Halogen Bond in Medicinal Chemistry

Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Fluorine in Medicinal Chemistry

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Fluorine atom has been playing a prominent role in drug discovery, and the applications of fluorine atom in the design of drug and agricultural chemicals are continuing to grow as our knowledge and understanding of how to take full advantage of the unique properties. This has been facilitated by the development of innovative synthetic methodology which providing access to new **fluorinated building blocks**. While early applications of fluorine as a bioisostere focused on the relatively simple replacement of hydrogen atoms in drug molecules, often as a means of influencing metabolism, the last 30 years has been broader deployment of fluorine and fluorinated building blocks in the construction of more sophisticated structural arrangements that are able to emulate and influence a number of more traditional functionalities (**Figure 41**). [1-2]

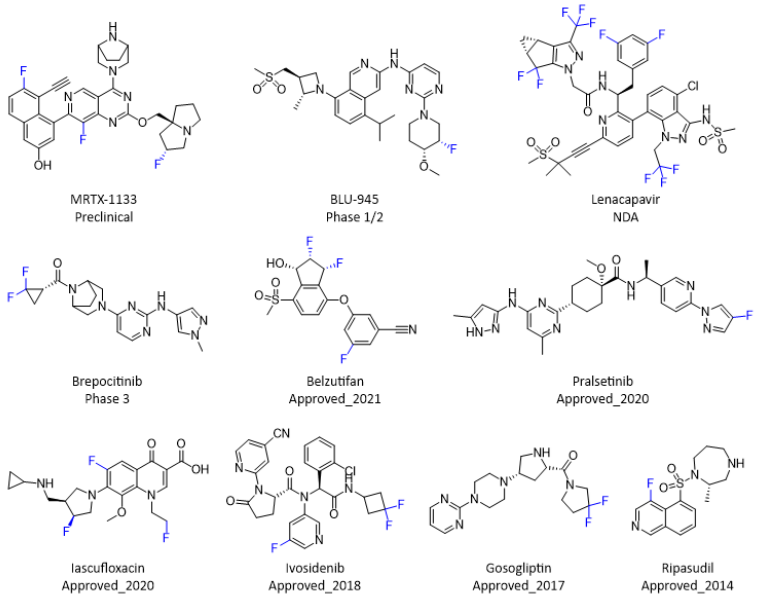


Figure 41. Representative fluorine-containing drug and clinical candidate molecules

Fluorine atom can exert plenty of positive influences on molecules, including increasing potency by forming a critical interaction with the protein, increasing solubility by forming an intramolecular hydrogen bond, reducing hERG inhibition by modulating basicity of nitrogen atom, and reducing metabolism by blocking metabolic sites.

In a series of potent inhibitors of BTK, a fluorine scan identified a site for substitution that led to a 400-fold enhancement of potency by comparison of the matched pair of BTK inhibitors **108** and **109** where the introduction of a single fluorine atom increased potency by two orders of magnitude (**Figure 42**). [3] An X-ray co-crystal structure of compound **109** provided some understanding of the SAR observation. The fluorine atom of compound **109** was observed to be close to the protonated amine of Lys, the ortho C-H of Phe and a conserved water molecule. Like nitrogen-walking described previously, fluorine-walking is also an important tactic for medicinal chemists to explore potential interactions with protein. Therefore, a quick access of diverse fluorine-containing building blocks is of great value for drug discovery campaign to understand structure-activity and structure-property relationship.

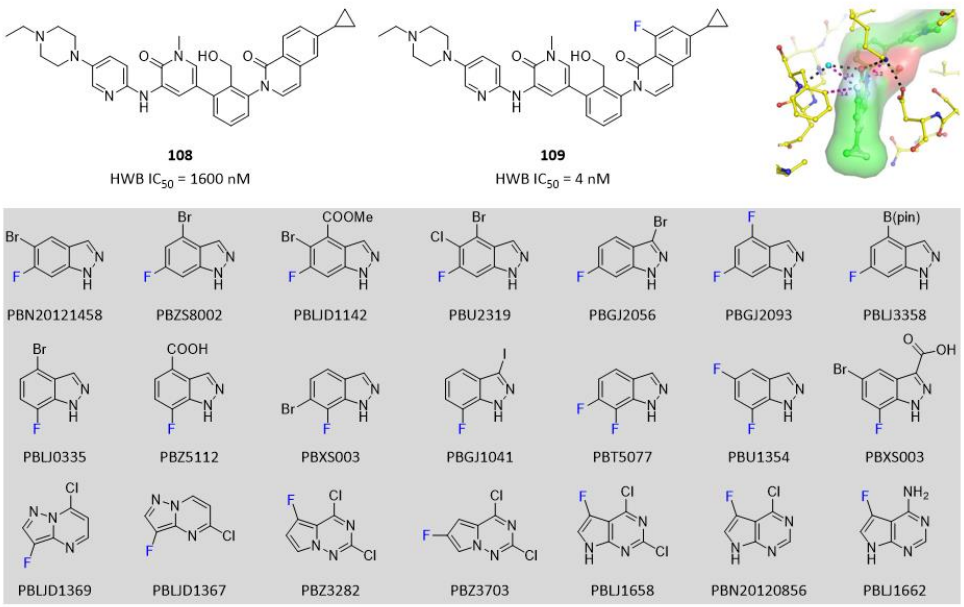


Figure 42. Key interactions between fluorine atom and BTK

A dramatic fluorine effect was observed by comparison of compound **110** and **111**, with the latter 30-fold more potent than the former. With regard to the remarkable fluorine phenomenon, an X-ray structure of compound **111** revealed that the fluorine of compound **111** was located close to the terminal carboxamide in Gln530 with a F-N distance of 2.97 A and functioned as a hydrogen bond acceptor (**Figure 43**). [4] Additionally, the introduction of fluorine also strengthened the hydrogen bond interaction between the amidecarbonyl group of compound **111** and Ser555. Therefore, carboxylic acid building blocks with a fluorine atom at alpha-position are of great interest for medicinal chemists in this kind of context.

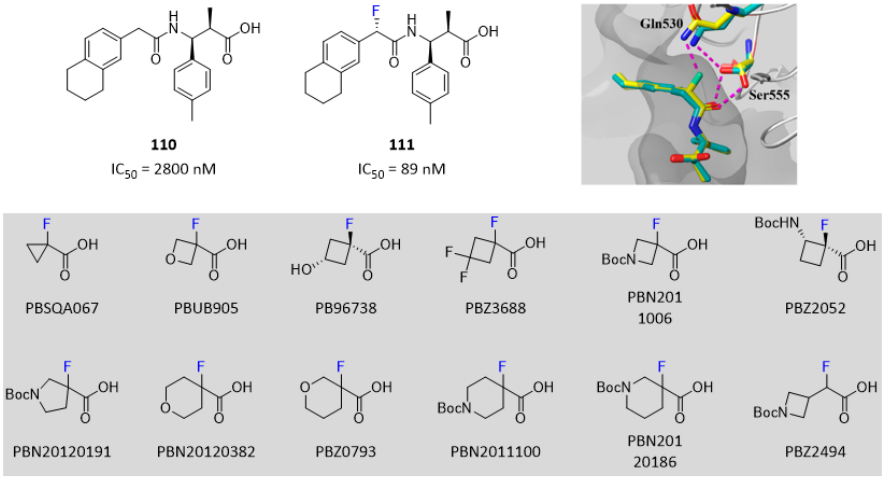


Figure 43. Introduction of fluorine increased potency by 40-fold.

Introduction of two fluorine atoms in compound **113** on methyl group of compound **112** displayed improved biochemical potency by 10-fold. An X-ray co-crystal structure of an analogue compound revealed a critical interaction between one fluorine atom with Ser774, explaining the observation (**Figure 44**). [5]

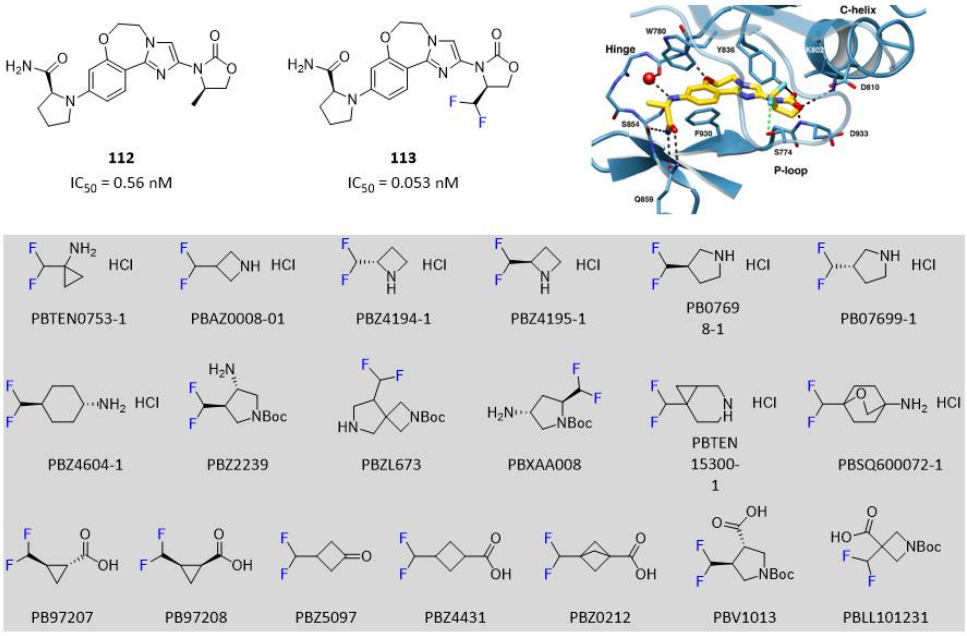


Figure 44. Difluoromethyl increased potency by forming an interaction with Ser774 (PDB code: 8EXU).

Difluoro- compound **115** demonstrated a 4-fold increase in CBP inhibitory potency, compared to methyl compound **114**. To further understand the increased CBP potency of compound **115**, an X-ray co-crystal structure of compound **115** in CBP bromodomain was obtained. The crystal structure revealed that additional favorable dipolar interaction between the partial negative charge on the fluorines of the difluoromethyl and the positively charged guanidine on Arg1173 was observed (**Figure 45**). [6]

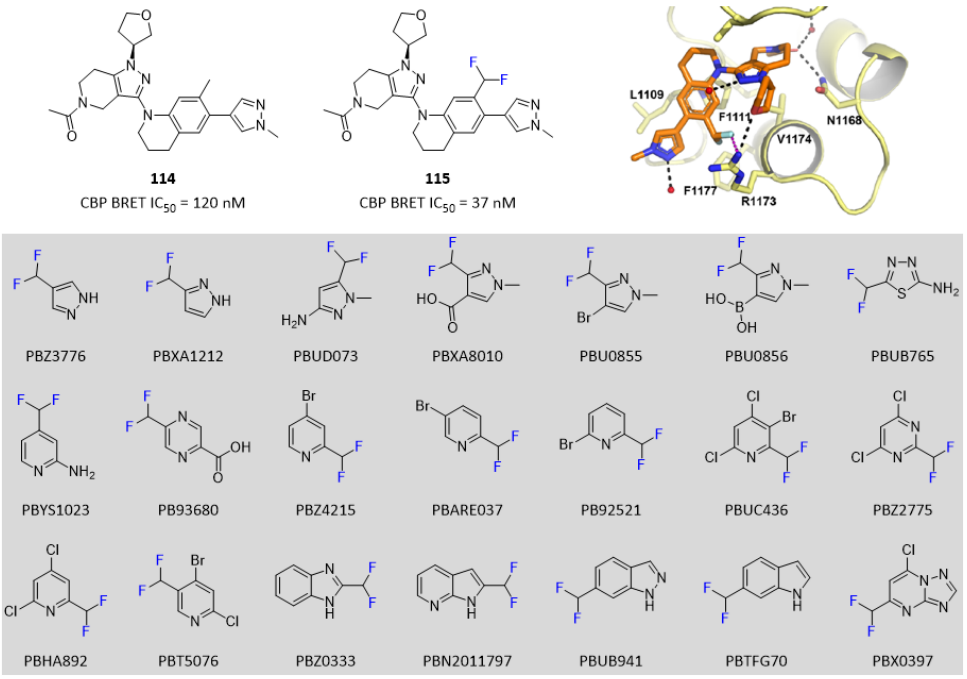


Figure 45. Interaction between negatively charged fluorine and positively charged Arg1173 (PDB code: 5W0I)

A weak but nevertheless interesting interaction between the CF_3 moiety and electron rich centers of protein, such as COOH, amide carbonyl and oxygens of serine, threonine and tyrosine, that involves tetrel CF_3-O bonding has recently been reported. [7] The geometry of the interaction of

electron rich species with the sigma-hole associated with the CF_3 substituent is highly directional in nature, optimal at an angle of 180° to the Ar-sp^3 carbon bond (**Figure 46**).

Two examples were depicted in **Figure 46**: in the first case, the side chain carboxylate of Asp312 interacted with the CF_3 of the inhibitor, while in the second case, the oxygen atom of Tyr246 was the partnering element.

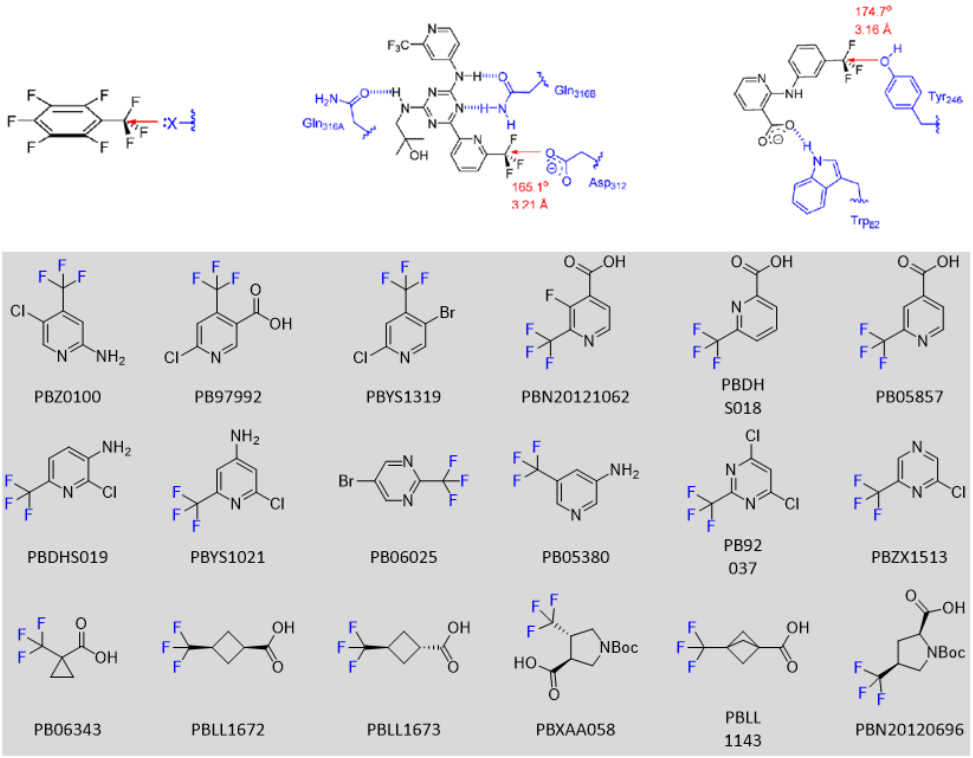


Figure 46. Key interactions between CF_3 and electron rich centers of the protein

Compound **116** exhibited a weak hERG inhibition at 44 uM. Estimate for effective therapeutic plasma concentration for compound **116** was typically in the range of 2 to 10 uM free concentration. The resulting ratio for hERG IC_{50}/free drug concentration < 22 reflected a high risk for QT prolongation signals in man. A recent analysis of human thorough QT studies at Pfizer demonstrated that a hERG IC_{50} within 60-fold of the effective therapeutic plasma concentration results in an 82% chance of causing a significant signal in a human thorough QT study. [8] Therefore, the team aimed to further reduce hERG inhibition of compound **116**. To reduce the risk of a positive signal in the human thorough QT study, the team aimed for a > 100 ratio of hERG IC_{50}/free drug concentration, which translated approximately into a hERG IC_{50} target of > 200 uM.

It is well-established that pKa has an impact on hERG inhibition. [9] The team explored reduction of pKa through substitution at the 3-position of the piperidine moiety with electron-withdrawing substituents, specifically both cis- and trans-substitution with hydroxyl, methoxy and fluoro groups (**Figure 47**). [10] All of these strategies worked, with cis-fluoro substitution in compound **117** decreasing hERG inhibition to 233 uM which meet criteria of target product profile and advanced into phase 1 clinical studies. Addition of a substituent adjacent to -NH_2 results in two chiral centers making molecule more complexed, so an efficient access of chirally pure building blocks is of great value for medicinal chemists.

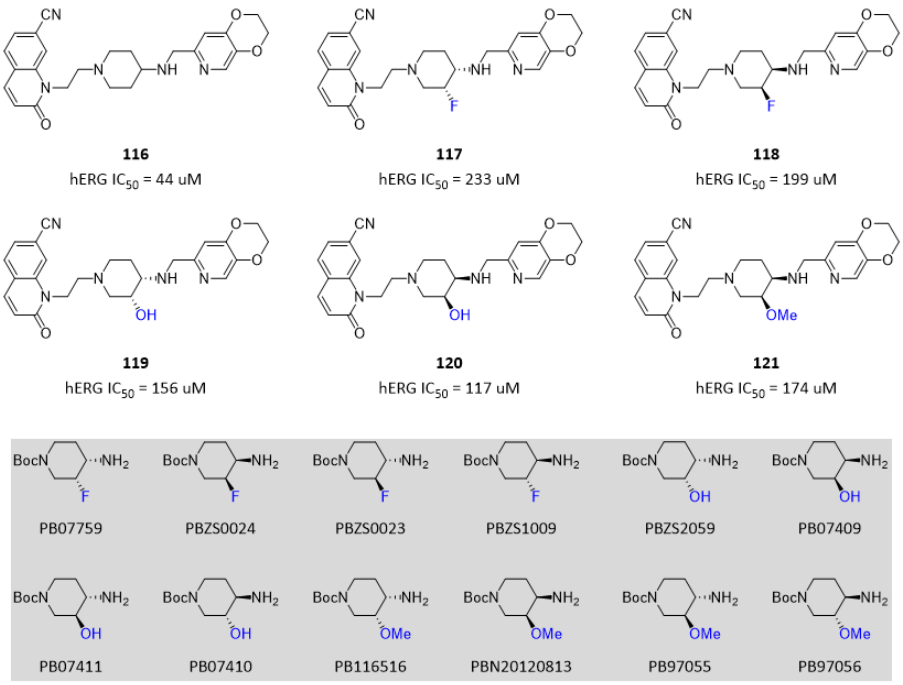


Figure 47. Impact of F-, -OH and –OMe on hERG inhibition

Another example is that reduction in the electron density of the pyridine heterocycle of JAK3 inhibitor **122** was examined as an approach to reduce the affinity of this compound for the hERG channel. As captured in **Figure 48**, the installation of a fluorine atom in the piperidine ring reduced hERG binding by an order of magnitude in both cis- compound **123** and trans- compound **124**. [11]

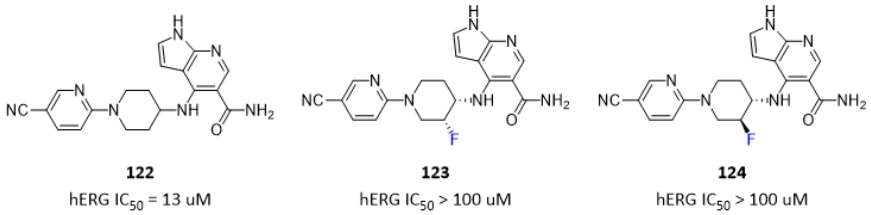


Figure 48. Fluorine substitutions impact hERG inhibition.

In part because of the strength of the C-F bond, fluorine is often used to overcome issues associated with poor metabolic stability, where it may be deployed as the direct replacement for a metabolically liable H atom in both aromatic and aliphatic settings. In the course of discovering oral EP300/CBP inhibitors, compound **125** was found to be metabolically unstable. Two fluorine atoms were introduced on cyclohexane ring to block the metabolic site. As expected, the *in vitro* microsome stability of compound **126** was increased by about 16-fold compared to compound **125**, which translated into *in vivo* PK with AUC improved by about 8-fold and oral bioavailability improved by 3-fold compared to compound **125**. As discussed in this example, difluoro-aliphatic building blocks have been widely used by medicinal chemists to circumvent the metabolism issue (**Figure 49**). [12]

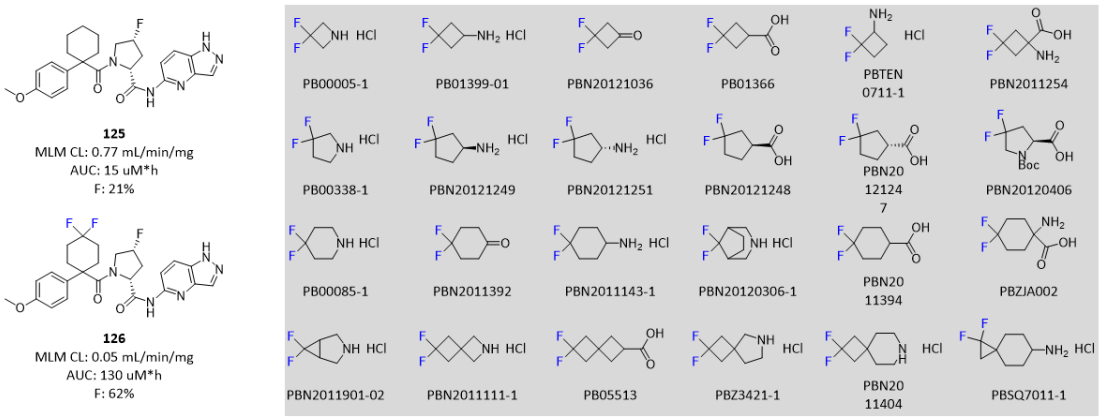


Figure 49. Two fluorine atoms block the metabolic site and improve PK profile.

Compound **127** exhibited good potency, but suffered from poor metabolic stability with just 8% remaining after incubation in mouse microsome. Introduction of two fluorine atoms on cyclopetane ring in compound **128** exhibited improved microsome stability (**Figure 50**). [13] Hydroxylation process of compound **129** caused rapid in vivo clearance from mouse plasma. Compared to compound **129**, the anti-fluoro on cyclobutane ring of compound **130** exhibited lower clearance and increased oral bioavailability. [14]

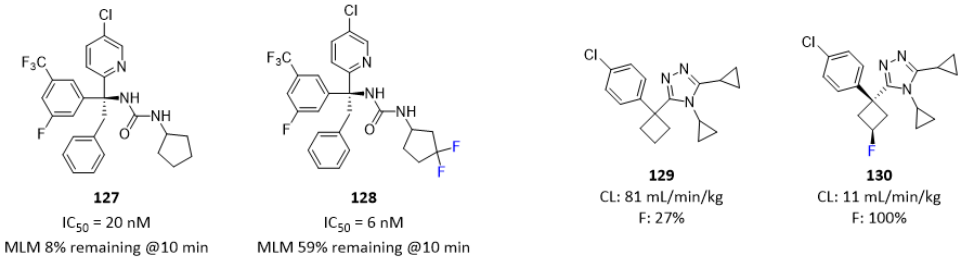
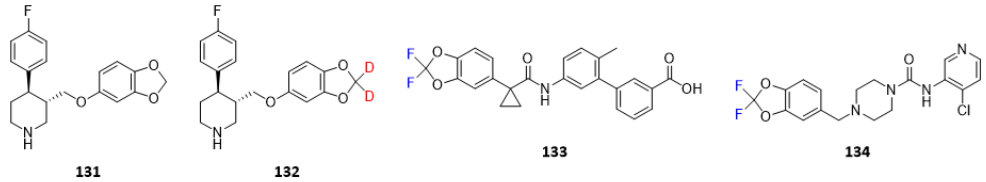


Figure 50. Fluorine atom improved microsome stability and oral bioavailability.

The 1,3-benzodioxole moiety is a structural element in prevalent natural products and in small-molecule candidates or drugs. However, this moiety is susceptible to metabolism by CYP450 enzymes following a pathway that leads to the formation of a carbine intermediate that binds to the Fe atom of the enzyme tightly (**Figure 51**). This carbine-bound intermediate is referred to as a metabolite intermediate complex that inactivates the enzyme until the complex degrades, which relieves the inhibition, with the methylenedioxy carbon atom released as carbon monoxide. However, this step generates a catechol than can be subject to bioactivation by oxidizing enzymes, including CYP450, to afford quinone derivatives that are highly reactive toward both soft and hard nucleophiles. Consequently, the moiety is considered to be a structural alert because it can be associated with drug-drug interaction, metabolic activation, and toxicities that includes hepatotoxicity. For example, despite its relatively low clinical dose of 10-50 mg, the antidepressant drug Paroxetine (**111**) is metabolized by CYP2D6 in a fashion that leads to inhibition of the enzyme, inhibiting both its own metabolism and that of other drugs that are cleared by CYP2D6.
An appreciation of these problems has prompted the design of 1,3-benzodioxole replacements that would abrogate this metabolic pathway while preserving the physicochemical properties. Deuteration of the methylene moiety represents the most conservative isosteric substitution that can slow this metabolic process while preserving biological activity and has been successful in the context of compound **132**, a deuterated derivative of compound **131** (**Figure 51**). [15]

Fluorination offers a more definitive solution, although the effects on biological potency are less predictable with increases, decreases and minimal changes described that show dependence on the specific target or chemotype within a target. Lumacaftor (**133**) has been approved by FDA for the treatment of cystic fibrosis (**Figure 51**). [16] Compound **134** is a clinically evaluated, mechanism-based inhibitor of FAAH for which the 2,2-difluorobenzo[d][1,3]dioxole heterocycle was observed to be metabolically stable (**Figure 51**). [17]



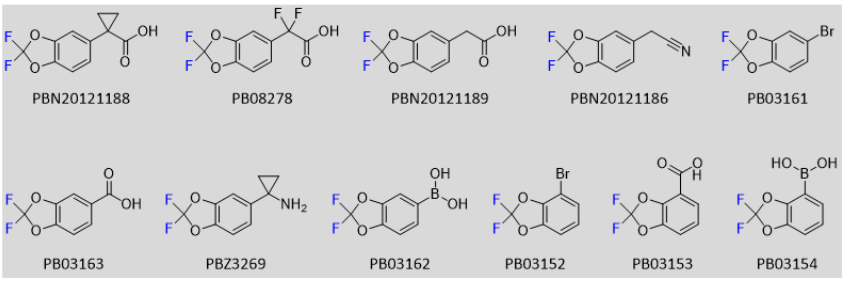


Figure 51. 2,2-Difluorobenzo[d][1,3]dioxole heterocycle is more metabolically stable.

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