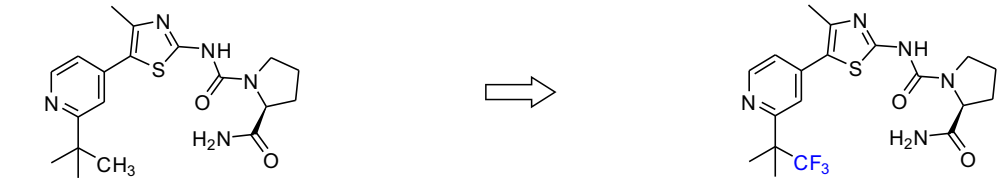


2b Cortisol

Figure 2. Florinef and Cortisol

The fluorine effect can be profound and magic (**Figure 3**) in terms of molecule properties. It can improve potency, block metabolic soft spots and decrease clearance (**Figure 4**), reduce pK_a (**Figure 5**), boost permeability, and impact aqueous solubility[1]. Thus, fluorine is more and more widely deployed by medicinal chemists in the drug design because of its unique properties.

Figure 3. Magic Fluorine in Drug Design[1]



RLM clearance, 77 μL/min/mg
rat clearance *in vivo*, 39 μL/min/kg

29 μL/min/mg
10 μL/min/mg

Figure 4. Fluorine can reduce clearance

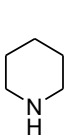
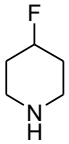
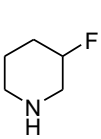
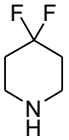
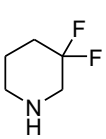
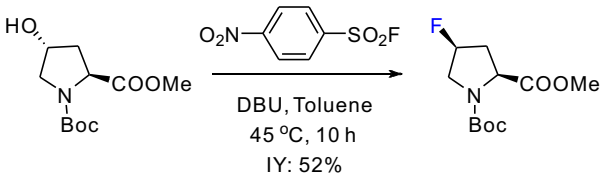
						
Predicted pK_a	σ-bond path 1 σ-bond path 2 Δ pK_a		γ-F=-0.7 γ-F=-0.7 -1.4	β-F=-1.7 δ-F=-0.3 -2.0	γ-F=-1.4 γ-F=-1.4 -2.8	β-F=-3.4 δ-F=-0.6 -4.0
Observed pK_a	pK_a Δ pK_a	11.1	9.4 -1.7	9.3 -1.8	8.5 -2.6	7.4 -3.7

Figure 5. Fluorine can reduce pK_a

Fluorine Chemistry

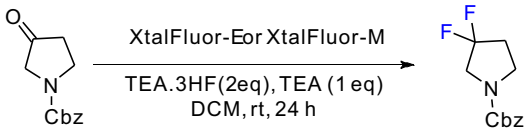
Chemists at PharmaBlock have been using versatile fluorine chemistry to synthesize novel fluorinated building blocks and keep optimizing the process for large scale manufacturing of fluorine-containing products.

1) Deoxyfluorination of alcohol:



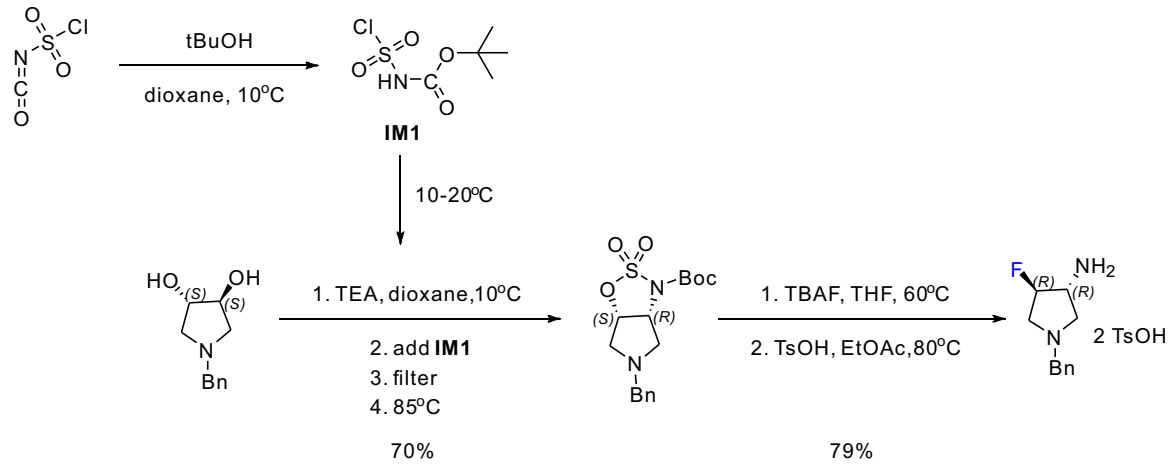
Ref. Large-Scale Practical Synthesis of Boc-Protected 4-Fluoro-l-Proline *Org. Process Res. Dev.* **2020**, *24*, 1609-1613

2) Deoxyfluorination of ketone:



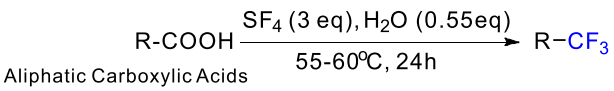
Ref. Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling *J. Org. Chem.* **2010**, *75*, 3401-3411

3) Fluorination of Sulfonate:

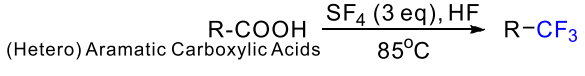


Ref. Enantiospecific Synthesis of (3R,4R)-1-benzyl-4-fluoropyrrolidin-3-amine Utilizing a Burgess-type Transformation *Org. Process Res. Dev.* **2019**, *23*, 1970-1978

4) Deoxyfluorination of carboxylic acid:

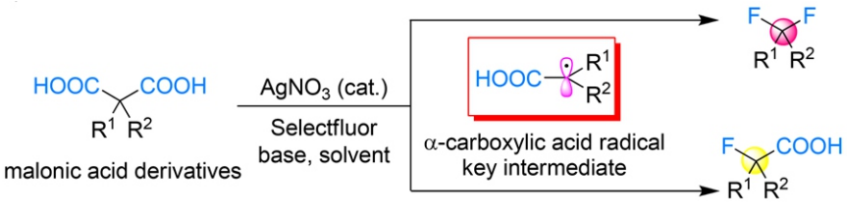


Ref. Deoxofluorination of Aliphatic Carboxylic Acids: a Route to Trifluoromethyl-Substituted Derivatives *J. Org. Chem.* **2019**, *84*, 16105-16115



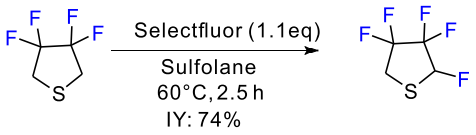
Ref. Deoxofluorination of (Hetero) aromatic Acids *J. Org. Chem.* **2020**, *85*, 3110-3124

5) Decarboxylative fluorination:



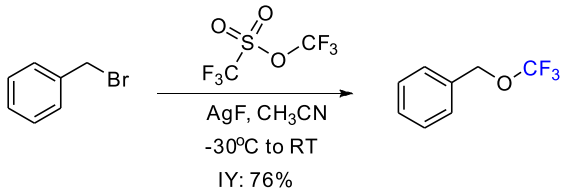
Ref. Ag-Catalyzed Chemoselective Decarboxylative Mono-and gem-Difluorination of Malonic Acid Derivatives
J. Am. Chem. Soc. **2019**, *141*, 5617-5622

6) Fluorination of thioethers:



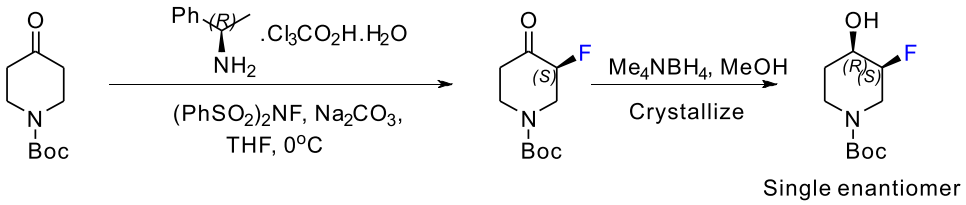
Ref. Tetrafluorothiophene S,S-Dioxide: A Perfluorinated Building Block *J. Org. Chem.* **2013**, *78*, 12330-12337

7) Trifluoromethoxylation of active halides:



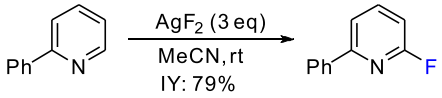
Ref. A deeper insight into direct trifluoromethoxylation with trifluoromethyl triflate *J. Fluorine Chem.* **2010**, *131*, 200-207

8) Enantioselective Alpha Fluorination of Ketones:



Ref. Enantioselective Synthesis of cis-3-Fluoropiperidin-4-ol, a Building Block for Medicinal Chemistry *J. Org. Chem.* **2013**, *78*, 8892-8897

9) Fluorination of Pyridines and Diazines:



Ref. Site-Selective C-H Fluorination of Pyridines and Diazines with AgF_2 *Org. Synth.* **2017**, *94*, 46-53

Building Blocks Containing Fluorine

PharmaBlock has conducted a systematic study on marketed, clinical and preclinical drug structures containing fluorine, our chemists constantly monitor the latest researches to design and synthesize new fluorinated building blocks that can be used to explore structure-activity relationship (SAR) and structure-property relationship (SPR). We offer >5,000 unique fluorinated building blocks from gram to kilogram scale with most of them in stock (**Figure 6**).

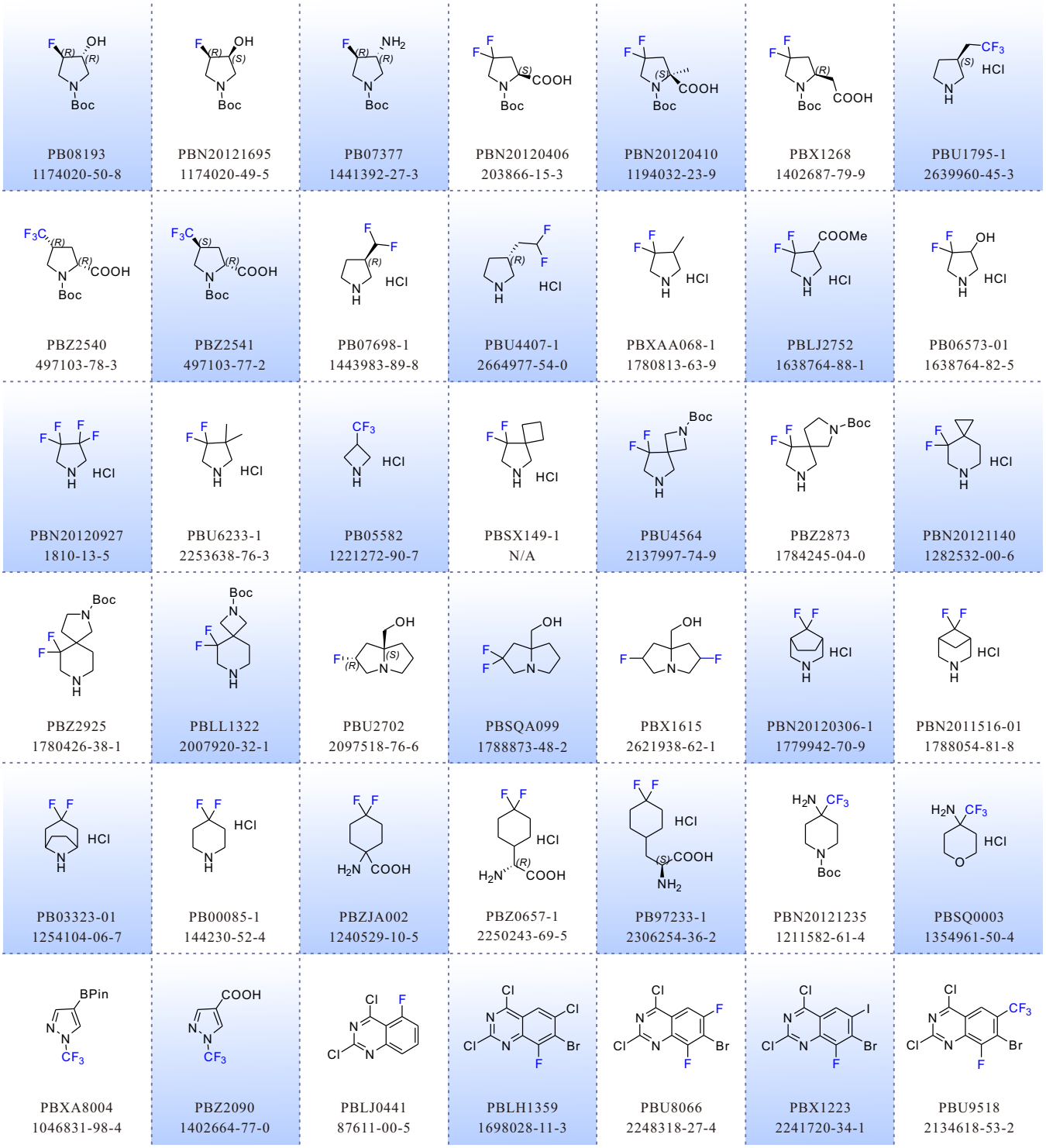


Figure 6. Representative fluorinated building blocks at PharmaBlock

Fluorine-containing Fragment Library

Fluorine gains popularity in drug discovery as it accounts for ~50% of blockbuster drugs. In addition, F^{19} NMR becomes a powerful screening tool especially in fragment based drug discovery (FBDD) due to the unique properties of F^{19} such as 100% natural abundance, zero background in native proteins/nucleic acids, large chemical shift range and sensitivity to the chemical environment. Inspired by this powerful discovery technology, Pharmablock has built a collection of >700 fluorine containing fragments that fits rule of three and other selection criteria (some representative structures shown in **Figure 7**). Moreover, we keep expanding our collections by regularly adding novel fragments into our inventory.

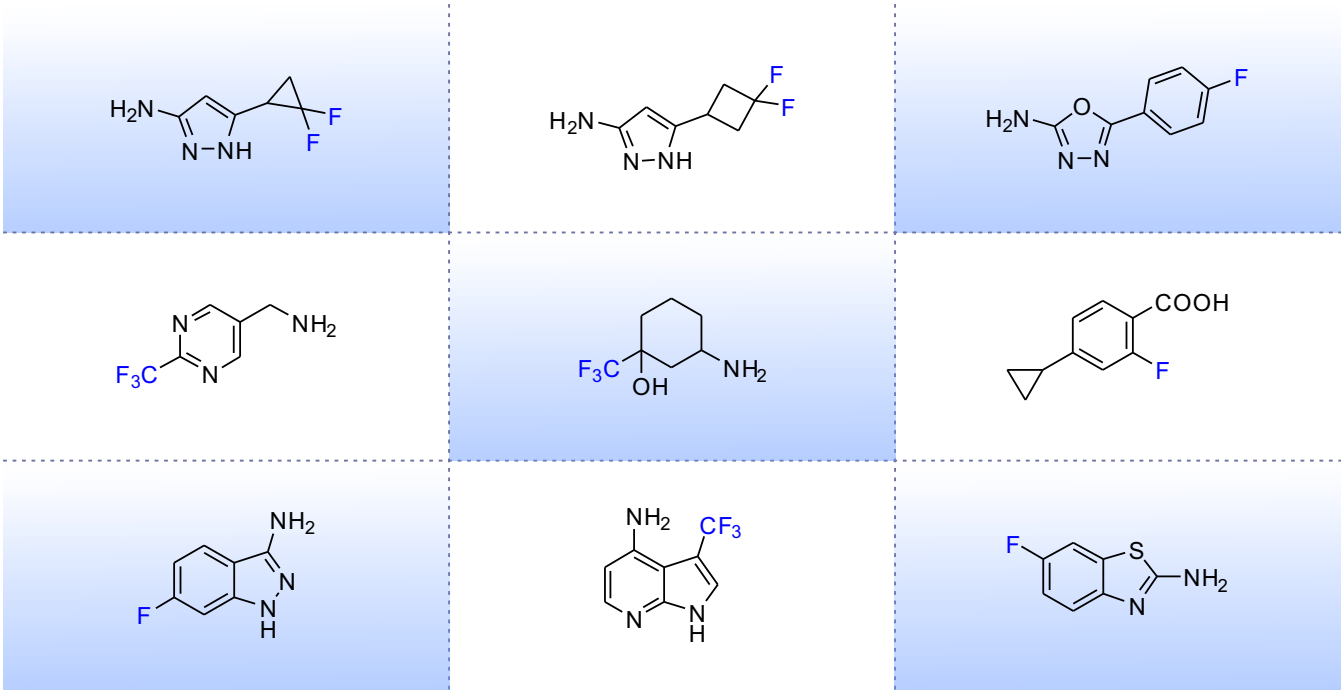


Figure 7. Representative fragments at PharmaBlock

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[7] Dual inhibition of TYK2 and JAK1 for the treatment of autoimmune diseases: discovery of PF-06700841. Andrew Fensome *et al. J. Med. Chem.* **2018**, *61,* 8597-8612.
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[11] Biological utility of fluorinated compounds: from materials design to molecular imaging, therapeutics and environmental remediation. Cheng Zhang *et al. Chemical Reviews* **2022**, *122* (1) , 167-208.

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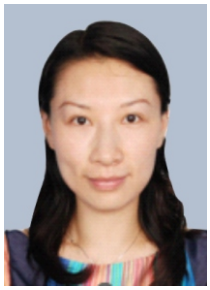

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