Halogen Bond in Medicinal Chemistry

Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Noncovalent Sulfur Interactions in Medicinal Chemistry

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Like halogen bond, there can be seen from the front and side view of thiophene ring that a region of positive, σ-hole-like potential exists near the sulfur atom (**Figure 34**). [1] The presence of σ-hole on sulfur atom is available for interaction with electron donating atoms, particularly nitrogen and oxygen. For instance, most commonly sulfur-containing heterocycles can participate in attractive nonbonding interactions that are proving to be useful in the control of molecular conformation. As illustrated in **Figure 34**, there is a sulfur-long pair interaction in 2-(2'-thienyl)pyridine which causes "s-*cis*-locked" conformational preference. One of the earliest examples of an intramolecular N-S interaction that stabilized a specific conformation was reported in 1976. The small molecule single X-ray structure of compound **92** revealed a *syn*, coplanar arrangement of the electron-donating guanidine N atom and the acceptor S atom of the thiadiazole ring. [2]

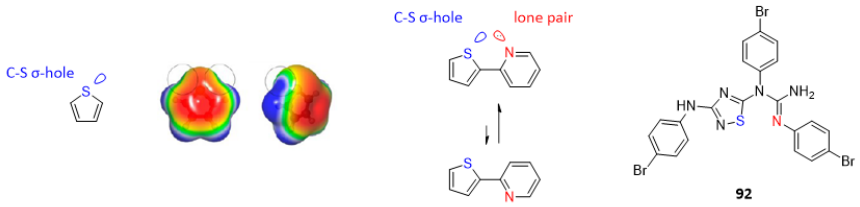

Figure 34. Illustration of σ-hole on sulfur atom and associated intramolecular interaction

Single replacement of oxygen atom in compound **93** with sulfur atom in compound **94** increased both Aurora A and Aurora B inhibition by at least 300-fold (**Figure 35**). Modeling of the heterocyclic core of compound **94** suggested that the two heterocyclic rings adopted a coplanar conformation in which the thiazole sulfur atom and the quinazoline N-3 atom were oriented proximal to each other. [3]

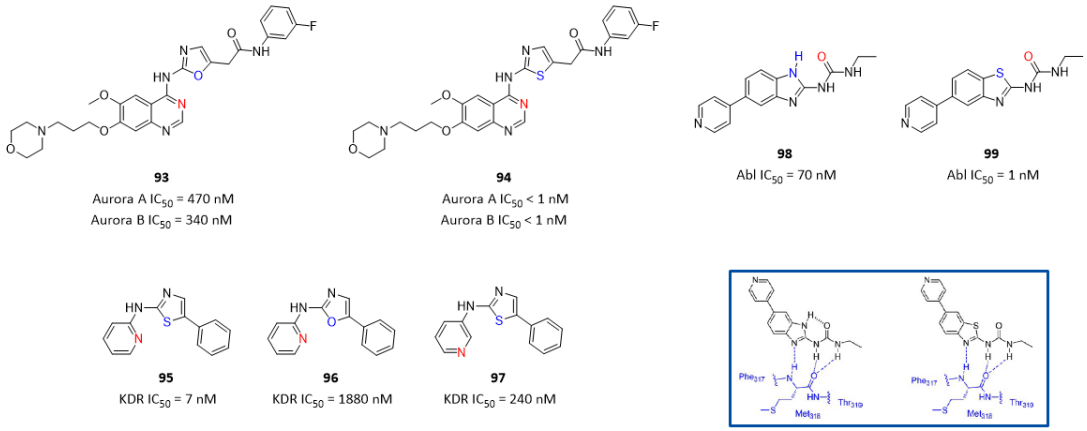

Figure 35. Intramolecular interaction between sulfur atom and nitrogen atom increased inhibition.

It was interesting to observe that a basic nitrogen atom in heteroaryl rings *ortho*- to the 2-amino group in compound **95** increased KDR inhibition by at least 30-fold, compared to isomer **97** with a *meta*- nitrogen. Single replacement of sulfur atom in compound **95** with oxygen atom in compound **96** decreased inhibition by at least 260-fold. Both two observations indicated that there was a key intramolecular interaction between sulfur atom and nitrogen atom in compound **95**, constraining binding favored conformation (**Figure 35**). [4]

There was 70-fold difference in potency between compound **98** and **99**, although both compounds had binding favored conformation resulted from intramolecular hydrogen bond and S-N interaction respectively. Calculations suggested that the difference in potency was more a function of desolvation costs, which are higher for the more basic compound **98** (**Figure 35**). [5]

In order to discover highly selective PI3K inhibitors based on primary hit compound **100**, replacing amide moiety in compound **100** with pyridine moiety in compound **101** maintained same desired conformation. Co-crystal structure of compound **101** in PI3K revealed that the pyridine ring was coplanar with the thiazole and with the nitrogen of the pyridine pointing inward. It was interpreted that long pair-sulfur interaction stabilized this conformation (**Figure 36**). [6]

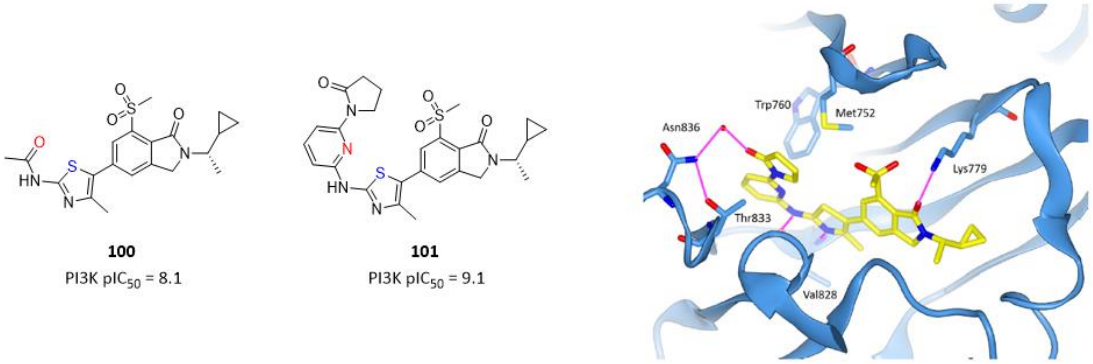

Figure 36. Co-crystal structure of compound **101** in PI3K revealed intramolecular interaction between S-N locked binding desired conformation. (PDB code: 7OIL)

As revealed above, intramolecular interaction between the sulfur atom in thiazole or fused-thiazole rings and adjacent nitrogen or oxygen plays a critical role in locking favored conformation. Thiazole or fused-thiazole building blocks are of great value (**Figure 37**).

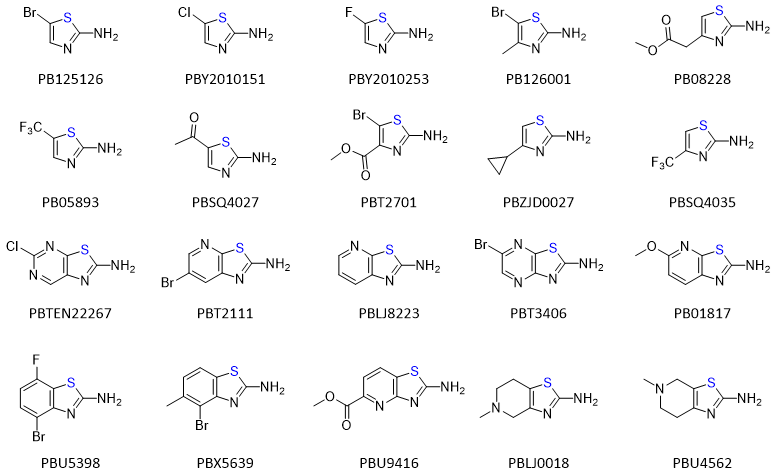

Figure 37. Thiazole and fused-thiazole building blocks

An intramolecular O-S interaction plays a role in orienting the thiazolopyridine heterocycle of the factor Xa inhibitor Edoxaben (**102**), which was approved for the prevention of venous thromboembolism following lower-limb surgery. In the crystal structure of the structurally related factor Xa inhibitor **103**, the close contact between the thiazole S and adjacent amide carbonyl O atom was considered to contribute to the correct alignment of the whole molecule (**Figure 38**). [7]

Thiazole-2-carboxylic acid building blocks are of great value for incorporation of O-S interaction into molecule.

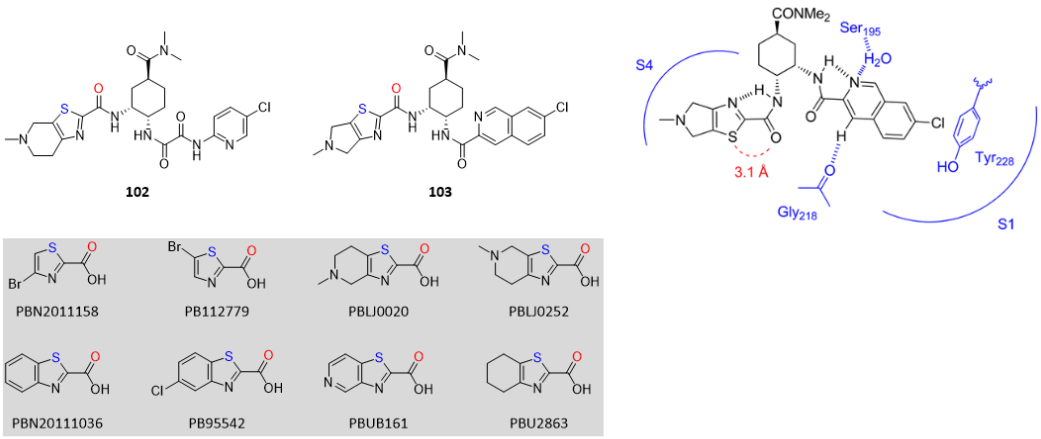

Figure 38. Intramolecular O-S interaction in Edoxaben and its analogues.

Compound **105** is a potent inhibitor of SIRT family members with IC_{50} values of 15 nM, 10 nM and 33 nM respectively, while the analogous compound **104** is about 10-fold weaker. These data are consistent with the co-crystal structure of SIRT3 with an analogue. The orientation of the 2-carboxamide is coplanar with the thienyl ring such that the oxygen atom lies proximal to the sulfur atom to facilitate a 1,4-electrostatic interaction. This topology facilitates four hydrogen bond interactions between the amide moiety and elements of the protein and a structural bridging water molecule (**Figure 39**). [8]

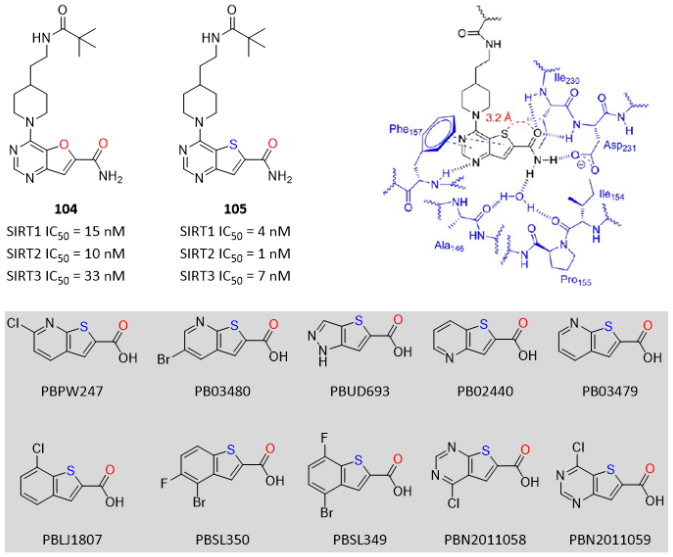

Figure 39. Key O-S contact was revealed in co-crystal structure in SIRT3 protein.

An X-ray co-crystal structure of compound **107** confirmed that the key enzyme-inhibitor interaction was preserved as the topology of the carboxamide moiety favored by close O-S interaction. The importance of this interaction on biological activity was understood by the dramatic difference in potency that was observed between compound **107** and close isomer compound **106**, with the latter 1500-fold weaker than the former. This was attributed to distortion of the carboxamide moiety of compound **106** from planarity, which resulted in a poor alignment for the important hydrogen bond with the protein (**Figure 40**). [9]

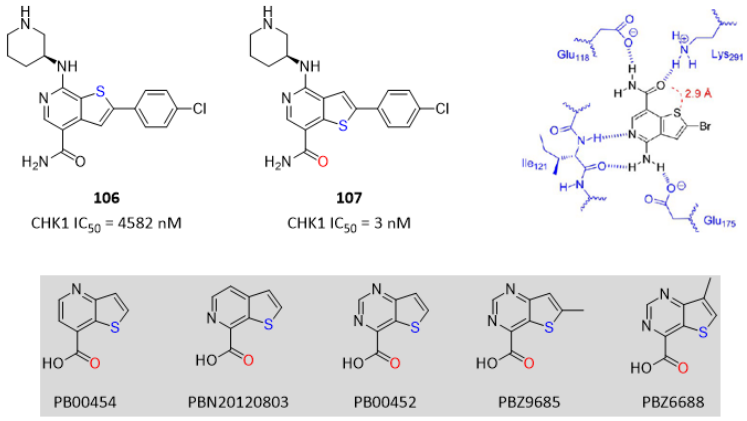

Figure 40. Key O-S contact was revealed in co-crystal structure in CHK1 protein.

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