



ASSOLOMBARDA
Confindustria Milano Monza e Brianza

Co-cristalli di 3-iodopropinil butilcarbammato (IPBC)

Alogeni – nuove opportunità nella formazione di co-cristalli farmaceutici.

Speaker

Giancarlo Terraneo

12 ottobre 2016

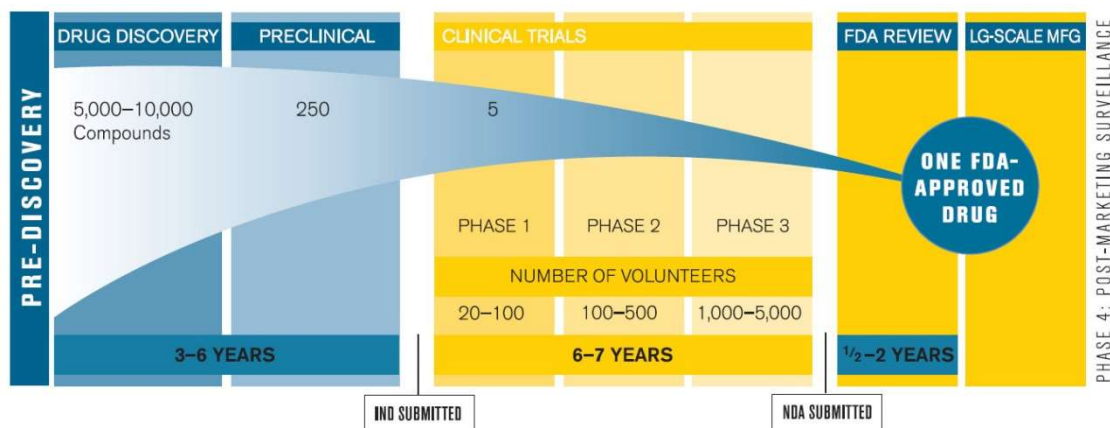




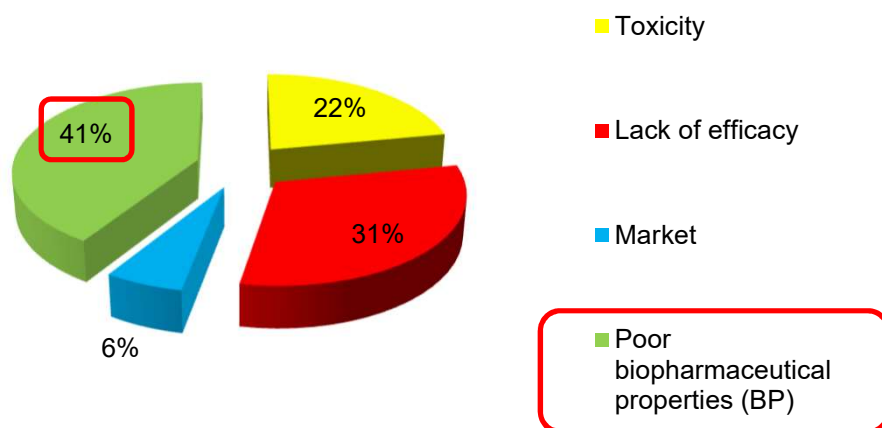
Time to develop a new drug



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Time to develop a drug	10-15 years
Cost of R&D	1.3 bl \$
Drug approved by FDA in 2016	16



Poor BP properties means:

- low solubility
- low permeability
- low stability
- bad technological properties

. Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2010 (Washington, DC: PhRMA, March 2010).

. Kerns, E.H.; Di, L. *Drug-Like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*; Elsevier, Amsterdam, **2008**, 7-9;

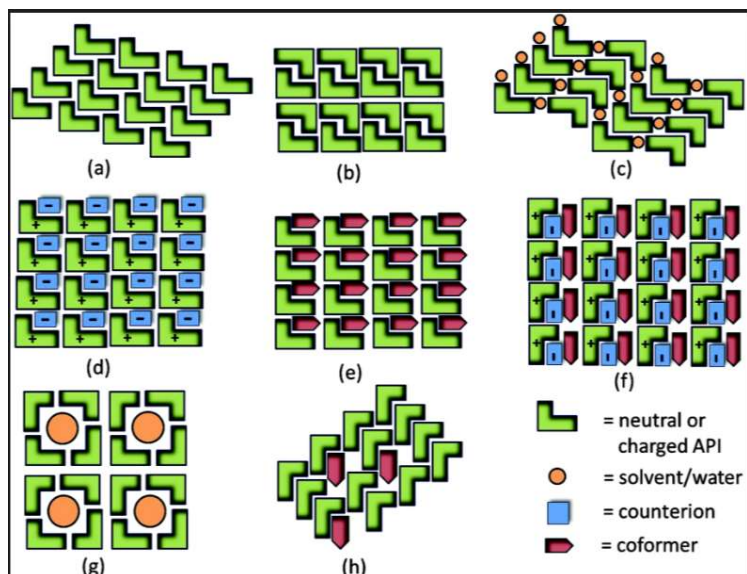


Polymorphs and co-crystals research



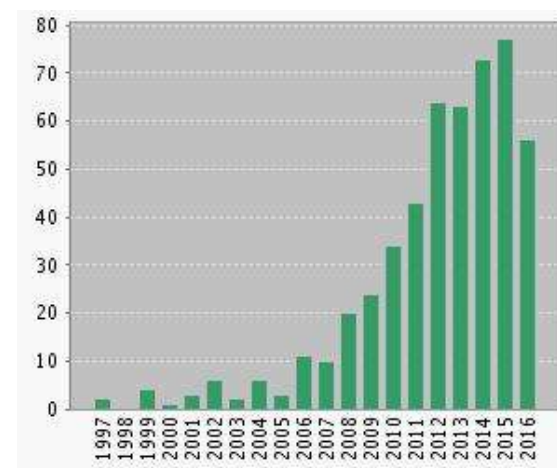
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Salt, solvate and co-crystal



CCF: co-crystal former

publications about API cocrystals



A single API can be provided in different crystalline forms and cocrystallized with a several number of CCF:

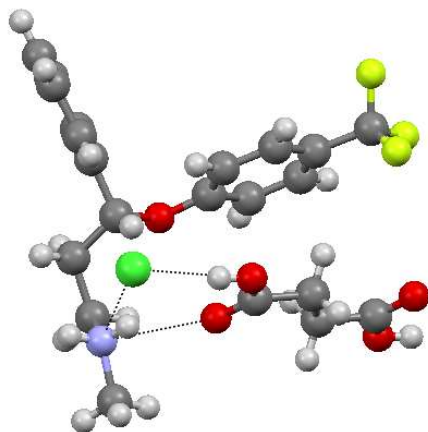
- the best solubility profile for the desired application
- the best crystal shape for the industrial production

... and also, from the patent point of view, every different crystalline form can be patented as a new pharmaceutical entity.



Hydrogen bonded Pharmaceutical cocrystals

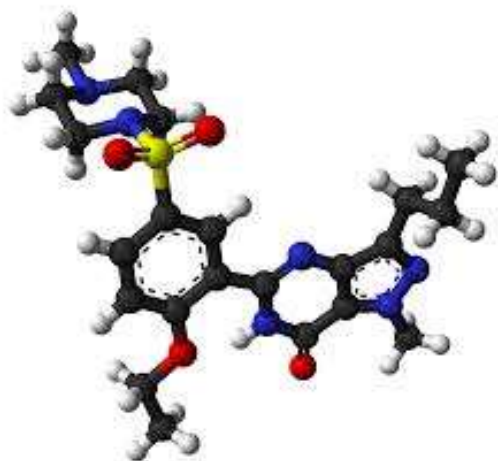
Pharmaceutical cocrystals of fluoxetine hydrochloride (Prozac®)



Fluoxetine HCl : succinic acid cocrystal exhibited an approximately twofold increase in aqueous solubility after only 5 min

Childs, J. *et al* J. Am. Chem. Soc. 126, 13335

Pharmaceutical cocrystals of sildenafil (Viagra®)



An intrinsic dissolution study in simulated gastric body fluid (pH 1.2) shows that the sildenafil : acetylsalicylic acid cocrystal exhibits an intrinsic dissolution rate (IDR) of ca. twofold comparing to sildenafil citrate under the same conditions

Zegarac, M. *et al* WO 2007/080362 A1



Why to use halogens?



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Drugs approved by FDA



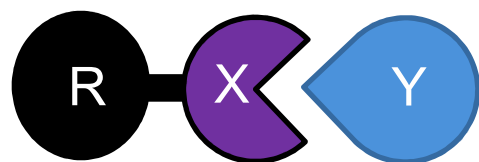
- Introducing an halogen atom(s) in selected positions of the molecular structure is one of the most common procedures for lead optimization in Medicinal chemistry

- **BUT** sometimes the introduction of halogens decrease dramatically API's biodisponibility

X could be a new tool for:

- Provide cocrystals with a new approach
- Improving and overcoming undesired properties of halogenated APIs

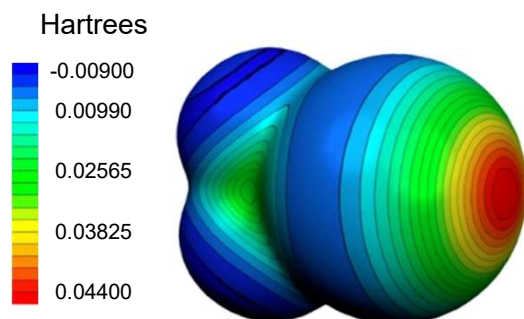
Halogen Bonding (XB): *any noncovalent interaction involving halogens as electron density acceptors.*¹



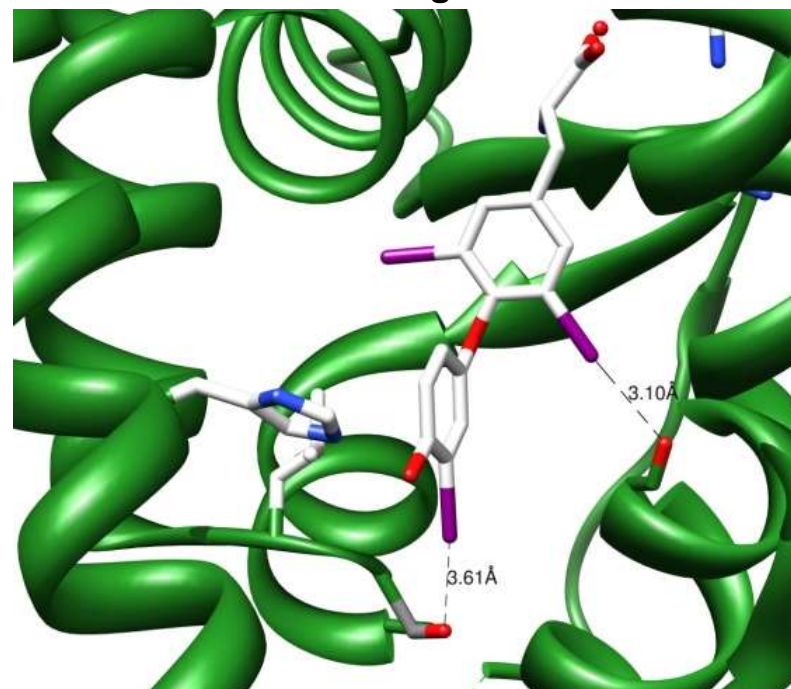
X= halogen (I>Br>Cl>F), XB donor

Y= Lewis base, XB acceptor

Electrostatic potential surface of CF₃I



T3 hormone inside its receptor's ATP binding site



[1] A more detailed definition can be found at <https://www.degruyter.com/view/j/pac.2013.85.issue-8/pac-rec-12-05-10/pac-rec-12-05-10.xml>

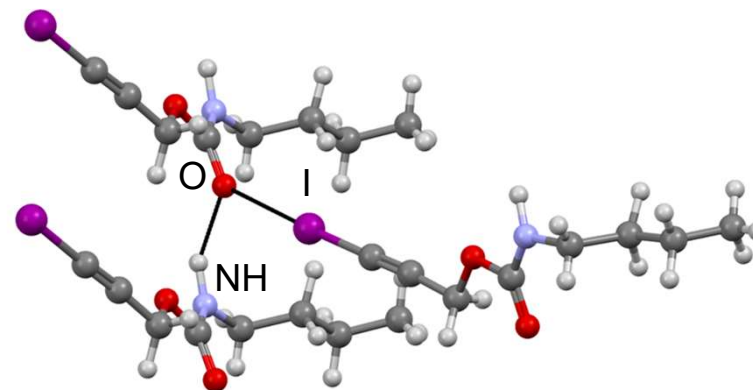
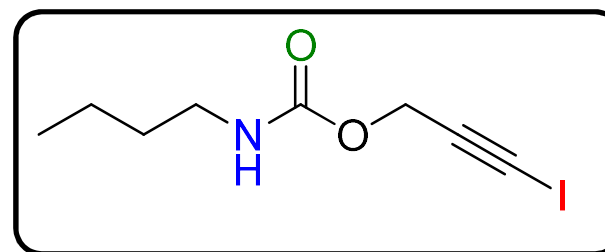


Iodopropynyl Butyl Carbamate (IPBC)



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- *It's the world's widest used antifungal product¹*
- *It's the most used preservative in wood products, paints, coatings, textiles and plastics,*
- *In cosmetics it is part of the composition of at least 191 products.*
- *Low water solubility (0.15-0.19 mg/ml) ²*
- *Powders are cohesive.*



The pure IPBC³ HB and XB are competing for the same acceptor.

[1] Hosomi M. Proceedings of the 25th Annual Meeting of the Society for Antibacterial and Antifungal Agents, **1998**, Japan, 97–98.

[2] Rioux, M.; Ciccognani, D. *Ind. Lubr. Tribol.* **2002**, 54, 215–218.

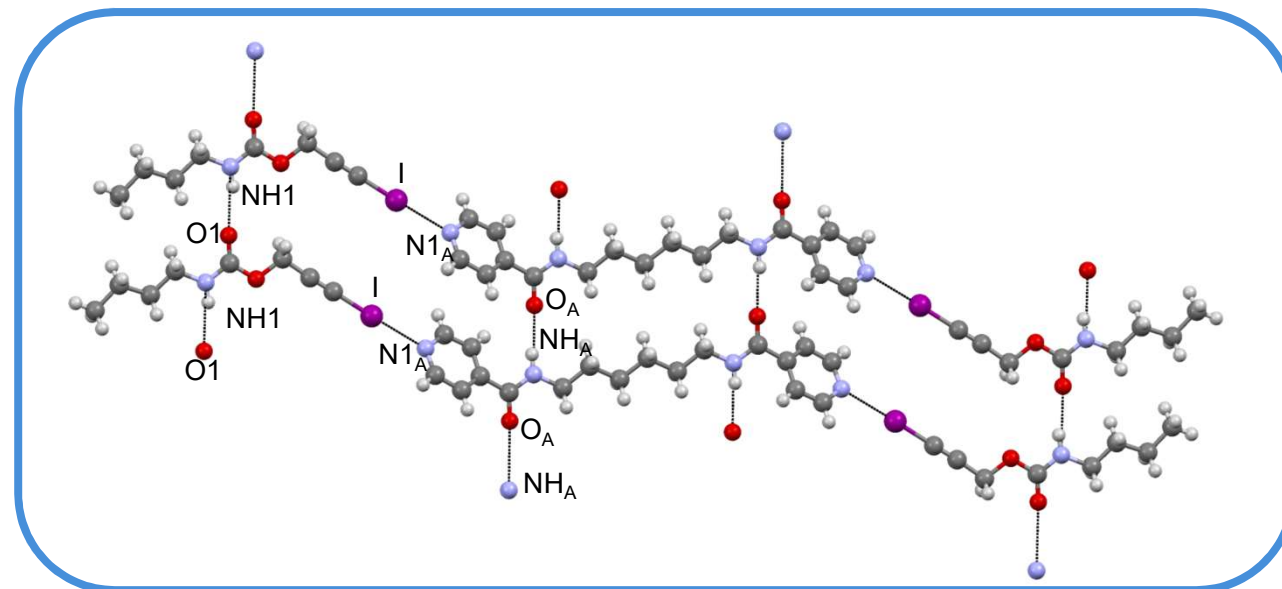
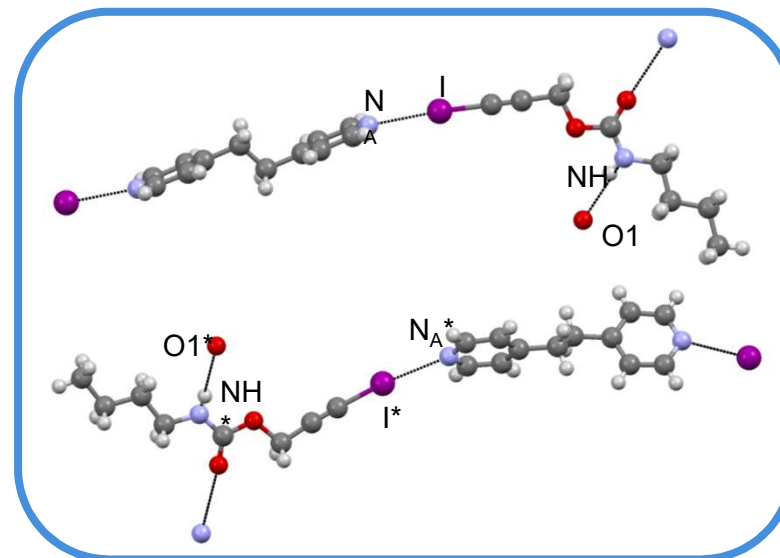
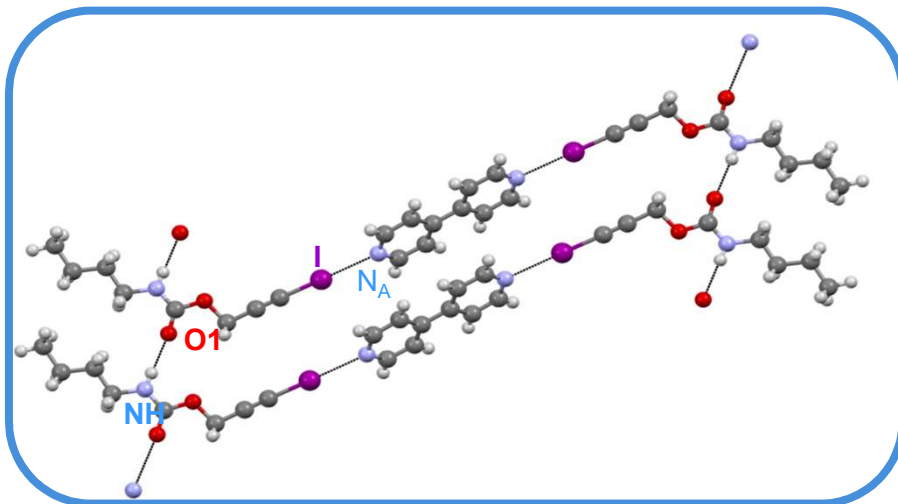
[3] Avtomonov, E. V.; Gruning, R.; Lorberth, J. Z. *Naturforsch. B* **1997**, 52, 256 (CSD code: TOYPUS).



IPBC co-crystals



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Mol. Pharmaceutics, **2013**, 10 (5),
pp 1760–1772

PCT/EP2013/057384
EP2836074A1, US20150051280



IPBC co-crystal

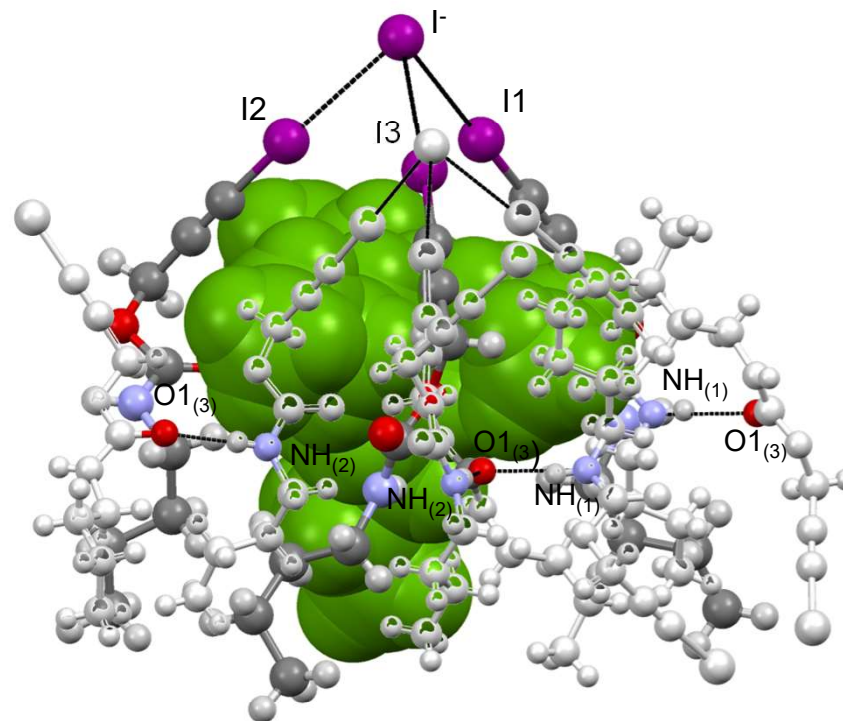


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m.p.	45 °C
m.p. API:	63-65 °C
m.p. CCF	280 °C

-C≡C- IR SHIFT (cm ⁻¹)		
IPBC	CO-CRYSTAL	SHIFT
2198	2185	-13

interaction	distance	angle
I1...I2	3.489 Å	172.70°
I1...I3	3.483 Å	174.84°
I1...I4	3.490 Å	179.38°
N1...O1*	2.883 Å	165.23°
N2...O1*	2.959 Å	177.27°



Mol. Pharmaceutics, **2013**, 10 (5), pp 1760–1772

PCT/EP2013/057384

EP2836074A1, US20150051280



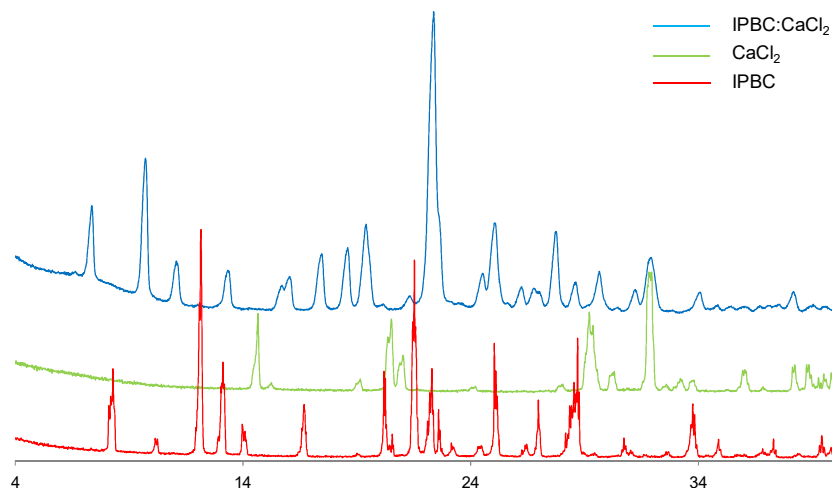
IPBC co-crystal



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API : CCF	4 : 1
m.p.	83 °C
m.p. API:	63-65 °C
m.p. CCF	30-45.5-176-260-772 °C

-C≡C- IR SHIFT (cm⁻¹)		
IPBC	CO-CRYSTAL	SHIFT
2198	2187	-11



CRYSTAL	¹³ C SSNMR chemical shift (C3)
IPBC:BYP	+9.8 ppm
IPBC:BYPET H	+8.1 ppm
IPBC:TBAI	+7.1/+8.7/+10.1 ppm
IPBC:CaCl₂	+7.1 ppm (br)

IR and SSNMR studies indicate the presence of two independent sets of IPBC molecules in the cell, one of which is involved in a NH···O HB while in the other the carbamate moiety is not involved in this interaction.



Angle of repose



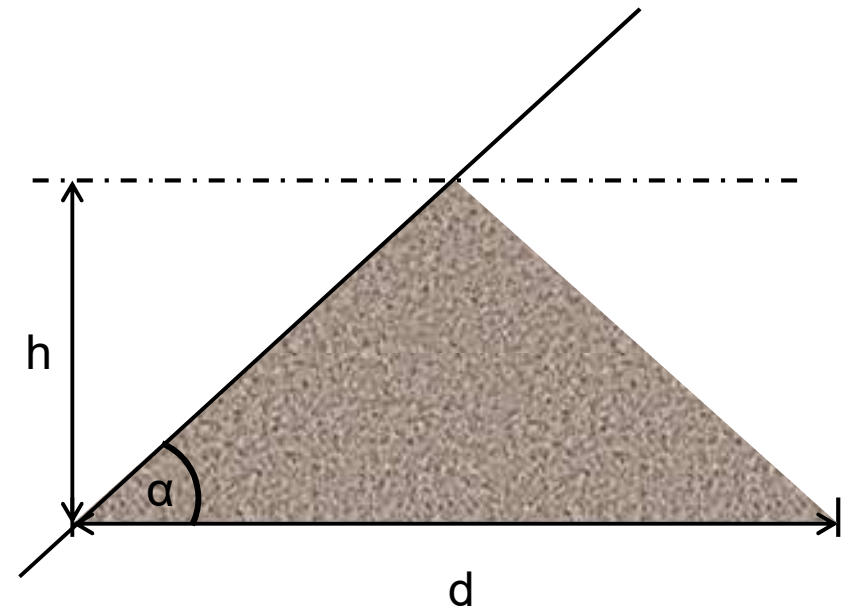
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Angle of repose¹ is the angle formed with an horizontal base made by a cone of powder.

Is a measure of the flow properties of a powder

Poorly flowing powders give high angle values

Powders with good flow properties give low angle values



$$\tan(\alpha) = \frac{h}{0.5 \times d}$$

The automatic handling devices that are used in the industrial manufacturing need powdered materials with good flow properties. Poorly flowing powders are a major technological issue.

[1] European Pharmacopoeia 7th ed. 2010; 2.9.36, 308–311.



Angle of repose



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IPBC → powders are very cohesive, the cone partially retain the shape of the funnel termination. Angle of repose is hardly measurable.

Powders have bad flow properties.

IPBC:CaCl₂ → powders are perfectly flowing out of the funnel and spread over the flat surface. Angle of repose is very low (13°-20°).

Powders are free-flowing.

IPBC



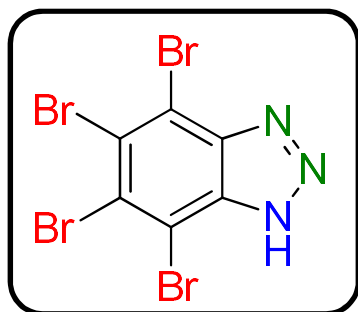
α not measurable

IPBC:CaCl₂

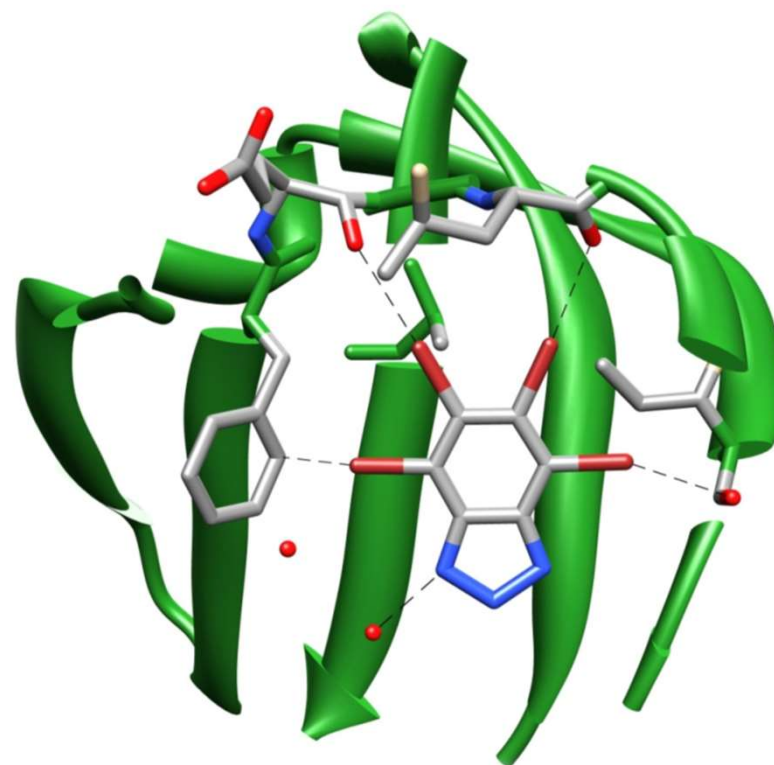


$\alpha = 13^\circ$ (average)

IPBC/CaCl₂ powders have the right flow characteristics for the application to industrial manufacturing automated feeding/handling devices.



Interaction pattern of TBBt inside CDK2



- TBBt is a selective inhibitor of CK2 (Caseine Kinase 2, a serine/threonine-selective protein kinase); it is a prototype anticancer drug.¹
- Crystal structures with CK2 and CDK2 (Cyclin-dependent kinase 2, also known as cell division protein kinase 2) indicate that the API is interacting with the two proteins via XBs.²

[1] Zien, P.; Duncan, J. S.; Skierski, J.; Bretner, M.; Litchfield, D. W.; Shugar, D. *Biochim. Biophys. Acta* **2005**, 1754, 271–80.

[2] Auffinger, P.; Hays, F. a; Westhof, E.; Ho, P. S. *P. Natl. Acad. Sci. USA* **2004**, 101, 16789–94.



Tetrabromobenzotriazole (TBBt)

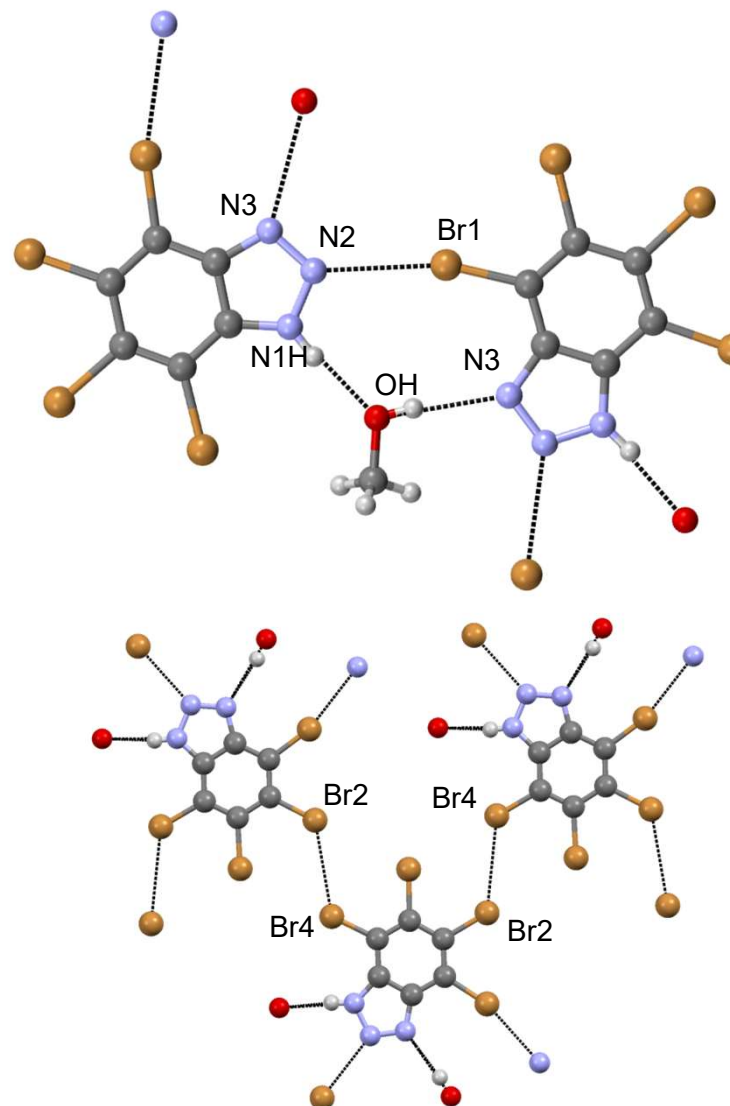


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m.p. 130 °C

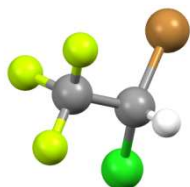
m.p. API 262-264 °C

interaction	distance	angle
N1H...O	2.773 Å	172.8°
OH...N3	2.945 Å	170.5°
Br1...N2	2.914 Å	164.4°
Br2...Br4	3.607 Å	126.3°



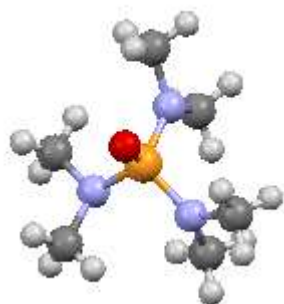


Halothane

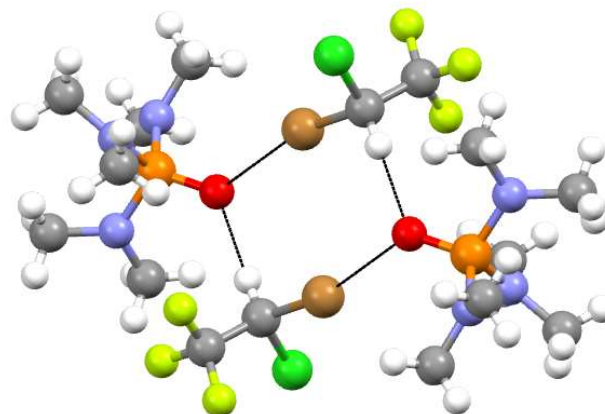


Halothane
mp = - 118 °C

- General anaesthetic
- Included in the WHO Model List of Essential Medicines



HMPA
mp = 7 °C



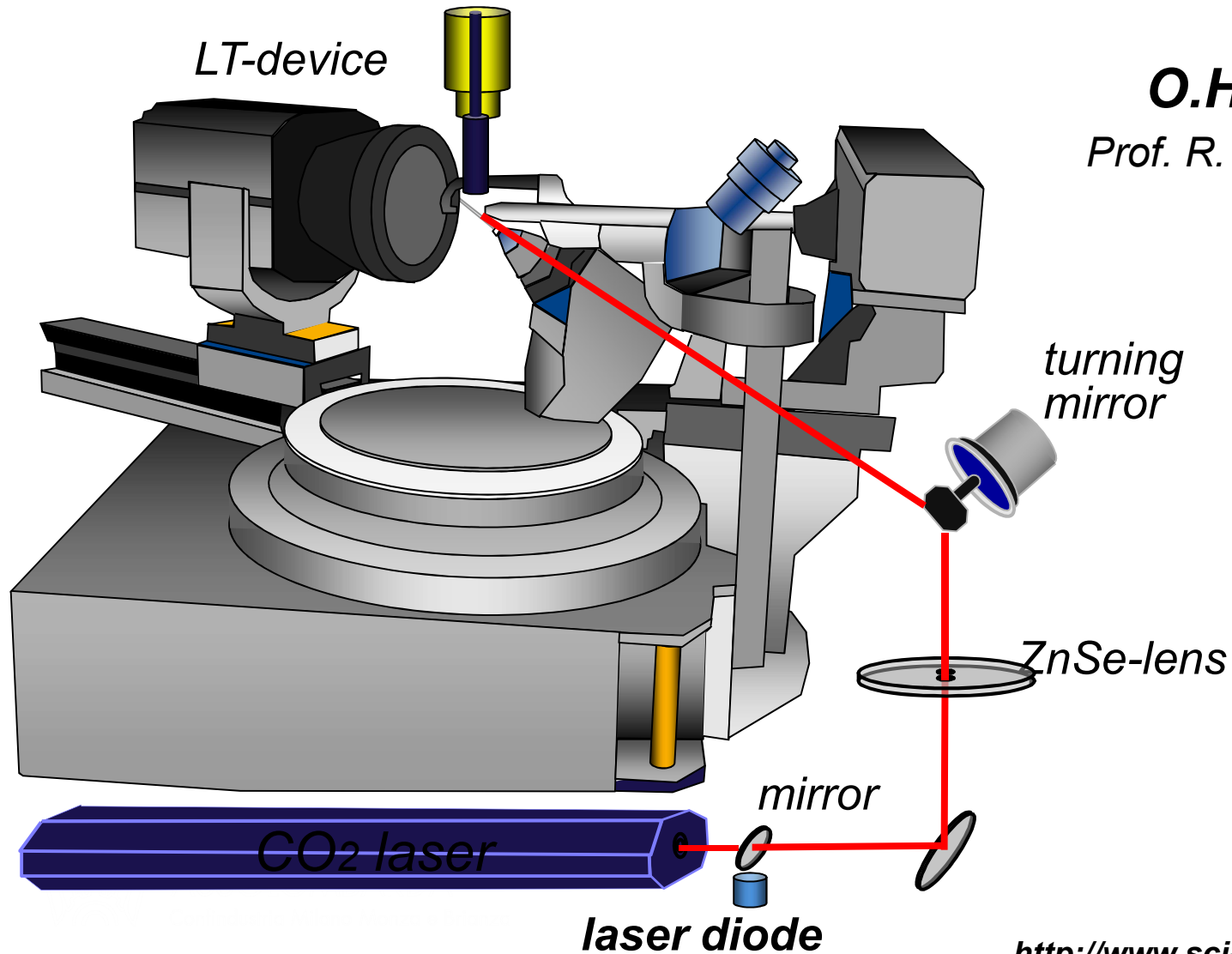
C-Br...O distance: 2.887 Å ($N_c = 0.86$)
C-H...O: 2.135 Å ($N_c = 0.79$)
C-Br...O angle: 165.94



In situ-cryocrystallization: Optical Heating and Crystallization Device

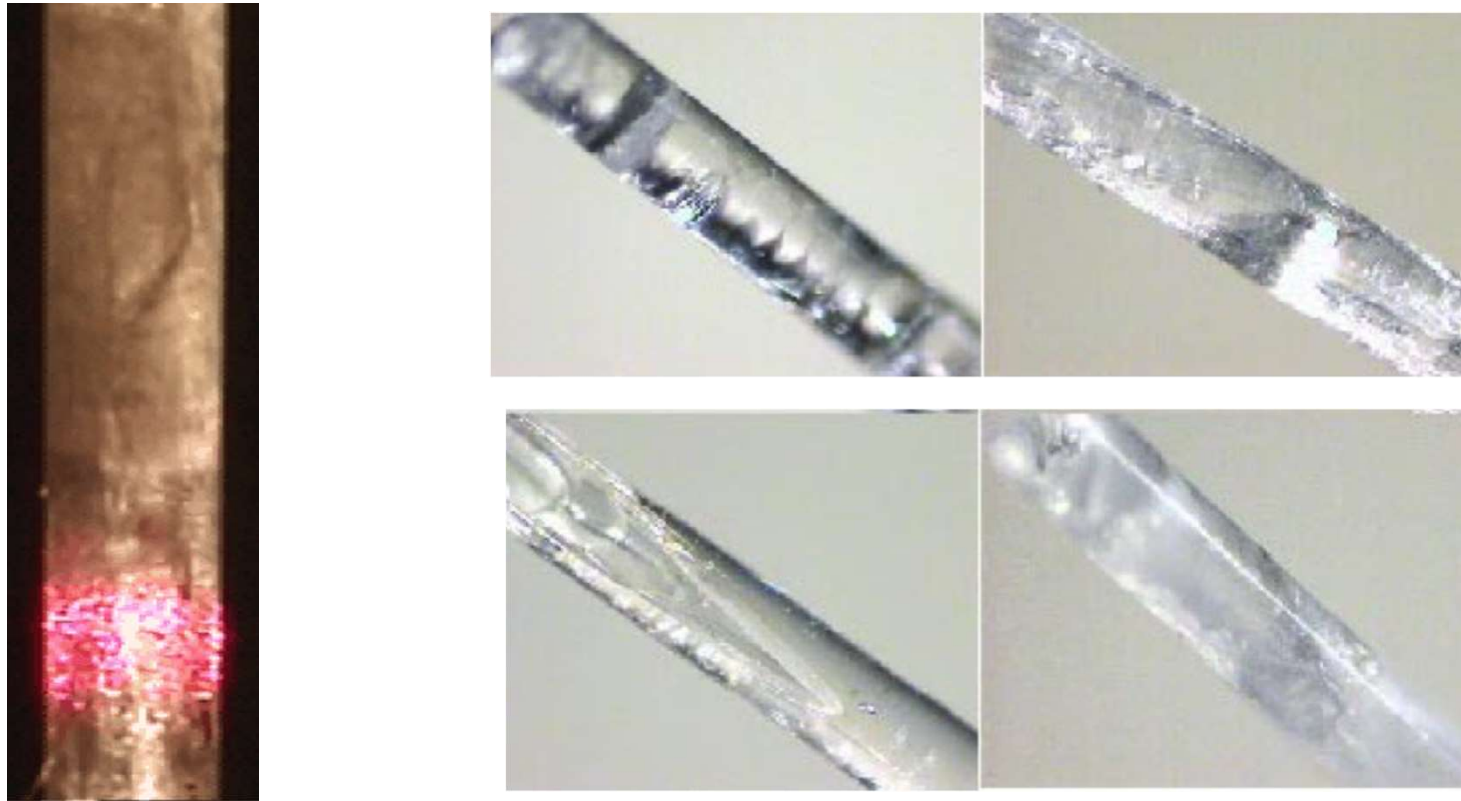


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<http://www.sci-ohcd.eu/>

In situ-cryocrystallization: Optical Heating and Crystallization Device



Crystals were formed below RT and were repeatedly molten and solidified in situ by the use of an IR laser



Single crystal X-ray crystallography

Bruker KAPPA APEX II, CCD area detector, Kappa geometry, Mo source, TRIUMPH Monochromator (Brilliance beam comparable to a micro-focus source)



Microcrystalline powders X-ray crystallography

Bruker D8 Advance, LynxEye detector, Cu source, temperature controlled stage, grazing Incident stage.



Top 200 Pharmaceutical Products



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Top 200 Pharmaceutical Products by US Retail Sales in 2011

Compiled and Produced by the Njardarson Group (The University of Arizona): Edon Vitaku, Elizabeth A. Iardi, Jón T. Njardarson

