Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Scaffold Hopping in Medicinal Chemistry

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In medicinal chemistry, scaffold hopping is a strategy for designing new drug molecules by replacing the core structure or scaffold of an existing drug molecule with a structurally different one while still retaining the key biological activity. This can be done by identifying common features or pharmacophores of the original scaffold and the desired scaffold, and then using computational or medicinal methods to design and optimize new molecules with similar activity. In the practice, scaffold hopping is carried out for different purposes. For example, one might be interested in circumventing an intellectual property position by identifying novel chemical entities having a desired activity, improving ADMET profile, or decreasing toxicity. [1]

The past 10 years witnessed great success in discovery and development of BTK inhibitors. **Ibrutinib** (**135**) was the first BTK inhibitor approved for the treatment of several B cell malignancies. [2] However, due to its binding to BTK in its active conformation, **Ibrutinib** not only potently inhibits BTK, but also inhibits all kinases which carry a Cys at the same position as BTK. Consequently, it is associated with several side effects, such as skin rash and diarrhea which are well associated with EGFR inhibition, and platelet disfunction which is resulted from TEC and SRC inhibition. Second generation of BTK inhibitors, **Acalabrutinib** [3] and **Tirabrutinib** [4], were discovered by employing scaffold hopping strategy based on **Ibrutinib**. Althought both of them retain a similar binding mode to BTK as **Ibrutinib**, they offer an overall improved selectivity profile against other kinases and therefore reduce side effects observed in treatment with **Ibrutinib** (**Figure 52**).

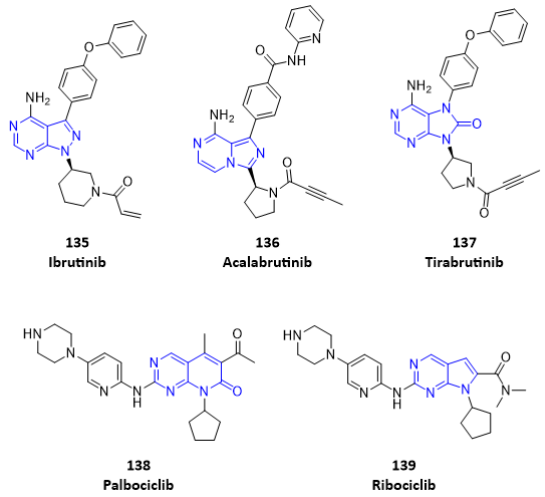

Figure 52. BTK inhibitors and CDK4/6 inhibitors approved by FDA

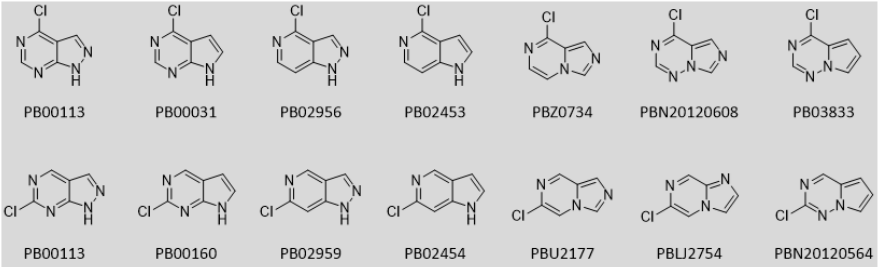

Figure 53. Building blocks for systematic scaffold hopping studies

Discovery of CDK4/6 inhibitors is another well-known example, representing the high value of scaffold hopping. CDK4/6 inhibitors brought as remarkable influence as BTK inhibitors for the

treatment of cancers and became a new standard of care of patients with advanced hormone receptor-positive breast cancer. [5] **Palbociclib** (**138**) and **Ribociclib** (**139**) were the first two drugs approved by FDA. [6] Obviously, there are several common features in structures of **Palbociclib** and **Ribociclib**, and the most distinct difference is the two scaffolds used (**Figure 52**). An efficient access of a set of diverse building blocks is considered of great value for medicinal chemists to conduct SAR/SPR studies by scaffold hopping (**Figure 53**).

In order to discover selective oral inhibitors of ERK1/2, previous scaffold hopping efforts based on compound **140** with a pyrrolo-pyrazinone scaffold generated compound **141** with an imidazo-pyrazinone scaffold. It was remarkable than a nitrogen atom in the scaffold of compound **141** increased aqueous solubility significantly by 55-fold and reduced metabolism in human microsome. The same trend was observed in paired compounds **142** and **143**. In addition, compounds **141** and **143** also demonstrated improved kinase selectivity to compounds **140** and **142** respectively (data not shown, **Figure 54**). Further lead optimization based on compound **143** generated a clinical candidate **AZD0364** for the treatment of NSCLC. [7]

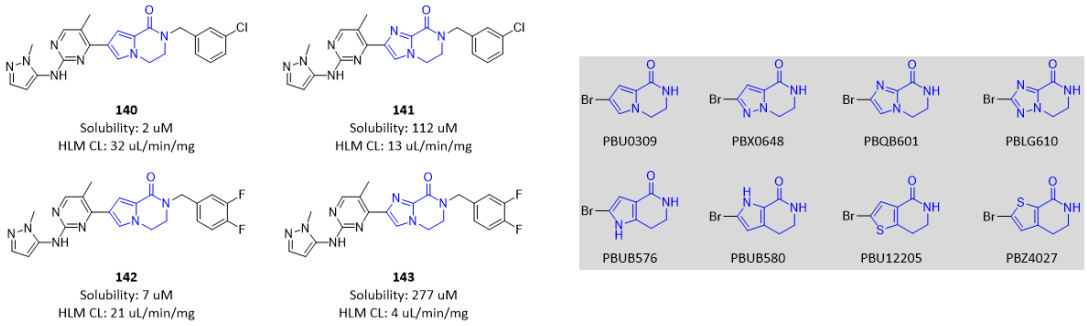

Figure 54. Scaffold hopping increased aqueous solubility and reduced metabolism.

Filgotinib (**144**) is one of second-generation JAK inhibitors with high JAK1 selectivity against other JAK family members, which was approved for the treatment of autoimmune and inflammatory diseases, such as rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD). [8] The amide hydrolysis reaction and the corresponding metabolite **AMF** (**145**) of **Filgotinib** (**144**) is primarily mediated by CES2. Notably, its amide hydrolysis metabolite **AMF** (**145**) show much higher exposure, longer half-life but 10-fold lower potency than those of **Filgotinib** (**144**) in human. Besides, both **Filgotinib** (**144**) and **AMF** (**145**) are substrates of PgP, and potential inhibitors of organic anion transporting polypeptides. Hereby further investigations of drug-drug interactions based on these transporters in clinic is still ongoing. In order to circumvent amide hydrolysis, scaffold hopping studies based on **Filgotinib** (**144**) generated a novel clinical candidate **FZJ-003** (**146**) where a nitrogen atom was removed from core structure. It was extremely interesting that amide hydrolysis of **FZJ-003** (**146**) was not observed, which was reflected by higher exposure of **FZJ-003** (**146**) than **Filgotinib** (**144**) and almost no metabolite **FZJ-004** (**147**) of **FZJ-003** (**146**) was detected in PK studies (**Figure 55**). It was hypothesized that electron density of nitrogen of amide of **FZJ-003** (**146**) is higher than that of **Filgotinib** (**144**), which is resulted from the lower electron-withdrawing ability of imidazole ring of **FZJ-003** (**146**) than that of triazole ring of **Filgotinib** (**144**). In addition, compared to **Filgotinib** (**144**), **FZJ-003** (**146**) displayed 5-fold higher potency for JAK1 while maintaining similar selectivity against other JAK family members. [9]

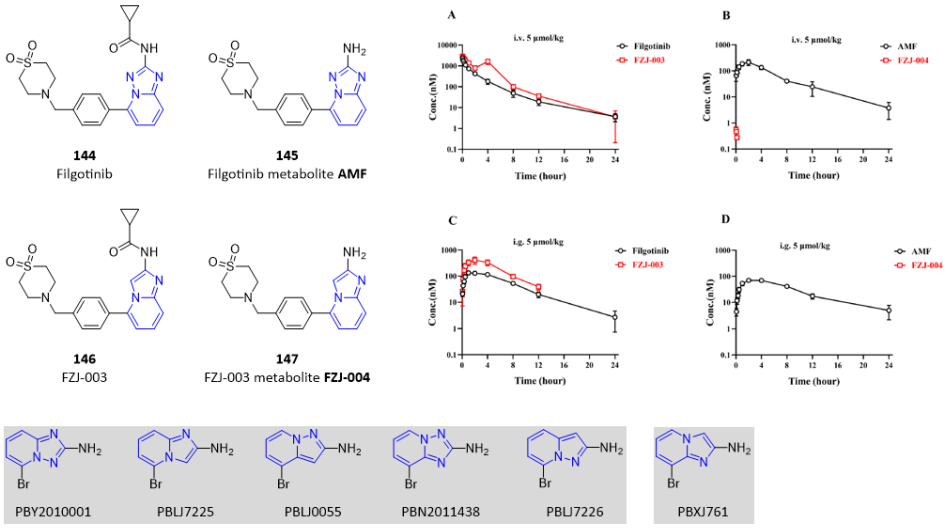

Figure 55. Novel scaffold in FZJ-003 resolved amide hydrolysis issue of Filgotinib.

Compound **148** was selected as a starting point for medicinal chemistry to discover novel CAMKK2 inhibitors. The team employed scaffold hopping by replacing 7-azaindole ring in compound **148** with a variety of diverse scaffolds. In summary, most of scaffolds exhibited robust CAMKK2 enzyme inhibition, such as furopyridine ring in compound **149**, thienopyridine ring in compound **150**, pyrazolopyridine ring in compound **151** and pyrazolopyrimidine in compound **152**. Among of them, compound **150** demonstrated comparable potency to compound **148**. [10] Dihalo- scaffolds are critical starting materials for quick access of these compound for evaluation. (**Figure 56**)

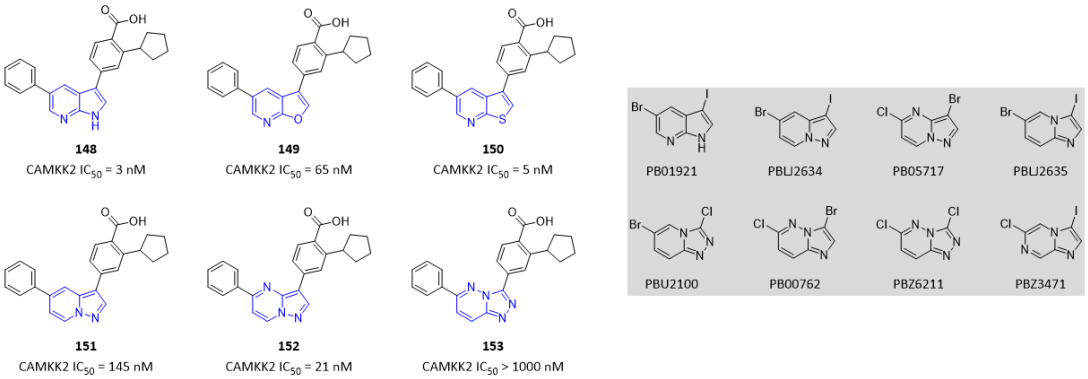

Figure 56. Scaffold hopping identified novel CAMKK2 inhibitors.

To further evaluate fused 5,6-ring structures as CAMKK2 inhibitors, the team switched from 3,5-ring substitutions as depicted in **Figure 56** to 2,4-ring substitutions as depicted in **Figure 57**. All of these compounds, compound **154** with an imidazopyridine core structure, compound **155** with a thienopyrimidine core structure and compound **156** with a reverse thienopyrimidine core structure, exhibited high CAMKK2 inhibition. Besides three scaffold used by the team in **Figure 57**, there are several other novel scaffolds which could potentially be employed by the team to further explore SAR and SPR.

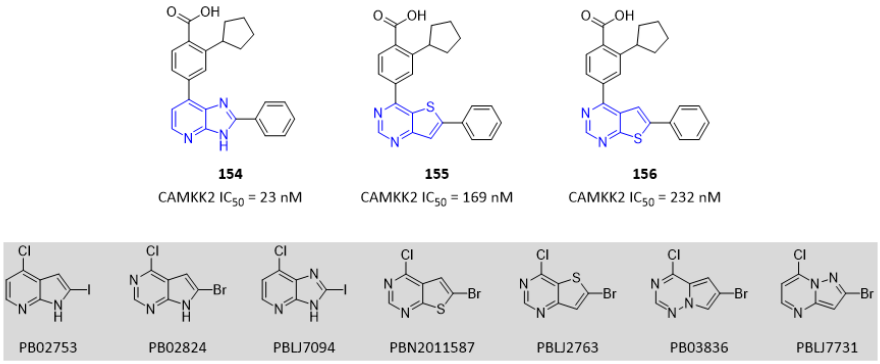

Figure 57. Scaffold hopping identified novel CAMKK2 inhibitors.

In order to discover a novel NIK inhibitor which is sufficient for robust *in vivo* evaluation of NIK pharmacology, the team tried several scaffolds with some of them represented in **Figure 58**. Comparing compound **157** and compound **158**, it was found that an additional nitrogen atom in the scaffold of compound **158** increased NIK binding affinity by at least 1500-fold. This observation can be explained by a potential intramolecular hydrogen bond between hydrogen of amide and the nitrogen atom, which lock the molecule in a binding favorable conformation as shown in the X-ray structure of an analogue. [11] Elimination of nitrogen from pyridine ring of compound **158** generated compound **159** with NIK binding affinity kept. It can be concluded that the nitrogen atom has no interaction with NIK protein, and this why compound **160** and **161** also displayed high NIK binding affinity.

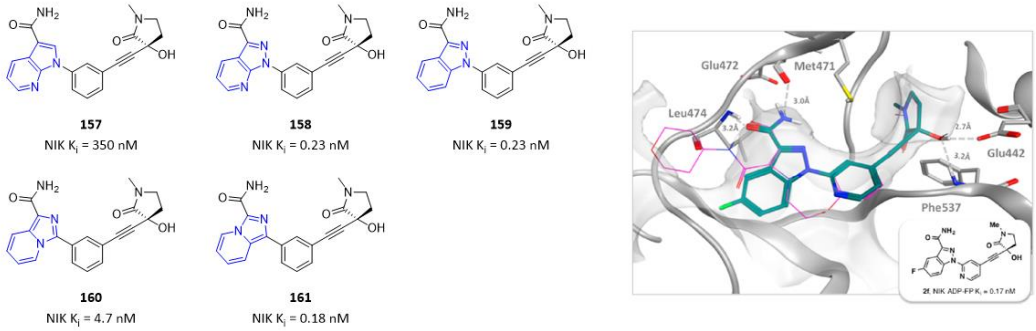

Figure 58. Scaffold hopping identified novel highly potent NIK inhibitors. (PDB code: 6G4Z)

Ester scaffold building blocks listed in **Figure 59** are essential starting materials for quick access of designed molecules in above medicinal campaign. Furthermore, building blocks which can offer C-C linking are of great value for medicinal chemists.

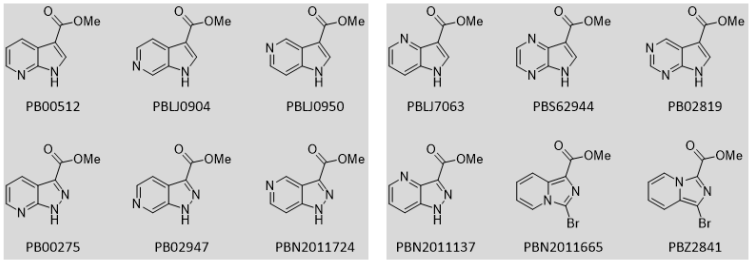

Figure 59. Ester building blocks used in scaffold hopping in above discovery campaign

In order to discover GCS inhibitors with a novel scaffold, the team screened internal library and identified a hit compound **163** which was structurally distinct from previously reported GCS inhibitors. Hit-to lead optimization was started by scaffold hopping. Isoindolinone core in compound **162** displayed improved potency, but reduced significantly solubility due to enhanced

lipophilicity. In order to circumvent solubility issue, a nitrogen atom was introduced at another position on the core to reduce lipophilicity. The introduction of a nitrogen atom in compound **164** and in compound **165** was well tolerated in terms of GCS inhibitory potency, and compound **165** demonstrated significantly improved solubility. Further optimization based on compound **165** by exploration of substitutions on two phenyl rings generated lead compound **166**. Although compound **166** showed encouraging *in vivo* activity, oral administration of compound **166** at 30 or 100 mg/kg daily for 3 days reduced body weight. The team hypothesized that the observed body weight reduction was due to off-target inhibition of SERT with IC_{50} = 310 nM. SERT inhibition was reportedly induces hypophagia and reduces body weight in rats. With this in mind, the team continued to optimize by scaffold hopping, and found that pyridazin-3-one core in compound **167** exhibited comparable potency while decreasing efflux ratio which potentially benefit BBB-penetration. Removing fluorine from compound **167** generated compound **168** which exhibited 3-fold increased GCS potency (**Figure 60**). Compound **168** has no SERT inhibitory activity with IC_{50} > 10 uM, and showed no reduction in body weight at any dose examined, indicating that compound **168** has a safer off-target toxicology profile than compound **166**. [12]

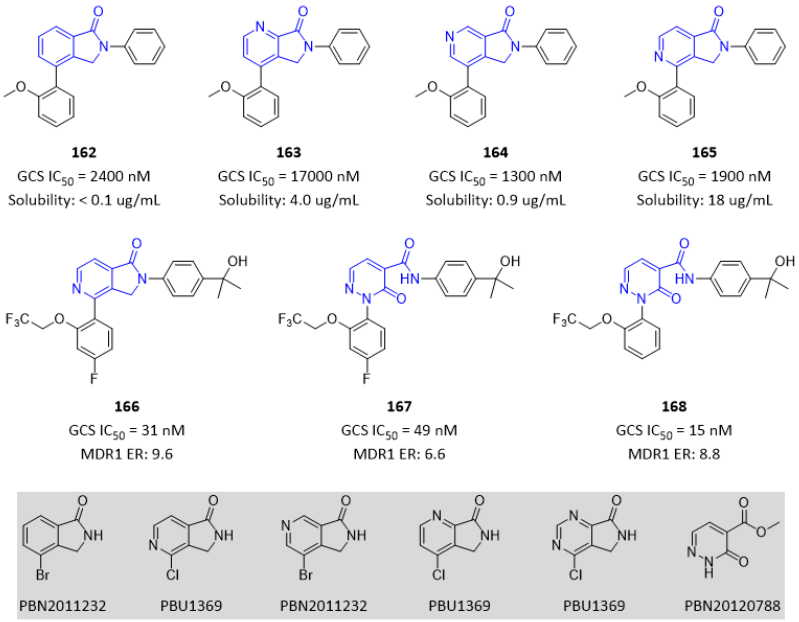

Figure 60. Scaffold hopping resolved toxicity issue.

A new chemical series, triazolo[4,5-b]pyridine, has been identified as an inhibitor of PIM-1 by scaffold hopping strategy. Comparing compound **169** with an imidazolo[1,2-b]pyridazine core and compound **170** with a triazolo[4,5-b]pyridine core, it was extremely interesting that FLT-3 selective compound **169** was changed to PIM-1/2/3 selective compound **170** by a simple scaffold hopping. The same trend was also observed in pair compound **171** and **172**. [13] It was notable that compound **171** was discontinued from phase 1 clinical trials, because it failed to demonstrate a safe therapeutic window (**Figure 61**).

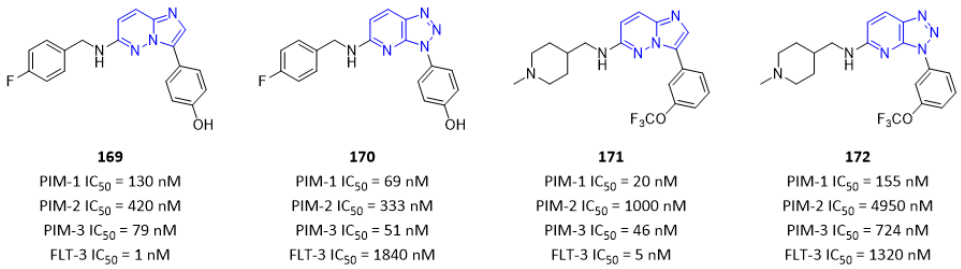

Figure 61. Scaffold hopping resolved selectivity issue.

In order to discover small-molecule inhibitors of TNFalpha, the team examined naphthyridine scaffolds as alternatives to the quinolone core in compound **173**. Compound **174** with a 1,5-naphthyridine core showed comparable potency, while compound **175** with a 1,7-naphthyridine core and compound **176** with a 1,8-naphthyridine core lost potency a lot. This observation can be explained due to better pi-stacking capability of 1,5-naphthyridine in compound **174** with Tyr135. In addition, in the case of 1,7-naphthyridine in compound **175** and 1,8-naphthyridine in compound **176**, the additional nitrogen atom is placed in a hydrophobic environment leading to a significant desolvation penalty, thereby lowering the potency in the binding assay (**Figure 62**). [14]

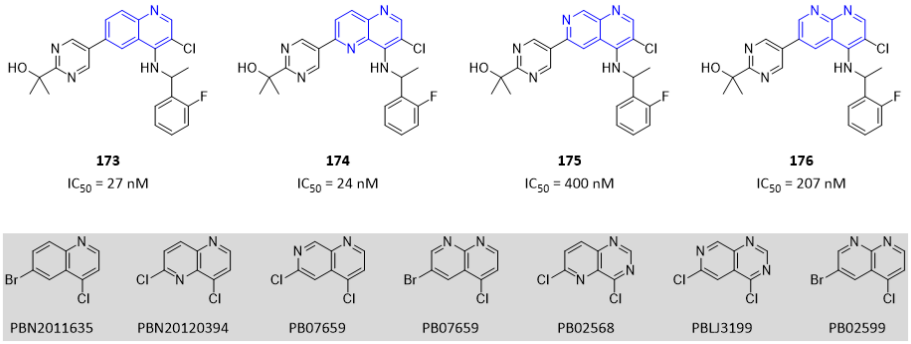

Figure 62. Naphthyridine scaffolds impacted potency in different way.

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About Author

Jin Li

Senior Director

10+ years' experience in organic chemistry
3+ years' experience in medicinal chemistry
10+ patents and papers published
Inventor of 2 clinical candidates
Email: li_jin@pharmablock.com

Contact Us

PharmaBlock Sciences (Nanjing), Inc.
Tel: +86-400 025 5188
Email: sales@pharmablock.com

PharmaBlock (USA), Inc.
Tel(PA): +1(877)878-5226 Tel(CA): +1(267) 649-7271
Email: salesusa@pharmablock.com

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