One Health drugs against parasitic vector borne diseases in Europe and beyond
OneHealth*drugs* Cost Action CA21111

Role of crystal engineering in repurposing drugs for therapy of antiparasitic vector-born disease: structure-property relationship

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The aim of drug repurposing for antiparasitic therapy

To leverage the utilization of the approved drugs or that what previously are investigated toward phases of clinical trail for treatment of the original diseases redirecting their well-establish pharmacokinetics and safety in validation the new therapies compared to their initial pharmacological treatments.

Cons of Drug Repurposing

- ✓ Limited specificity & efficacy
- ✓ Risk of failure and adverse effects
- ✓ Lack of Intellectual Property Protection

Pros of Drug Repurposing

- ➢ Saving time and money
- ➢ Expanding therapeutic opportunities to address unmet medical needs

Inbound repurposing of drugs to the field of infectious diseases.

Shared Property	Emerging Target/MoA	Drug
High rate of cell division	Microtubule sp.	Mebendazol
Fast rate of DNA synthesis	Topoisomerase	Quinolones
High demand of nucleotides	Pyrimidine synthesis	Antifolates, DHODH inhibitors
High rate of protein turnover	Proteasome	Proteasome inhibitors
High metabolic rate	Glycolysis	Antimycin A
Enhanced redox metabolism	Activation of prodrugs	Artemisinin
Cellular signaling pathways	Protein kinases	Sunitinib

Similarities between parasites and tumor cells, and how they can be exploited as drug targets

Molecule	Original Purpose	Envisaged New Purpose
Cisplatin	Cancer	Antibacterial
Eflornithine	Cancer	Human African trypanosomiasis
Gallium nitrate	Cancer	Pseudomonas aeruginosa
Miltefosine	Cancer	Leishmaniasis
Mitomycin C	Cancer	Microbial persisters
Niclosamide	Snail control	Antibacterial, antiviral, antifungal
Thalidomide	Morning sickness	Leprosy
Toremifene	Cancer	Bacterial biofilm

Role of Crystal engineering in Repurposing Drugs for Antiparasitic treatment

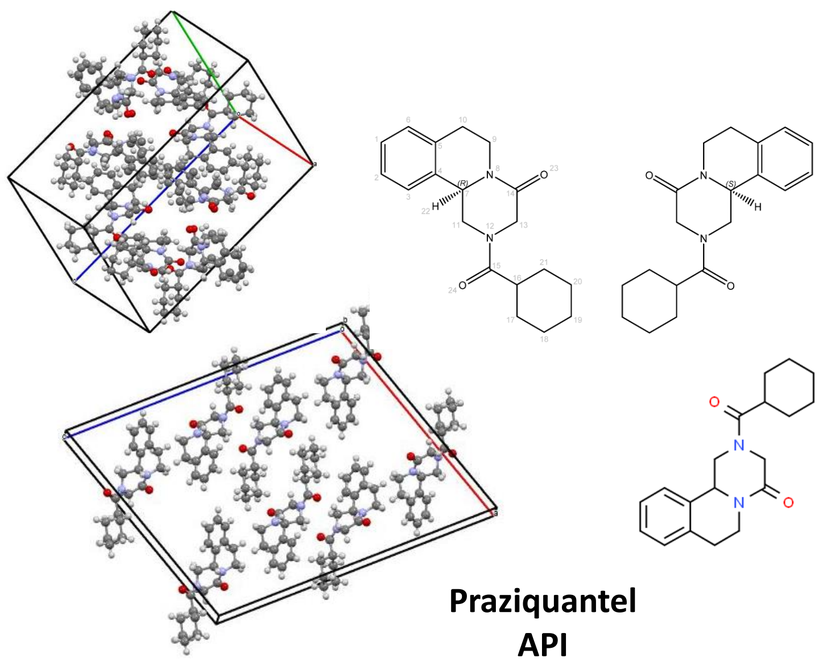
- Crystal engineering utilizes the chemical information of small-molecule crystal structures in the Cambridge Structural Database (CSD).
- Interaction surfaces and shapes of molecules in experimentally determined small-molecule crystal structures can serve as effective tools in drug discovery.
- Electron density-based intermolecular boundary surfaces in small-molecule crystal structures and in target protein pockets are utilized to identify potential ligand molecules from the CSD – based on 3D shape and intermolecular interaction matching.
- Bridging small-molecule crystallography and protein crystallography

Advantage of Crystal engineering in Assessment of the Drug-likeness of the Ligands

- The distributions of number of H-bond donors and acceptors,
- Molecular weights, Log P (cLogP, the logarithm of partition coefficient between n-octanol and water)[21] polar surface area (PSA)
- Desirable absorption or permeation based on Lipinski's empirical rules

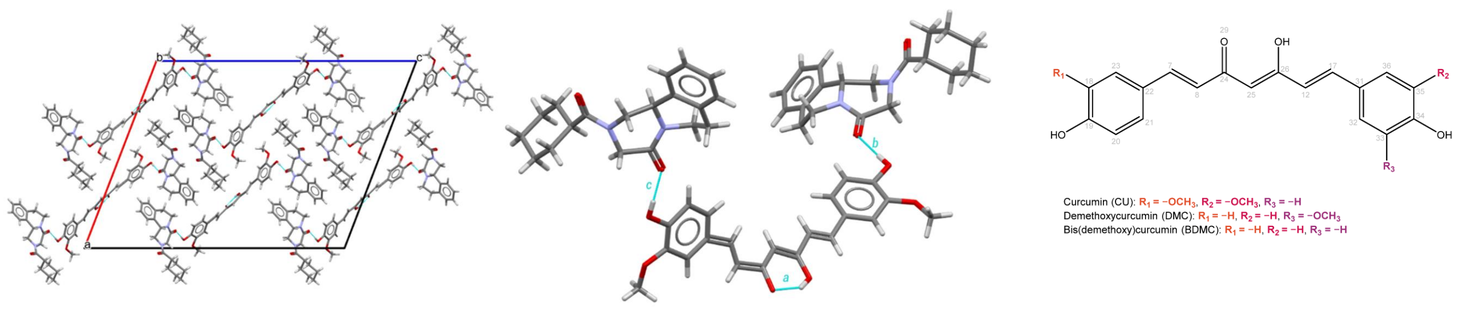
Workflow in Crystal Engineering

API → Computational Screening for potential Coformers → Ranking & analyses crystals prediction → Experimental design → Optimizing solid-state properties → Refinement/ Recalculate of computational screening (optional)



Praziquantel API

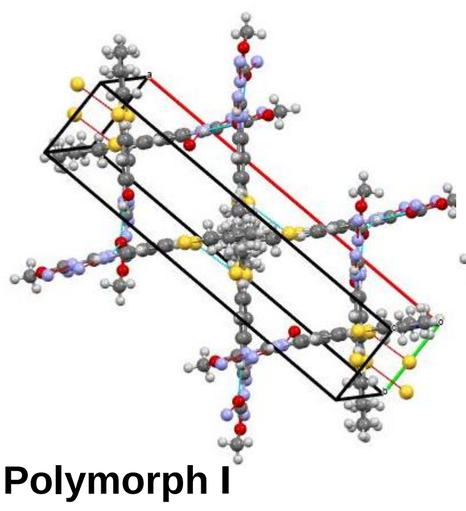
Model1: Cocrystal Praziquantel/ Curcumin 2:1 M/M



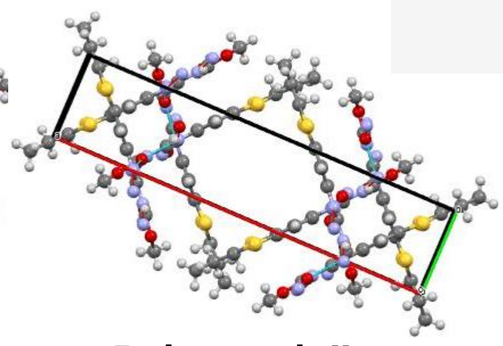
Curcumin Coformerl

Crystals **2024**, *14*(2), 181

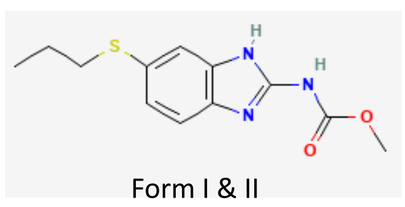
Model 2: Polymorphism of Ablendazole



Polymorph I



Polymorph II



Form I & II
Enantiotropicaly related
Form II less soluble at ambient T, more stable
0.0228 mg/mL in water at 25 °C
high permeability (log P 2.54)

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