CO-CRYSTALS DESIGN OF VELPATASVIR AND LITHOSPERMIC ACID APPLYING MOLECULAR MODELING

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Introduction

Inflammatory diseases originate from multiple biological systems and an abundance of P2X7R is observed in inflammation-modulating cells, making it a promising target for treatment. In recent decades, there has been a significant search for safe and effective anti-inflammatory molecules due to treatment failures caused by side effects and interactions with existing drugs. Two potent compounds - velpatasvir (VEL) and lithospermic acid (LIT) - were selected through our previous analysis of thousands of molecules for their high affinity for P2X7. VEL, an approved drug, is classified as class IV in the biopharmaceutical classification system, indicating difficult bioavailability. LIT is a natural product. One strategy to modulate a drug's pharmacokinetic properties, such as solubility, is to form co-crystals with suitable co-formers. Molecular modeling and computational chemistry techniques for co-crystal drug design continue to lack comprehensive rationalization in optimizing experimental design. This study aimed to provide significant theoretical information utilizing advanced quantum calculations to investigate crystalline systems.

Material and Methods

First, Avogadro, MOPAC2016, CSD-Mercury, and Molegro Virtual Docker programs were used for virtual screening of a molecule library of 107 co-formers. Next, USPEX and Quantum Espresso were employed for optimization of co-crystal structures using quantum relaxation calculations and enthalpy of formation (Figure 1).

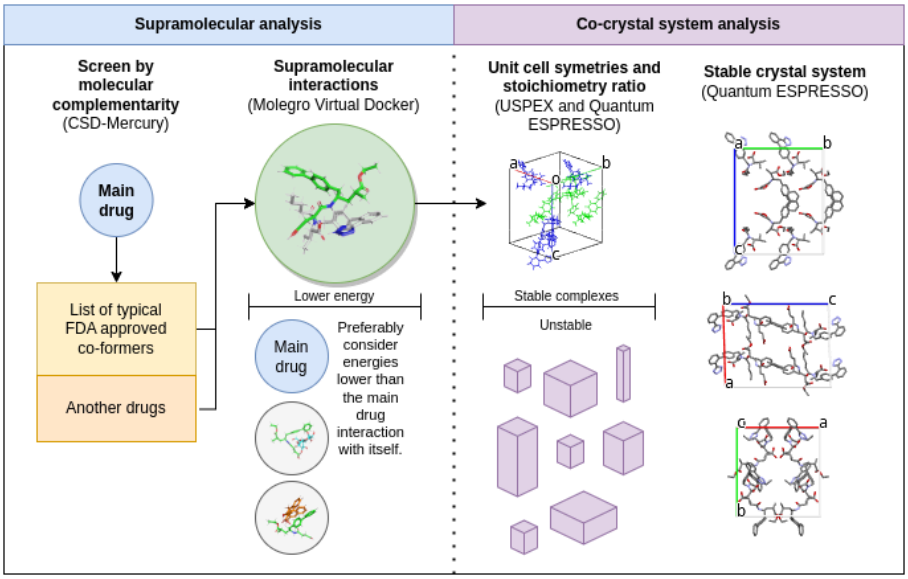

Figure 1. Two major analyses for screening potential co-crystal crystalline systems.

Results and Discussion

Supramolecular analyses of VEL and LIT, combined with a library of 107 co-formers defined as Generally Recognized as Safe (GRAS), indicated a higher affinity preference between them compared to the other compounds. Supramolecular interactions between VEL and LIT can be observed in Figure 2.

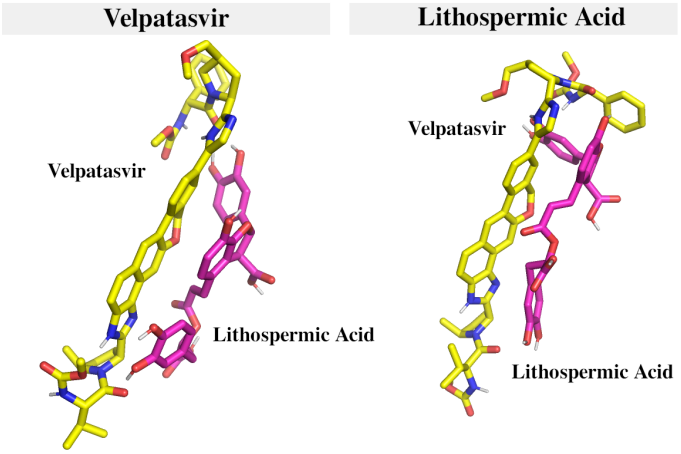

Figure 2. Supramolecular interactions between velpatasvir and lithospermic acid.

Preliminary results in the first stage of quantum relaxation calculations of co-crystal unit cells suggest that VEL could form a co-crystal with LIT with a stoichiometry of 1:1. The stability observed suggests that they will also remain stable in high-pressure calculations that may alter the volume of the hypothetical co-crystals. The results of co-crystal design can provide important data to guide the stages of experimental development, including the rationalization of solvents and active pharmaceutical ingredients (APIs) during the recrystallization phases. Many molecules considered first choices in experimental tests were discarded during the screening stages, including citric acid, malonic acid, sorbic acid, saccharin, and others.

Conclusion

VEL and LIT cloud provide a dual-action product for anti-inflammatory diseases through modulation of the P2X7 receptor. The most stable ratios and symmetries will be proposed for re-co-crystallization and dissolution studies. Novel co-crystals are important to pharmaceutical research, as it involves exploring new patents, mitigating risks in high-cost formulations, and providing insights for selecting methods to scale up production on an industrial level.

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