Crystal morphology prediction of structures determined by X-ray powder diffraction

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

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  - Dr. Letícia Kuplich
  - Dr. Amanda L. Ibiapino
  - Dr. Laysa P. de Figueiredo

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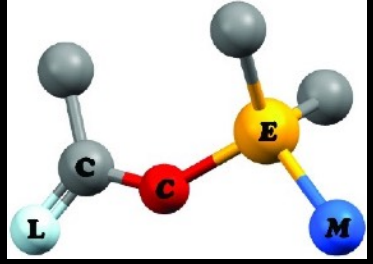
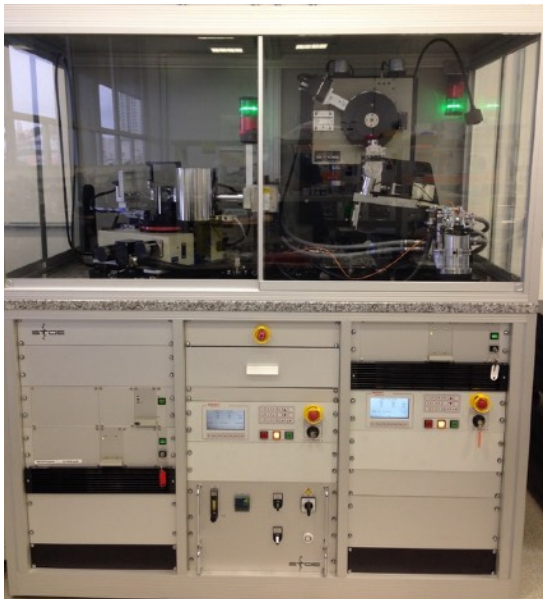
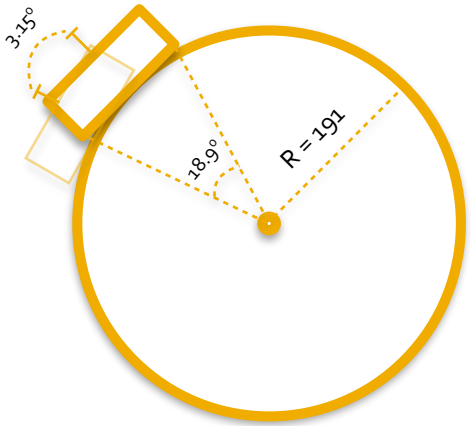
Experimental details



Stoe® STADI-P X-ray Powder Diffractometer (fully functional @ LC*CEM*)





- Variable counting time (VCT) acquisitions
- Transmission geometry → capillaries or acetate-cellulose foils
- CuKα_1 radiation (λ = 1.54056 Å)

LASSBio-1773/1774		LASSBio-1755	
2θ range (°)	Time (s)	2θ range (°)	Time (s)
5-26.000	100	6-28.035	100
26.015-45.950	200	28.050-47.985	200
45.965-65.900	400	48.000-68.985	400
65.915-90.050	800	69.000-100.485	800

Discovery of new lead-compounds

Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio®)

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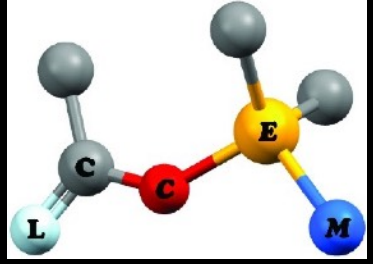

inct instituto nacional de ciência e tecnologia de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

Research program to develop a series of compounds with anti-inflammatory, antinociceptive, anticancer, antidiabetes activities by structural modifications of some prototype compounds

(In this presentation) Studies devoted to the discovery of:

new oral hypoglycemiant with dual activity **hypoglycemiant and anti-inflammatory** and antinociceptive and anti-inflammatory

LASSBio-1755

LASSBio-1773

LASSBio-1774

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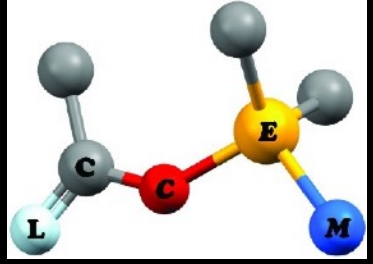
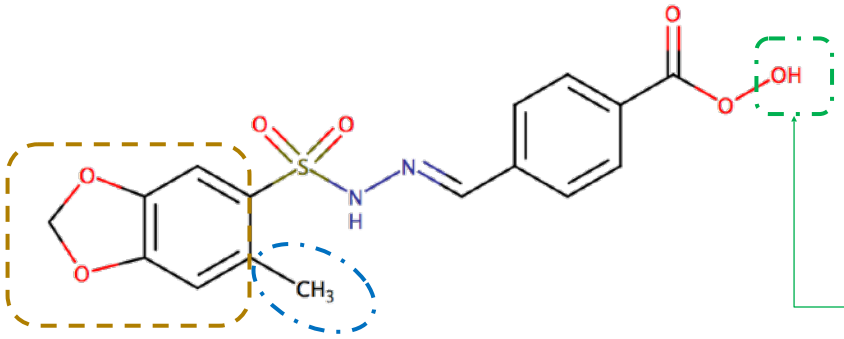
LASSBio-1773 and LASSBio-1774

Synthesis procedure

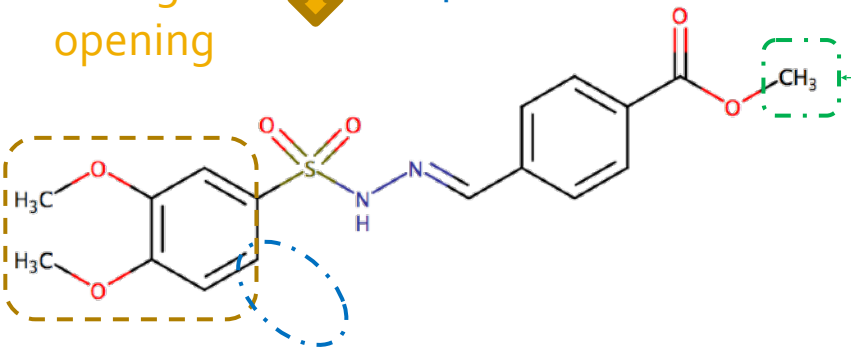


LASSBio-1471



Ring opening

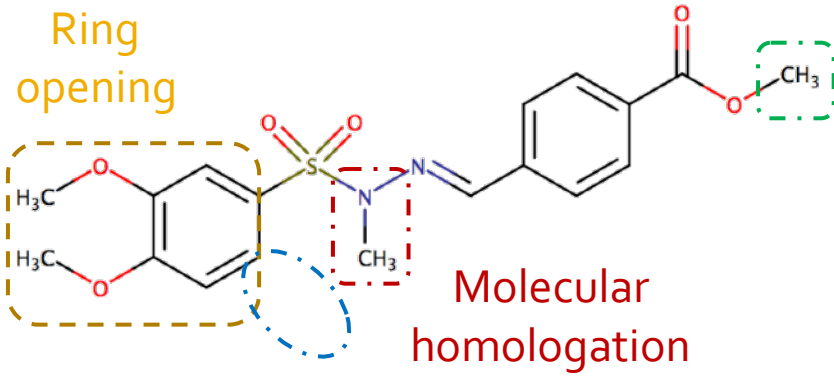
Molecular simplification



Methylation

LASSBio-1773

LASSBio-1774



Ring opening

Molecular homologation

Molecular simplification

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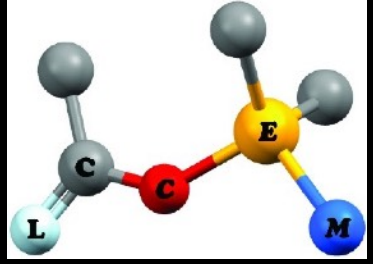
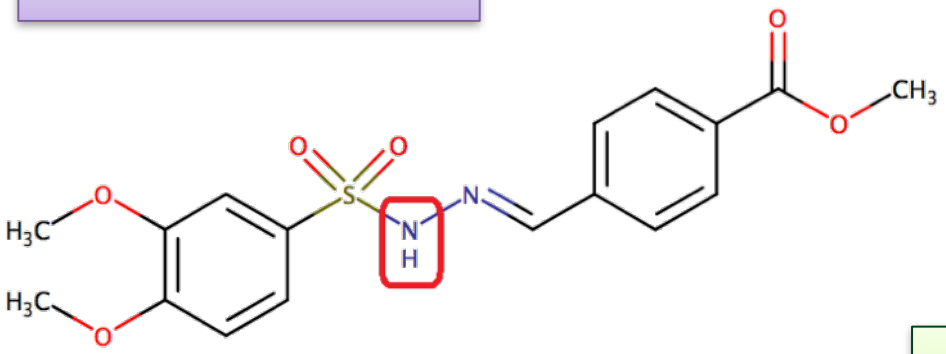
Structural modification

LASSBio-1773 and LASSBio-1774



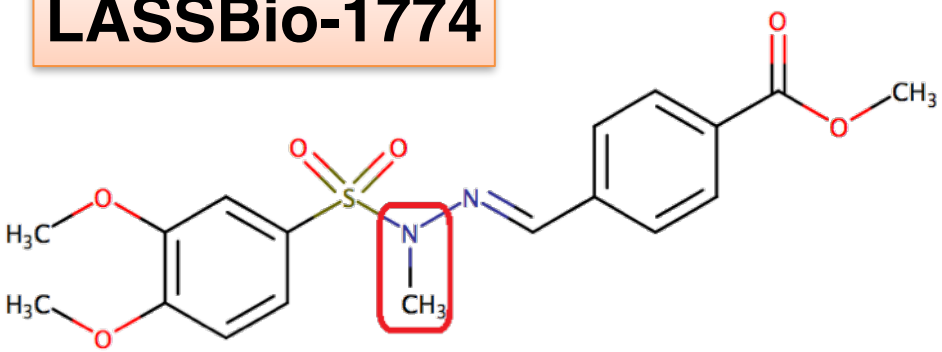
LASSBio-1773



- ✓ *PPARγ antagonist*
- ✓ Hypoglycemic activity

- ✓ **Samples:** *powders*
- ✓ **Aspect:** *white crystalline solids*

LASSBio-1774



- ✓ *PPARγ agonist*
- ✓ Hypoglycemic and **anti-inflammatory** activities

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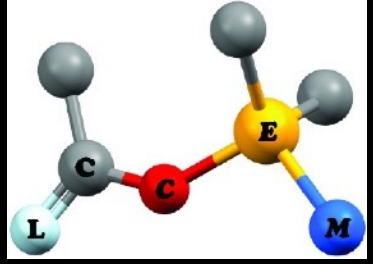
X-ray powder diffraction



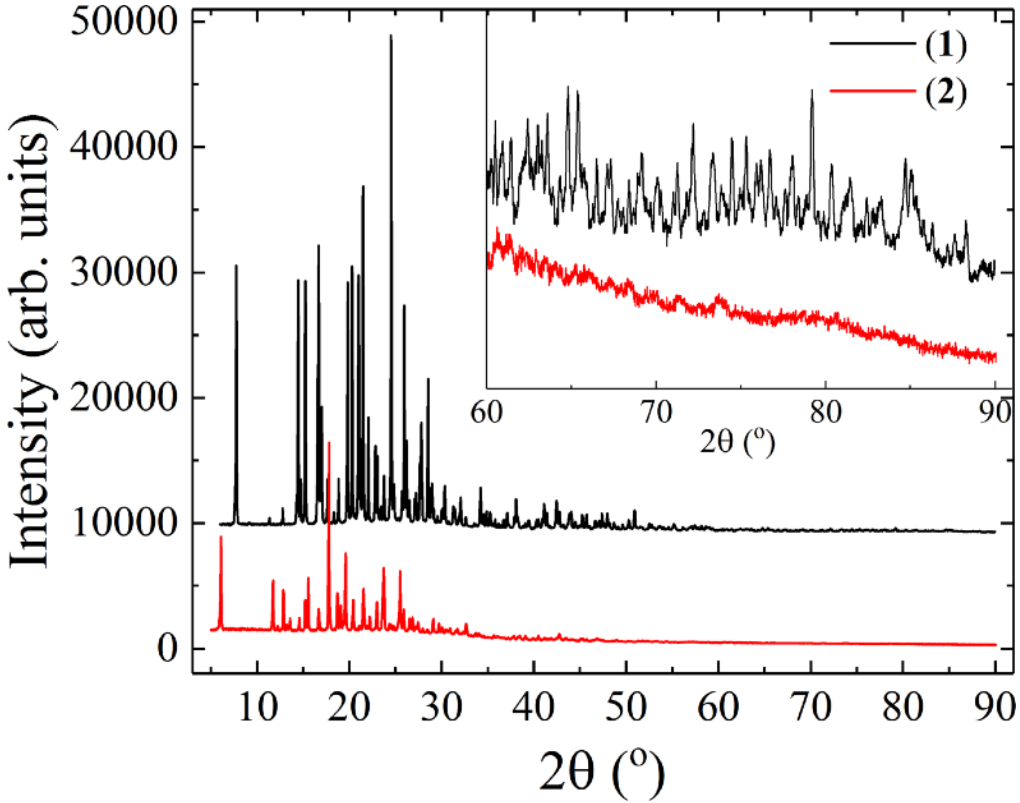
PAPER

Check for updates

Cite this: *New J. Chem.*, 2017, 41, 6464

Structural and physicochemical characterization of sulfonylhydrazone derivatives designed as hypoglycemic agents†

Amanda L. Ibiapino,[a] Laysa P. de Figueiredo,[a] Lídia M. Lima,[bc] Eliezer J. Barreiro,[bc] Francesco Punzo[d] and Fabio F. Ferreira*[a]



(1) - LASSBio-1773
(2) - LASSBio-1774

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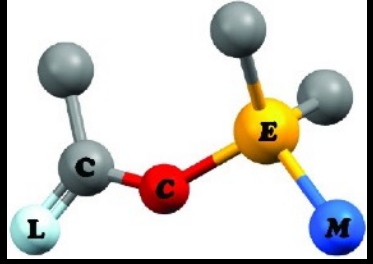
LASSBio-1773

Structure determination



1) Indexing procedure

✓ ***Crystal system***

Orthorhombic

✓ ***unit cell parameters***

a = 22.7330(6) Å;

b = 10.6880(4) Å;

c = 7.2519(2) Å;

✓ ***unit cell volume***

V = 1762.32(1) Å^3

✓ ***formula unit(s) per unit cell***

Z = 4

Z' = 1

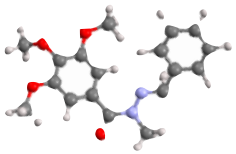
2) Space group determination

✓ ***space group***

$P2_12_12_1$

3) Structure determination

simulated annealing



4) Rietveld refinement

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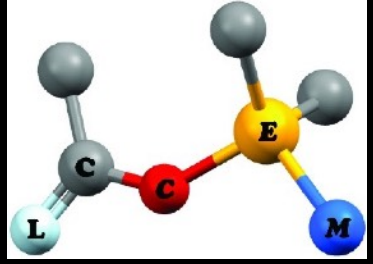
Structure determination



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1) Indexing procedure

✓ ***Crystal system***

Orthorhombic (*Pbca*)

✓ ***unit cell parameters***

a = **28.9007(11) Å;**

b = **15.0348(4) Å;**

c = **9.1482(2) Å;**

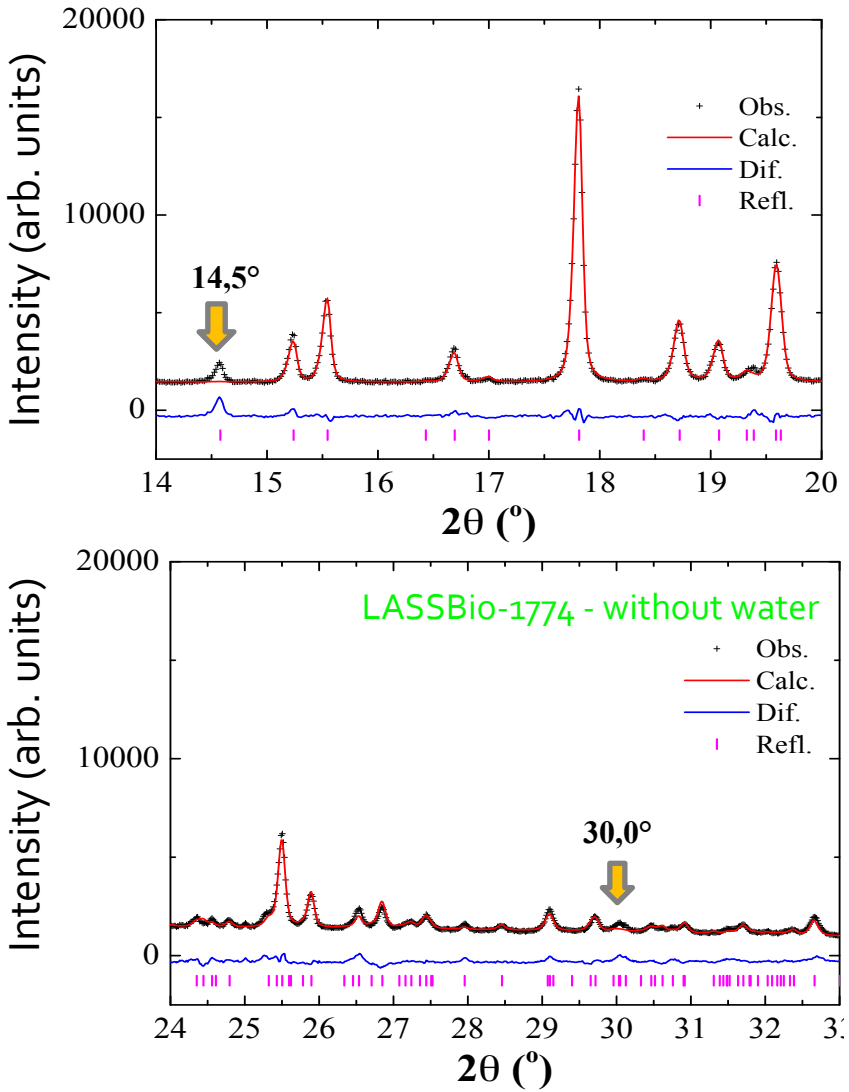
✓ ***unit cell volume***

V = **3975.1(2) Å³**

✓ ***formula unit(s) per unit cell***

Z = **8**

Z' = **1**



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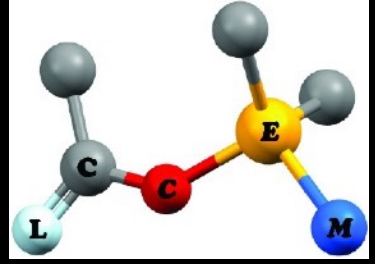
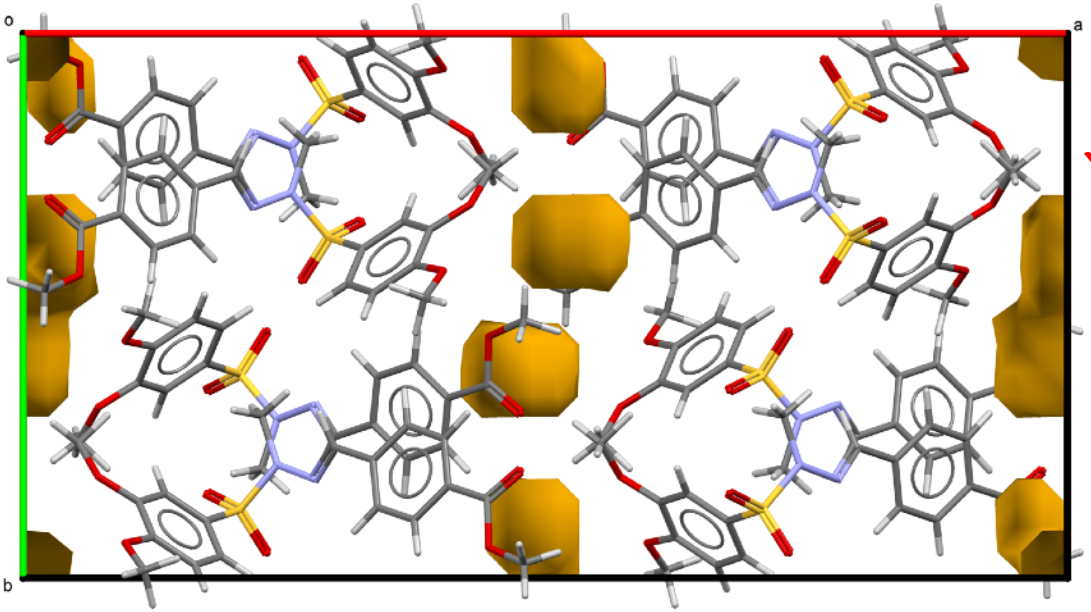
Voids





*Packing along the **c**-axis*

✓ **"Voids" within the unit cell**

Volume: ~ 179.4 Å^3

Volume: water (H_2O)

Volume: ethanol (C_2H_6O)

$\bar{v}_i^H = 5.08$ Å^3, $\bar{v}_i^O = 11.39$ Å^3 and $\bar{v}_i^C = 13.87$ Å^3

Hoffmann, D. W. M., Acta Cryst. (2002). B57, 489-493

Volume: ~22 Å^3

8 *voids*: ~176 Å^3

Volume: ~70 Å^3

8 *voids*: ~ 560 Å^3

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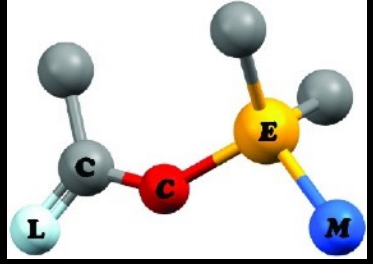
LASSBio-1774

Structure re-determination



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1) Indexing procedure

✓ ***Crystal system***

Orthorhombic

✓ ***unit cell parameters***

a = **28.9030(10) Å**;

b = **15.0357(3) Å**;

c = **9.1476(1) Å**;

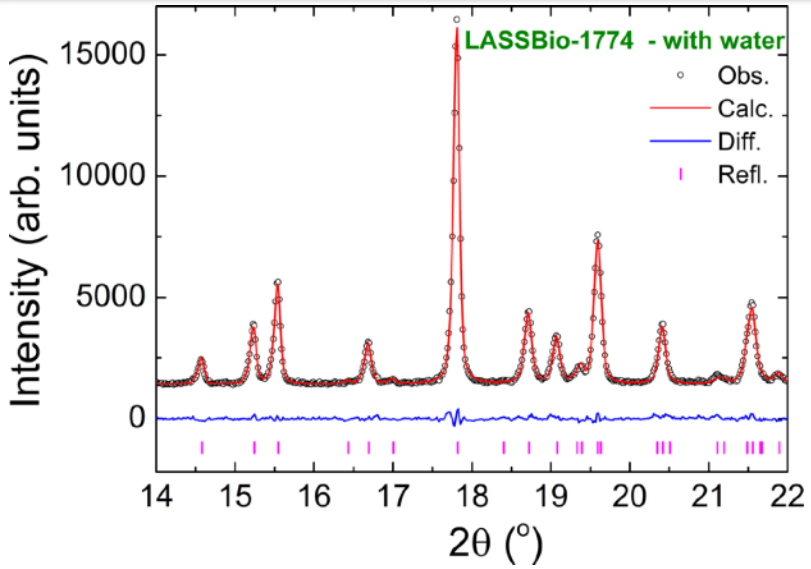
✓ ***unit cell volume***

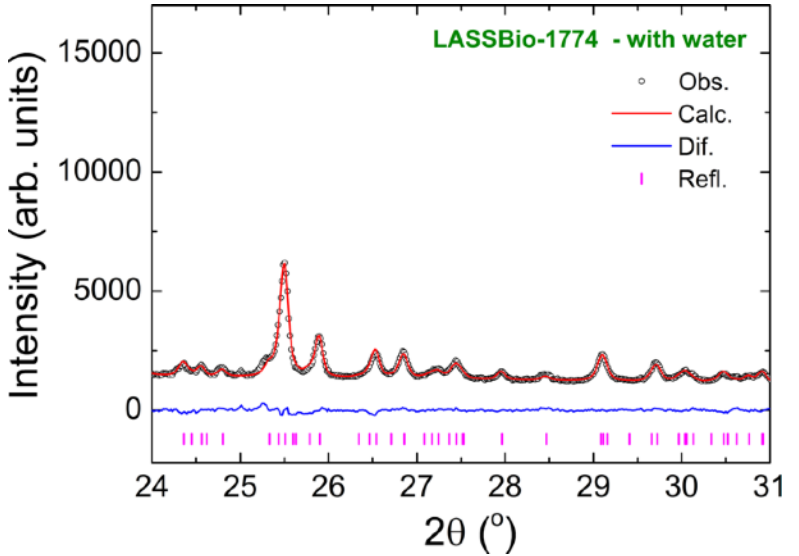
V = **3975.40(8) Å^3**

✓ ***formula unit(s) per unit cell***

Z = **8**

Z' = **1**





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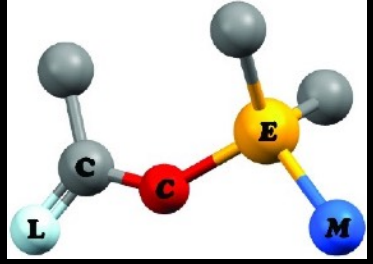
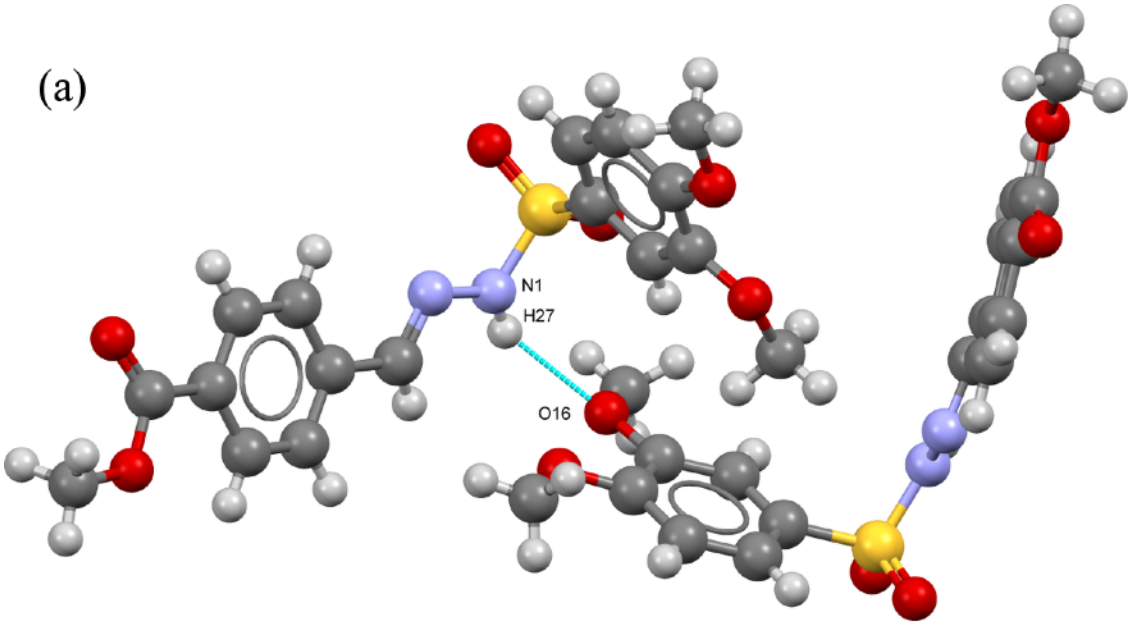
LASSBio-1773 and LASSBio-1774

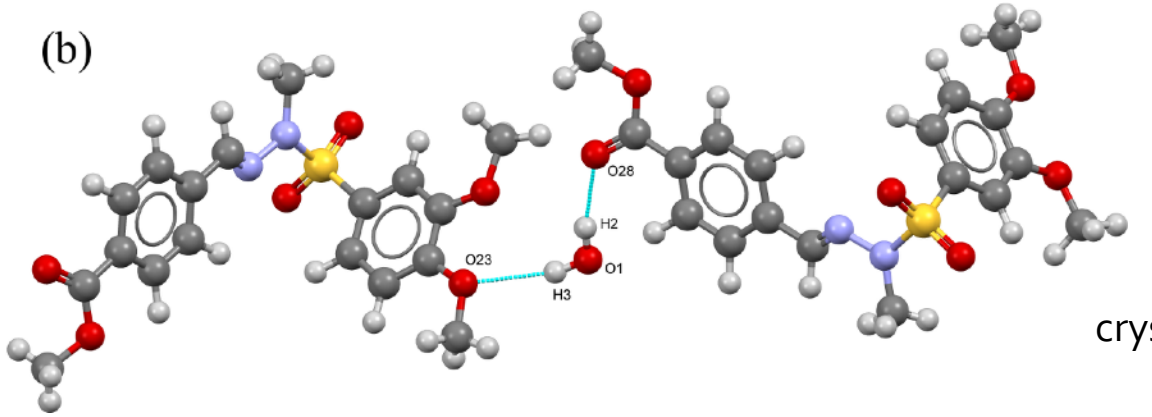
Hydrogen interactions





folded shape with an apical polar part and two mainly apolar wings

crystallized in water



mainly a non-polar landscape has been transformed in a clearly polar one in all the considered crystal faces

crystallized in a mixture of ethanol/water

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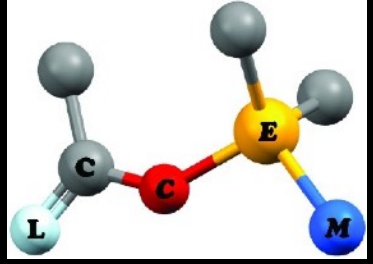
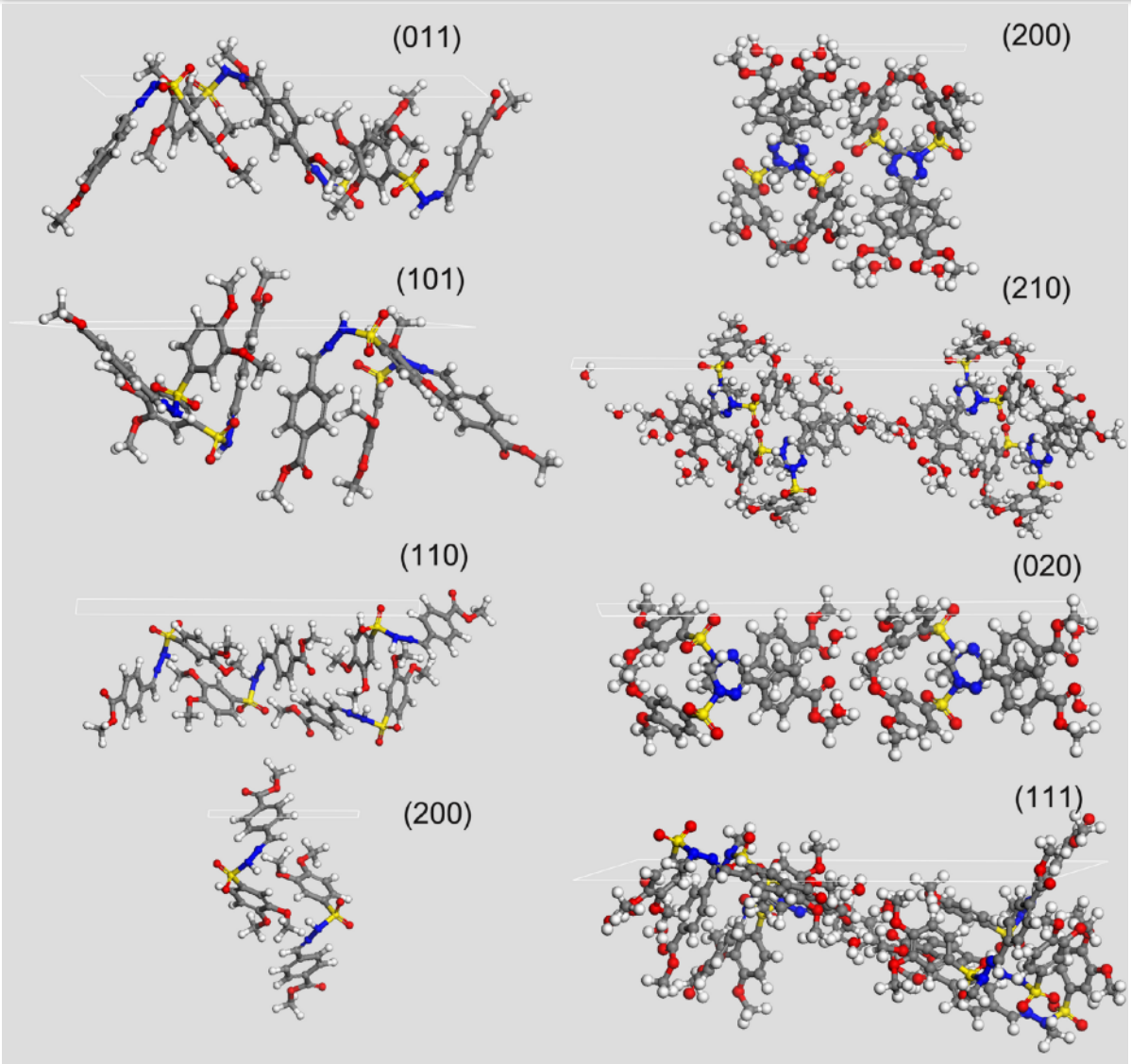
Morphology prediction

LASSBio-1773 and LASSBio-1774





Growth morphology method

The growth morphology (GM) method can predict the shape of a crystal more accurately than the BFDH method because it takes the energetics of the system into account

The crystallization energy, E_{cr}, is defined as:

$$E_{cr} = E_{slice} + E_{att}$$

E_{slice} = energy resulting from the lateral interaction of each formula unit within a slice

E_{att} = energy released as a consequence of the vertical interaction of the formula unit with an underlying slice

$$G_r \propto E_{att}$$

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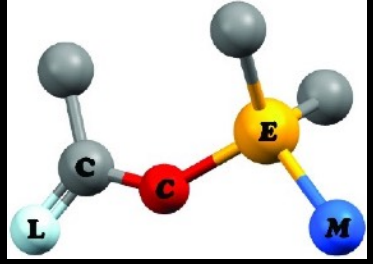
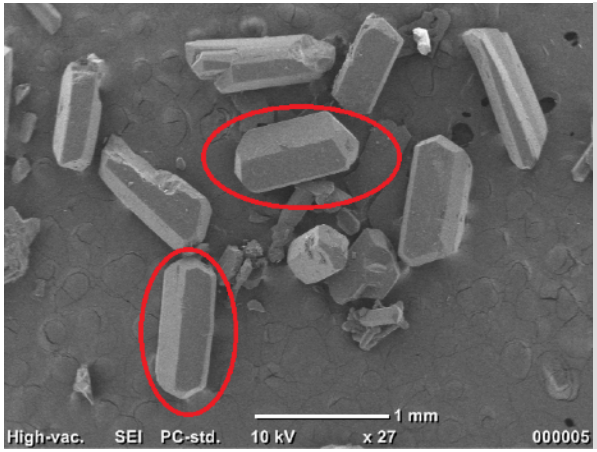
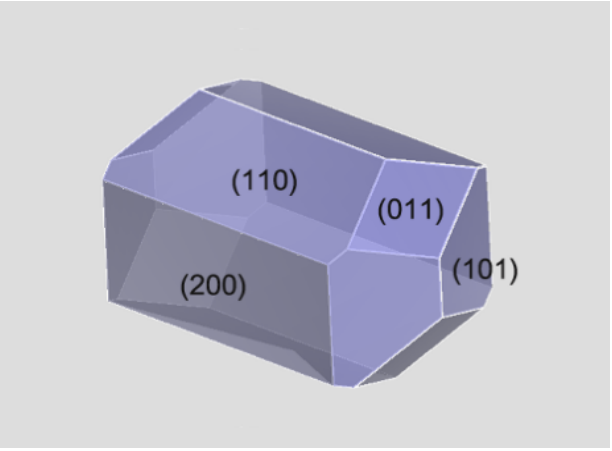
Morphology prediction

LASSBio-1773



SEM *Simulation (Growth morphology)*





Comparison between the SEM image and morphology prediction

hkl	Multiplicity	*dhkl* (Å)	E_{att}(Total) (kcal mol^{-1})	Total Facet Area (%)
(110)	4	9.6624	-120.7005	43.74
(200)	2	11.3564	-126.2876	24.32
(101)	4	5.9917	-180.9218	18.57
(011)	4	6.8973	-177.3885	13.37

Morphologically Important (MI) faces

% depends on d_{hkl} as well as on E_{att}

Potential effect of solvents in the growth mechanism of crystal faces

(200) E_{att} = *-126.2876 kcal.mol^{-1}*

(101) E_{att} = *-180.9218 kcal.mol^{-1}*

(011) E_{att} = *-177.3885 kcal.mol^{-1}*

apolar

(110) E_{att} = *-120.7005 kcal.mol^{-1}*

polar

Growth of face (110)

Strategy: use of less polar solvents, with water excess, during the crystallization of **LASSBio-1773**

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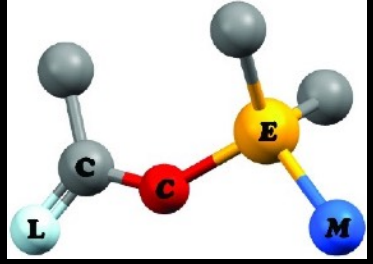
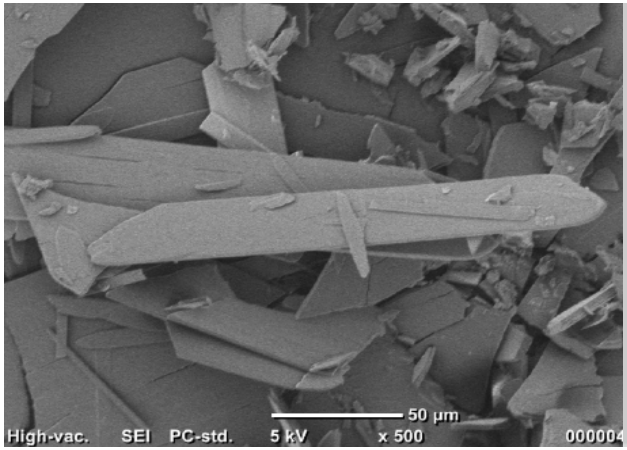
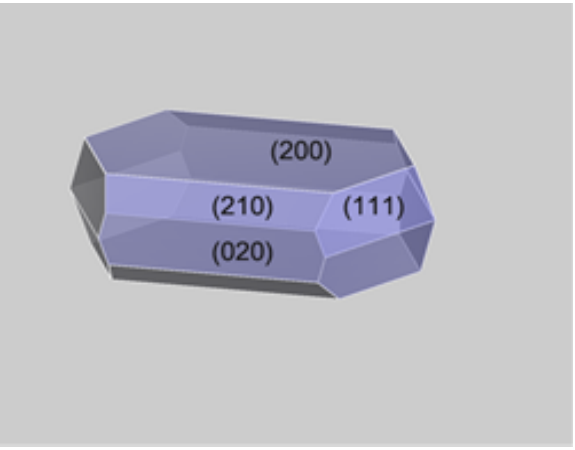
Morphology prediction

LASSBio-1774



SEM *Simulation (Growth morphology)*





Comparison between the SEM image and morphology prediction

hkl	Multiplicity	*dhkl* (Å)	E_{att}(Total) (kcal mol^{-1})	Total Facet Area (%)
(200)	2	14.4516	-87.4231	44.39
(210)	4	10.4192	-154.3096	17.12
(20)	2	7.5179	-178.4827	11.19
(111)	8	7.5441	-235.5099	27.30

Potential effect of solvents in the growth mechanism of crystal faces

(200) E_{att}= *-87.4231 kcal.mol^{-1}*

(210) E_{att}= *-154.3096 kcal.mol^{-1}*

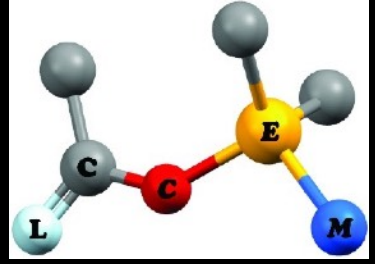
(020) E_{att}= *-178.4827 kcal.mol^{-1}*

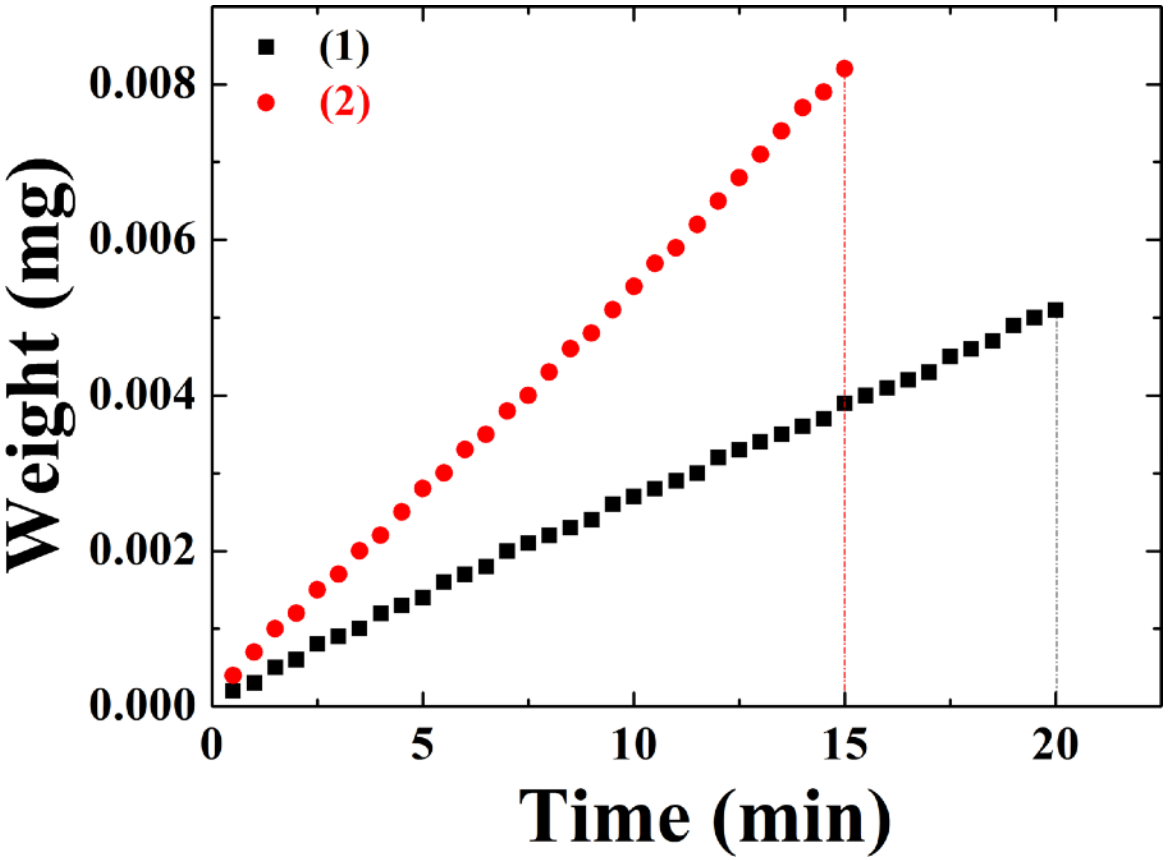
(111) E_{att}= *-235.5099 kcal.mol^{-1}*

polar

Favors the solubility in polar solvents

Intrinsic dissolution rate (IDR)





Comparison between the dissolution profiles

**Experimental conditions: dissolution medium - phosphate buffer (pH = 6.8) at 37°C*

LASSBio-1773

IDR : 6.4(6) $\mu g \cdot cm^{-2} \cdot min^{-1}$

LASSBio-1774

IDR: 15.9(6) $\mu g \cdot cm^{-2} \cdot min^{-1}$

Poor solubility

values below 100 $\mu g \cdot cm^{-2} \cdot min^{-1}$

New J. Chem., 2017, 41, 6464--6474

LASSBio-1755

Synthesis procedure

Journal of Molecular Structure 1146 (2017) 735–743

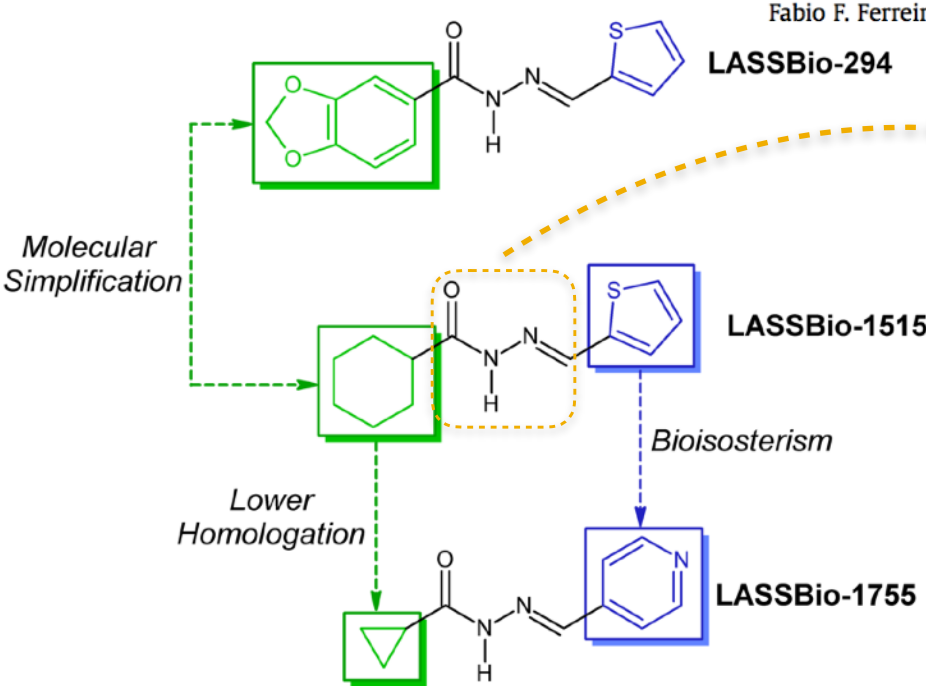
Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

A combined experimental and *in silico* characterization to highlight additional structural features and properties of a potentially new drug

Isadora T.S. Bastos [a], Fanny N. Costa [b], Tiago F. Silva [c], Eliezer J. Barreiro [c, d], Lídia M. Lima [c, d], Delson Braz [e], Giuseppe M. Lombardo [f], Francesco Punzo [f], Fabio F. Ferreira [b, *], Regina C. Barroso [a]



N-acylhydrazone privileged structure

J. Mol. Struct. 1146 (2017) 735 - 743

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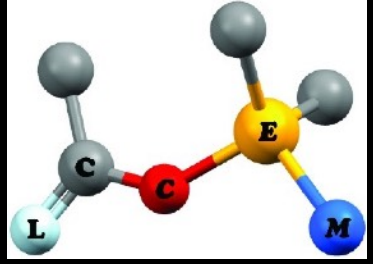
LASSBio-1755

Structure determination



1) Indexing procedure

✓ ***Crystal system***

Triclinic

✓ ***unit cell parameters***

a = 4.8594(2) Å;
b = 9.3162(5) Å;
c = 11.3701(5) Å;
α = 73.400(4)°;
β = 78.088(3)°;
γ = 82.640(4)°

✓ ***unit cell volume***

V = 479.70(4) Å^3

✓ ***formula unit(s) per unit cell***

Z = 2
Z' = 1

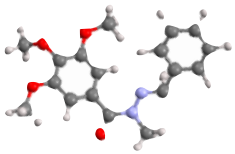
2) Space group determination

✓ ***space group***

$P\bar{1}$

3) Structure determination

simulated annealing



4) Rietveld refinement

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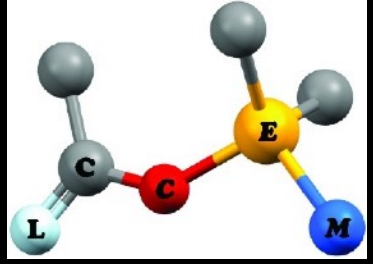
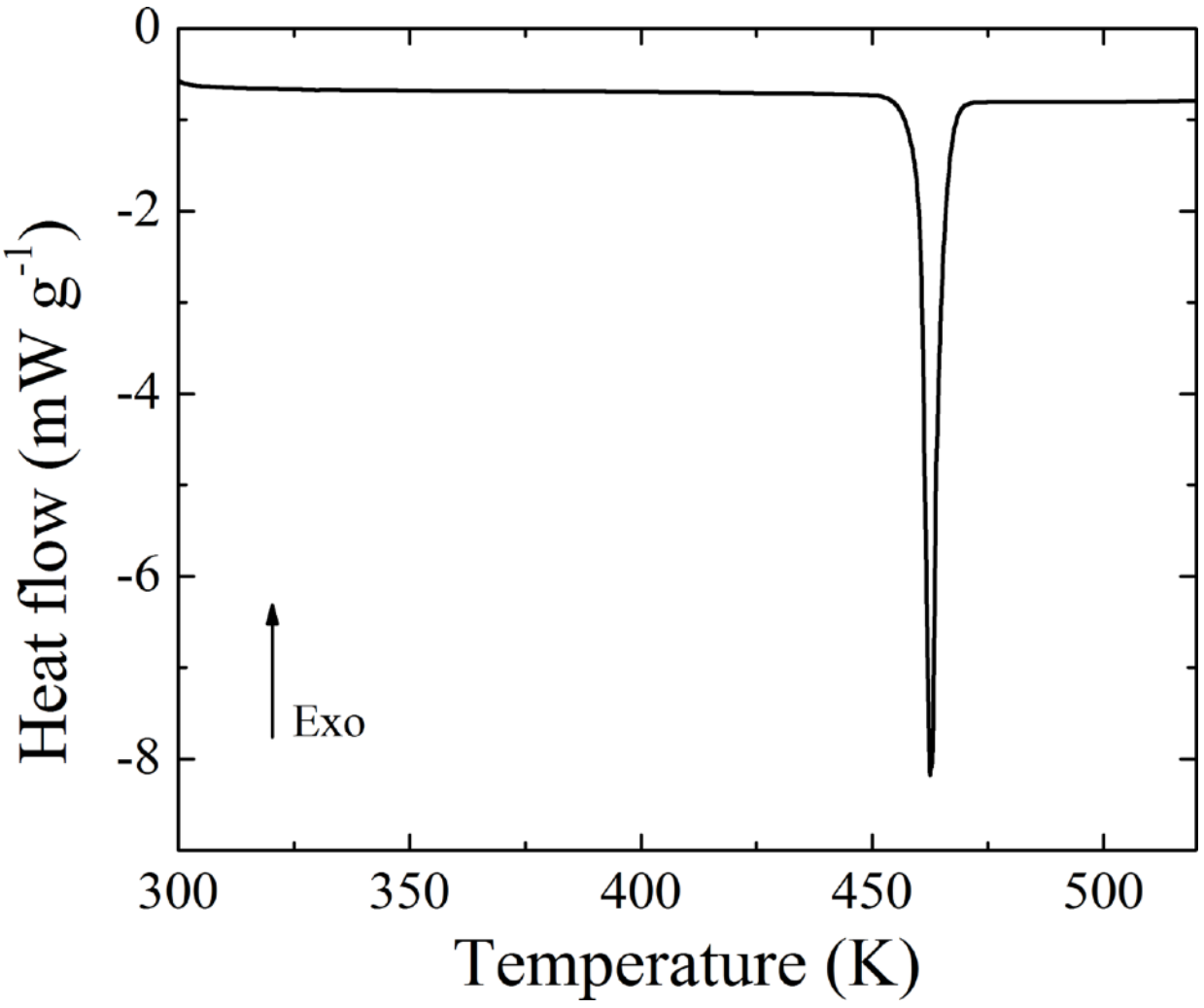
DSC scan





well-defined melting behavior with a sharp minimum

melting temperature (460.81 K)

high purity and a relative good stability

enthalpy of fusion ΔH_f = 30.43 kJ mol^{-1}

No tendency for polymorph formation

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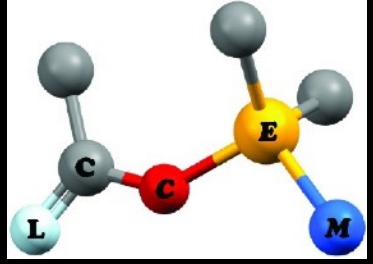
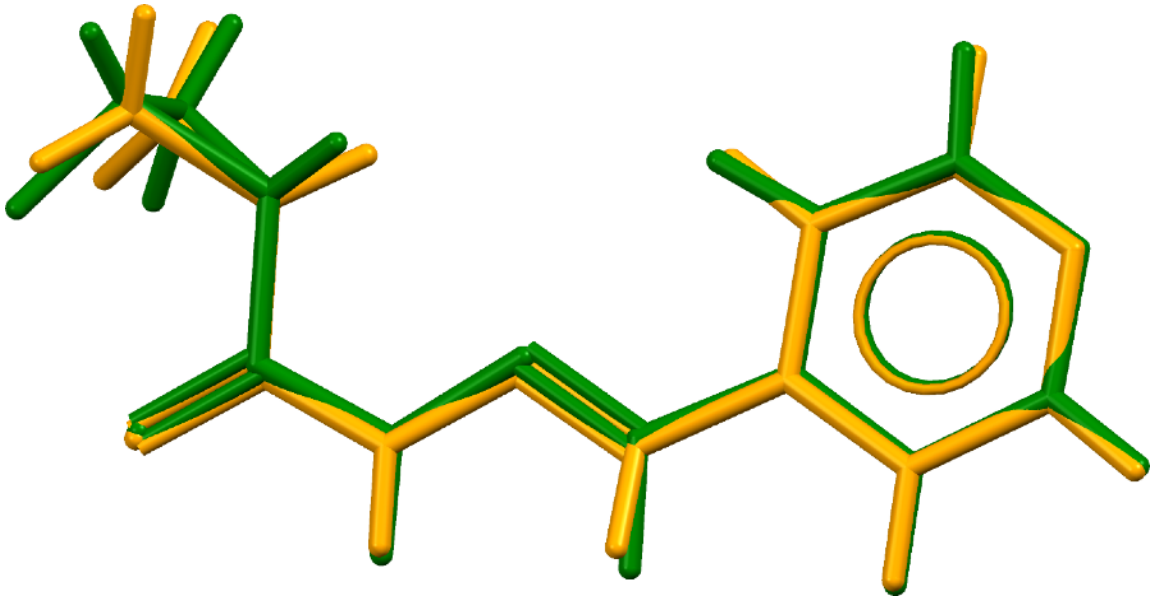
X-ray powder diffraction

Overlay of structures





RMS = 0.0189
MD

RMS = 0.0952
XRPD

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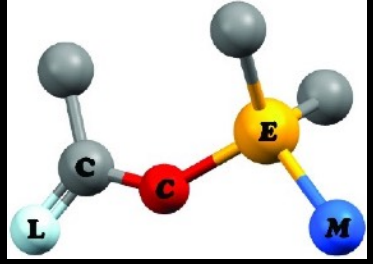
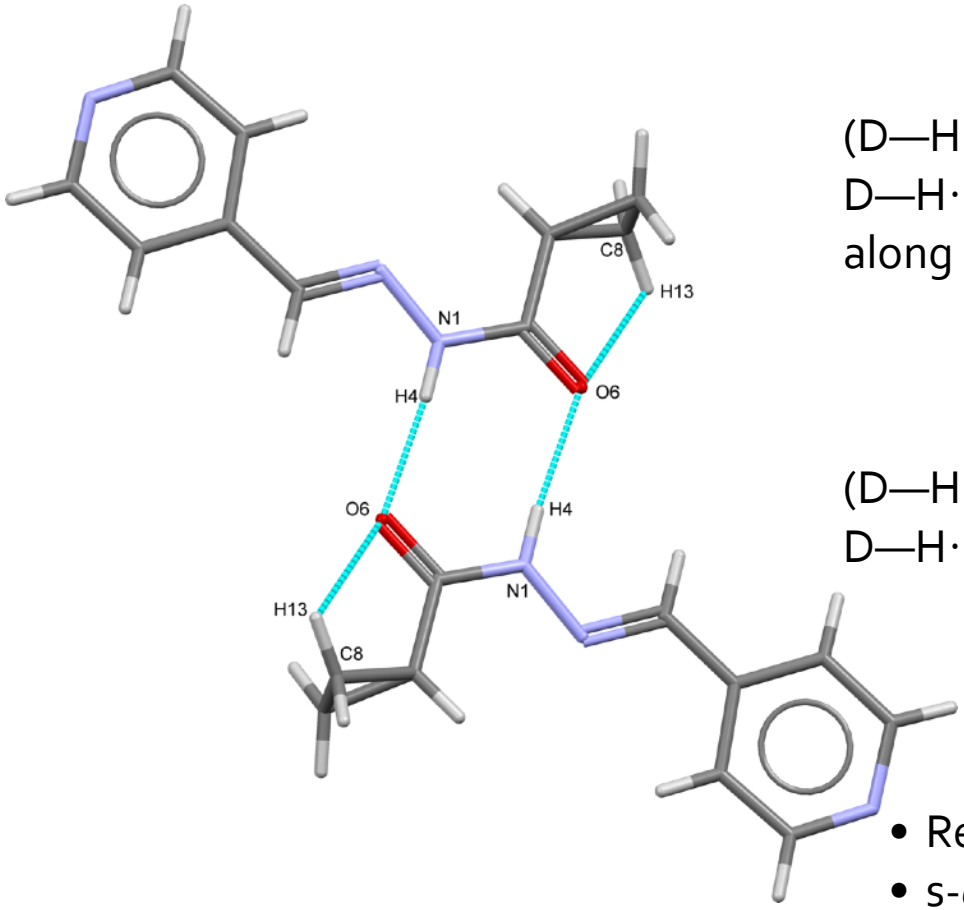
Hydrogen interactions





Intramolecular bond

N(1)—H(4)···O(6)

(D—H = 0.86(2) Å, H···A = 1.97(2) Å, D···A = 2.78(2) Å
D—H···A = 156.4(19)°)
along x, 1 y, 1 z

weak intermolecular bond

C(8)—H(13)···O(6)

(D—H = 0.96(3) Å, H···A = 2.42(2) Å, D···A = 2.83(3) Å
D—H···A = 105.8(16)°)

- Relative configuration *E* of the imine double bond
- s-*cis* conformation of the amide function of the *N*-acylhydrazone compound

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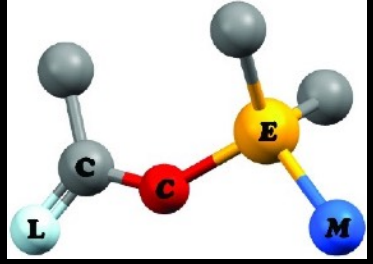
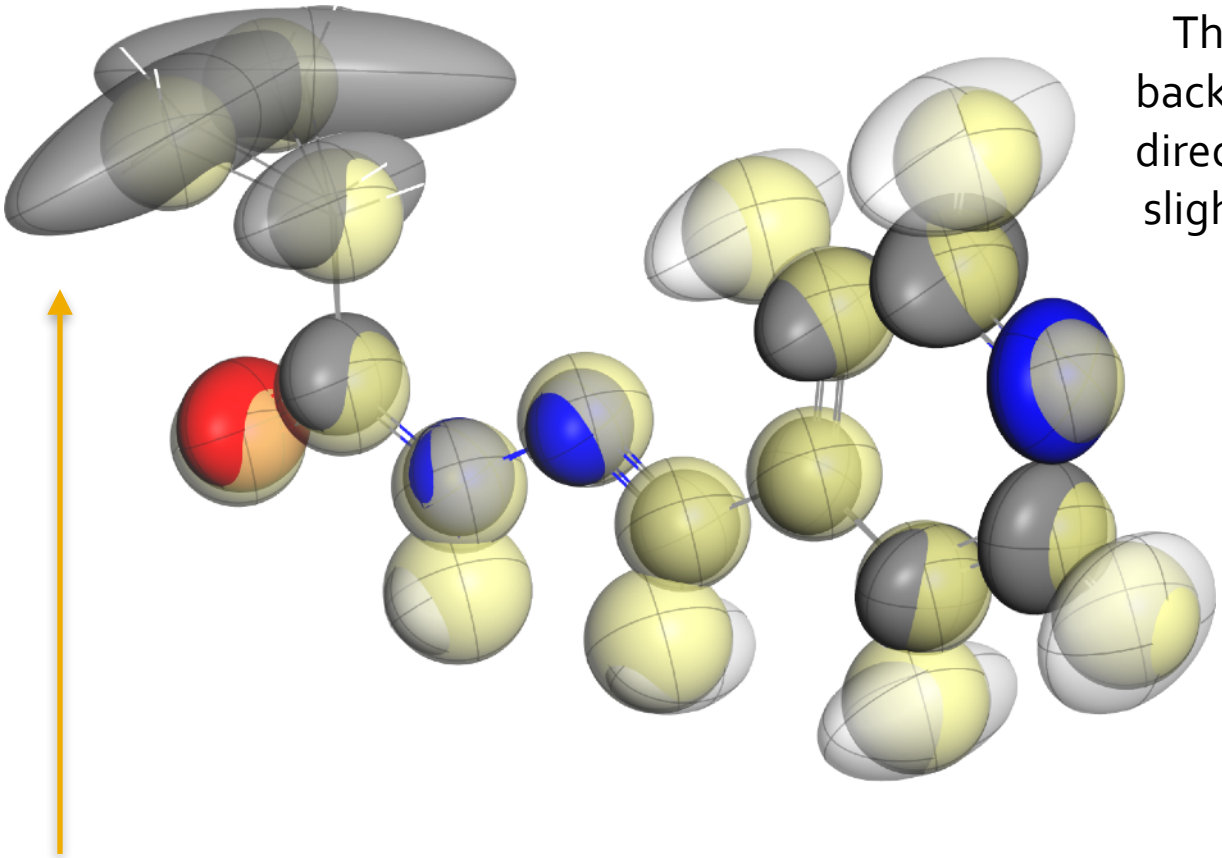
ADPs calculation





The adp motions in the molecule backbone points mostly in the same direction, while the two rings show a slightly different movement around their equilibrium

cycloalkylic moiety does not show a fairly good overall estimation of the app volume

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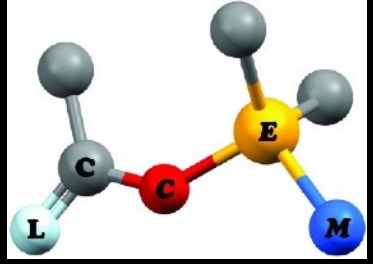
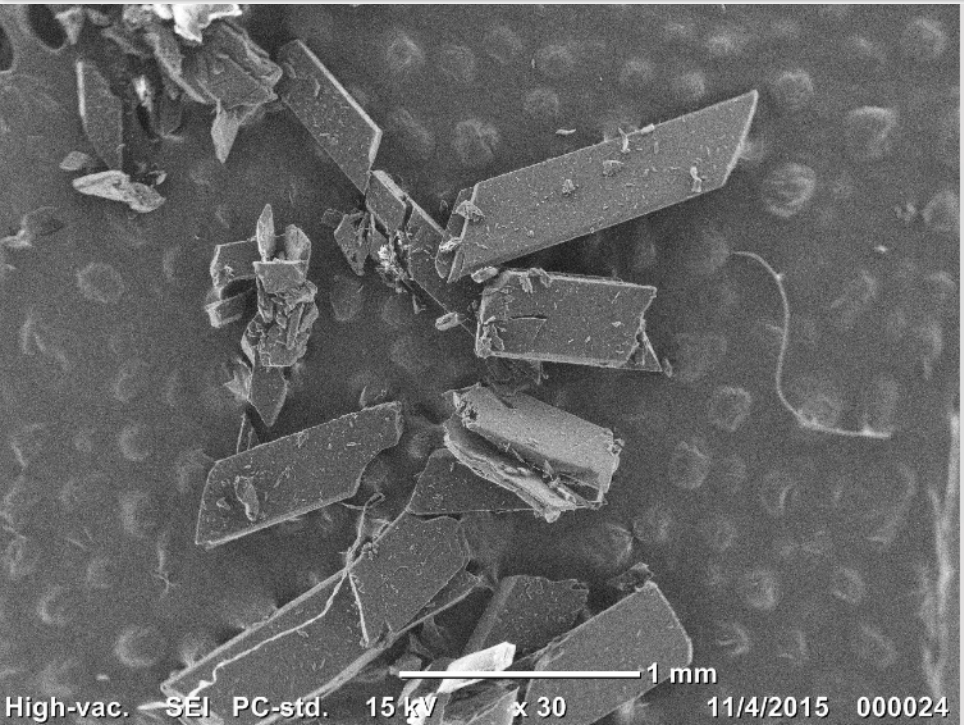
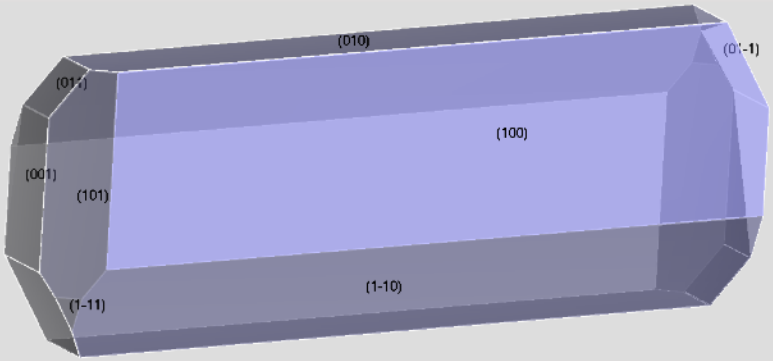
Morphology prediction







- Very good agreement between the experimentally inferred SEM images and the computationally derived crystal habit

- Growth rate of the crystal face is inversely proportional to the interplanar spacing d_{hkl}

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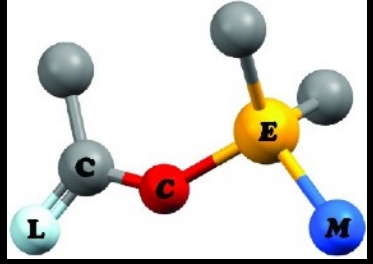
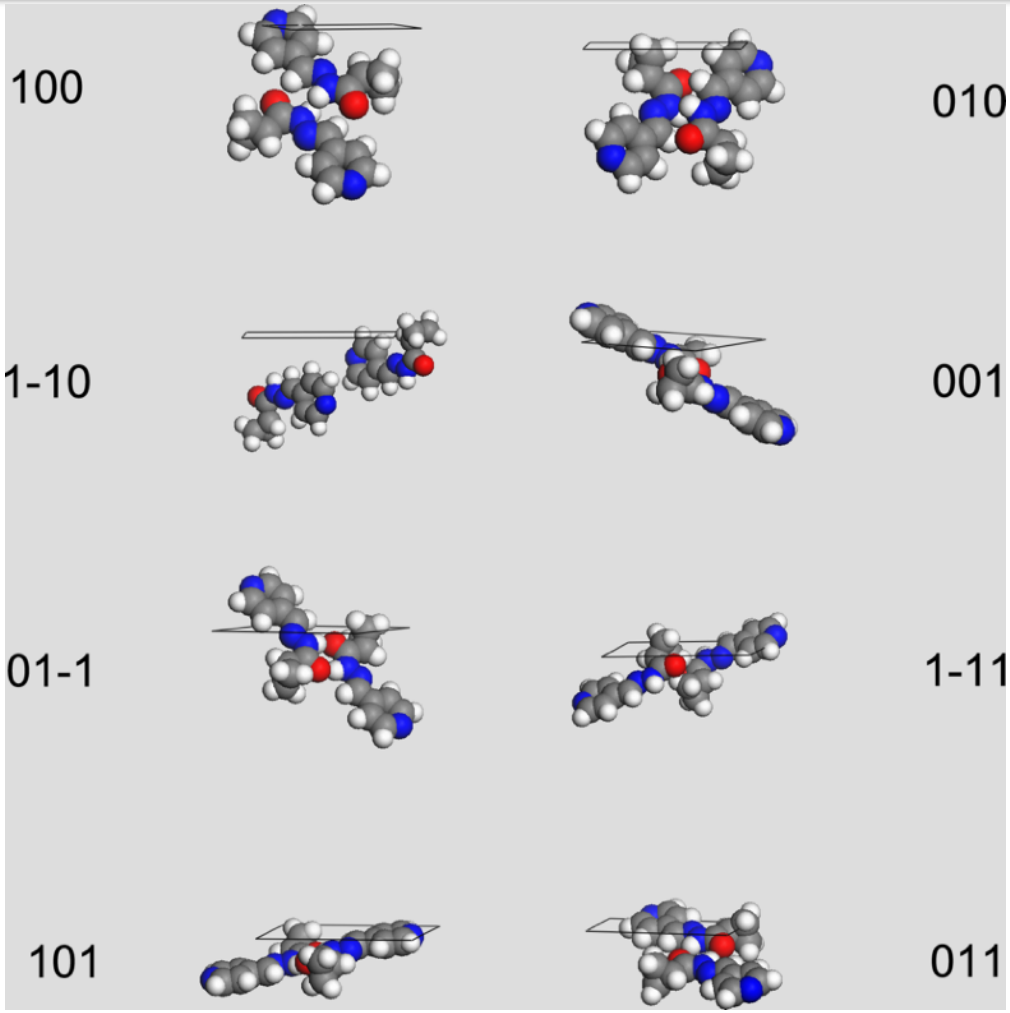
Morphologically important faces





Morphologically important (MI) faces have the largest d_{hkl} values

Use of the attachment energy (E_{att})

hkl	Multiplicity	d_{hkl} (Å)	E_{att} (Total) (kcal mol^{-1})	Total Facet Area (%)
(001)	2	10.6842	-16.2911	29.71
(010)	2	8.9036	-15.1595	29.24
(011)	2	7.9662	-16.7300	20.17
(101)	2	4.6534	-35.9330	7.21
(111)	2	4.4862	-37.6315	4.95
(112)	2	3.9747	-36.2963	0.22
(10$\bar{2}$)	2	3.9100	-32.0516	6.27
($\bar{1}$11)	2	3.8375	-33.8921	2.23

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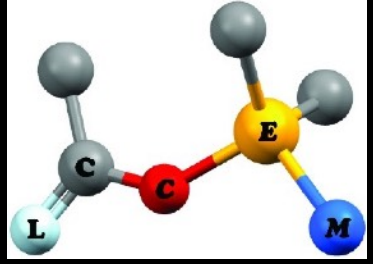
A series of different compounds

Morphologically important faces - on going work

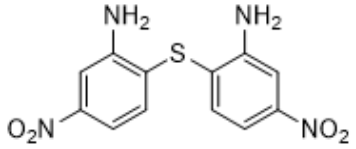


Single S bond → double single S bond

Change of functional groups from NO_2 to Cl

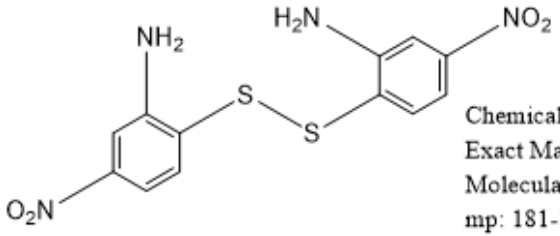
Complete change of functional groups

1D



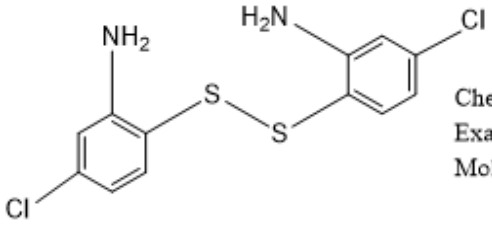
Chemical Formula: $C_{12}H_{10}N_4O_4S$
Exact Mass: 306.04
Molecular Weight: 306.30

2E



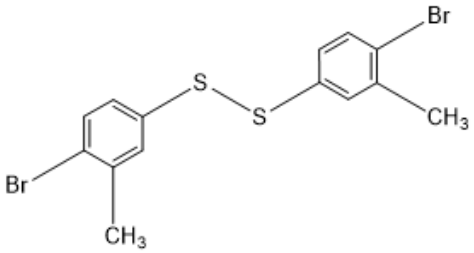
Chemical Formula: $C_{12}H_{10}N_4O_4S_2$
Exact Mass: 338.01
Molecular Weight: 338.36
mp: 181-182 (177-178)

3E



Chemical Formula: $C_{12}H_{10}Cl_2N_2S_2$
Exact Mass: 315.97
Molecular Weight: 317.26

9E



Chemical Formula: $C_{14}H_{12}Br_2S_2$
Exact Mass: 401.87
Molecular Weight: 404.18

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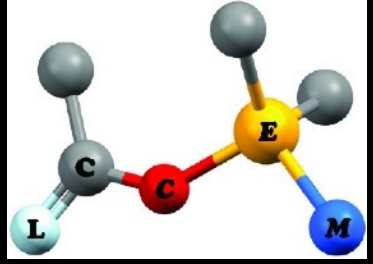
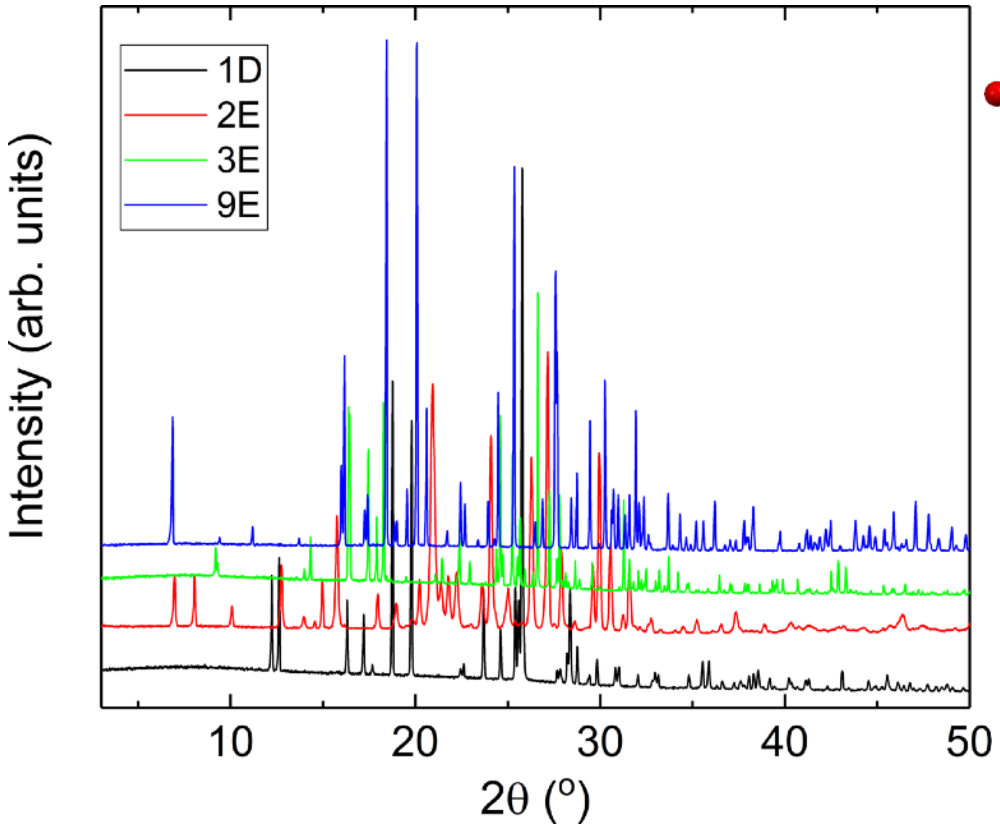
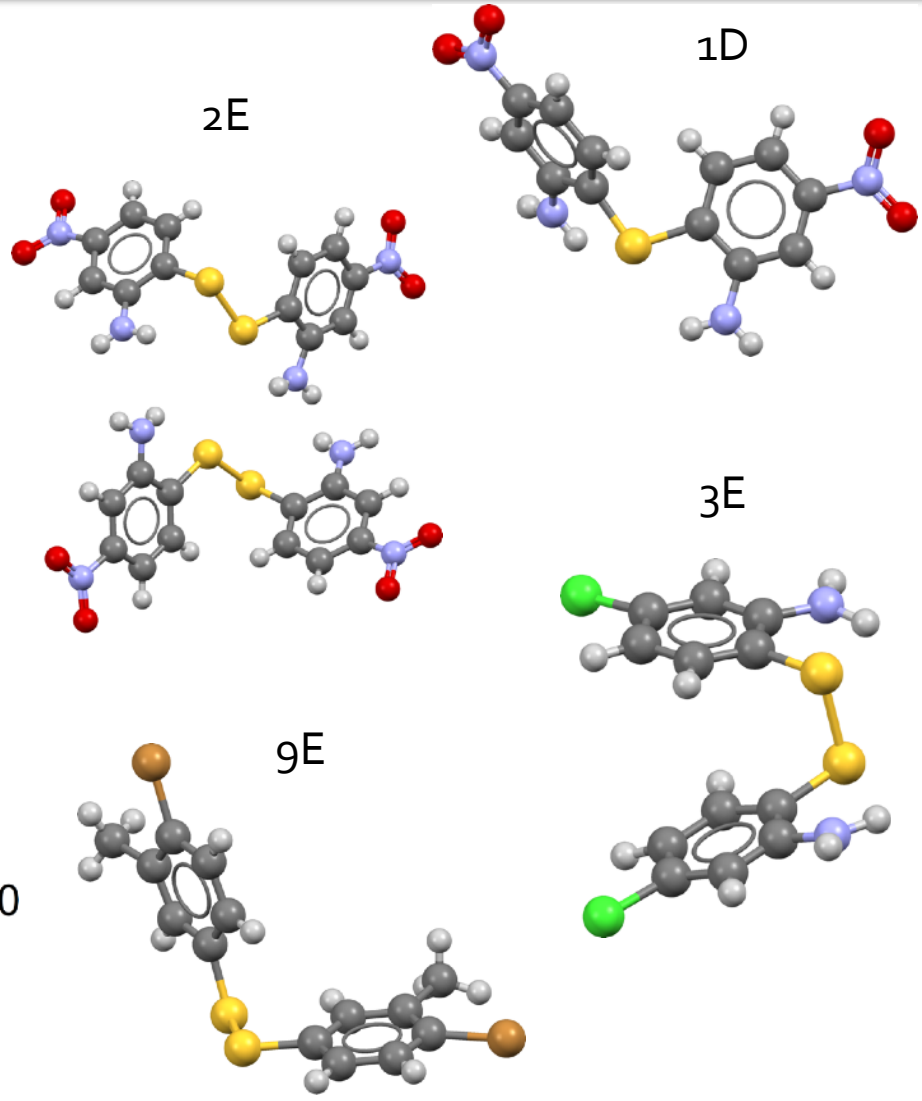
A series of different compounds

Morphologically important faces - on going work







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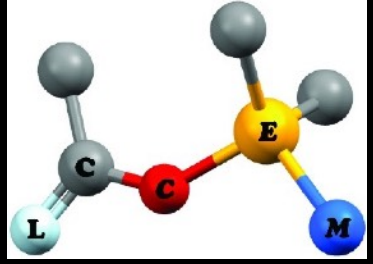
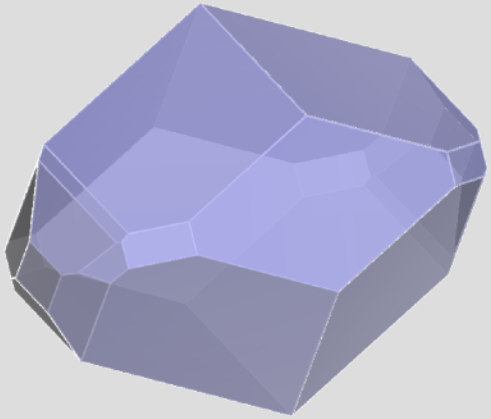
A series of different compounds

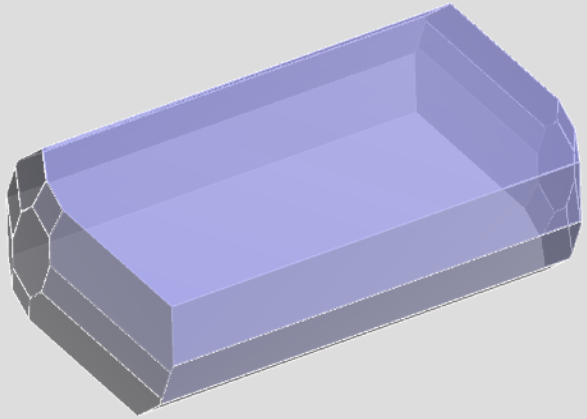
Morphologically important faces - on going work



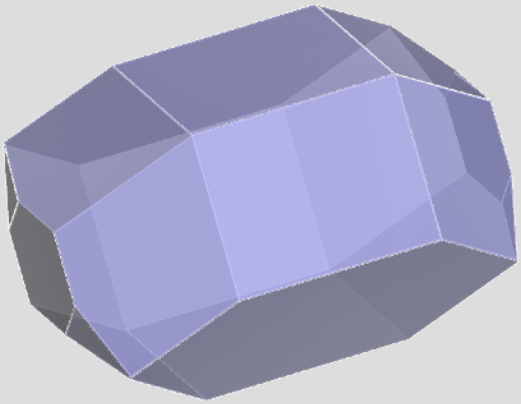
1D



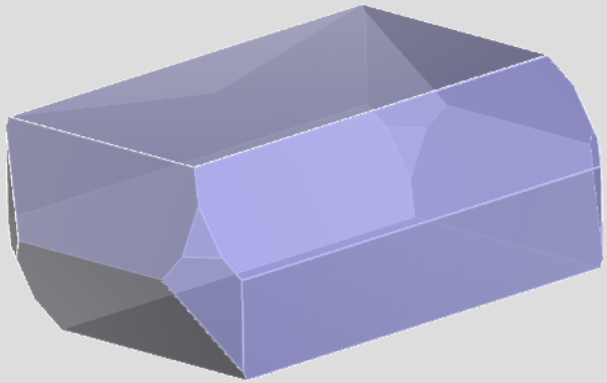
2E



3E



9E



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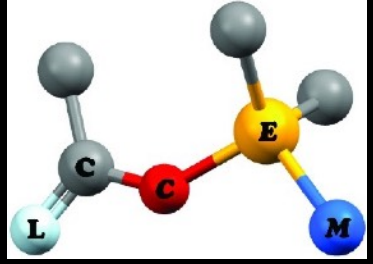
The case of spironolactone

ongoing work



- A diuretic steroidal aldosterone agonist
- Poor water solubility and dissolution rate
- Two polymorphs and 5 solvates described in the literature
  - only 4 crystal structures reported

- Recrystallized from:
- acetone: WUWROW (CSD Refcode)
- acetonitrile: KIKWUW (CSD Refcode)
- ethyl acetate (only space group and unit cell parameters reported so far)

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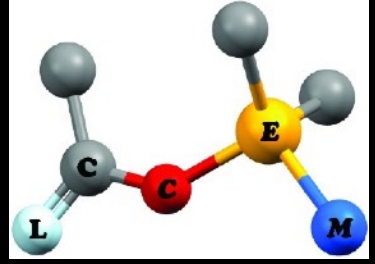
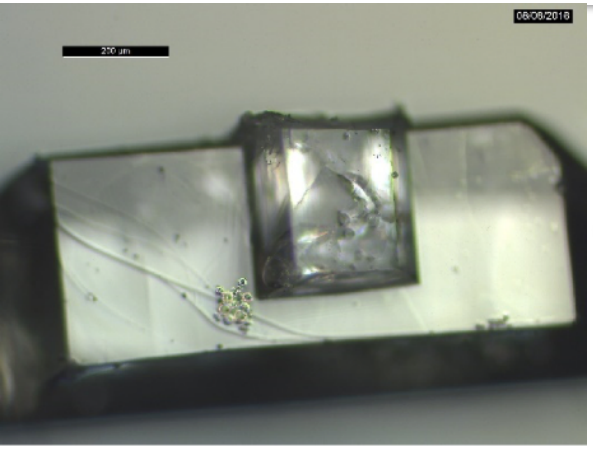
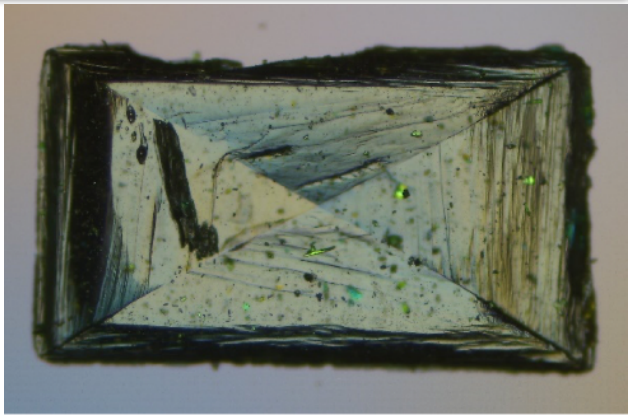
The case of spironolactone

ongoing work

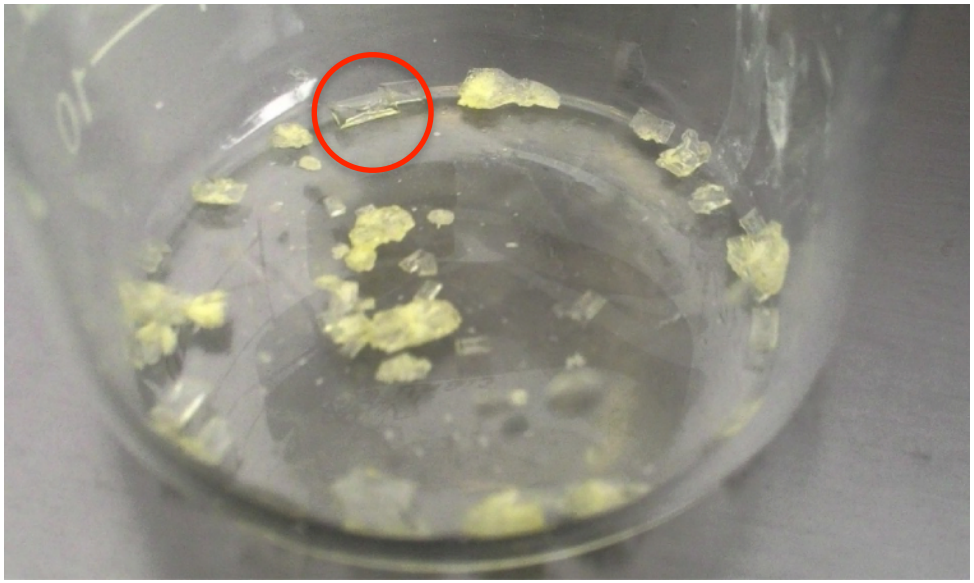




Optical microscopy



Spironolactone recrystallized in acetone



Mobile phone camera

The case of spironolactone

ongoing work

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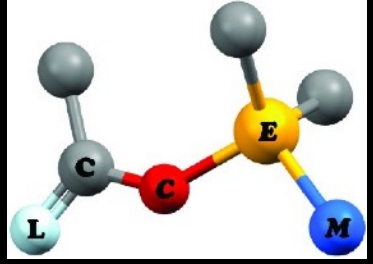
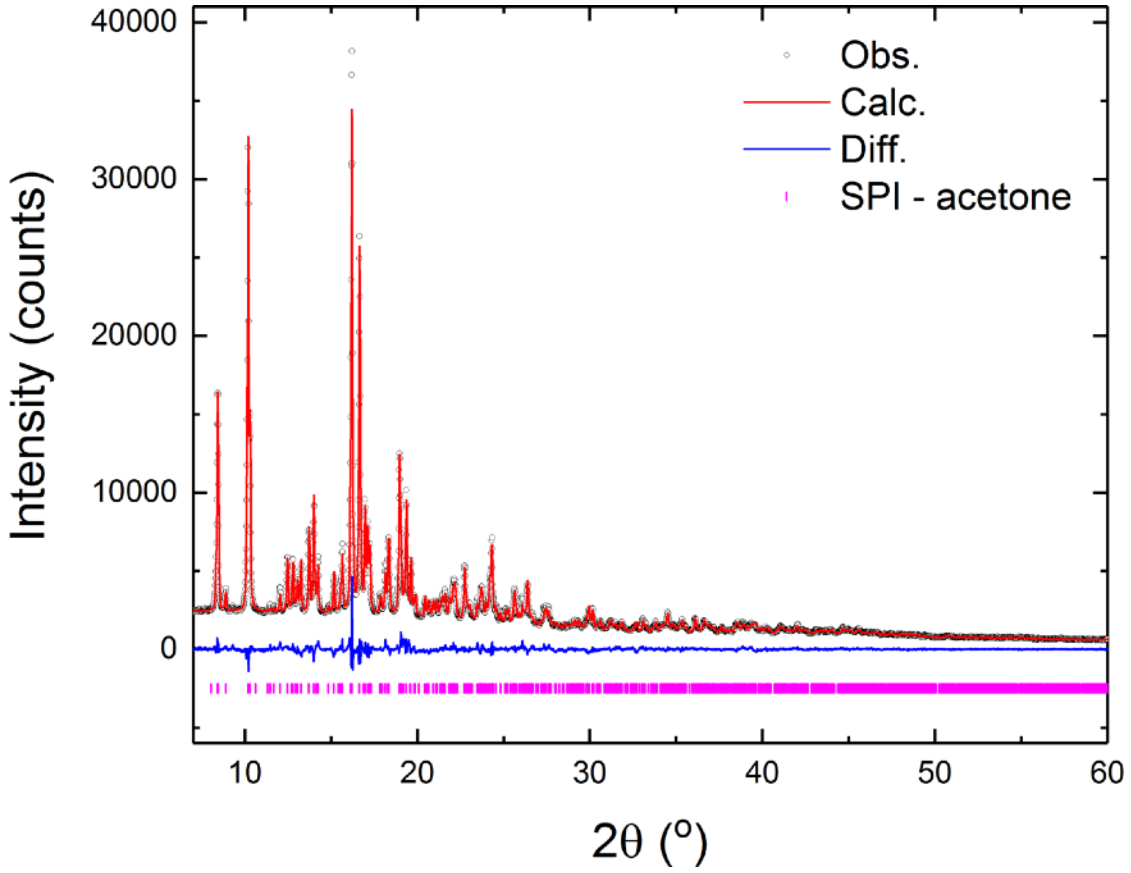


Agafonov [1] describes forms I and II → we have obtained the hydrated form, described by Takata [2]

- Structure contains disorder
- Fractional coordinates not refined

ATPRCL01	Spironolactone Form II
ATPRCL10	Spironolactone Form I
WUWROW	Spironolactone hydrate



[1] V.Agafonov, B.Legendre, N.Rodier, Acta Crystallogr.,Sect.C:Cryst.Struct.Commun. (1989), 45, 1661
[2] N.Takata, R.Takano, H.Uekusa, Y.Hayashi, K.Terada, Cryst.Growth Des. (2010), 10, 2116

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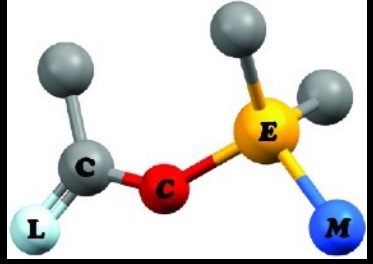
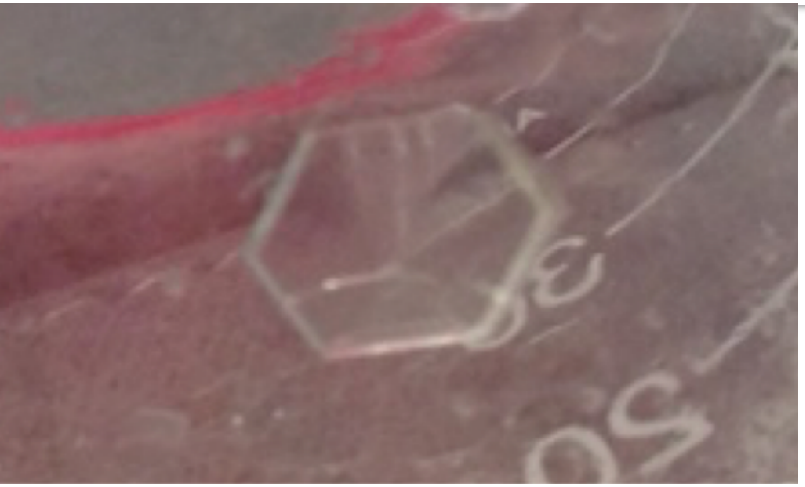
The case of spironolactone

ongoing work

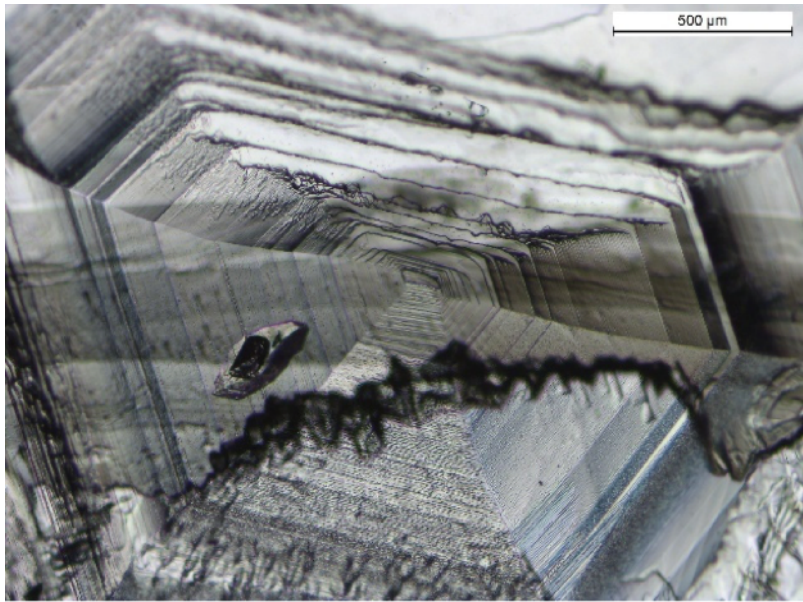




Mobile phone camera

Spironolactone recrystallized in acetonitrile

Optical microscopy



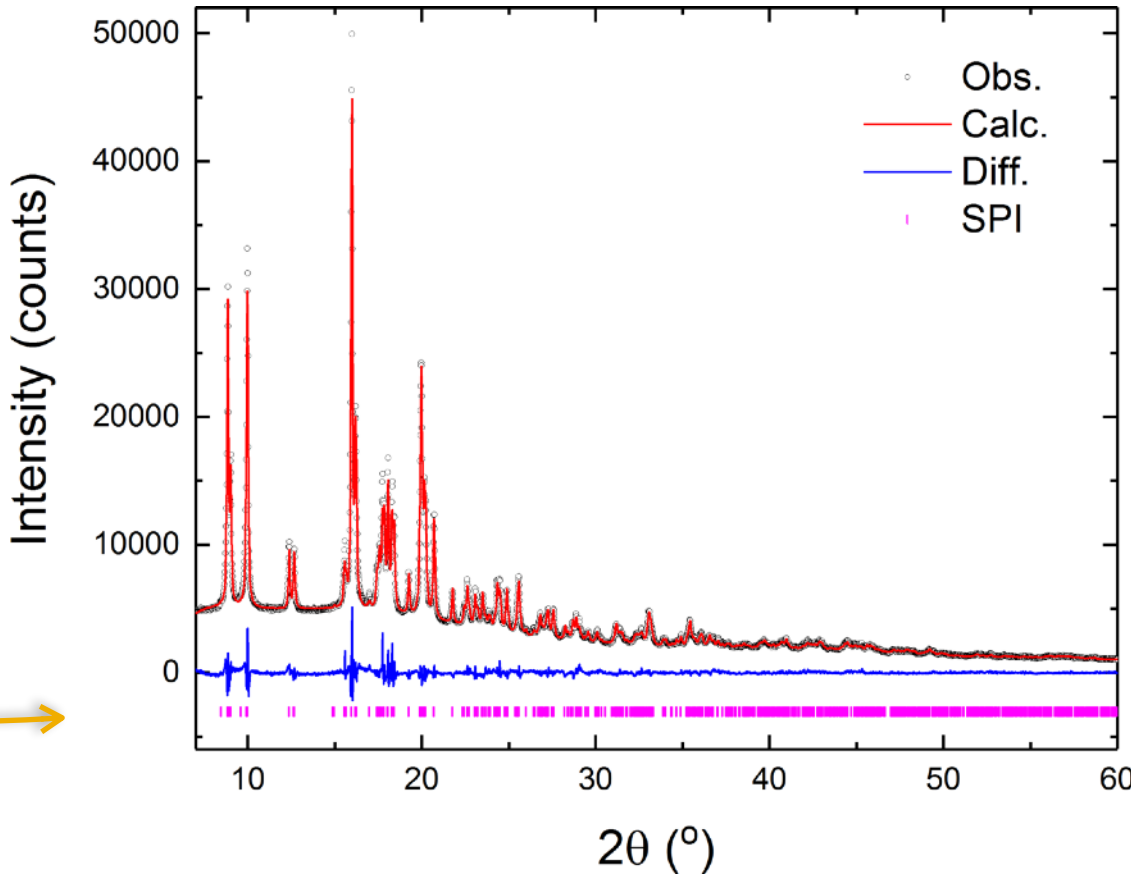
The case of spironolactone

ongoing work

Form III described by Agafonov et al. [1]

- Structure contains disorder
- Fractional coordinates not refined

KIKWUW: Spironolactone acetonitrile solvate (Form III)



[1] V.Agafonov, B.Legendre, N.Rodier, Acta Crystallogr.,Sect.C:Cryst.Struct.Commun. (1991), 47, 365

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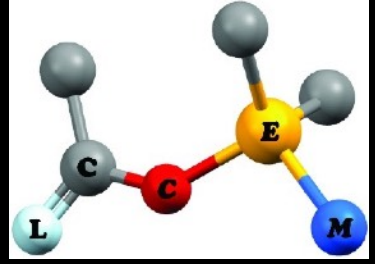
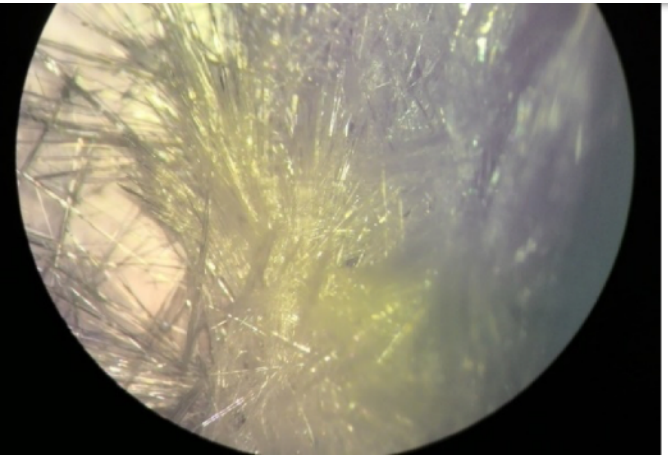
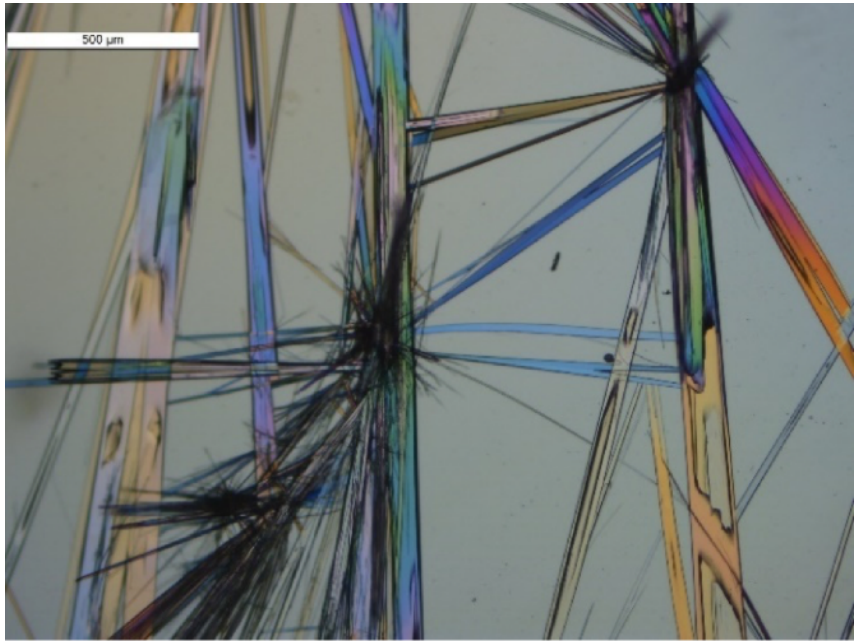
The case of spironolactone

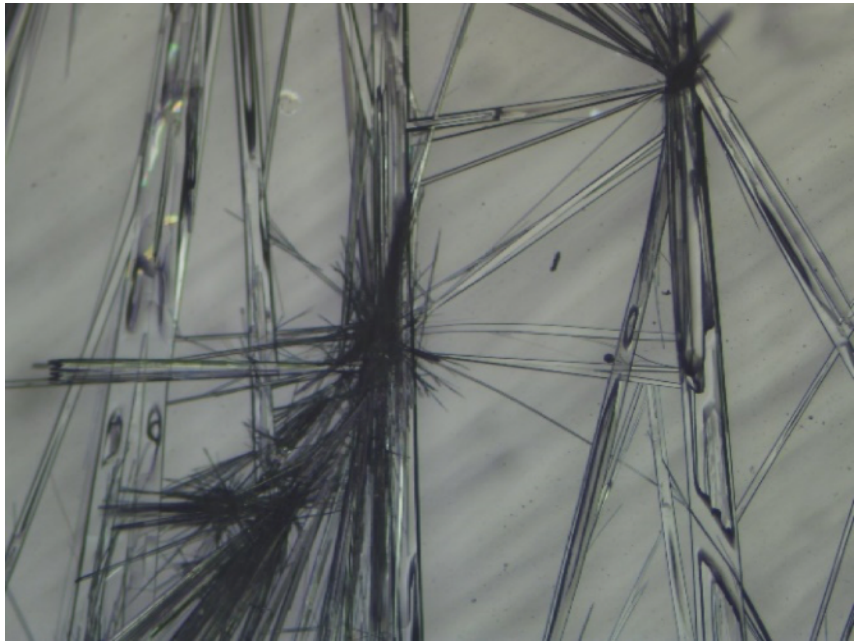
ongoing work





Spironolactone recrystallized in ethyl acetate





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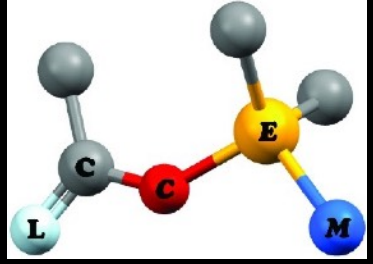
The case of spironolactone

ongoing work



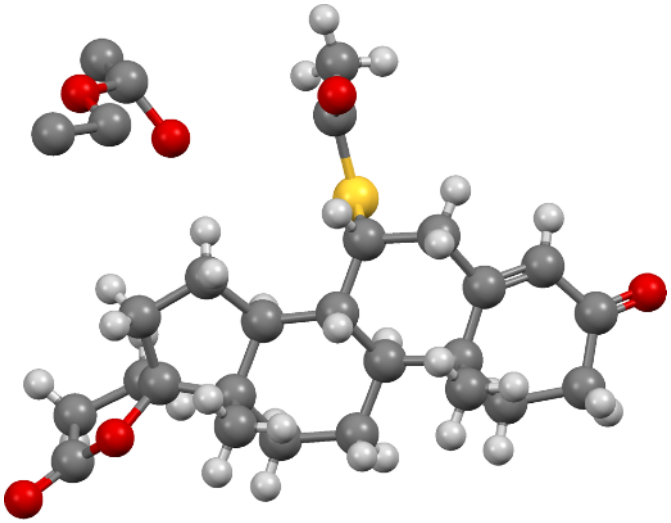
Hydrated form described by Takata [1]

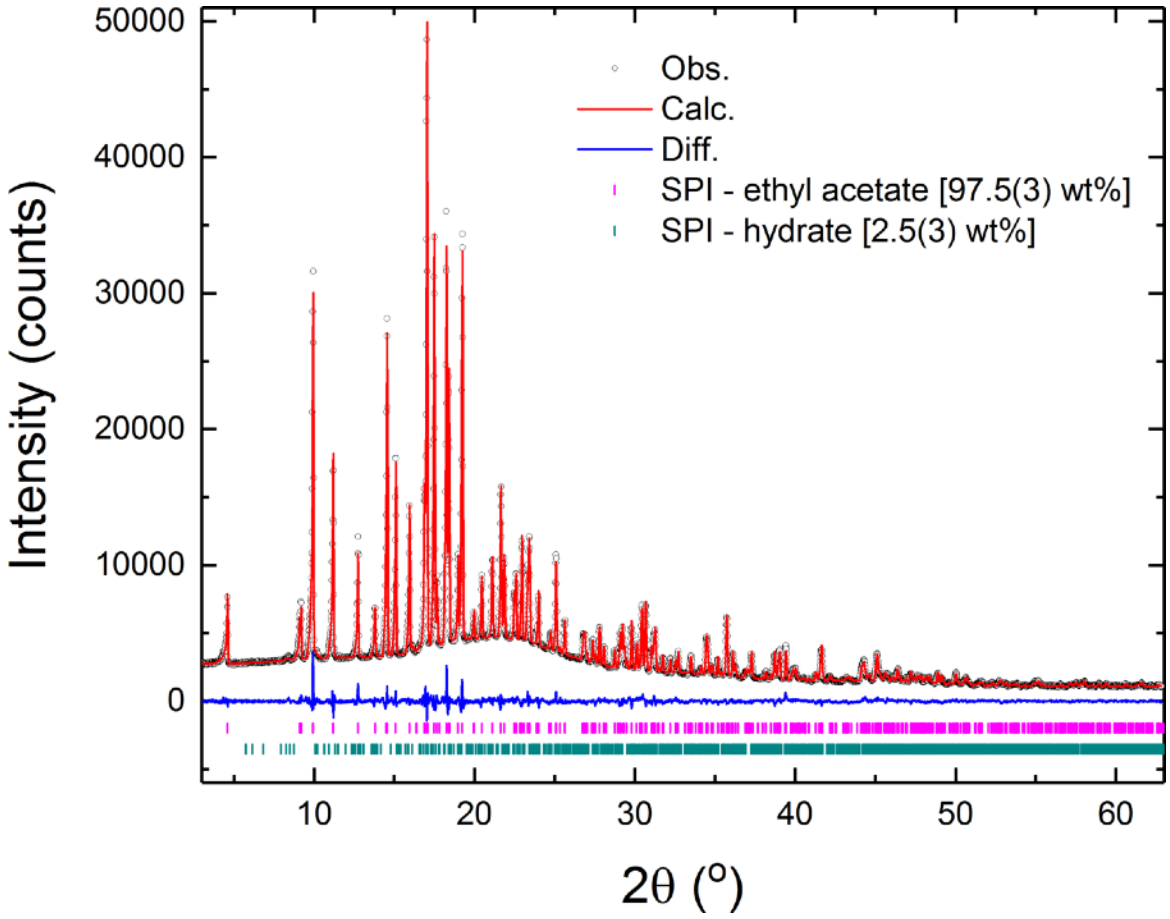
WUWROW Spironolactone hydrate

Spironolactone ethyl acetate

↓

structure proposed in our group





[1] N.Takata, R.Takano, H.Uekusa, Y.Hayashi, K.Terada, Cryst.Growth Des. (2010), 10, 2116

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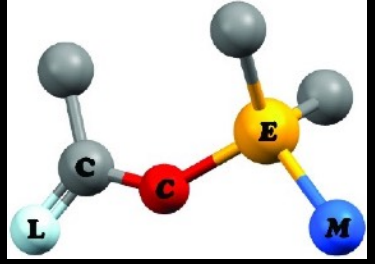
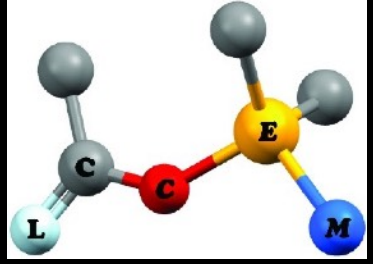
Summary



- LASSBio-1773 and LASSBio-1774: anhydrous and hydrated samples => tendency for a methylated compound to retain solvents within the crystal structure?!
- LASSBio-1755: ADPs calculation proved to be a useful approach using powder data
- XRPD is a fast tool to avoid the bottleneck provided by the need of harvesting good quality crystals
- Crystal Morphology Prediction (CMP) as a way to get valuable information regarding crystal habit
- Low cost POLYMORPH/SOLVATE SCREENING


UFABC

Acknowledgements



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