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Repurposing Aspirin and Simvastatin into a Bioavailable Co-Crystal with Enhanced Anti-Breast Cancer Activity

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INTRODUCTION & AIM

INTRODUCTION

- **Breast carcinoma,** a principal contributor to global cancer-related morbidity and mortality, highlighting a critical demand for innovative therapeutic modalities.
- **Conventional chemotherapeutic** agents are frequently limited by non-specific biodistribution and dose-limiting systemic toxicities which has catalysed the investigation of alternative paradigms, including pharmaceutical repurposing and the engineering of multi-component crystalline forms.
- **Aspirin**, a canonical nonsteroidal anti-inflammatory drug (NSAID), demonstrates documented chemo preventive and antitumor properties via irreversible inhibition of cyclooxygenase (COX) isoforms and potentiating mitochondrial apoptotic pathways
- **Simvastatin**, a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, has revealed pleiotropic anti-neoplastic effects independent of its lipid-lowering activity.
- The **drug-drug co-crystal (DDC)** approach constitutes a supramolecular strategy to coalesce two active pharmaceutical ingredients (APIs) into a singular, homogeneous crystalline lattice under non-covalent interactions.
- DDC are fundamentally optimized critical quality attributes, such as aqueous solubility, dissolution kinetics, and solid-state stability, thereby potentially augmenting in vivo bioavailability without chemical modification of the constituent APIs.

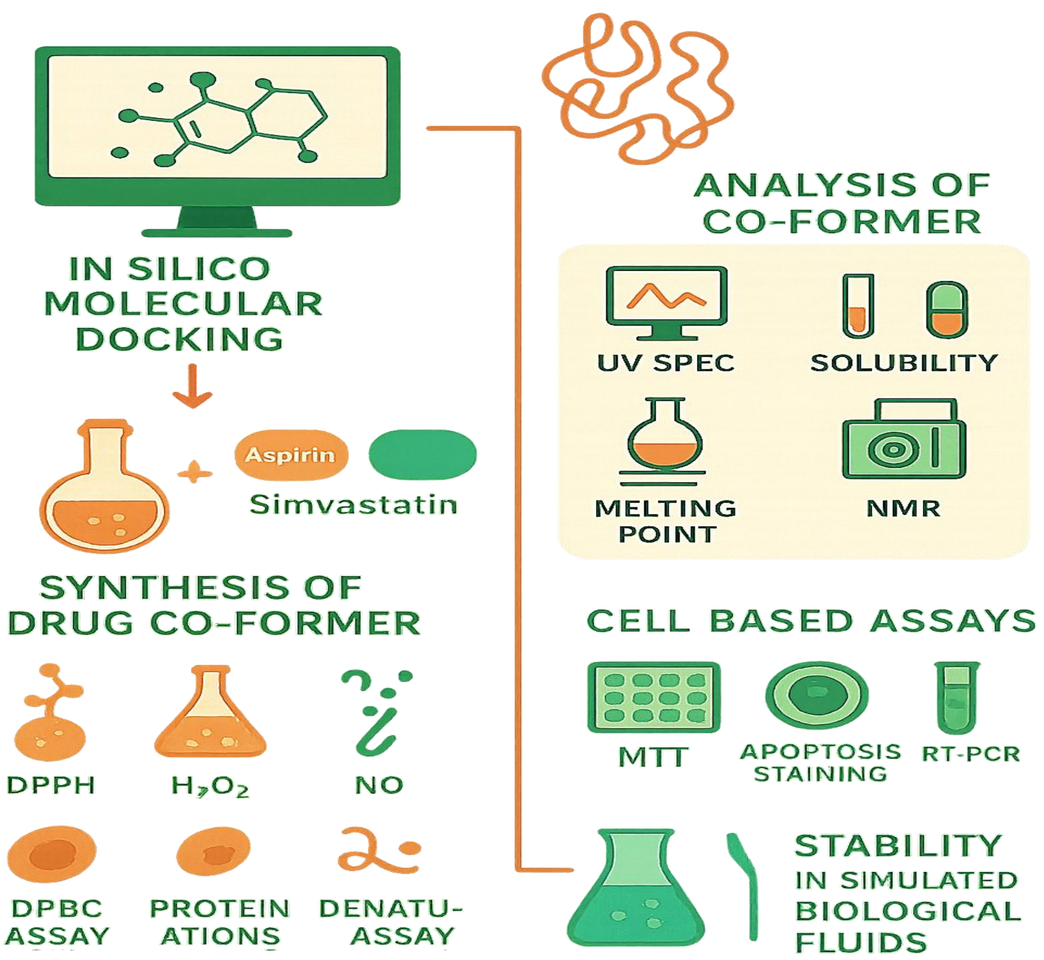
AIM

Mechanochemical synthesis, comprehensive solid-state characterization, and preclinical biological profiling of a novel **Aspirin–Simvastatin Co-crystal** as a prospective synergistic entity for the management of breast cancers.

OBJECTIVES:

1. **Computational Design and Solid-State Synthesis:** To computationally validate the synergistic potential of Aspirin and Simvastatin via molecular docking against key oncogenic targets, followed by the mechanochemical synthesis of a novel Aspirin-Simvastatin co-crystal, with its formation unequivocally confirmed by a suite of solid-state characterization techniques.
2. **Comprehensive Preclinical Biological Profiling:** To conduct a comparative evaluation of the co-crystal's bioactivity, assessing its enhanced antioxidant and anti-inflammatory properties, and its superior efficacy against MCF-7 breast cancer cells.
3. **Physicochemical and Biopharmaceutical Assessment:** To determine the developed co-crystal's physicochemical stability and simulate its gastrointestinal dissolution profile to predict in vivo performance and potential for improved oral bioavailability.

METHOD



RESULTS & DISCUSSION

Physiochemical Analysis

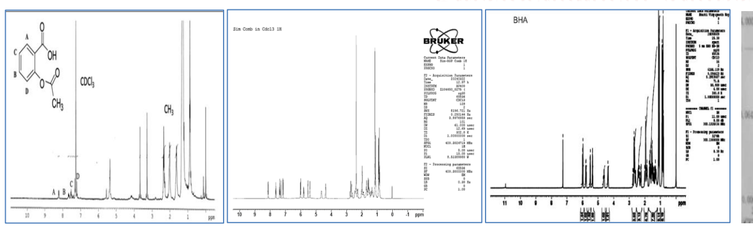


Figure 1: NMR 1H of Aspirin, DDC and Simvastatin respectively

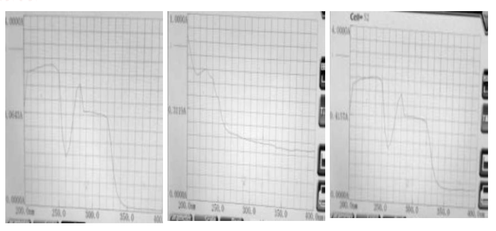


Figure 2: λmax analysis of pure compounds and synthesized DDC

In-Silico Analysis

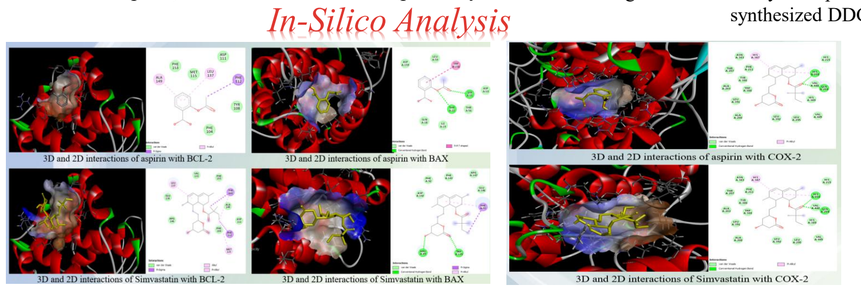


Figure 3: 2D, 3D Interactions of Key Oncogenic Markers with Aspirin and Simvastatin

Cell-Free Assays

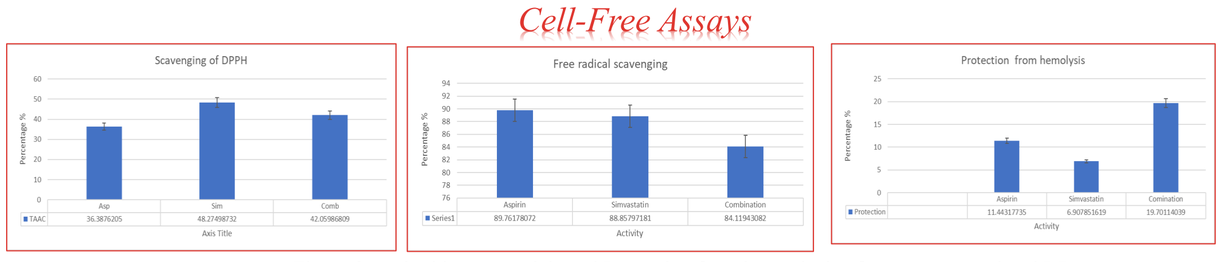
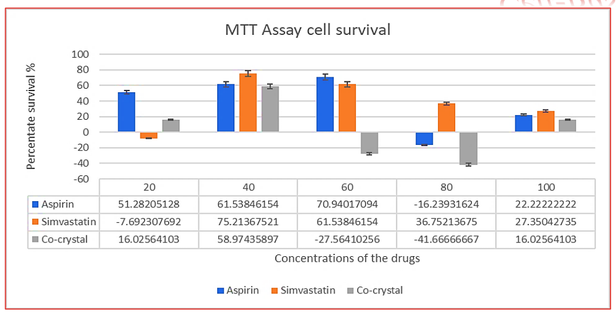


Figure 3:Antioxidant potentials and Protection from haemolysis of pure compound and DDC

Cell-Based Assays



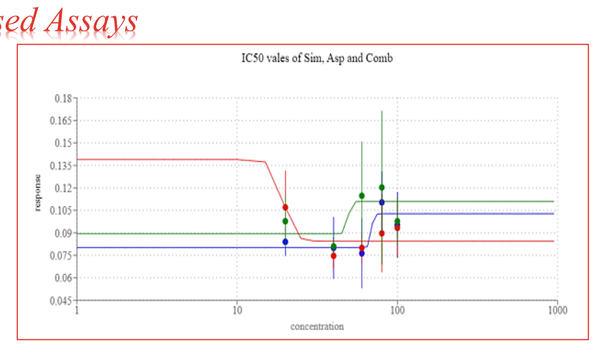


Figure 4:Cytotoxicity analysis and calculated IC_{50} values, on MCF-7 cells

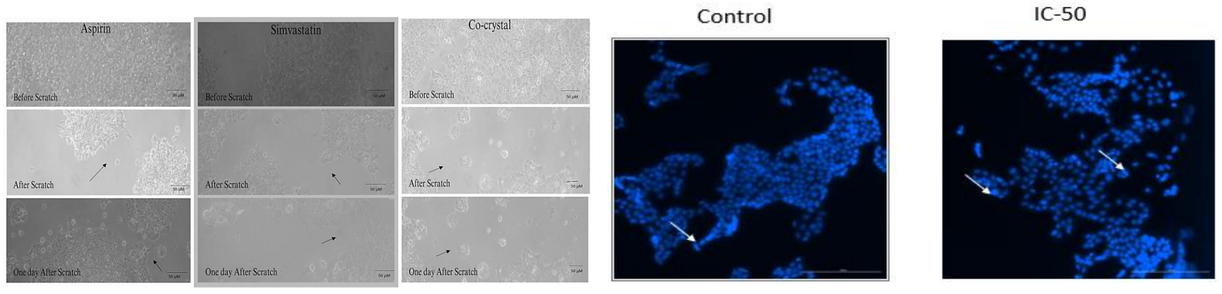


Figure 5:Antiproliferative effect of synthesized Co-former at IC50 value, by scratch assay and Apoptosis Assay by Hoechst staining (MCF-7 cell line)

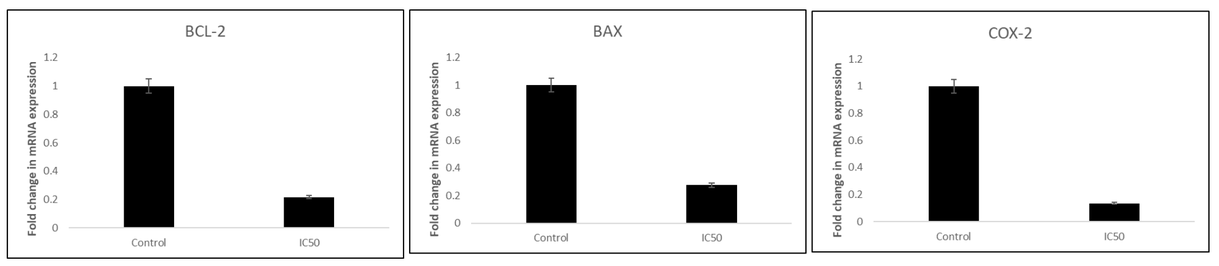


Figure 6: RT-PCR analysis of Key oncogenic marker genes in MCF-7 cell line treated with IC50 values of synthesized co-former

CONCLUSION

- **Successful Co-crystal:** A novel Aspirin-Simvastatin co-crystal with enhanced solubility and stability was formed.
- **Potent Anti-cancer Activity:** It demonstrated superior anti-proliferative effects against breast cancer cells, outperforming the parent drugs.
- **Pro-apoptotic Mechanism:** Activity is driven by inducing apoptosis via key gene regulation (↓BCL-2/COX-2, ↑BAX).
- **Promising Candidate:** This co-crystal is a rational, repurposing strategy for a potentially faster route to breast cancer therapy.

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3. Patel, K., Li, H., & Zaworotko, M. J. (2024). Targeting apoptosis in cancer therapy: The role of co-crystals in modulating BCL-2 family proteins. *Crystal Growth & Design, 24*(1), 456–470. https://doi.org/10.1021/acs.cgd.3c01102