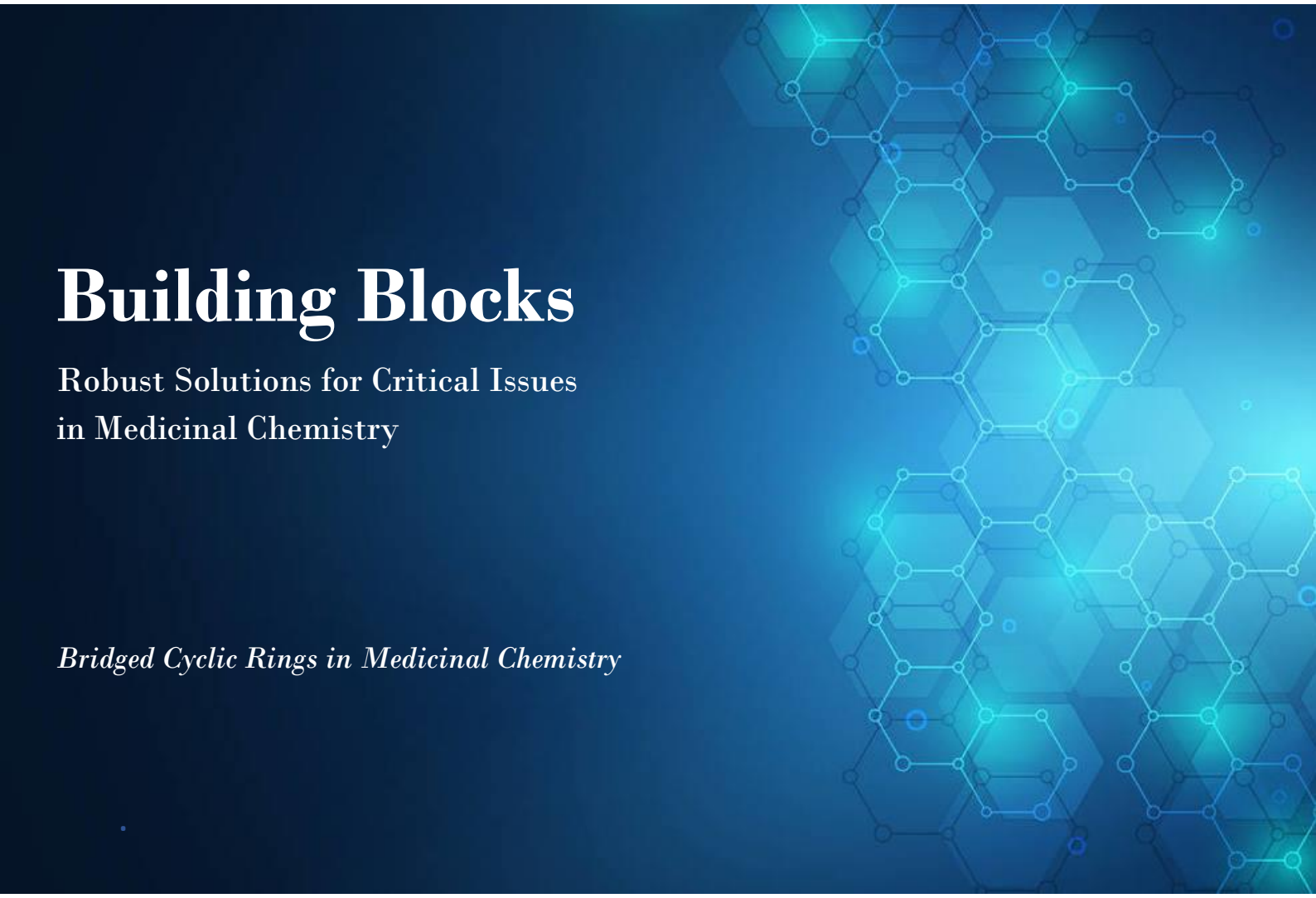

Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Bridged Cyclic Rings in Medicinal Chemistry

Bridged Cyclic Rings in Medicinal Chemistry

Like spirocyclic rings and fused cyclic rings, bridged cyclic ring system is also one of the most popular focus of modern medicinal chemistry, as can be seen by a wide range of applications of bridged cyclic rings in approved drug and clinical candidate molecules (**Figure 111**).

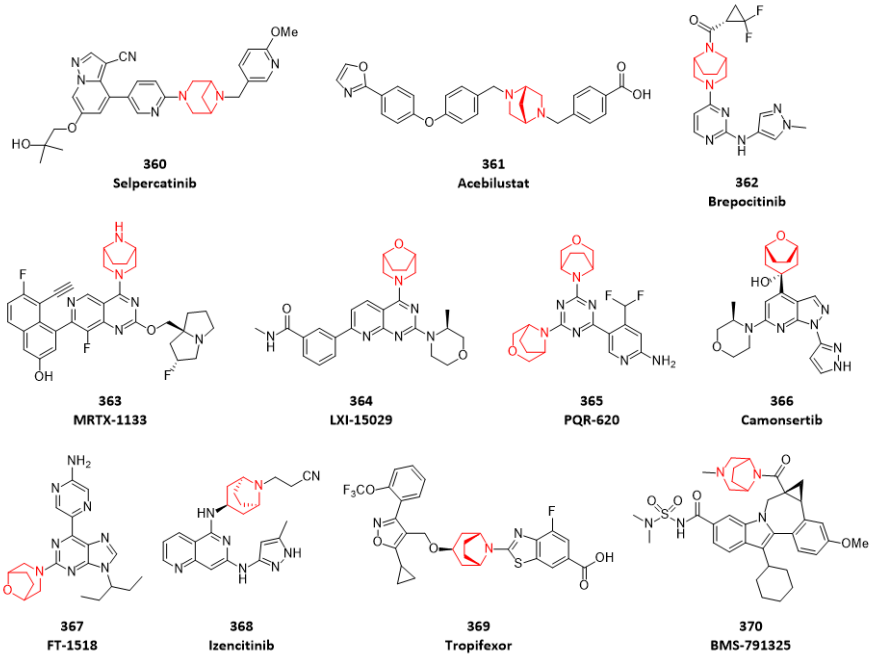

Figure 111. Approved drug and clinical candidate molecules containing bridged cyclic rings

Bridging piperazines, piperidines, morpholines and other mono-rings with one, two or even more carbon atoms can confer them with unexpected observations due to conformational restrictions (**Figure 112**). For instance, it was recommended that medicinal chemists consider the use of one-carbon bridges as a potential strategy to modulate the physicochemical properties of morpholines and piperazines, especially in cases where issues are observed with metabolism, hERG inhibition, or other detrimental properties correlated with lipophilicity. In addition, specific benefits, particularly where the conformational restrictions can potentially be used to improve selectivity or increase potency via subtly changing the shape of the moiety. [1]

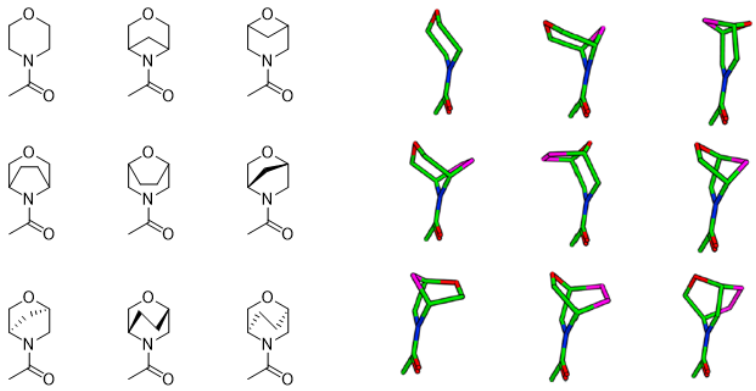

Figure 112. 3-D models of various bridged N-acetylmorpholines (bridged carbons are shown in purple)

In the course of discovery of clinical candidate **Brepocitinib** (compound **362**), a variety of bridged rings were examined in compound **371**, **372**, **373**, **374**, **375**, **376** and **362**. A clear stereochemical

preference is evident from the biochemical activity of compound **371** and compound **372**. Potency against TYK2 improved for compound **374**, compound **375** and compound **376** compared to compound **373**, presumably due to improved hydrophobic interactions of bridged carbon atoms with the residues at the bottom of the binding site. Among of these compounds, compound **376** containing 3,8-diazabicyclo[3.2.1]octane ring demonstrated the highest potency. Further optimization led to discovery of clinical candidate **Brepocitinib** (compound **362**). To better understand the TYK2 potency, a crystal structure of compound **362** bound to TYK2 was obtained. The ethylene bridge of the [3.2.1]-diazabicycle projects into the lower hydrophobic portion of the binding site (**Figure 113**). [2]

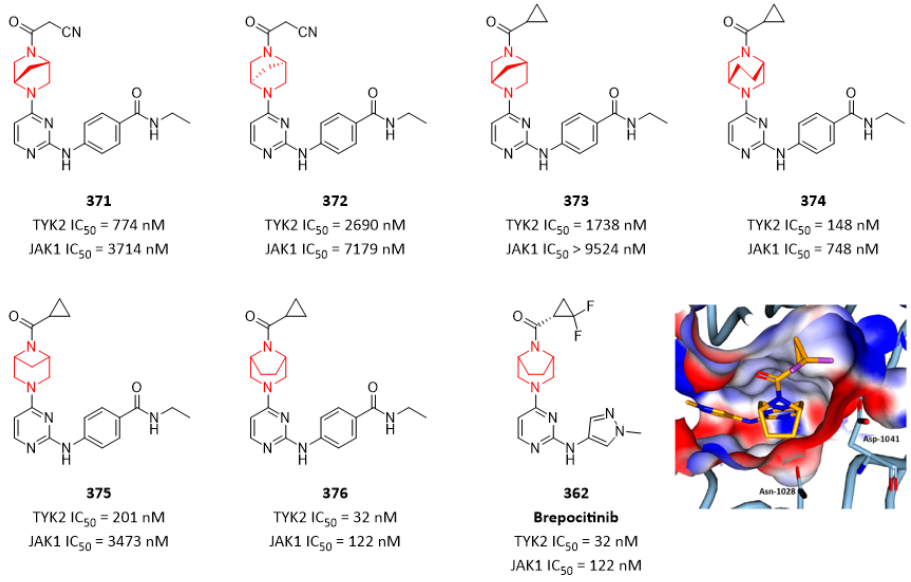

Figure 113. Bridged cyclic rings used in discovery of **Brepocitinib** (PDB code: 6DBM)

As described in above case story, an efficient access of diverse **bridged piperazine building blocks** is of great value for quick exploration of SAR and SPR (**Figure 114**).

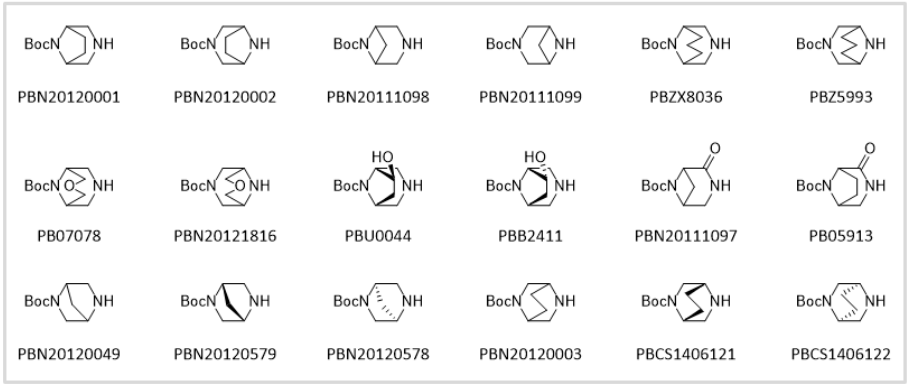

Figure 114. Bridged piperazine building blocks

In order to discover novel KRAS G12D inhibitor, like discovery of **Brepocitinib** (compound **362**) in above, a variety of bridged rings were examined in compound **378**, **379**, **380**, **381**, and **363**. Comparing with compound **377**, all rigidification of bioactive conformation with bridged piperazine increased affinity. Among of them, compound **381** containing a [3.2.1]bicyclic diamino substituent had a 200-fold greater affinity than compound **377**. The X-ray structure of compound **381** bound to KRAS G12D revealed that two-carbon bridge of the bicyclic group occupies a small pocket, while

one of the endo C-Hs forms a non-classical hydrogen bond with the Gly10 carbonyl oxygen (**Figure115**). [3]

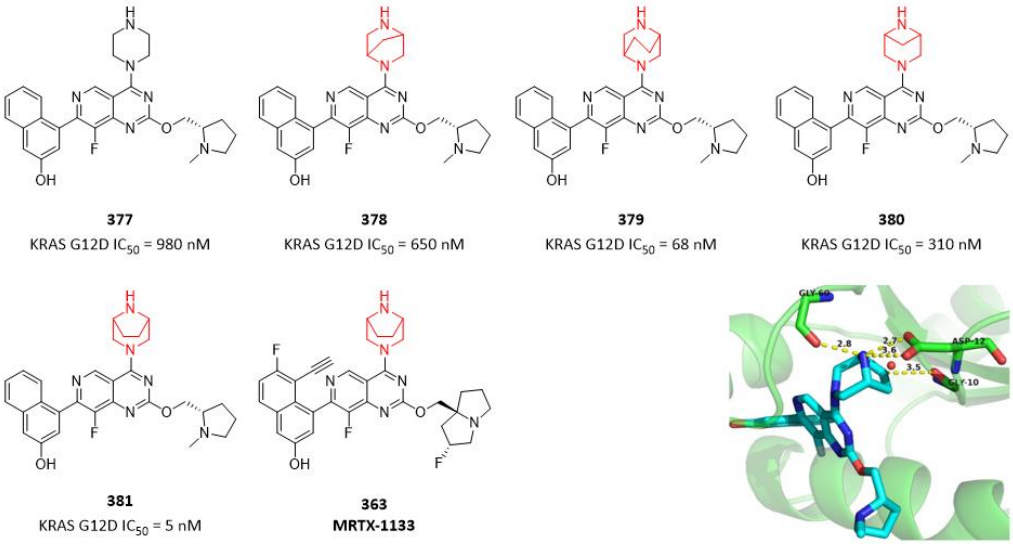

Figure 115. Bridged cyclic rings used in discovery of **MRTX-1133** (PDB code: 7RT1)

In the last section "**Fused Cyclic Rings in Medicinal Chemistry**", we described further optimization of compound **358** which suffered poor oral exposure. Besides fused cyclic rings, the team also investigated bridged cyclic piperazines for improving oral exposure. As shown in compound **382** and compound **383**, 3,8-diazabicyclo[3.2.1]octane ring increased oral exposure by 4-fold and 6-fold respectively (**Figure 116**). However, compound **383** decreased cellular potency by 4-fold. [4]

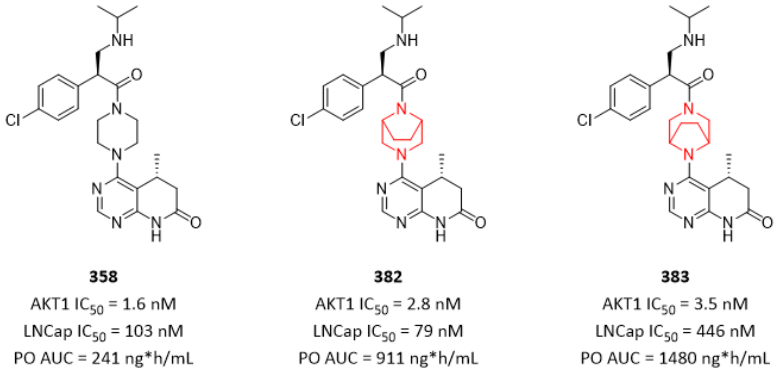

Figure 116. Bridged rings increased oral exposure.

In the course of discovery of clinical candidate **BMS-791325** (compound **370**) as a potent allosteric inhibitor of the hepatitis C virus NS5B polymerase, a variety of bridged cyclic rings were examined to address off-target activities, most notably hPXR transactivation which led to identification of compound **384**. Compound **384**, containing a 3,6-diazabicyclo[3.1.1]heptane ring, had a highly potency and no hPXR issue, but inhibited CYP3A4 with IC_{50} = 14 uM. It was interesting that in compound **370** (**BMS-791325**), containing a 3,8-diazabicyclo[3.2.1]octane ring, demonstrated no CYP3A4 inhibition (**Figure 117**). [5] X-ray structure of compound **370** bound in NS5B revealed that additional contacts between two-carbon bridge of the bicyclic group and proximal protein residues L492, T399 and A400 were observed.

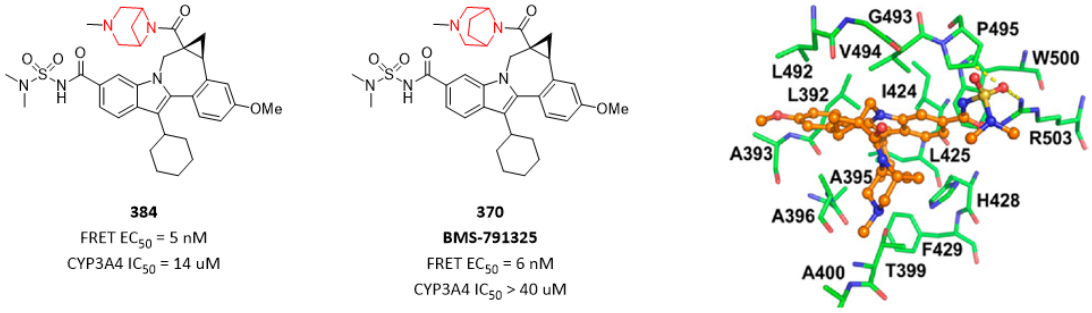

Figure 117. 3,8-Diazabicyclo[3.2.1]octane ring address CYP3A4 inhibition.

Compound **385** was identified as a potent, brain-penetrant and selective M1R antagonist, but showed low metabolic stability and inhibition against hERG. To address these issues, many bridged cyclic rings in compound **386** (**PIPE-359**), compound **387** and compound **388** were examined. A 3,8-diazabicyclo[3.2.1]octane ring in compound **386** (**PIPE-359**) not only increased activity, but also improved metabolic stability and hERG inhibition. However, in compound **387** and compound **388**, two bridged cyclic rings displayed inferior activity (**Figure 118**). [6]

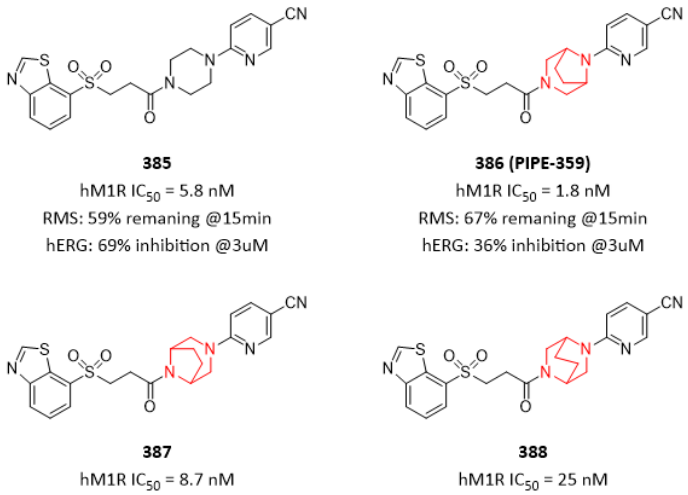

Figure 118. 3,8-Diazabicyclo[3.2.1]octane ring address metabolic stability and hERG inhibition issues.

In order to discover FGFR2 and FGFR3 dual inhibitors with high selectivity against FGFR1 and FGFR4, compound **389** was selected as starting point. Encouraged by previous work, piperazine bearing 2,6-dimethyl group displayed improved FGFR3 potency in comparison to unsubstituted piperazine, suggesting an opportunity to enhance potency and selectivity by introduction of carbon bridge on piperazinone ring. Pleasingly, compound **390**, featuring an ethylene bridge between C-2 and C-6 of the piperazinone, displayed single-digit-nanomolar potency against FGFR3 while maintaining good selectivity against FGFR1 (16-fold). Further optimization led to identification of more promising compound **391**. Docking of compound **391** in binding site revealed that the bridged piperazinone occupies the pocket under the P loop, wherein the ethylene bridge is oriented toward a hydrophobic groove formed by Leu624 and Ala634, placing the amide carbonyl group in the proper position to form a strong hydrogen bond with the catalytic Lys508 (**Figure 119**). [7]

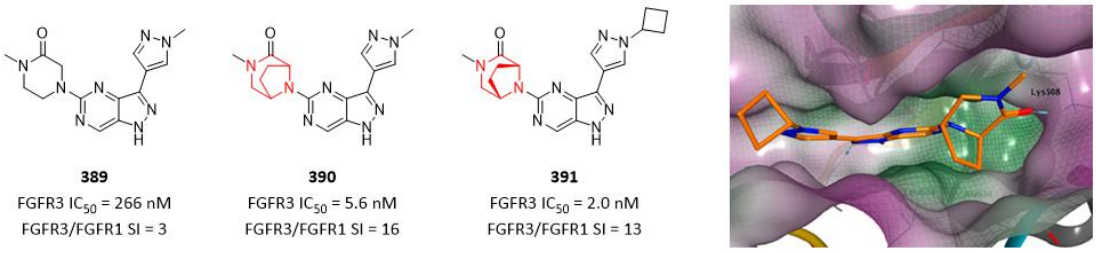

Figure 119. Bridged piperazinone increased both potency and selectivity.

In the course of discovery of clinical candidate **PQR-620** (compound **365**) as a highly potent and selective mTORC1/2 inhibitor, a variety of bridged cyclic rings were investigated to improved selectivity against PI3K. Compound **392**, featuring two morpholines, displayed a high potency, but suffured a low selectivity against PI3K. 8-Oxa-3-azabicyclo[3.2.1]octane ring in compound **393** increased selectivity significantly while keeping a comparable potency. 2-Oxa-5-azabicyclo[2.2.1]heptane ring in compound **394** also increased selectivity significantly while keeping a comparable potency. However, in compound **395** 2-oxa-5-azabicyclo[2.2.1]heptane ring decreased potency dramatically, indicating a preference of chiral conformation. 3-Oxa-6-azabicyclo[3.1.1]heptane ring in compound **396** decreased potency dramatically, although selectivity index was increased to 49 (**Figure 120**). [8]

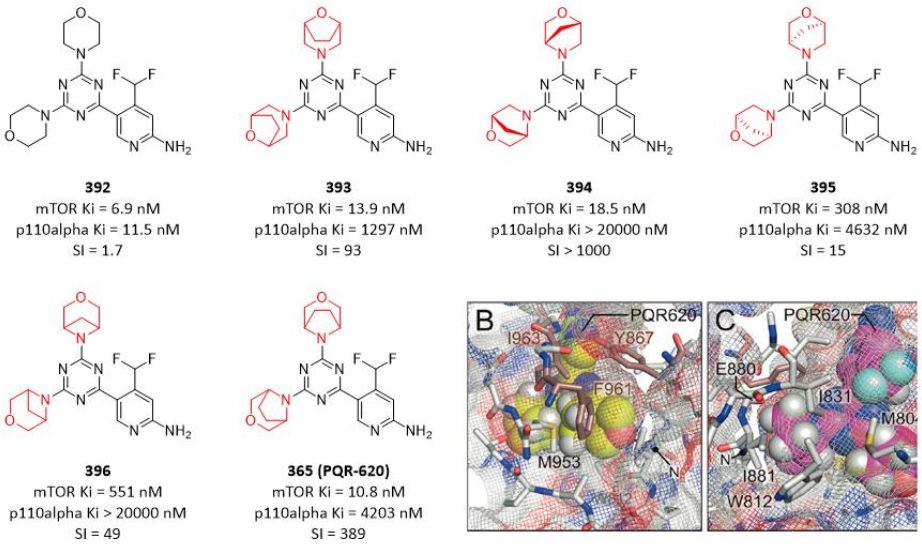

Figure 120. Bridged cyclic rings increased selectivity due to steric clash with protein.

3-Oxa-8-azabicyclo[3.2.1]octane ring in compound **365** (**PQR-620**) increased selectivity significantly with SI = 389, while keeping a comparable potency. Computational modeling studies were used to elucidate the binding mode of compound **365** and ultimately provided structural features defining the compound's high selectivity toward mTOR versus PI3K. The ethylene bridge of the morpholine pointing toward Val882 can take two main conformations, with the bridge oriented toward Met953 defined as bridge-up, or toward Ile881 defined as bridge-down. The bridge-up conformation induces steric clashes within a region of the ATP-binding pocket that has previously been identified as very rigid in PI3K and is defined by residues Tyr867, Phe961 and Ile963. The bridge-down conformation generates steric clash within the backbone of Ile881 and Glu880 and side chains of Ile831 and Ile881. Steric clashes, and as a consequence the weakening of the essential hydrogen bond to the PI3K hinge region explain the reduced affinity of compound **365** for PI3K (**Figure 120**). [8]

As described in above case story, an efficient access of diverse **bridged morpholine building blocks** is of great value for quick exploration of SAR and SPR (**Figure 121**).

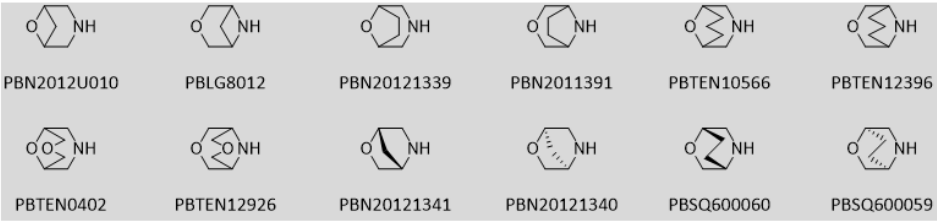

Figure 121. Bridged morpholine building blocks

The trend of selectivity against PI3K in above case story (**Figure 120**) was also observed in another series of mTOR inhibitors. Compared to compound **397** with morpholine ring unsubstituted, 8-oxa-

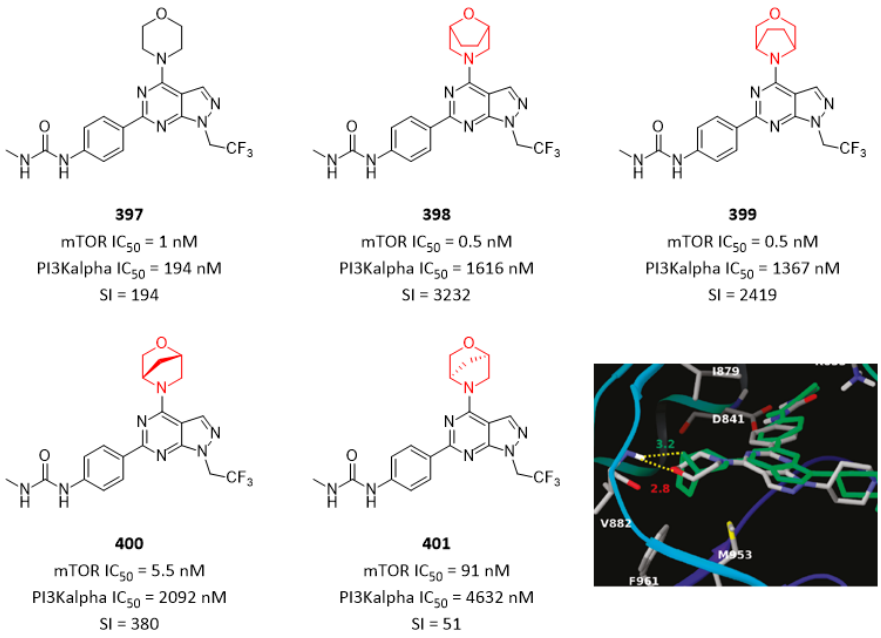

Figure 122. Bridged morpholines increased selectivity due to steric clash.

3-azabicyclo[3.2.1]octane ring in compound **398** and 3-oxa-8-azabicyclo[3.2.1]octane ring in compound **399** both increased selectivity significantly, while keeping comparable potency. However, 2-oxa-5-azabicyclo[2.2.1]heptane rings in compound **400** and compound **401** decreased potency. Docking of the bridged morpholine analogue suggests that a single amino acid difference between mTOR and PI3K causes a difference in the depth of the morpholine binding pockets that is responsible for the increased selectivity observed. Modeling indicates that Phe961 of PI3K is too large to comfortably accommodate the ethylene-bridged morpholine, causing displacement of the morpholine oxygen away from its hydrogen bonding partner, the backbone NH of Val882 (**Figure 122**). [9]

In order to obtain an orally available GSM without covalent binding and phototoxicity, compound **402** was identified as a promising starting point, which has moderate potency and very low human plasma-free fraction and low solubility. By exploring replacements for the central ring with various bridged, bicyclic or azaspiro-piperidine analogues, it was realized that the best replacement was [3.2.1] bridged piperidine as existed in compound **403**. Compound **403** gave an excellent

improvement in potency along with decreased protein binding with human plasma free fraction increased to 40% compared to compound **402**. The potency improvement can be caused by a most favorable conformational change due to the repulsion between the bridge and the lone electron pair from the piperidine nitrogen that enforces an almost linear orientation of the two exit vectors from the piperidine, enabling an optimal binding to gamma-secretase (**Figure 123**). [10]

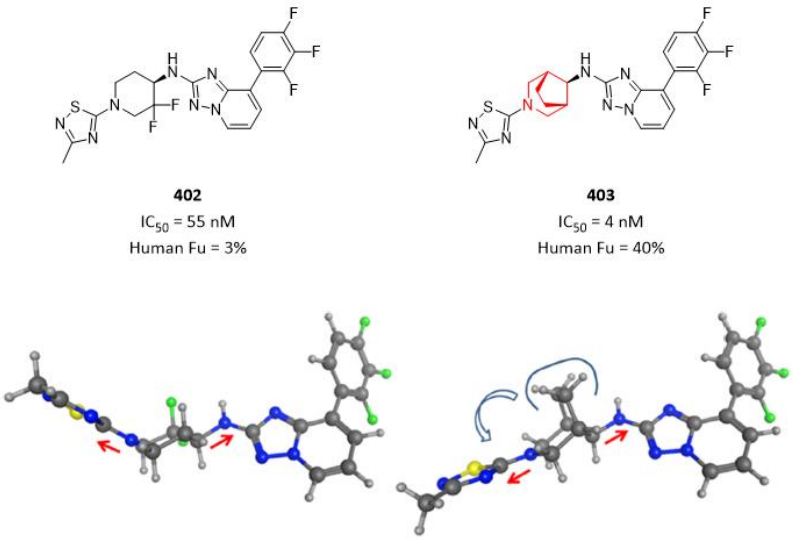

Figure 123. Bridged piperidine increased potency by conformational modulation.

In the course of discovery **EPZ030456** (compound **406**) as the first orally bioavailable small-molecule SMYD3 inhibitor, compound **404** was identified as a promising starting point. Further restriction of conformational freedom with the bridged piperidine core, compound **405**, gave a 17-fold potency improvement over compound **404**. Further optimization led to identification of **EPZ030456** (compound **406**) which displayed stronger potency in cellular assay and demonstrated superior PK profile. To better understand binding model, X-ray crystal structure of compound **406** bound to **SMYD3** was obtained (**Figure 124**). [11]

As described in above two case stories where various bridged piperidine were used to solve critical issues in medicinal chemistry, it is obvious that an efficient access of diverse bridged piperidine building blocks is of great value for medicinal chemists (**Figure 124**).

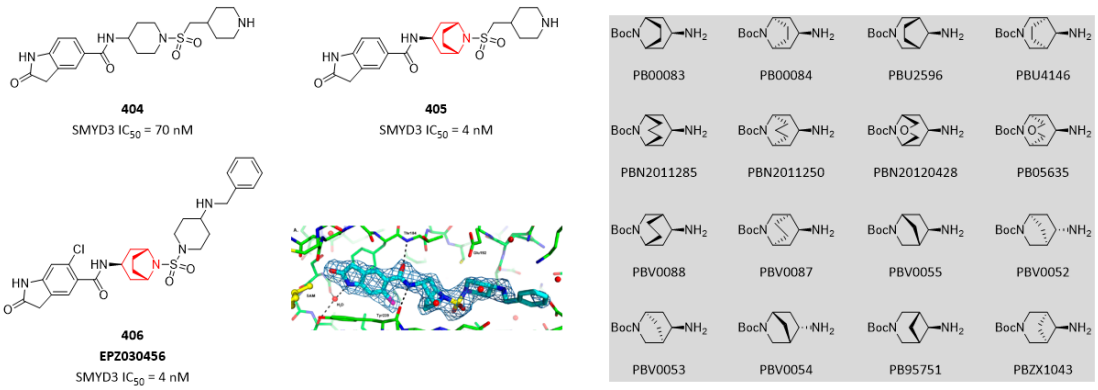

Figure 124. Bridged piperidine increased potency and related building blocks

It was found that compound **408** can fully antagonize an agonist response, while compound **407** can antagonize to approximately 20% of maximum. Taken together with the pharmacology results, the

conformational analysis of compound **407**, compound **408** and compound **409** led the team to propose the agonist conformation hypothesis shown in **Figure 125**. Compound **407** can explore the agonist and antagonist forms from the accessible axial and equatorial conformations and shows partial agonist activity. Compound **408** is constrained to the antagonist conformation and is an antagonist. The agonist conformation is energetically preferred by compound **409**, and this accounts for the greater functional response observed. Complete switching in the functional profile can be attributed to conformational differences in the ligand. [12]

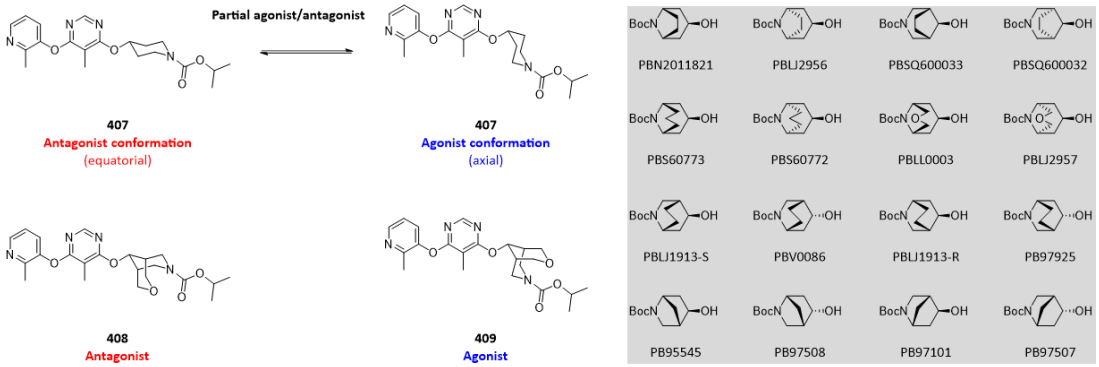

Figure 125. Conformational differences changed mechanism of action.

In order to discover potent, selective, and brain-penetrant LRRK2 inhibitors, the team identified compound **410** as a promising lead compound with high potency. However, this compound suffered very low solubility (< 2 uM), which hinder further development. To address this critical issue, the team focused on disrupting planarity through the introduction of additional complex Fsp^3-riched fragment in the solvent front. With respect to design, the team sought to incorporate fused and/or bridged bicyclic ring systems that, in addition to improving solubility, could also decrease oxidative metabolism of the pyrrolidine and potentially reduce P-gp efflux by further masking the tertiary alcohol polarity. This design logic resulted in the synthesis of azabicyclo[2.1.1]hexane compound **411**, which demonstrated a significantly increased solubility while keeping a comparable potency (**Figure 126**). [13] This kind of caged pyrrolidine building blocks are of great value for exploring SAR and SPR.

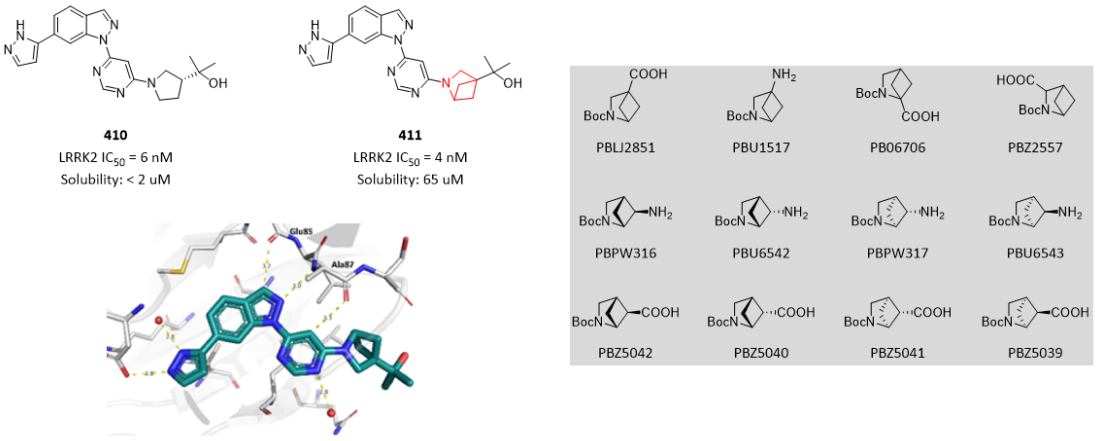

Figure 126. Caged pyrrolidine increased aqueous solubility. (PDB code: 8E80)

Initial evaluation of the SAR from the HTS screen suggested that the diazepane ring found in compound **412** was essential for GCSi activity. Substituted with ethyl group in compound **413**

caused > 10-fold lower potency. However, cyclizing the ethyl group into a 1,4-diazabicyclo[3.2.2]nonane in compound **414** improved the potency > 1000-fold (**Figure 127**). [14]

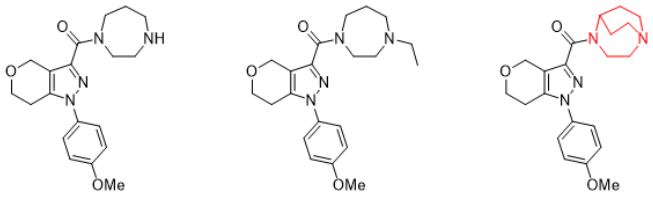

Figure 127. 1,4-Diazabicyclo[3.2.2]nonane increased potency significantly.

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