# Crystal Engineering for Sustainable Antimalarial Therapies: Combating Drug Resistance through Sulfadoxine–Ascorbic Acid Cocrystal Design

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**Abstract.** Malaria remains a leading cause of morbidity and mortality in sub-Saharan Africa, with Plasmodium falciparum increasingly resistant to existing antimalarial drugs. This study explores the use of crystal engineering to design sustainable, synergistic formulations aimed at mitigating drug resistance. Sulfadoxine (SAD), an antifolate used in sulfadoxine–pyrimethamine therapy, was co-crystallized with ascorbic acid (ACA) to form a redox-active cocrystal system designed to improve stability, bioavailability, and reduce environmental impact during production. Computational modelling using Density Functional Theory (DFT) was combined with experimental mechanochemical screening via liquid-assisted grinding (LAG). The SAD–ACA heterodimer showed a lower binding energy (–81.6 kJ $mol^{-1}$) than corresponding homodimers, indicating predicted cocrystal stability. The resulting solid form was characterised using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Findings confirm the formation of a novel cocrystal phase, evidenced by a distinct single melting endotherm and new PXRD peaks compared to the parent compounds. This work aligns with Sustainable Development Goals (SDGs) 3, 9, and 12, highlighting advances in health, innovation, and responsible production. The study demonstrates that green cocrystallization strategies can support the development of more stable, effective, and environmentally sustainable antimalarial therapies.

**Keywords:** antimalarial resistance; crystal engineering; cocrystallization; sustainability.

## 1 Introduction

### 1.1 Global malaria burden

According to the World Malaria Report [1], 247 million malaria cases and 619 000 deaths occurred globally in 2021, with 95% of cases in the WHO African Region [1] . Nigeria, the Democratic Republic of the Congo, Uganda, and Mozambique accounted for nearly half of

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global cases. In Sudan, malaria remains endemic, with over 75% of the population at risk of infection [2]. Despite sustained vector-control measures, rising insecticide and drug resistance continue to hinder progress toward malaria elimination.

### 1.2 Antimalarial drug resistance crisis

Resistance to 4-aminoquinolines, antifolates, and artemisinin derivatives has severely undermined treatment efficacy [3]. The emergence of partial artemisinin resistance in Africa, associated with *Plasmodium falciparum* Kelch13 mutations, prompted the WHO 2022 strategy to contain resistance through surveillance and optimized therapeutic use [1, 4]. New drug-delivery strategies that enhance bioavailability, stability, and sustainability are therefore urgently needed.

### 1.3 Sustainability and pharmaceutical imperative

The pharmaceutical sector faces increasing pressure to minimize its ecological footprint [5]. Green chemistry and solid-form engineering provide pathways to more sustainable manufacturing. Cocrystallization, which relies on non-covalent interactions between an active pharmaceutical ingredient (API) and a pharmaceutically acceptable coformer, can modify physicochemical properties without altering pharmacological activity [6].

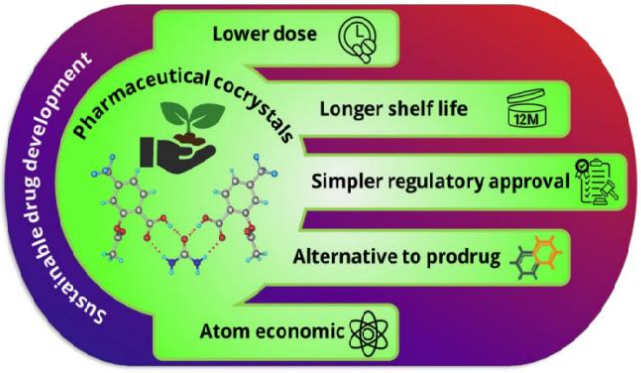


**Fig. 1.** The role of co-crystallization in sustainable drug development [6].

### 1.4 Aim of the present work

This research investigates sulfadoxine–ascorbic acid (SAD–ACA) cocrystal formation using computational (DFT) and mechanochemical (LAG) methods, supported by DSC and PXRD characterization, to enhance the solubility and stability of sulfadoxine, contribute to sustainable manufacturing, and provide a potential approach to address antimalarial resistance.

## 2 Literature Review

### 2.1 Mechanisms of resistance and therapeutic gaps

The life cycle of *P. falciparum* offers multiple drug targets, yet adaptive mutations continually erode treatment efficacy. Folate-pathway inhibitors such as sulfadoxine–pyrimethamine face high-level resistance due to *dhps* and *dhfr* gene mutations [3]. Partial artemisinin resistance further threatens first-line artemisinin-based combination therapies (ACTs) [7, 8]The World Health Organization [1] has therefore called for innovative chemotypes, improved combination therapies, and novel drug-delivery systems to sustain malaria control.

### 2.2 Cocrystallization in drug design

Cocrystals are defined as crystalline single-phase solids composed of two or more neutral molecular species in a definite stoichiometric ratio [5, 9]. They can modify solubility, melting point, mechanical properties, and stability through supramolecular synthons such as amide–carboxylic acid and amide–hydroxyl hydrogen bonds. Several FDA-approved drugs (e.g., Entresto®, Steglatro®, Seglentis®) attest to the translational potential of this approach [10].

### 2.3 Sustainability of pharmaceutical cocrystals

Cocrystal engineering supports eco-friendly drug development by enabling solvent-free synthesis, lower energy use, and improved manufacturability. Mechanochemical processes such as liquid-assisted grinding (LAG) avoid hazardous solvents and reduce waste [11]. Cocrystals have also been described as “molecular-level green innovations” supporting Sustainable Development Goals (SDGs) [5].

### 2.4 Antimalarial cocrystals and prior research

Previous studies have explored cocrystallization of plant-derived antimalarial compounds [12] and classical antimalarials such as artemisinin and lumefantrine [13]. However, literature on sulfadoxine cocrystals remains scarce. The present work extends this field by combining an antifolate drug with an antioxidant, Generally Recognized As Safe (GRAS), coformer to generate a potentially synergistic and sustainable antimalarial formulation.

## 3 Methodology

### 3.1 Materials

Sulfadoxine (SAD, ≥98%) and ascorbic acid (ACA, ≥99%) were purchased from Sigma-Aldrich (UK) and used as received without further purification. The compounds were selected for their complementary functional groups—sulfonamide and carboxylic acid/hydroxyl groups—which favour hydrogen-bond formation. Both compounds have low toxicity profiles, are readily available, and are compatible with environmental sustainability goals.

### 3.2 Computational modeling

Molecular conformations of SAD and ACA were extracted from the Cambridge Structural Database (CSD refcodes DOLJIX01 and COFKOA). Hydrogen atom positions were optimized

and partial atomic charges calculated using the ORCA quantum chemistry software package employing the r2SCAN-3c density functional theory (DFT) method [14]. A conformational scan of SAD was performed to explore torsional flexibility and possible tautomeric forms. Dimerization energies were calculated using the *mol_dimer* program employing a drift-free differential-evolution optimizer (K = 0.5, F = 0.98, Gmax = 50 000, Np = 120). Binding energies were further refined at the r2SCAN-3c level of theory.

### 3.3 Experimental mechanochemical screening

A 1:1 molar ratio of SAD and ACA was ground in a Retsch MM200 ball mill at 25 Hz for 30 min. Liquid-assisted grinding (LAG) was performed using 20 μL of ethanol as the grinding solvent. The resulting powder was analysed by powder X-ray diffraction (PXRD) using Cu Kα radiation (λ = 1.5406 Å). Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed to characterize the resulting solid phase [11].

### 3.4 Sustainability assessment

The environmental performance of the LAG process was evaluated qualitatively using established green chemistry metrics, including atom economy, solvent minimization, energy efficiency, and waste reduction [15]. The sustainability outcomes were mapped to United Nations Sustainable Development Goals (SDGs) 3 (Good Health and Well-being), 9 (Industry, Innovation and Infrastructure), and 12 (Responsible Consumption and Production).

## 4 Results

### 4.1 Computational outcomes

The relaxed potential-energy surface revealed two possible sulfadoxine conformers separated by a high rotational barrier to interconversion, confirming the predominance of the crystal-structure conformation. Dimerization analyses indicated that SAD–ACA complexes form multiple hydrogen-bond networks involving sulfonamide N–H···O and hydroxyl O–H···O interactions. The predicted binding energy difference (≈ –33 kJ mol$^{-1}$) strongly favoured heteromolecular pairing, supporting the likelihood of cocrystal formation [9].

The calculated binding energies show that the SAD–ACA heterodimer is more stable than the corresponding homodimers (Table 1).

**Table 1.** Calculated binding energies for SAD, ACA and SAD–ACA dimers (kJ mol$^{-1}$)

| System | ΔE (optimized DFT) |
|---|---|
| SAD–ACA | **–81.6** |
| SAD–SAD | –73.4 |
| ACA–ACA | –56.3 |
| Predicted ΔE for heterodimer stability | –33.5 |

The optimized dimer geometries further illustrate the intermolecular interactions responsible for cocrystal formation and confirm the structural complementarity between SAD and ACA (Figure 2).

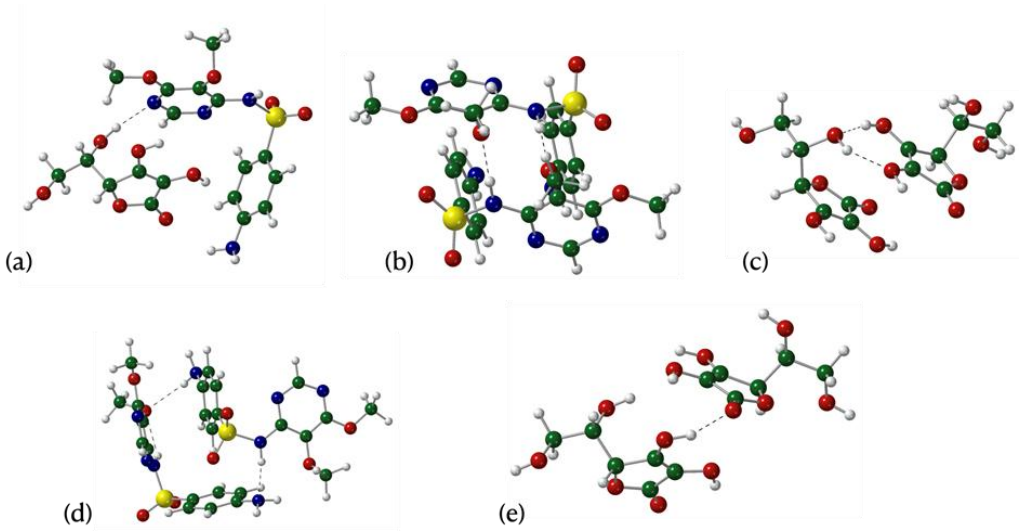


**Fig. 2.** Comparison of mol dimer located pairs for (a) SAD-ACA, (b) SAD-SAD, (c) ACA-ACA and the optimised dimers extracted from (d) SAD and (e) ACA crystal structures.

The significantly lower binding energy of the SAD–ACA heterodimer compared to the SAD–SAD and ACA–ACA homodimers indicates stronger intermolecular interactions between the two components. This thermodynamic favourability suggests that the formation of a SAD–ACA cocrystal is energetically preferred, providing a stable lattice structure consistent with experimental observations.

### 4.2 Experimental characterization

PXRD patterns of the ground sample displayed the appearance of a new diffraction peak at 19.272° (2θ), which was absent in both parent compounds, indicating the formation of a new crystalline phase rather than a physical mixture. The emergence of this distinct peak, along with minor shifts in the original peaks, confirms structural reorganization consistent with cocrystal formation (**Figure 3**).

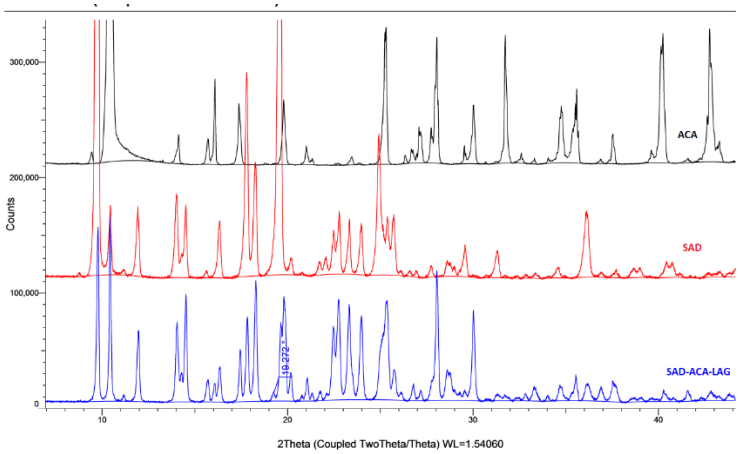


**Fig. 3.** Powder X-ray diffraction (PXRD) patterns of pure ascorbic acid (ACA), sulfadoxine (SAD), and the SAD–ACA cocrystal prepared by liquid-assisted grinding (LAG).

DSC thermograms exhibited a single sharp endotherm at approximately 165 °C, intermediate between the melting points of sulfadoxine (175 °C) and ascorbic acid (190 °C), further supporting the presence of a new solid form (**Figure 4**).

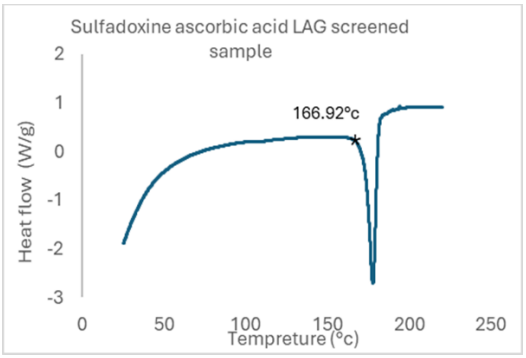


**Fig. 4.** DSC thermogram of sulfadoxine, ascorbic acid, and the LAG-screened SAD–ACA sample.Correlation between computational and experimental data.

The experimentally observed stability corresponds with the theoretical prediction of the favourable SAD–ACA binding energy. This agreement underscores the reliability of molecular-level computational screening for guiding sustainable formulation design [16].

## 5 Discussion

### 5.1 Mechanistic rationale for synergy

Cocrystallization of SAD with ACA offers both physicochemical and pharmacological advantages. Ascorbic acid's antioxidant capacity may help mitigate oxidative stress associated with malaria infection and reduce oxidative degradation of SAD during storage. The hydrogen-bonded heterosynthon stabilizes SAD's sulfonamide group, enhancing dissolution and potentially improving oral bioavailability [13].

### 5.2 Combating drug resistance

Drug resistance in *P. falciparum* is linked to genetic mutations (e.g., *K13*, *dhps*, *dhfr*) that reduce drug accumulation and binding (Blasco *et al.*, 2017). Sustained drug exposure at sub-therapeutic levels accelerates resistance development. By improving solubility and pharmacokinetic stability, SAD–ACA cocrystals could maintain effective plasma concentrations, potentially delaying resistance development [8]. Furthermore, combination with redox-active coformers could target parasite oxidative stress pathways synergistically.

### 5.3 Sustainability advantages

Mechanochemical synthesis requires minimal solvent and energy compared with traditional crystallization methods, while the Generally Recognized As Safe (GRAS) status of ascorbic acid supports regulatory safety and environmental compatibility. Such green approaches can significantly reduce the ecological footprint of pharmaceutical production by lowering $CO_2$ emissions, solvent waste, and processing time (Friščić *et al.*, 2020). This strategy aligns directly with the United Nations Sustainable Development Goals (SDGs), particularly SDG 3 (Good Health and Well-being) by contributing to malaria control through accessible therapies; SDG 9 (Industry, Innovation and Infrastructure) by advancing sustainable pharmaceutical manufacturing; and SDG 12 (Responsible Consumption and Production) by promoting solvent-free, low-waste production methods.

### 5.4 Future directions

Future work should focus on comprehensive physicochemical characterization, including solubility, dissolution rate, and hygroscopicity, together with *in vitro* cytotoxicity and antiplasmodial assays to evaluate biological efficacy [13]. Additional studies are needed to assess the scalability and environmental life cycle impact of the mechanochemical process, as well as to explore ternary cocrystals incorporating other GRAS coformers to fine-tune solubility, stability, and drug-release kinetics for optimized therapeutic performance.

## 6 Conclusion

This study demonstrates the potential of crystal-engineering strategies to address both therapeutic and environmental challenges associated with antimalarial drug development. The sulfadoxine–ascorbic acid cocrystal, validated computationally and experimentally, represents a promising sustainable formulation with improved physicochemical stability and potential pharmacological synergy. Integrating green manufacturing and molecular design offers a

pathway toward resilient, accessible, and environmentally responsible therapies to combat malaria and global drug resistance [15].

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