



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA



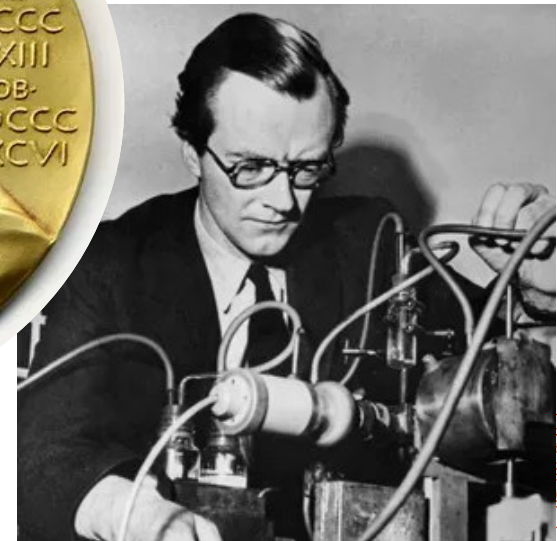
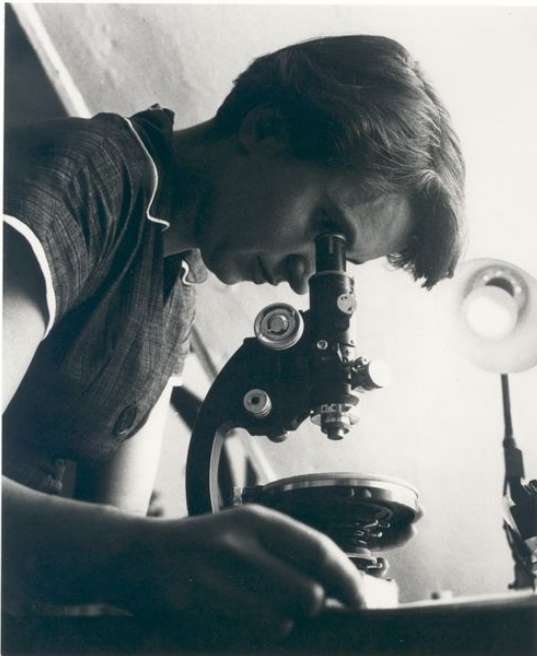
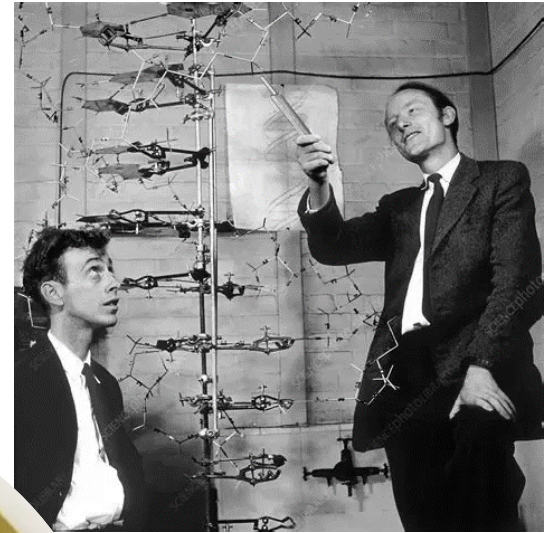
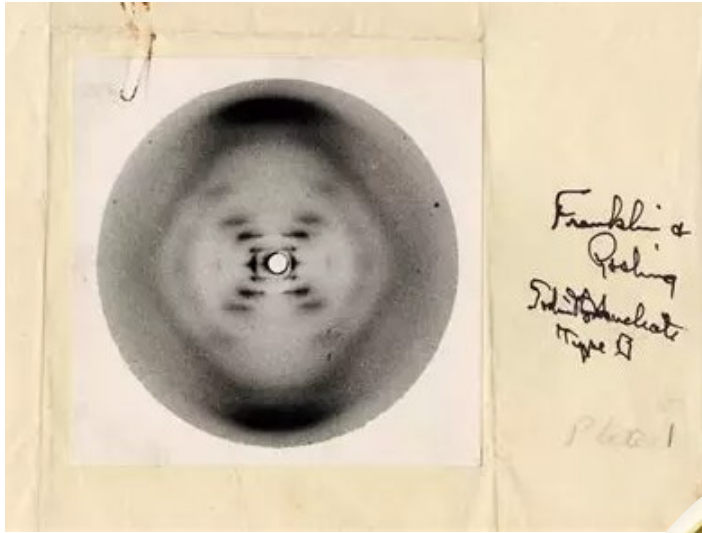
Centro Interdipartimentale
Grandi Strumenti
CINQUANTA

Perché abbiamo ancora bisogno della diffrazione di raggi X su cristallo singolo

Lucia Maini

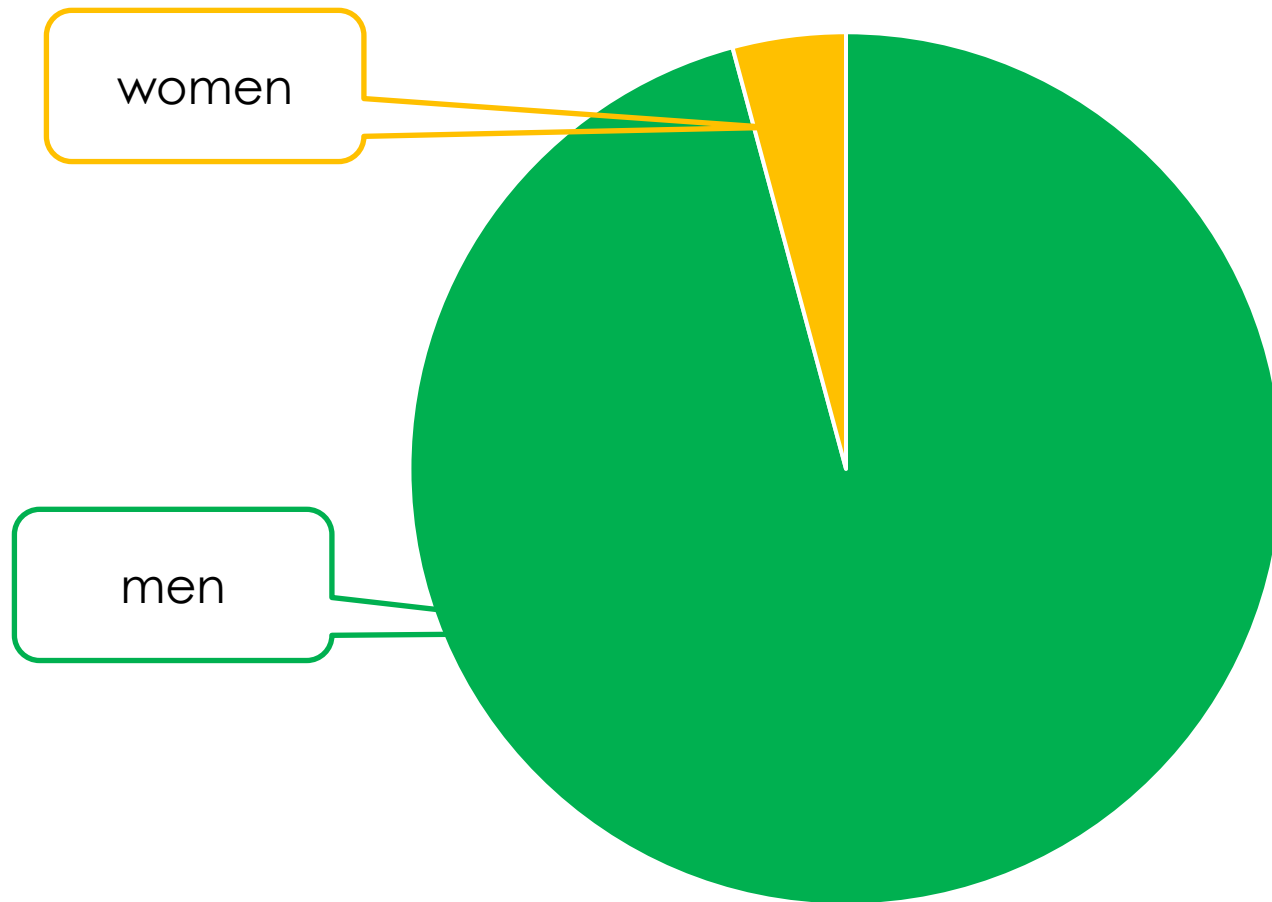
Dipartimento di Chimica Giacomo
Ciamician

The discovery of molecular structure of DNA



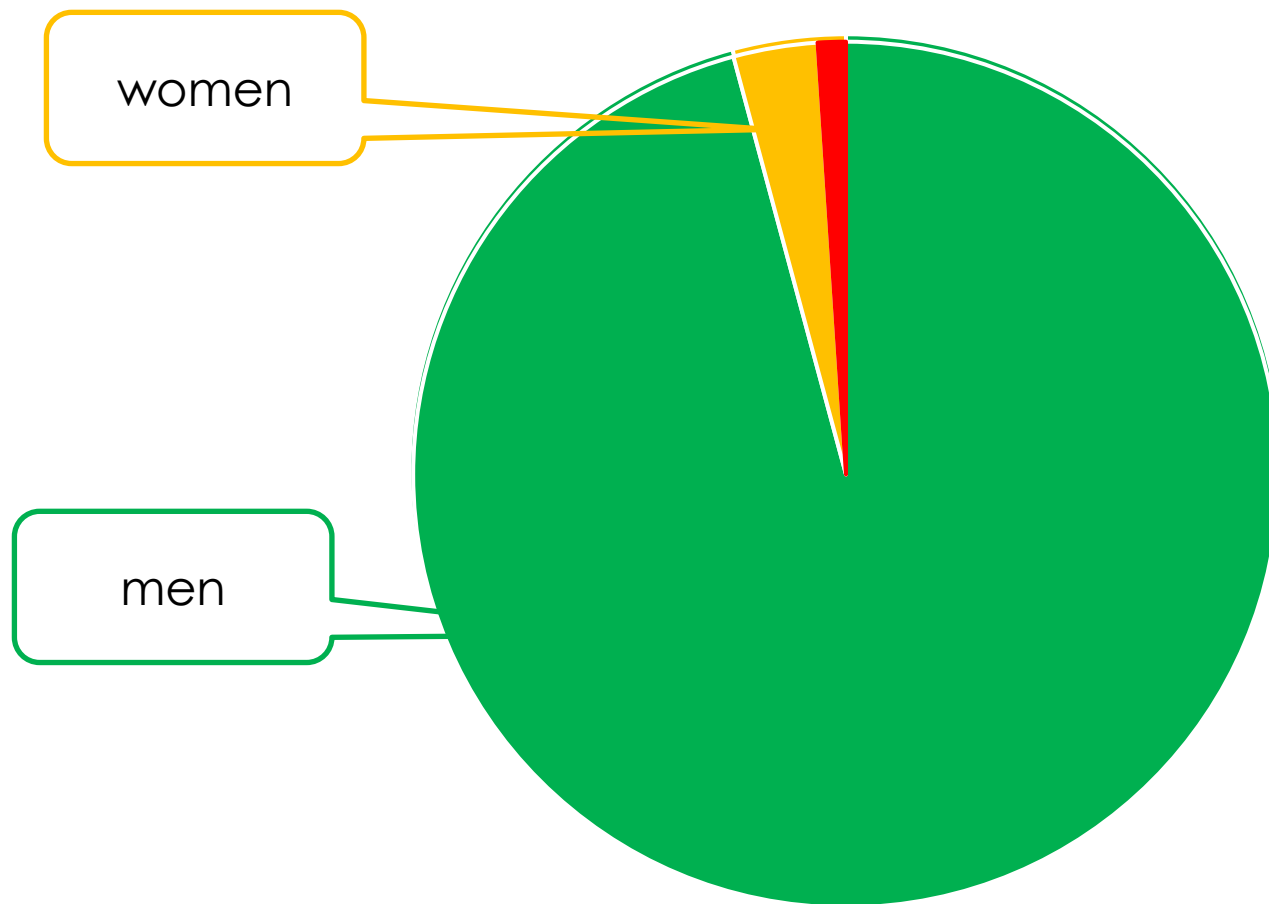
Crystallography supports women

Chemistry nobel prize (tot 191)



Crystallography supports women

Chemistry nobel prize (tot 191)

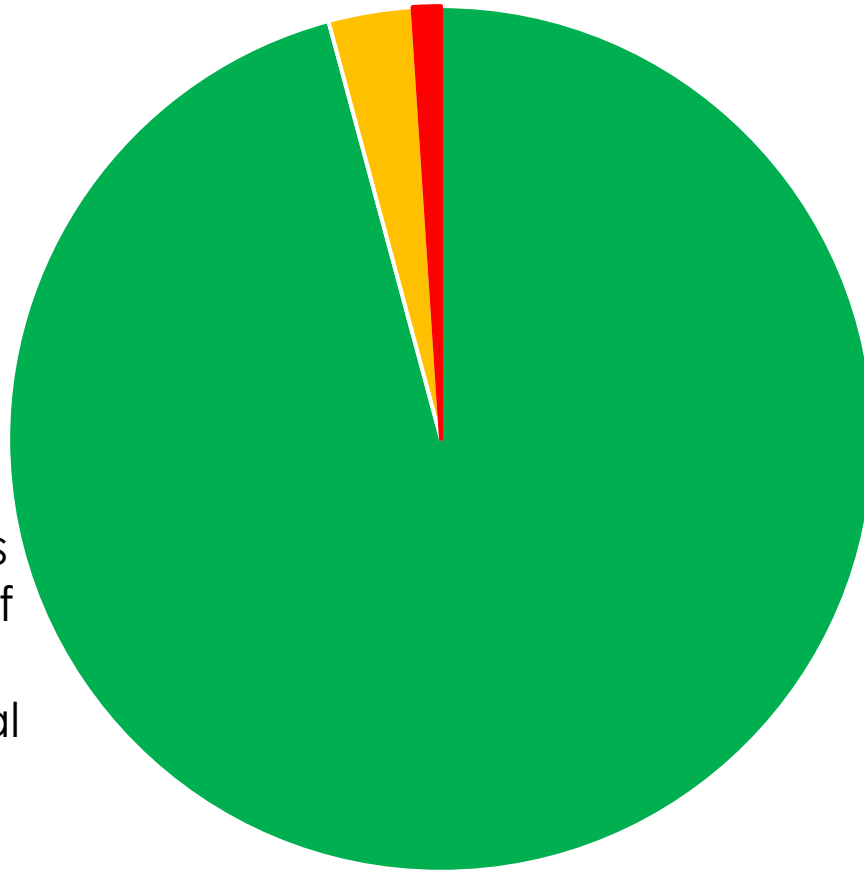


Crystallography supports women



1964 Dorothy C. Hodgkin

for her determinations
by X-ray techniques of
the structures of
important biochemical
substances

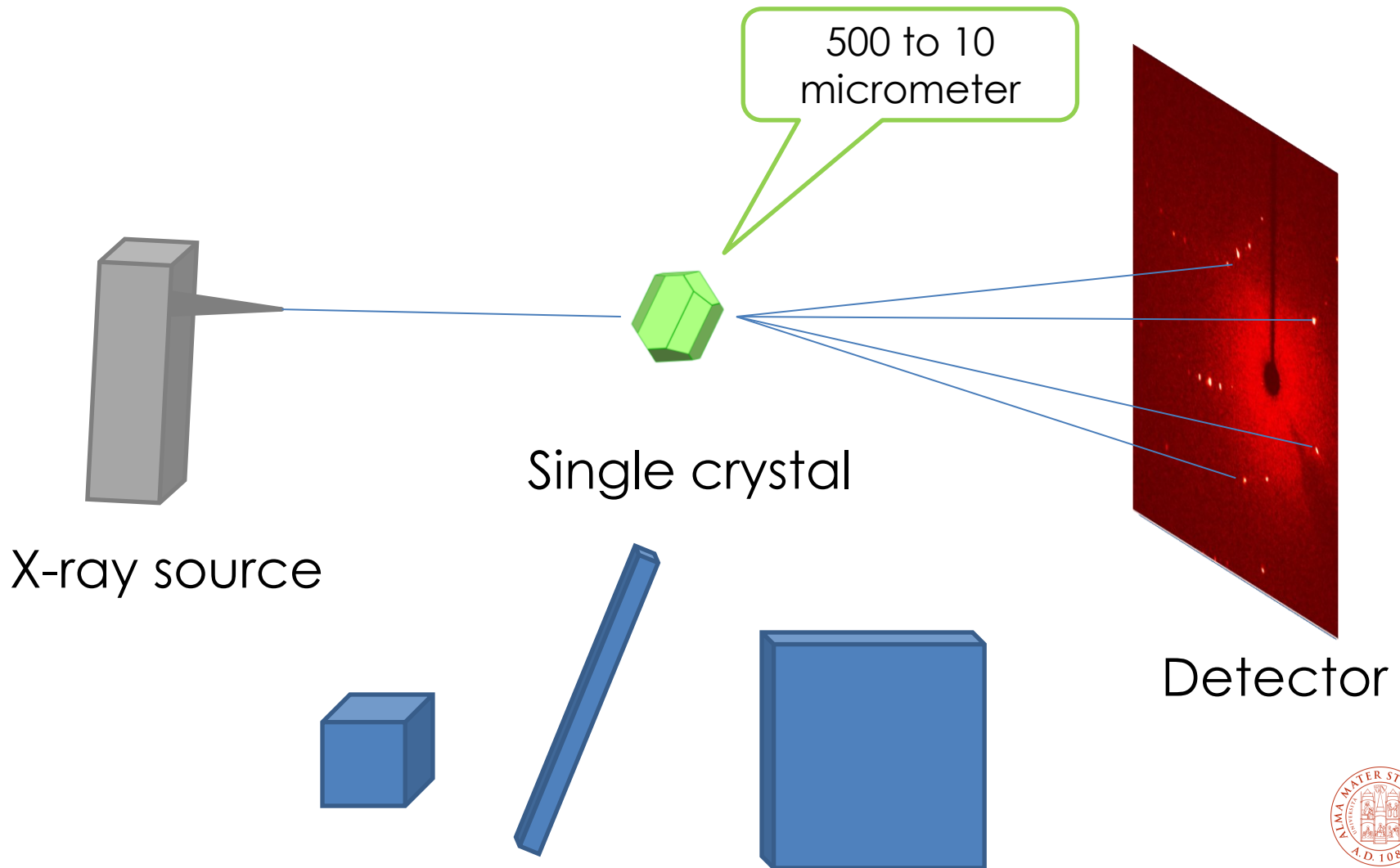


2009 Ada Yonath
for studies of the
structure and
function of
the ribosome.



How Single crystal X-ray diffraction works?

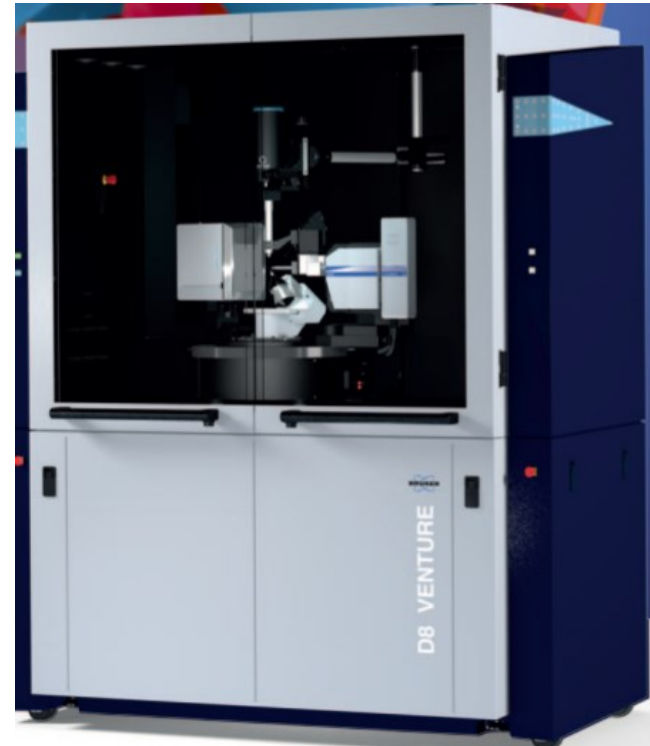
Collecting the data



Diffractometers



Area detector
single X-ray radiation (Mo)



Area detector
double X-ray radiation (Mo,Cu)
Microfocus source



Innovation in the X-ray source



Metal-Ceramic Sealed Tube



Micro-focus X-ray Source (IpS)



METALJET

brilliance

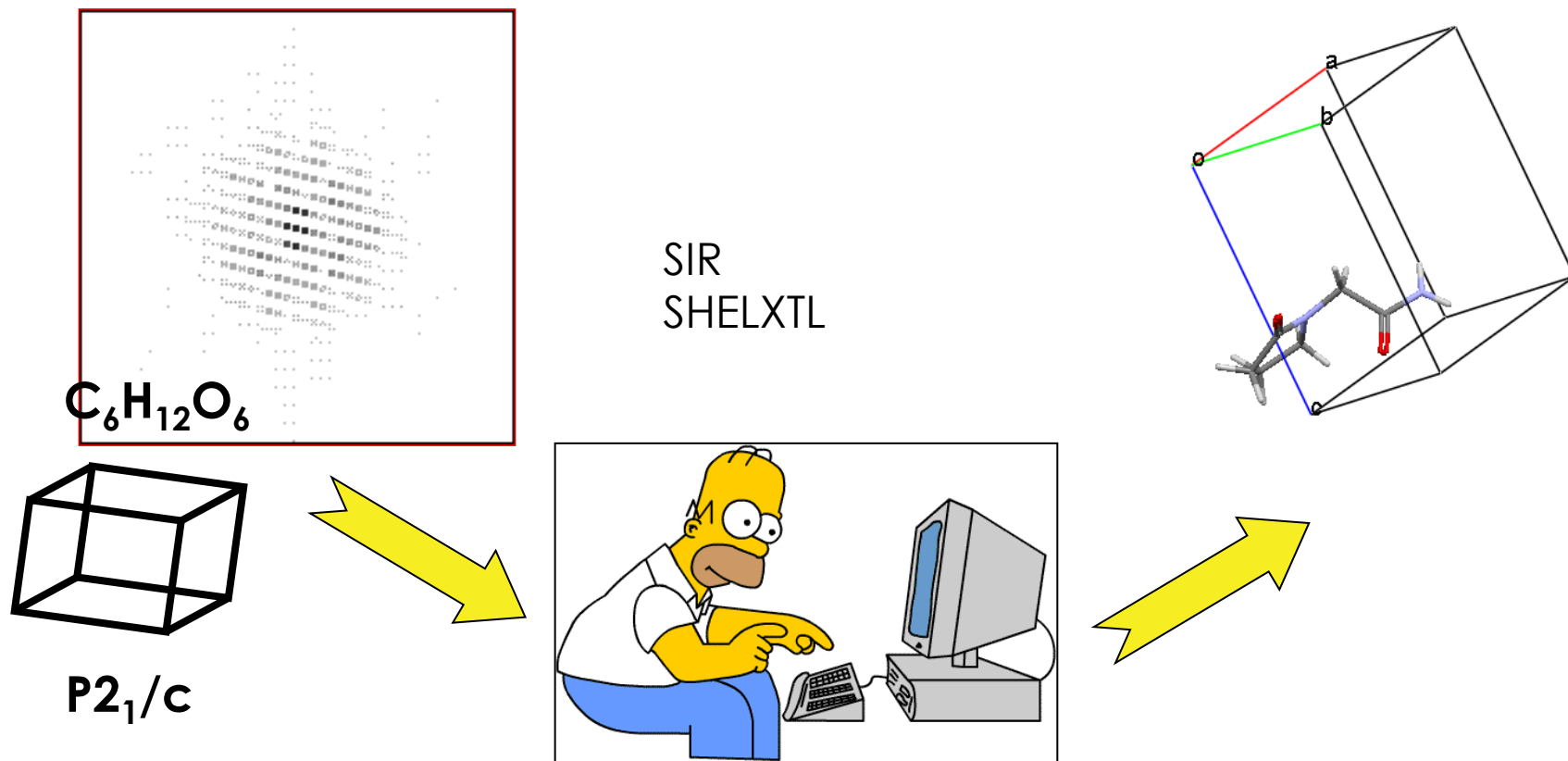
time

crystal size

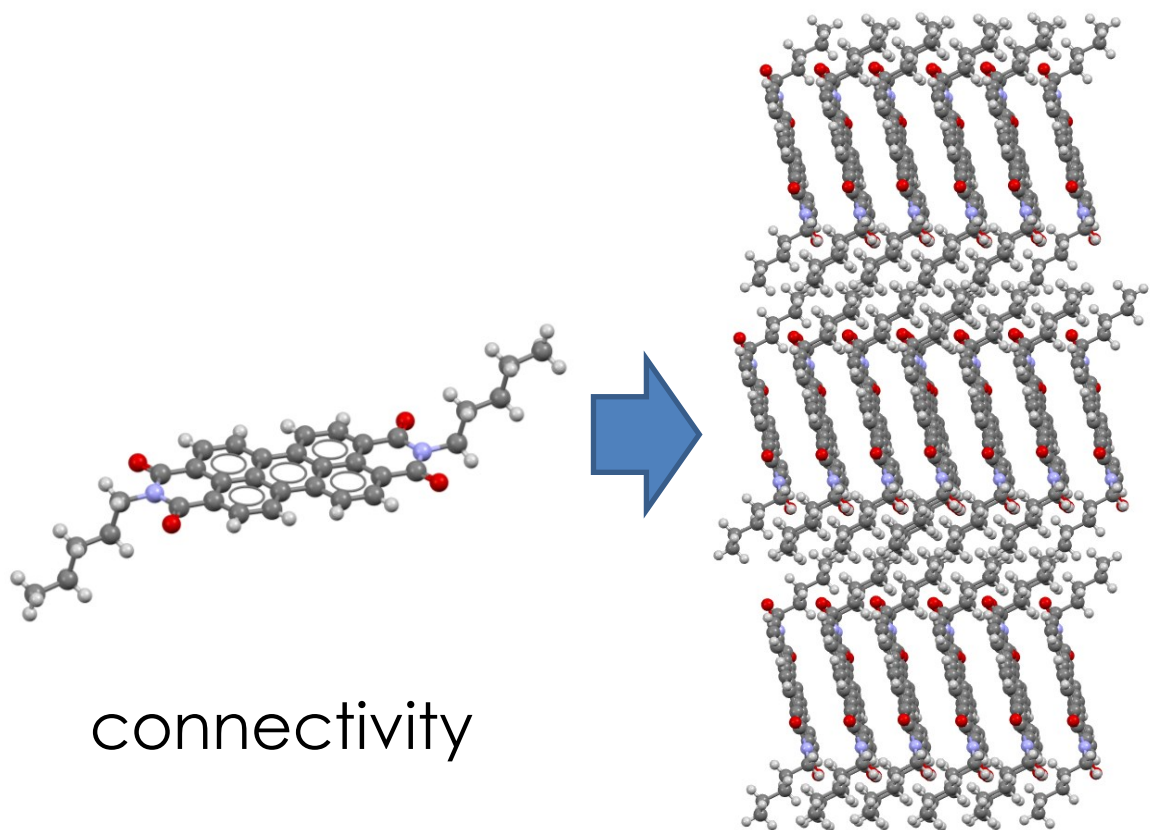


From reciprocal to direct space

Structure determination

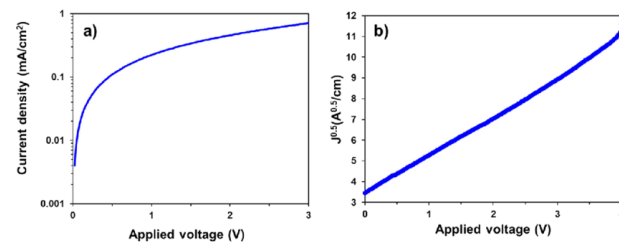


Why the structure is so Important?



connectivity

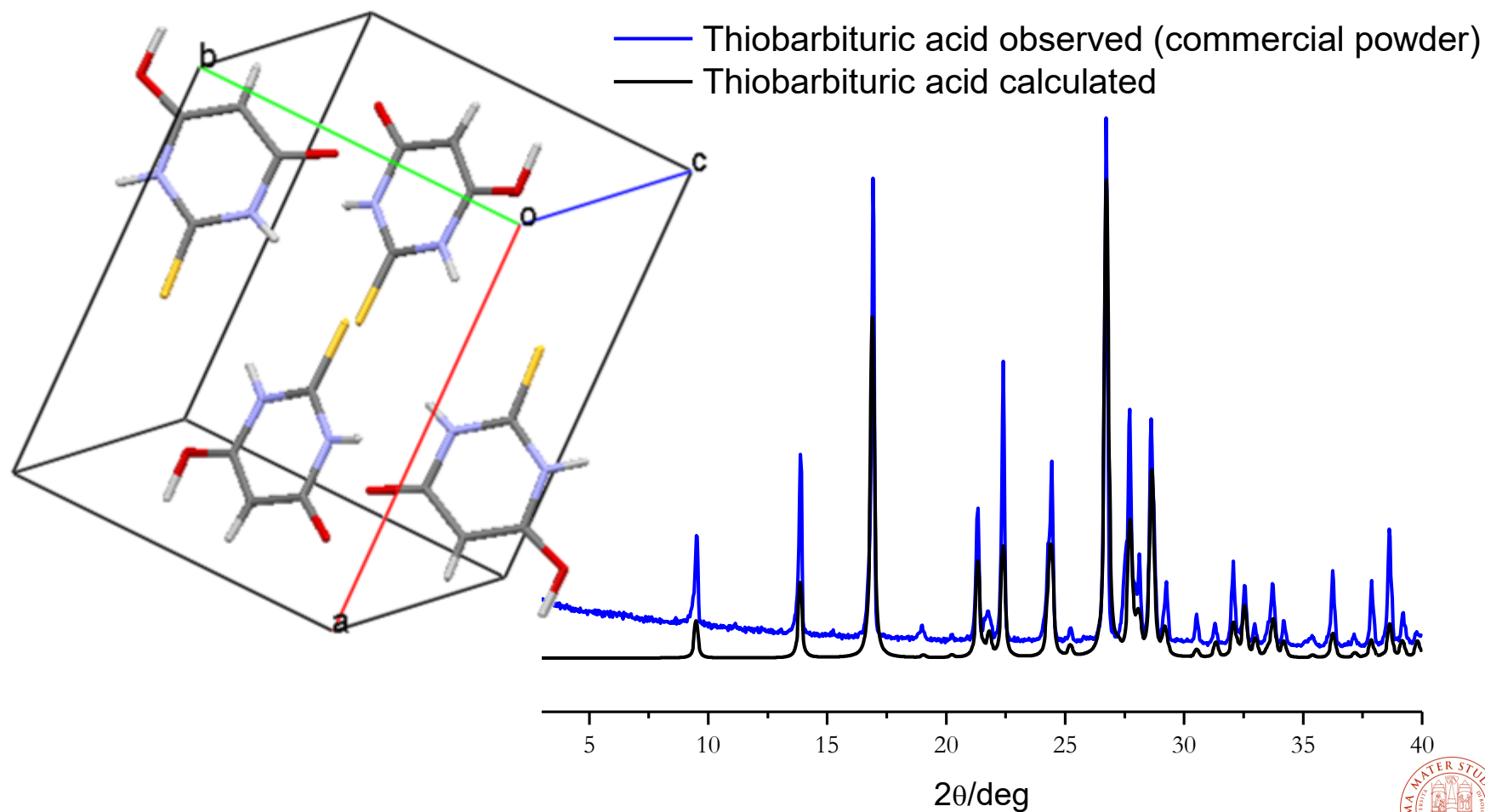
Crystal packing
molecular interactions



properties



Simulated or calculated powder diffractogram



Some examples from my research

- Active Pharmaceutical Ingredient (API)
- Organic molecular material
- Hybrid Coordination Polymer (HCP)

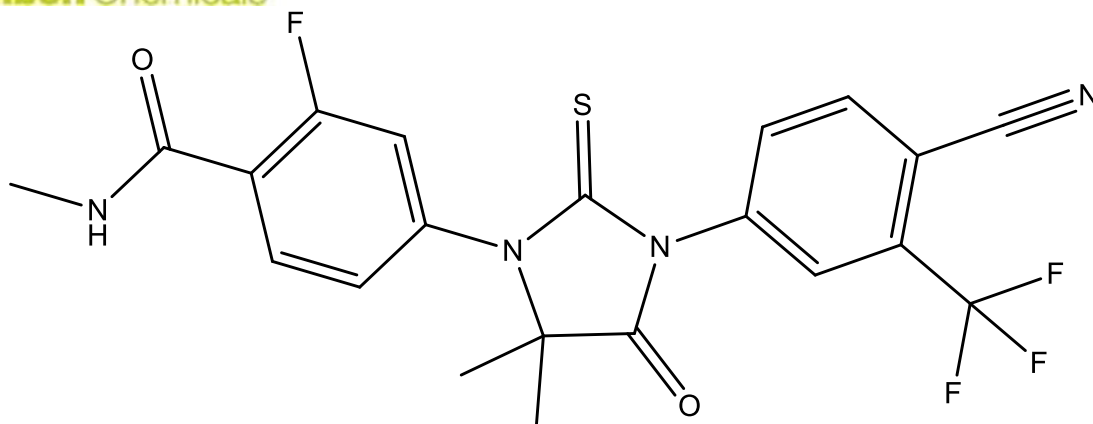


Some examples from my research

- **Active Pharmaceutical Ingredient (API)**
- Organic molecular material
- Hybrid Coordination Polymer (HCP)



Enzalutamide



Francesco Farinella



Enzalutamide for the treatment of metastatic castration-resistant prostate cancer.

Marked by Astellas as anhydrous form called R1

Patent expires in 2017

Polymorph screening to enter in the market

Maini, L.; Braga, D.; Farinella, F.; Melotto, E.; Verzini, M.; Brescello, R.; Michieletto, I.; Munari, I. Crystal Forms of Enzalutamide and a Crystal Engineering Route to Drug Purification. *Cryst. Growth Des.* **2018**. <https://doi.org/10.1021/acs.cgd.7b01613>.



Crystal structure :R1

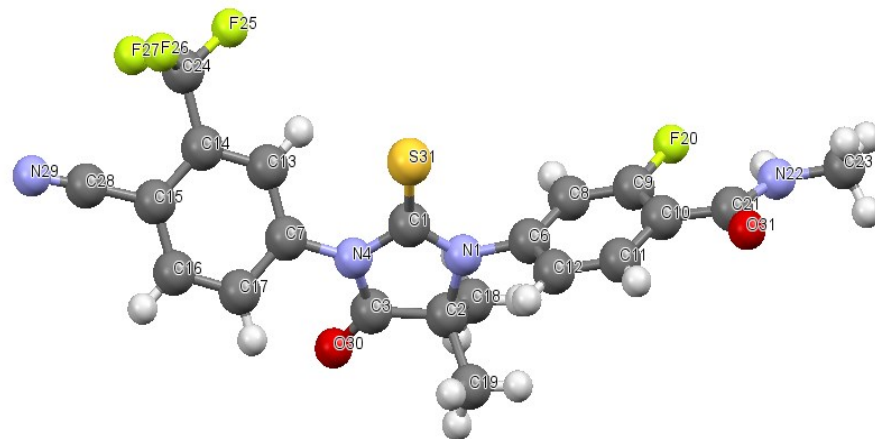
From **isopropyl alcohol**:

Monoclinic $P2_1/n$

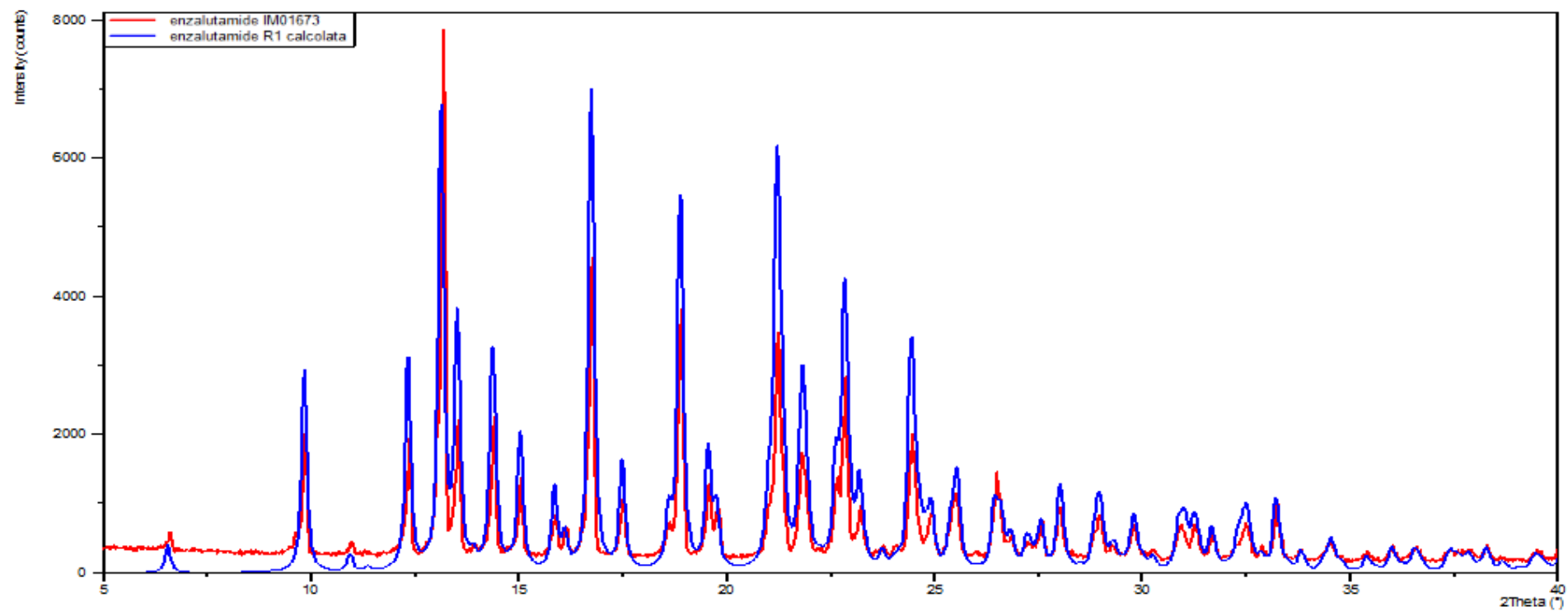
$a = 8.4972(4) \text{ \AA}$, $b = 26.9629(13) \text{ \AA}$, $c = 9.5571(5) \text{ \AA}$, $\beta = 93.739(4)^\circ$

Volume = $2184.96(19) \text{ \AA}^3$

ASU: 1 molecule of enzalutamide



Calculated vs experimental



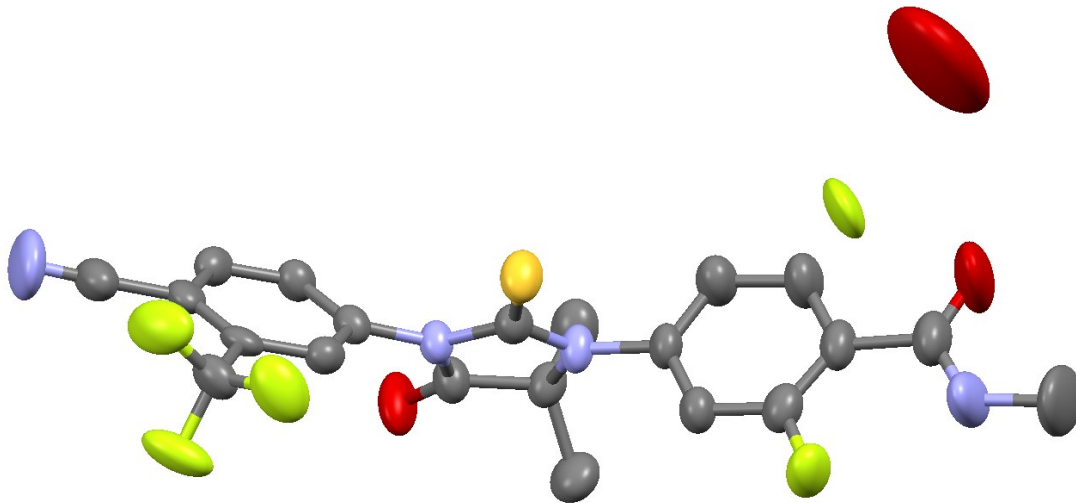
Crystal structure :R2

Crystals **from methanol**

Monoclinic $P2_1/c$

$a = 18.3659(12)\text{\AA}$, $b = 15.2025(12)\text{\AA}$, $c = 8.0136(8)\text{\AA}$, $\beta = 90.049(7)^\circ$ e volume = $2237.5(3)\text{\AA}^3$

ASU: 1 molecule enzalutamide and $\frac{1}{2}$ molecule of solvent



No clear description of the solvent. It has been modelled as 1 atom of oxygen placed on the inversion center

F disordered



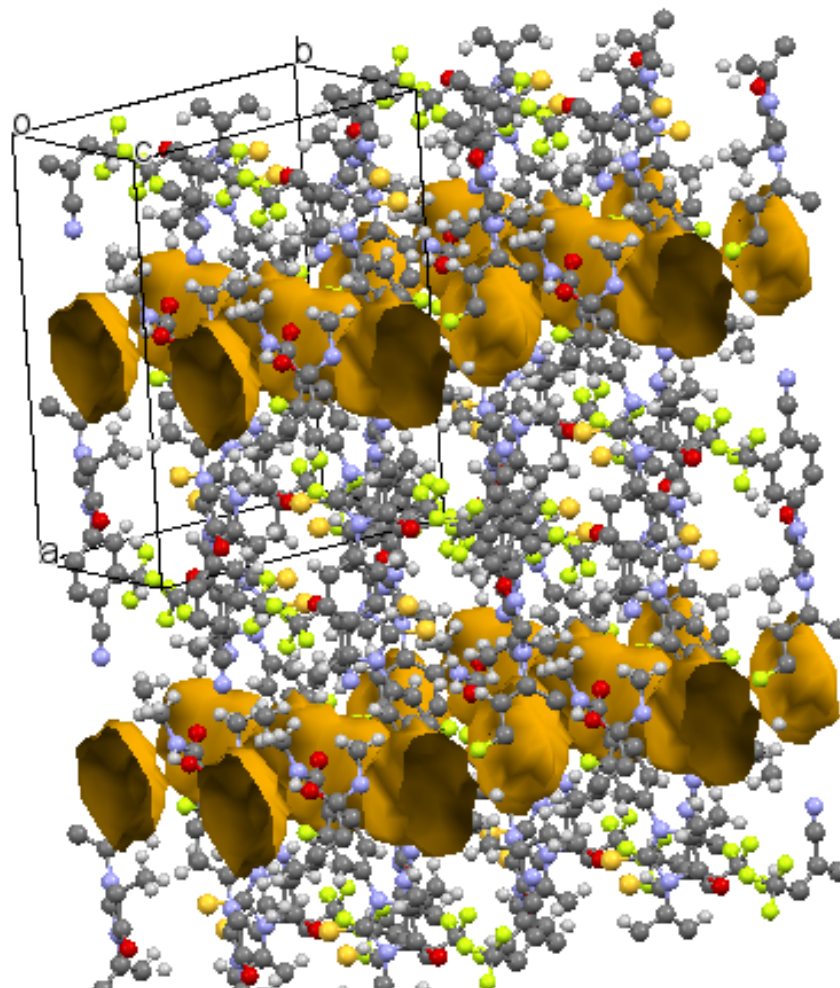
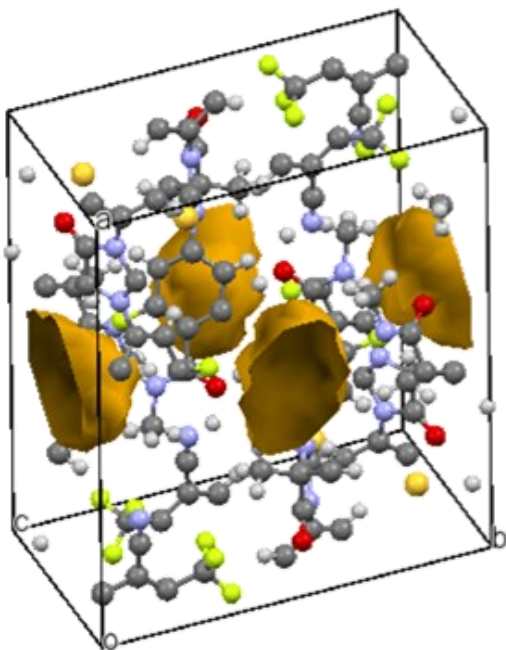
Packing of R2

Volume of void in the unit cell $108 \text{ \AA}^3$
(excluding solvent)

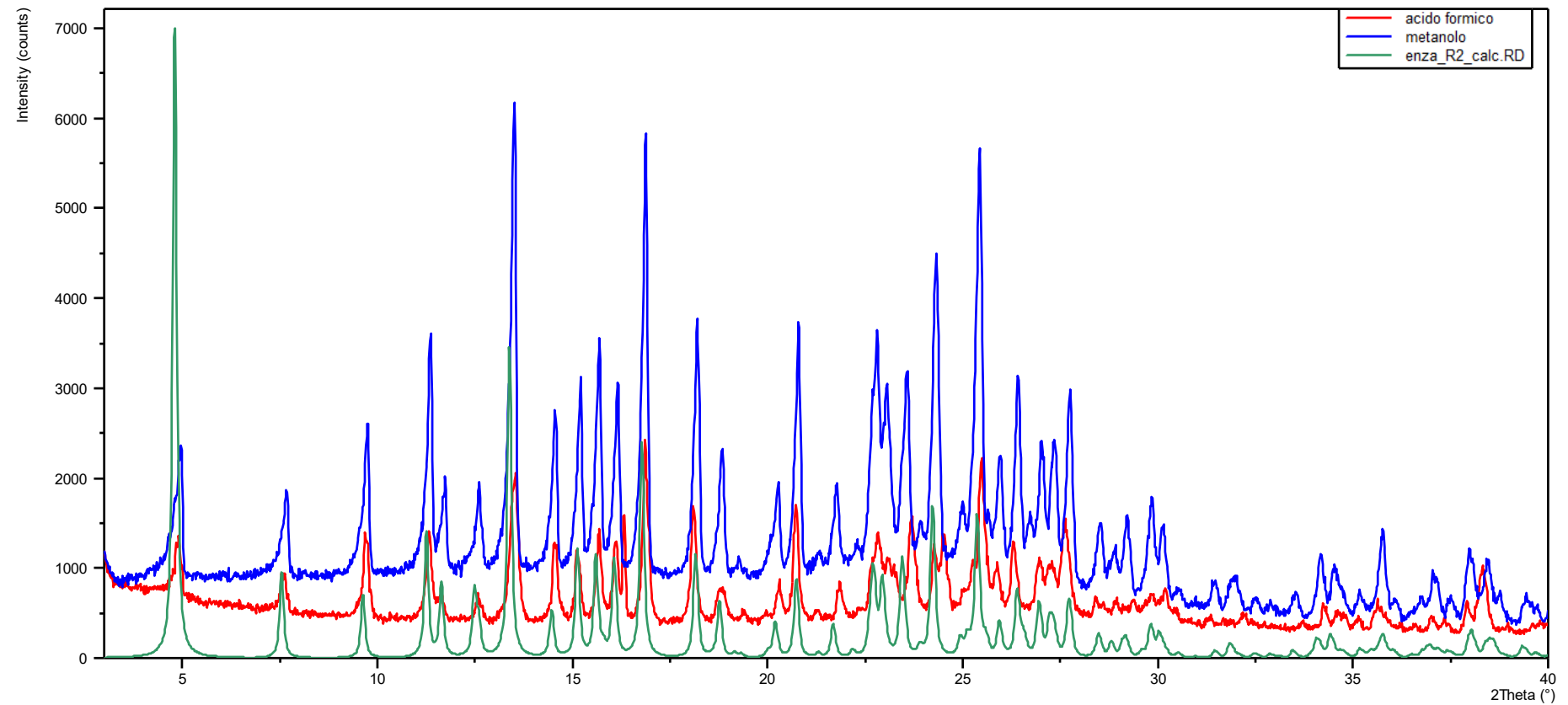
Volume H_2O $21.6 \text{ \AA}^3 \rightarrow 4$ molecules

Volume MeOH $45.6 \text{ \AA}^3 \rightarrow 2$ molecules

Volume HCOOH $46.8 \text{ \AA}^3 \rightarrow 2$ molecules



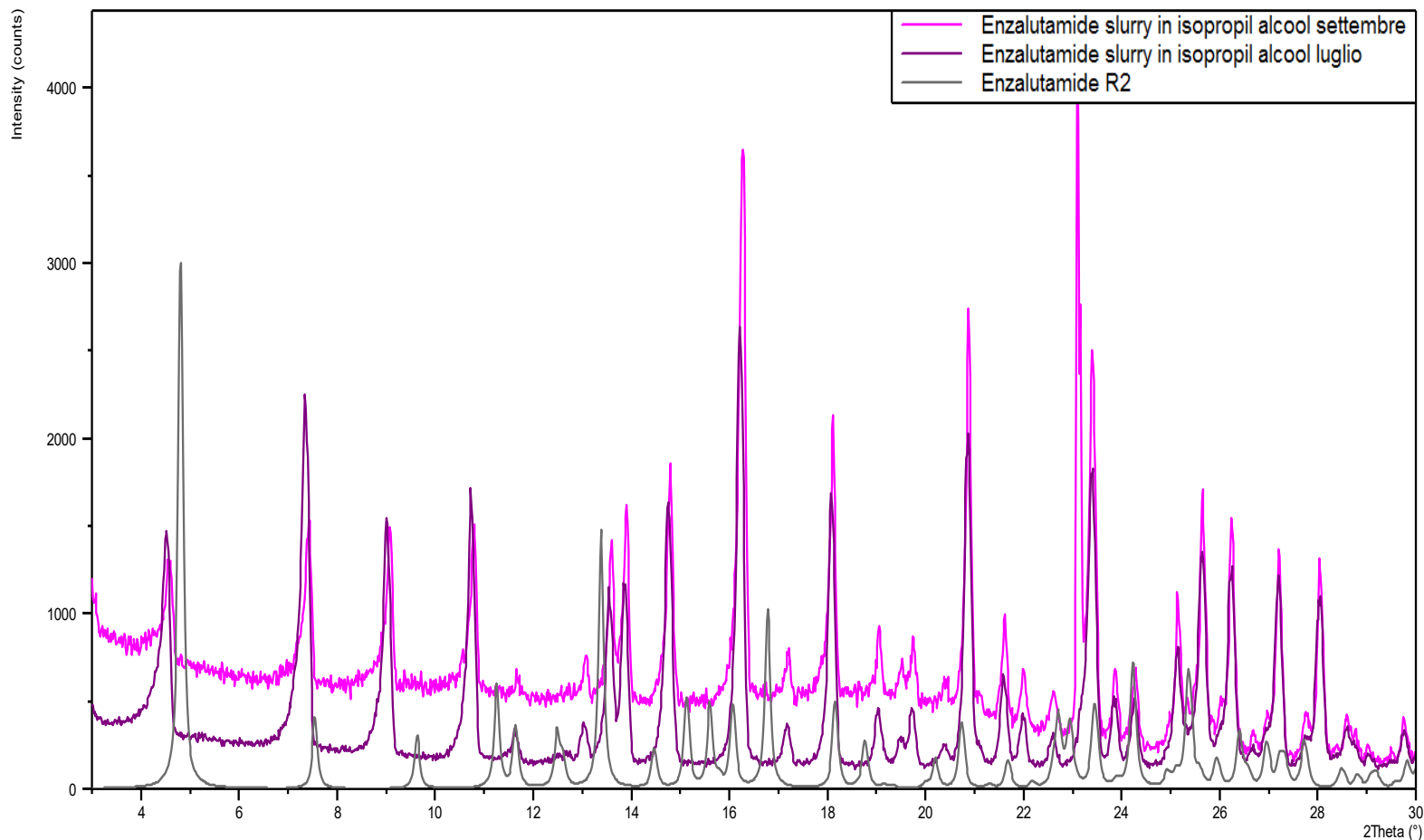
Slurry experiment (R2)



Methanol and formic acid



Slurry in isopropyl alcohol

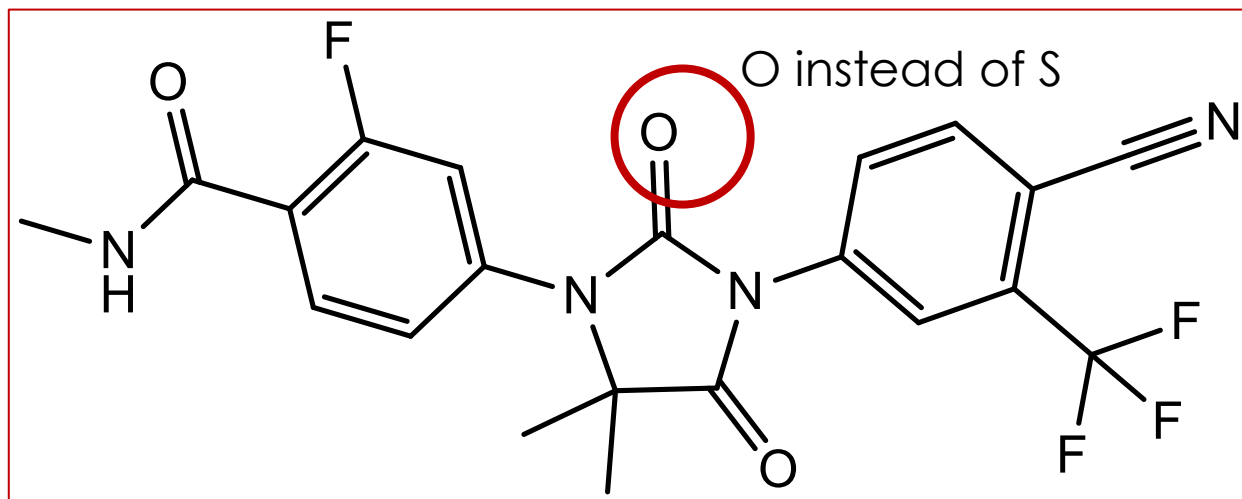


New form called **R3-** (S-enza isopropylate)



An unexpected result

One of the impurity to avoid is



Impurity J



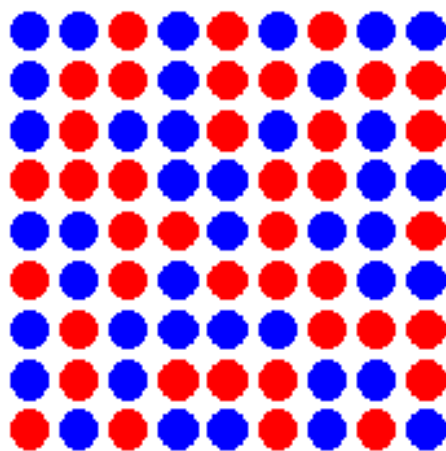
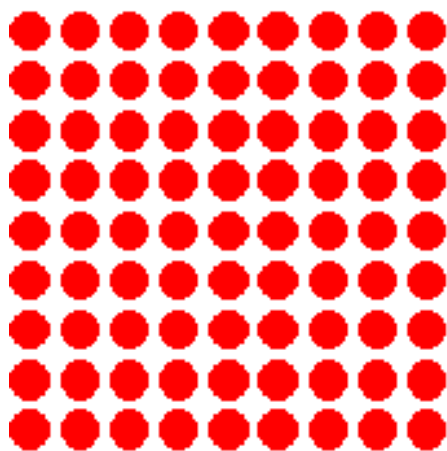
	Impurity J	Enzalutamide R1
	P2 ₁ /n	P2 ₁ /n
a (Å)	8.0639(5)	8.4972(4)
b (Å)	25.7007(19)	26.9629(13)
c (Å)	9.9640(6)	9.5571(5)
β (°)	95.005(6)	93.739(4)
V (Å ³)	2057.1(2)	2184.96(19)

isomorphic



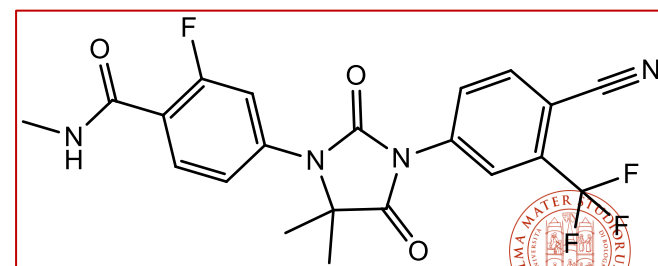
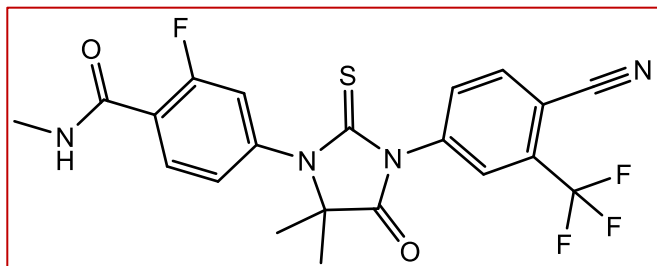
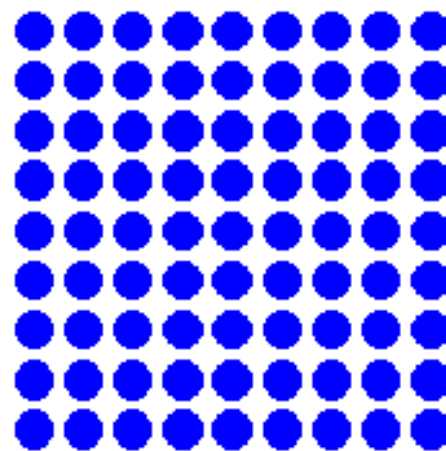
Solid solution

Enzalutamide
R1



I

Impurity J
Form I

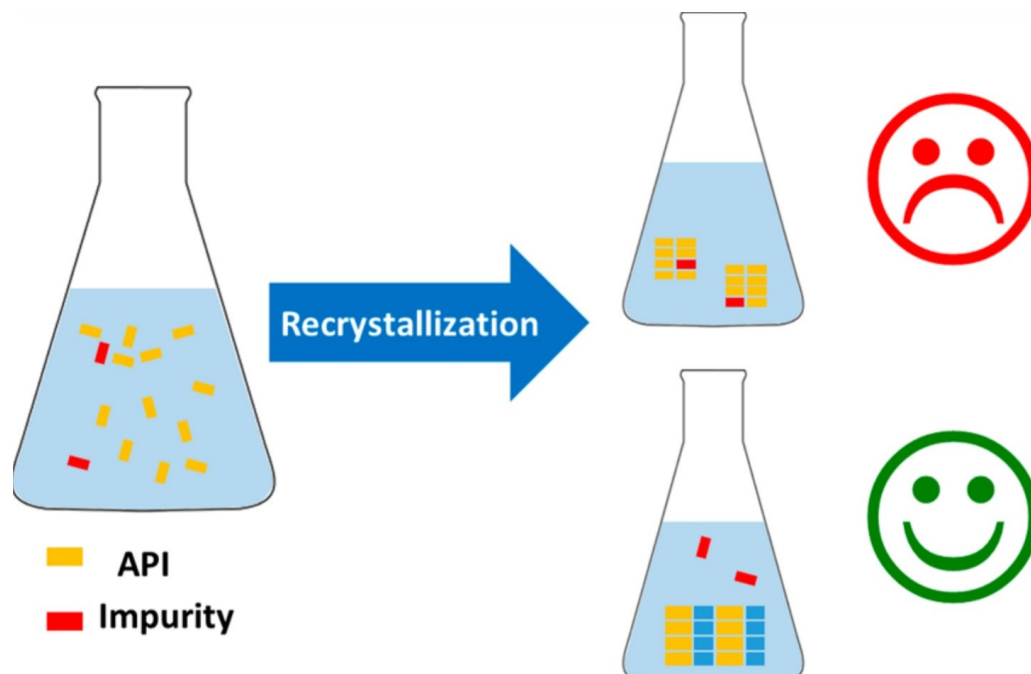


Old process:

The crude enzalutamide is re-crystallized in isopropyl alcohol as R1 (anhydrous form) **three time** for purification.

New process:

One recrystallization of enzalutamide as form R3 reduce all the impurities to acceptable values.(included the amount of impurity J)



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- **Organic molecular material**
- Hybrid Coordination Polymer (HCP)

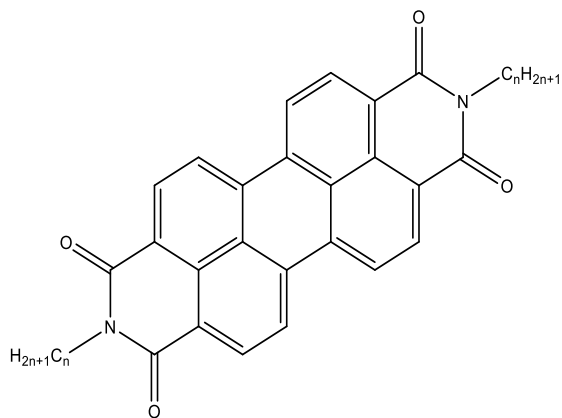


PERYLENE DIIMIDES

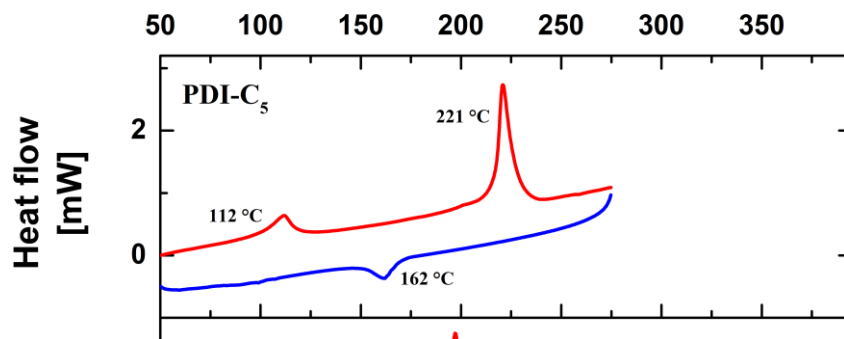
Francesco Marin



- Excellent stability thermal, chemical and photostability.
- Application as industrial pigments.
- Well known n-type organic semiconductors.
- Potential application in devices (OFETs, solar cells, laser etc.).

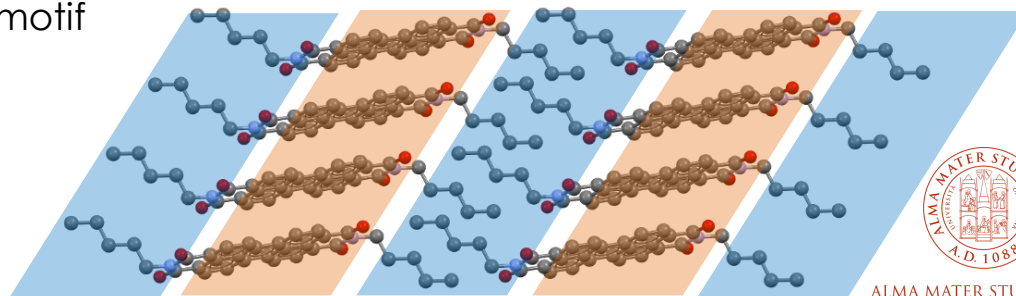
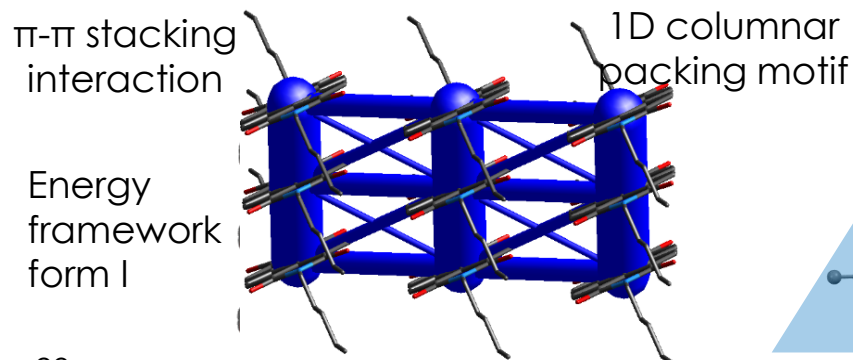
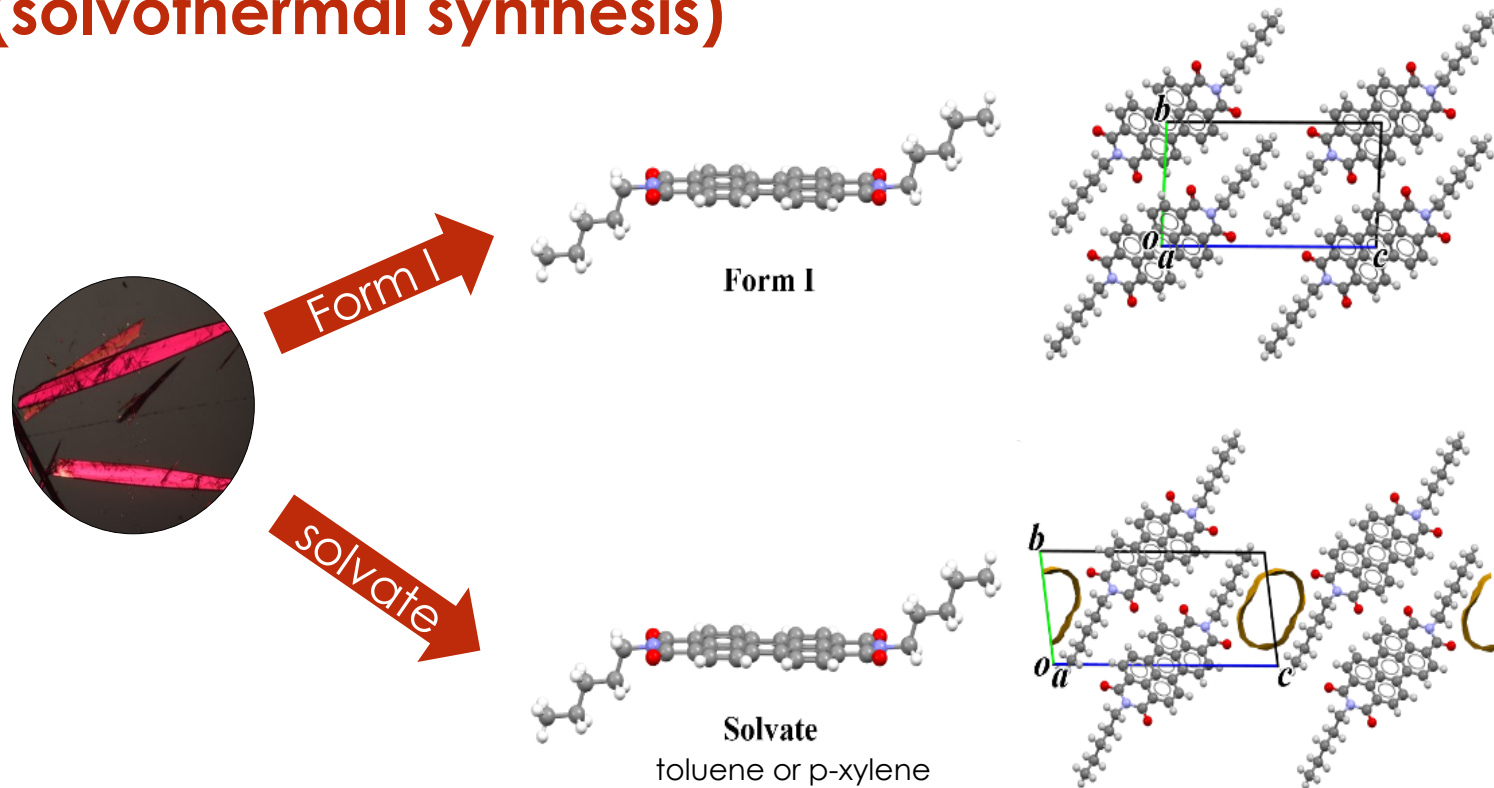


With $n = 5$

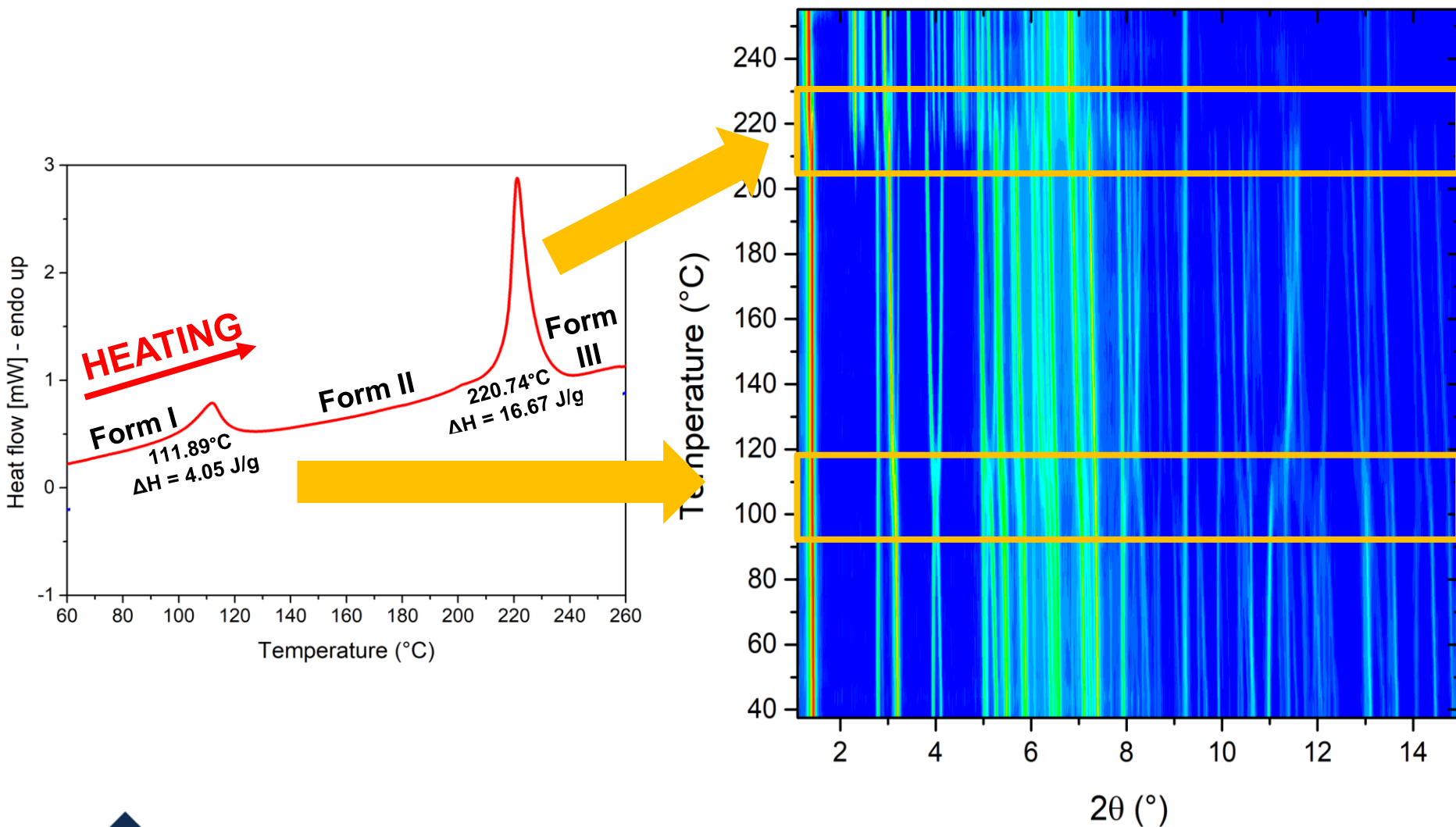


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Polymorph screening: Recrystallization of PDI-C5 (solvothermal synthesis)



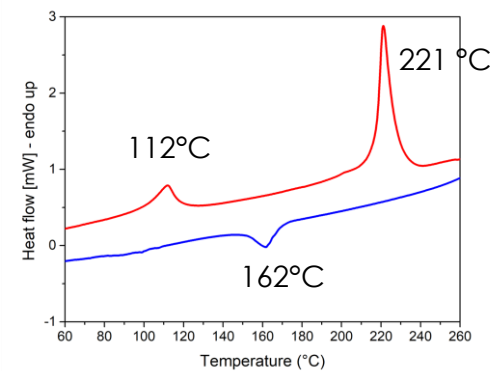
Thermal treatment: high temperature polymorphism



Hot stage microscopy



- Transition I $\rightarrow$ II NOT observed
- Transition II $\rightarrow$ III upon heating
- Reverse transition upon cooling

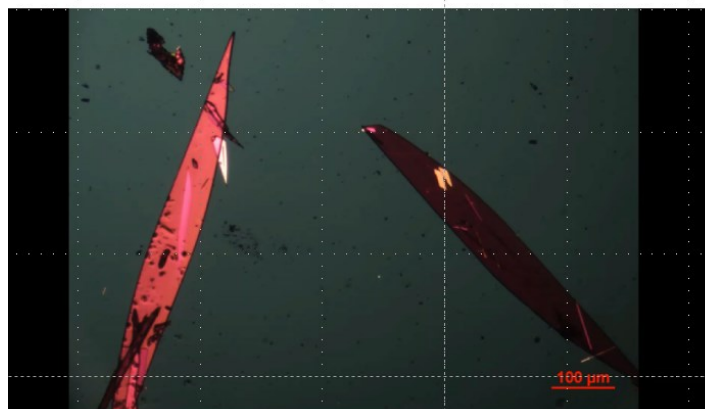


Why different behaviour?

COOLING

thermal expansion coefficient

Big crystals

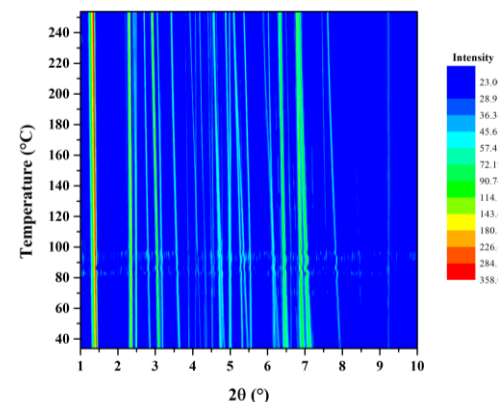
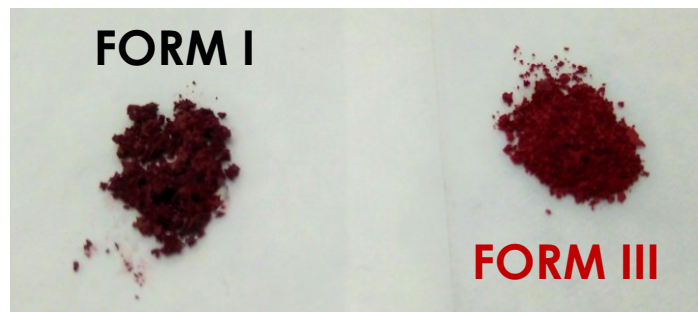


Form III

Axes	$\alpha_i [10^{-6} \text{ K}^{-1}]$
X_1	-56.4
X_2	114
X_3	337
V	395

Organic system $\alpha_V = 169 \text{ MK}^{-1}$

Powder

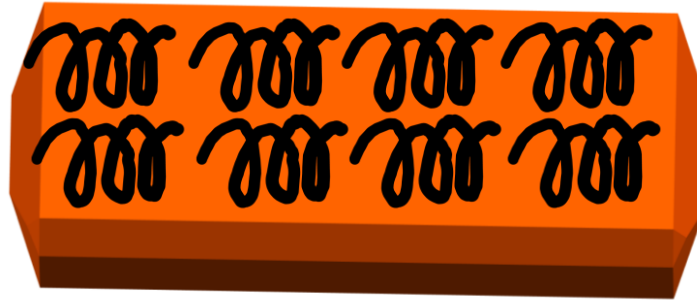
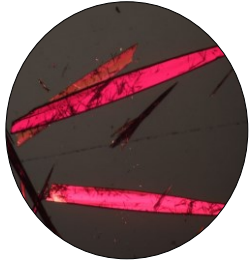


Marin, F.; Tombolesi, S.; Salzillo, T.; Yaffe, O.; Maini, L. Thorough Investigation on the High-Temperature Polymorphism of Dipentyl-Perylenediimide: Thermal Expansion vs. Polymorphic Transition. *J. Mater. Chem. C* **2022**, 10 (20), 8089–8100. <https://doi.org/10.1039/D1TC06132A>.

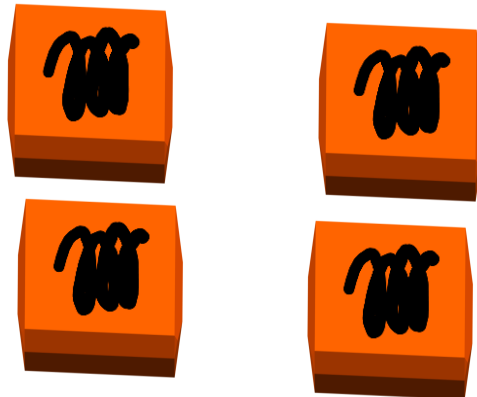
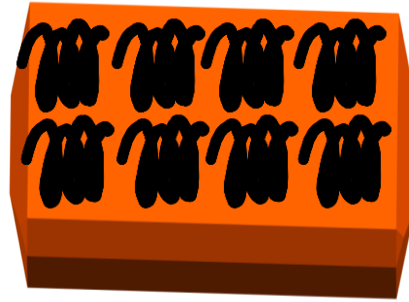
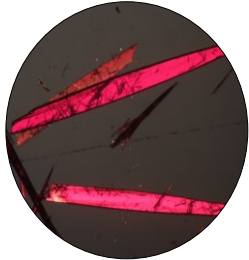


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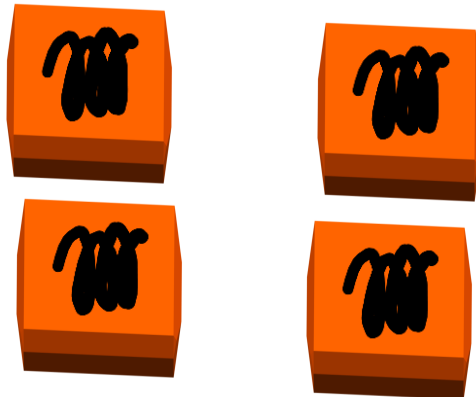
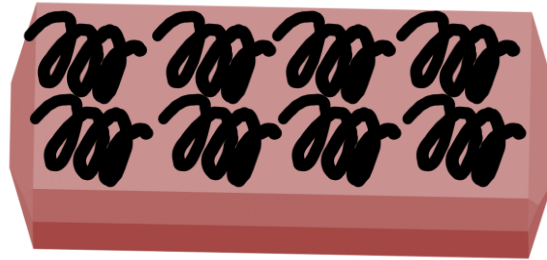
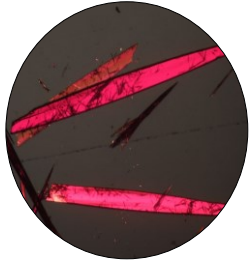
Thermal compression



Thermal compression



Thermal compression

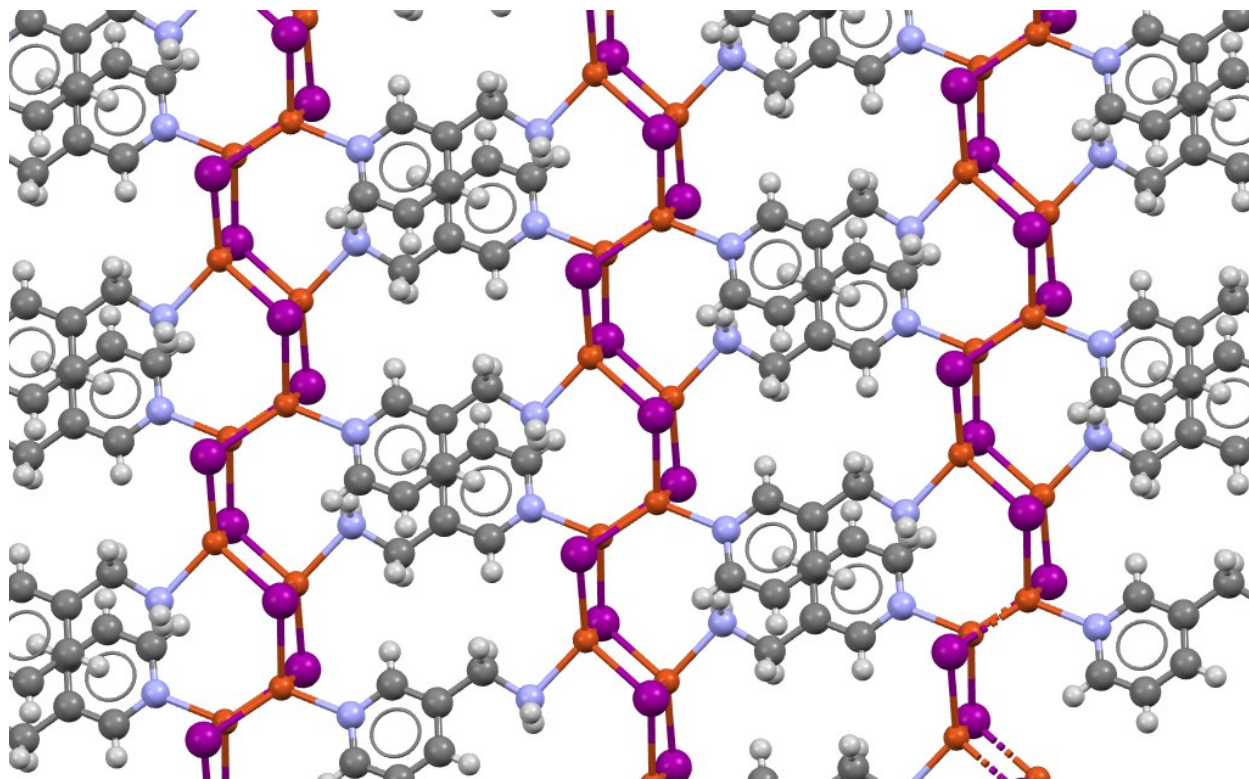
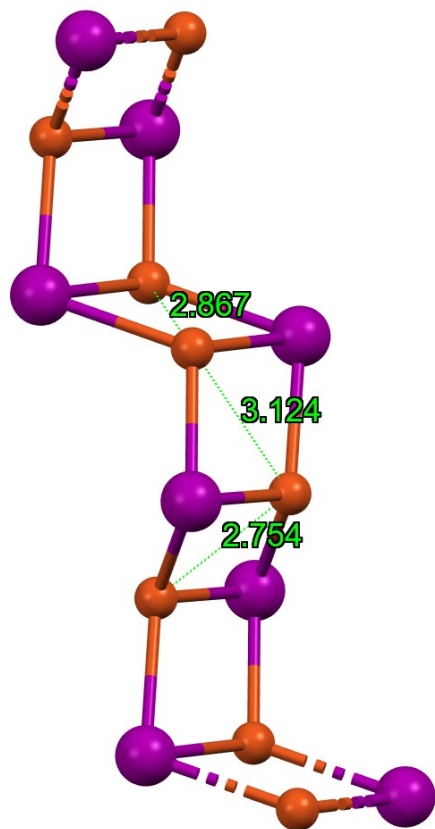


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- Organic molecular material
- **Hybrid Coordination Polymer (HCP)**

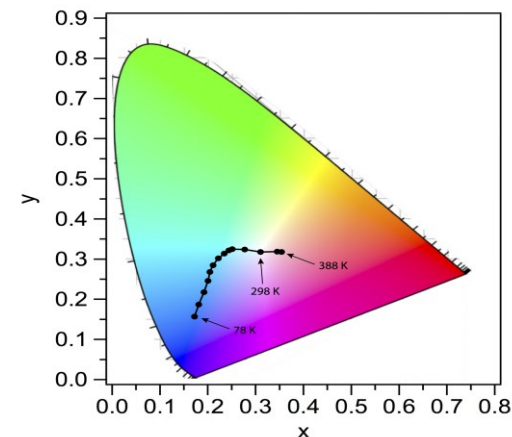
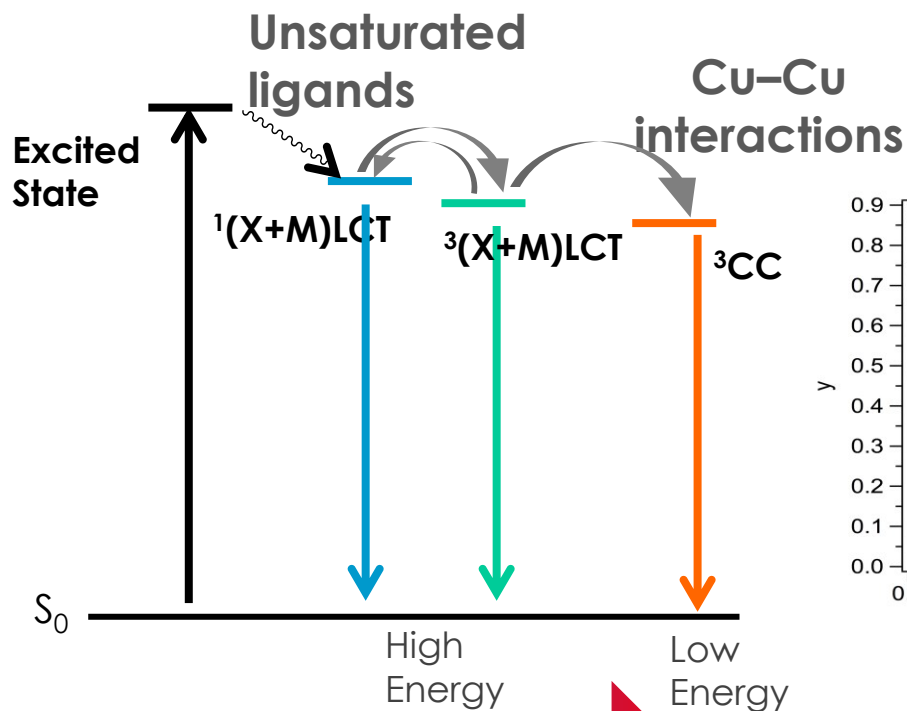
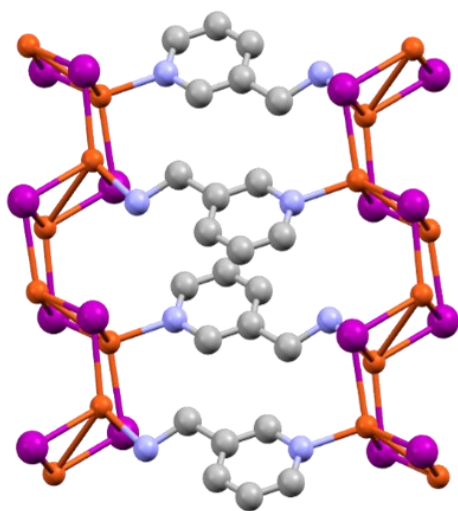
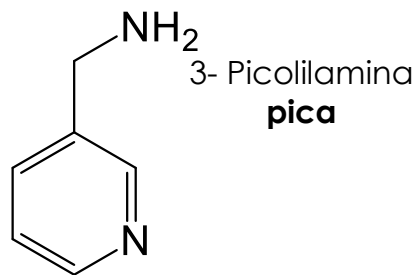


Copper Iodide based Hybrid Coordination Polymer



Inorganic
double stair

Stimuli responsive Hybrid Coordination polymer



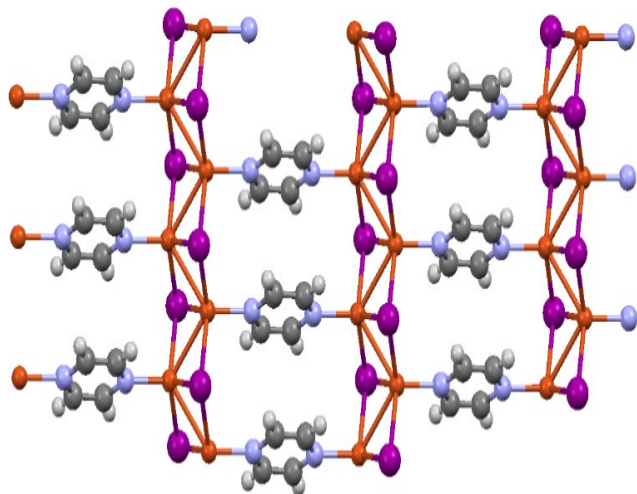
F. Farinella
PhD

Farinella, F.; Maini, L.; Mazzeo, P. P.; Fattori, V.; Monti, F.; Braga, D. White Luminescence Achieved by a Multiple Thermochromic Emission in a Hybrid Organic-Inorganic Compound Based on 3-Picolylamine and Copper(II) Iodide. *Dalt. Trans.* **2016**, 45 (44), 17939–17947. <https://doi.org/10.1039/C6DT03049A>.

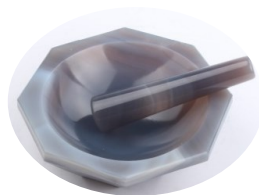


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Mechanochromic compound



Unsaturated organic ligand
metallophilic interaction



Alma Idea-MEMENTO 2022 PRIN-STIGMA 2022 Chiara Gualandi, Damiano Genovese, Daniele Fazzi

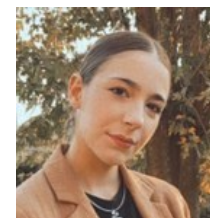
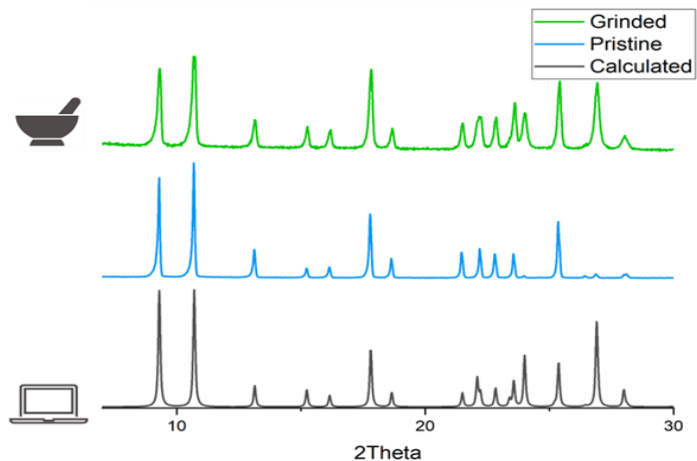
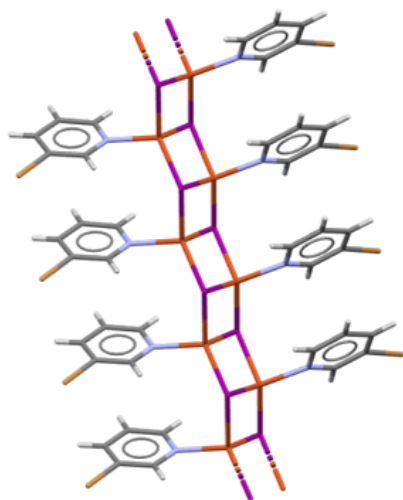
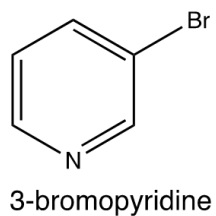


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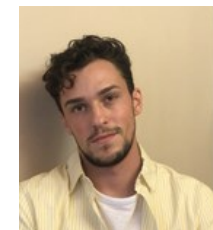
Mechanochromic HCP



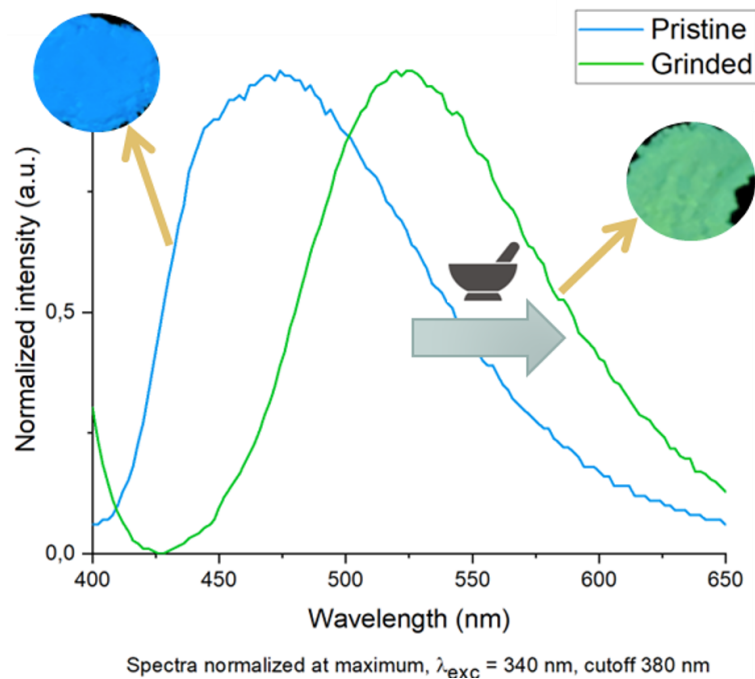
Cambridge Structure Database



Laura Contini



Lorenzo Gatti

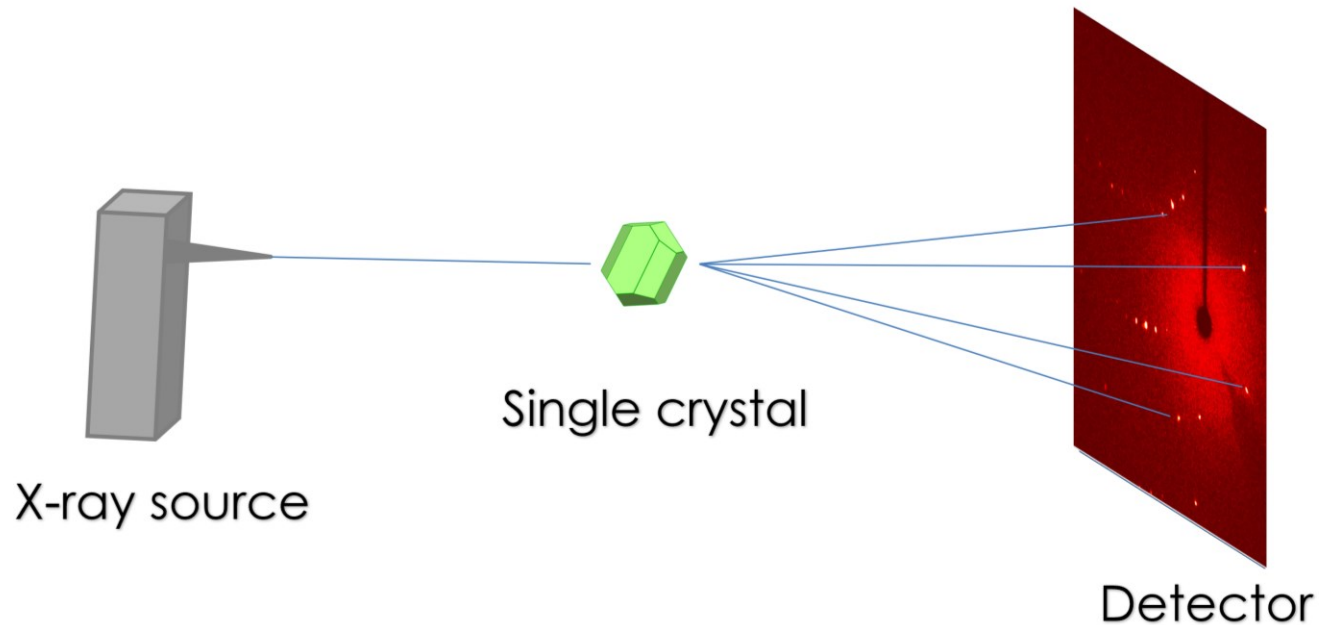


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Conclusion

- To understand, optimize desired properties it is important to know the structure



Molecular Crystal Engineering Group





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