

CA21111 - One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs)

1st Meeting, Modena 23-24 January 2023

**Crystal engineering for antiparasitic drug
multicomponent crystal:
crosscut in drug discovery and drug development**

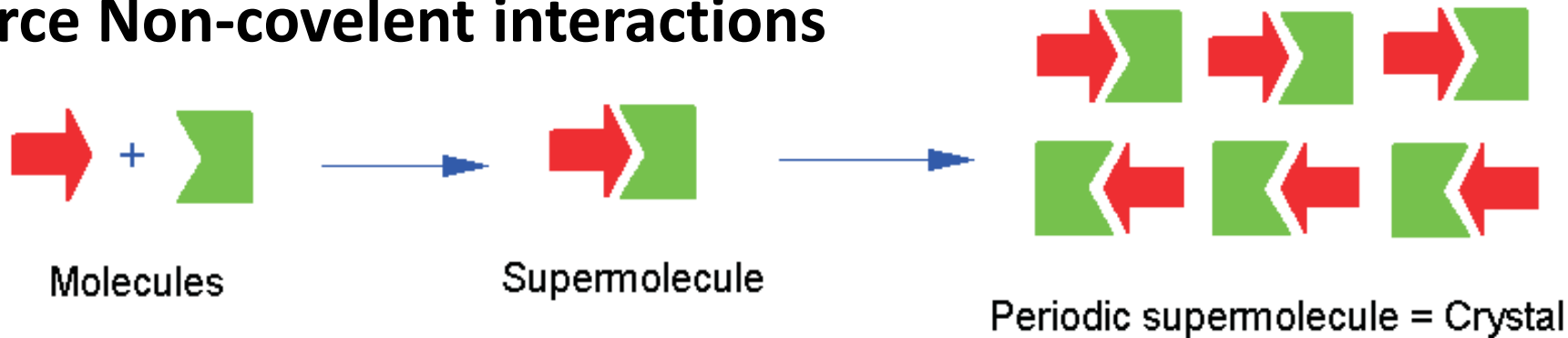
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^aFaculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip, North Macedonia

Correspondence email: aleksandar.cvetkovski@ugd.edu.mk

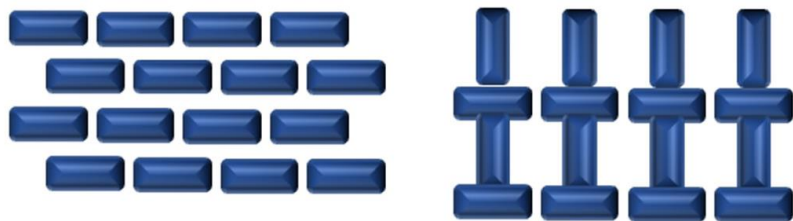
What is Crystal engineering?

Driving force Non-covalent interactions

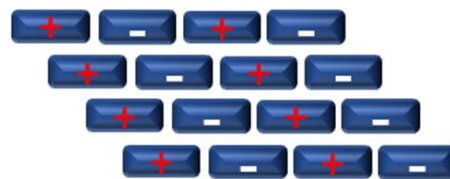


Beyond covalent bond chemistry

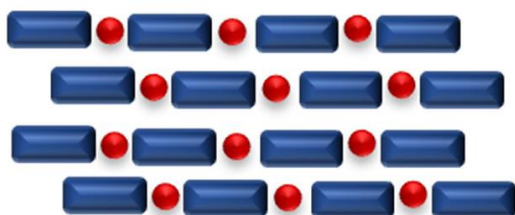
Polymorphs



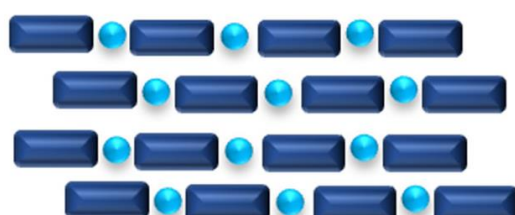
Salts



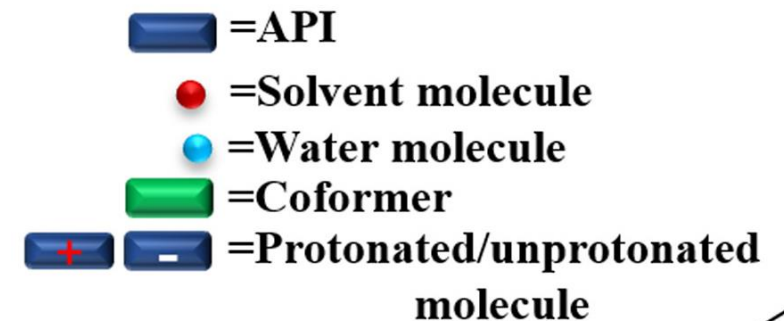
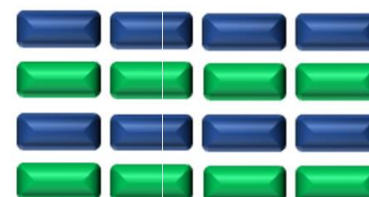
Solvates



Hydrates



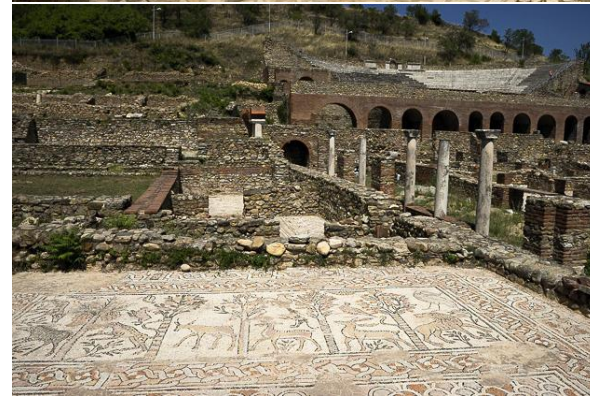
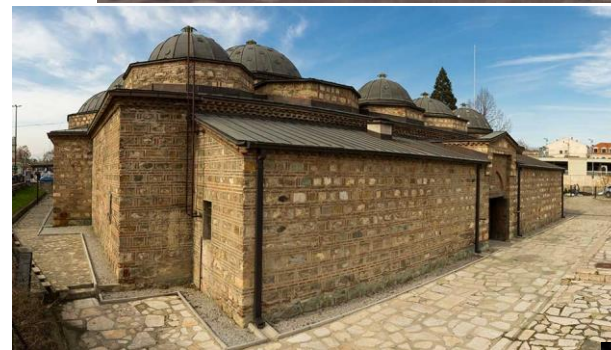
Cocrystals



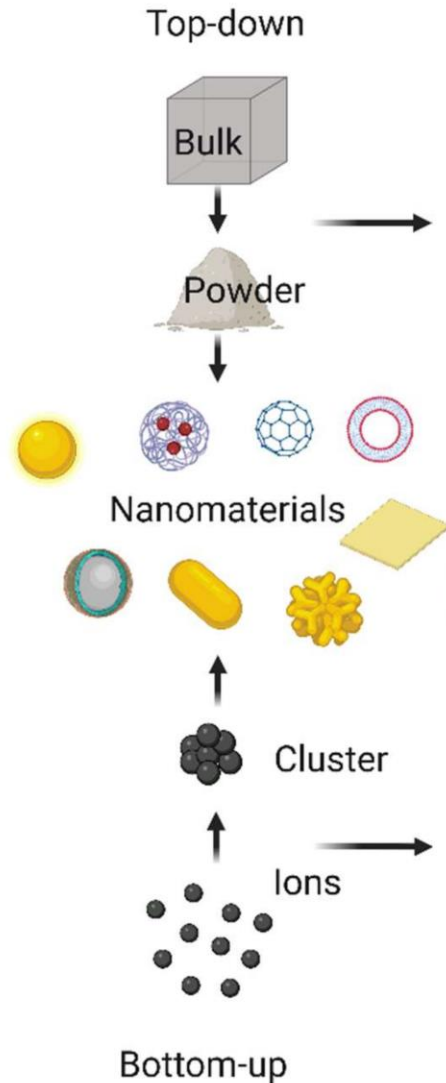
Inspired in history and cultural heritage for designing Crystals with desirable properties

Roma, Italy

Skopje, N Macedonia



Top-down Synthesis



Segmentation into microfractions to nanoparticles.

MECHANICAL: Ball milling, mechanical attrition, mechanical grinding.

PHYSICAL: Thermal evaporation, thermal pyrolysis, nano-spraying.

ADVANTAGES: Low-cost and large-scale production. Deposition on large substrates. Low environmental impact.

DISADVANTAGES: Broad size distribution. Varied particle shapes. High product impurities.

Bottom-up Synthesis

Assembling ions or molecules into nanoparticles.

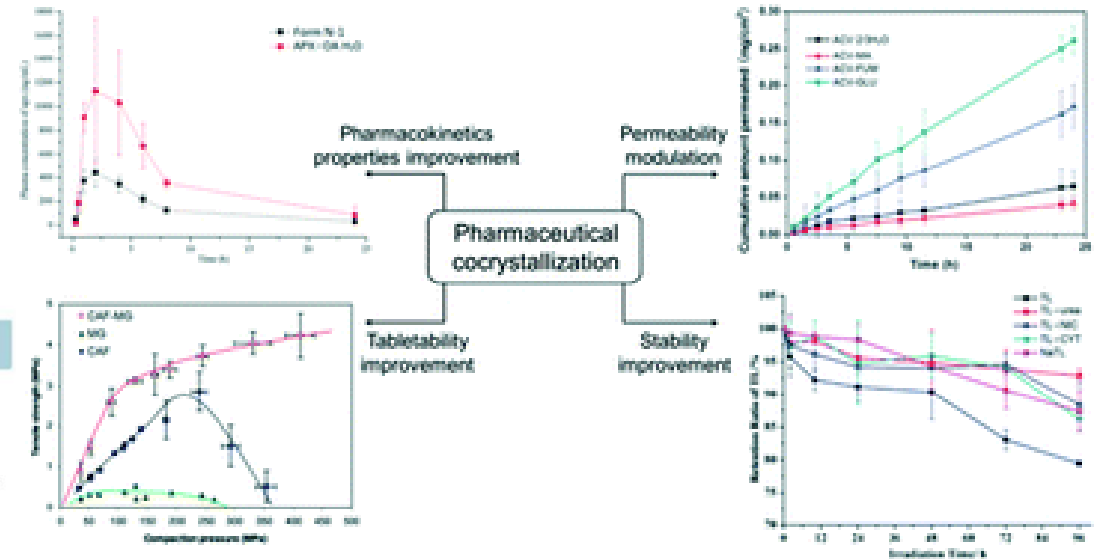
CHEMICAL: Polymerization, reduction, oxidation.

BIOLOGICAL: Plant extract, bacteria, fungi, algae.

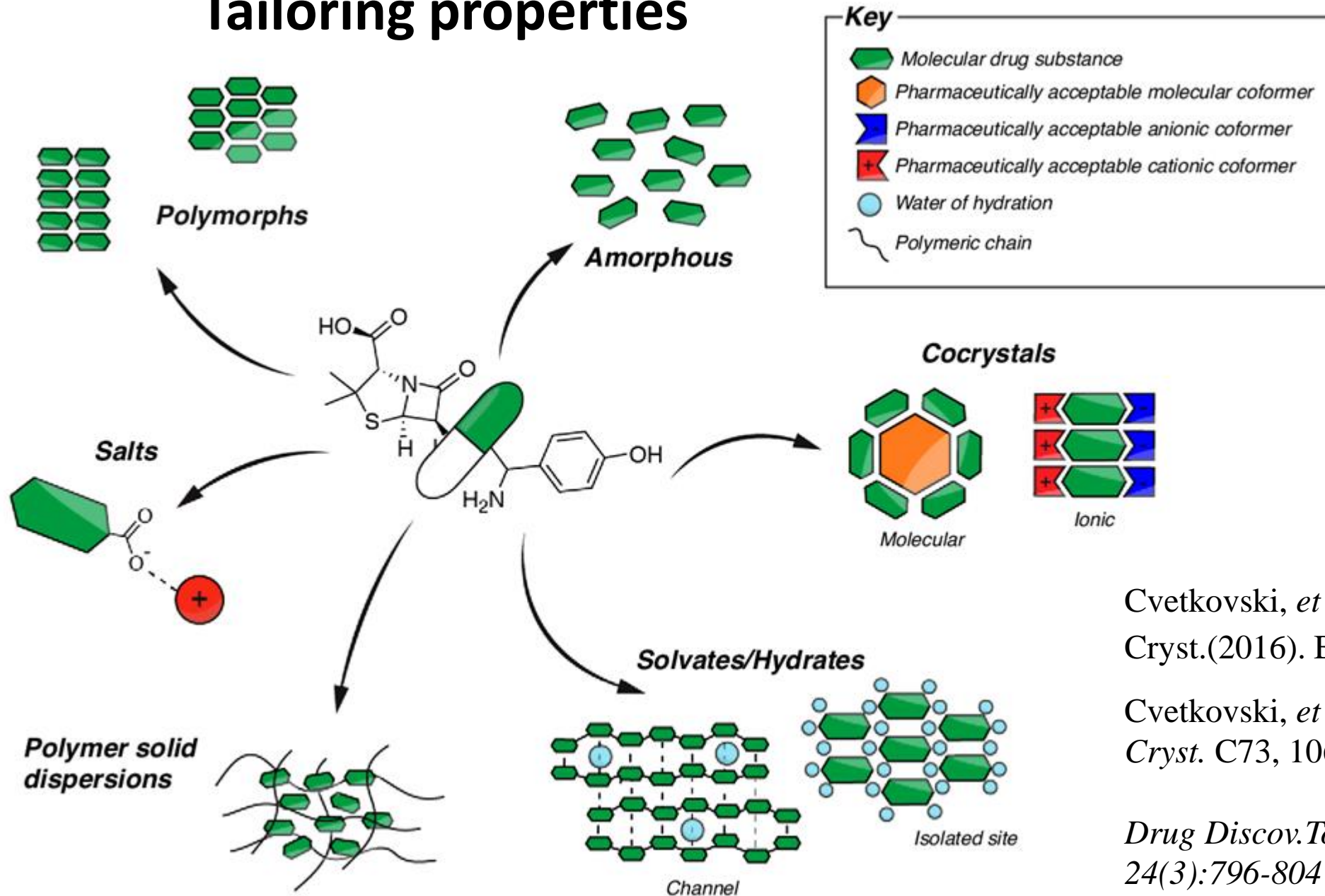
ADVANTAGES: Narrow size distribution. Particle shape and composition control. Suitable for lab.

DISADVANTAGES: High-cost production. Large-scale production difficult. Requires removal of by-products.

Green Chemistry



Tailoring properties

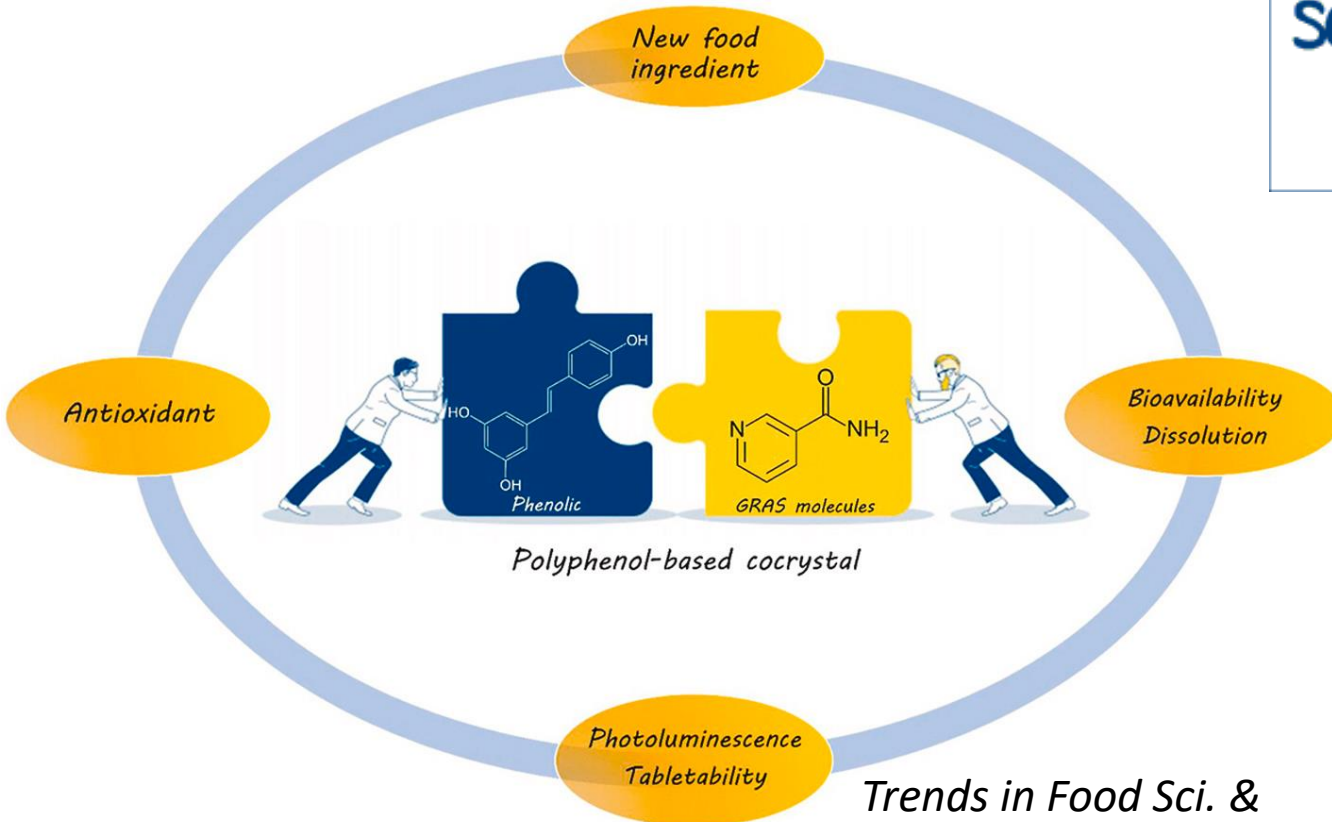


Cvetkovski, *et al.*, *Acta Cryst.*(2016). B72, 326–334.

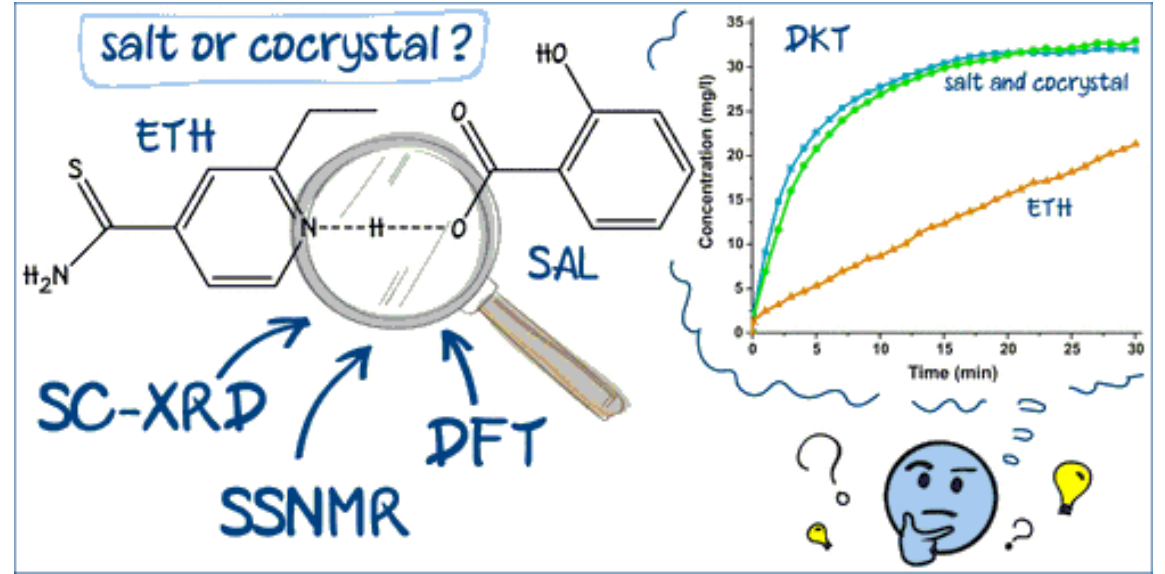
Cvetkovski, *et al.*, (2017). *Acta Cryst.* C73, 1064–1070

Drug Discov.Today, 2019
24(3):796-804

Molecular Interplay



Trends in Food Sci. & Tech., 110, 2021, 13-27



Cryst. Growth Des.
2020, 20, 2, 906–915

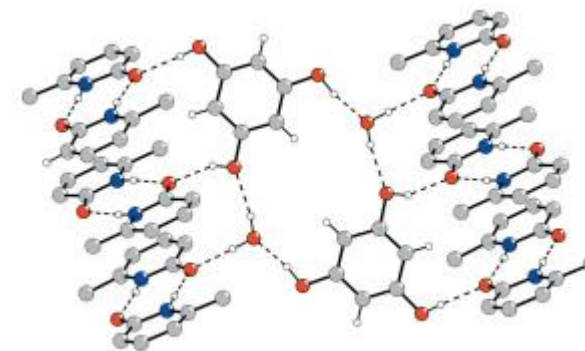
Supramolecular hydrogen-bonding patterns of co-crystals containing the active pharmaceutical ingredient (API) phloroglucinol and *N*-heterocycles

Aleksandar Cvetkovski,^a Valerio Bertolasi^b and Valeria Ferretti^{b*}

^aFaculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip The Former Yugoslav Republic of Macedonia, and ^bDepartment of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17-27, I-44121 Ferrara, Italy. *Correspondence e-mail: frt@unife.it

Received 9 February 2016

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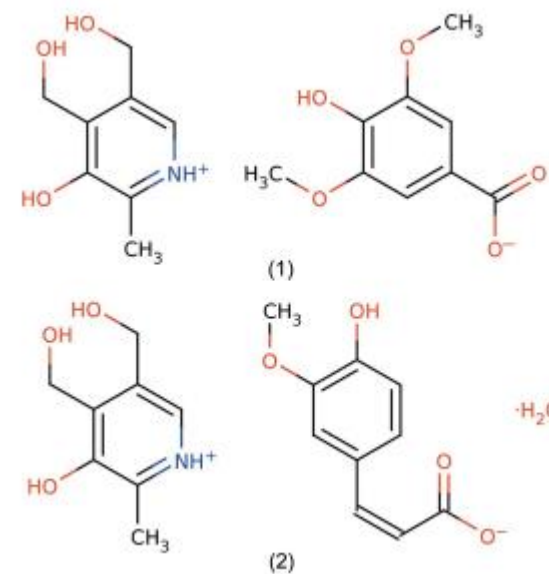


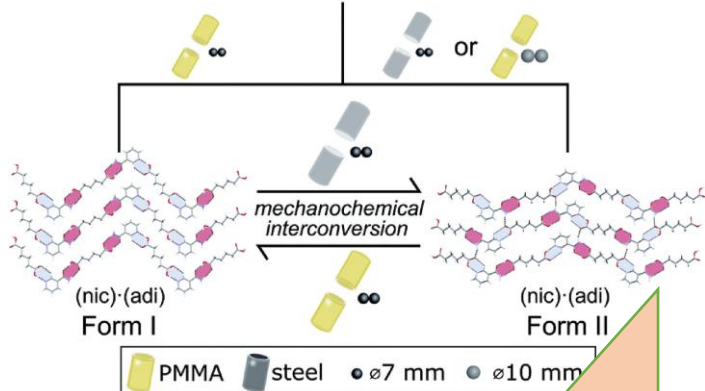
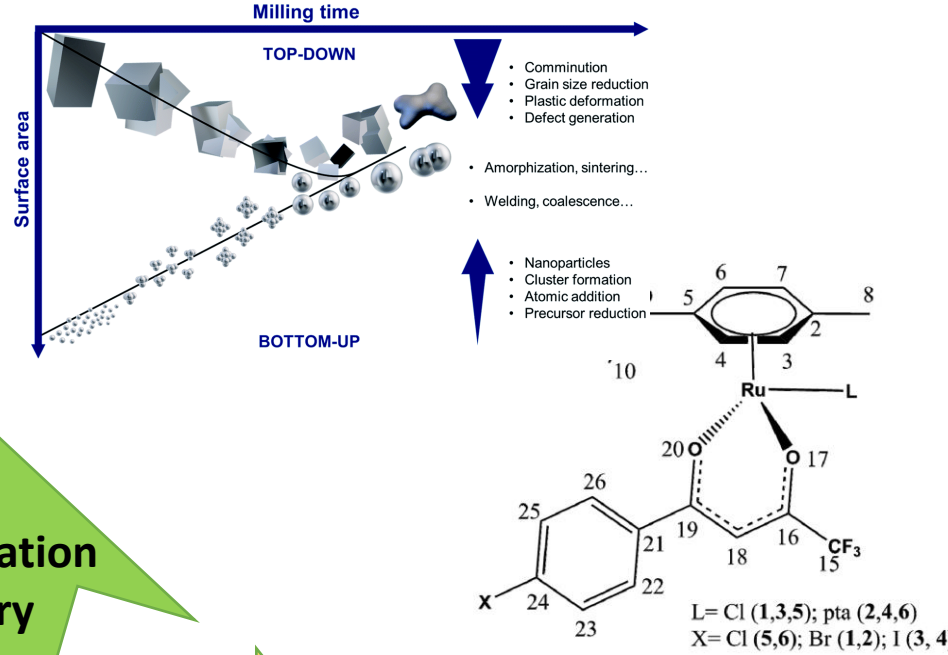
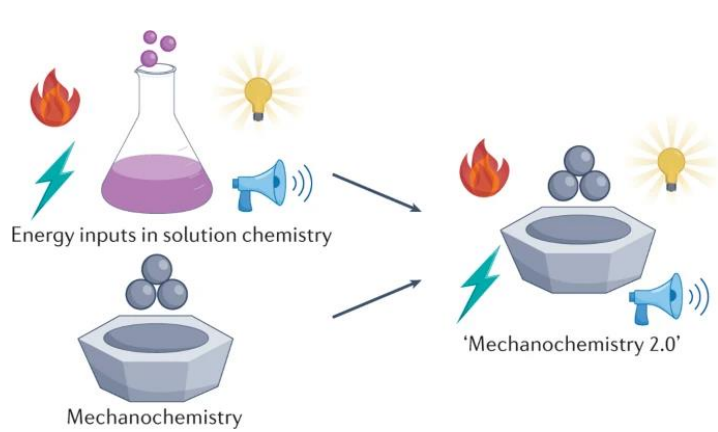
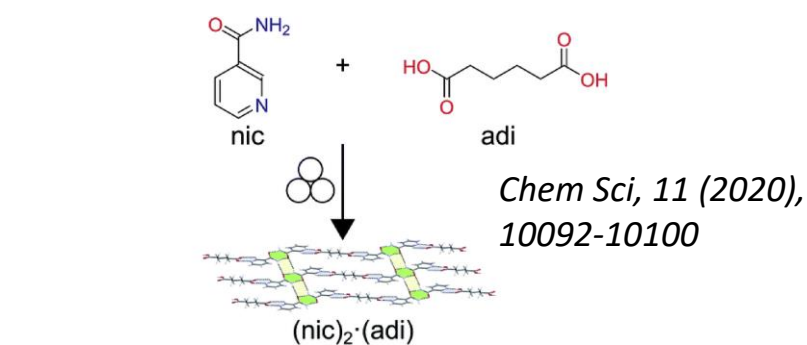
research papers

New pharmaceutical salts containing pyridoxine

Aleksandar Cvetkovski,^a Valeria Ferretti^{b*} and Valerio Bertolasi^b

^aFaculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip, The Former Yugoslav Republic of Macedonia, and ^bDepartment of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17, Ferrara I-44121, Italy. *Correspondence e-mail: frt@unife.it





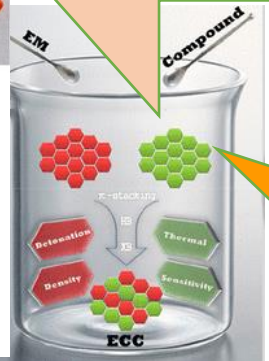
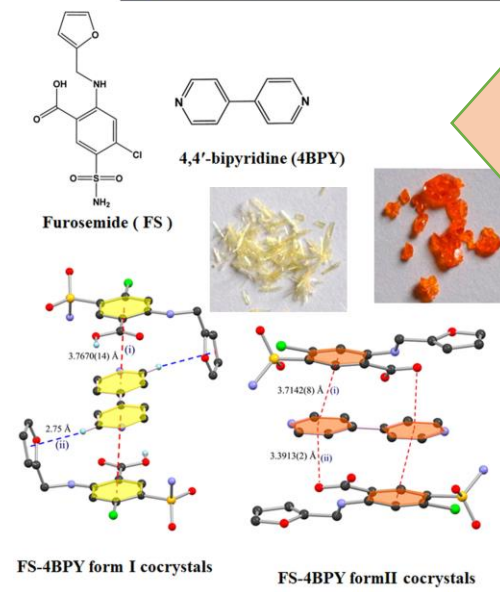
Mechanochemistry

Coordination chemistry

SUPRAMOLECULAR CHEMISTRY

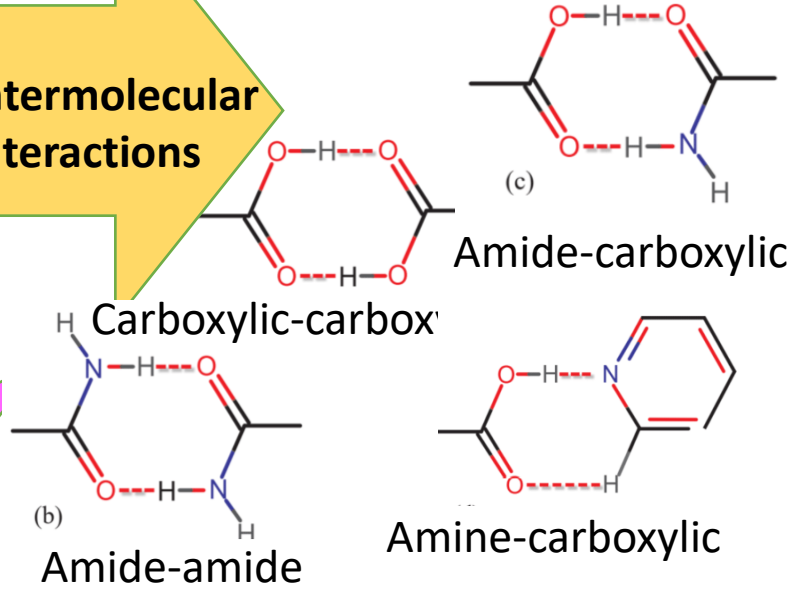
Pharma & Agrochemical applications

Intermolecular interactions



Energetic materials

Molecular capsules



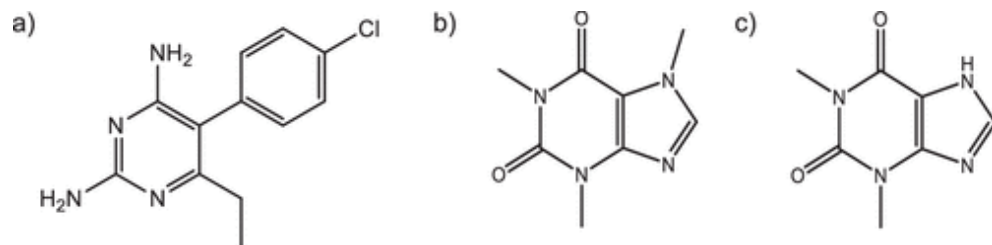
Cryst Growth Des, 15 (2015), 5858-5872

Cryst. Growth Des. 2022, 22, 2, 954-970

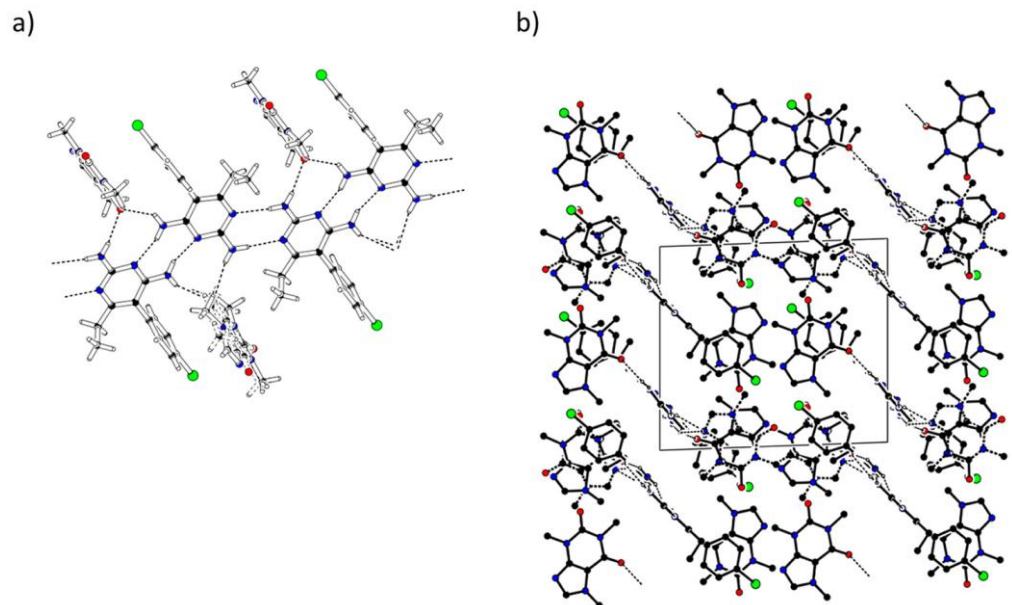
CrystEngComm, 2005, 7, 439-448

Case study: Pharmaceutical Co-crystals of antimalaric Pyrimethamine drug

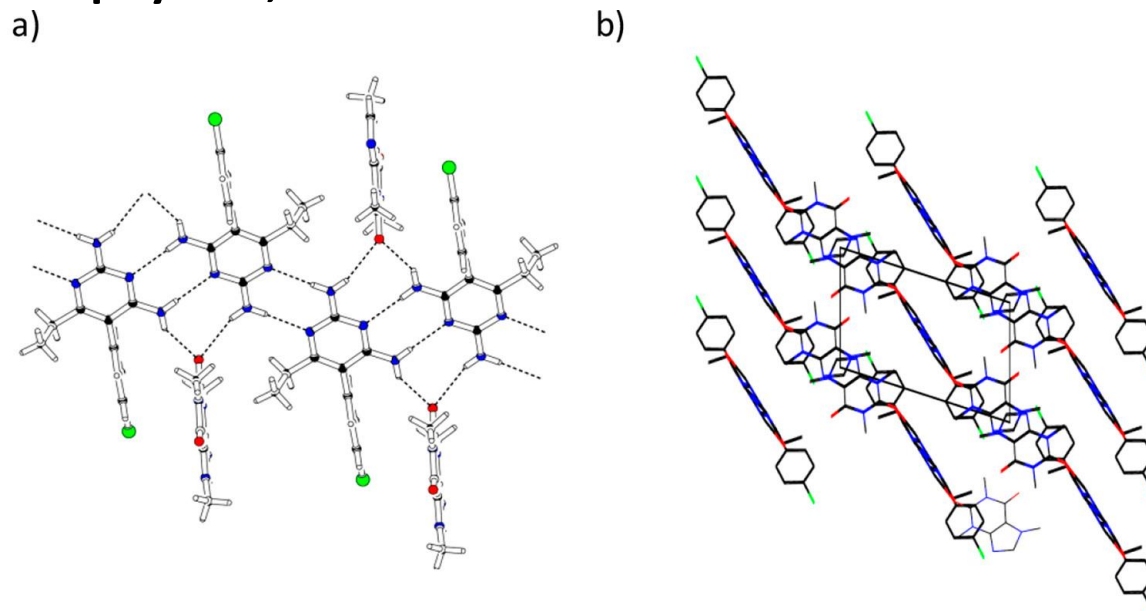
Crystal Growth & Design 2021, 21, 7, 3699-3713



(a) Pyrimethamine, PMA; (b) Caffeine, CAF; (c) Theophylline, THEO

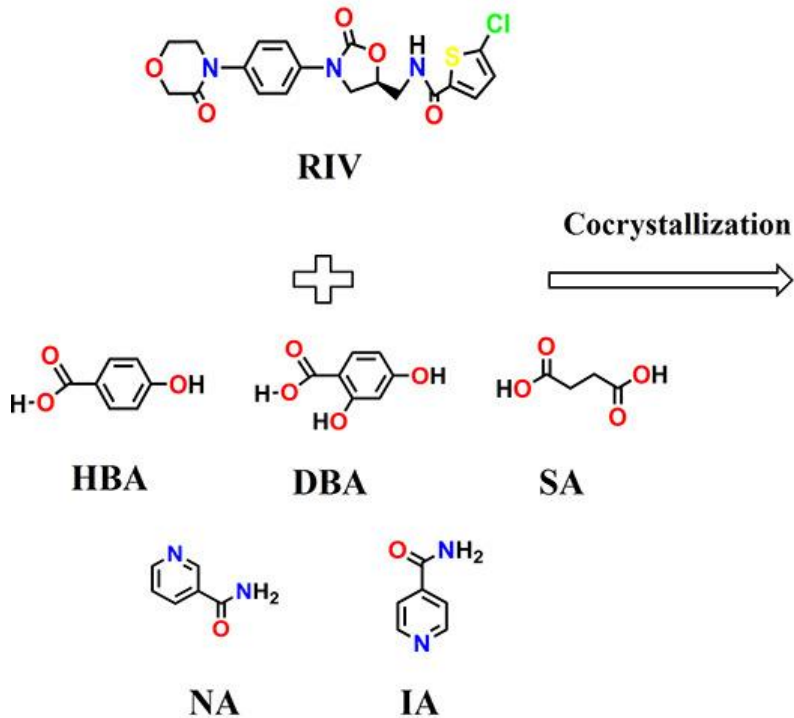


(1:1) Pyrimethamine:caffeine cocrystal, polymorph I, CCDC [1957393](#): (a) hydrogen-bonded ribbons joining pyrimethamine and caffeine molecules. (b) Unit cell packing viewed along the a axis.

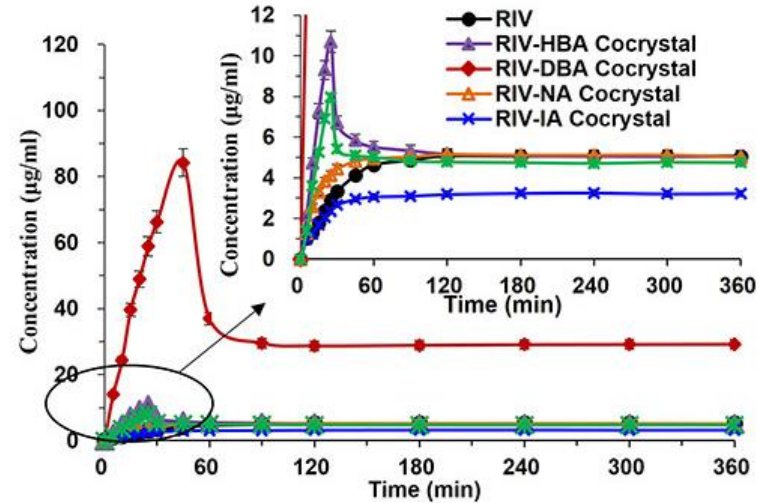


(1:1) Pyrimethamine:caffeine cocrystal, polymorph II, CCDC [1906084](#): (a) hydrogen-bonded ribbons joining pyrimethamine and caffeine molecules. (b) Packing of the chains in the unit cell, viewed along the b axis. Some atoms were omitted to improve clarity.

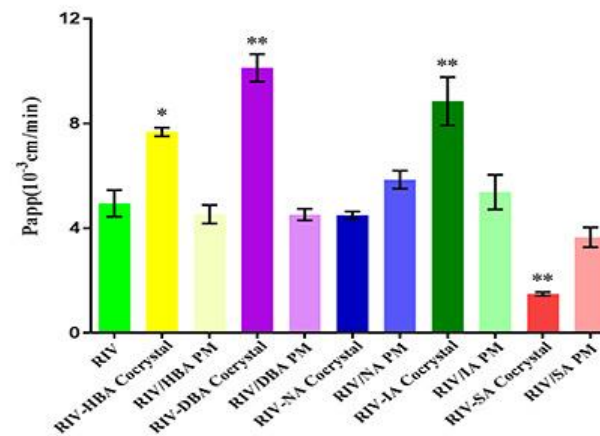
Case study: Improved Pharmacokinetics of Rivaroxaban toward co-crystallization



1. Solubility, and dissolution studies

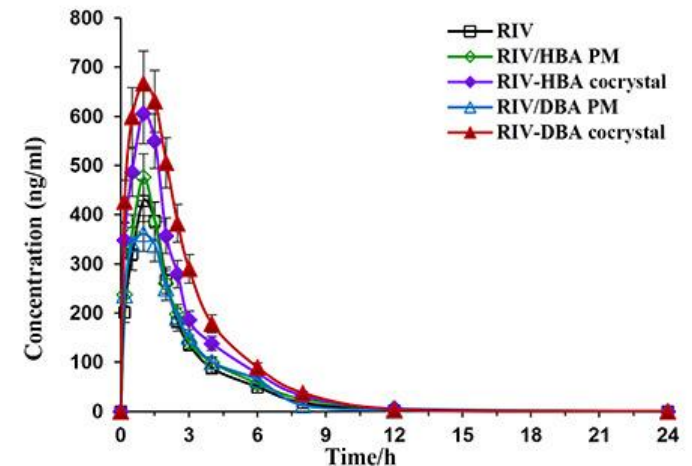


2. Permeation studies across Cell Monolayers



Rivaroxaban (RIV) is a direct Factor Xa inhibitor anticoagulant, Oral bioavailability of RIV 60% (poor solubility). Five cocrystals with Co-formers: P-hydroxybenzoic acid (HBA), 2,4-dihydroxybenzoic acid (DBA), nicotinamide (NA), isonicotinamide (IA), succinic acid (SA)

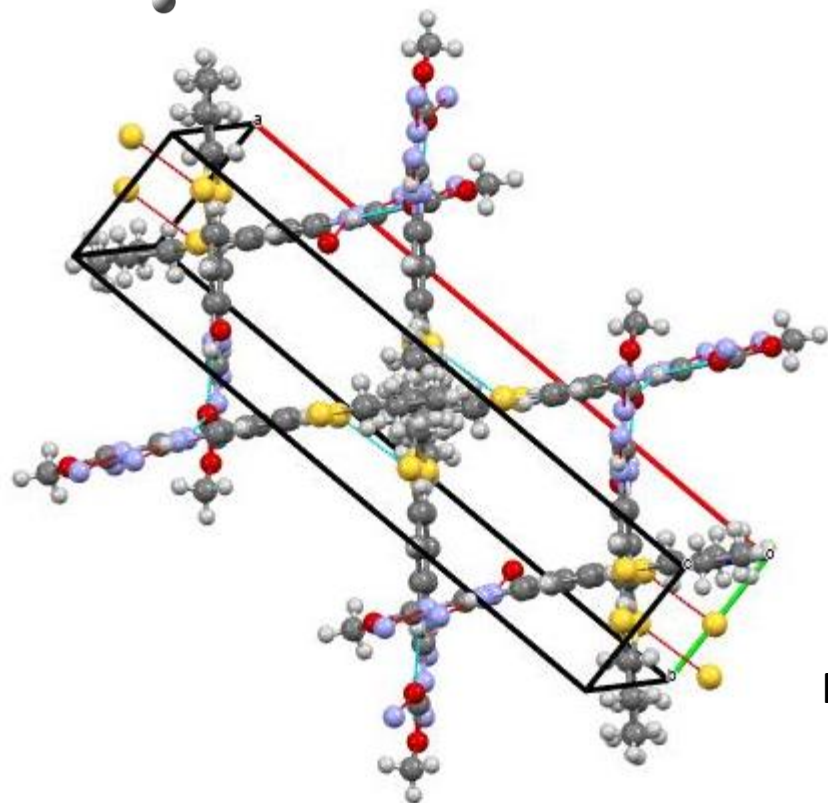
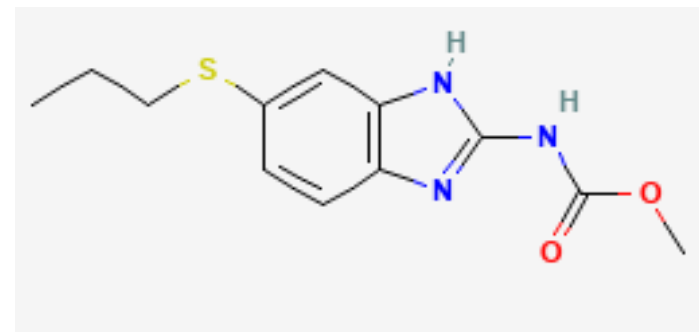
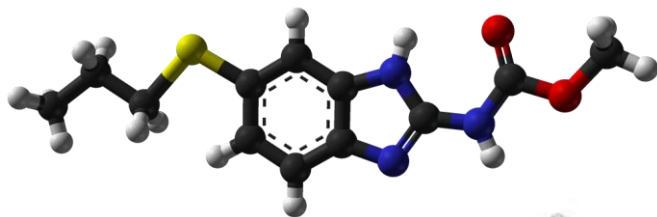
3. Pharmacokinetic studies in Beagle dogs



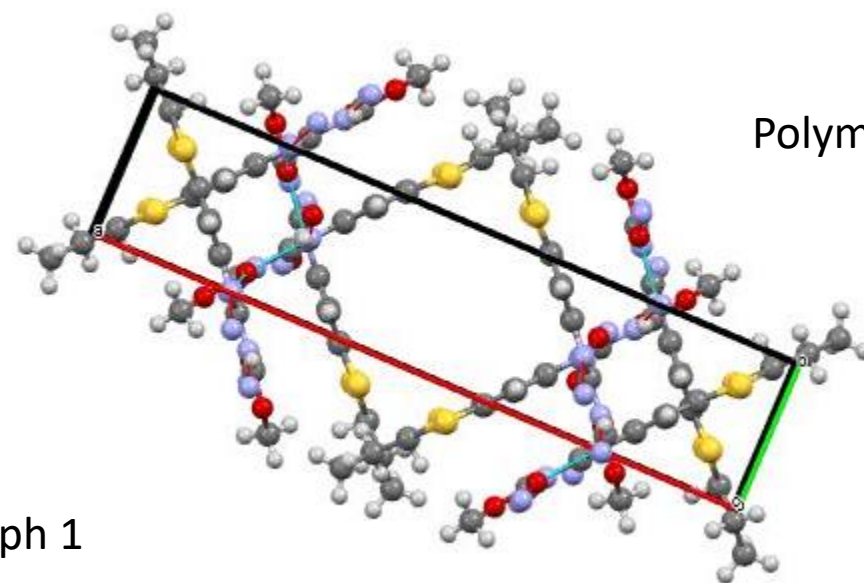
Int.J.Pharm: X 4 (2022) 100119

<https://doi.org/10.1016/j.ijpx.2022.100119>

Ablendazole, antiparasitic drug, crystal structures in CCDC, Cambridge Crystallography Database

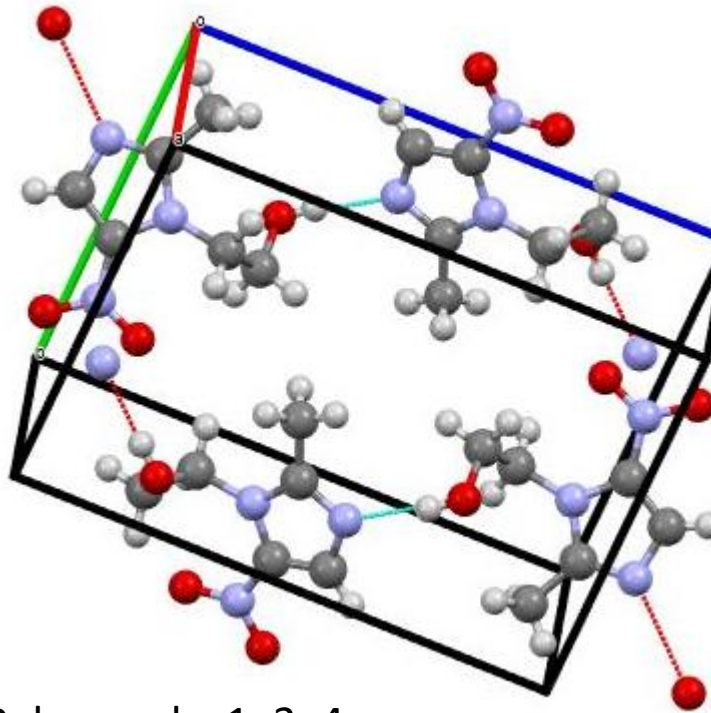


Polymorph 1

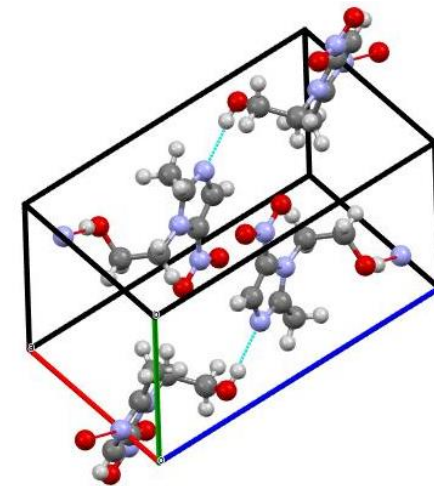
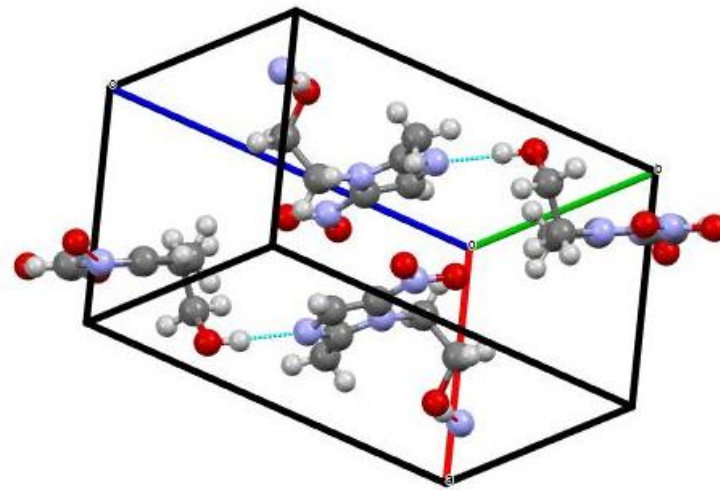
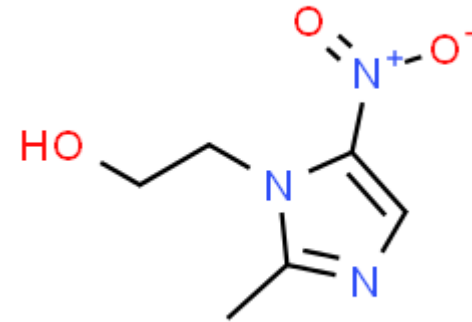


Polymorph 2

Metronidazole, antiparasitic drug, crystal structures in CCDC, Cambridge Crystallography Database

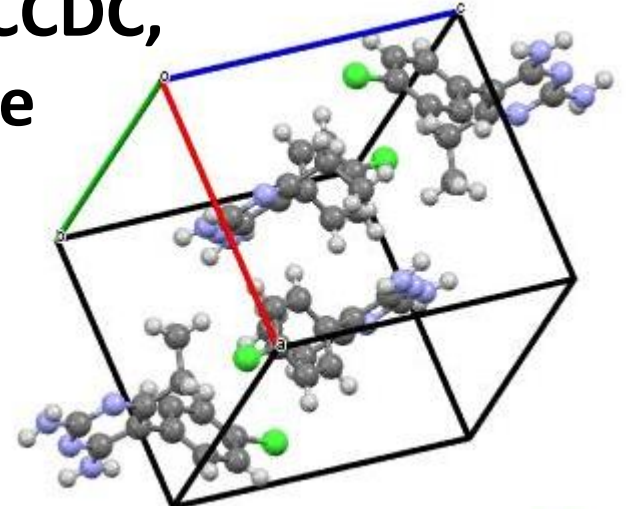
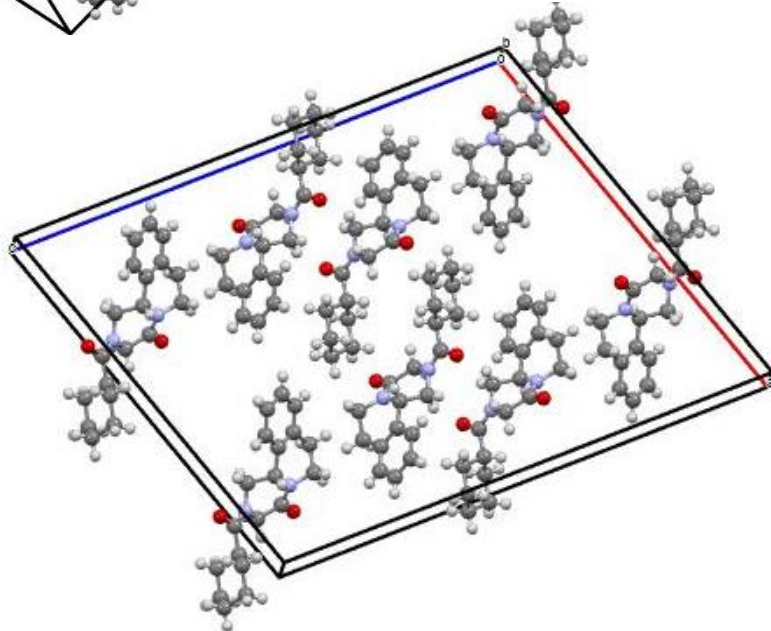
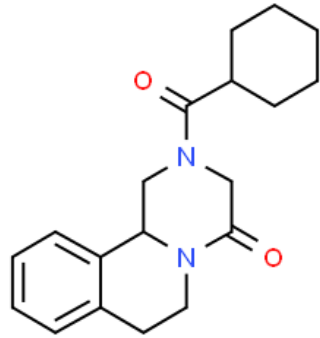
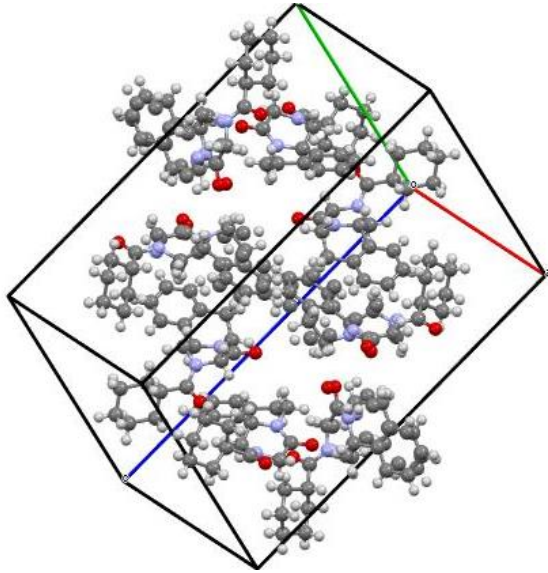


Polymorphs 1, 3, 4

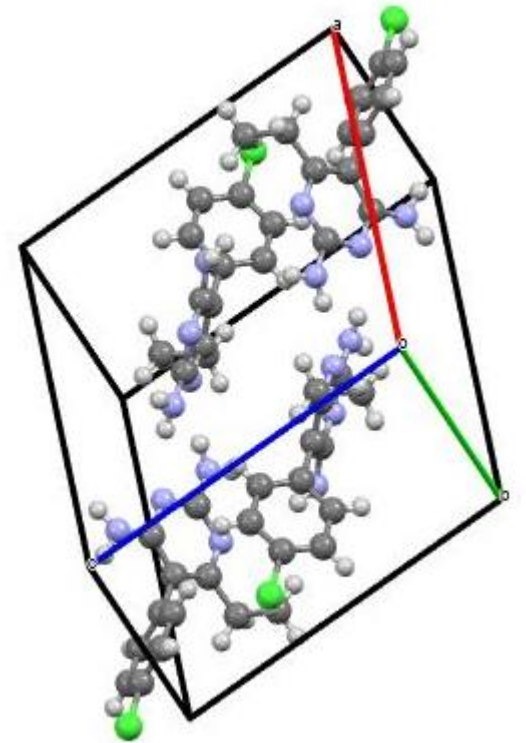
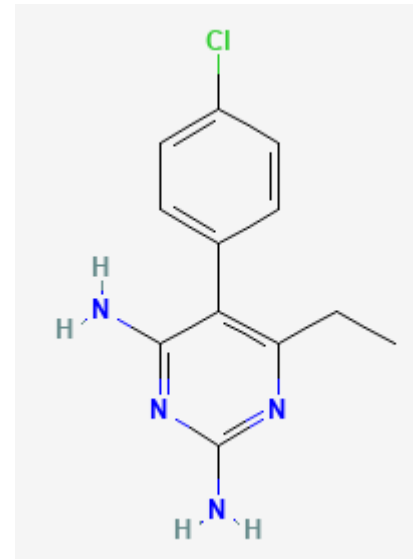


Antiparasitic drug, crystal structures in CCDC, Cambridge Crystallography Database

Praziquantel



Pyrimethamine



Future challenge for research on solid state of antiparasitic drugs

Filling the gap in improved bioavailability forward cocrystallization

Baruah JB1*, Khakhlary P 1 , Holland S2 & van Zyl RL2 Potent Anti-Malaria Salts, Co-Crystals and Derivatives of Aminoquinolines with Hydroxyaromatic Acids, Pharm. Bioprocess. (2016) 4(2), 031–040

Al Jalali V, Zeitlinger M. Systemic and Target-Site Pharmacokinetics of Antiparasitic Agents. Clin Pharmacokinet. 2020 Jul;59(7):827-847