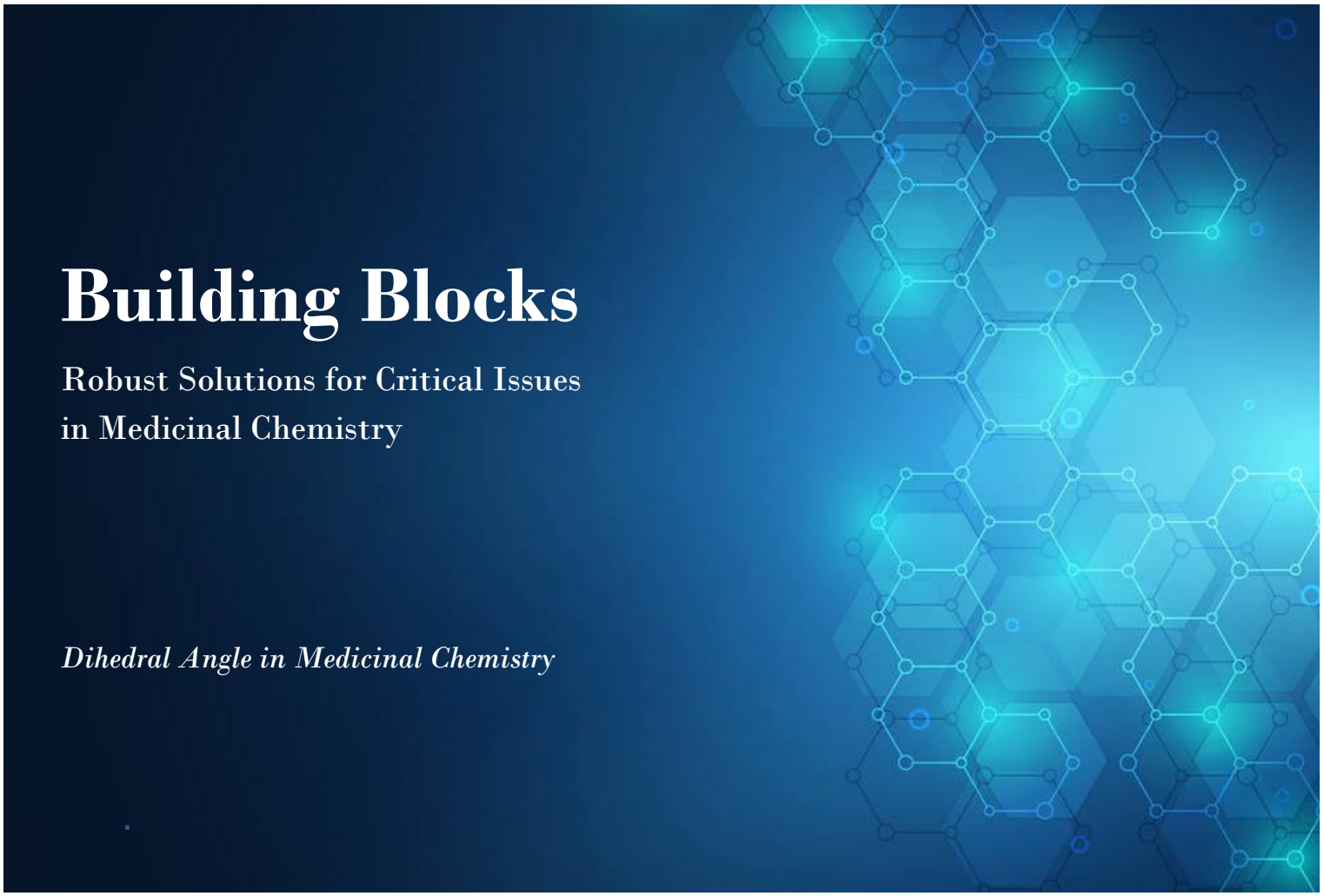

Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Dihedral Angle in Medicinal Chemistry

Dihedral Angle in Medicinal Chemistry

Dihedral angle-based drug design has been a commonly used approach for improving both activity or selectivity of molecules and conformation or orientation of molecules. For instance, small-molecule crystal data from the Cambridge Structural Database (CSD) revealed a dependence of the dihedral angle between the C=O and the phenyl ring on the size and polarity of R1 substituents (**Figure 16**). [1]

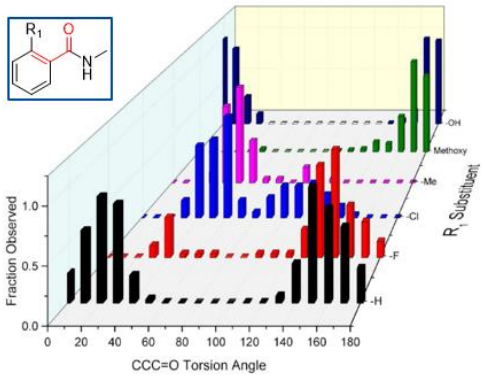

Figure 16. Distribution of relative fractions of C=C-C=O dihedral angle for various R1-substituted benzamides.

In the course of discovering a novel class of EZH2 inhibitors, there were two critical hypotheses: 1) the carbonyl oxygen makes an important hydrogen bond with the backbone NH of Tyr111 that is located approximately 50° above or below the plan of the phenyl ring; 2) the linker orients the dimethylpyridone and phenyl rings into an optimal binding geometry. [1,2] With this in mind, dihedral angle-based drug design strategy was used by introducing a Me or a Cl at the ortho-position of benzamide in compound **49** and **50** with activity increased by > 20-fold comparing to compound **48**. In conformation restricted six-membered lactam compounds **51**, **52** and **53**, the same trend was observed. An X-ray crystal structure of compound **54** bound to EZH2 revealed that carbonyl oxygen forms a hydrogen bond with the backbone NH of Tyr111 as expected (**Figure 17**).

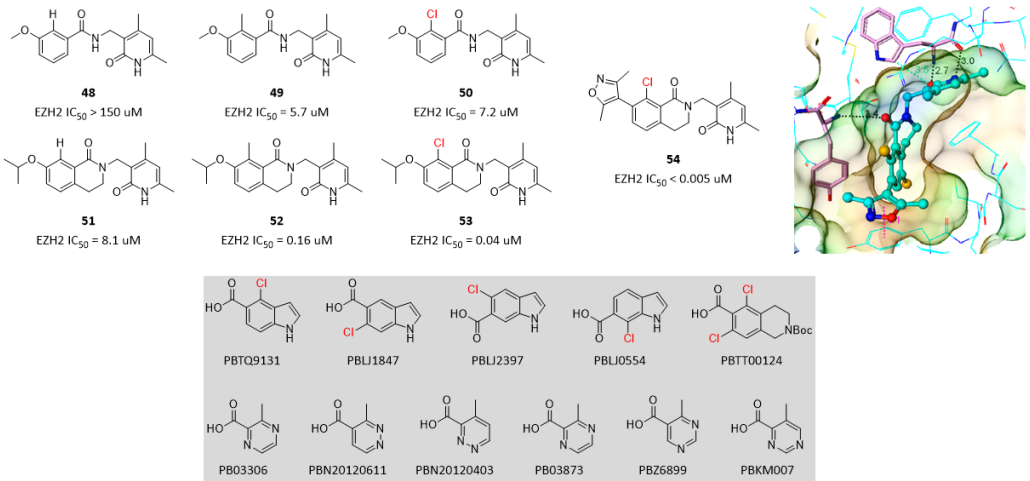

Figure 17. Impact of dihedral angle between amide and phenyl ring on EZH2 inhibition (PDB code: 6B3W).

Docking compound **55** into AKT protein revealed that a critical hydrogen bond interaction between Glu278 and the nitrogen on the piperidine ring was missing. It was assumed that hydrogen bond interaction might be formed through deflecting the piperidine by a certain angle. A fluorine atom

was incorporated at the ortho- position of amide in compound **56**, and docking revealed that a 43.2° dihedral angle was observed between the phenyl flat and amide flat, leading to the nitrogen on piperidine ring close to Glu278 and forming a stable hydrogen bond (**Figure 18**). [3] Consistent with docking result, compound **56** had 5-fold more potent AKT1 activity than compound **55**. It was also interesting that compound **56** had 16-fold less potent AKT2 activity than compound **55**, inhibition of which contributes to cutaneous toxicity.

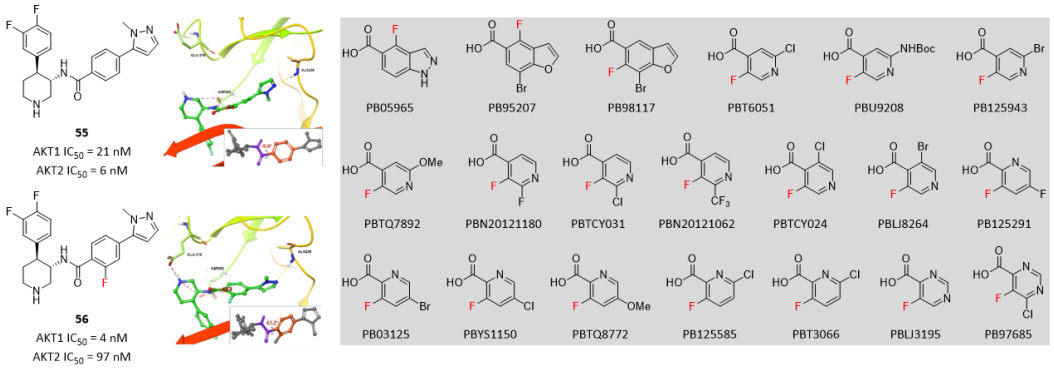

Figure 18. Impact of dihedral angle on AKT1 activity and selectivity against AKT2.

Besides impact on activity or selectivity, dihedral angle can also play influences on physicochemical properties of molecules significantly. [4] Molecular planarity and symmetry are known to influence crystal packing, and disruption of molecular planarity would be expected to decrease efficiency of crystal packing, consequently changing physicochemical properties such as solubility etc.

It was noteworthy that disruption of molecular planarity of compound **57** by incorporating two steric methyl groups in compound **58** had greatly improved solubility by 350-fold (**Figure 19**). [5] The similar strategy has been widely used to disrupt dihedral angle between two aromatic rings.

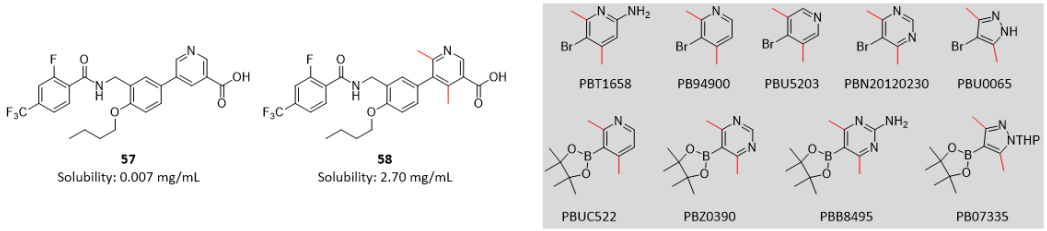

Figure 19. Two methyl groups disrupt molecular planarity and increase solubility significantly.

Besides biaryl structures as demonstrated in **Figure 19**, increase of dihedral angle by steric hinder was also useful for benzamide, anilide and phenylurea structures.

Transformation from compound **59** to compound **60** by adding chlorine caused an increase in solubility by at least 10-fold. The calculated LogP value of these two compounds are comparable which can't explain the solubility difference. This can be understood in terms of a conformational effect constraining the urea group to be orthogonal to the aromatic ring in compound **60**, whereas more planar conformations that may stack better in the solid state are permitted in the case of compound **59** (**Figure 20**). [6]

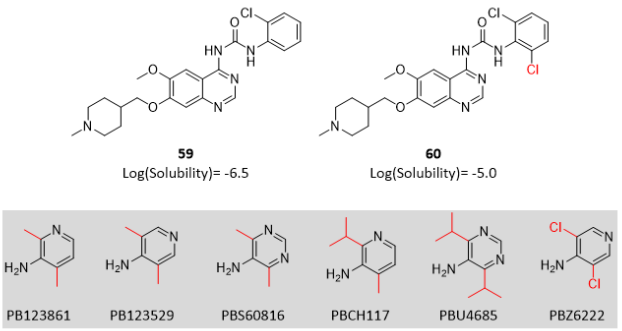

Figure 20. Improvement of solubility by ortho-substitution of a phenylurea.

In the course of discovering CDK inhibitors, it was found that introduction of a methyl group in compound **62** at the ortho-position of dimethylbenzamide compound **61** led to a 230-fold increase of aqueous solubility (**Figure 21**). [7]

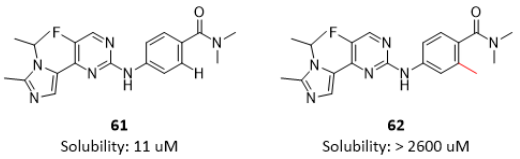

Figure 21. Improvement of aqueous solubility by ortho-substitution of benzamide.

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