Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Fused Cyclic Rings in Medicinal Chemistry

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There are three types of bicyclic aliphatic rings: spirocyclic, fused cyclic and bridged cyclic, all of which have been gaining substantial interest in medicinal chemistry. [1-3] Like spirocyclic rings, fused cyclic ring system is also one of the most popular strategies of modern medicinal chemistry, as can be seen by the number of publications and contributions to a variety of approved drugs and clinical candidates (**Figure 97**). The increase in rigidity resulting from fused cyclization can influence important factors, such as potency and selectivity. Furthermore, significant improvements in physicochemical properties, such as logD, lipophilicity and solubility, as well as ADMET properties, are achievable, ultimately leading to improved pharmacokinetic profiles. Recent advances in the development of synthetic methods and efficient supplies of diverse **fused cyclic building blocks** have allowed the introduction and increase in fused cycles in medicinal chemistry in the past decade.

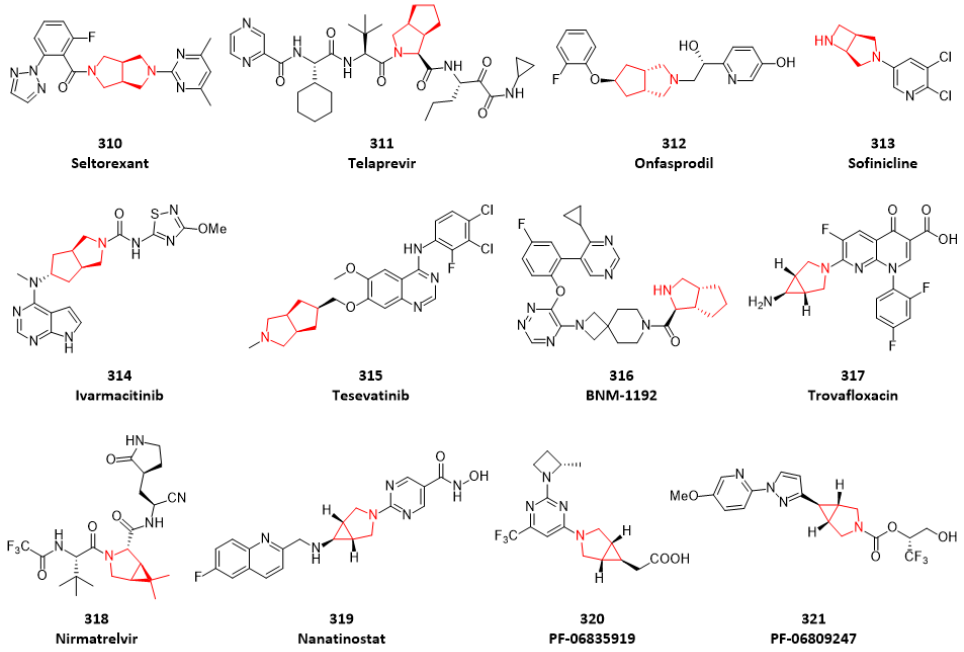

Figure 97. Fused cyclic rings in drug or clinical candidate molecules

In order to discover novel KHK inhibitors, compound **322** was identified as a promising hit. X-ray structure of compound **322** bound to KHK protein revealed that the cis-dihydroxypyrrolidine substituent is in line with the Arg108 residue at the polar back portion of the ATP binding site normally occupied by the triphosphate side chain in KHK. The team sought to exploit this vector in the direction of Arg108 in an effort to improve potency, possibly utilizing a Coulombic interaction. Additionally, a HydroSite calculation predicted a high-energy virtual water molecule in this pocket present within the hydrogen-bonding distance between Arg108, a backbone carbonyl oxygen atom of Thr253, and a backbone NH of Gly257 respectively, suggesting the possibility of making energetically favorable interactions with an appropriately chosen side chain attachment in this regioin. With this in mind, initial exploration of this vector by parallel medicinal chemistry using a diverse array of amines culminated in the identification of compound **323**, possessing a fused cyclic 3-azabicyclo[3.1.0]hexane ring system as one of the most potent neutral azetidine analogues among those tested from parallel medicinal chemistry effort (**Figure 98**). [4] X-ray structure of compound **323** bound in KHK protein showed that the terminal hydroxyl group on the newly

introduced 3-azabicyclo[3.1.0]hexane ring system effectively reached proximally to Arg108. This terminal hydroxyl group indirectly forms a hydrogen bond with Arg108 through a bound water, while within the hydrogen bond distance with the backbone carbonyl oxygen atom of Thr253. With compound **323** in hand, further optimization of the terminal polar groups was targeted as next design strategy to improve potency. Among the polar group known to interact with the arginine residue, the carboxylic acid group was considered as one of the top candidates given its potential to form a strong salt bridge with the guanidinium group of Arg108. This was proved by compound **324**, which demonstrated significantly increased potency by > 20-fold compared to compound **323**. X-ray structure of compound **324** bound to KHK protein displayed that the carboxylic acid group was well positioned to interact with cationic guanidinium group of Arg108. In addition, the backbone NH of Gly255 and Gly257, as well as a bound water nearby, were all within the hydrogen bond distance. Thus, a complex network of polar interactions through the carboxylic acid is likely responsible for the significant potency improvement. Further optimization based on compound **324** led to identification of clinical candidate **PF-06835919** (compound **320**).

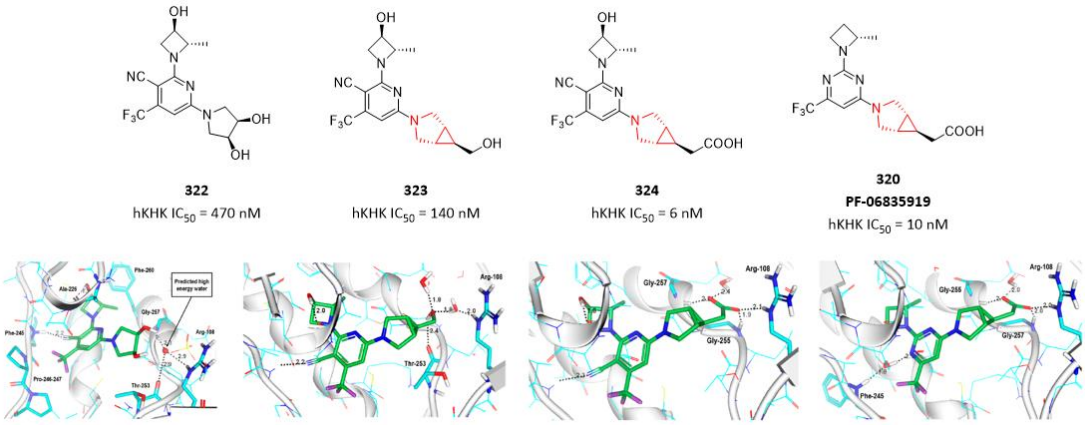

Figure 98. Fused 3-azabicyclo[3.1.0]hexane ring in KHK inhibitors (PDB codes: 6W0W, 6W0X, 6W0Y, 6W0Z)

In the course of discovery of MAGL inhibitor **PF-06795071** (compound **321**), the team previously identified a series of azetidine analogs such as compound **325**, which displayed excellent MAGL potency with IC_{50} = 0.3 nM and a good selectivity profile. However, in vivo PK-PD studies, only a transient elevation in 2-AG was observed. Cellular activity based protein profiling studies confirmed that this class of compounds covalently inhibited MAGL transiently and led the team to speculate that the azetidine adducts formed at the MAGL site were rapidly hydrolyzed from the enzyme. With an observation in mind that analogs containing larger ring cores, such as piperidines, resulted in improved MAGL adduct stability and thus prolonged PD effects, efforts to optimize the core system resulted in the discovery of compounds based on 3-azabicyclo[3.1.0]hexane ring system, such as compound **326**. Compound **326** retained MAGL potency with IC_{50} = 1.4 nM and had excellent selectivity. Despite a promising pharmacology profile, compound **326** had poor solubility (< 1 uM). To address this issue, the team systematically explored leaving group with the goal of improving drug-like properties, which led to discovery of clinical candidate **PF-06809247** (compound **321**) with significantly increased solubility. X-ray structure of compound **326** bound to MAGL protein revealed that 3-azabicyclo[3.1.0]hexane core with aryl pyrazole tail complements the shape of the lipophilic MAGL acyl chain binding pocket (**Figure 99**). [5]

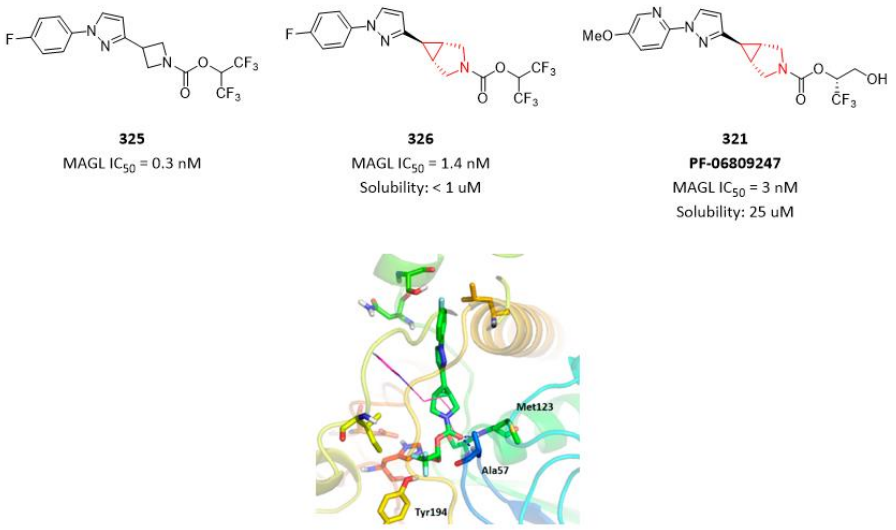

Figure 99. Fused 3-azabicyclo[3.1.0]hexane ring in MAGL inhibitors (PDB codes: 6BQ0)

PBTZ169 (compound **327**) is a promising compound which possesses extraordinary while-cell activity with a minimum inhibitory concentration (MIC) of 1 nM. While impressive, **PBTZ169** has liabilities emanating from its extremely poor solubility (< 0.01 ug/mL) that portend poor penetration. This may affect oral bioavailability (F) and volume of distribution (V_d), neither of which have been reported. To address this issue, disruption of molecular symmetry and planarity was used to improve aqueous solubility by replacing piperazine moiety with a wide variety of bioisosteric spirocyclic, fused cyclic and bridged cyclic diamines. This effort led to identification of compound **328** and compound **329** which possess a bridged cyclic ring and a fused cyclic ring respectively. Both compounds had high potency with MIC_{90} = 32 nM, although 15-fold less potent than **PBTZ169**. Fused 3-azabicyclo[3.1.0]hexane ring in compound **329** significantly increased aqueous solubility by at least 480-fold, while metabolic stability in both human and mouse liver microsome were both improved. However, compound **328** failed to improve solubility, and had a similar metabolic stability profile with **PBTZ169** (**Figure 100**). [6]

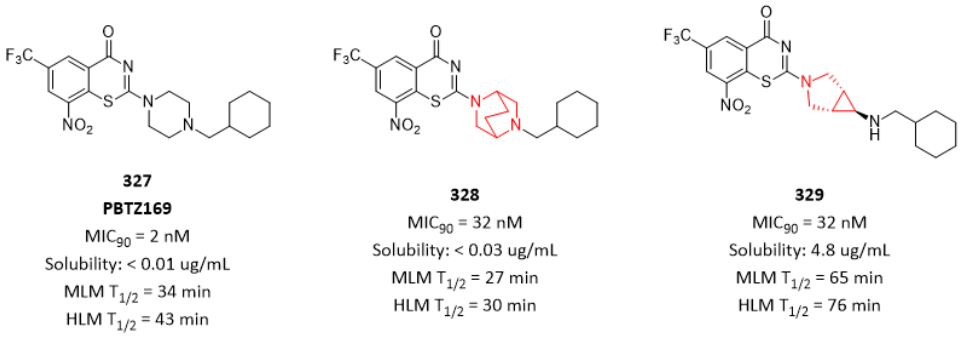

Figure 100. Fused 3-azabicyclo[3.1.0]hexane ring improved both solubility and metabolic stability.

To identify new potent and selective allosteric SHP2 inhibitors, the team led to discovery of a promising hit compound **330**, which exhibited modest SHP2 inhibition with IC_{50} = 225 nM. An attempt to optimize the novel amino moiety was undertaken with objectives: (a) maximize SHP2 inhibition; (b) remove secondary amine groups which are potentially detrimental to cell penetration; (c) make molecule constrained to likely control metabolic stability. With these goals in mind, a variety of fused cyclic diamines were examined and these efforts led to identification of compound **331** which possesses a bicyclo[3.1.0]hexane ring. Compound **331** had an excellent SHP2

inhibition with IC_{50} = 9 nM, and a modest pERK inhibition with IC_{50} = 210 nM. In order to further increase potency, a bicyclic pyrazopyrazole scaffold in compound **332** was employed with pERK inhibition increased by up to 10-fold. Despite promising in vitro potency, compound **332** inhibited hERG with IC_{50} = 58 nM. In order to address this critical issue, dichlorophenyl group was replaced by various bicyclic heterocycles. Among of them, indazole in compound **333** was found to decrease hERG inhibition while keeping excellent in vitro potency. Surprisingly, the corresponding 3-azabicyclo[3.1.0]hexane ring in compound **334** showed excellent in vitro potency and significantly lower hERG inhibition (**Figure 101**). [7]

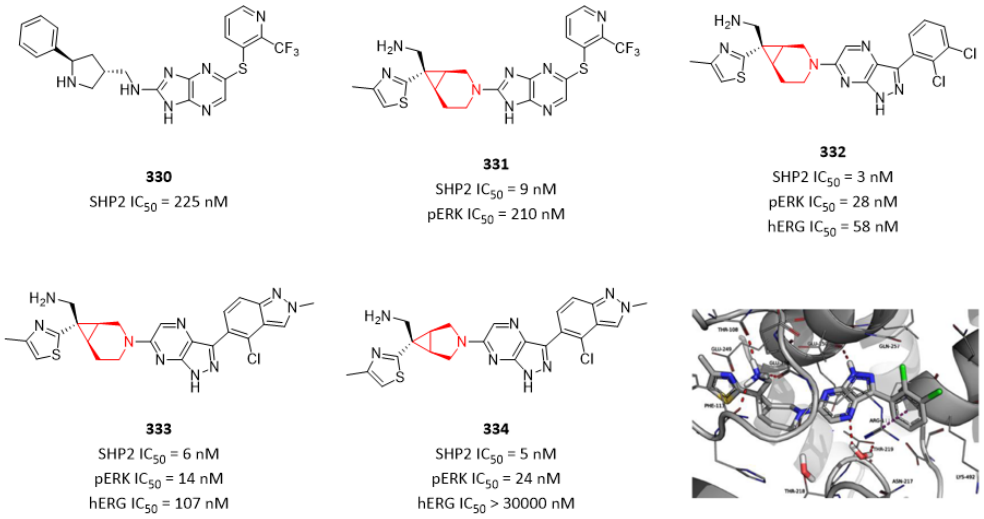

Figure 101. Fused 3-azabicyclo[3.1.0]hexane ring decreased hERG inhibition. (PDB code: 8CBH)

As can be seen in above case stories, a quick access of a diverse collection of fused cyclic building blocks is of great value for medicinal chemists to get SAR or SPR results in their program as soon as possible (**Figure 102**).

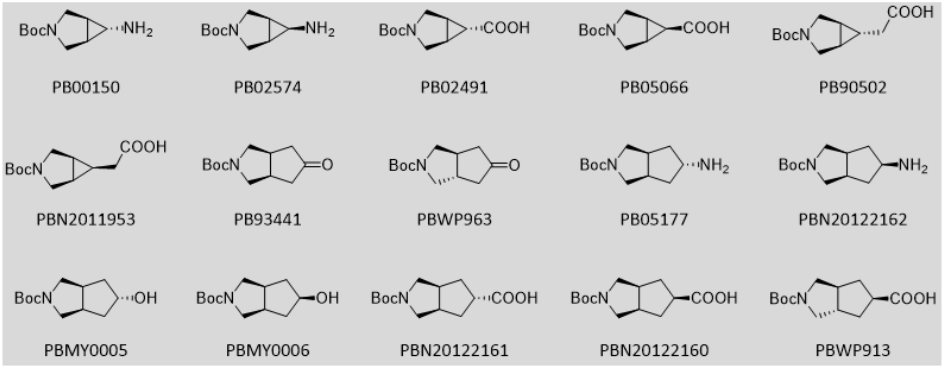

Figure 102. Fused cyclic building blocks with different functional groups

Discovery of compound **339** (**SAR707**) was started from reported compound **335**. Replacement of piperazine moiety with fused hexahydro-pyrrolo-pyrrole ring in compound **336** increased potency by 5-fold. SAR study around the left chain identified compound **337** as the most potent compound, which possesses a cyclopropane. Replacing pyridine with pyridazine in compound **338** didn't change potency. Surprisingly, in compound **339** (**SAR707**), phenyl ring increased SCD1 potency significantly by 25-fold (**Figure 103**). [8]

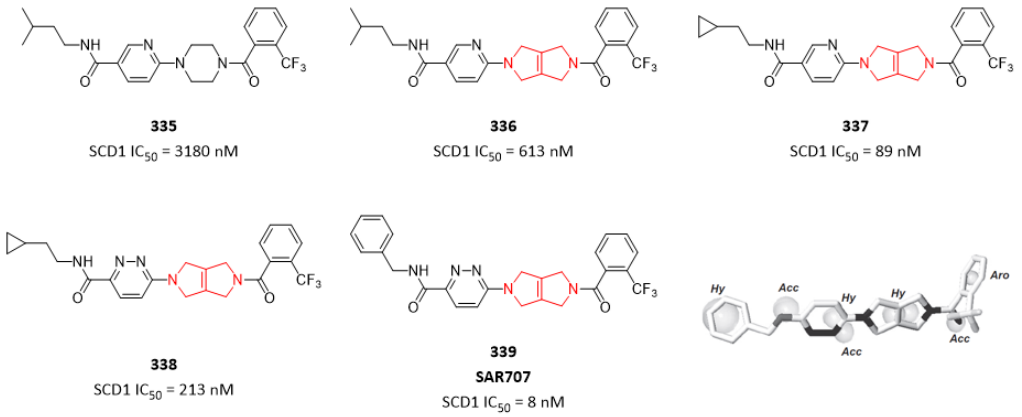

Figure 103. Fused hexahydro-pyrrolo-pyrrole ring in discovery of **SAR707**.

Compound **341** was discovered through an optimization program based on hit compound **340**, and potency was increased by 7-fold. However, compound **341** had CYP inhibition with IC_{50} = 7 uM for CYP3A4 and IC_{50} = 12 uM for CYP2D6 respectively. In order to address this critical issue, replacing piperazine with bioisosteres was employed. One piperazine isostere of interest was the fused octahydropyrrolo[3,4-c]pyrrole ring. As showed in compound **342**, fused octahydropyrrolo[3,4-c]pyrrole also increased potency by 7-fold, but still had CYP inhibition with IC_{50} = 6 uM for CYP3A4 and IC_{50} = 24 uM for CYP2D6 respectively. Further optimization led to compound **343** where adamantly group was replaced with a spirocyclic ring, which demonstrated no CYP3A4 and CYP2D6 inhibition (**Figure 104**). [9]

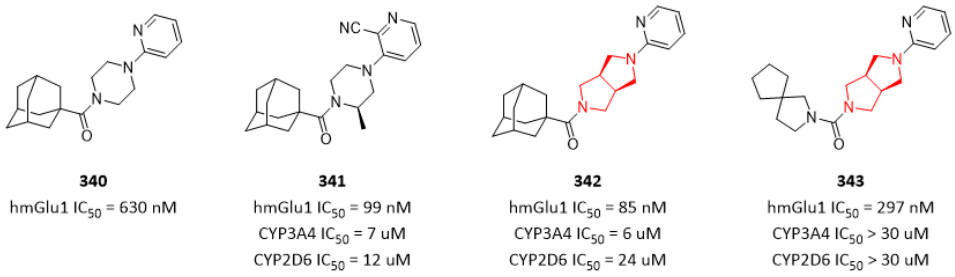

Figure 104. Fused octahydropyrrolo[3,4-c]pyrrole ring increased potency.

In order to discover novel, selective OX2R antagonists that were orally bioavailable and safe with an optimal pharmacokinetic profile for the treatment of primary insomnia, a high-throughput screening campaign was conducted identified a promising hit compound **344**. To further optimize compound **344**, the team decided to investigate SAR and selectivity of compounds with novel core structures. These efforts generated compound **345** possessing a fused octahydropyrrolo[3,4-c]pyrrole ring, which decreased potency significantly by 88-fold. Despite low potency, iterative SAR led to great improvements in both OX2R affinity and selectivity against OX1R, and culminated in discovery of clinical candidate **Seltorexant** (compound **310**) (**Figure 105**). [10]

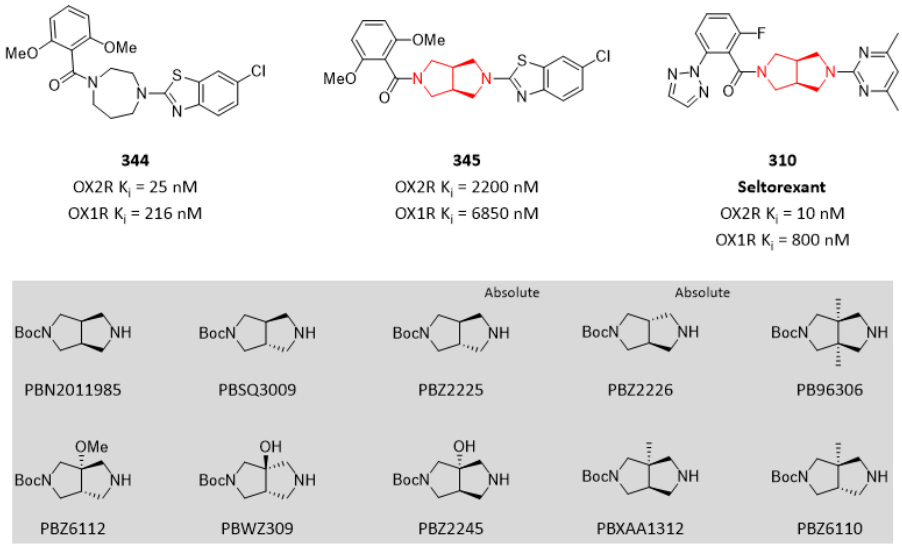

Figure 105. Fused octahydropyrrolo[3,4-c]pyrrole ring in selective OX2R antagonists

To optimize compound **346**, a series of potent neuronal nAChR ligands based on fused 3,8-diazabicylco[4.2.0]octane ring have been synthesized and evaluated for affinity and agonist efficacy at human high affinity nicotine recognition site and in a rat model of persistent nociceptive pain. Among of them, compound **347** and compound **348** exhibited equivalent or greater affinity relative to epibatidine, and demonstrated robust analgesic efficacy in the rat formalin model of persistent pain (**Figure 106**). [11] Fused 3,8-diazabicylco[4.2.0]octane ring was also used in discovery of novel dual orexin receptor antagonists via scaffold hopping approach based on compound **349** (**Suvorexant**). Compound **350** displayed comparable potency to compound **349** (**Suvorexant**). [12]

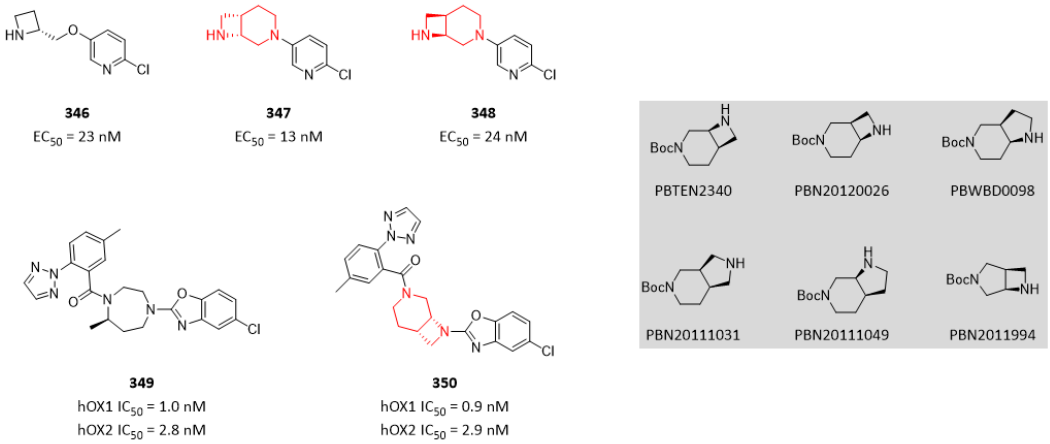

Figure 106. Fused 3,8-diazabicylco[4.2.0]octane ring used in drug discovery

Fused cyclic diamines have been widely used in discovery of novel antibacterial drugs. Based on compound **351**, an additional ring was formed to generate compound **352** which increased potency by 7-fold. However, compound **352** inhibited hERG with 36% inhibition at 100 uM. To address this critical issue, a polar oxygen atom was inserted in compound **353**, and interestingly hERG inhibition was not observed (**Figure 107**). [13] In another work, compound **354** was identified as a highly potent antibacterial inhibitor. Further optimization by introduction of a fused cyclic ring and two fluorine atoms, led to discovery of compound **355** which significantly increased antibacterial potency by 33-

fold. Furthermore, compound **355** also decreased *in vivo* clearance and increased *in vivo* exposure and oral bioavailability. [14]

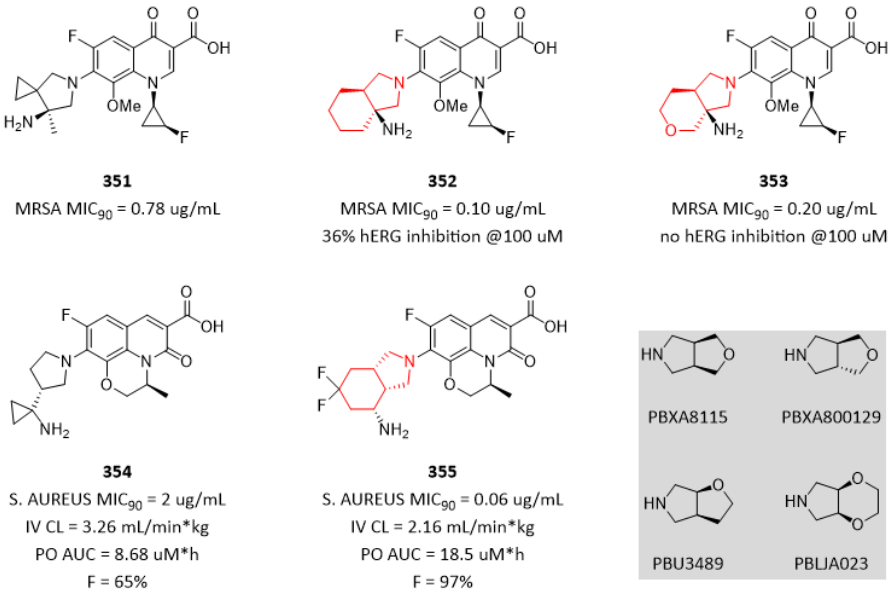

Figure 107. Fused cyclic rings used in discovery of novel antibacterial drugs

The fusion of a cyclopropane ring with two of the carbon of piperazine reduces the basicity of the nitrogen atom. This is attributed to a combination of the known effect of the cyclopropane ring on amine basicity which typically reduces pKa values by 1.15 units, coupled with an effect resulting from the two nitrogen atoms being slightly closer in proximity, disposing at a distance of 2.77 A compared to 2.86 A in the piperazine. The ring fusion also confers an element of conformational constraint. In an effort to assess the potential fused 2,5-diazabicyclo[4.1.0]heptane ring to substitute for the C-7 piperazine ring of compound **356**, analogue **357** was synthesized and evaluated for its in vitro antibacterial properties. The antibacterial potency of compound **357** was comparable to that of compound **356**. In the single crystal X-ray structure of compound **357**, the fused 2,5-diazabicyclo[4.1.0]heptane ring exists in a twist boat-like conformation that results in some distortion of cyclopropane ring (**Figure 108**). [15]

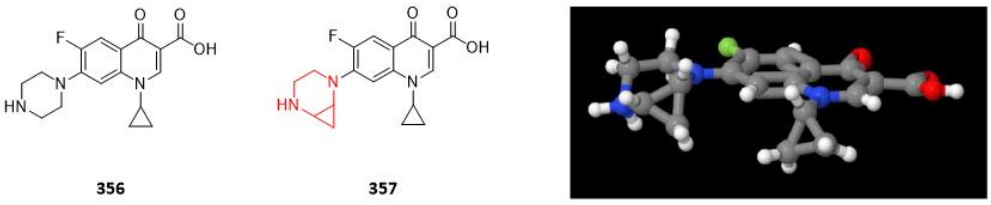

Figure 108. Conformation of fused 2,5-diazabicyclo[4.1.0]heptane ring

It would be greatly interesting to investigate conformation and impact on biological activity of other fused piperazine rings. An efficient access of this kind of building blocks can provide us more insights in potential applications in drug discovery (**Figure 109**).

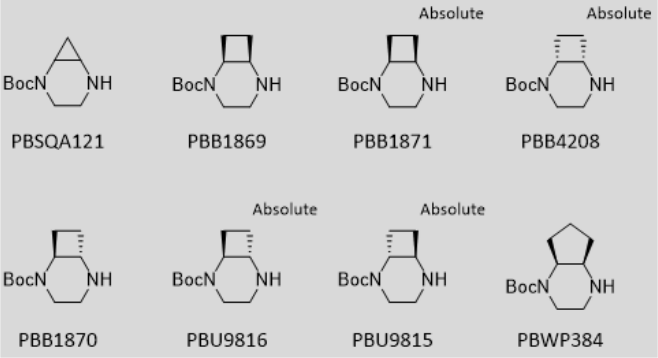

Figure 109. Fused piperazine building blocks

In the course of discovery of clinical candidate **NTQ1062** (compound **359**) as an AKT inhibitor, it was surprisingly to found that the inhibitory of fused piperazine compound **359** was improved by 4-fold compared with compound **358**, and more importantly the exposure was increased by 9-fold. The predicted binding model of compound **359** revealed that the distance between the sulfur in the amino acid residue of Met281 and the cyclopropyl was 3.6 A. The cyclopropyl ring has properties similar to those of carbon-carbon double bond of alkene. Therefore, it was speculated that additional sulfur-pi interaction might contribute to the increase in the potency of compound **359** (**Figure 110**). [16]

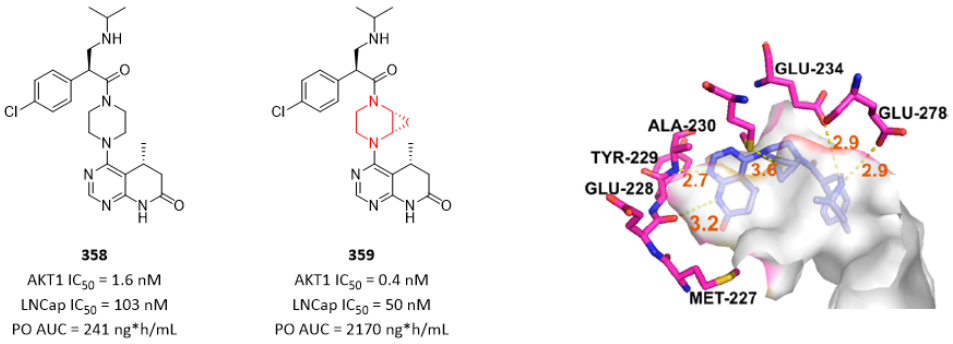

Figure 110. Fused piperazine increased both potency and exposure.

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