Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Aliphatic Rings as Bioisosteres of Phenyl Ring

Aliphatic Rings as Bioisosteres of Phenyl Ring

The high prevalence of benzene rings in marketed drugs reflects its fundamental importance as both a structural and pharmacophoric element in drug design. Meanwhile, its versatility qualifies it as the preeminent privileged scaffold. [1] However, there are several issues associated with phenyl ring, including low aqueous solubility, poor metabolic stability, membrane permeability, etc. To circumvent these drawbacks, significant effort has been dedicated to exploring the design of bioisosteric replacements for phenyl rings that would offer advantageous properties. [2] Among of them, sp^3-riched aliphatic rings, including monocyclic and bicyclic, have emerged as frequently used bioisosteres of the phenyl ring (**Figure 22**).

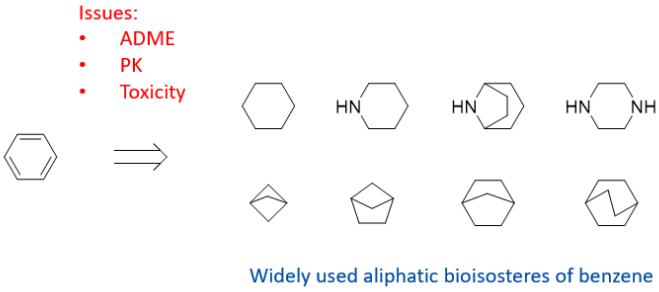

Figure 22. Sp^3-riched aliphatic rings as bioisosteres of the phenyl ring to circumvent critical issues.

Compound **63** (AMG-517) is Amgen's first-generation TRPV1 antagonist which was evaluated in clinical trials. However, it was found to have low aqueous solubility (< 1 ug/mL). The goal to identify a novel second-generation clinical candidate with increased aqueous solubility was achieved by replacing the phenyl ring with sp^3-riched aliphatic rings (**Figure 23**). [3] Cyclohexene in compound **64**, cyclohexane in compound **65** and piperidine in compound **66** were used as bioisosteres of the phenyl ring in compound **63**, and all of them increased aqueous solubility significantly. In studies of structure-solubility relationship, diverse cyclohexenyl boronic acid pinacol ester building blocks played crucial roles in quick synthesis of designed molecules.

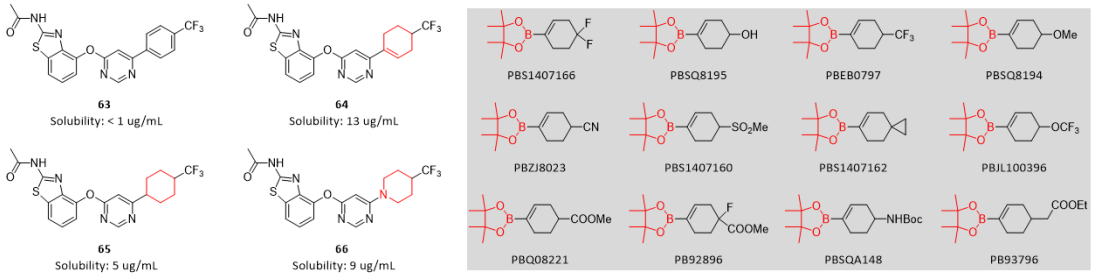

Figure 23. Cyclohexene, cyclohexane and piperidine increased aqueous solubility.

In the course of discovering a novel selective PDE9A inhibitor, compound **67** was identified as an early lead compound with excellent PDE9A inhibition and good selectivities against PDE family members (**Figure 24**). [4] However, in studies of PK profile of compound **67** in rats, high clearance and low bioavailability were observed, which was attributed to extensive phase 2 metabolism. Replacement of the 4-methylphenyl group in compound **67** with 4-dimethylpiperidine afforded compound **68**, which interestingly showed no phase 2 glucuronidation metabolism after incubation in rat hepatocytes. Although without phase 2 metabolism, oral bioavailability of compound **68** was slightly improved. It was found that the main clearance pathway of compound **68** was driven by

oxidative metabolism. It was hypothesized that cyclopropane can be metabolically more stable than the corresponding gem-dimethyl analogue. With this hypothesis in mind, compound **69** which has a spiro-piperidine motif was identified. It was extremely exciting that compound **69** (**BAY-7081**) improved bioavailability significantly. In the discovery campaign, diverse spiro-piperidine building blocks played crucial roles in quick synthesis of designed molecules.

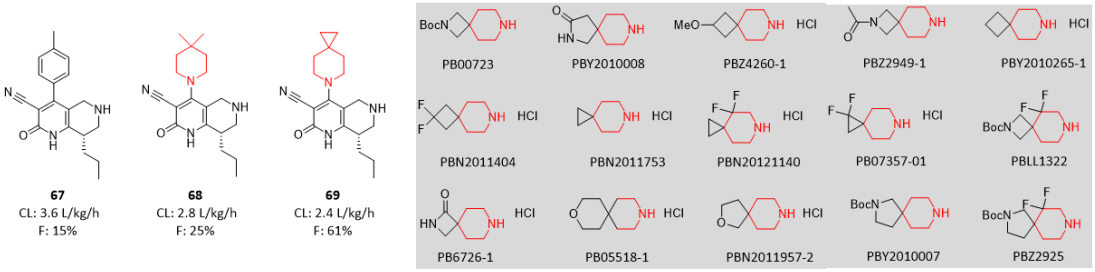

Figure 24. Piperidines as bioisosteres of the phenyl ring improved PK profiles.

Compound **70** was originally discovered as a novel potent SETD2 inhibitor (**Figure 25**). [5] The structure contains an aniline motif which impacts less-than-ideal pharmacokinetic properties and potential metabolism-derived toxicities. The team has experience before that saturating of the phenyl ring significantly improved the physicochemical properties of the series and avoided the potential AMES toxicity. With this in mind, replacement of the phenyl ring in compound **70** with cis-cyclohexane in compound **71** improved clearance and oral bioavailability significantly. There are two chiral centers on 1,3-disubstituted cyclohexane ring, and chirally pure bifunctional cyclohexane building blocks played crucial roles in quick SAR and SPR studies.

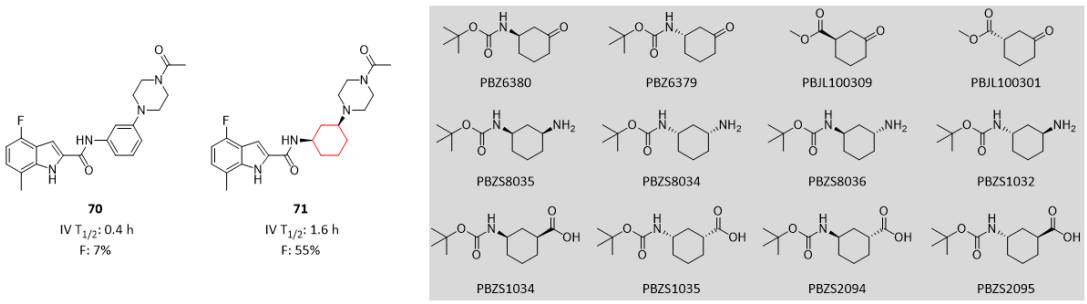

Figure 25. Cyclohexanes as bioisosteres of the phenyl ring improved PK profile.

Although bicylco[1.1.1]pentane (BCP) has a different stereoelectronic property compared to the 1,4-disubstituted phenyl ring, it shares comparable dihedral angle and similar distance and coplanar linear disposition of the substituents (**Figure 26**). [1] BCP system significantly increase aqueous solubility and noticeably decreases nonspecific binding. Consequently, the sp^3-riched BCP system serves as a nonclassical phenyl bioisostere to escape from flatland imposed by high aromatic ring count and modulate physicochemical properties during lead optimization. For instance, isosteric replacement of the 1,4-disubstituted phenyl ring with BCP has been shown to confer significant improved passive permeability and aqueous solubility. however, it should be noted that such bioisosteric replacement strategy will not be effective in lead compounds where a 1,4-disubstituted phenyl ring plays a pharmacophore role such as pi-pi stacking or pi-cation interactions with the aromatic or positively charged residue of the target protein. [6]

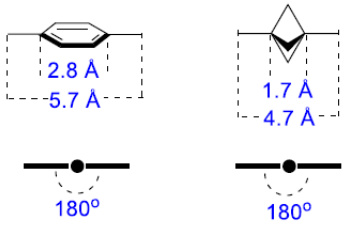

Figure 26. Geometrical parameters of phenyl ring and BCP ring

The significant advantage of the BCP moiety in compound **73** over the phenyl ring in compound **72** was manifested in physicochemical properties, with aqueous solubility increased by 360-fold and clearance decreased by at least 4-fold (**Figure 27**). It is noteworthy that this case story is one of the earliest examples using BCP as bioisostere of the phenyl ring. [7]

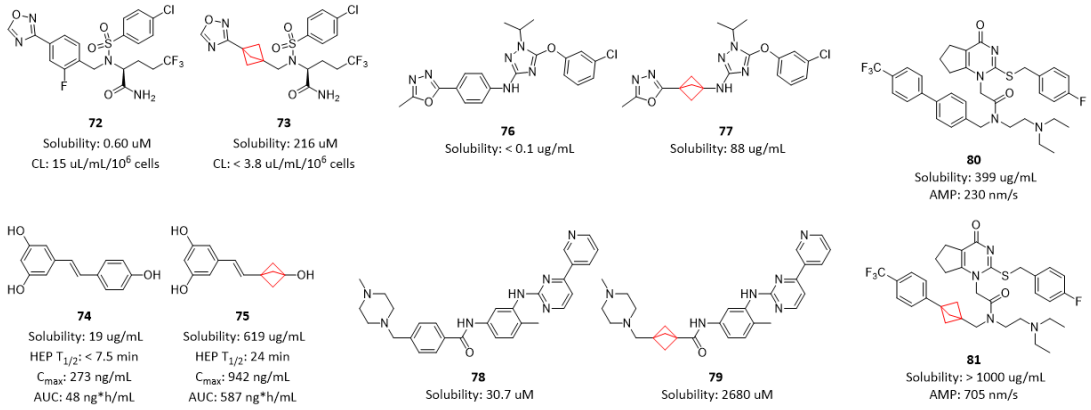

Figure 27. Representative examples where BCP improved ADME and PK profiles over the phenyl ring

The natural product **74** is associated with a wide range of biological activities. However, the poor bioavailability in preclinical species and humans has hampered its clinical progression, which can be attributed, in part, to metabolic modification of the phenolic hydroxyl moieties which are subjected to rapid first-pass glucuronidation or sulfation. An interesting approach to improve the pharmacokinetic profile of compound **74** conceived of replacing the phenol ring with a hydroxyl-substituted BCP moiety, explored in the context of compound **75** (**Figure 27**). [8] The BCP moiety dramatically increased aqueous solubility by 32-fold, and improved hepatocyte half-time by at least 3-fold which translated into 12-fold higher expousure.

The compound **76** exhibited a poor physicochemical profile, with an aqueous solubility of less than 1 ug/mL that was reflective of the overall planar nature of the structure (**Figure 27**). [9] The strategy adopted to address this deficiency was to replace the phenyl ring with a range of sp^3-riched bioisosteres. Among of them, BCP in compound **77** increased aqueous solubility significantly by at least 880-fold.

Despite the presence of the piperazine heterocycle, a basic element introduced to support salt formation as a means of enhancing aqueous solubility, the solubility of compound **78** is low at 0.01 mg/mL (**Figure 27**). [10] It was anticipated that reducing the aryl ring count by introducing the sp^3-riched, nonaromatic structural motifs would productively modulate physicochemical properties by lowering lipophilicity and enhancing aqueous solubility. This hypothesis was proved to be correct, with aqueous solubility increased by 87-fold in compound **79** in which BCP was used as bioisostere of the phenyl ring.

Compound **80** showed high membrane permeability and low aqueous solubility (BCS II). Based on assumption that reducing aromatic ring count and disrupting the planarity associated with the biaryl system would led to improved physicochemical profiles, the effect of replacing the central phenyl ring with a BCP isostere was examined in the compound **81** (**Figure 27**). [11] Compound **81** has both improved aqueous solubility and membrane permeability (BCS I).

With great success achieved in application of BCP as bioisostere of the phenyl ring, efficient access of diverse BCP building blocks is of substantial need, including monofunctional BCP building blocks (amines, carboxylic acids, etc.) and difunctional BCP building blocks (**Figure 28**).

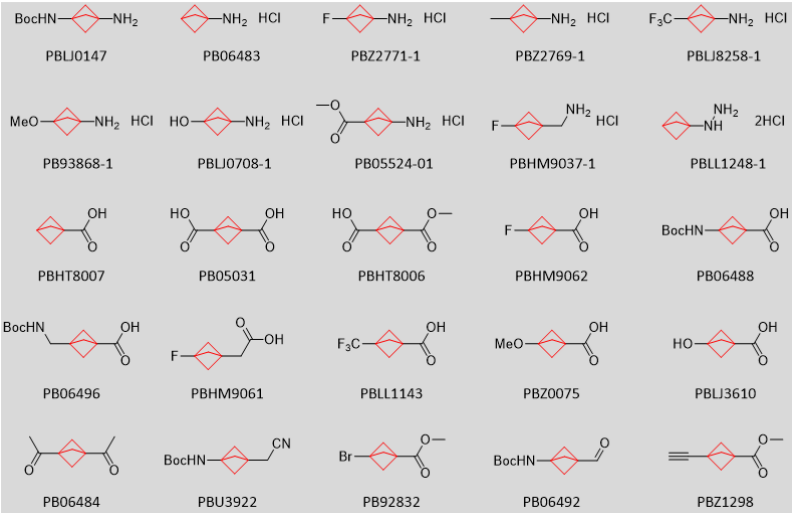

Figure 28. BCP building blocks have been widely used in medicinal chemistry.

Besides bicyclo[1.1.1]pentane (BCP) ring system, bicyclo[2.2.2]octane (BCO) ring system is another commonly used bioisostere of the phenyl ring by medicinal chemists. As part of a study of structurally novel HCV NS5A inhibitors, replacement of the biphenyl scaffold of compound **82** with alternative conformationally constrained spacers offering improved physicochemical properties was explored in a survey that included BCO-phenyl motif in compound **83**. The aqueous solubility was increased by 6-fold which was translated into high oral bioavailability (**Figure 29**). [12]

As described previously, compound **76** exhibited a poor physicochemical profile, with an aqueous solubility of less than 1 ug/mL that was reflective of the overall planar nature of the structure. The team also used BCO in compound **84** to replace the phenyl ring to improve aqueous solubility by at least 150-fold (**Figure 29**). [9]
Compound **85** caused only partial tumor regression in a mouse model attributed to low *in vivo* exposure. To address the PK deficiency, the benzoic acid was replaced with the conformationally rigid, sp^3-riched BCO ring system in compound **86**. C_{max} and AUC were improved dramatically by 5-fold and 11-fold respectively (**Figure 29**). [13]

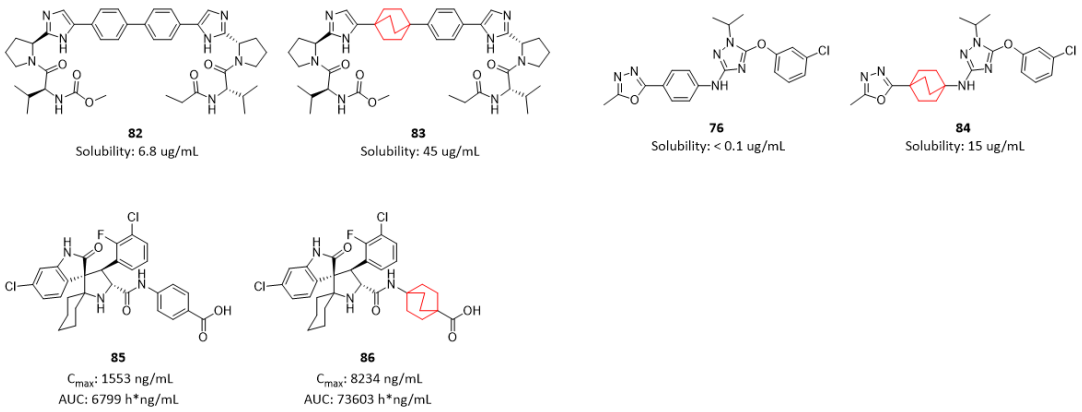

Figure 29. Representative examples where BCO improved ADME and PK profiles over the phenyl ring

Like BCP, great success was also achieved in application of BCO as bioisostere of the phenyl ring. Therefore, an efficient access of diverse BCO building blocks is of substantial need for medicinal chemists, including monofunctional BCO building blocks (amines, carboxylic acids) and difunctional BCO building blocks (**Figure 30**).

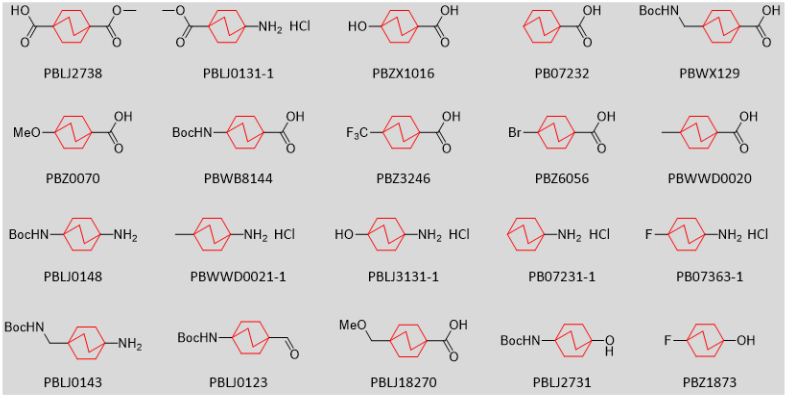

Figure 30. Like BCP, BCO building blocks have also been widely used in medicinal chemistry.

The altered geometries associated with the introduction of an oxygen atom into the skeleton of a BCP moiety confers plausible mimicry between 2-oxabicyclo[2.1.1]hexanes and *meta*-disubstituted benzene as depicted in **Figure 31**. [1]

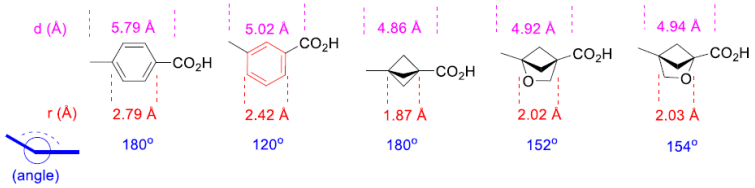

Figure 31. Geometric parameters of the phenyl ring and oxabicyclo[2.1.1]hexane ring system

Replacement of the phenyl ring of compound **87** with a 2-oxabicyclo[2.1.1]hexane ring system resulted in at least 6-fold improvement in aqueous solubility in both compound **89** and **90** (**Figure 32**). [14] Besides, there is a potentially IMHB between the ring oxygen atom and the amide N-H in compound **90**, which would reduce both the exposed polarity and solvation.

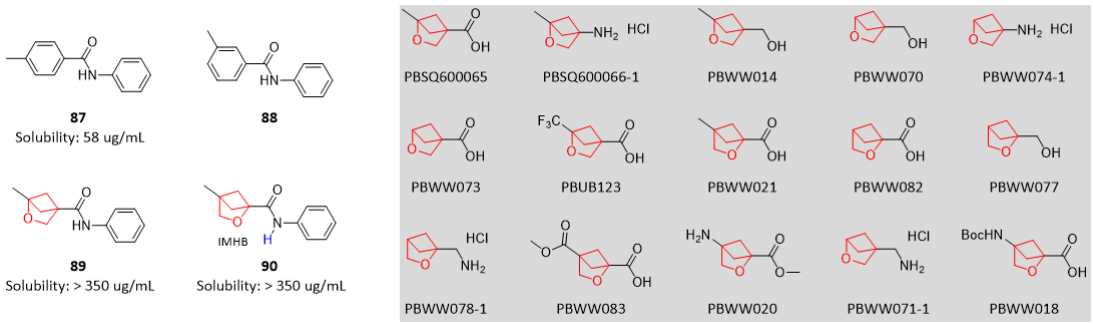

Figure 32. 2-Oxabicyclo[2.1.1]hexane moiety increased aqueous solubility.

As described previously, compound **76** exhibited a poor physicochemical profile, with an aqueous solubility of less than 1 ug/mL that was reflective of the overall planar nature of the structure. The team also used bridged piperidine in compound **91** to replace the phenyl ring to improve aqueous solubility by at least 1040-fold (**Figure 33**). [9] Besides, compound **91** exhibited improved potency by almost 10-fold.

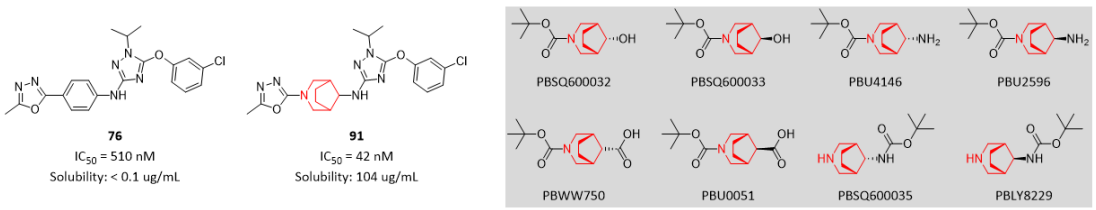

Figure 33. Bridged piperidine increased both aqueous solubility and potency.

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