Crystal Engineering Strategies to optimize the performance of Drugs and Nutraceuticals

Rafel Prohens

Overview

Crystal Engineering

- Why should a chemist be interested in crystals?
- How can crystals be engineered?

Nutraceutical Cocrystals

- Why do we need to improve Nutraceuticals?
- How can we improve Nutraceuticals?

Questions

Crystal Engineering

- **Why should a chemist be interested in crystals?**
- How can crystals be engineered?

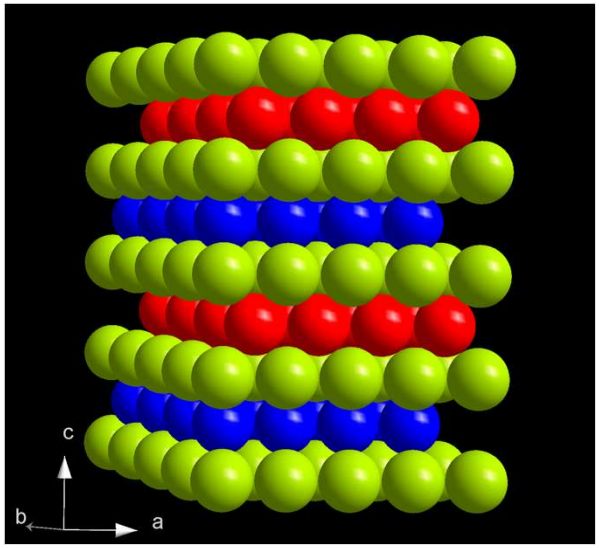
Nutraceutical Cocrystals

- Why do we need to improve Nutraceuticals?
- How can we improve Nutraceuticals?

Crystals are ubiquitous

Molecules

Nature



Versus

Order

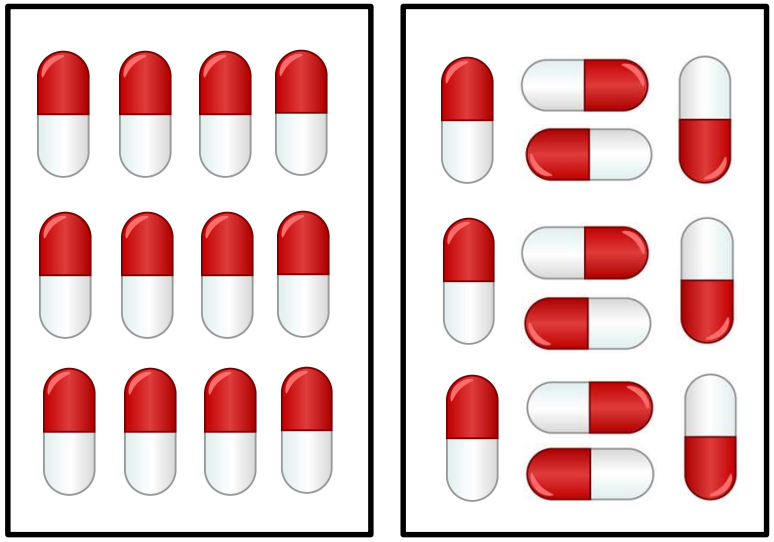
Disorder

$$\Delta G^0 = \Delta H^0 - T\Delta S^0$$

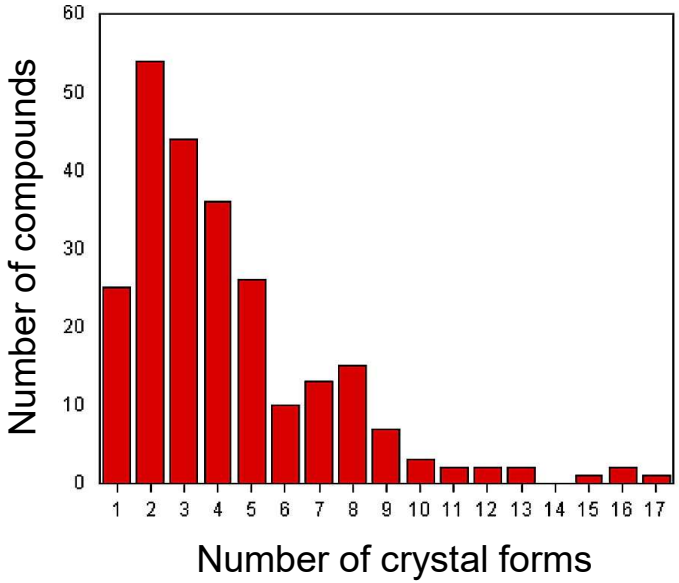
Intermolecular Interactions vs Entropy

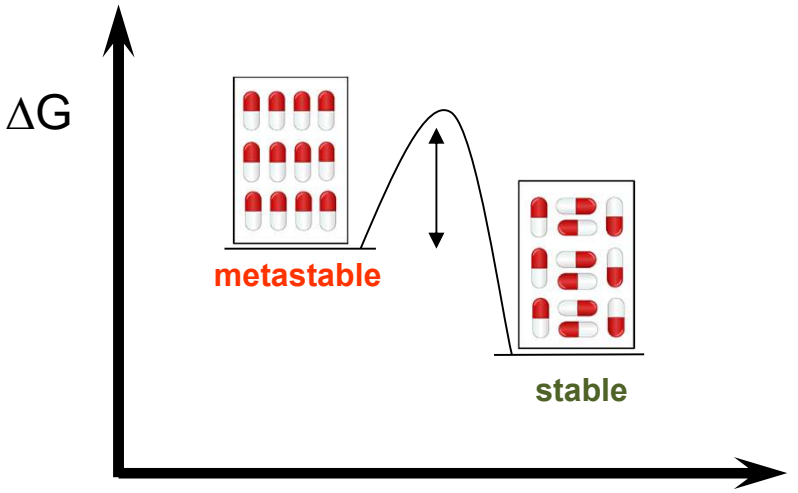
Why Crystals?

Drug Compound



POLYMORPHS

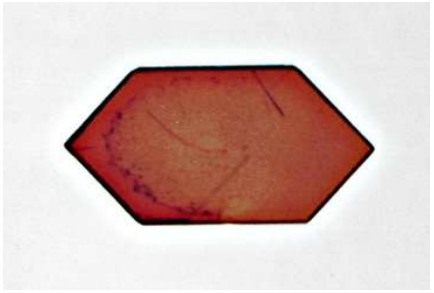


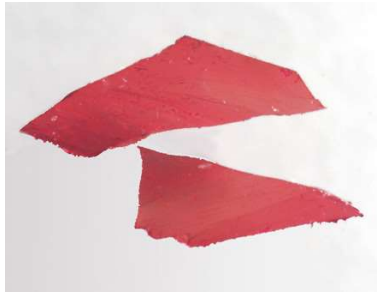


Crystal Growth & Design 2007, 7, 6, 1007-1026

Why Crystals?

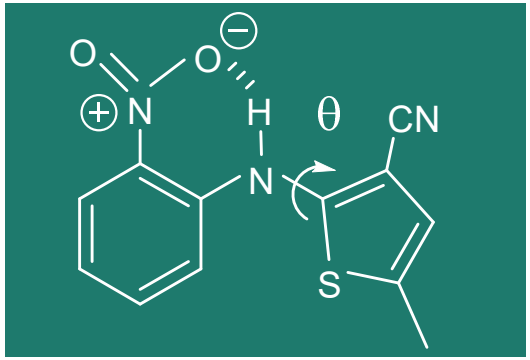
mp 112.7 °C
θ = 46.1°





θ = 39.4°

mp 114.8°C
θ = 52.6°



mp 106.2 °C
θ = 21.7°

θ = 104.1°

mp 109.8 °C
θ = 104.7°

J. Am. Chem. Soc. **2000**, *122*, 585

Questions

Crystal Engineering

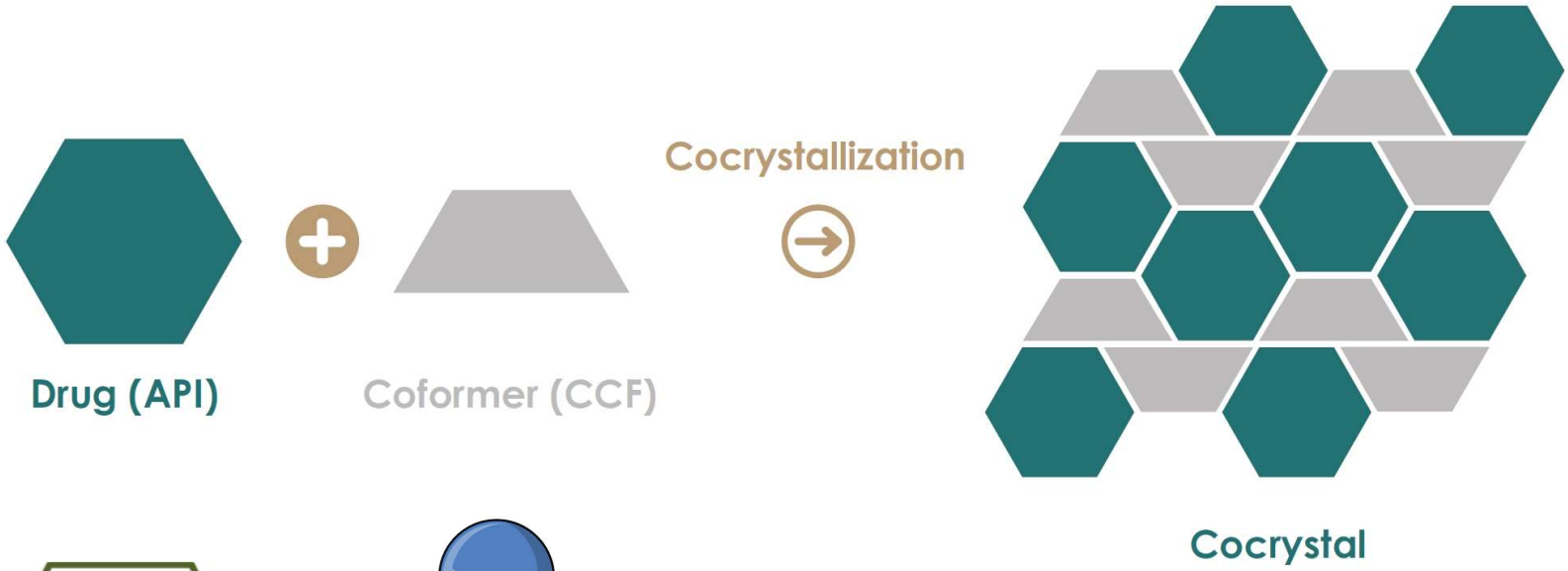
- Why should a chemist be interested in crystals?
- **How can crystals be engineered?**

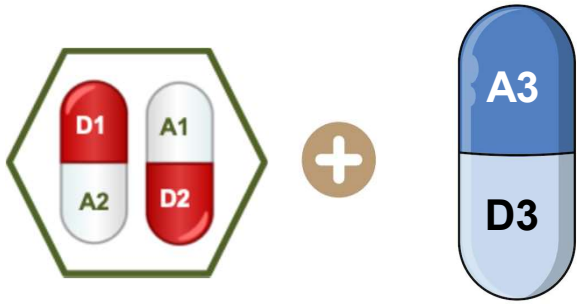
Nutraceutical Cocrystals

- Why do we need to improve Nutraceuticals?
- How can we improve Nutraceuticals?

How can crystals be engineered?

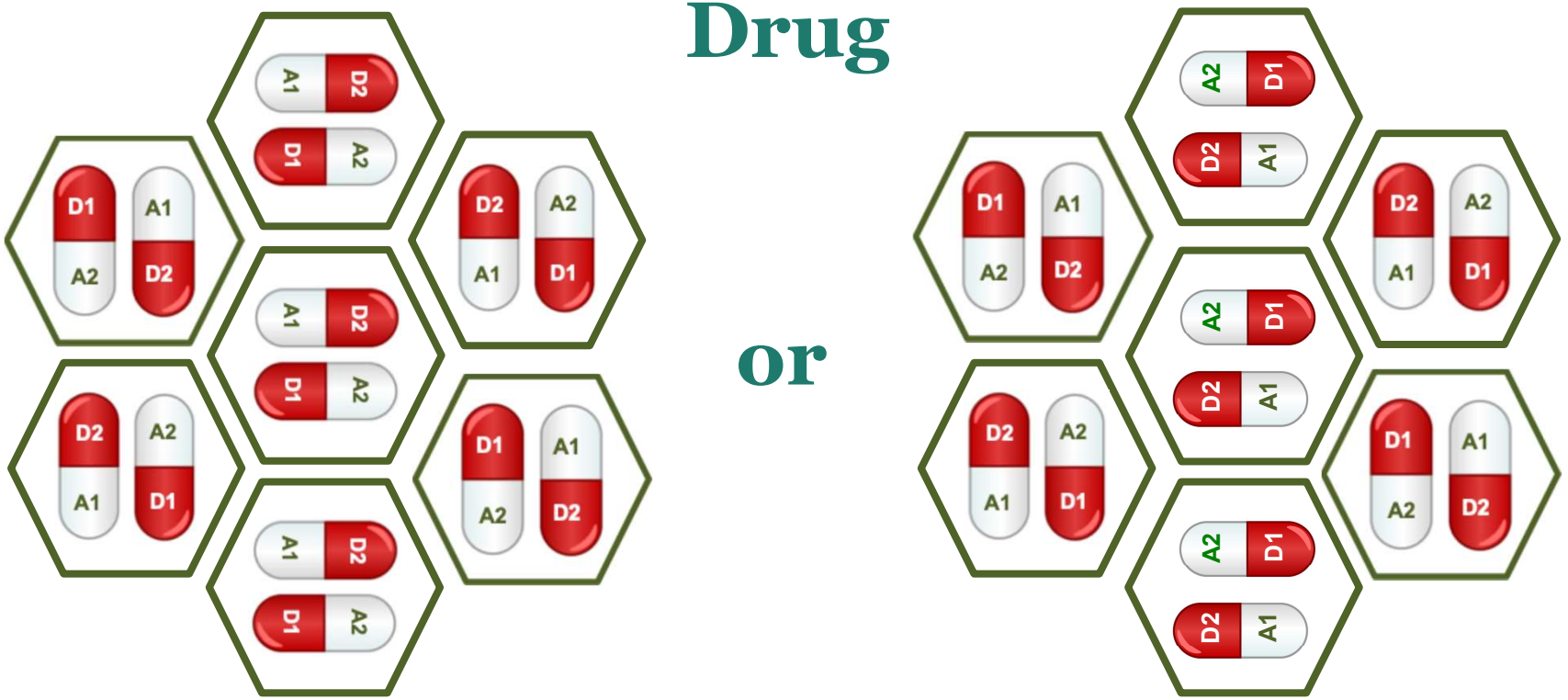
Cocrystalization is a process in which the Active Ingredient is processed with a coformer, resulting in a new crystal form containing both molecules linked by non-covalent interactions, such as hydrogen bonds.





Any interaction can be treated as a hydrogen bond

How can crystals be engineered?

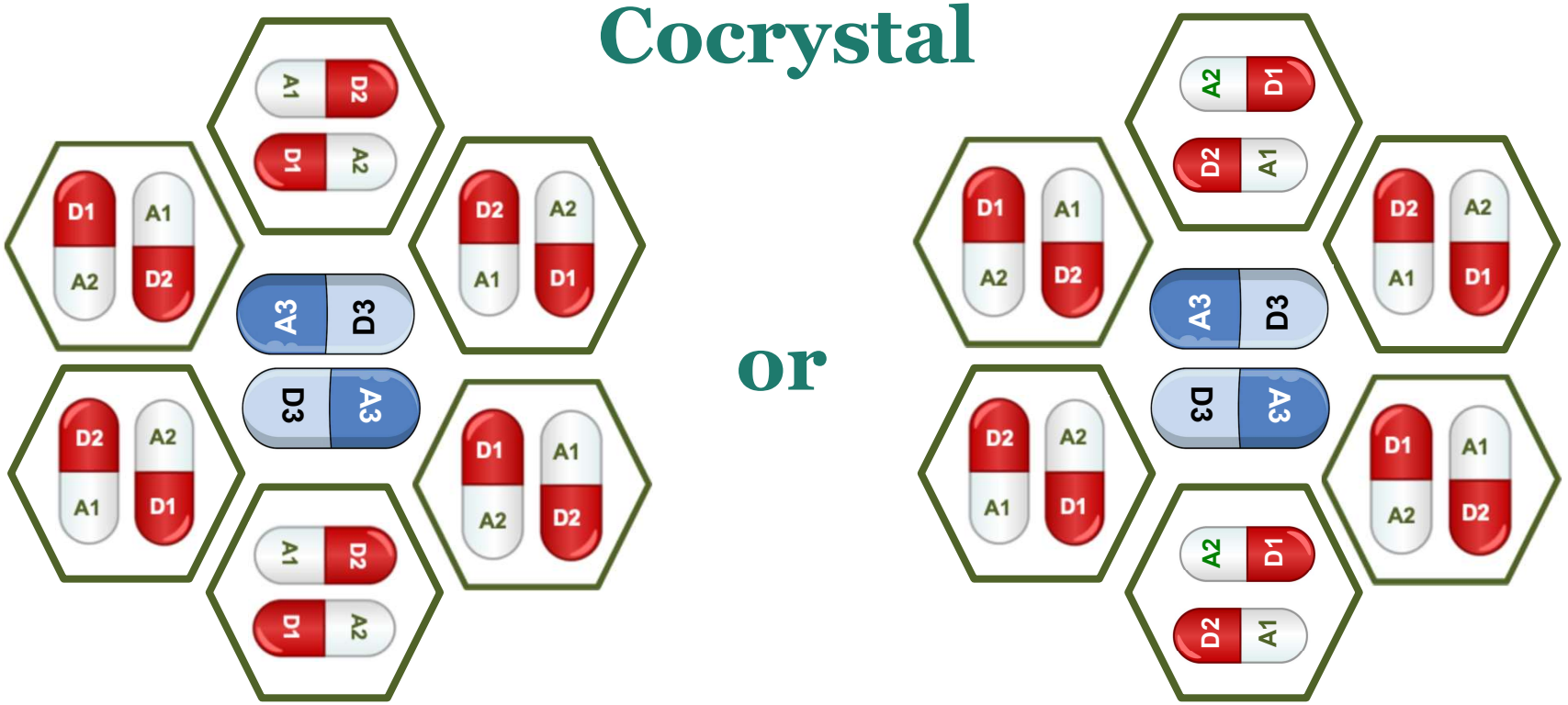


$$\Delta E = E_1 - E_2$$

Different arrangements in the crystal lattice have different energies

How can crystals be engineered?

Cocrystal

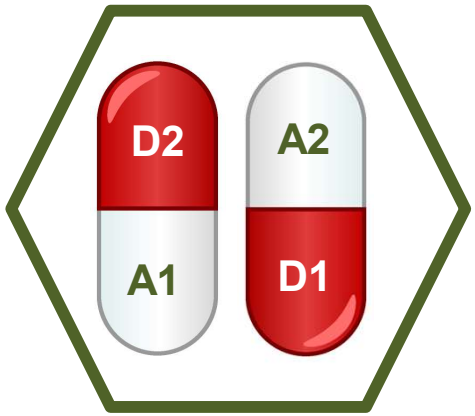


$$\Delta E = E_{cc} - nE_1 - mE_2$$

Different arrangements in the crystal lattice have different energies
Multiple combinations

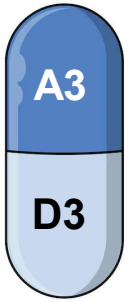
How can crystals be engineered?

Drug



+

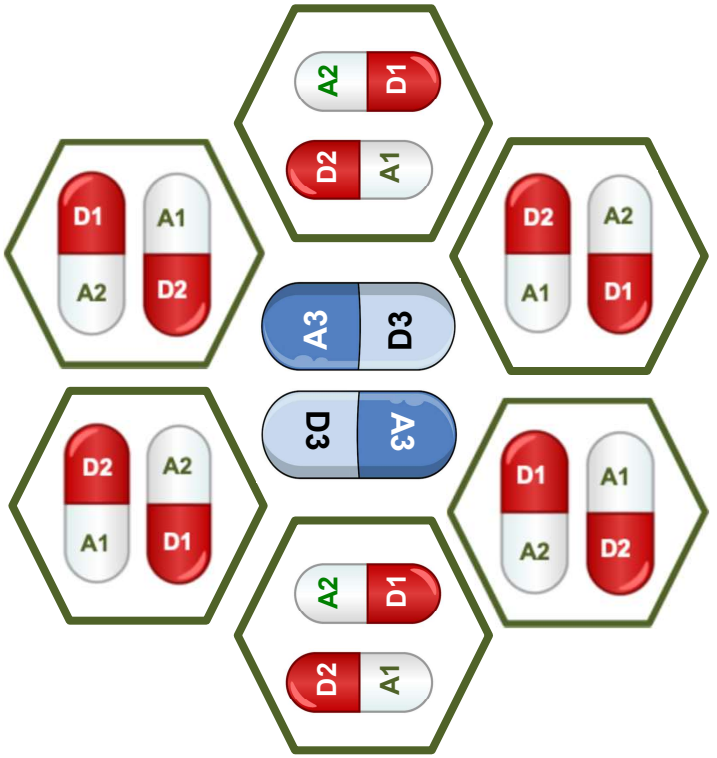
Coformer



$\Delta E = ?$

$\Delta E = E_{cc} - nE_1 - mE_2$

Cocrystal

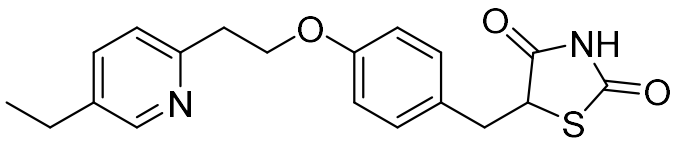


Related with Cocrystallization Probability

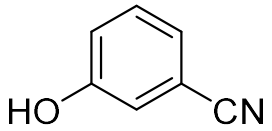
Musumeci, D; Hunter, C. A.; Prohens, R.; Scuderi, S.; McCabe, J.; *Chem Sci.*, **2011**, 2, 883-890

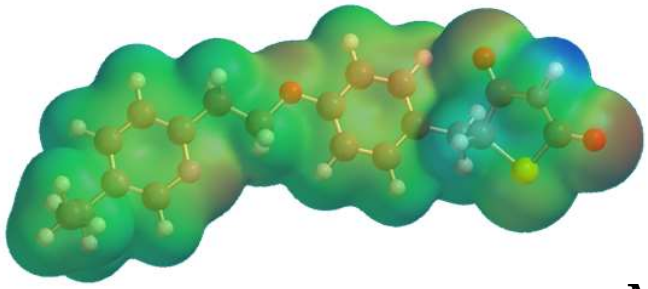
How can crystals be engineered?

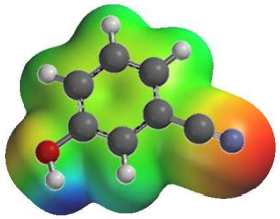
Intermolecular Interactions in organic materials are weak



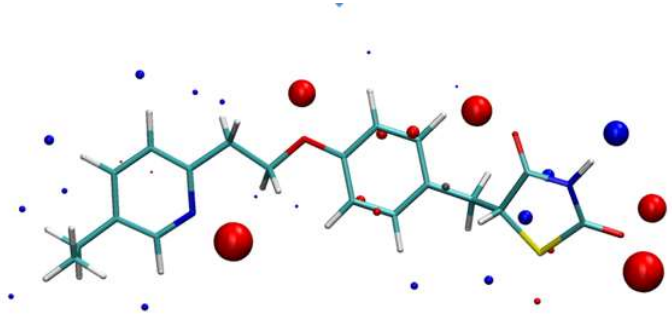
Molecular Structure

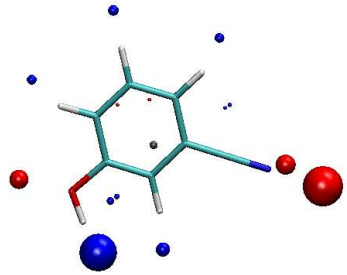






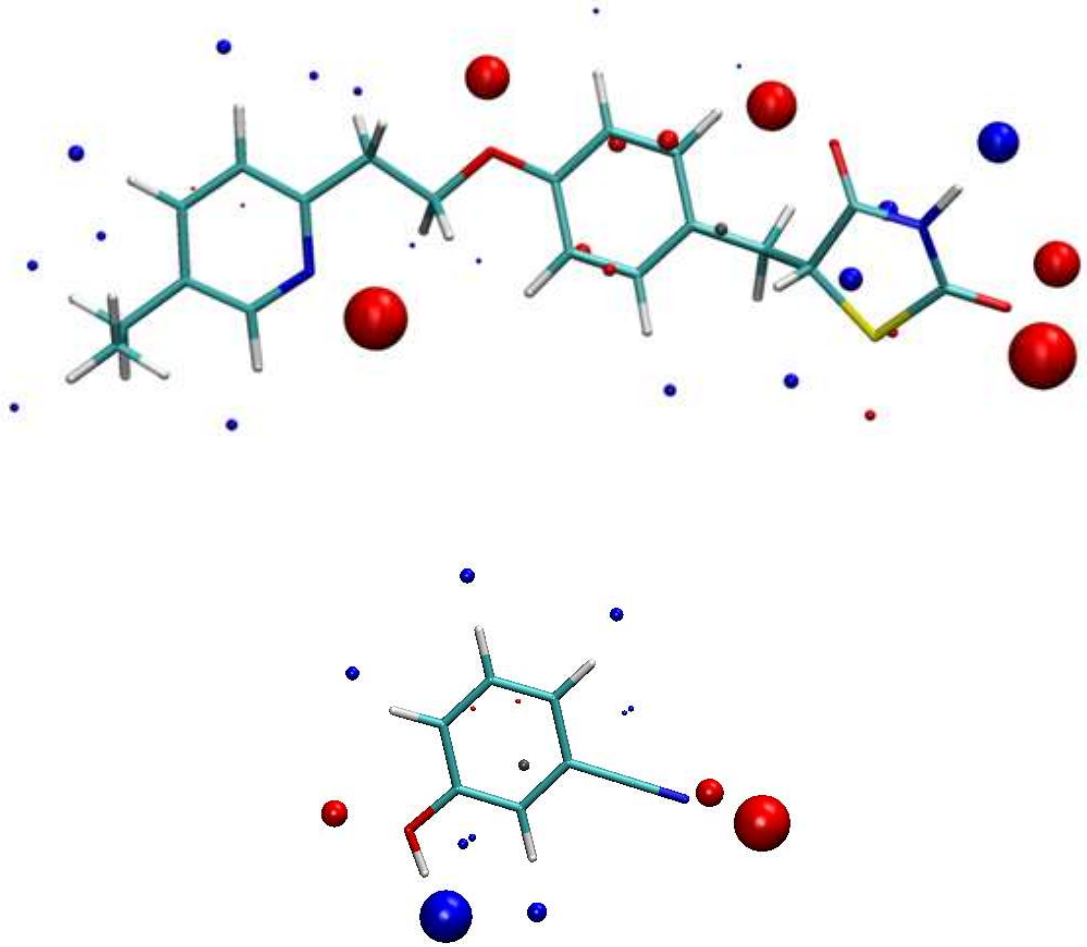
Molecular Electrostatic Potential



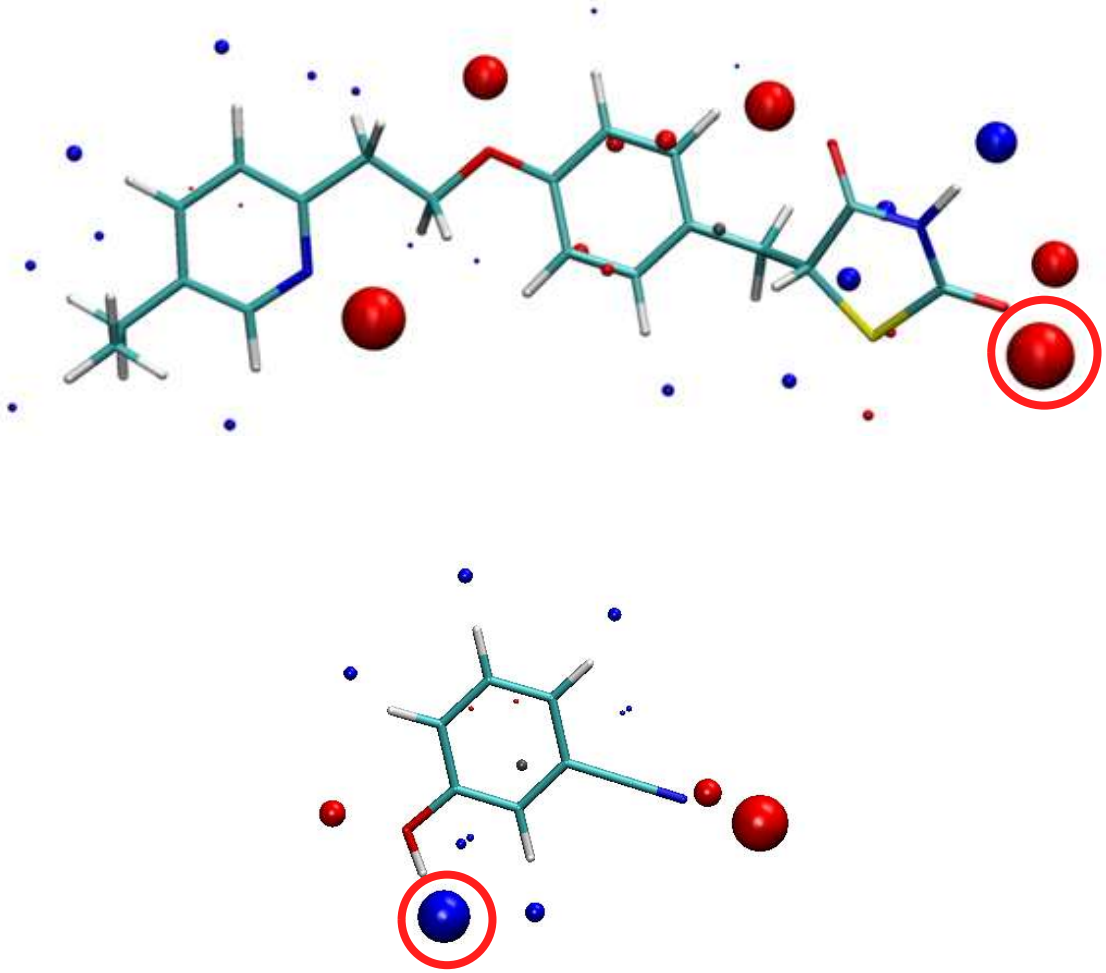


Surface Site Interaction Points

How can crystals be engineered?

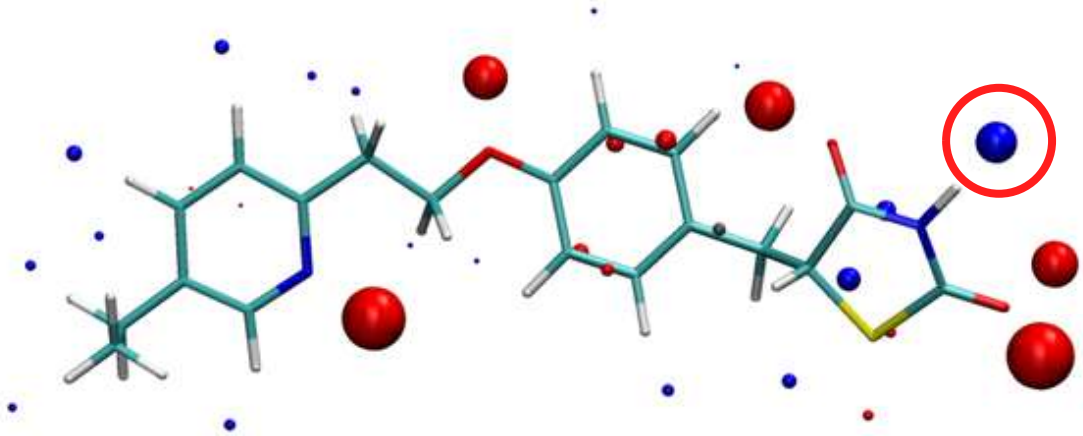


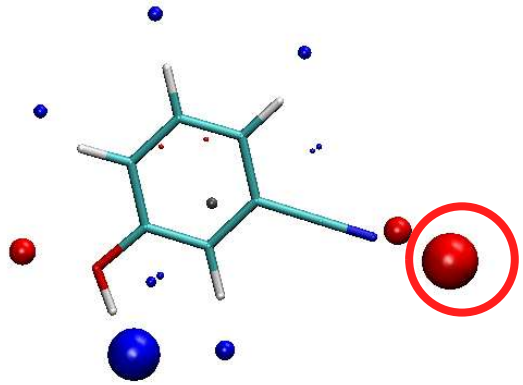
How can crystals be engineered?



$E = (\alpha_1 \times \beta_1) + \ldots$

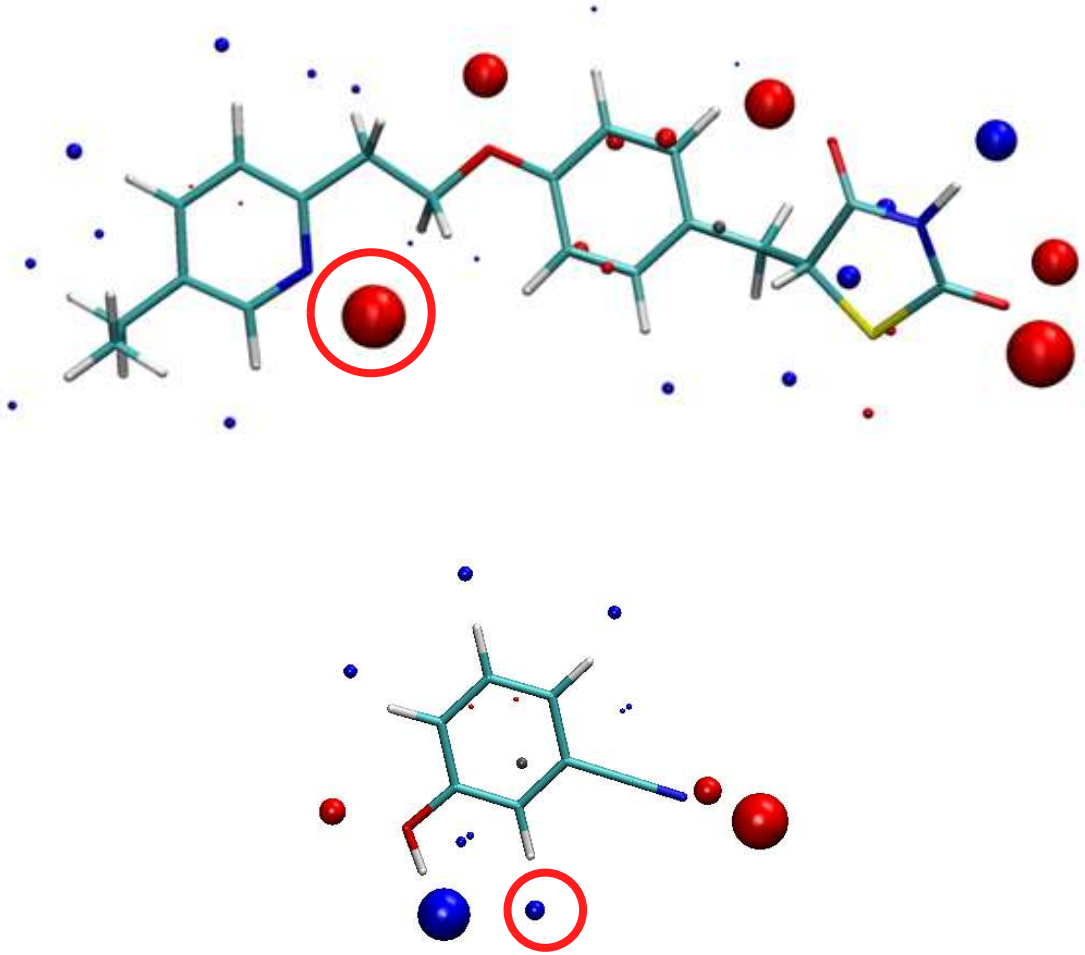
How can crystals be engineered?





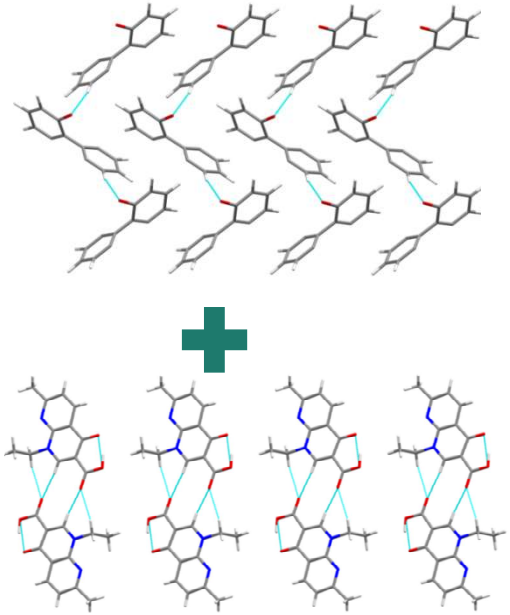
$$E = (\alpha_1 \times \beta_1) + (\alpha_2 \times \beta_2) + \ldots$$

How can crystals be engineered?

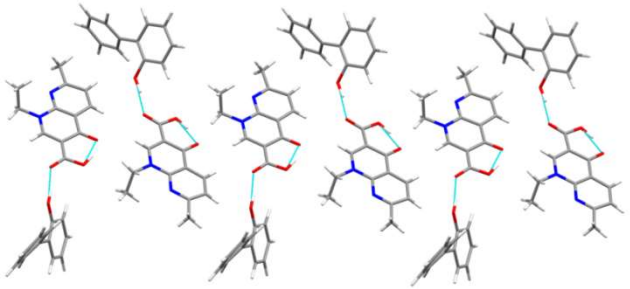


$$E = (\alpha_1 \times \beta_1) + (\alpha_2 \times \beta_2) + (\alpha_3 \times \beta_3) \ldots$$

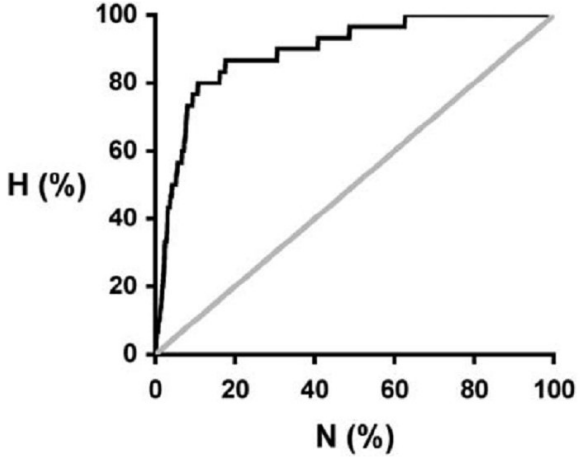
How can crystals be engineered?



$\Delta E = ?$



$$\Delta E = E_{cc} - nE_1 - mE_2$$



Related with Cocrystallization Probability

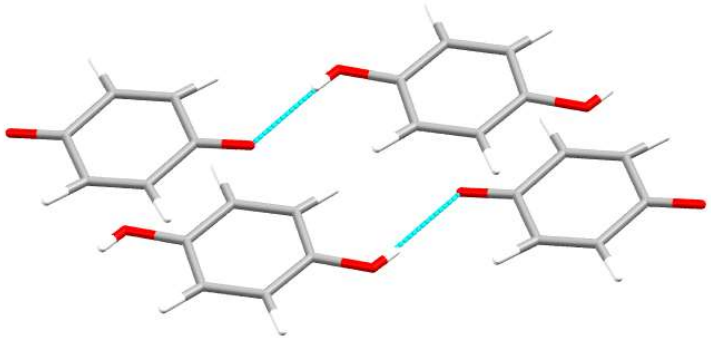
Chem Sci., **2011**, 2, 883-890

From discovery to marketed drug

Quinhydrone

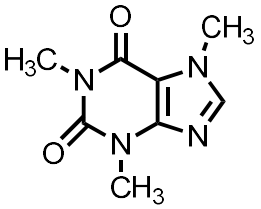
†

Quinone Hydroquinone

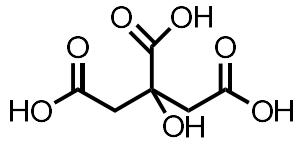


1844

Apnoea drug

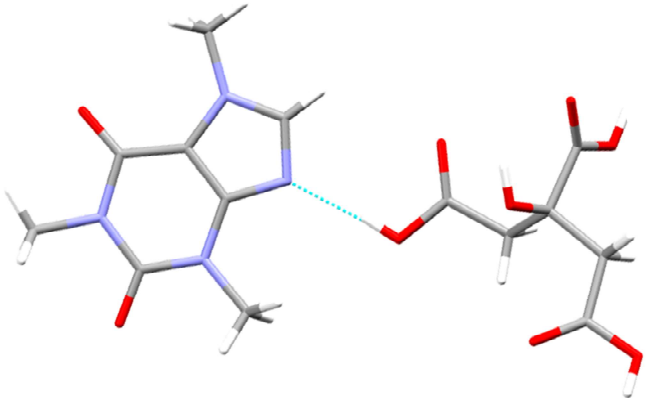


caffeine



citric acid

††



2007

† Wohler, **1844**

†† S. Karki, T. Friščić, W. Jones, W. S. Motherwell; *Mol. Pharm.*, **2007**, 4, 347-354

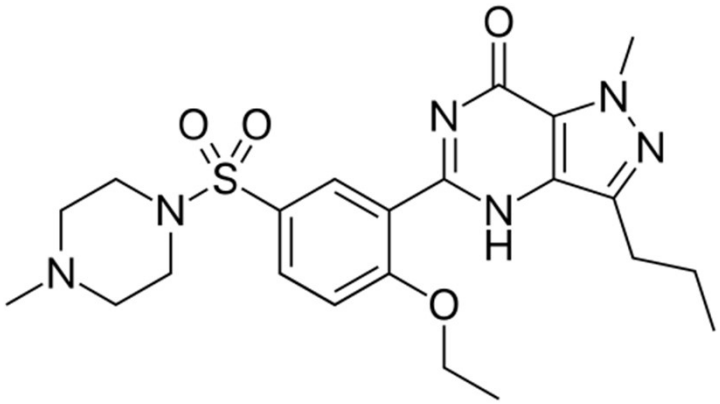
Recently, the **FDA** has published a *Guidance for Industry about the Regulatory Classification of Pharmaceutical CoCrystals*.

The **FDA** treats **cocrystals** as *"dissociable API-excipient molecular complexes"*. Thus, the cocrystal is regarded just as a drug product intermediate.

Many opportunities to improve physicochemical properties

How can crystals be engineered?

Sildenafil



Active principle of Viagra. Drug patented in 1996

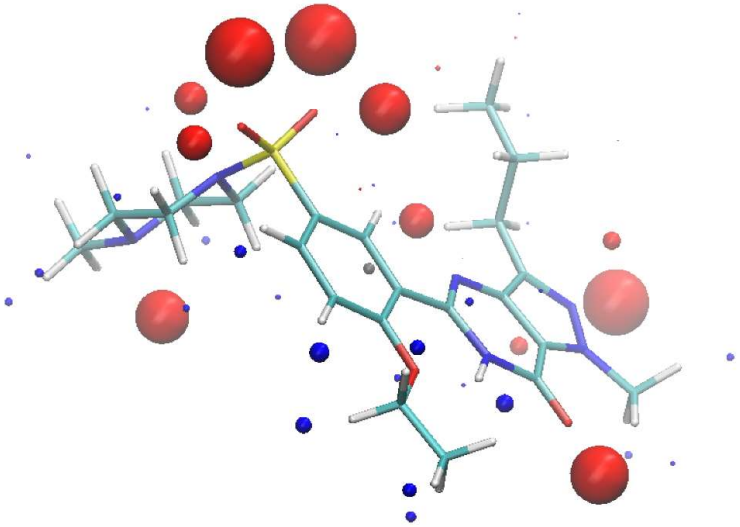
The API was initially studied for use in hypertension but it had little effect on angina so it was used for other applications

Cryst. Growth Des. **2018**, 18, 12, 7618–7627

How can crystals be engineered?

Virtual Cocrystal Screening

Sildenafil



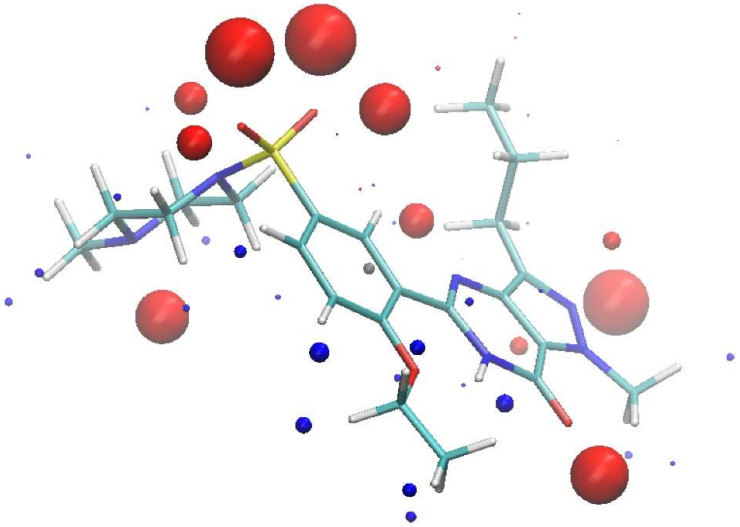
API structure

Library of potential coformers

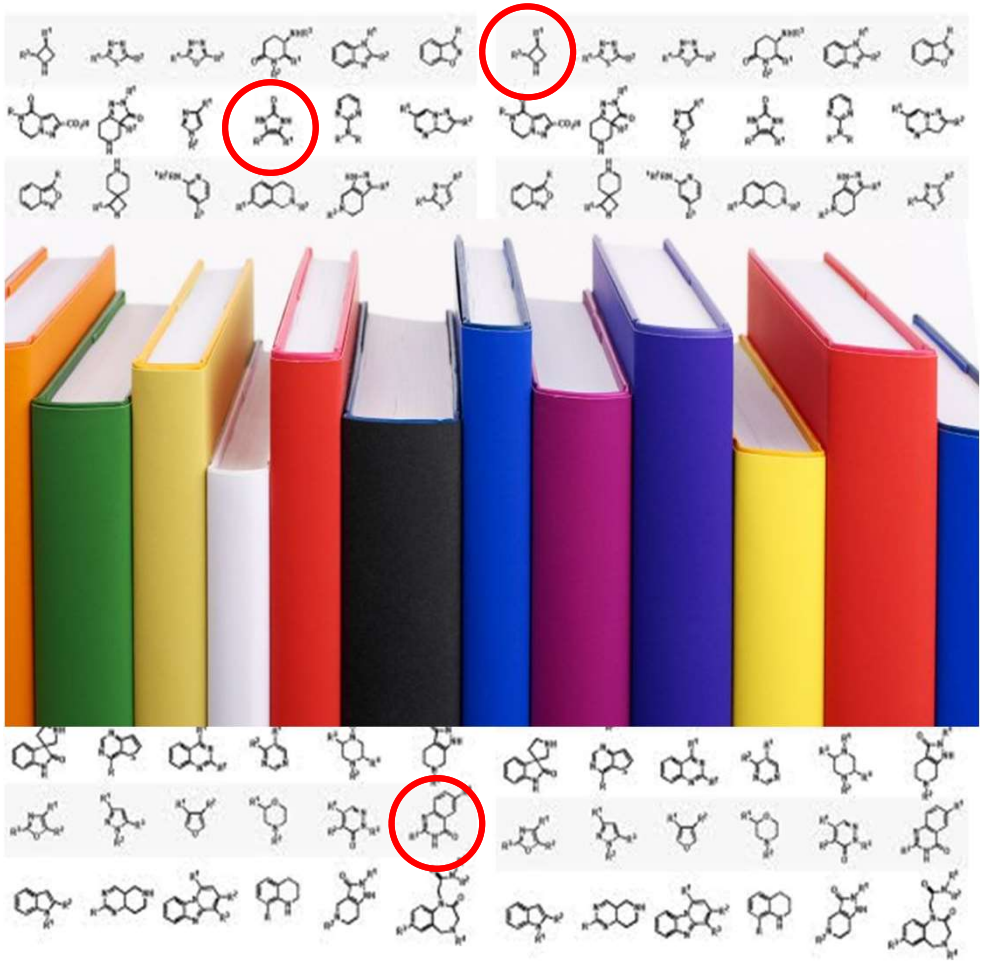
How can crystals be engineered?

Virtual Cocrystal Screening

Sildenafil



API structure

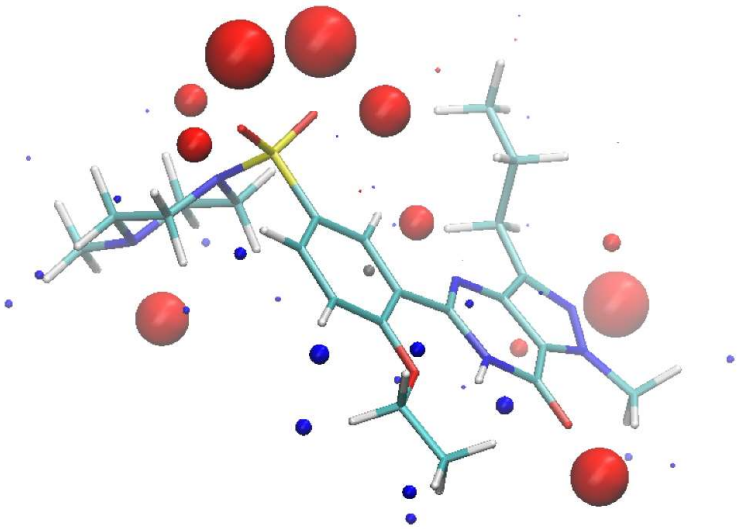


Library of potential coformers

How can crystals be engineered?

Virtual Cocrystal Screening

Sildenafil



API structure

coformer	ΔE/kJ mol^{-1}
quercetin	28.1
resveratrol	24.0
phloroglucinol	23.8
3,4-dihydroxybenzoic acid	21.7
resorcinol	19.3
tartaric acid	18.2
caffeic acid	17.8
myo-inositol	15.7
tert-butylhydroquinone	13.8
methyl gallate	13.5
3-hydroxybenzoic acid	13.1
4-hydroxybenzoic acid	12.9

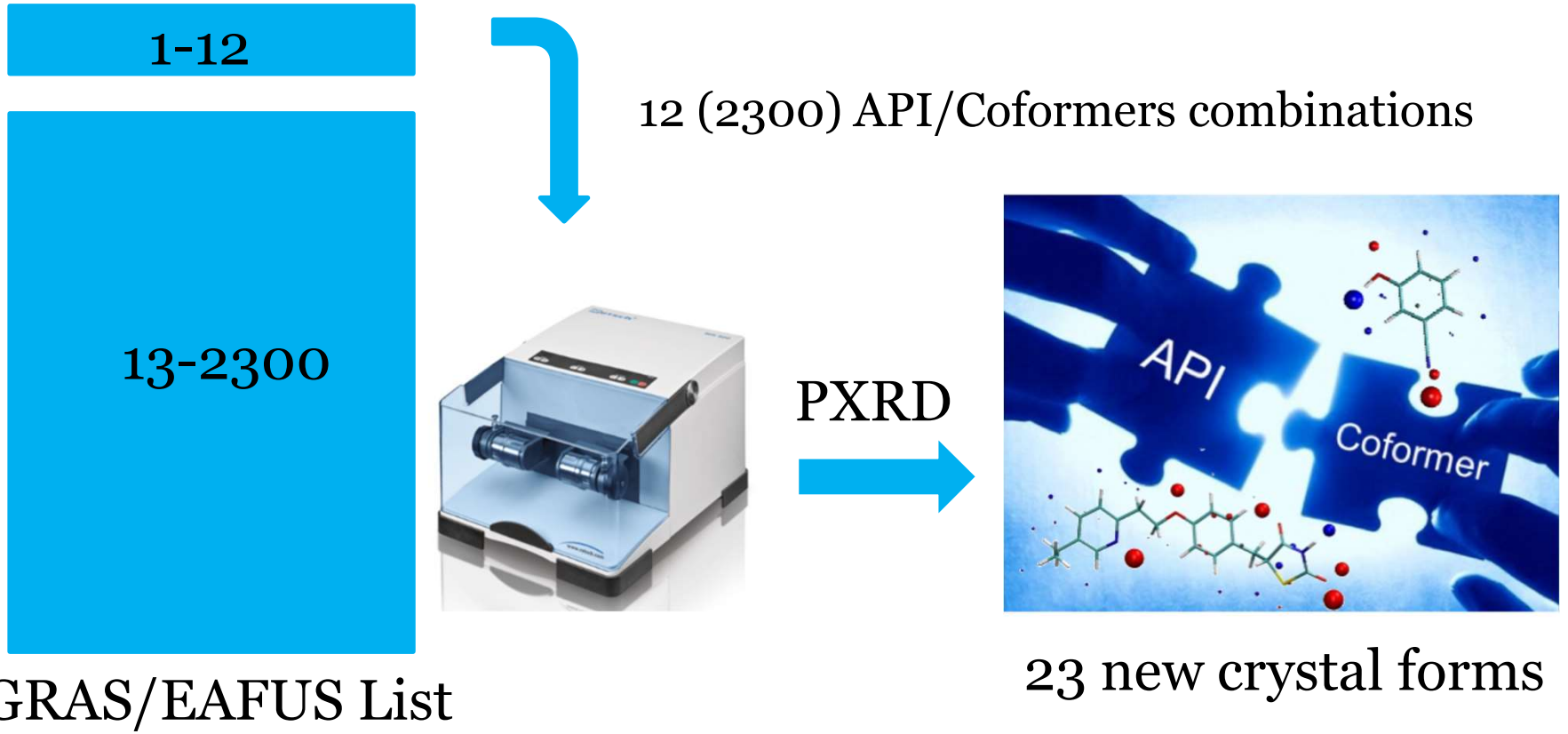
Library of potential coformers

How can crystals be engineered?

Sildenafil

Virtual and Experimental Cocrystal Screening

Selection of the coformer candidates



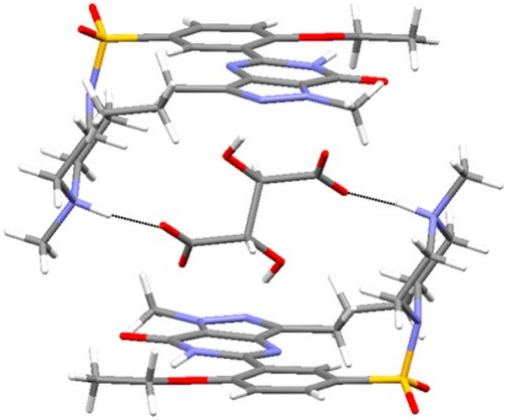
How can crystals be engineered?

Sildenafil

Virtual and Experimental Cocrystal Screening

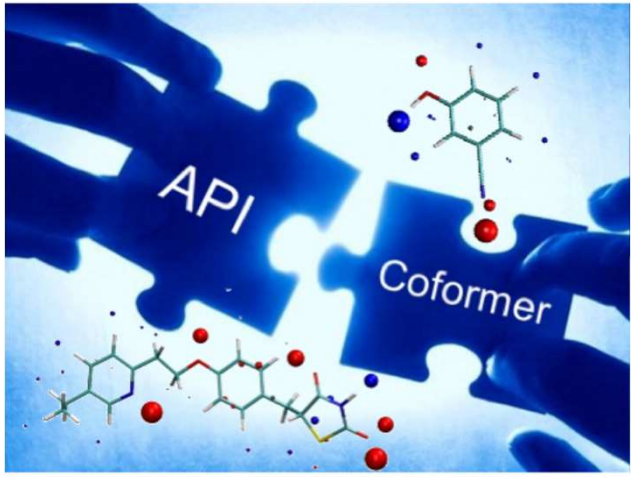
Selection of the coformer candidates

12 (2300) API/Coformers combinations



GRAS/EAFUS List

PXRD



23 new crystal forms

Questions

Crystal Engineering

- Why should a chemist be interested in crystals?
- How can crystals be engineered?

Nutraceutical Cocrystals

- **Why do we need to improve Nutraceuticals?**
- How can we improve Nutraceuticals?

Why do we need to improve Nutraceuticals?

•Life expectancy has been substantially improved worldwide

•This improvement in life expectancy has not been accompanied by the same increase in healthspan

•Longevity supplements are in pole position to be the first set of effective interventions to improve healthspanin aging population

•However, **many active ingredients** that are being researched and used **within longevity supplements**, mostly polyphenols, **show important problems related to their physicochemical properties**

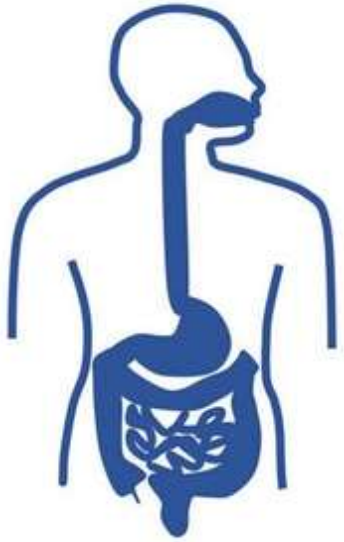
Why do we need to improve Nutraceuticals?

Three great limitations

Many Nutraceuticals used as potential pharmaceutical drugs, dietary supplements or added to functional food, show problems related with their physicochemical properties

Poor stability

Poor aqueous solubility



Low bioavailability

Questions

Crystal Engineering

- Why should a chemist be interested in crystals?
- How can crystals be engineered?

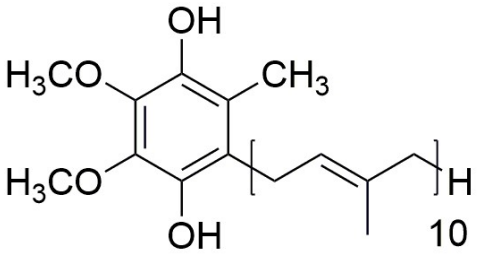
Nutraceutical Cocrystals

- Why do we need to improve Nutraceuticals?
- **How can we improve Nutraceuticals?**

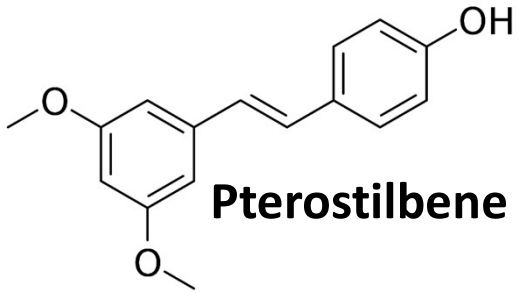
How can we improve Nutraceuticals?

Four Case Studies

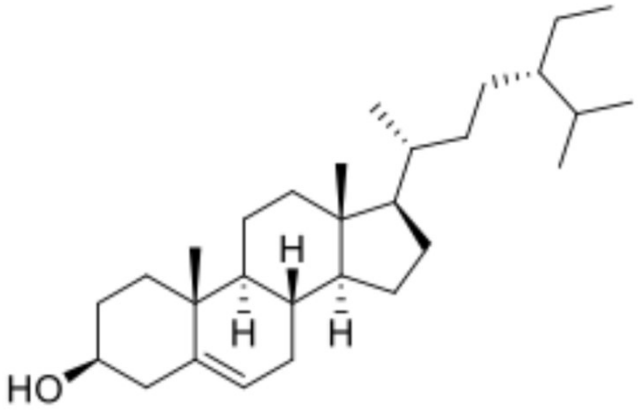
Nutraceuticals with physicochemical limitations solved by means of cocrystallization



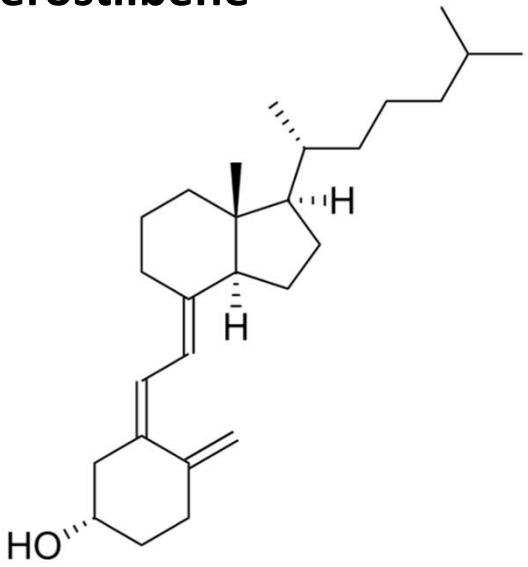
Ubiquinol



Pterostilbene



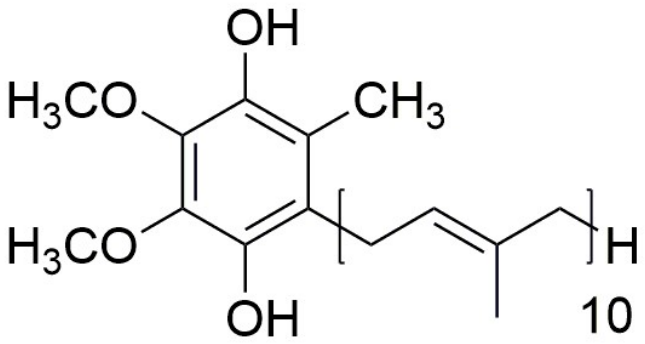
β-sitosterol



Cholecalciferol

How can we improve Nutraceuticals?

Ubiquinol



Coenzyme Q10 is a vitamin-like compound. Ubiquinol is the reduced form of Ubiquinone but more bioavailable and highly unstable

Present in many different food sources, supports optimal heart health, energy production, prevents damage by oxidative stress, etc.

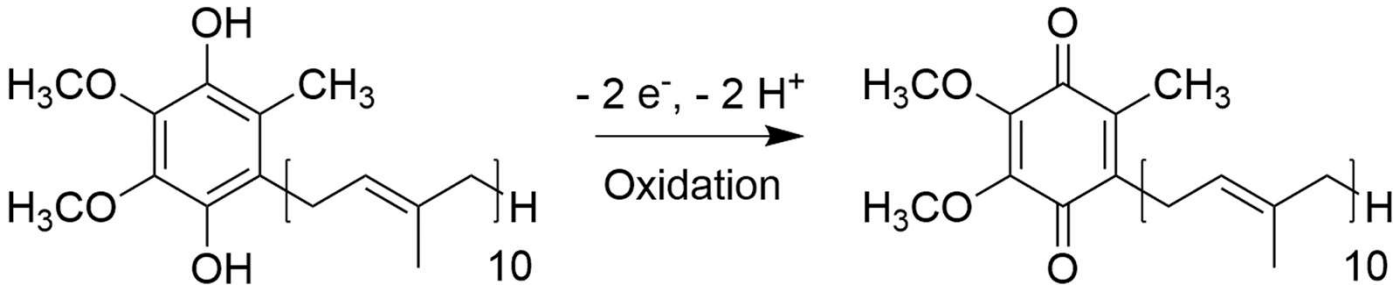
Limitations

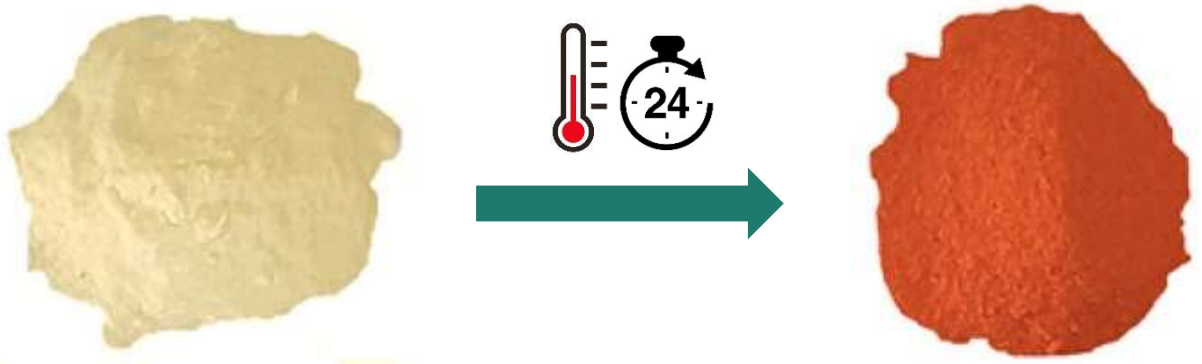
- 

Very low chemical stability

How can we improve Nutraceuticals?

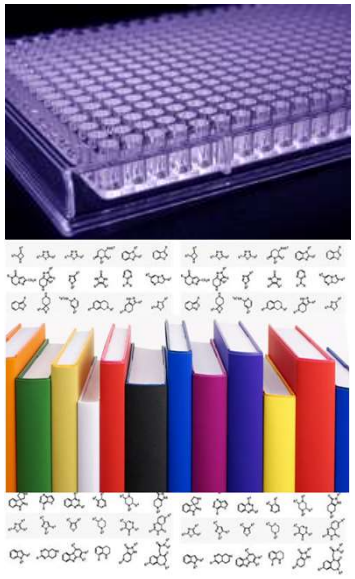
Ubiquinol





How can we improve Nutraceuticals?

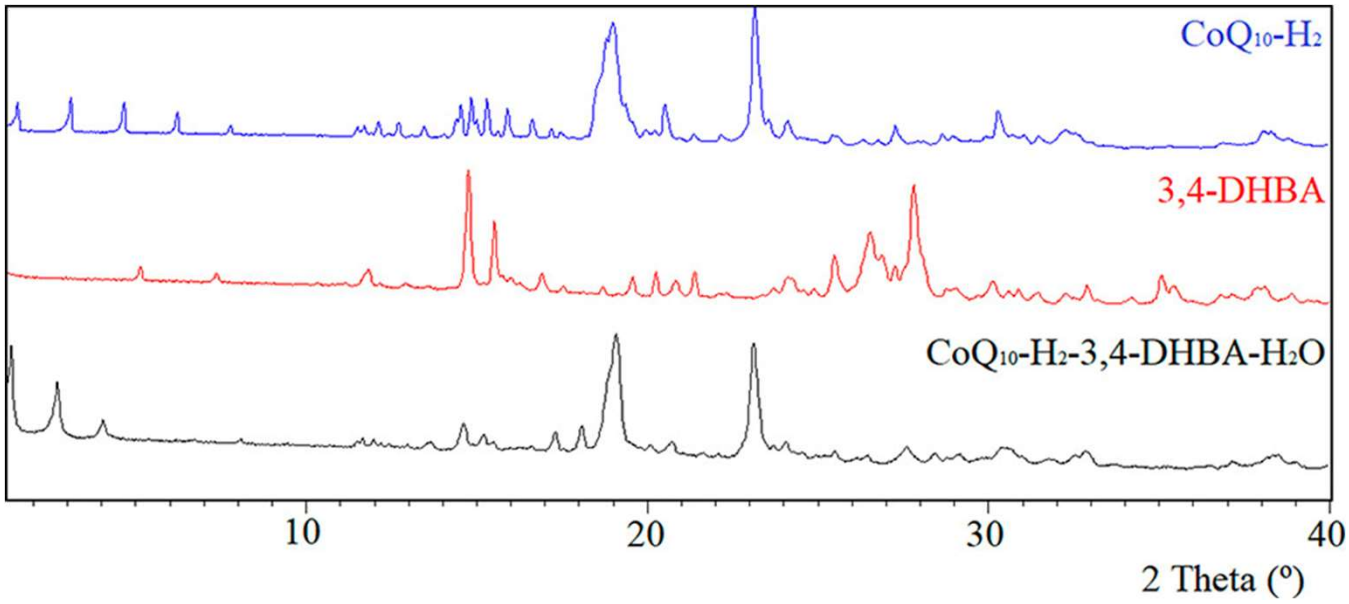
Ubiquinol



Cocrystal Screen

5 new solid forms from 11 coformers

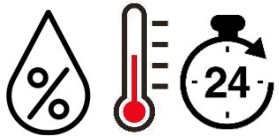
3,4-dihydroxybenzoic acid
3-hydroxybenzoic acid
3,5-dihydroxybenzoic acid
2,5-dihydroxybenzoic acid
Resorcinol

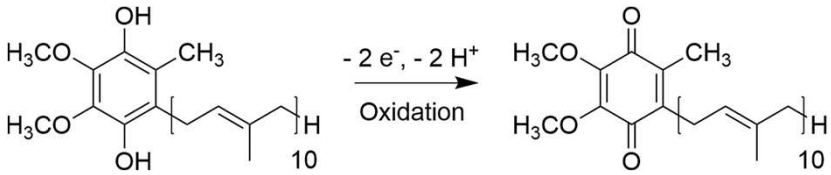


How can we improve Nutraceuticals?

Ubiquinol

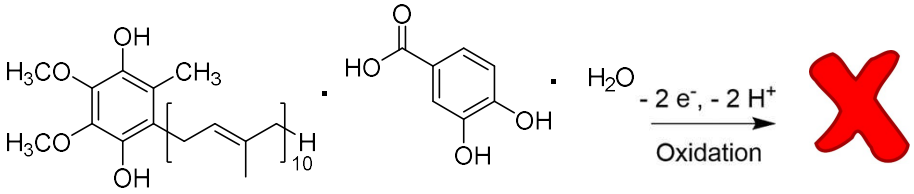
Normal Storage Conditions
25ºC / 60% RH



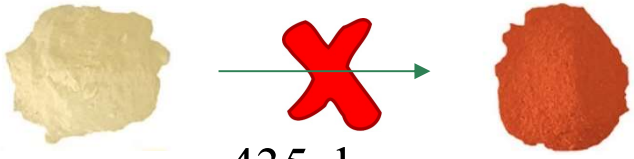


26 days

Stress Storage Conditions
40ºC / 75% RH



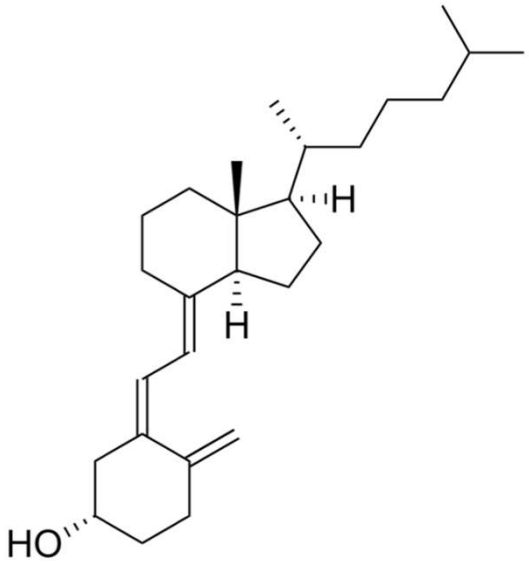
Cocrystal monohydrate



435 days

How can we improve Nutraceuticals?

Cholecalciferol



Vitamin D_3 (Cholecalciferol) is naturally synthesized in skin. It is important for maintaining calcium levels and promoting bone health and development, but also for the immune system

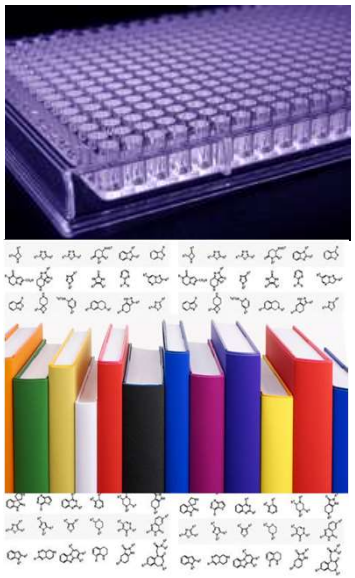
Limitations

- 

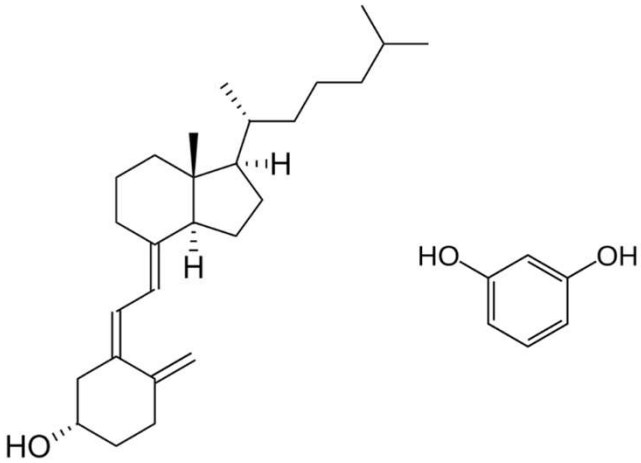
Very low chemical stability

How can we improve Nutraceuticals?

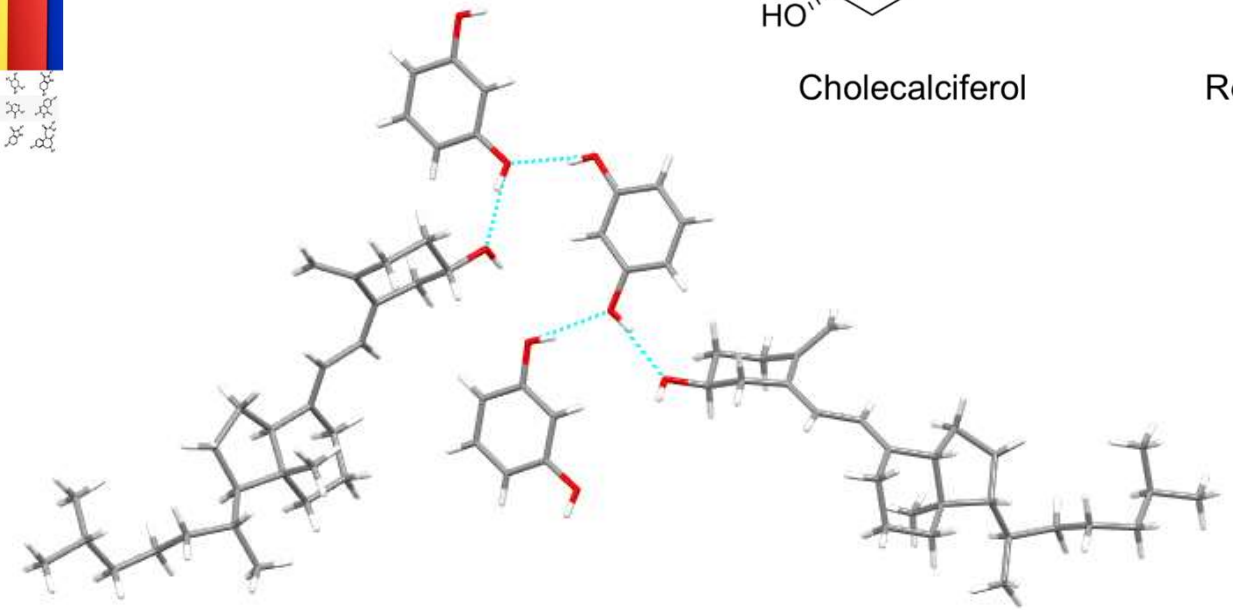
Cholecalciferol



Cocrystal Screen

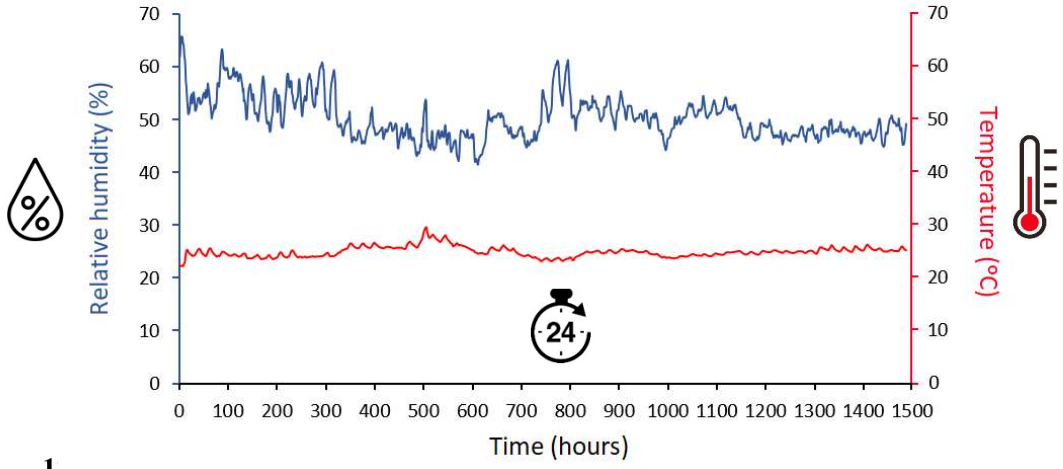


Cholecalciferol Resorcinol

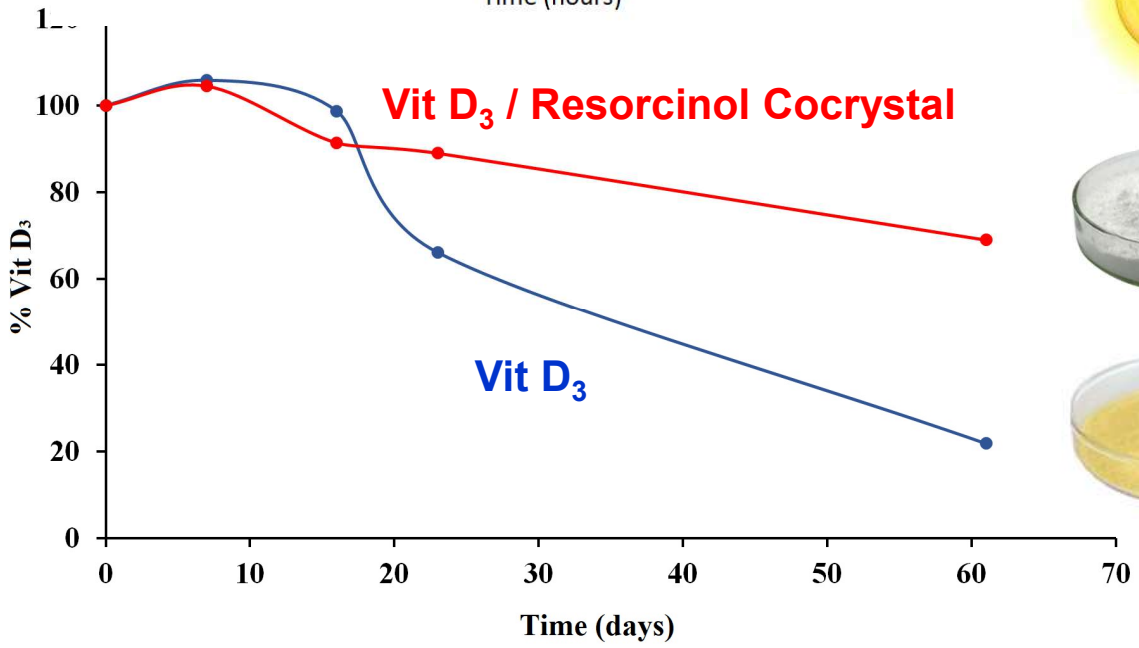


How can we improve Nutraceuticals?

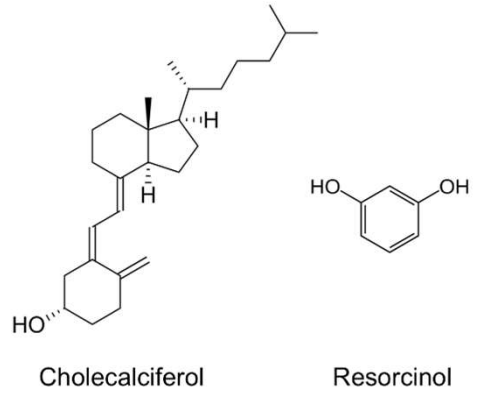
Cholecalciferol



Evolution of content of Vit D_3 in the cocrystal *vs* the commercial Vit D_3 against irradiation of 5000 lx at 25 °C.

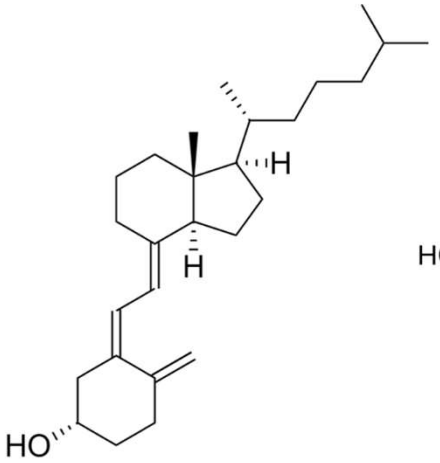


Cocrystal

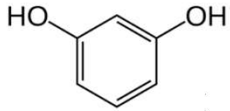


How can we improve Nutraceuticals?

Cholecalciferol



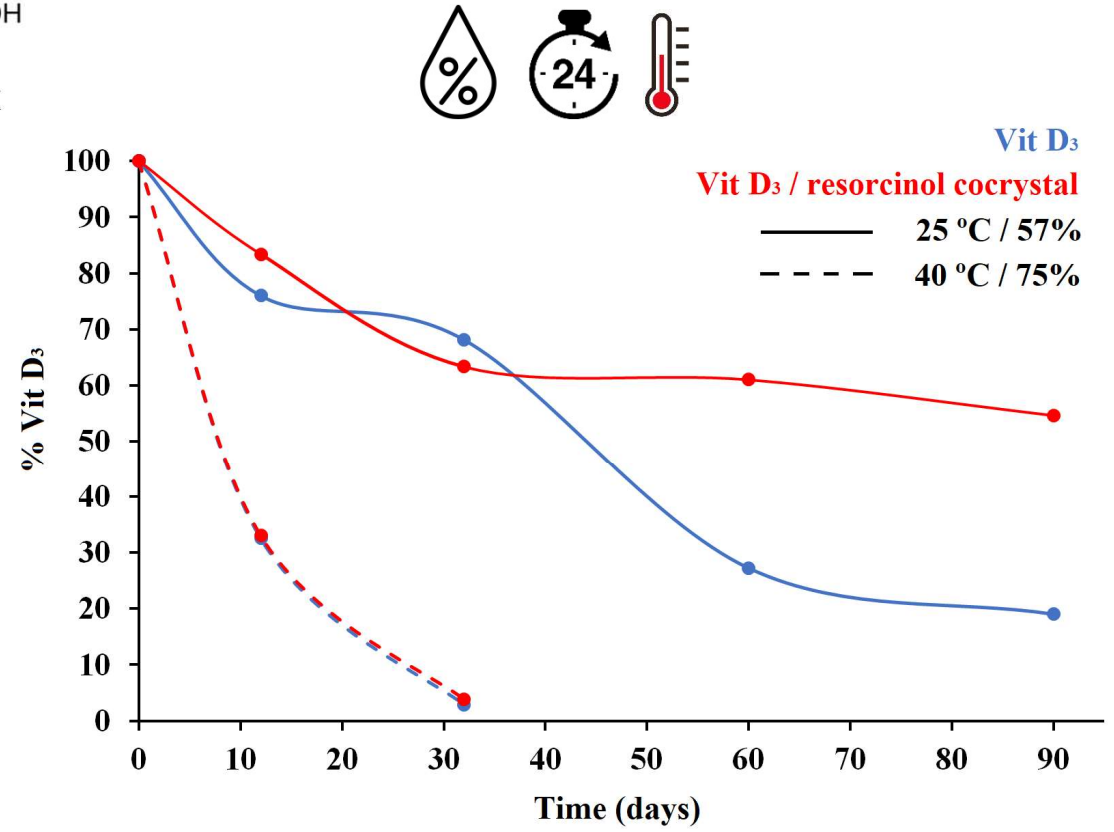
Cholecalciferol



Resorcinol

Nutritional additive	mg/kg
Copper	4,35
Zinc	17,92
Manganese	5,39
Iodine	137
Selenium	91
Cobalt	47
Zinc	5

Evolution of content of cholecalciferol (Vit D_3) in the cocrystal *vs* the commercial cholecalciferol in the mineral and vitamin premix.



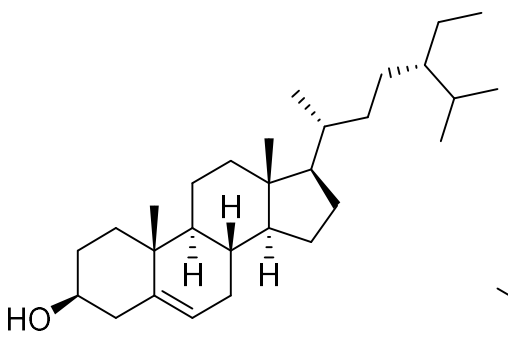
How can we improve Nutraceuticals?

β-sitosterol

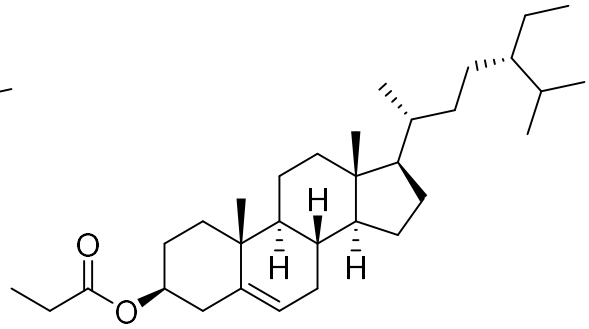
- ✓ Phytosterols (PSs) are substances similar in structure to cholesterol, present in plants. β-sitosterol is the more common phytosterol.

How can we improve Nutraceuticals?

β-sitosterol



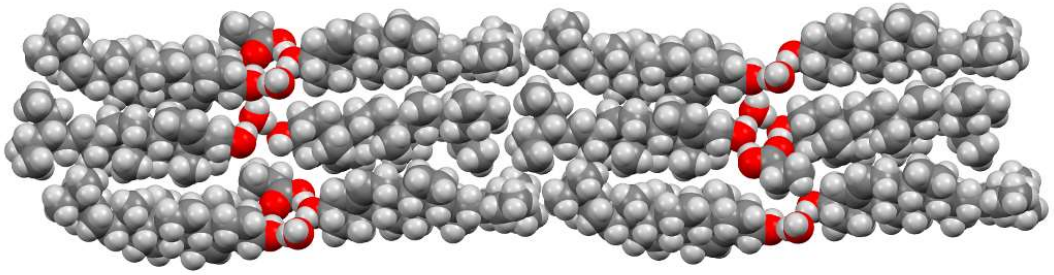
β-sitosterol



propionate ester of β-sitosterol

B–sitosterol has **low water solubility**. Its ester form improve its solubility, but doubles its manufacturing cost and easily degrades, leading to off-flavor issues.

Propionic acid β-sitosterol Cocrystal

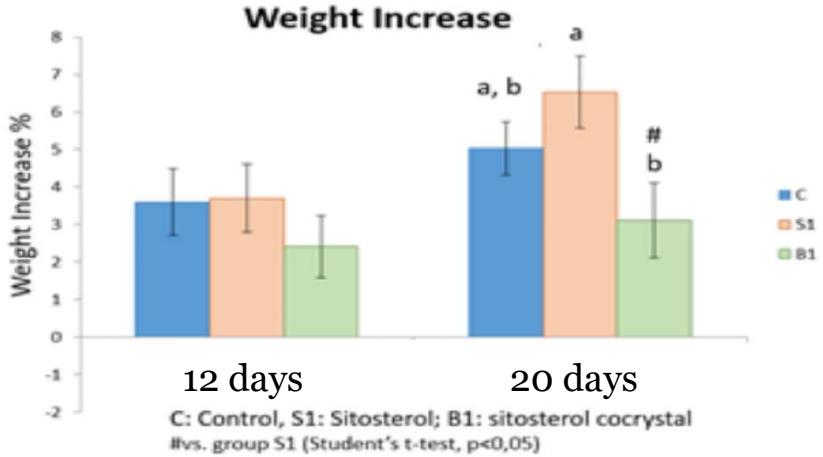


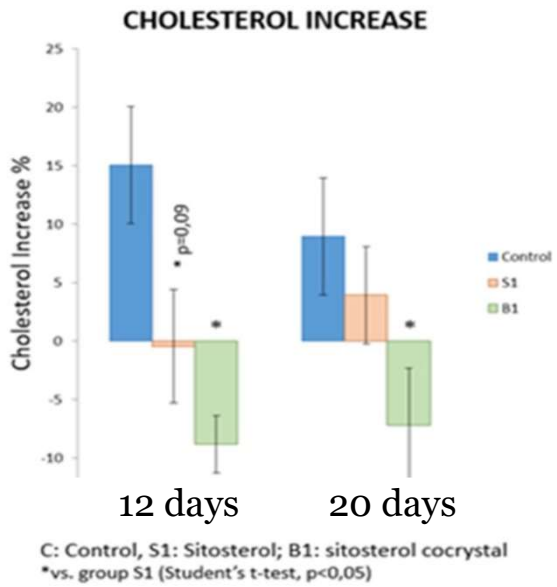
Compound	Log S	[API] (mg/ml)
β-Sitosterol	-6.07 (0.08)	0.36 (0.06)
β-Sitosterol cocrystal	-5.3 (0.2)	2.5 (1)

How can we improve Nutraceuticals?

β-sitosterol

In vivo study (22 days analysis in hamsters with obesogenic diet giving an equivalent to human dose of free β-sitosterol and the cocrystal).

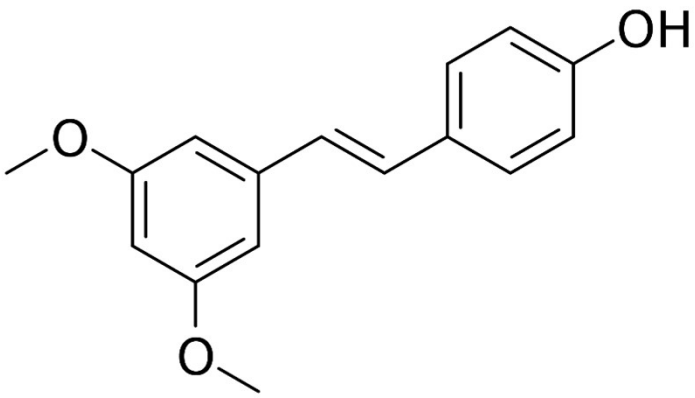




β–sitosterol cocrystal reduced the cholesterol increase much better than β–sitosterol itself in in vivo study in hamsters fed with an **obesogenic diet** (22 days), with equivalent doses. Also, improved effect on **obesity** (the increase in body weight was lower and the proportion of small adipocytes was higher).

How can we improve Nutraceuticals?

Pterostilbene



Stilbenoid found in many natural sources like blueberries

Potent antioxidant used in longevity supplements with brain health and anti-cancer properties

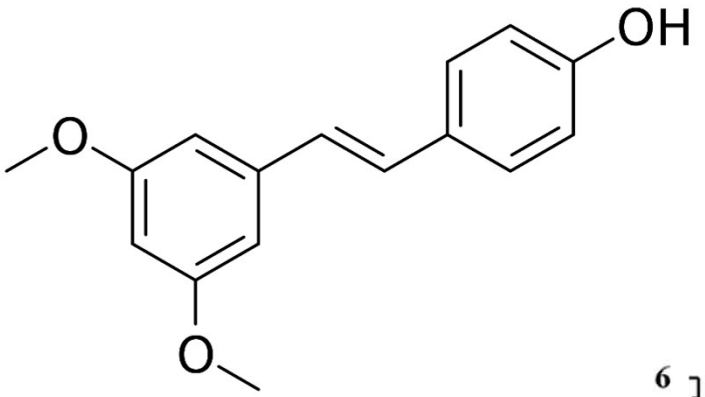
Limitations

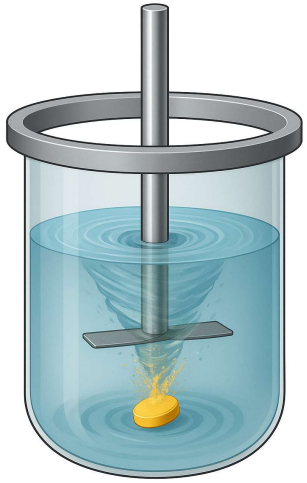
Poor aqueous solubility

Low bioavailability, only 5-16% of the total intake.

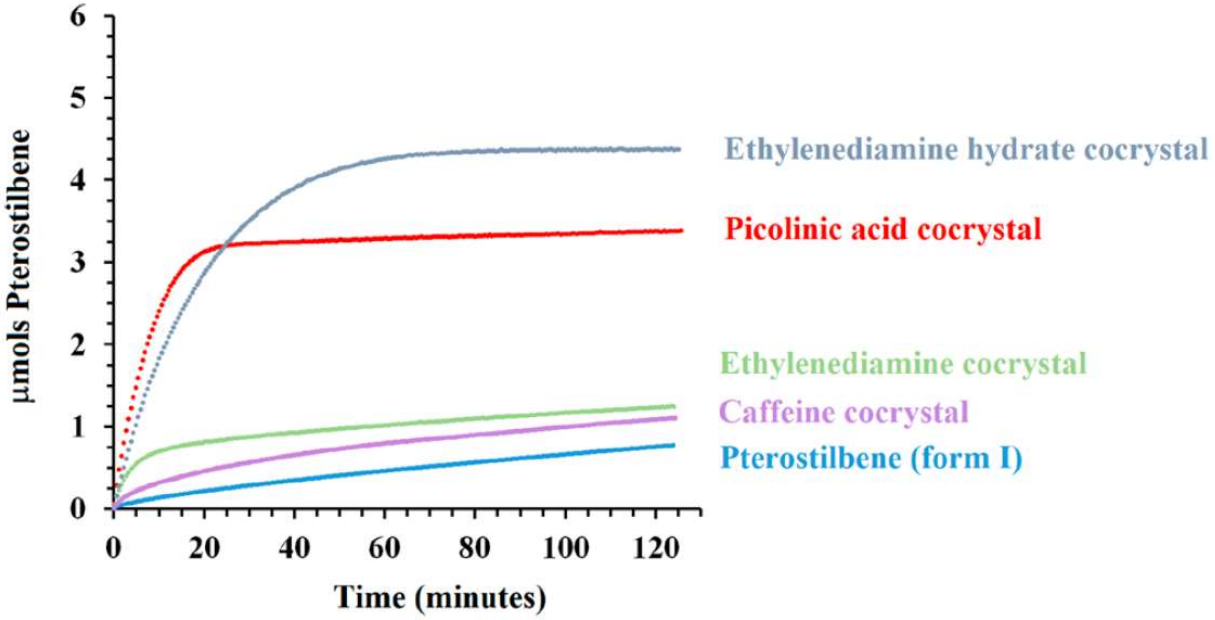
How can we improve Nutraceuticals?

Pterostilbene





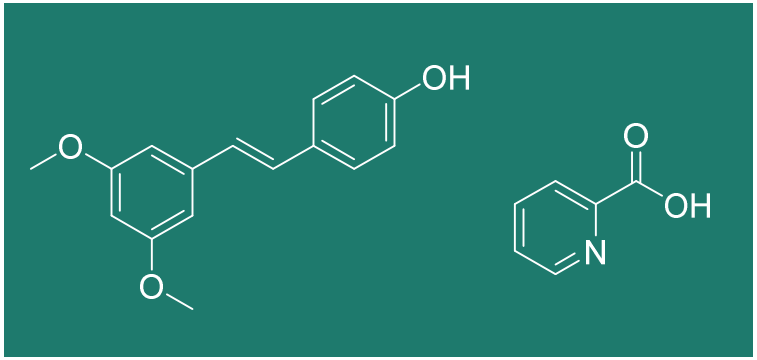
Cocrystal Screen produced 4 new cocrystals
Dissolution profiles in FaSSIF shows large improvement for two new cocrystals



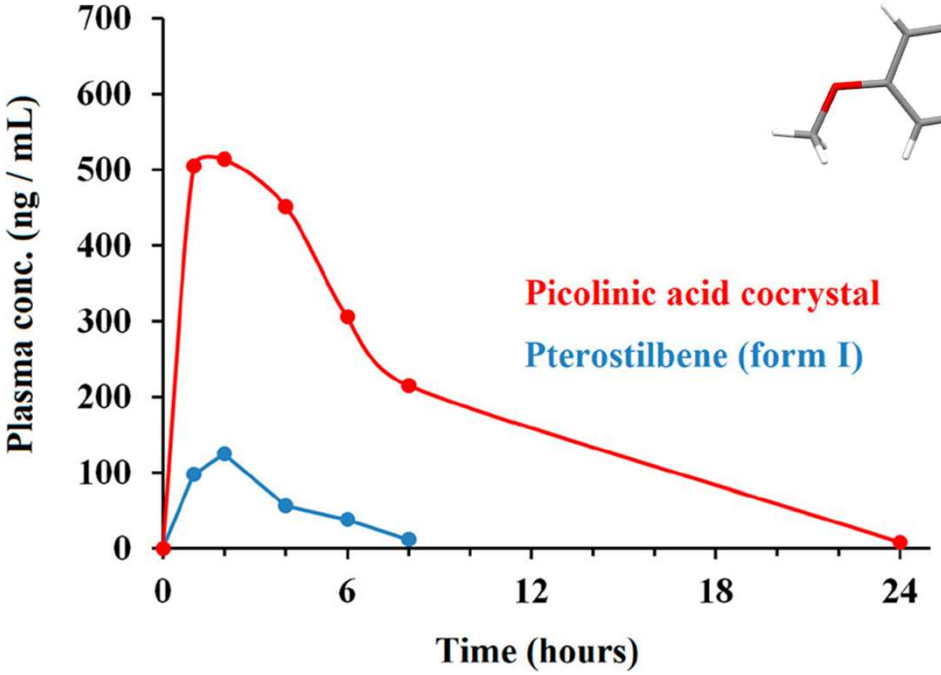
Crystal Growth & Design **2021**, 21, 4, 2315-2323

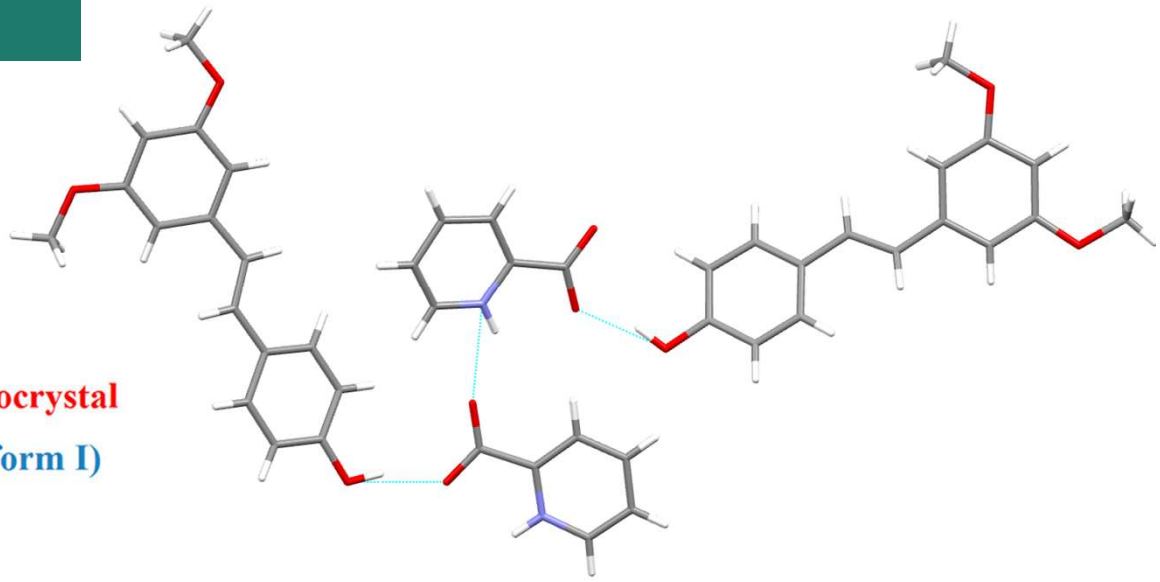
How can we improve Nutraceuticals?

Pterostilbene



Picolinic acid cocrystal is chosen for regulatory issues and because it shows a relative 10-fold improvement in oral bioavailability in rats

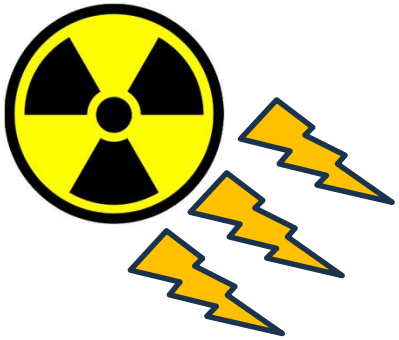




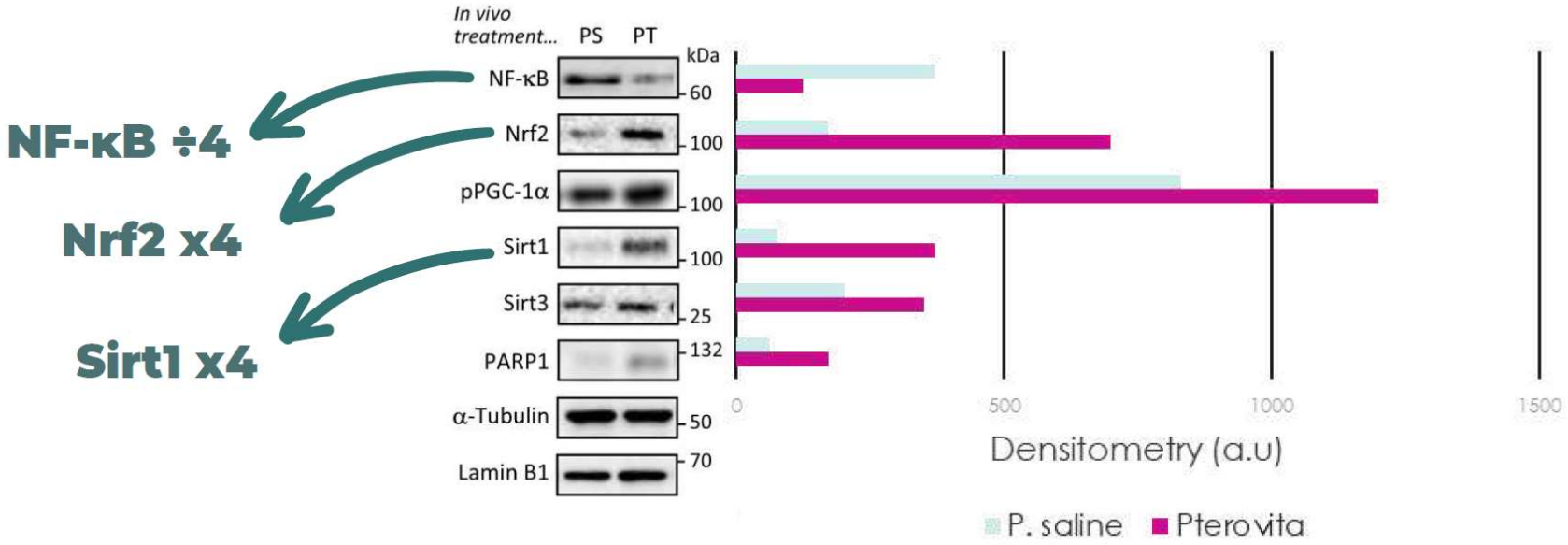
Crystal Growth & Design **2021**, 21, 4, 2315-2323

How can we improve Nutraceuticals?

Pterostilbene

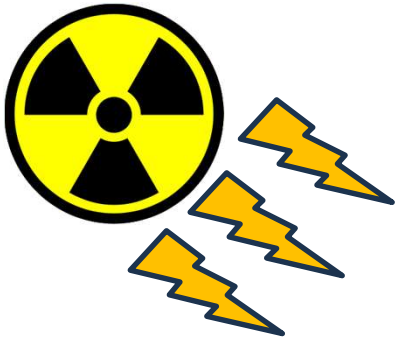


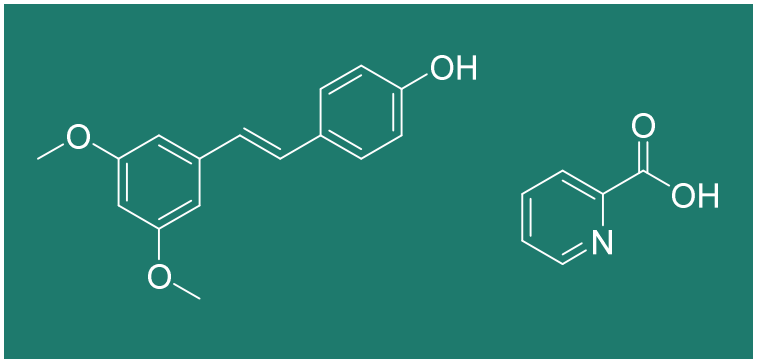
Antioxidant and antiaging activity with *in vivo* accelerated aging model (irradiated mice, LD50/30 7.2 Gy) achieving 100% survival after 90 days



How can we improve Nutraceuticals?

Pterostilbene





Applications to human health

Skin care (cosmetics)

Skin care (radiotherapy)

Well-being: nutritional supplements

ACKNOWLEDGEMENTS

Prof. Chris Hunter

Dr. Rafa Barbas

Dra. Lídia Bofill