Systematic Coformer Screening, Preparation, and Solid-State Characterization of 6-Mercaptopurine Cocrystals

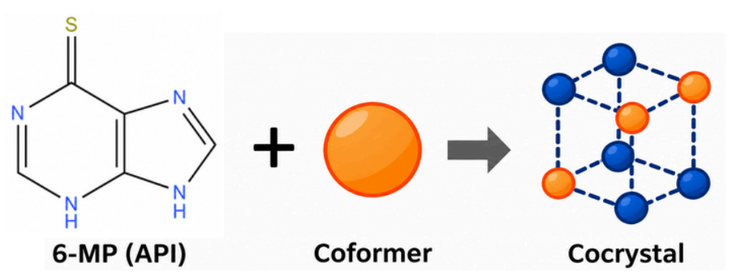
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ABSTRACT

Coformer selection is a critical step in pharmaceutical cocrystal development, yet conventional screening often requires substantial time and material resources. In this study, 6-mercaptopurine (6-MP) was selected as the active pharmaceutical ingredient, and a COSMO-RS/LDA screening model was applied to evaluate 13 candidate coformers. The model used mixing free energy (Gmix), molecular volume, and the third-order hydrogen-bond donor moment (MHBdon3) as descriptors. Malonic acid was the only candidate with a predicted probability above the cutoff value of 0.40 and was therefore selected for experimental validation. 6-MP–malonic acid samples were prepared by neat grinding and liquid-assisted grinding, followed by PXRD, FTIR, DSC, TG, and DTG analyses. Samples prepared by neat grinding and ethanol-assisted grinding exhibited solid-state characteristics distinct from those of the starting materials, supporting the formation of a new 6-MP–malonic acid solid phase.

1. Background & Objective

Pharmaceutical Cocrystal：



- Purine-based antimetabolite drug with low aqueous solubility.
- Preserves the covalent structure of 6-MP(API).
- Modifies molecular packing and intermolecular interactions.

Coformer Screening：

Candidate coformers A B C ···

Trial-and-error Time- and resource-intensive

Computational Screening

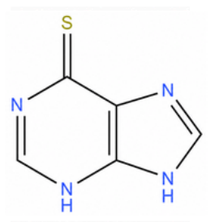
- Predict Coformer Potential
- Improve Screening Efficiency

Research Objective：

To screen potential coformers for 6-MP and evaluate new solid-phase formation through experimental validation.

2. Research Framework

01 Computational Screening：



+ Coformer → **TmoleX** (Molecular modeling) → **COSMOthermX** (Descriptor Calculation) → **LDA model** (P > 0.40)

Model Development and Parameter Selection：

Parameter	Selected Condition	Model Performance	
Feature Set	Gmix + Volume + MHBdon3	Total Accuracy	72.23%
Calculation Level	B3LYP/def2-TZVPD, ε = 78.4	Positive Accuracy	67.33%
Classification Cutoff	P > 0.40	Specificity	78.15%

An LDA model was trained using 515 reported cocrystal formation and non-formation cases.

02 Experimental Preparation：

Sample Preparation：



NG
LAG – EtOH （η=0.25 μL/mg）
LAG – ACN （η=0.25 μL/mg）
API ：Coformer ＝ 1：1(mole)
20Hz / 30min

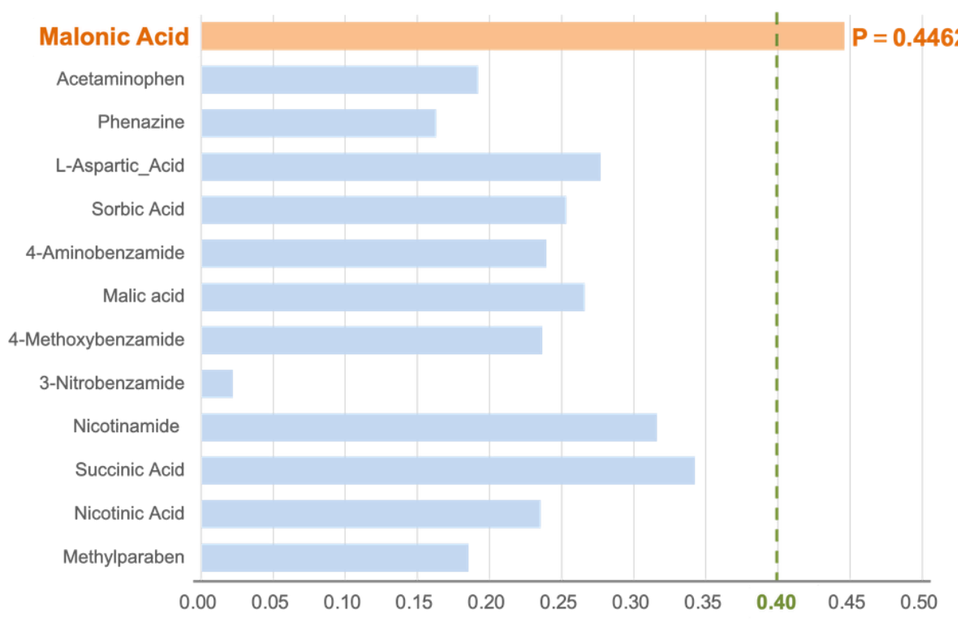
Solid-State Characterization：

 PXRD

 FTIR

 DSC、TG-DTG

3. Model Screening Results



4. PXRD Analysis

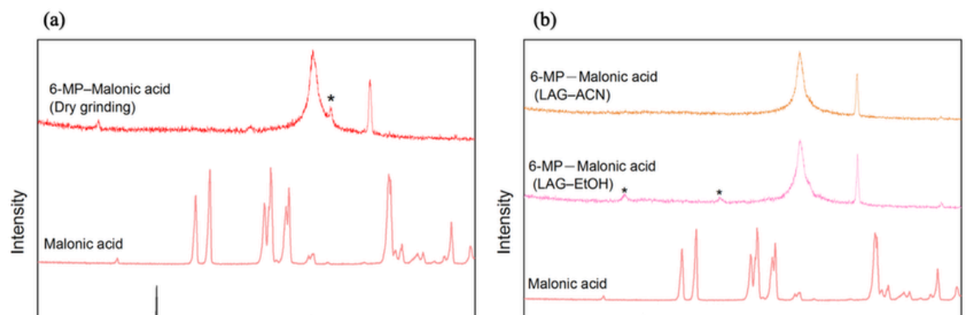
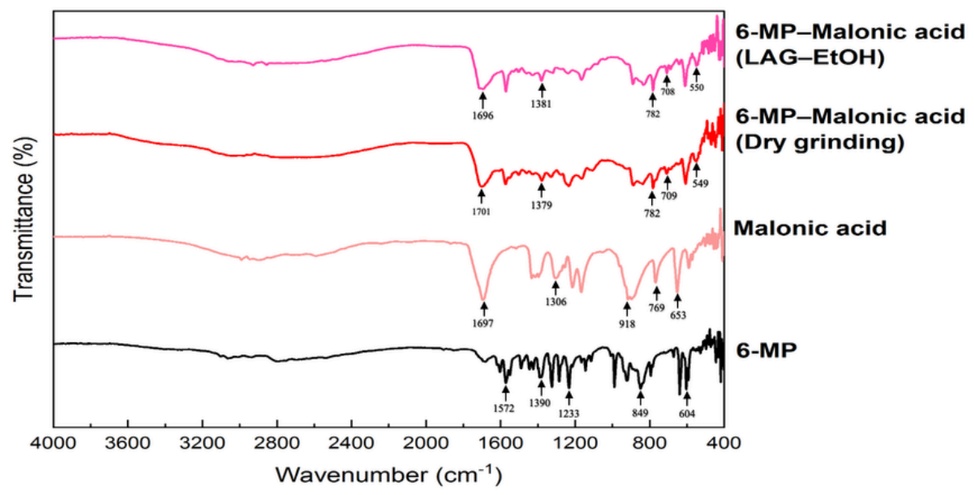
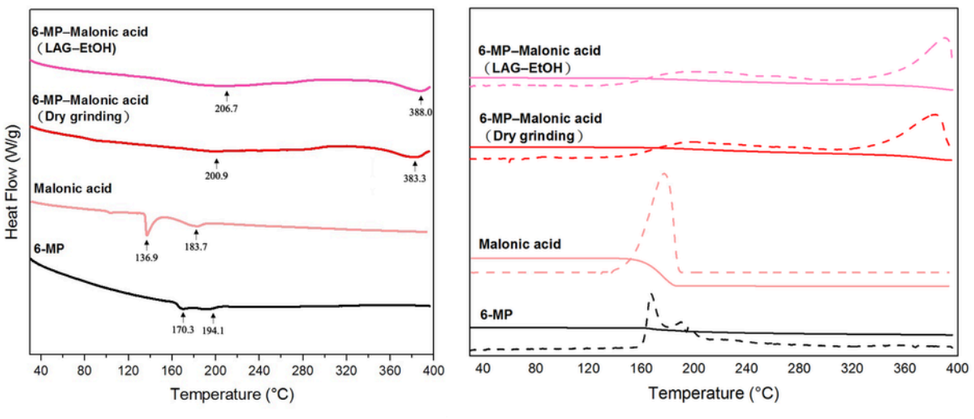


Figure (b) LAG – ACN：No new peaks ; excluded from further analysis.

5. FTIR Analysis



6. Thermal Analysis



conclusion

1. The COSMO-RS/LDA model using B3LYP/def2-TZVPD (ε = 78.4) and Gmix + Volume + MHBdon3 identified Malonic acid as the only candidate exceeding the cutoff (P = 0.4462 > 0.40) among 13 coformers.
2. PXRD, FTIR, and thermal analyses of NG and LAG–EtOH samples support the possible formation of 6-MP–Malonic acid cocrystals.
3. Future Work: Optimize grinding conditions, evaluate solubility and dissolution behavior, and validate additional coformers.