Research Center for Molecular Recognition and Synthesis
Department of Chemistry, Fudan University

Strategies for Structural Optimization of Drugs for Acute Liver Injury

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Date: 2025.04.11

CONTENT

- Background of Acute Liver Injury (ALI)
- Strategies for structural optimization of drugs for ALI
  - Molecular hybridization
  - Scaffold hopping
  - Conformational restriction
- Summary and outlook

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- Background of ALI
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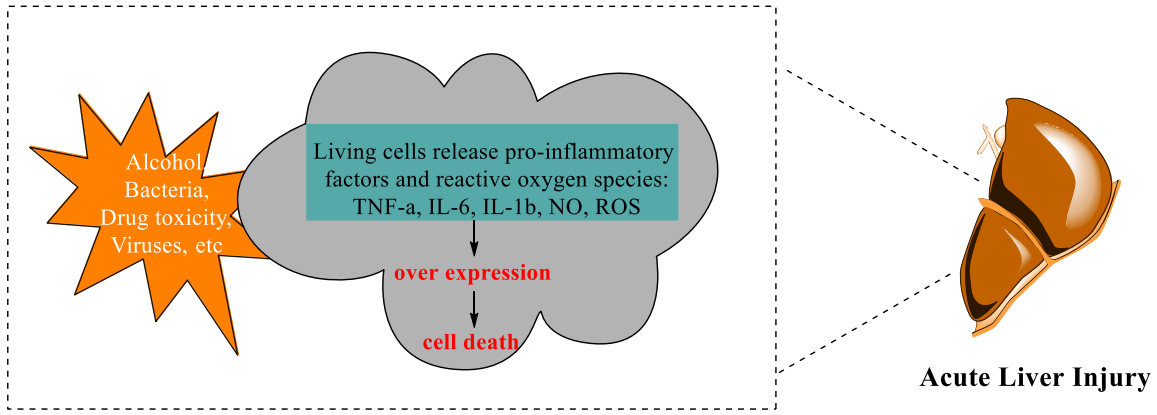
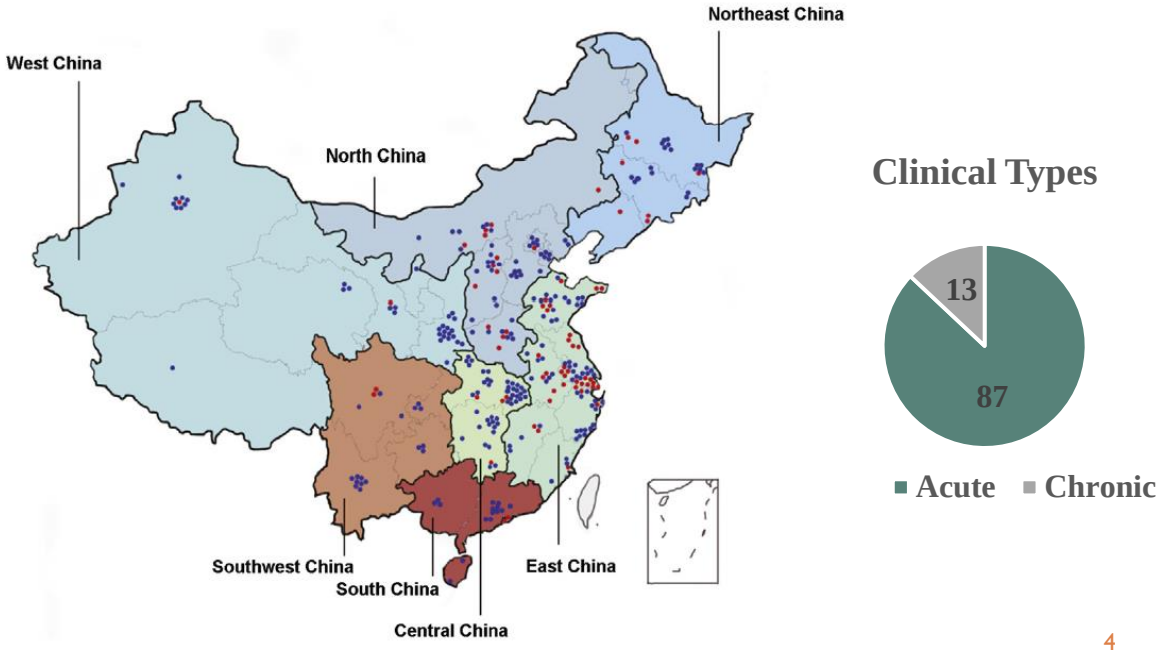
Background——Definition of ALI

☐ Acute Liver Injury (ALI)

Acute liver injury (ALI) is a common clinical disease caused by **drugs**, **alcoholism**, **hepatitis virus**, **bacterial infection**, etc., which can progresses to severe life-threatening acute liver failure with poor survival rate.



- **Epidemiological data come from a total of 25,927 confirmed DILI cases, hospitalized from 2012 - 2014 at 308 medical centers in mainland China.**



The **annual incidence rate** in mainland China was **23.80 / 100,000 persons.**

- *Cell Death Dis.* **2019**, *10*, 313.
- *J. Med. Chem.* **2013**, 247, 115013.
- *Gastroenterology* **2019**, *156*, 2230-2241.

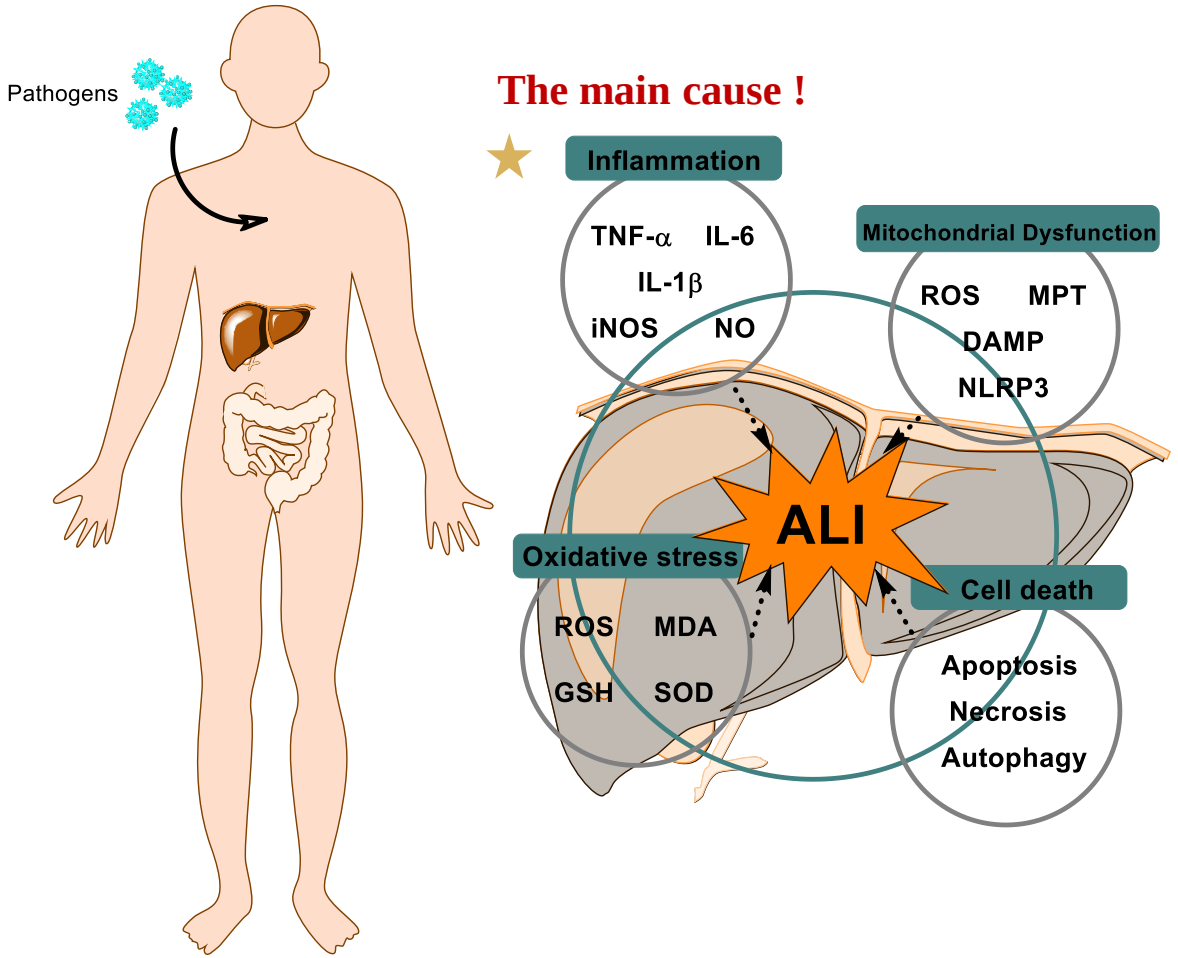
Background——Pathogenesis of ALI

- **The pathogenesis of ALI and their relationships.**

Clinical biomarkers:

Alanine Aminotransferase (**ALT**)

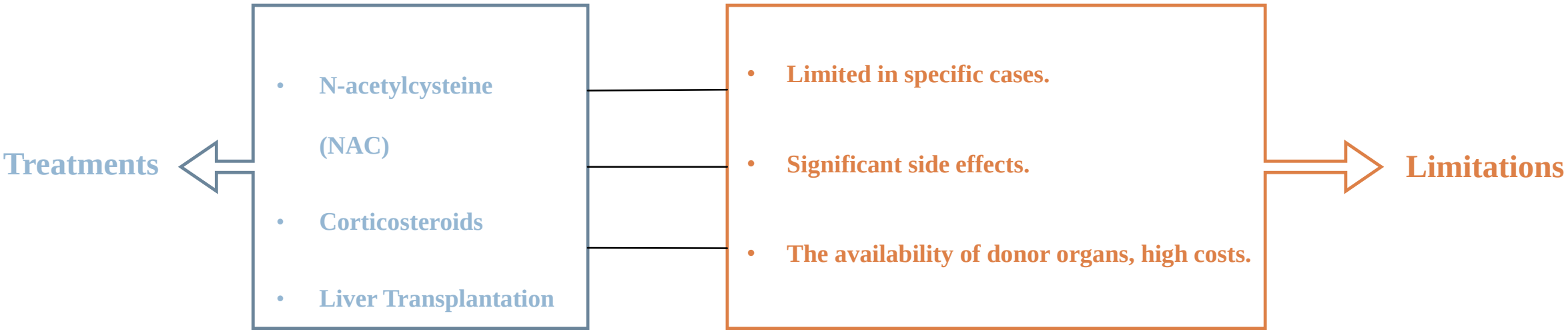
Aspartate Aminotransferase (**AST**)



- *J. Hepatol.* **2019**, *70*, e424-e427.
- *ACS Nano* **2024**, *18*, 20772−20791.
- *Nat. Commun.* **2023**, *14*, 7527.
- *Gut* **2017** ,*66*, 716-723.

Background——Current treatments and limitations

☐ Clinical treatments



There is an urgent need for **novel and effective therapeutic drugs** for acute liver injury.

- *Clin. Pharmacol. Ther.* **2021**, *101*, 531-540.
- *Nat. Rev. Dis. Primers.* **2019**, *5*, 59.

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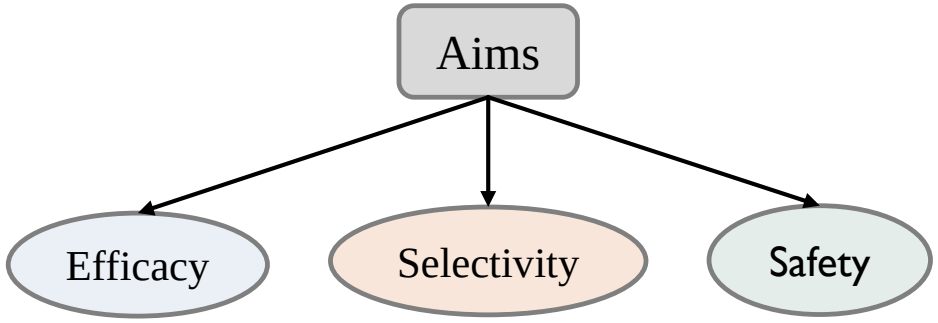
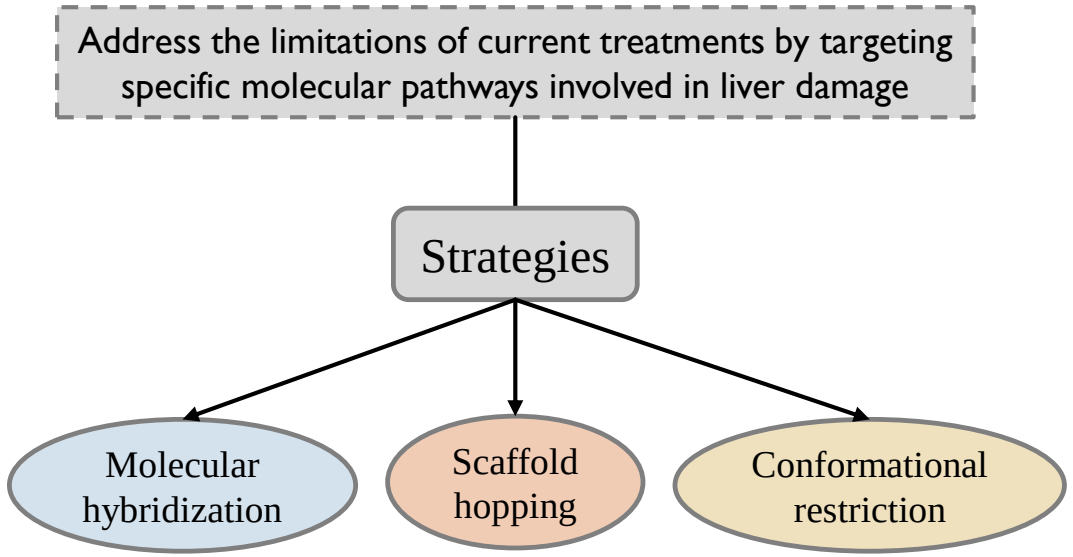
Strategies for structural optimization of drugs for ALI

- **Structural optimization**



- **Structural optimization of drugs for ALI**

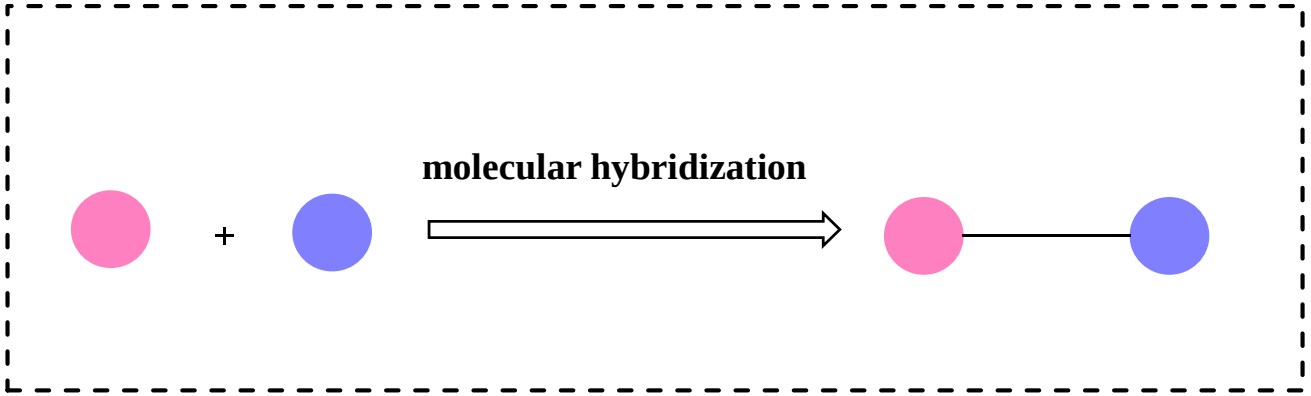


Strategies——Molecular hybridization

- **Molecular hybridization**

1 + 1 > 2

Molecular hybridization refers to the combination of two or more pharmacophores with different biological activities through chemical bonding to form new hybrid molecules.

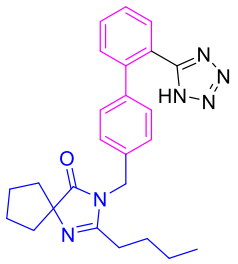


Strategies——Molecular hybridization

- FDA-approved drugs based on molecular hybridization strategies

From drug to drug

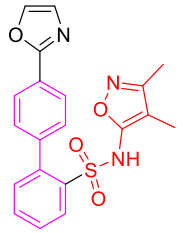
BMS:



Irbesartan
AT_1RK_i = 0.8 nM
ET_ARK_i > 10 μM

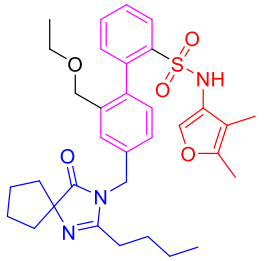
An angiotensin II subtype 1 receptor (AT1R) inhibitor used to treat high blood pressure (hypertension)

+



BMS-193884
AT_1RK_i > 10 μM
ET_ARK_i = 1.4 nM

A selective, orally active ETAR inhibitor used to treat cardiovascular disease. Terminated in Phase II.



Sparsentan
AT_1RK_i = 0.8 nM
ET_ARK_i = 9.3 nM
FDA approved in 2023
for the treatment of IgA nephropathy

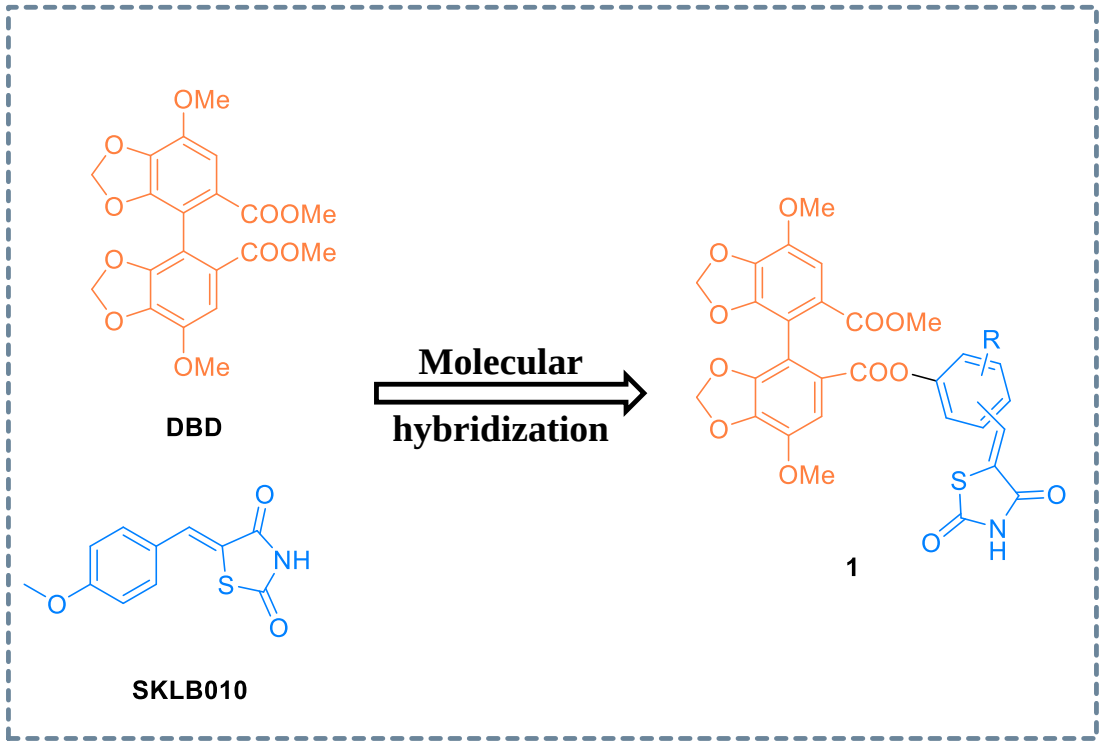
Antihypertensive effect.
Vascular endothelial protection

• *J. Med. Chem.* **2005**, *48*, 171-179.

Strategies——Molecular hybridization

- The application of **molecular hybridization strategies** in the treatment of ALI.

Chen L. [a]



Parents molecules:

- **Bifendate (DBD)**

A synthetic intermediate of Schizandrin C (isolated from **Wuweizi**).

【clinically used 】

【low cost 】

【minimal side effects】

- **SKLB010**

Thiazolidine-2,4-dione (TZD) derivatives.

【Inhibit pro-inflammatory cytokines 】

【Decrease ALT and AST】

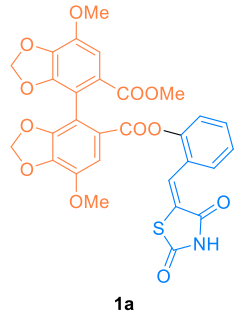
[a] state key laboratory of biotherapy, west china hospital, west china medical school, sichuan university

Eur. J. Med. Chem. **2011**, *46*, 5941-5948.

Strategies——Molecular hybridization

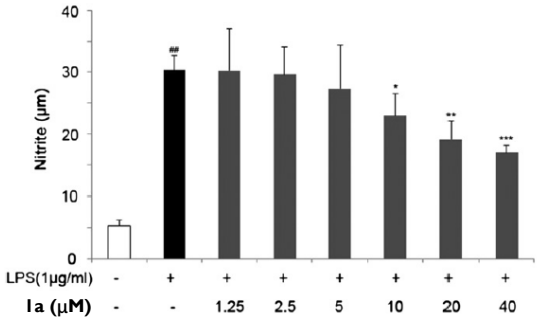
- The application of **molecular hybridization strategies** in the treatment of ALI.

- **Hybrid molecule 1a**



1a

- **Compound 1a inhibited NO release in cells**



- **Compound 1a decreased AST and ALT levels in ALI mice.**

Table 1 Effects of **1a** and **DBD** on ALT and AST.

	ALT (U/L)	AST (U/L)
Blank	39.57	99.17
Control	3343.23	2008.33
DBD	**1490.50**	**1016.62**
1a	**168.42**	**620.13**

*Con A: Concanavalin A is used to induce acute liver injury.

1a had superior protective effects against liver damage.

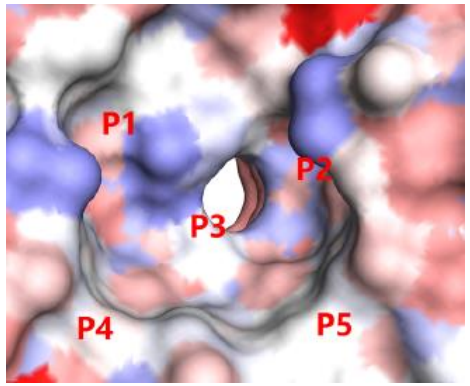
* By testing LPS induced excessive production of NO in RAW264.7 cells is a common **cell inflammatory model.**

Strategies——Molecular hybridization

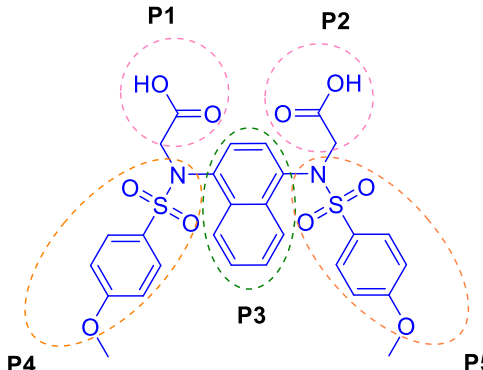
- The application of **molecular hybridization strategies** in the treatment of ALI.

  - **Brief background: Nrf2** is a key transcription factor that controls cells' defense system – turning it on helps cells fight off all sorts of damage like inflammation and oxidative stress. Directly blocking Keap1−Nrf2 protein−protein interactions is a solid way to activate Nrf2.

You Q. [b]

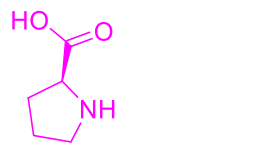


Subpockets of Keap1−Nrf2 ETGE complex



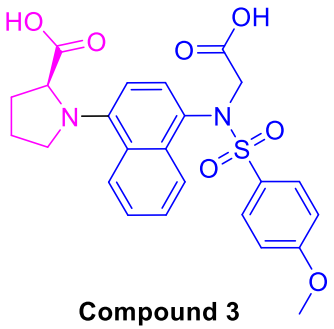
Mv: 615
Keap1 IC_{50}: 28.6 nM

Reported compound **2**



Proline

Molecular hybridization



Compound 3
Mv: 484
Keap1 IC_{50}: 43 nM

The **Pro** substituent might create a unique way to precisely control the combined effects of P1 and P4 subpockets!

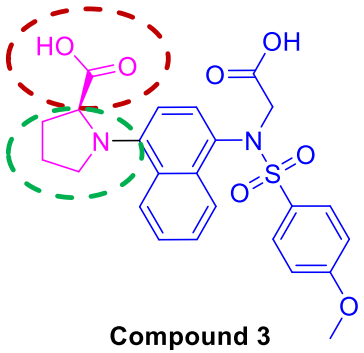
The high polar and symmetric structure of compound **2** can result in poor physicochemical and drug-like properties

- [b] China Pharmaceutical University
- *J. Med. Chem.* **2019**, *62*, 6796−6813.

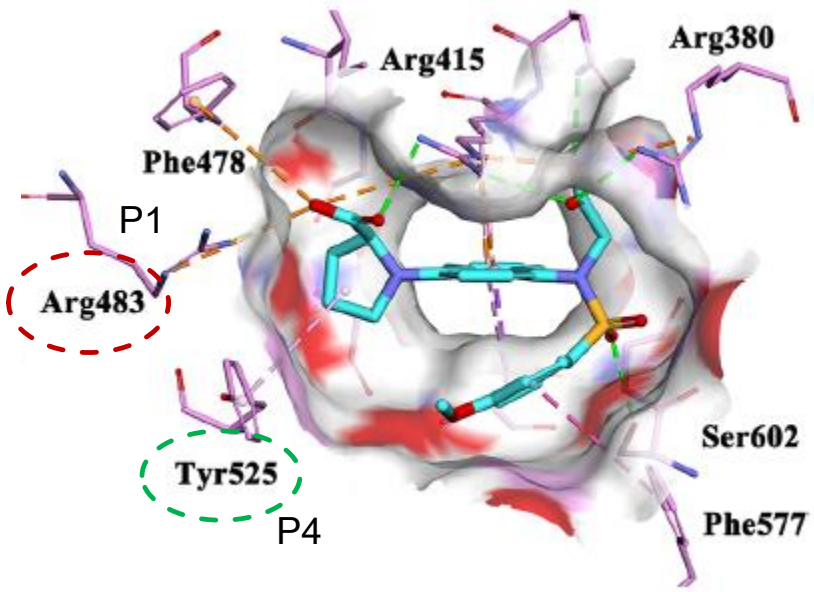
Strategies——Molecular hybridization

- The application of **molecular hybridization strategies** in the treatment of ALI.

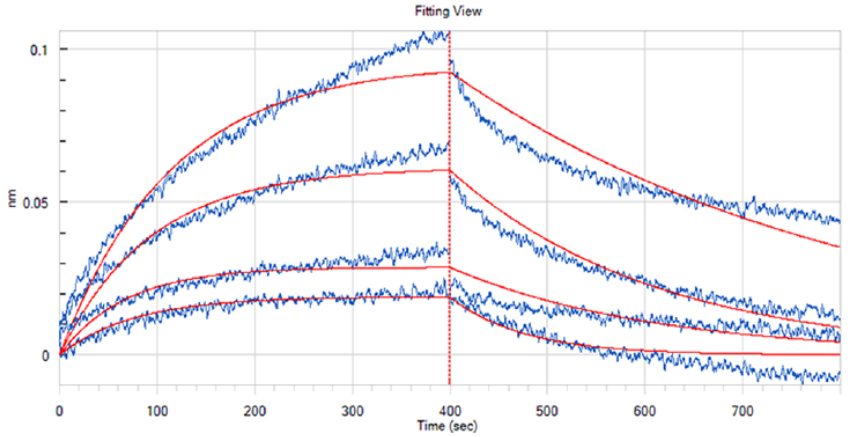
➢ **Molecular docking studies**:
proposed binding mode of **compound 3** with **Keap1**.



Compound 3
Mv: 484
IC_{50}: 43 nM



➢ **BLI assay:**
the affinity of **compound 3** with **Keap1.**



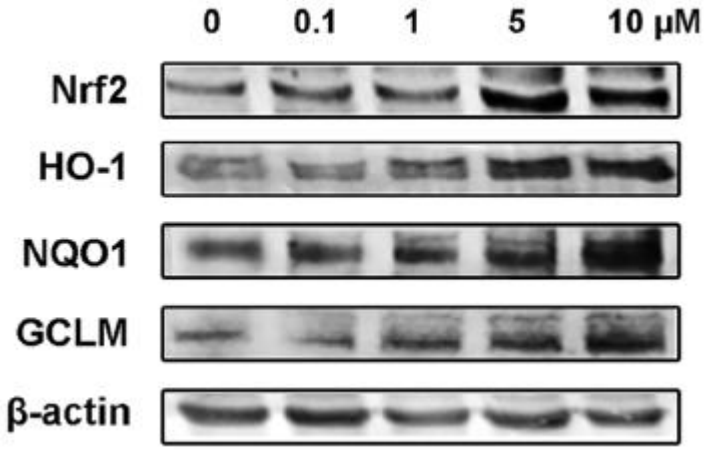
KD (nM)	k_{on} (1/Ms)	k_{dis} (1/s)
28.5	1.68E+05	4.79E-03

Compound 3 could bind to Keap1 with **nM-level** affinity**!**

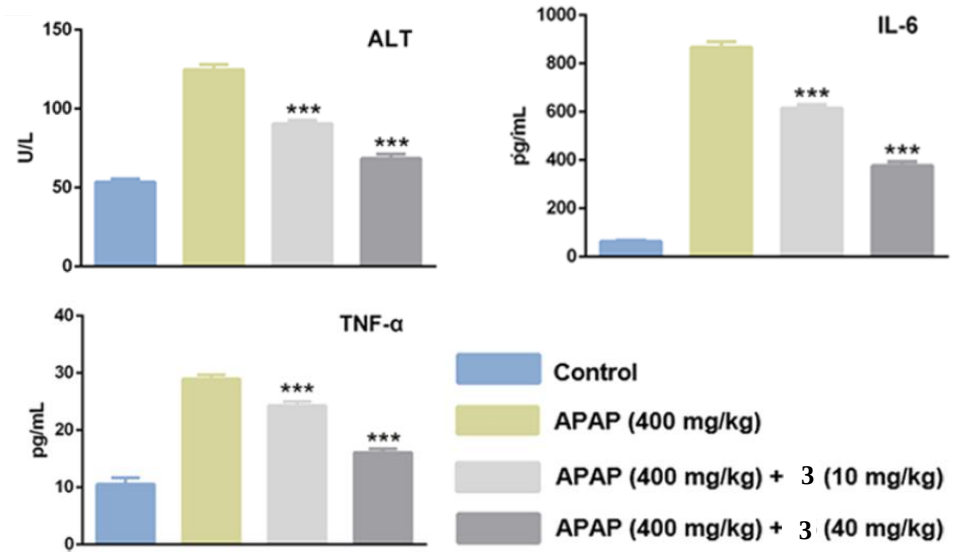
Strategies——Molecular hybridization

- The application of **molecular hybridization strategies** in the treatment of ALI.

➢ **Compound 3** could up-regulate the protein level of Nrf2 and its downstream signaling pathways in **L02 cell**.



• **Compound 3** could inhibit the level of ALT、TNF-α and IL-6 in **ALI** mice.



*APAP: Paracetamol is used to induce acute liver injury.

Indicating the therapeutic efficacy of 3 against acute liver injury in vivo.

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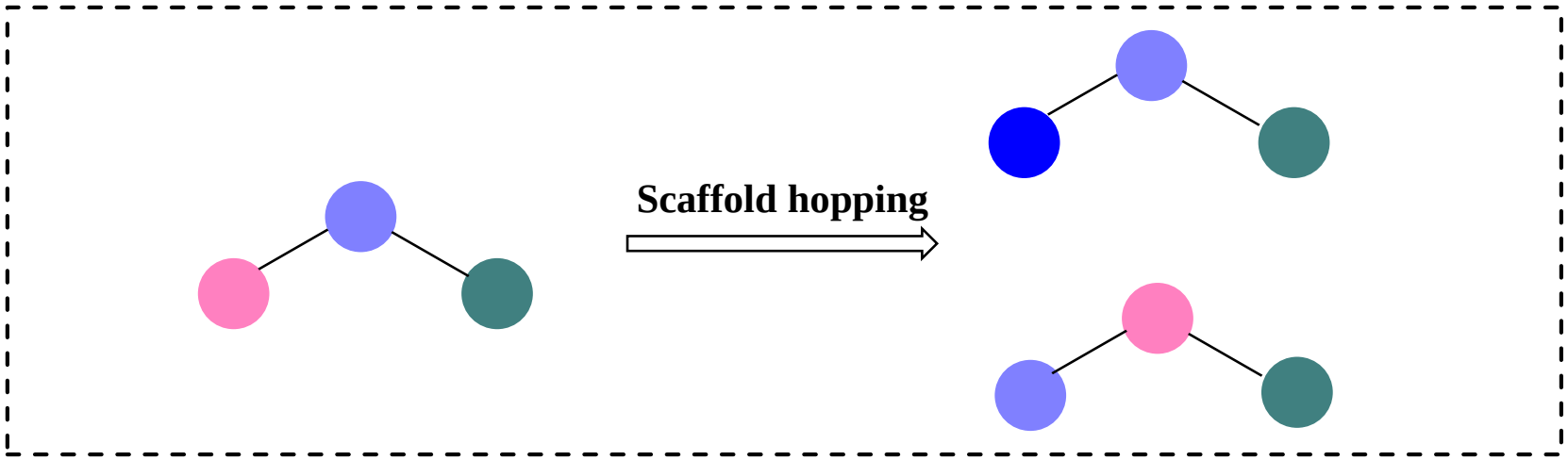
Strategies——Scaffold hopping

☐ Scaffold hopping

Scaffold hopping refers to generating completely **novel molecular frameworks** while maintaining similar binding properties, 3D shape, and electrostatic characteristics as the original molecule.



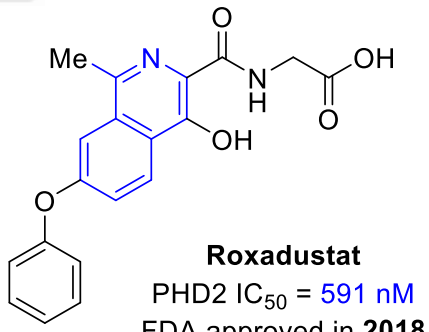
Strategies——Scaffold hopping

- FDA-approved drugs based on **Scaffold hopping** strategies

From drug to drug

- For the treatment of **chronic kidney disease**

Astellas Pharma Inc.

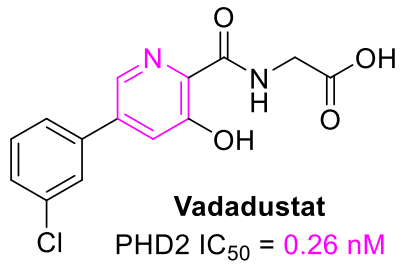


Roxadustat
PHD2 IC_{50} = 591 nM
FDA approved in **2018**

Scaffold hopping

2000-fold improvement

Akebia Therapeutics Inc.



Vadadustat
PHD2 IC_{50} = 0.26 nM
F(%) = 121
FDA approved in **2020**

2000-fold improvement in IC50 value against PHD2
outstanding bioavailability exceeding 90% at 20 mg/kg.

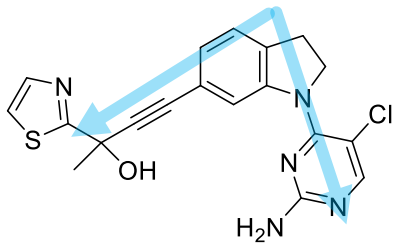
- *N Engl J Med.* **2019**, *381*, 1001–1010.

Strategies——Scaffold hopping

- The application of **scaffold hopping strategies** in the treatment of ALI.

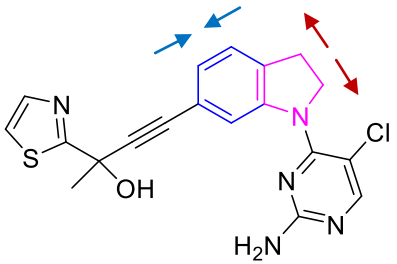
Chen Y. [b]

Brief background: blocking NIK (NF-κB inducing kinase) dramatically reduces pro-inflammatory cytokines and liver damage markers, which which suggests that **NIK inhibitor** could serve as a promising drug candidates for ALI.

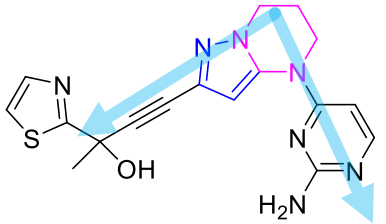


B022
first reported NIK inhibitor

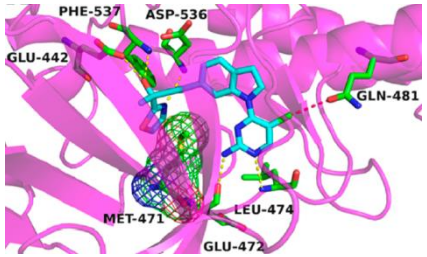
Rational design



Scaffold hopping



4
retain the special angle
improve pocket occupancy

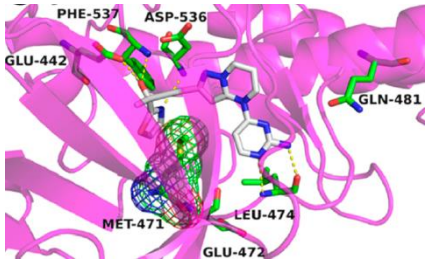


Expanding the pink ring,

to enhance hydrophobic interactions

Compressing the blue ring,

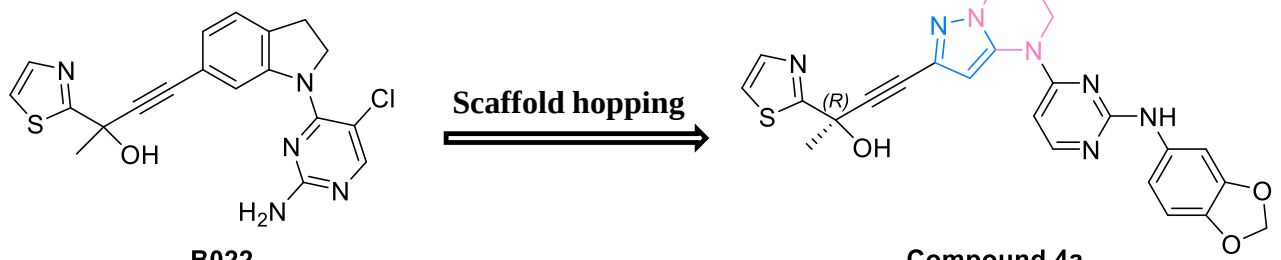
to achieve tighter binding.



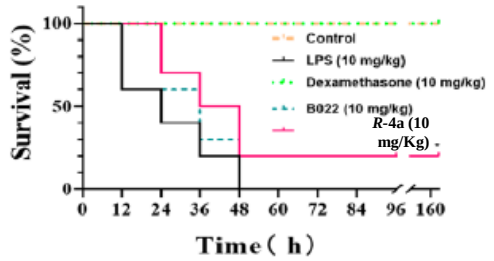
- *J. Med. Chem.* **2024**, *67*, 5617−5641.

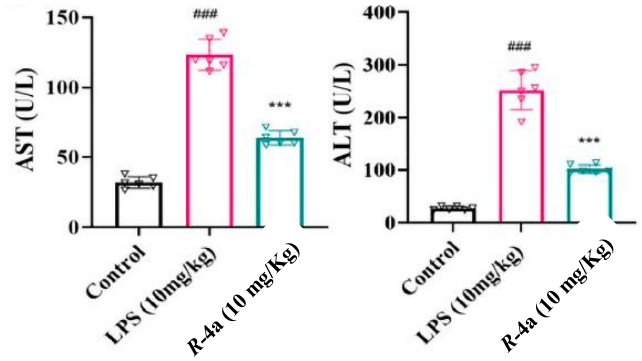
Strategies——Scaffold hopping

➢ **From B022 to (*R*)-4a.**



➢ ***R*-4a exhibits great anti-inflammatory activity in Vivo**

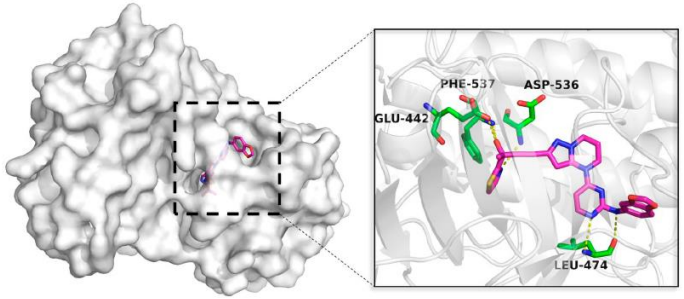




*LPS: Lipopolysaccharides is used to induce acute liver injury.

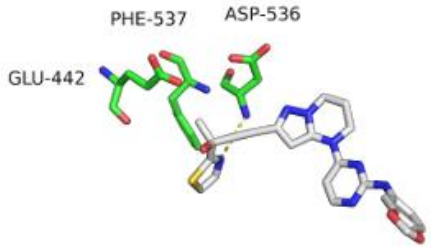
➢ **Molecular docking simulations**

- Binding mode of *R*-**4a with NIK**



Five hydrogen bonds formed

- Binding mode of *S*-**4a with NIK**



The activity loss of *S*-**4a** may correlates with the loss of critical hydrogen bonds.

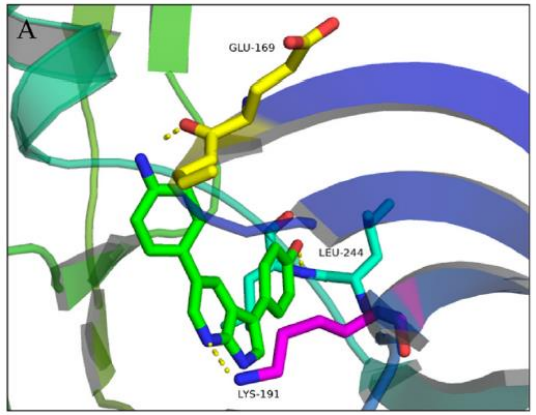
R-**4a** exhibits **excellent protective effects against liver damage**.

Strategies——Scaffold hopping

- The application of **scaffold hopping strategies** in the treatment of ALI.
  - **Brief background**: Clk1 inhibition effectively induces autophagy and is a validated target for autophagy-related diseases. However, most Clk1 inhibitors lack kinase selectivity, mainly due to Dyrk1A off-target effects.

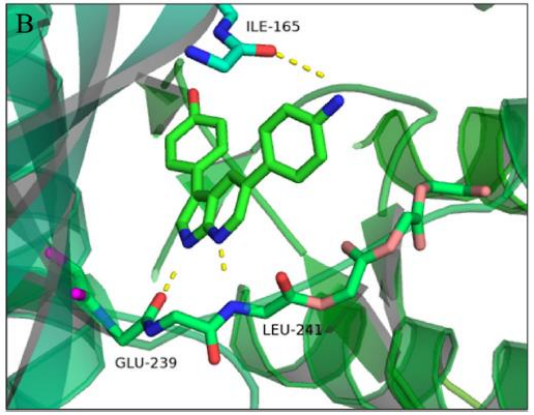
Chen L. [a]

➢ Binding mode of **Zhou 9h** with **CLK1**

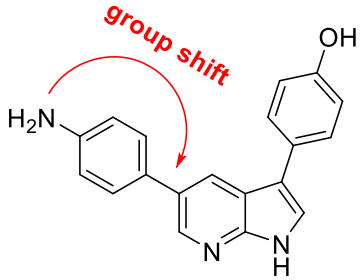


docking scores : -9.9

➢ Binding mode of **Zhou 9h** with **Dyrk1A**



docking scores : -12.8



Compound Zhou-9h
CLK1 IC_{50} = 34 nM
DYRK1A IC_{50} = 43 nM

dual-target compound

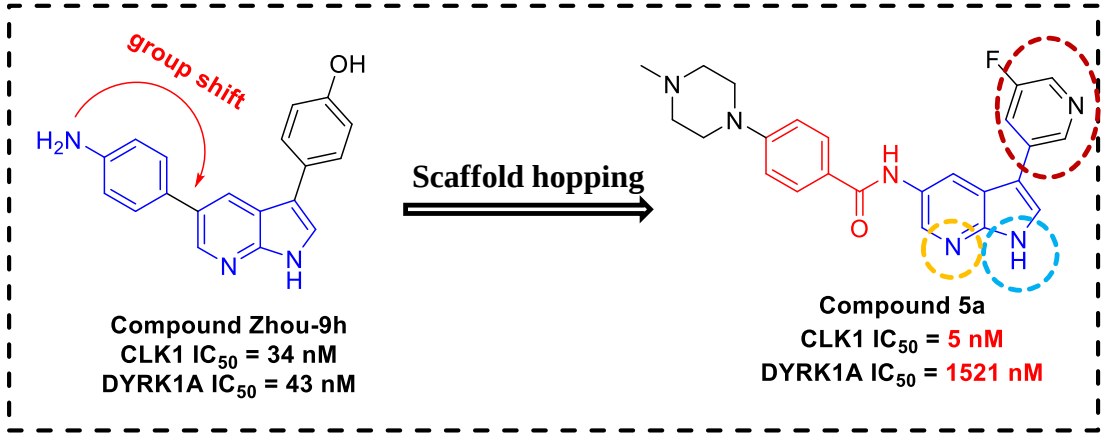
lacking the necessary flexibility
aniline moiety has potential hepatotoxicity

No selectivity

- [a] state key laboratory of biotherapy, west china hospital, west china medical school, sichuan university
- *Eur. J. Med. Chem.* **2023**, *250*, 115168.

Strategies——Scaffold hopping

- **From Zhou-9h to 5a.**

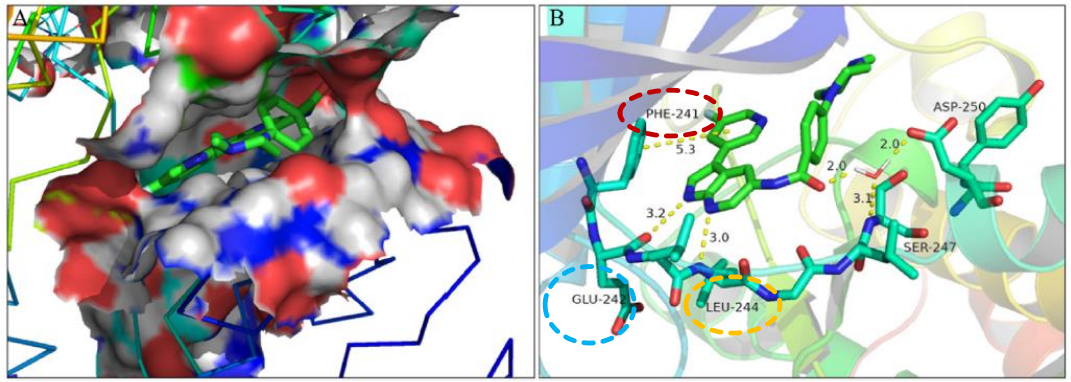


Compound Zhou-9h
CLK1 IC_{50} = 34 nM
DYRK1A IC_{50} = 43 nM

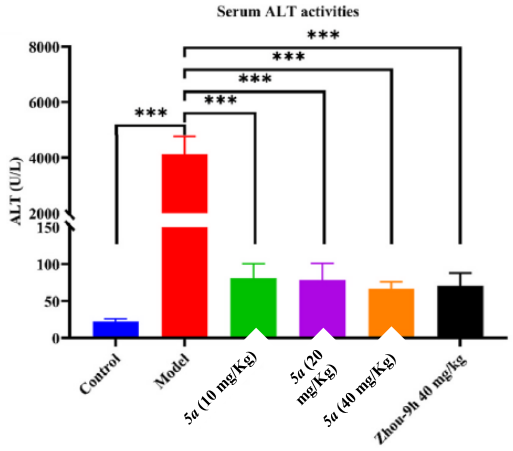
Compound 5a
CLK1 IC_{50} = 5 nM
DYRK1A IC_{50} = 1521 nM

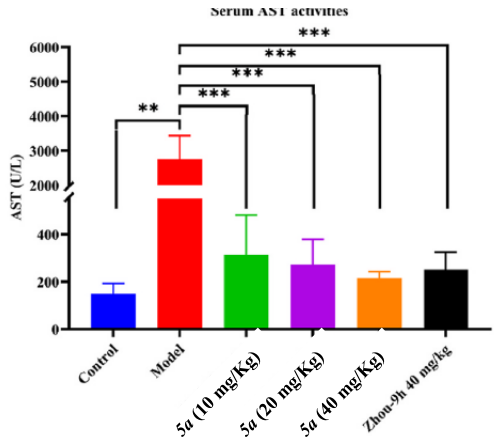
- **Molecular docking result of 5a in the Clk1 protein**

5a has high affinity and selectivity for Clk1



- **5a reduced serum AST/ALT levels in ALI mice.**





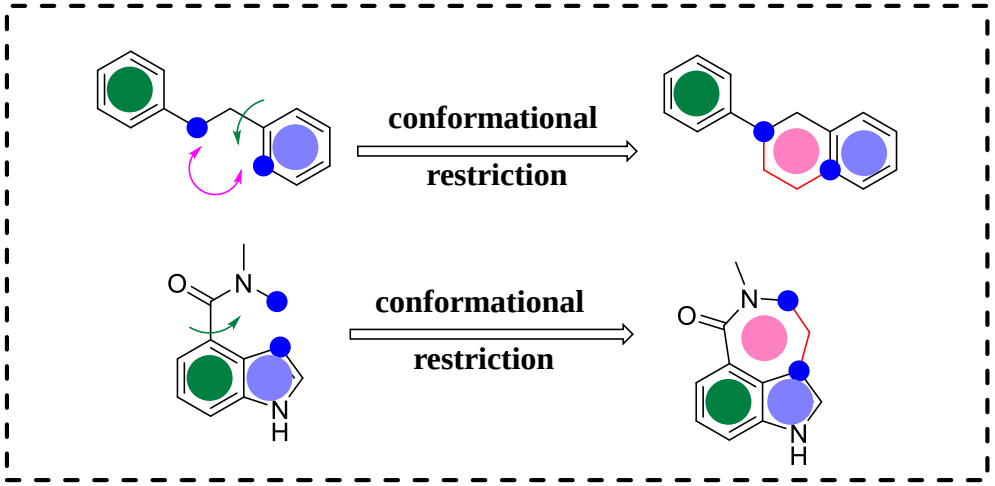
CONTENT

- Background of ALI
- Strategies for structural optimization of drugs for ALI
  - Molecular hybridization
  - Scaffold hopping
  - Conformational restriction
- Summary and outlook

Strategies——Conformational restriction

☐ Conformational restriction

It refers to the appropriate conformational restriction of drug molecules to reduce the conformational production of weak, ineffective or even negative effects, and promote their binding to the target.



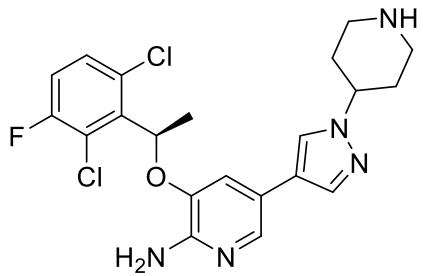
Strategies——Conformational restriction

- FDA-approved drugs based on **conformational restriction** strategies

From drug to drug

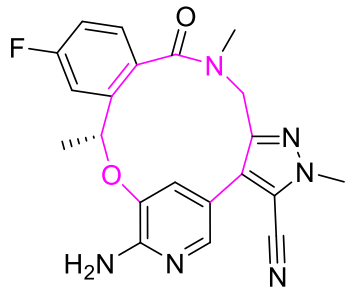
Pfizer:

- For the treatment of ALK-positive non-small cell lung cancer



Crizotinib
ALK cell IC_{50} = 80 nM
ALK-L1196M cell IC_{50} = 843 nM

Conformational restriction
over 40-fold boost



Lorlatinib
ALK cell IC_{50} = 1.3 nM
ALK-L1196M cell IC_{50} = 21 nM
FDA approved in 2021
cross the blood-brain barrier way better

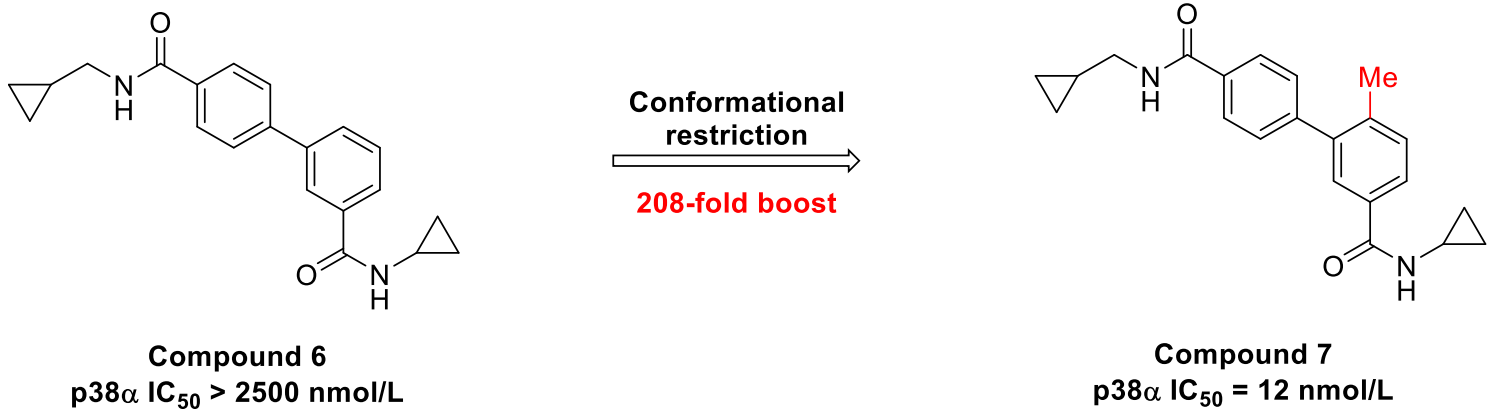
Lancet Oncol. **2018**, *19*, 1654-1667.

Strategies——Conformational restriction

- FDA-approved drugs based on **conformational restriction** strategies

GSK:

- p38α kinase inhibitors



Compound 6
p38α IC_{50} > 2500 nmol/L

Compound 7
p38α IC_{50} = 12 nmol/L

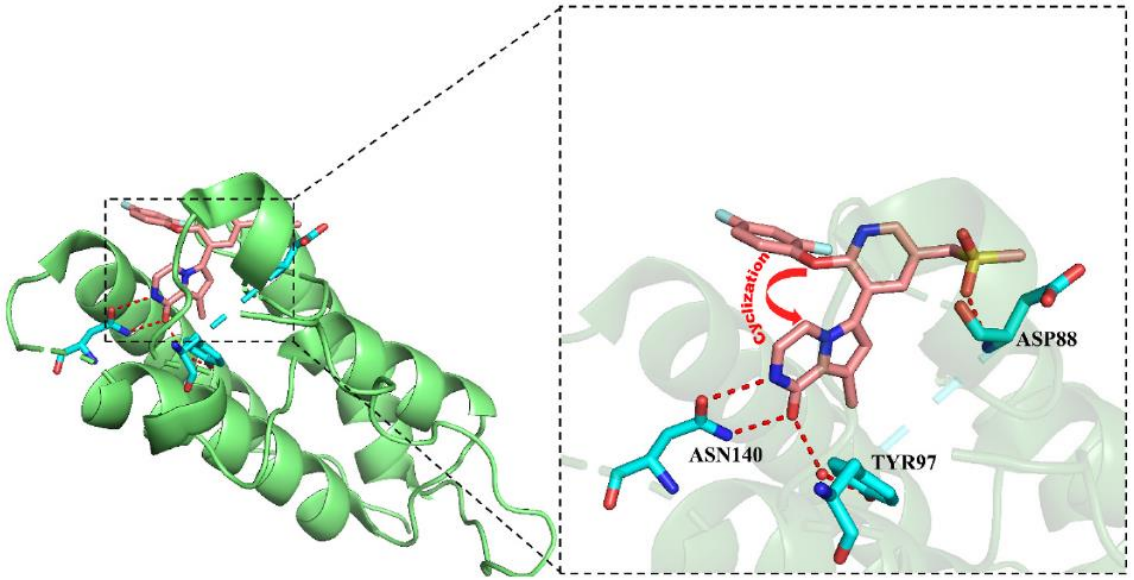
Bioorg. Med. Chem. Lett. **2008**, *18*, 4428–4432.

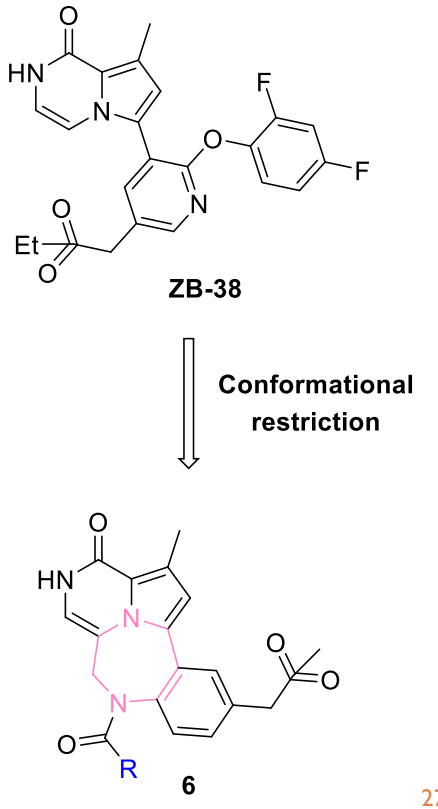
Strategies——Conformational restriction

- The application of **conformational restriction strategies** in the treatment of ALI.

Brief background: the BET family of proteins acts like molecular switches in our cells by grabbing onto acetylated histones. No BET-targeting drugs are on the market yet. BRD4, a key BET member, turns on genes involved in inflammation and fibrosis, making **BRD inhibitors** a promising drug candidates for ALI.

Zhou B. [c]





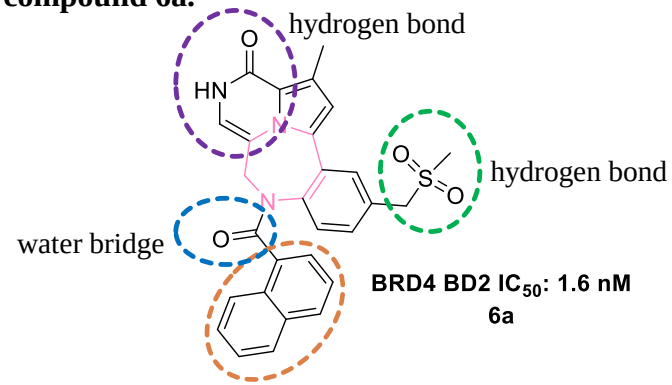
This ring could lock the benzene part into BRD4's hydrophobic WPF pocket

[c] University of Chinese Academy of Sciences

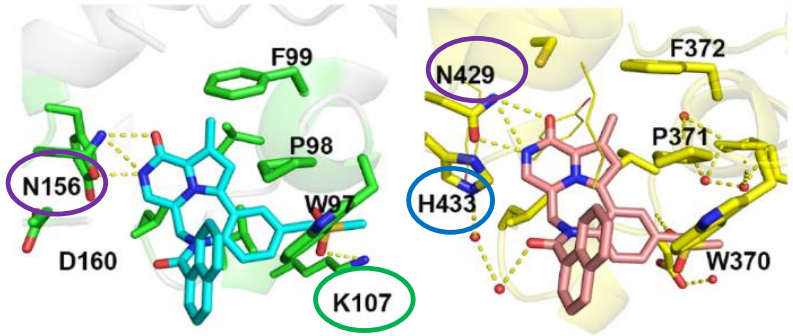
EUR. J. MED. CHEM. **2023**, *247*, 115023.

Strategies——Conformational restriction

- **Selective compound 6a.**

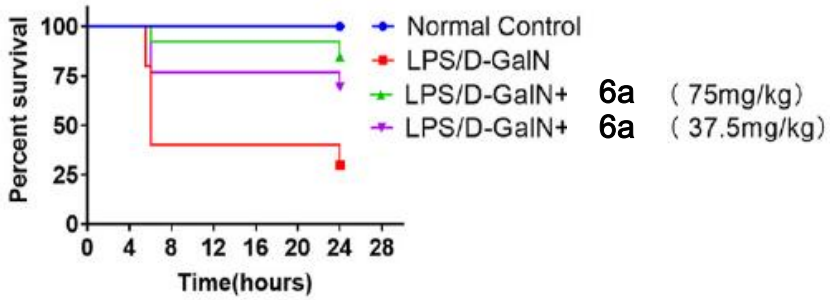


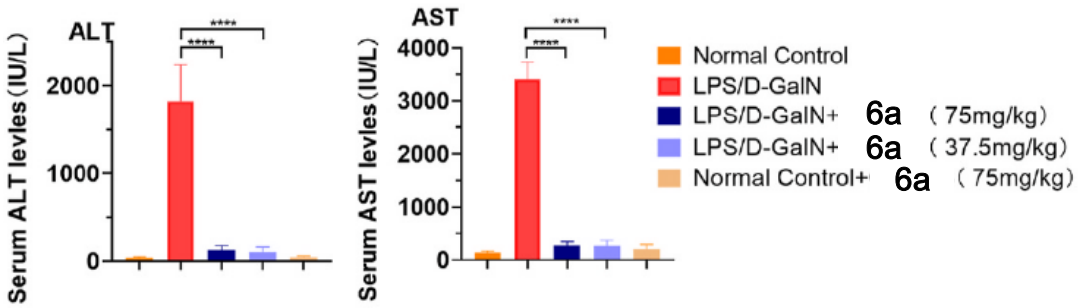
- **Co-crystal structures of BRD2 BD1 and BRD2 BD2 in complex with 6a.**



6a binds to **BET** proteins with **high affinities**

- **6a alleviates acute liver injury in mice.**





*LPS: Lipopolysaccharides is used to induce acute liver injury.
*D-GalN: D-galactosamine is a specific liver sensitizing agent.

These results demonstrate that **6a** exhibits **robust anti-inflammatory activity** in vivo.

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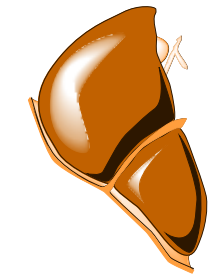
Summary



Acute Liver Injury

clinical treatments

NAC corticosteroids liver transplantation

cases side effects costs

limitations

Structural Optimization

Molecular hybridization

Scaffold hopping

Conformational restriction

Efficacy

Selectivity

Safety

Limitations of the structural optimization strategies

Molecular hybridization

- **Activity and stability** of heterozygous molecules
- Properties of **linkers**
- Potential risk of **toxic side effects**

Scaffold hopping

- Uncertain **activity** of new structures
- A large amount of synthesis and screening work

Conformational restriction

- Decreased **flexibility**
- **Advanced computational simulation technology** is required

Outlook

What can AI do in the field of drug structure optimization?

- **Target Discovery and Validation**

  Eg: AlphaFold (DeepMind)

- **Virtual Screening**

  Eg: Schrödinger's Glide

- **Molecular Property Prediction**

  Eg: DeepChem (open-source tool)

- **De Novo Drug Design**

  Exscientia's AI Platform: AI-generated immuno-oncology candidate drug (EXS-21546)

- **Synthetic Route Planning**

  Eg: Synthia

- **Automated Laboratories**

  AI-powered robots complete the "design - synthesis - testing" loop.

Thanks for your attention!

Speaker: Wenqing Li

Supervisor: Prof. Shengming Ma

Dr. Chengbin Yang

Date: 2025.04.11