Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Sulfone in Medicinal Chemistry

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The sulfone moiety has been frequently used in medicinal chemistry to optimize potency and physicochemical properties. There are several examples of approved drugs and clinical candidates containing sulfone moiety (**Figure 152**). The sulfone moiety has been found to function as important pharmacophore responsible for a range of biological activities in many therapeutic areas. Its ability to confer conformational constraint, serve as hydrogen bond acceptor, and influence proximal functionality by virtue of its electron-withdrawing property has been exploited to maximize interactions with proteins in order to optimize affinity or potency. Besides, sulfone moiety can be used as one of ketone isosteres that offers increased polarity while avoiding the potential for ketone reduction, and as one of carboxylic acid isosteres that is devoid of the burden of the charge of the carboxylate. In addition, sulfone moiety is very polar that can lower the overall lipophilicity and improve aqueous solubility and metabolic stability of a molecule, which can lead to an overall improvement of ADMET. [1]

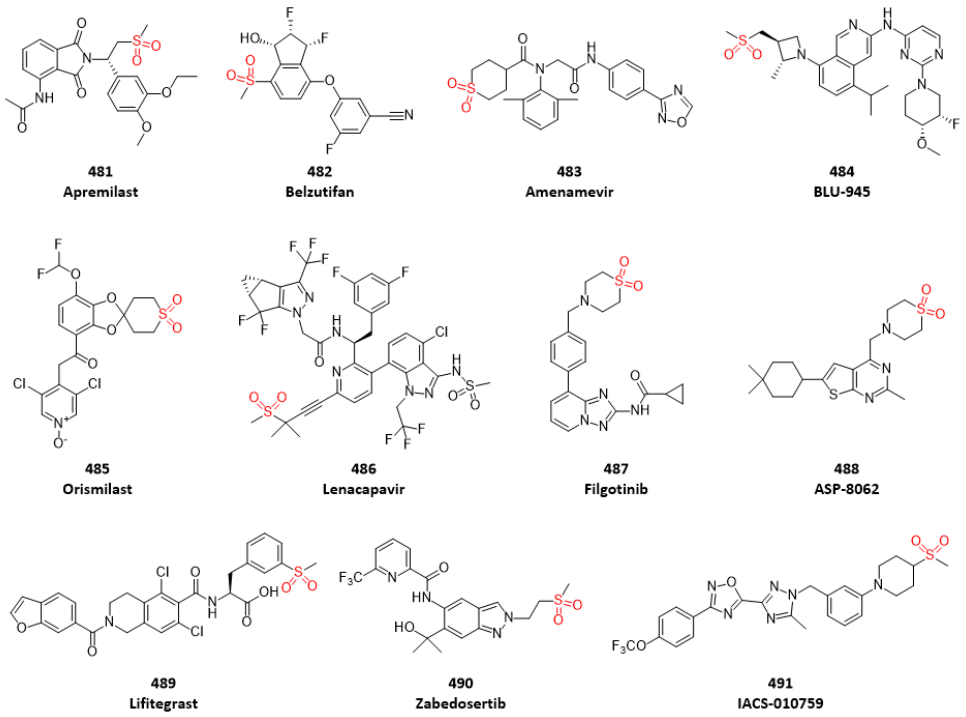

Figure 152. Approved drug and clinical candidate molecules containing sulfone

In the course of discovery of **BLU-945** (compound **484**), a reversible, potent, and wild-type sparing next generation EGFR mutant inhibitor for the treatment-resistant non-small cell lung cancer, compound **492** was identified as a potent and selective lead compound. However, compound **492** suffered a low metabolic stability in human microsome. To address this problem, it was identified that 3-position of the azetidine ring was a vector to explore the addition of polar substituents to tune properties. Among of substituents explored by the team, sulfone-containing compound **493** was distinctly superior, with excellent stability in human microsome and increased potency compared to compound **492**. In order to explain observed potency increasing, X-ray crystal structure of compound **493** bound to EGFR LR/TM revealed that this improvement could be attributed to two hydrogen bonds between sulfone moiety and two Lys716 and Lys728 in the front pocket of protein (**Figure 153**). [2] Further optimization based on compound 493 led to discovery of **BLU-945** (compound **484**).

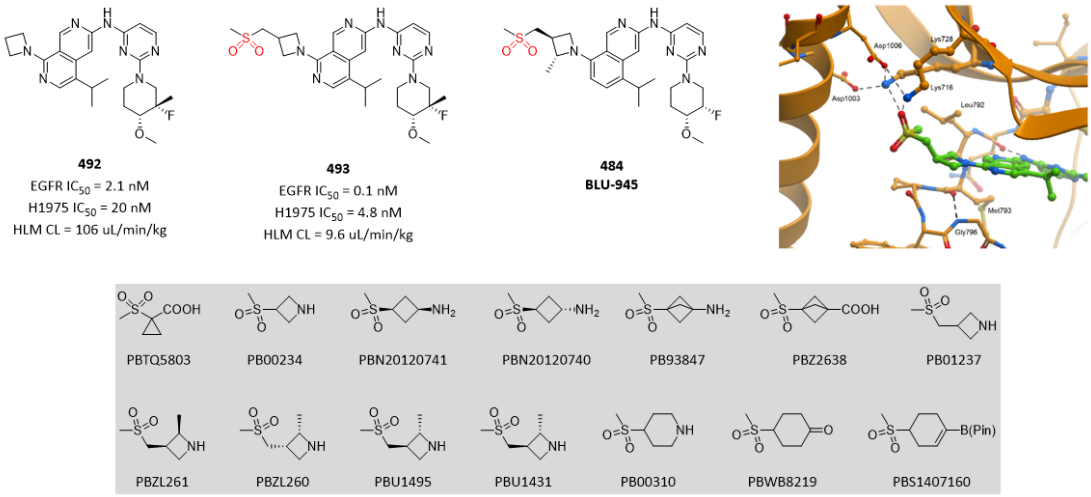

Figure 153. Sulfone moiety increased both metabolic stability and potency. (PDB code: 8D76)

In order to increase ATAD2 potency and selectivity against BRD4 of hit compound **494**, several analogues with increased polarity were synthesized and evaluated. The most promising compound **496** containing sulfone moiety achieved this goal. To better understand the interactions made by the cyclic sulfone, X-ray crystal structure of compound **496** bound to ATAD2 was obtained. There are two polar interactions made by the two sulfone oxygen atoms, each of which accepts hydrogen bonds from the guanidinium group of Arg1077 (**Figure 154**). [3]

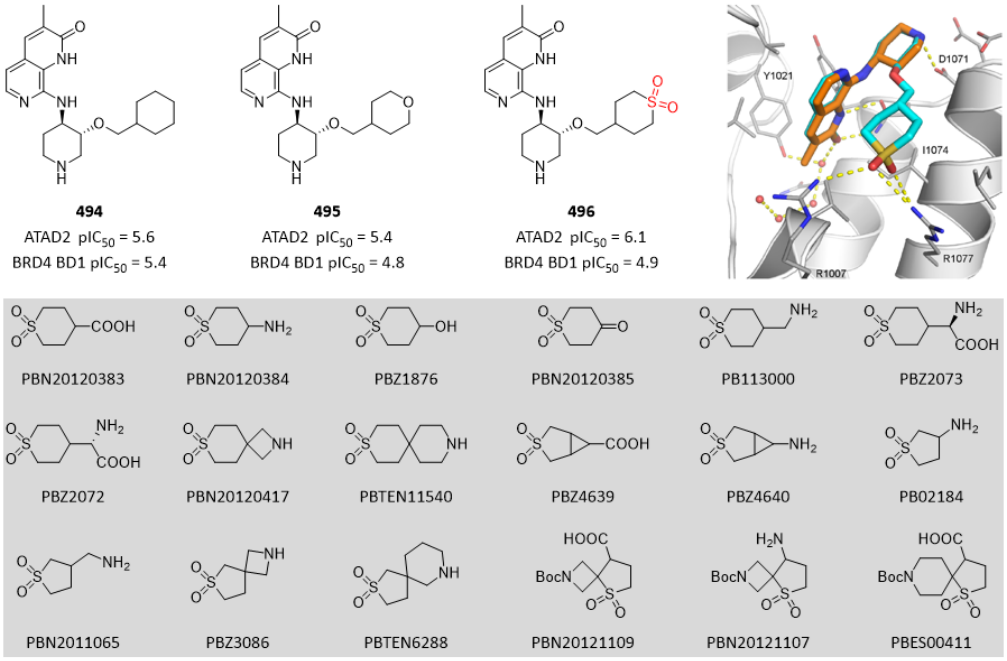

Figure 154. Sulfone moiety increased both potency and selectivity. (PDB code: 5A82)

The enhanced selectivity over BRD4 of compound **496** relative to compound **494** is due to both increased ATAD2 potency and decreased BRD4 activity. The ATAD2 potency gain arises from the new direct hydrogen bonds to the arginines and the displacement of the weakly bound water molecules. The reduction of BRD4 activity presumably results from placing polar sulfone oxygen atoms in an unfavorable lipophilic location. The tetrahydropyran compound **495** is intermediate in polarity between the compound **494** and compound **496**, and shows intermediate selectivity.

Compound **497** was identified as a novel, potent V1b antagonist. However, this compound suffered a high *in vivo* clearance. To address this critical issue, several polar moieties were introduced into

molecules, as exemplified by compound **498** and compound **499** (**Figure 155**). The in vivo clearance was well consistent with polarity of oxygen atom and sulfone moiety. [4]

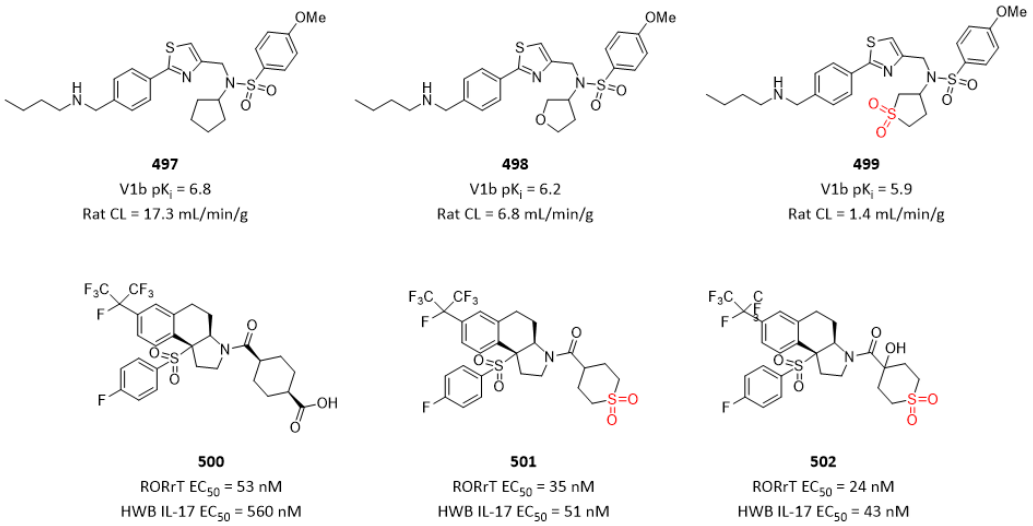

Figure 155. Sulfone moiety improved physicochemical properties of molecules due its high polarity.

Comparing compound **500** and compound **501**, as RORgammaT antagonists, sulfone moiety increased human whole blood potency by at least 10-fold, although both compounds have similar enzymatic RORrT potency. This is probably due to poor permeability of carboxylic acid in compound **500**. Therefore, cyclic six-membered sulfone can be used as one excellent surrogate for carboxylic acid (**Figure 155**). [5]

Piperidine ring often causes hERG inhibition due to basicity of nitrogen. To address this problem, electron-withdrawing atom(s) are introduced, as exemplified by difluoropiperidine, morpholine, etc. Due to the most electron-withdrawing property of sulfone, thiomorpholine dioxide is less basic than morpholine and difluoropiperidine. Therefore, thiomorpholine dioxide is often used when reduction of basicity is desired and specially when avoiding hERG inhibition liability (**Figure 156**).

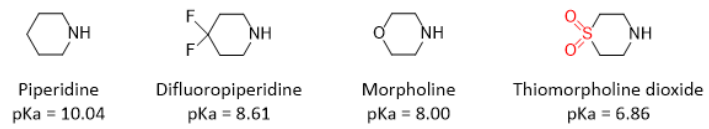

Figure 156. Comparison of pKa values (calculated by ChemDraw software)

Compound **503** was a potent, selective CB2 receptor agonist. However, this compound inhibits hERG with 88% inhibition at 100 uM. As described above, hERG ion channel is well known for its preference of ligands with a basic amine group. To address this issue, general strategies were employed to reduce basicity of nitrogen of piperidine by introducing a fluorine atom in compound **504**, introducing two fluorine atoms in compound **505**, replacing piperidine with morpholine in compound **506** and replacing piperidine with thiomorpholine dioxide in compound **507**. The extent of decreasing hERG inhibition is consistent with the ability of reducing basicity of nitrogen atom (**Figure 157**). [6]

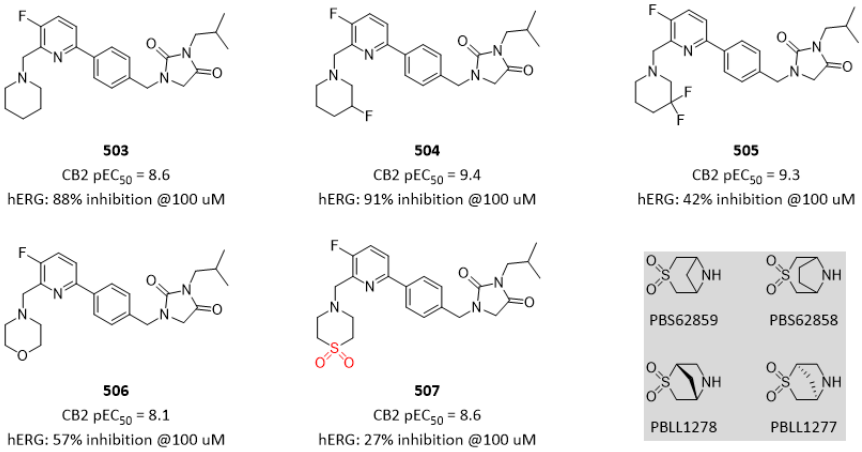

Figure 157. Sulfone moiety in thiomorpholine dioxide decreased hERG inhibition.

In the course of discovery of **Filgotinib** (compound **487**) as a JAK1 selective inhibitor, it was found that replacing morpholine in compound **508** with N-methyl piperazine in compound **509** lost potency completely, while sulfone moiety in **Filgotinib** (compound **487**) increased both potency and metabolic stability in rat liver microsome. X-ray crystal structure of **Filgotinib** (compound **487**) bound to JAK2 revealed that the terminal thiomorpholine dioxide group packs against the glycine rich loop, forming polar interactions with main chain atoms of this flexible loop (Gly861, Ser862), the side chain of Val863, and the catalytic Lys882 and Asp994 of the DFG segment (**Figure 158**). [7]

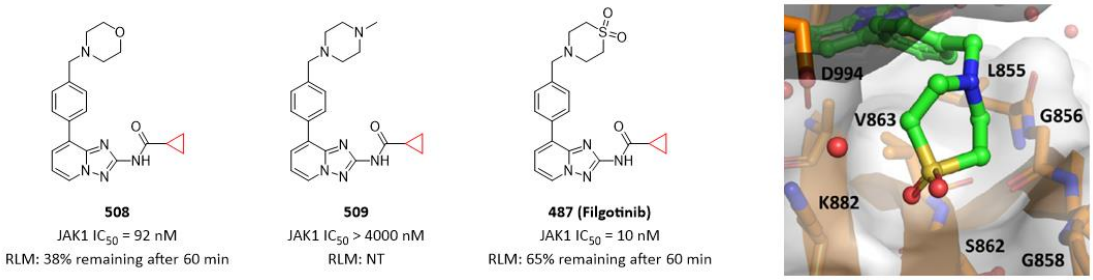

Figure 158. Sulfone moiety increased both potency and metabolic stability. (PDB code: 4P7E)

References

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