

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

**Workshop: Novel leads and drugs and their mechanism of action in the field of vector borne parasitic disease**

**Online Meeting, 15<sup>th</sup> May 2023**

**From drug discovery to drug development:**

**The role of intermolecular interactions in drug solid forms**

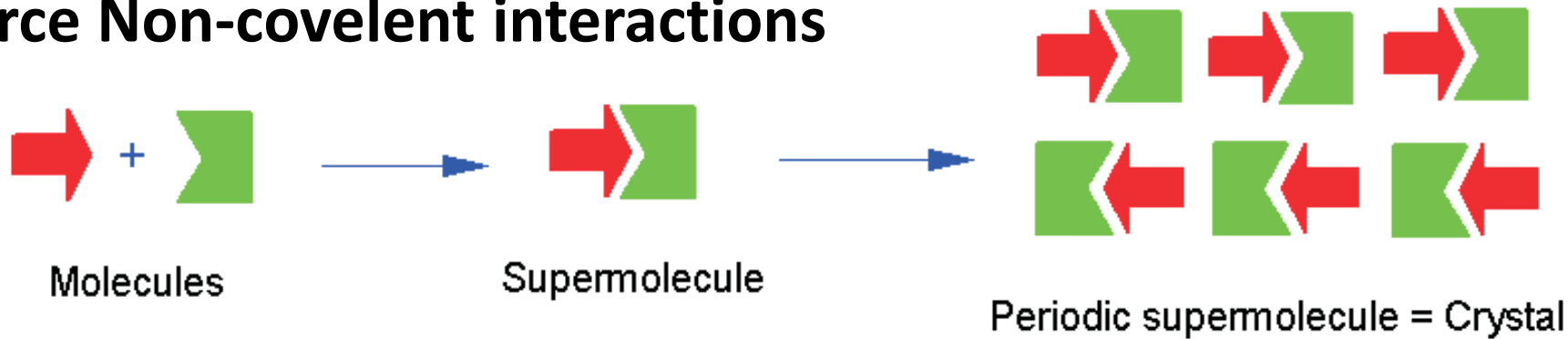
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Correspondence email: [aleksandar.cvetkovski@ugd.edu.mk](mailto:aleksandar.cvetkovski@ugd.edu.mk)

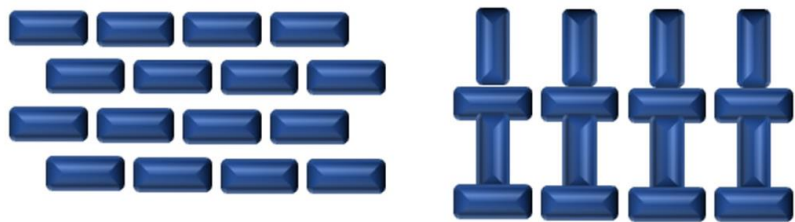
# What is Crystal engineering?

Driving force Non-covalent interactions

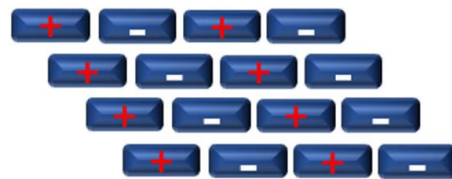


Beyond covalent bond chemistry

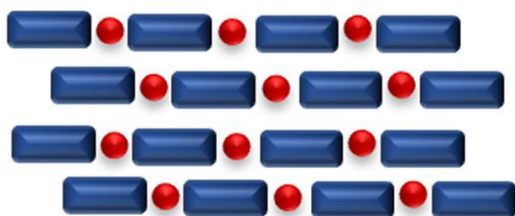
Polymorphs



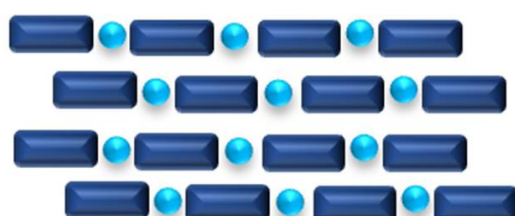
Salts



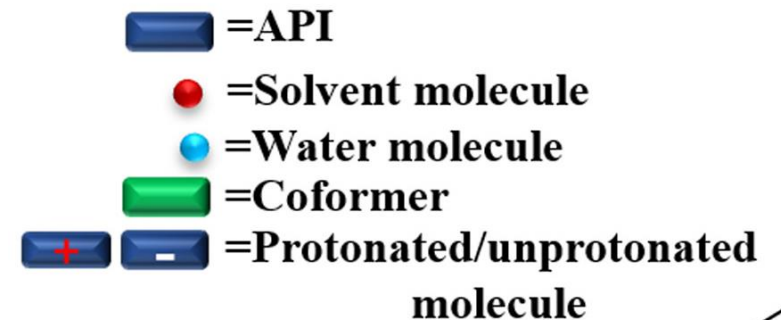
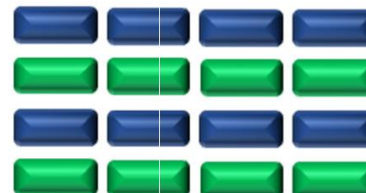
Solvates



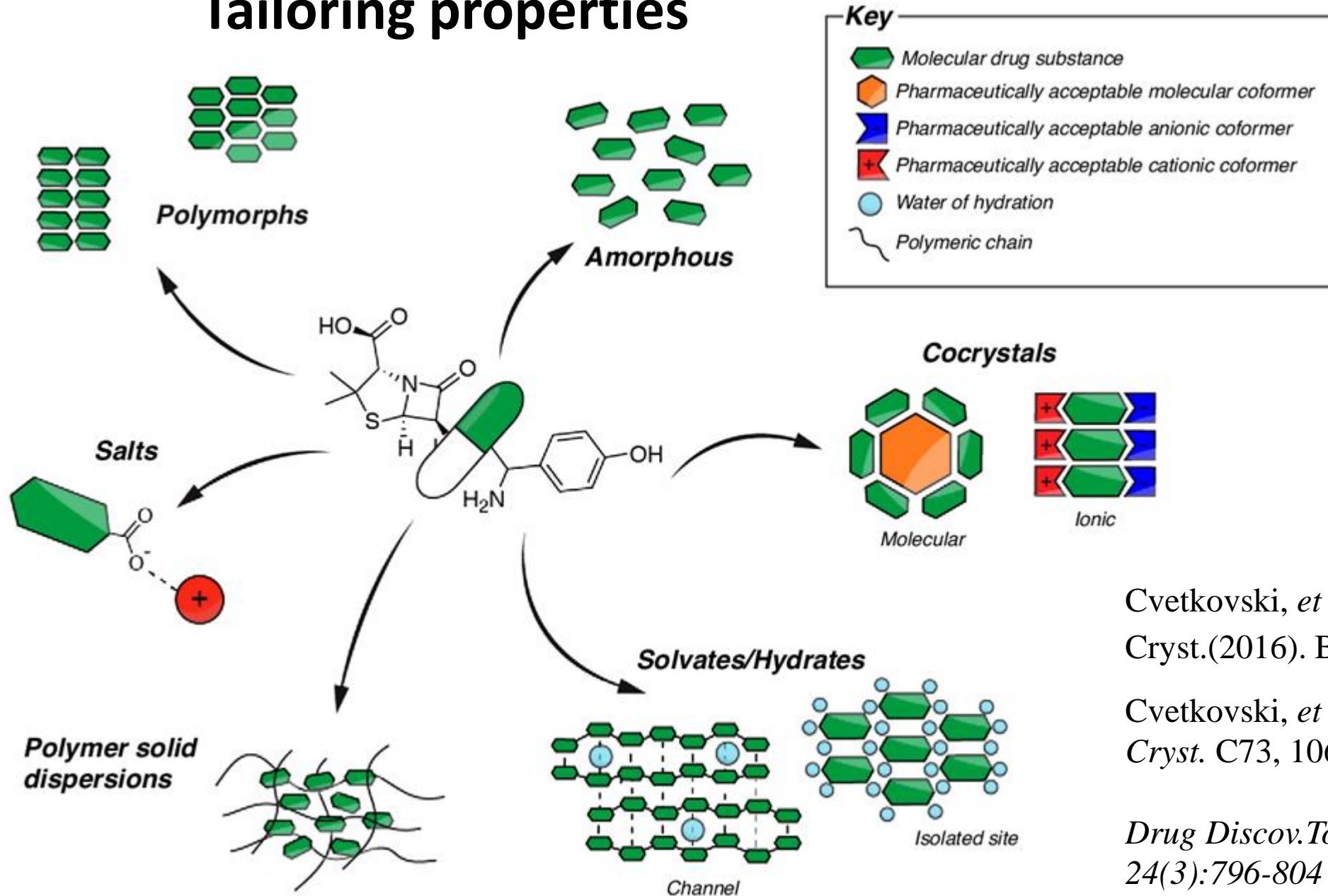
Hydrates



Cocrystals



# 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

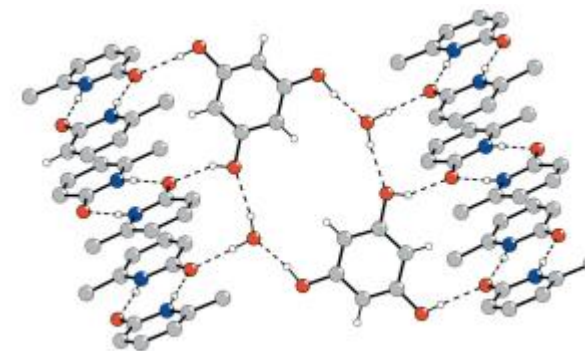
## Supramolecular hydrogen-bonding patterns of co-crystals containing the active pharmaceutical ingredient (API) phloroglucinol and *N*-heterocycles

Aleksandar Cvetkovski,<sup>a</sup> Valerio Bertolasi<sup>b</sup> and Valeria Ferretti<sup>b\*</sup>

<sup>a</sup>Faculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip The Former Yugoslav Republic of Macedonia, and <sup>b</sup>Department of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17-27, I-44121 Ferrara, Italy. \*Correspondence e-mail: frt@unife.it

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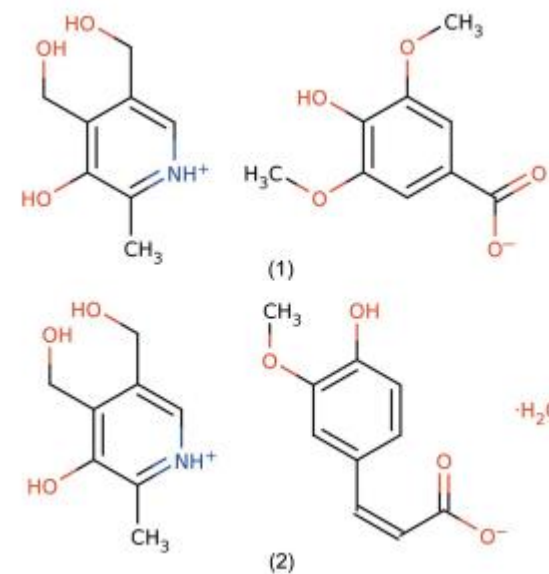


## research papers

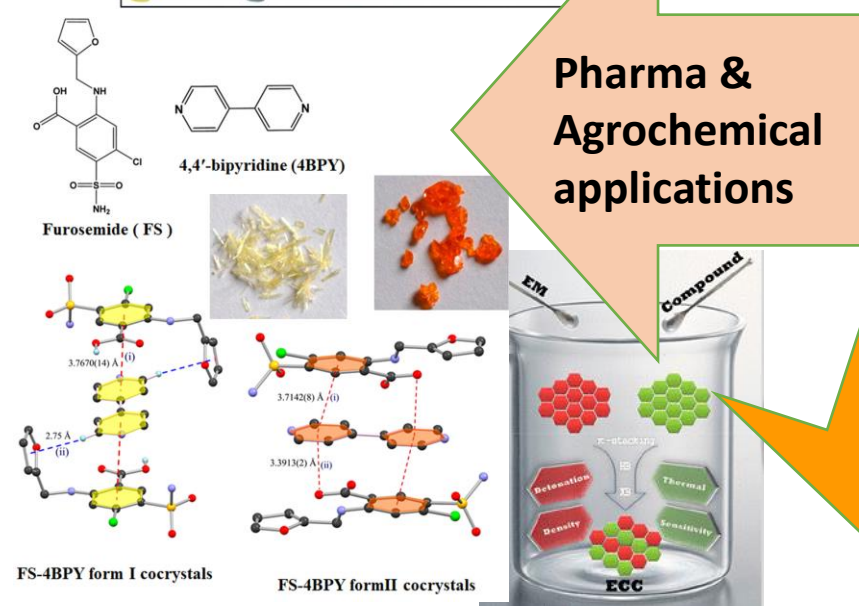
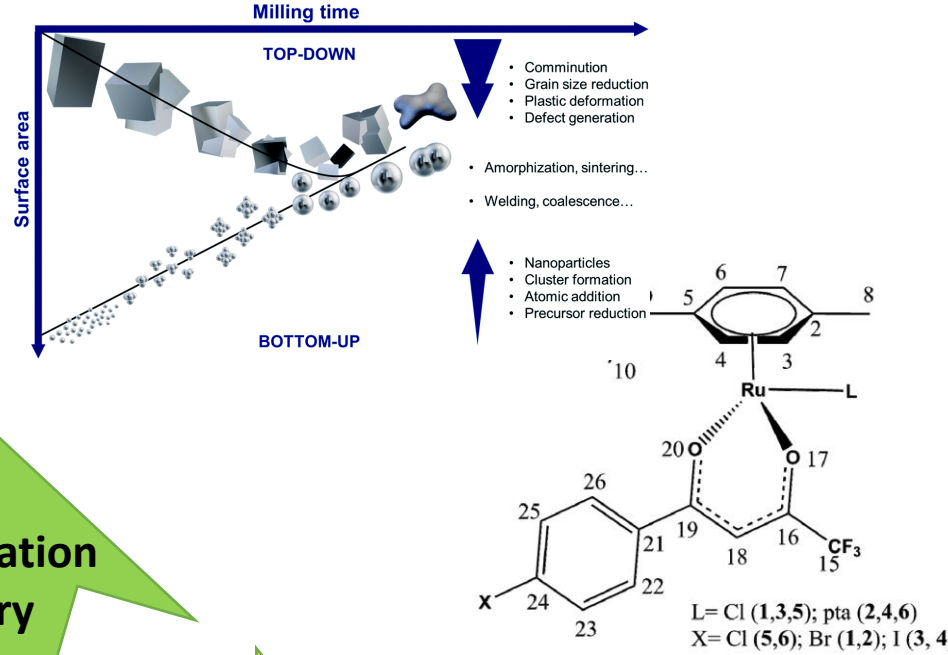
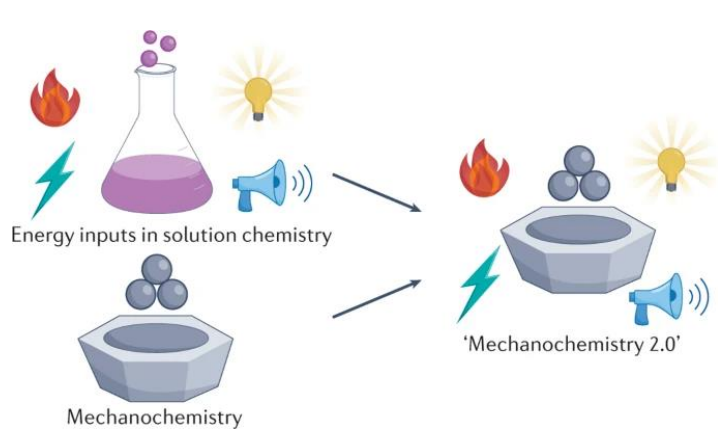
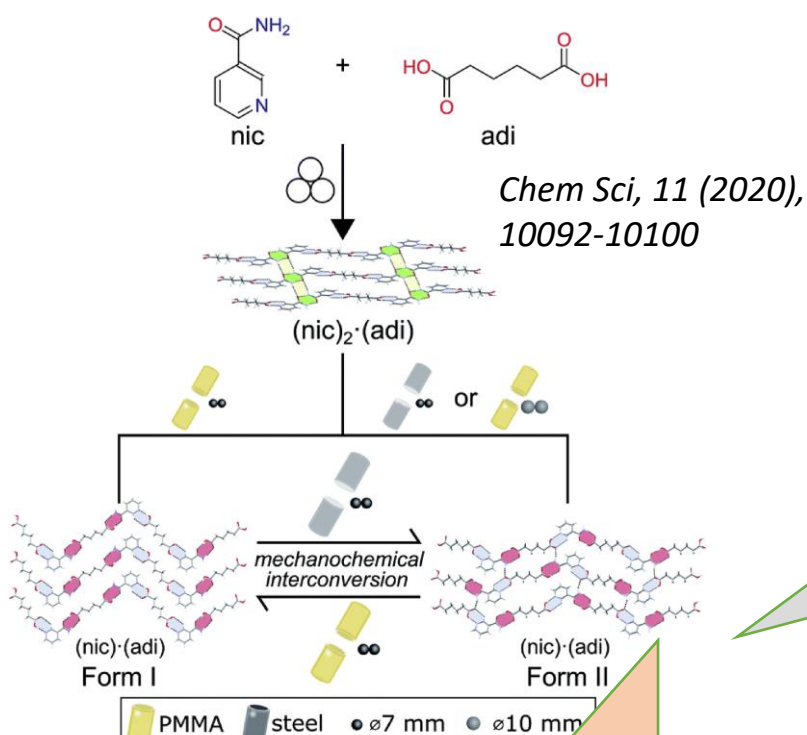
## New pharmaceutical salts containing pyridoxine

Aleksandar Cvetkovski,<sup>a</sup> Valeria Ferretti<sup>b\*</sup> and Valerio Bertolasi<sup>b</sup>

<sup>a</sup>Faculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip, The Former Yugoslav Republic of Macedonia, and <sup>b</sup>Department of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17, Ferrara I-44121, Italy. \*Correspondence e-mail: frt@unife.it



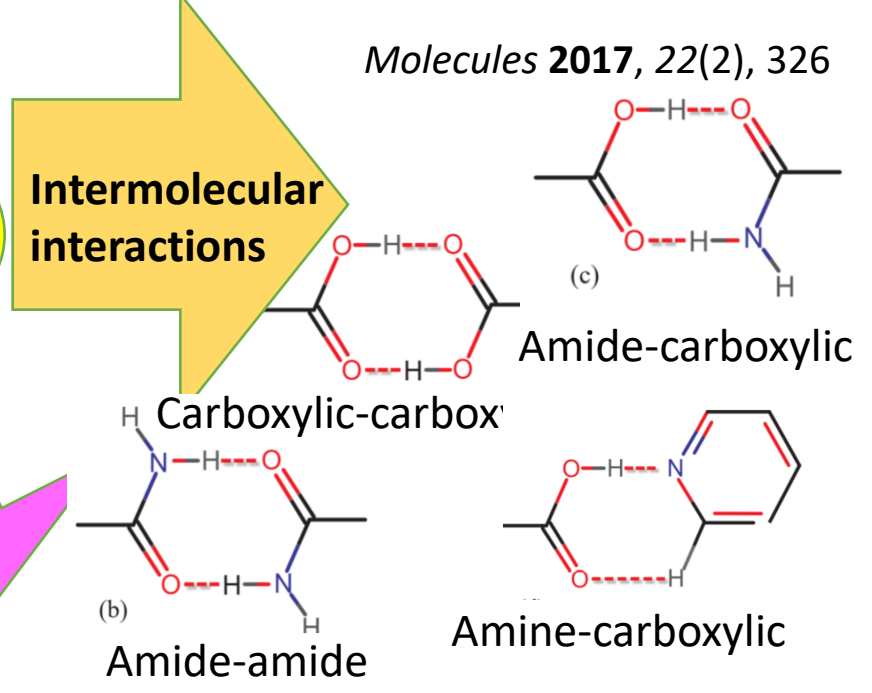




**Mechanochemistry**

**Coordination chemistry**

**SUPRAMOLECULAR CHEMISTRY**



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

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

*CrystEngComm*, 2005, 7, 439-448

*Molecules* 2017, 22(2), 326

# Case study 1: Antiparasitic Drug Praziquantel

Praziquantel (PZQ), an anthelmintic drug used in developing countries for the treatment of schistosome infections

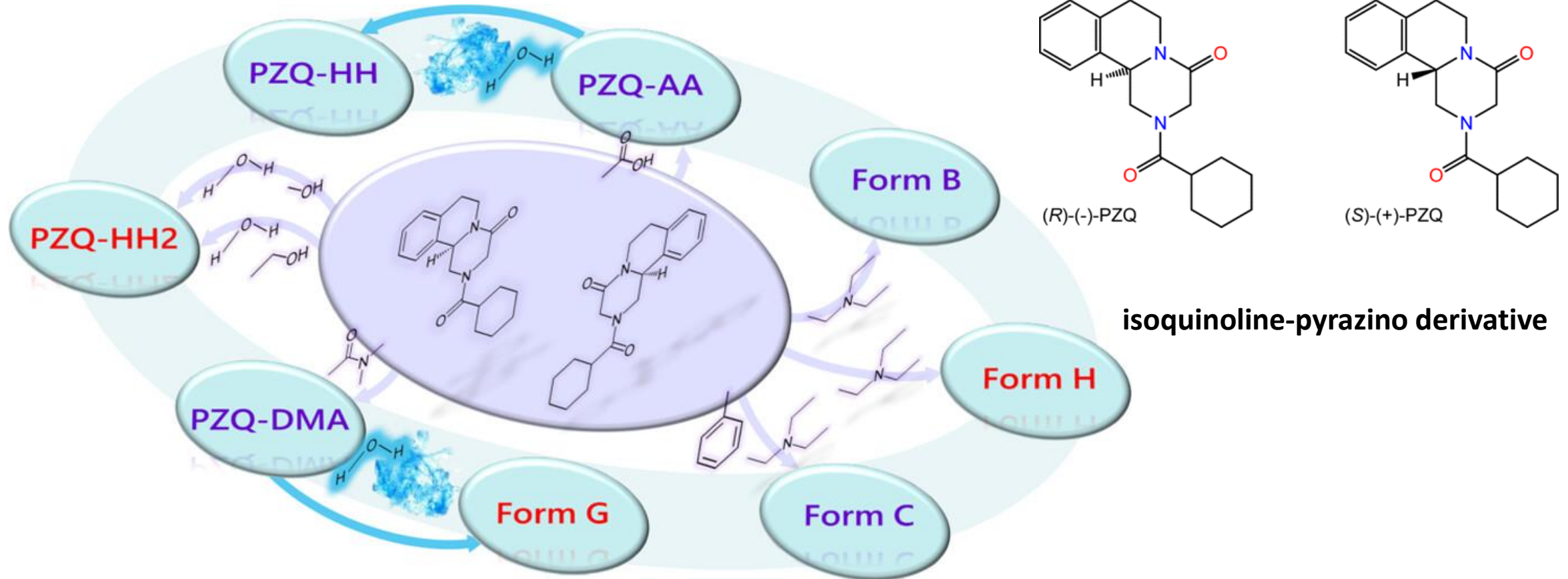
78 developing countries in the tropics and subtropics and it affects 210 million people approximately, causing two hundred thousand deaths every year.

92% of people who need treatment for schistosomiasis live in Africa and, behind of malaria, is the second of the most prevalent diseases that affects African children.

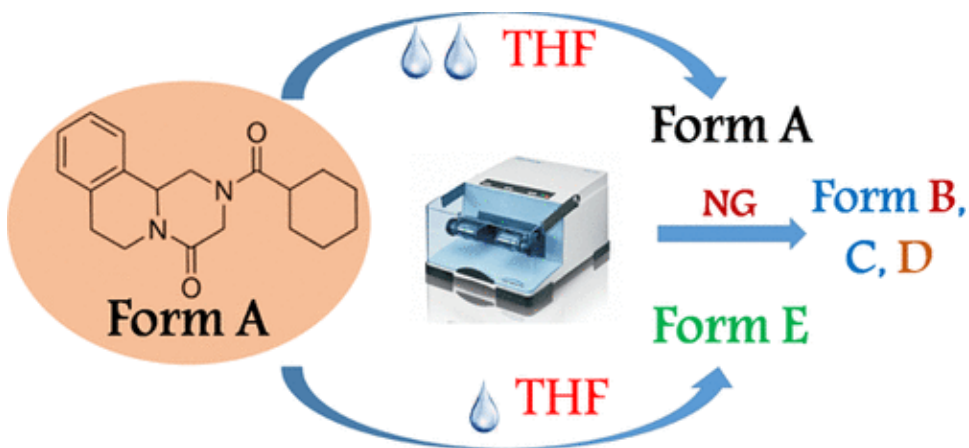
## **raziquantel (PZQ) advantages (essential drug, WHO):**

- ✓ Active against every Schistosomas species
- ✓ Administration is orally,
- ✓ Few side effects,
- ✓ High efficiency,
- ✓ low toxicity.

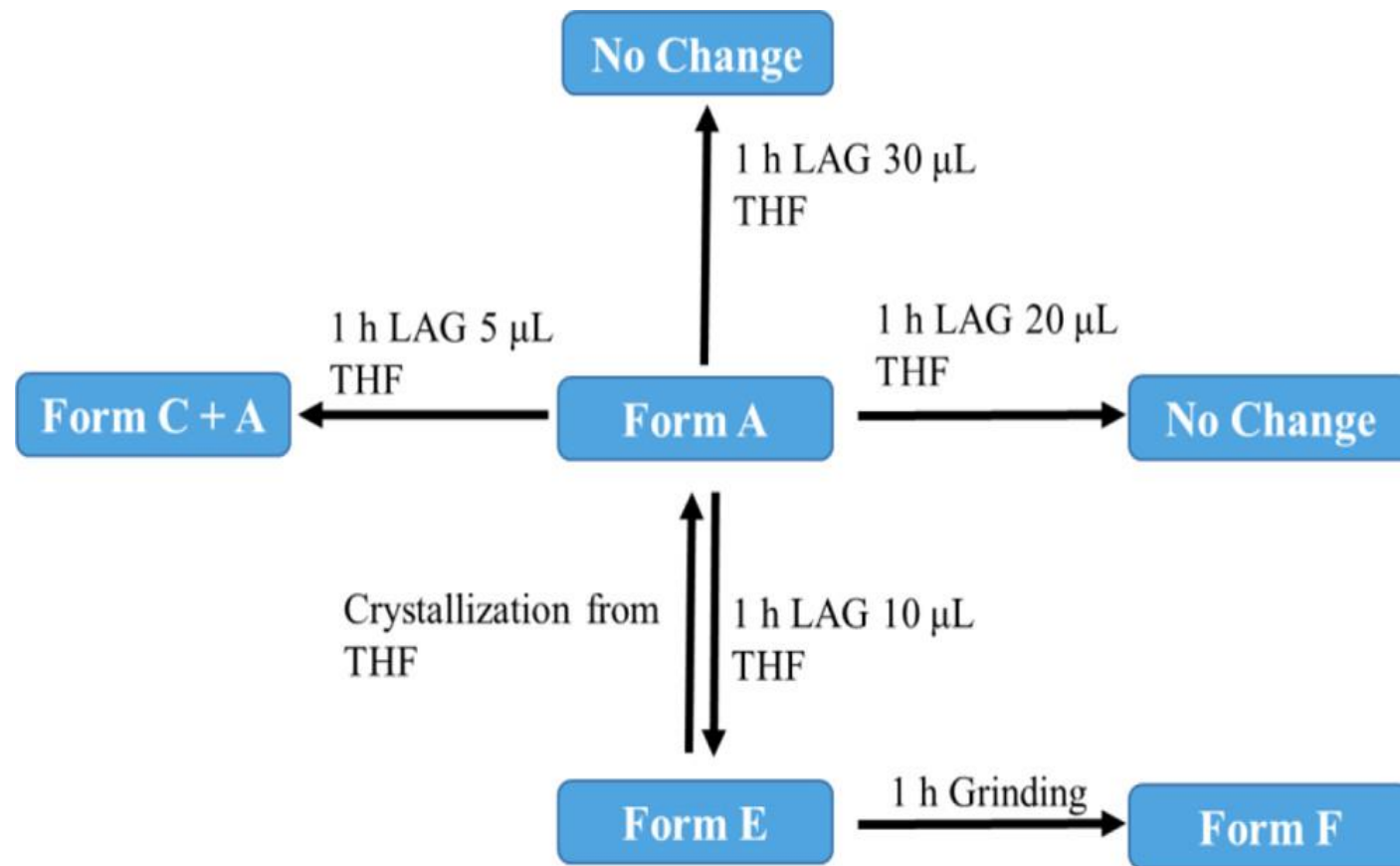
# Polymorphism of Praziquantel: Role of Cooling Crystallization in Access to Solid Forms and Discovery of New Polymorphs



# Case Study 1: Role of Mechanochemistry in Solid Form Selection and Identification of the Drug Praziquantel



formation of partial solid solutions of the racemic compound with the enantiomer.



*Cryst. Growth Des.* 2021, 21, 10, 5854–5861

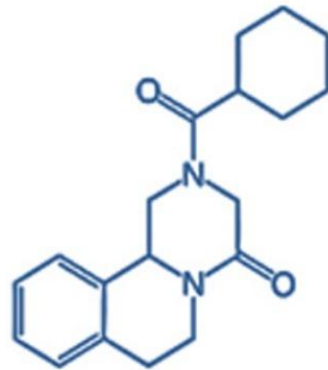
Grinding Experiments with PRA at Different Amounts of THF in Liquid-Assisted Grinding (VALAG)



# Case Study 1: Development of flexible and dispersible oral formulations containing praziquantel for potential schistosomiasis treatment of pre-school age children

## Formulation challenges

- BCS class II drug
- High dose burden
- Bitter taste
- Micronised drug

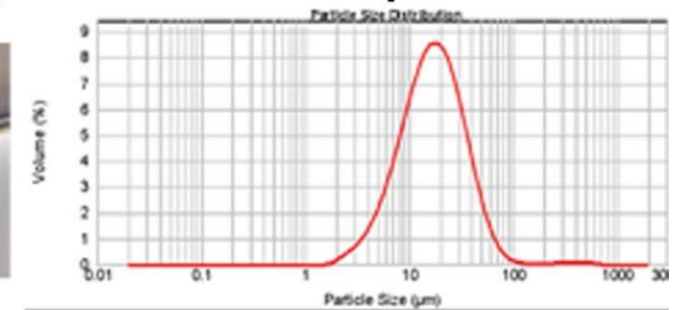
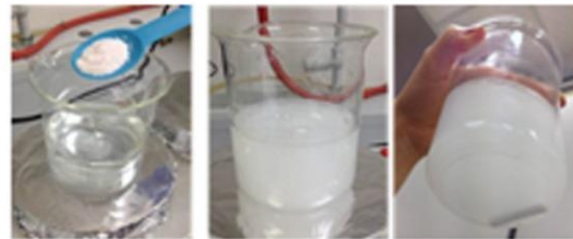


Praziquantel ( $\pm$ )



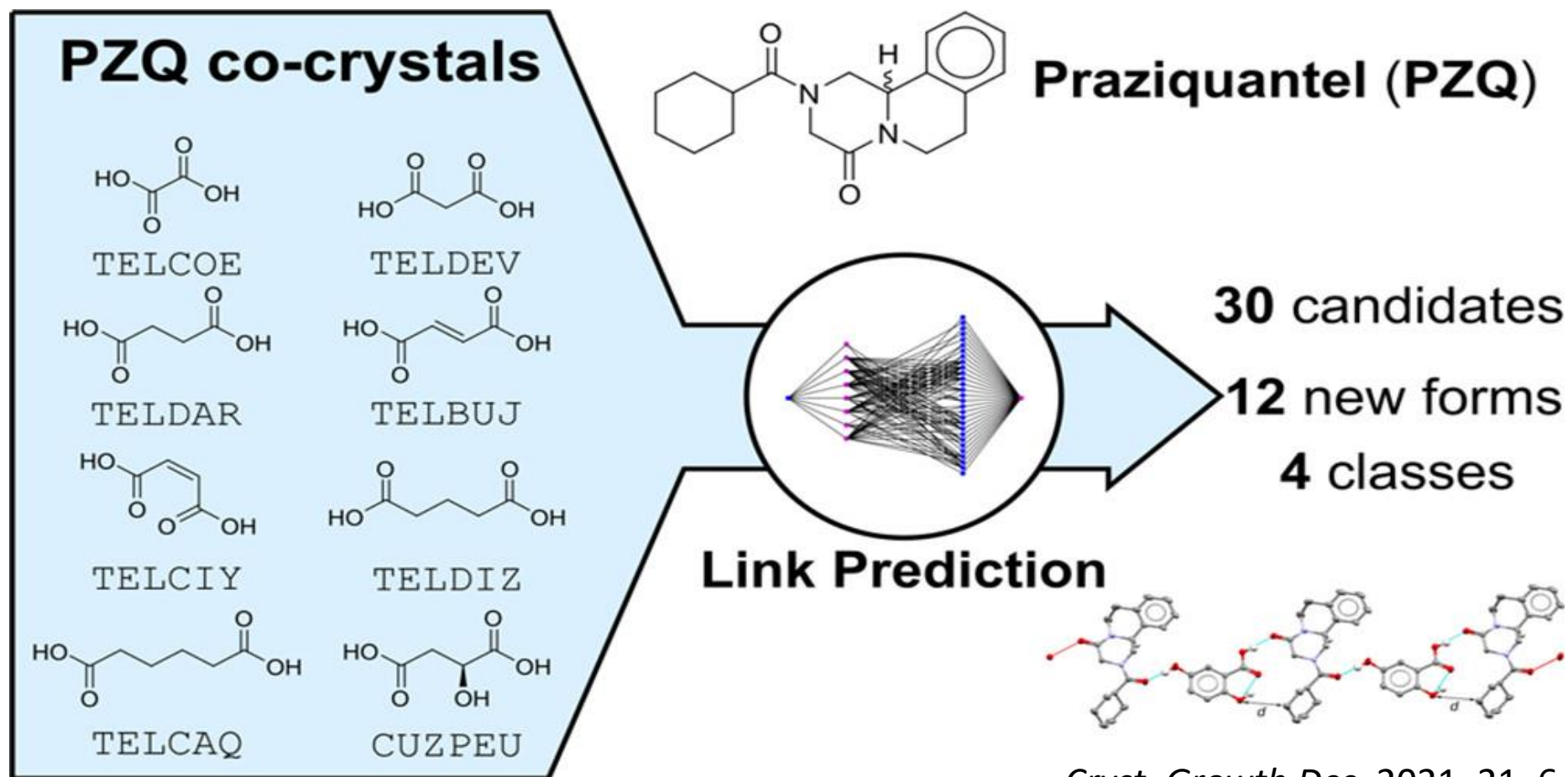
## Achievements

- Taste masked granules for dose flexibility
- Extemporaneous aqueous fine suspension

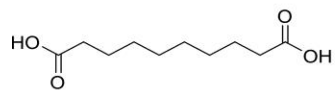


- Manipulation with milk and fruit juice
- Stability in ICH IVb climate zone

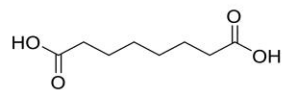
# Case Study1. Cococrystals of Praziquantel: Discovery by Network-Based Link Prediction



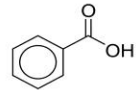
# Coformers for co-crystallization



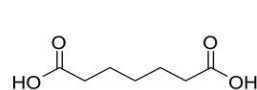
Sebacic acid  
**1**



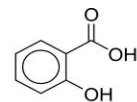
Suberic acid  
**2**



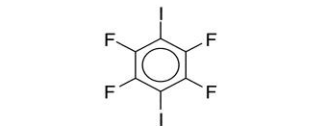
Benzoic acid  
**3**



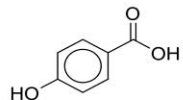
Pimelic acid  
**4**



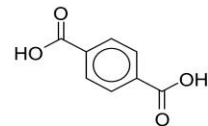
Salicylic acid  
**5**



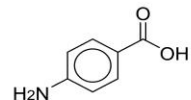
1,4-Diiodotetrafluorobenzene  
**6**



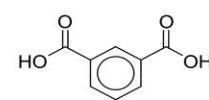
4-Hydroxybenzoic acid  
**7**



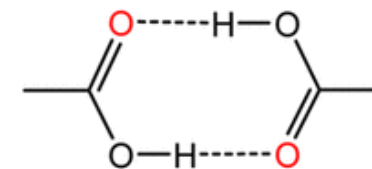
Terephthalic acid  
**8**



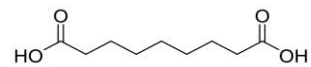
4-Aminobenzoic acid  
**9**



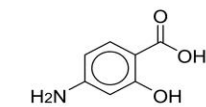
Isophthalic acid  
**10**



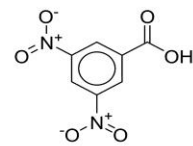
**A**



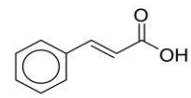
Azelaic acid  
**11**



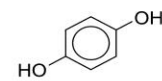
4-Aminosalicylic acid  
**12**



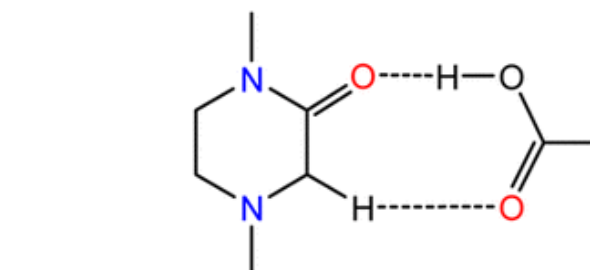
3,5-Dinitrobenzoic acid  
**13**



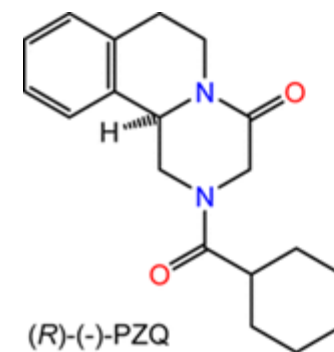
*trans*-Cinnamic acid  
**14**



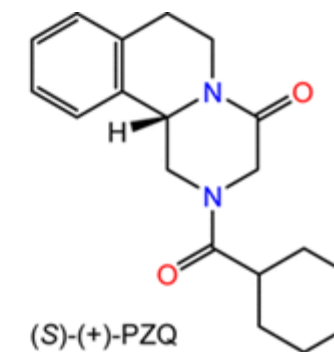
Hydroquinone  
**15**



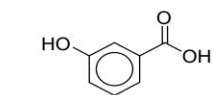
**B**



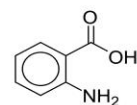
(*R*)-(-)-PZQ



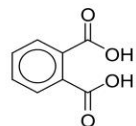
(*S*)-(+)-PZQ



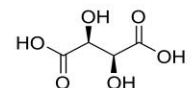
3-Hydroxybenzoic acid  
**16**



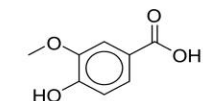
Anthranilic acid  
**17**



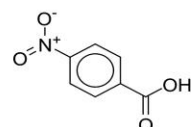
Phthalic acid  
**18**



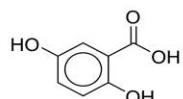
D-(-)-Tartaric acid  
**19**



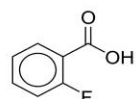
Vanillic acid  
**20**



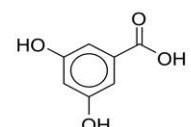
4-Nitrobenzoic acid  
**21**



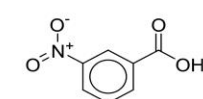
2,5-Dihydroxybenzoic acid  
**22**



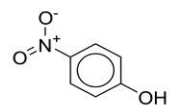
2-Fluorobenzoic acid  
**23**



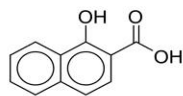
3,5-Dihydroxybenzoic acid  
**24**



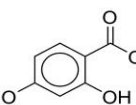
3-Nitrobenzoic acid  
**25**



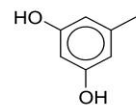
4-Nitrophenol  
**26**



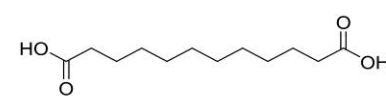
1-Hydroxy-2-naphthoic acid  
**27**



2,4-Dihydroxybenzoic acid  
**28**



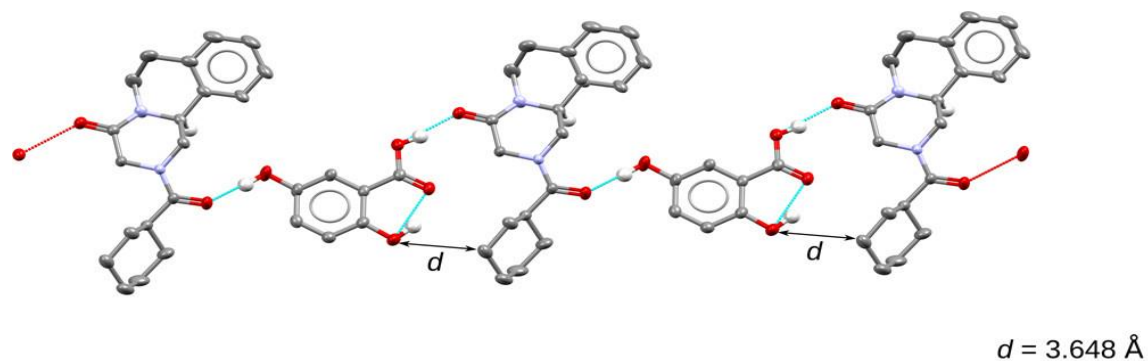
Orcinol  
**29**



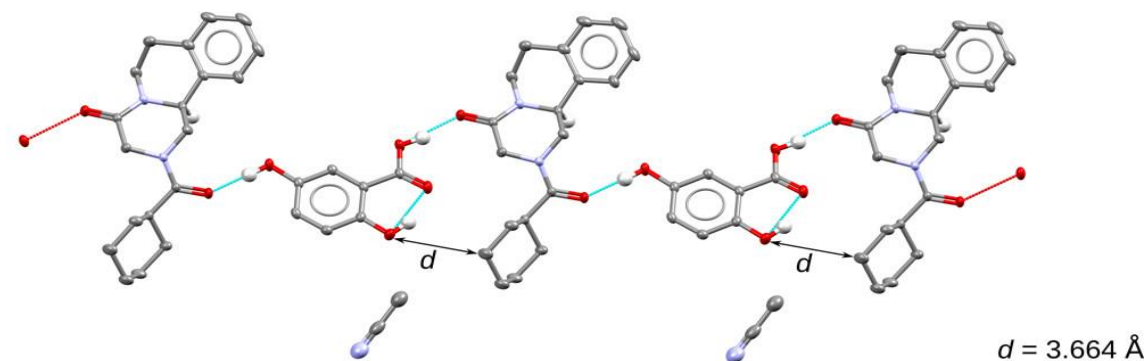
Dodecanedioic acid  
**30**

# Cocrystals of Praziquantel: Discovery by Network-Based Link Prediction

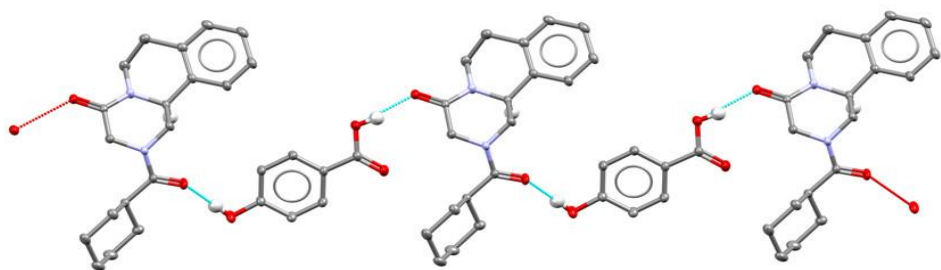
*Cryst. Growth Des.* 2021, 21, 6, 3428–3437



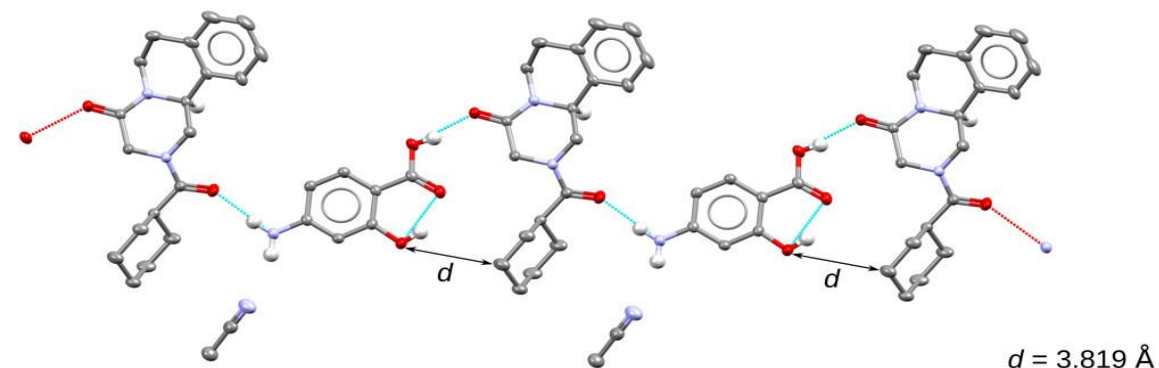
(a)



(b)

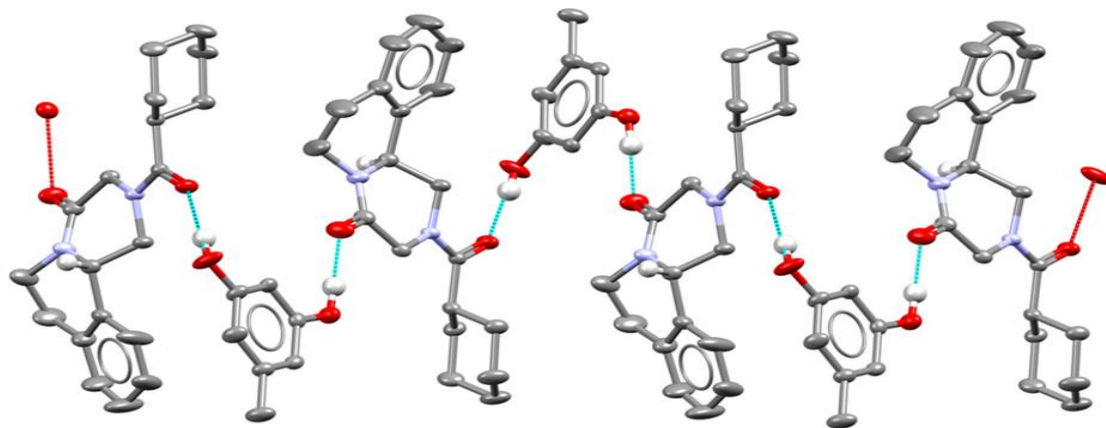


(c)

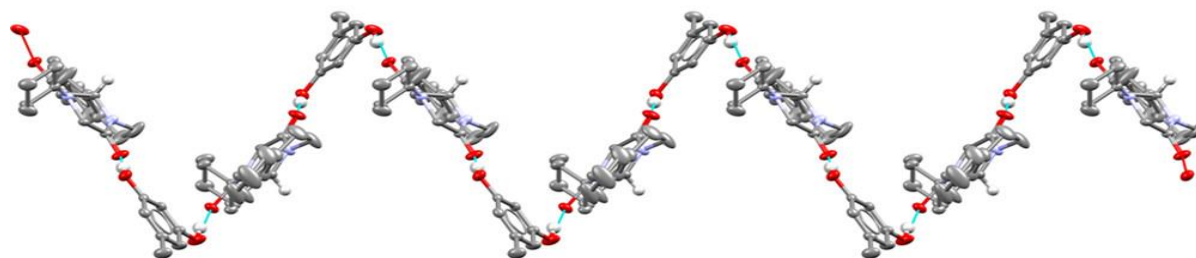
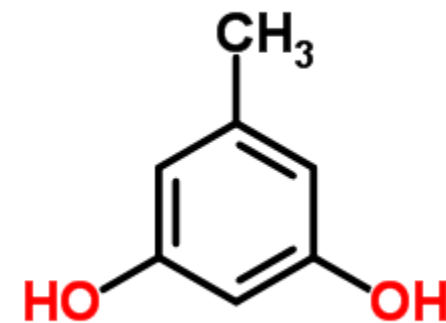


(d)

- a) Cocrystal with 2,5-dihydroxybenzoic acid (b) Cocrystal solvate with 2,5-dihydroxybenzoic acid and MeCN  
c) Cocrystal with 4-hydroxybenzoic acid (d) Cocrystal solvate with 4-aminosalicylic acid and MeCN.



(a)



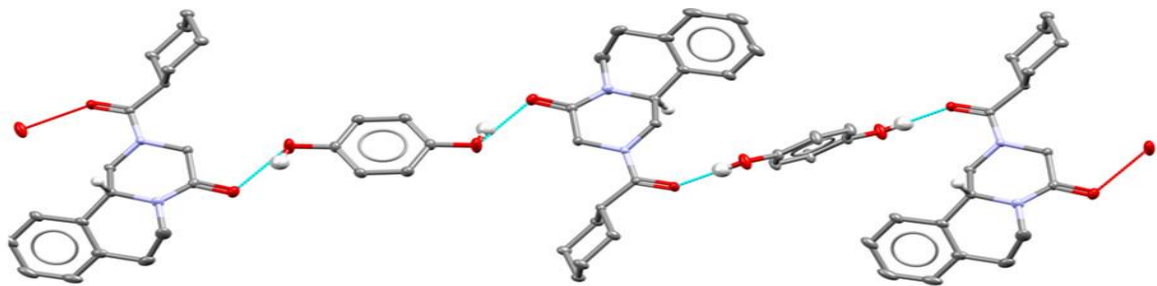
(b)

(a) Structure of the cocrystal containing (S)-PZQ and orcinol .

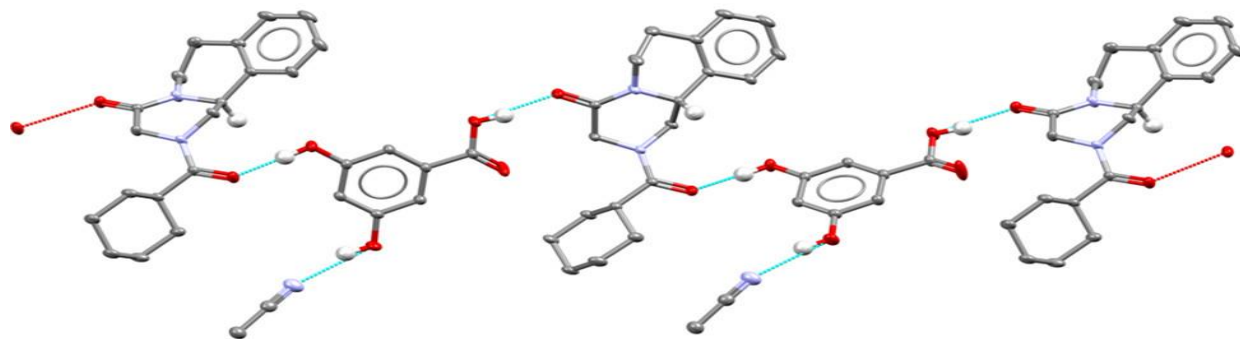
(b) Enantiopure zigzag chain of (S)-PZQ and orcinol running along the [010] direction.

Chains with an identical chirality stack on top of each other.

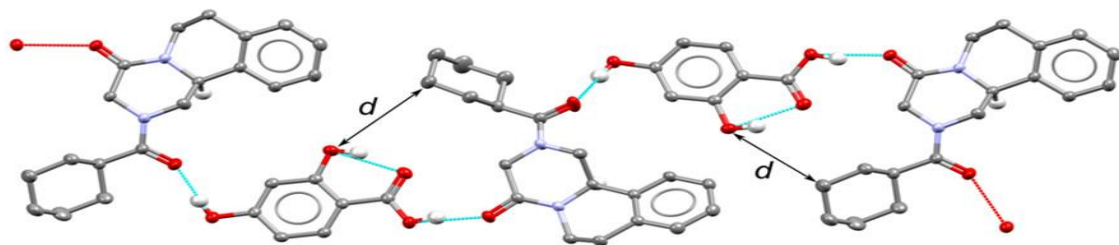




(a)



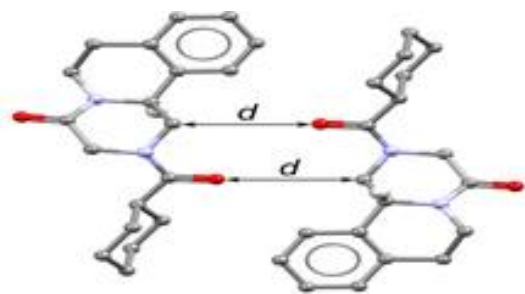
(b)



(c)

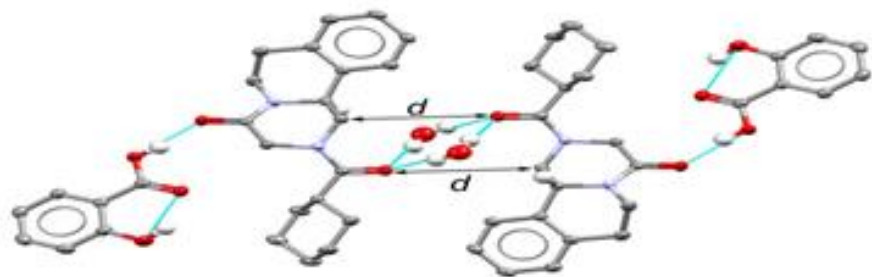
$d = 4.380 \text{ \AA}$

- (a) Cocrystal with hydroquinone
- (b) Cocrystal solvate with 3,5-dihydroxybenzoic acid and MeCN.
- (c) Cocrystal with 2,4-hydroxybenzoic acid



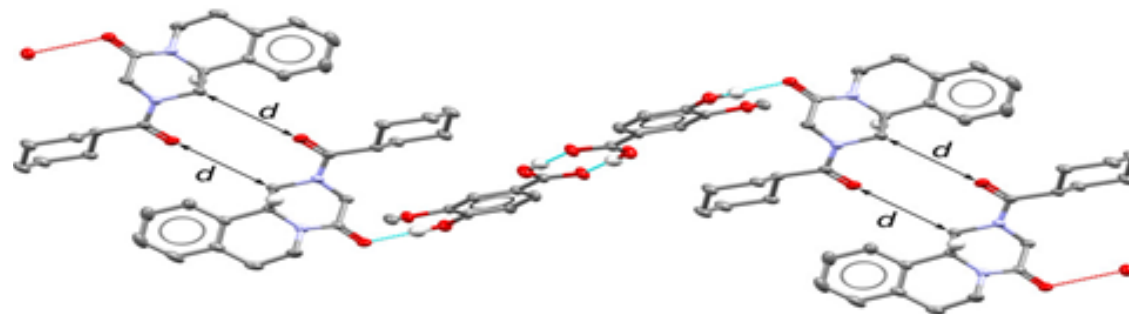
(a)

$d = 3.914 \text{ \AA}$



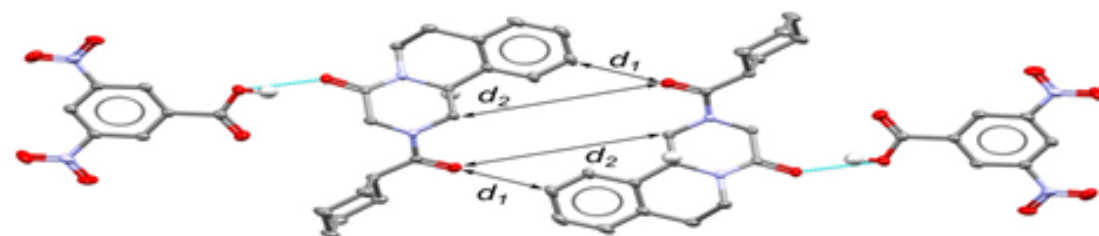
(b)

$d = 4.494 \text{ \AA}$



(c)

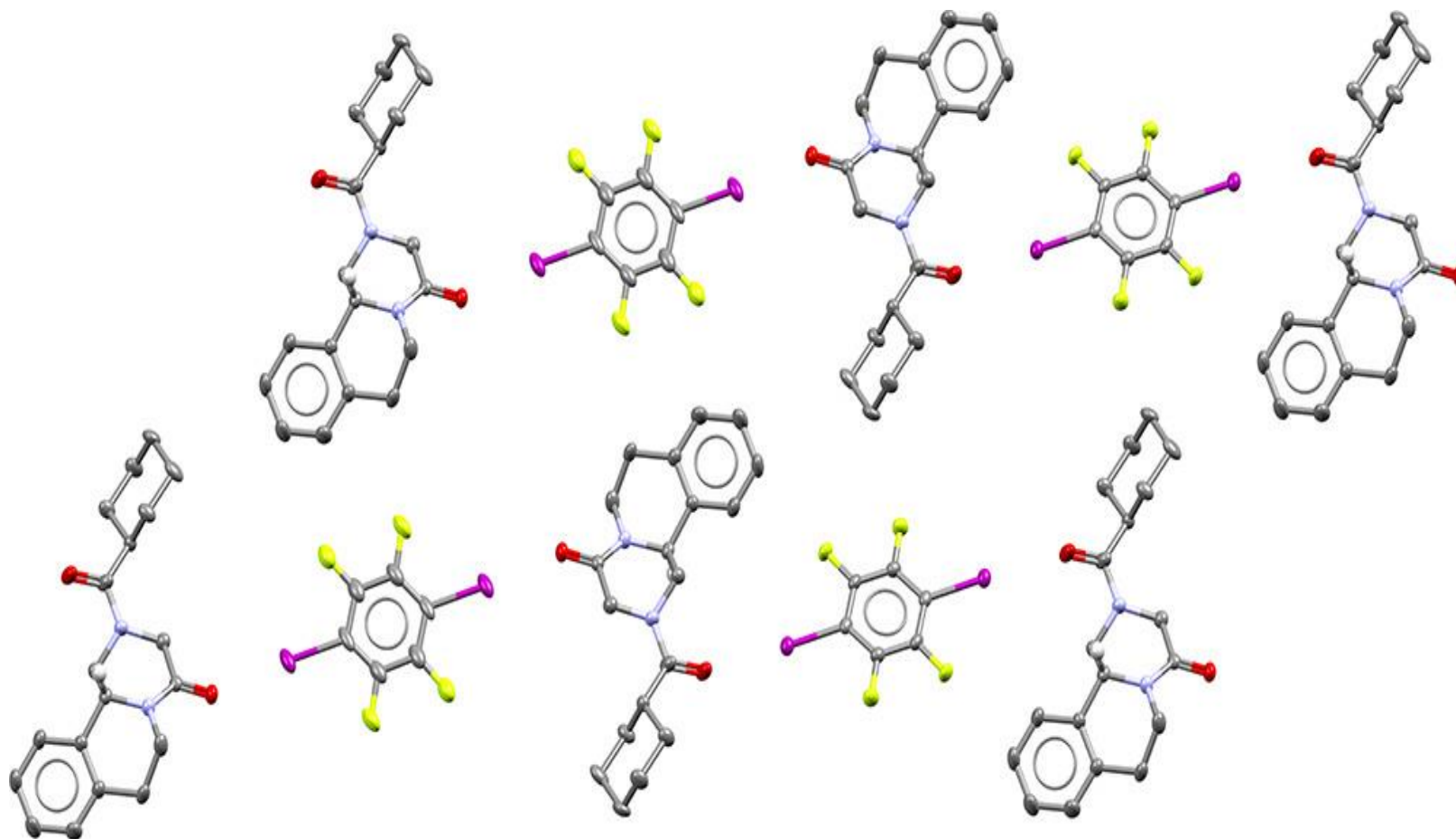
$d = 4.007 \text{ \AA}$



(d)

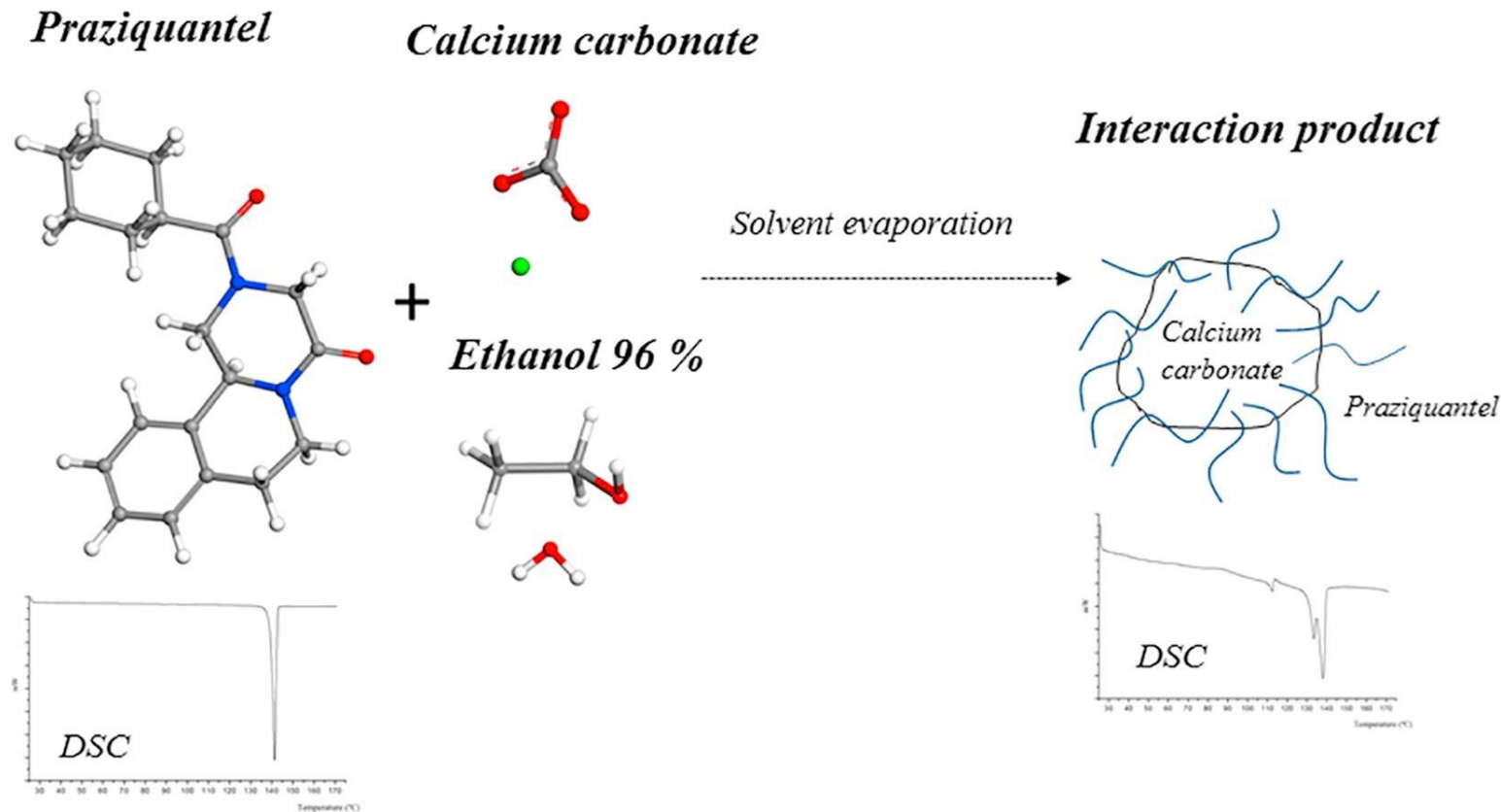
$d_1 = 3.143 \text{ \AA}$   
 $d_2 = 6.366 \text{ \AA}$

- (a) Racemic polymorph of Praziquantel (TELCEU01)
- (b) Cocrystal hydrate with salicylic acid
- (c) Cocrystal with vanillic acid
- (d) Cocrystal with 3,5-dinitrobenzoic acid



Racemic halogen-bonded network structure  
cocrystal of PZQ and 1,4-diiodotetrafluorobenzene

# Conformational polymorphic changes in the crystal structure of the chiral antiparasitic drug praziquantel and interactions with calcium carbonate



Thank you for your attention