

Application of Scaffold Hopping in Drug Discovery

Mar 2023



Introduction

The general goal of drug discovery is the rapid identification of novel compounds, which are active against a preselected biological target relevant to a disease with sufficient safety and drug-like properties. Scaffold hopping is a central task of modern medicinal chemistry for rational drug design, which is widely used by medicinal chemists to discover equipotent compounds with novel backbones and improved properties toward known hit molecules. Most used methods in Scaffold hopping include topology-based hopping (**Figure 1**)^{1,2}, heterocycle replacements (**Figure 2**)³, ring opening (**Figure 3**)⁴ or ring closure (**Figure 4**)⁴, and etc.

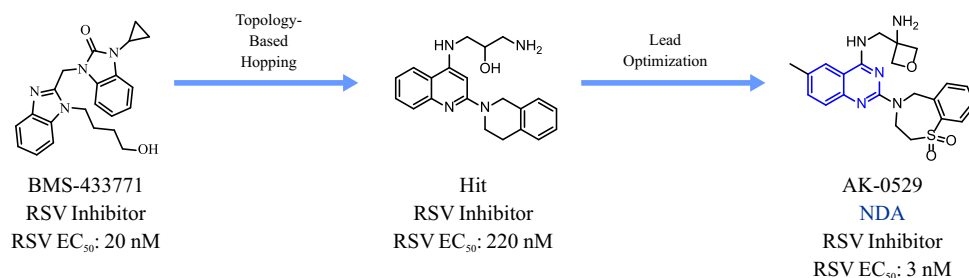


Figure 1. Using Topology-based Hopping Method to Identify a Novel RSV Drug

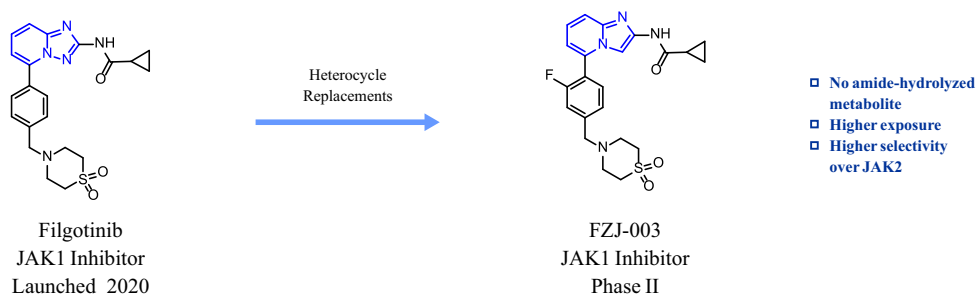


Figure 2. Using Heterocycle Replacements Method to Identify a Novel JAK1 Inhibitor

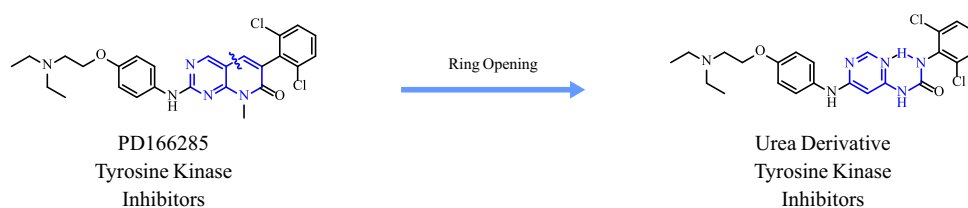


Figure 3. Using Ring Opening Method to Identify a Novel Tyrosine Kinase Inhibitors

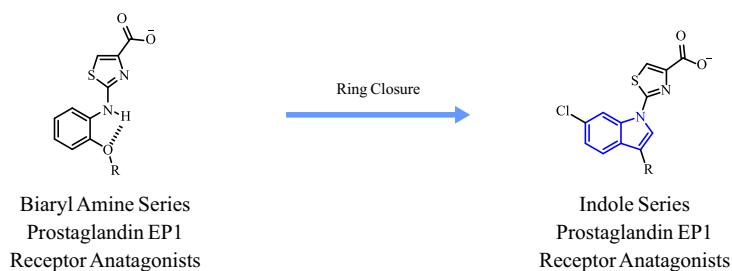
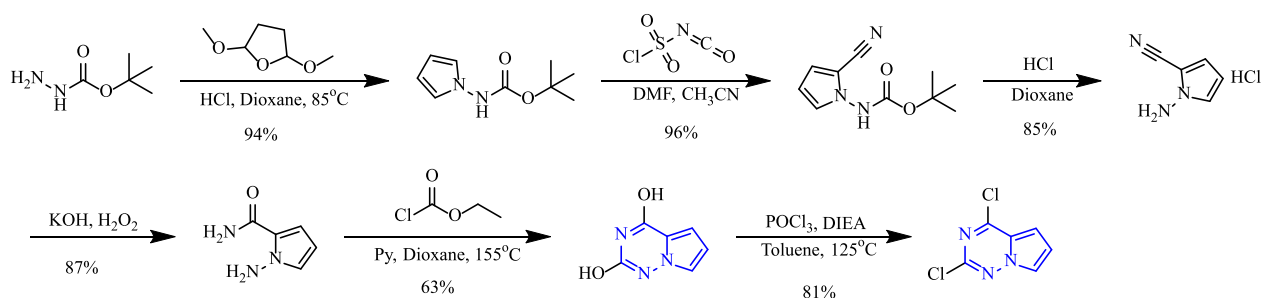


Figure 4. Using Ring Closure Method to Identify a Novel Prostaglandin EP1 Receptor Antagonists

Heterocyclic chemistry Developed at PharmaBlock

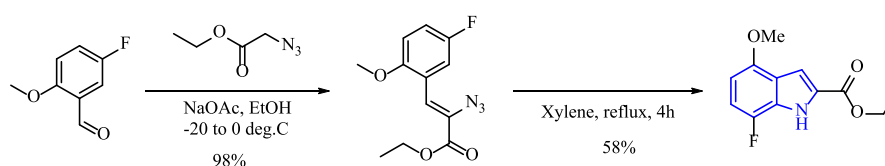
The core structures of drug molecules are generally heterocyclic compounds, and heterocycle replacement is a commonly used scaffold hopping method. PharmaBlock has rich experience in heterocyclic chemistry, and has a large number of heterocyclic products in stock. We can also provide customized synthesis services for our customers. Here are some common methods for the synthesis of heterocyclic compounds.

1) Synthesis of pyrrolo[2,1-f][1,2,4]triazine derivatives

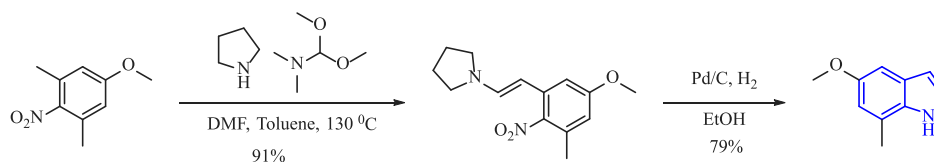


WO2008005956 A2

2) Synthesis of indole derivatives

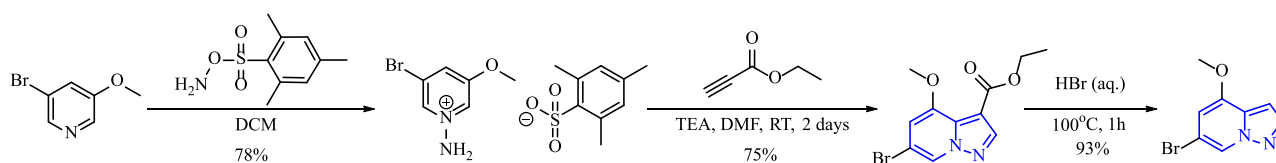


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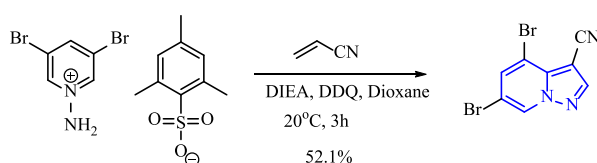


CN112457235

3) Synthesis of pyrazolo[1,5-a]pyridine derivatives

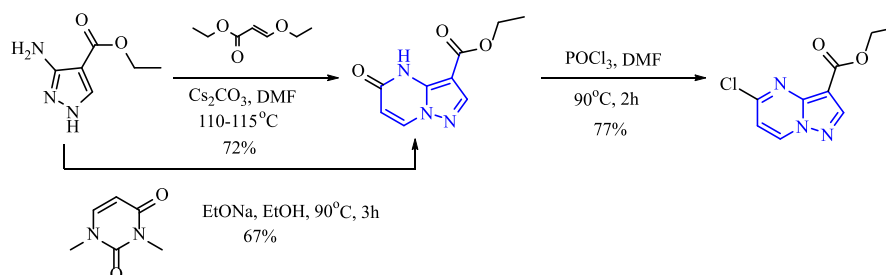


WO2022037643 A1



WO2019075114 A1

4) Synthesis of pyrazolo[1,5-a]pyrimidine derivatives

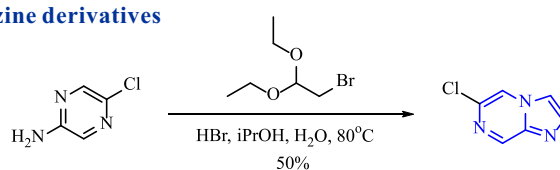


European Journal of Medicinal Chemistry. **2020**, *190*, 112092.

WO2017007759 A1

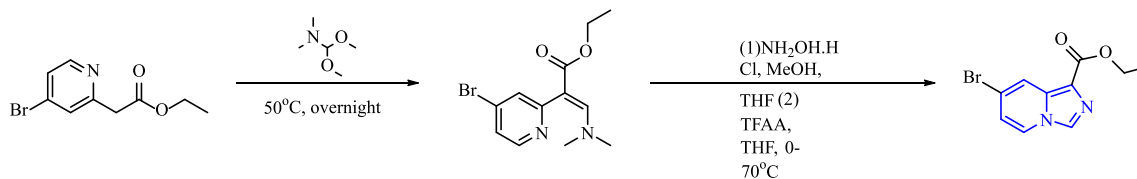
WO2015073267 A1

5) Synthesis of imidazo[1,2-a]pyrazine derivatives

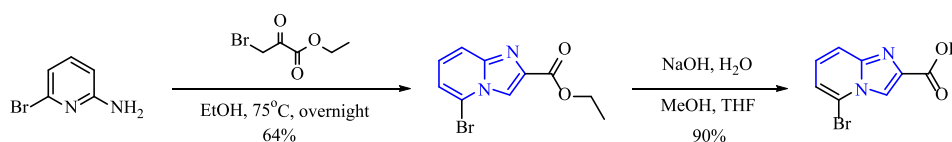


WO2016050165 A1

6) Synthesis of imidazo[1,5-a]pyridine and imidazo[1,2-a]pyridine derivatives

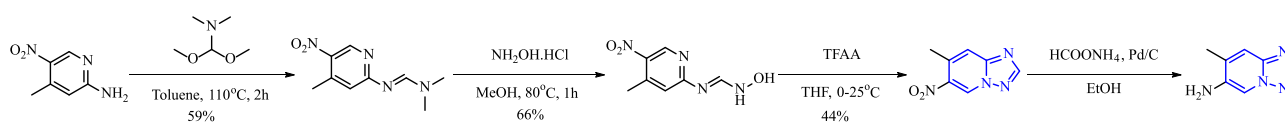


Organic Letters. **2021**, *23(12)*, 4694-4698



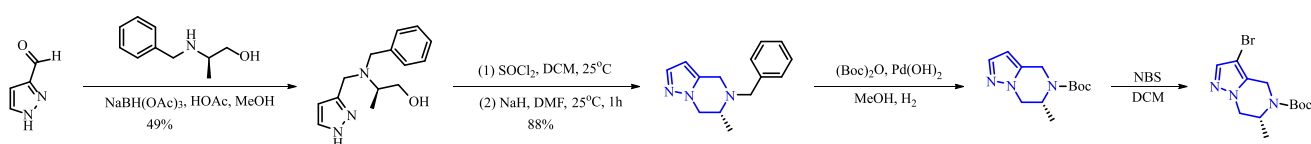
WO2017223239 A1

7) Synthesis of [1,2,4]triazolo[1,5-a]pyridine derivatives



WO202221697 A1

8) Synthesis of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine derivatives



ACS Medicinal Chemistry Letters. **2015**, *6(1)*, 37-41

Building Blocks Containing Heterocycles

PharmaBlock has conducted a systematic study of clinical and preclinical drug molecules, and our chemists continue to pay attention to the latest research, design and synthesize a large number of new heterocyclic building blocks, which can be used to explore structure-activity relationship (SAR) and structure-property relationship (SPR). We offer more than 10000 unique heterocyclic building blocks, ranging from grams to kilograms, most of which are in stock (**Figure 5**).



Figure 5. Representative building blocks containing heterocycles at PharmaBlock

References

- [1] Discovery of Benzoazepinequinoline (BAQ) Derivatives as Novel, Potent, Orally Bioavailable Respiratory Syncytial Virus Fusion Inhibitors. Xiufang Zheng, Chungeng Liang, Lisha Wang, Hongying Yun *et al. J. Med. Chem.* **2018**, *61*, 22, 10228–10241.
- [2] Discovery of Ziresovir as a Potent, Selective, and Orally Bioavailable Respiratory Syncytial Virus Fusion Protein Inhibitor. Xiufang Zheng, Lu Gao, Lisha Wang, Hongying Yun *et al. J. Med. Chem.* **2019**, *62*, 13, 6003–6004.
- [3] Contributions of intestine and liver to the absorption and disposition of FZJ-003, a selective JAK1 inhibitor with structure modification of filgotinib. Yu Zhuang *et al. Eur. J. Pharm. Sci.* **2022**, *175*, 106211-106219.
- [4] Classification of Scaffold Hopping Approaches. Hongmao Sun *et al. Drug Discov Today.* **2012**, *17*, 310-324.
- [5] Mastalerz, Harold; Wittman, Mark D.; Zimmermann, Kurt; Saulnier, Mark G.; Parthi, Upender; Vyas, Dolatrai M.; Zhang, Guifen; Johnson, Walter Lewis; Frennesson, David B.; Sang, Xiaopeng; Liu, Peiying; Langley, David R.; Pyrrolotriazine kinase inhibitors. WO2008005956 A2, **2008**
- [6] Corbett, Jeffrey Wayne; Elliott, Richard Louis; Freeman-Cook, Kevin Daniel; Griffith, David Andrew; Phillion, Dennis Paul; Pyrazolospiroketone acetyl-CoA carboxylase inhibitors. WO2009144554 A1, **2009**
- [7] CN112457235, **2021**
- [8] Zhu, Yongqiang; Liu, Zhaogang; Feng, Chao; Chen Hao; Xu, Kaikai; Wang, Jia; Shi, Jingmiao; Heteroaromatic ring compound as RET kinase inhibitor, and preparation and use thereof. WO2022037643 A1, **2022**
- [9] *European Journal of Medicinal Chemistry.* **2020**, *190*, 112092.
- [10] Reynolds, Mark; Eary, Charles Todd; Formulations comprising 6-(2-hydroxy-2- methylpropoxy)-4- (6-(6-(((6-methoxy-pyridin-3-yl)methyl)-3,6-diazabicyclo [3.1.1] heptan-3-yl) pyridin-3-yl) pyrazolo[1,5-a]pyridine-3-carbonitrile. WO2019075114 A1, **2019**
- [11] Cui, Jingrong J.; Rogers, Evan W.; Diaryl macrocycle polymorph. WO2017007759 A1, **2017**
- [12] Xi, Ning; Li, Minxiong; Li, Xiaobo; Substituted heteroaryl compounds and methods of use. WO2015073267 A1, **2015**
- [13] Jin, Yunzhou; Bu, Ping; He, Qi; Lan, Jiong; Zhou, Fusheng; Zhang, Liang; He, Xiangyu; Azabicyclo derivatives, process for preparation thereof and medical use thereof. WO2016050165 A1, **2016**
- [14] *Organic Letters.* **2021**, *23(12)*, 4694-4698
- [15] Bourque, Elyse Marie Josee; SK-Erlj, Renato; CXCR4 inhibitors and uses thereof. WO2017223239 A1, **2017**
- [16] Swami, Archana; Rakshe, Vishal; Prodeus, Aaron; Maetani, Micah; Parmar, Rubina Giare; Lipid nanoparticle compositions. WO2022221697 A1, **2022**
- [17] *ACS Medicinal Chemistry Letters.* **2015**, *6(1)*, 37-41

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