

Aula 10 – 29/07

Tópicos Especiais em Química Medicinal

Tópicos Especiais
em Química Medicinal

Código: **BMF-777**

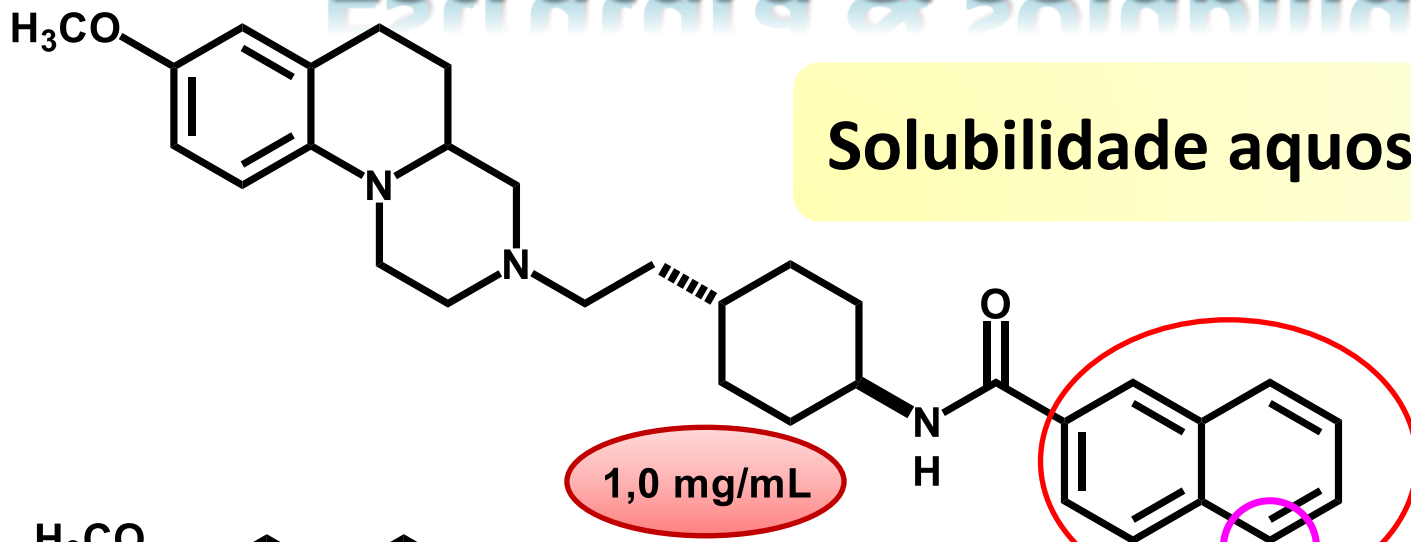
Carga Horária: 45 horas

Créditos: 3 créditos



Estrutura & solubilidade...

Solubilidade aquosa



1,0 mg/mL

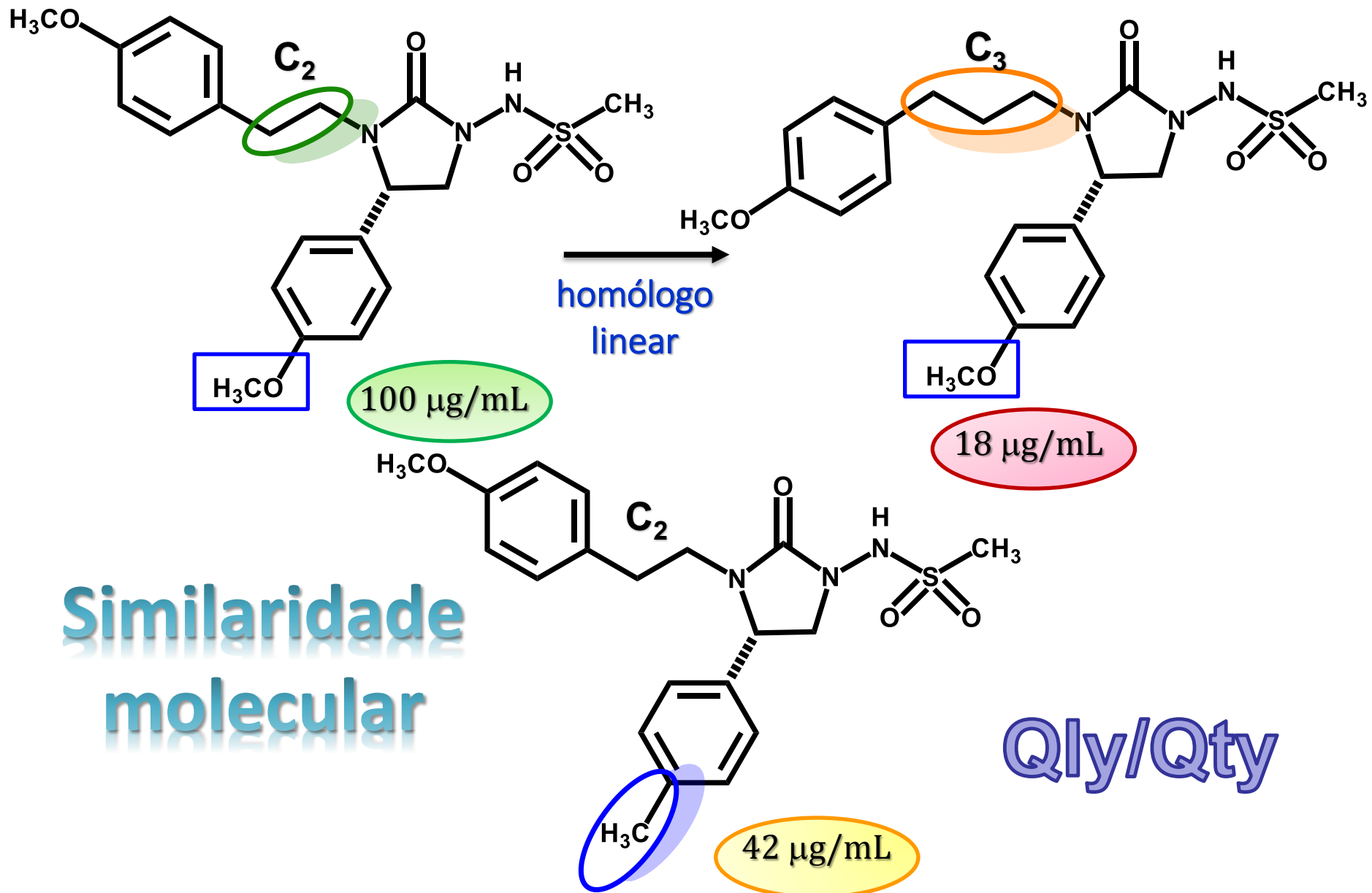
isósteros

Similaridade
molecular

51,0 mg/mL



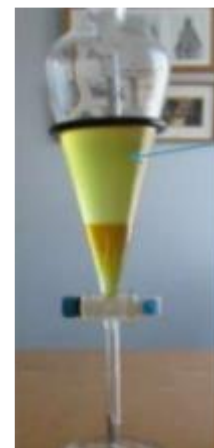
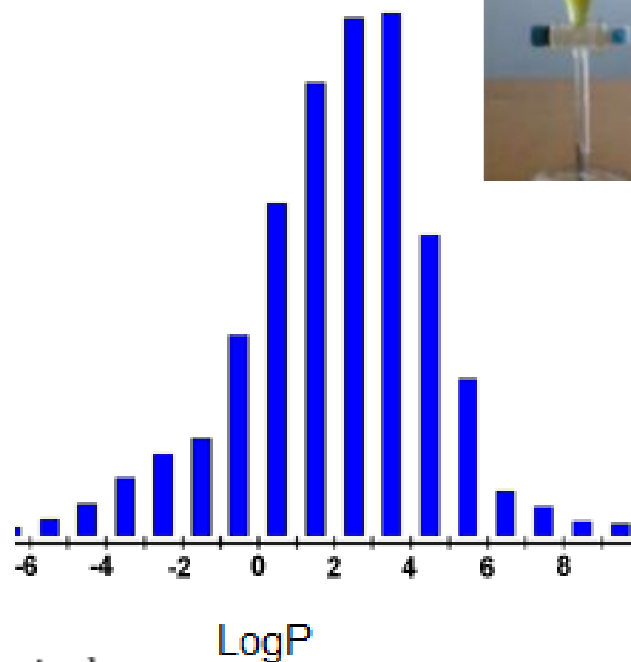
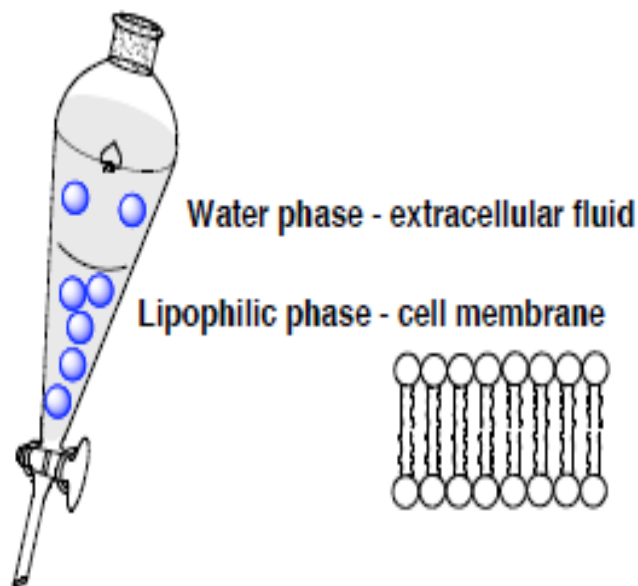
Homologia & solubilidade...



Coeficiente de Partição

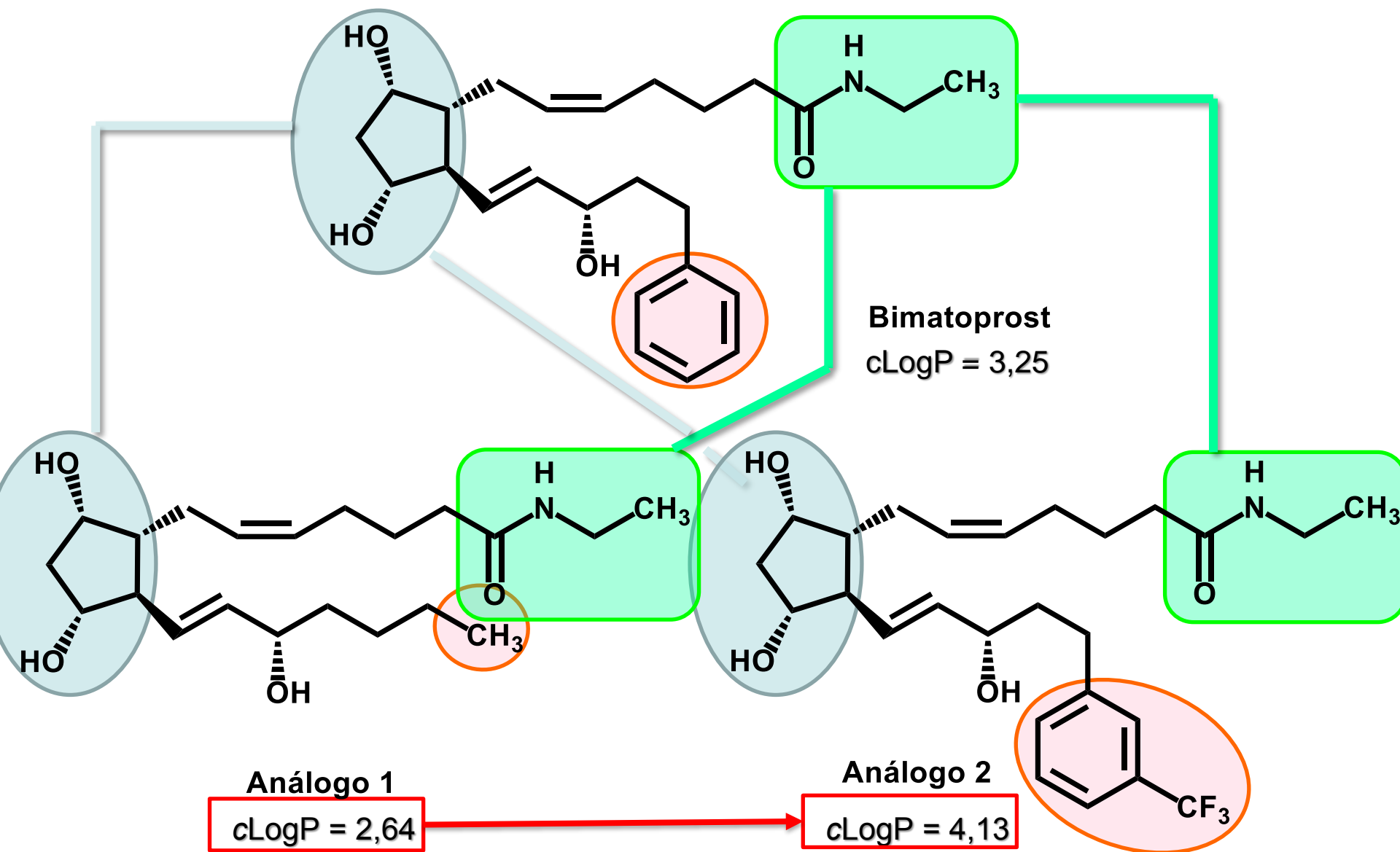
LogP

$\log P$ - P: Partition coefficient between *n*-octanol and water



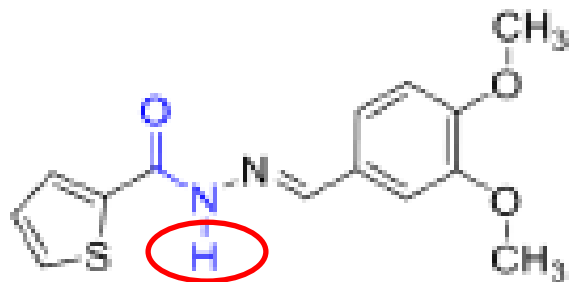
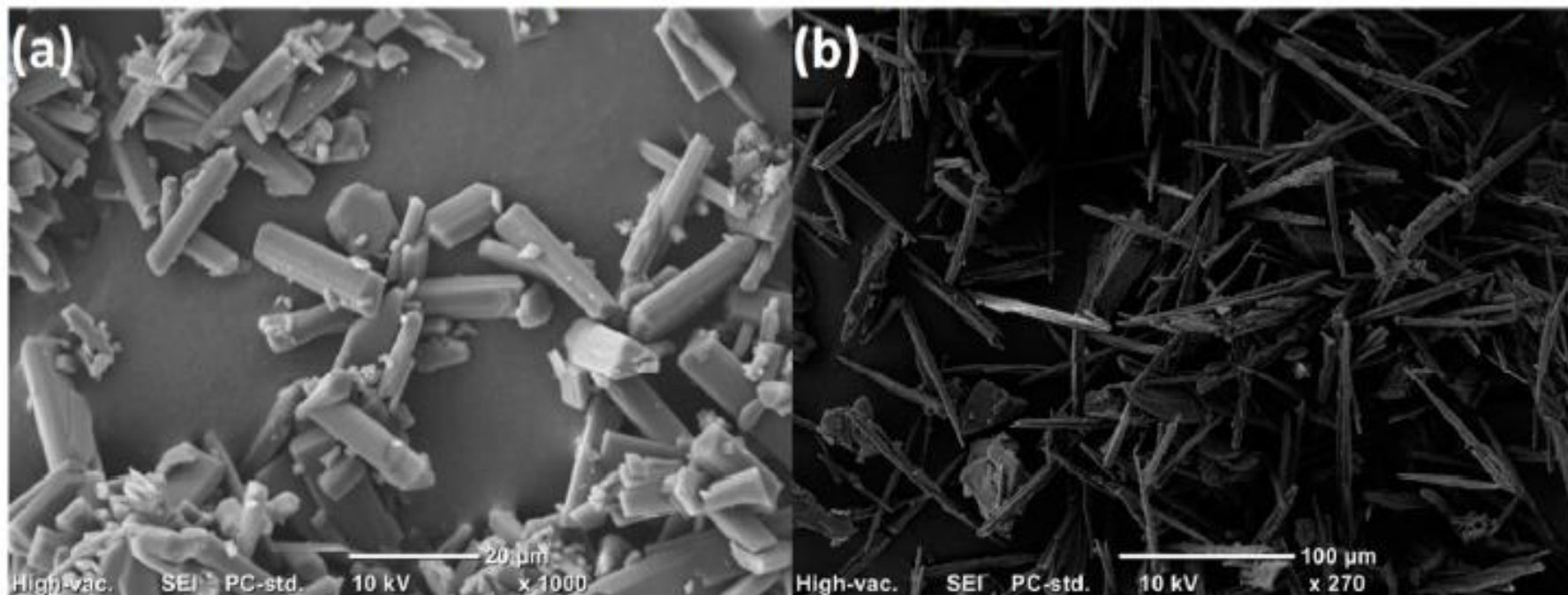
$$\log P_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}^{\text{un-ionized}}}{[\text{solute}]_{\text{water}}^{\text{un-ionized}}} \right)$$

Solubilidade X cLog P

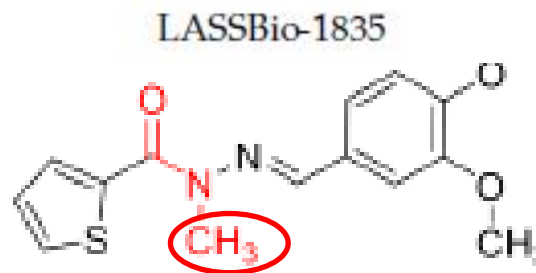


Conformação & solubilidade

Scanning electron microscopy (SEM) image

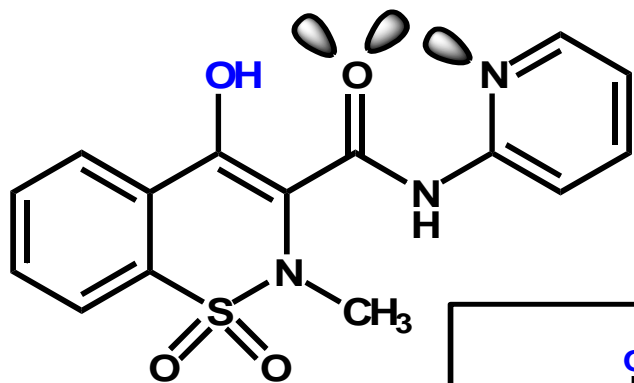


LASSBio-1834



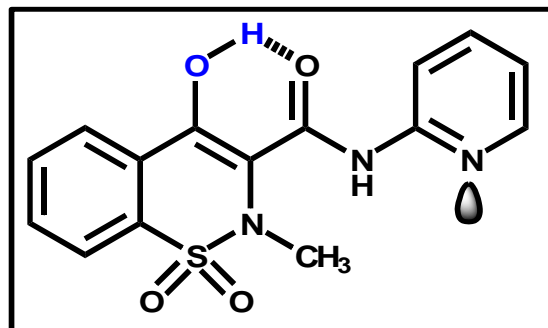
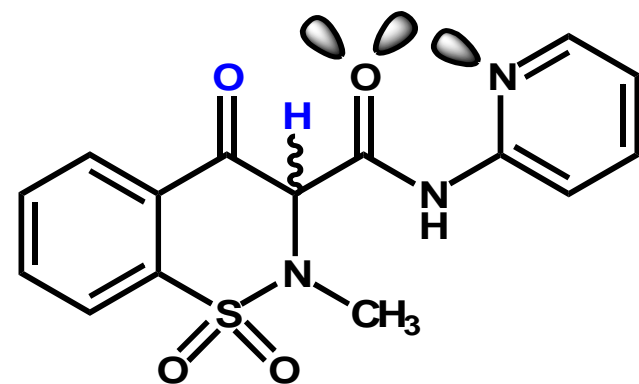
LASSBio-1835

Tautomeria

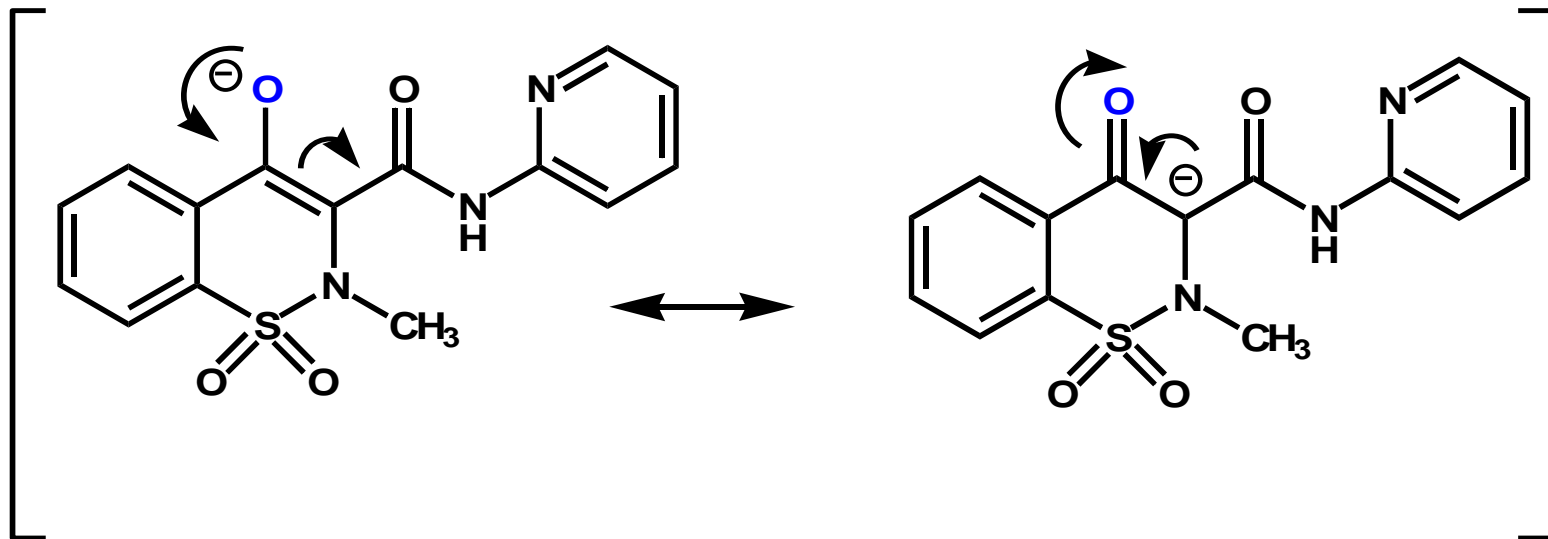


$C_{15}H_{13}N_3O_4S$

Piroxicam



B:

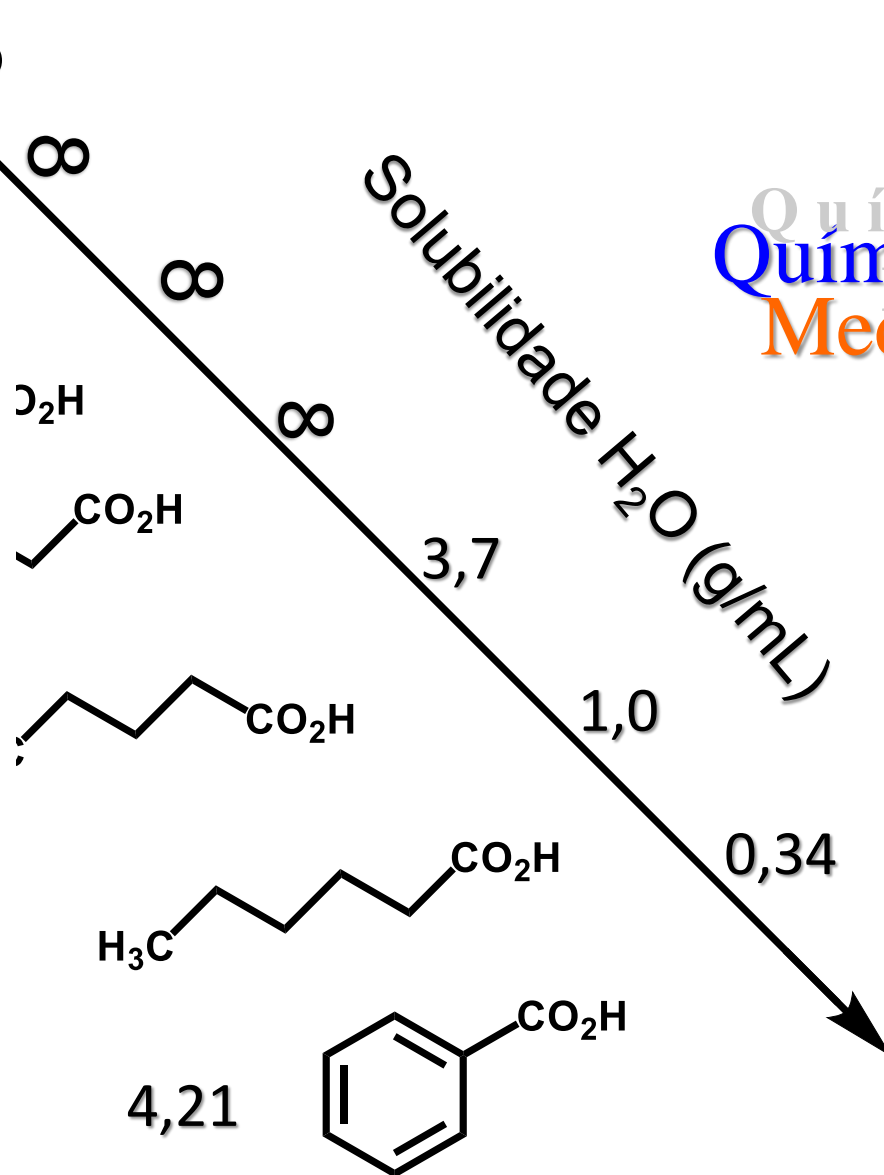


Propriedades moleculares

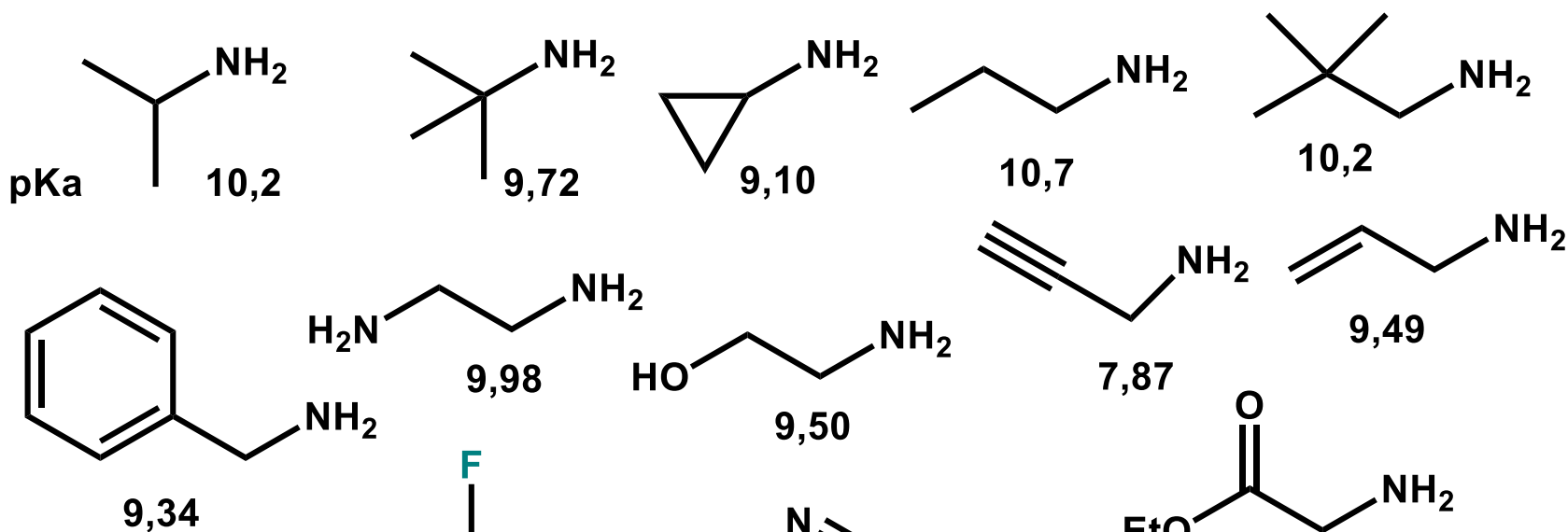
Química
Medicinal

27C H—CO₂H

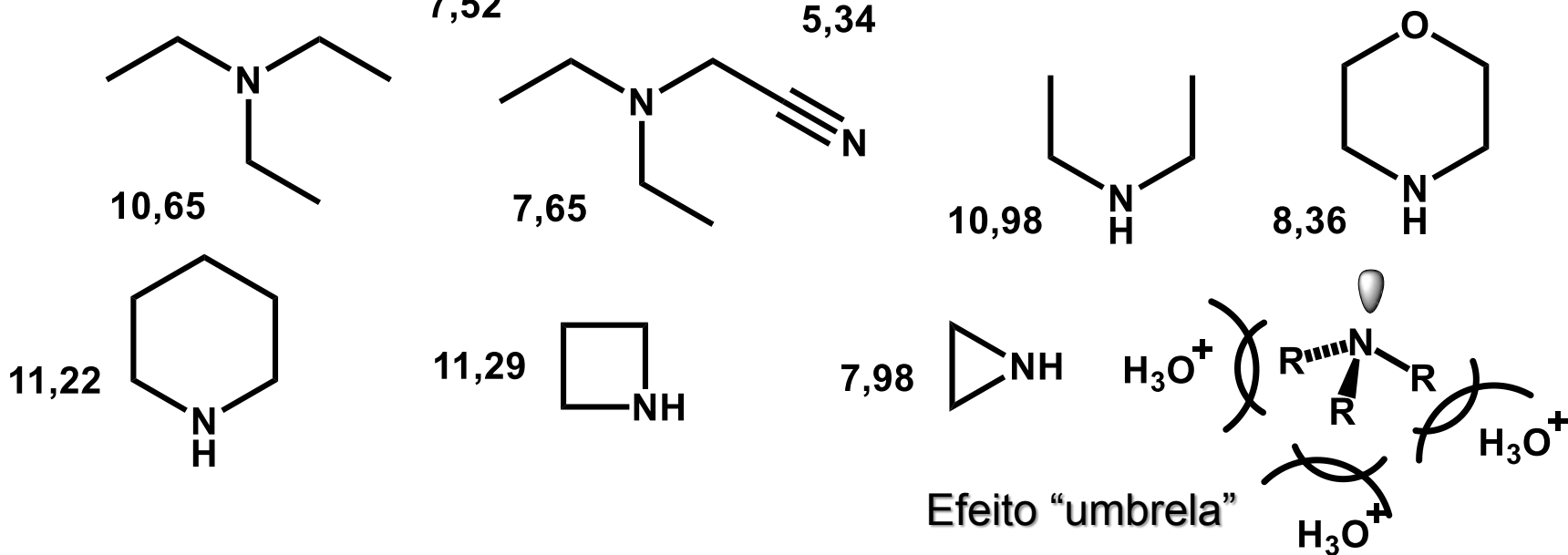
Fluido	pH
Humor aquoso	7.2
Sangue	7.4
Colon	5-8
Duodeno (vazio)	4.4-6.6
Duodeno (alimentado)	5.2-6.2
Saliva	6.4
Intestino Delgado	6.5
Estômago (vazio)	1.4-2.1
Estômago (alimentado)	3-7
Suor	5.4
Urina	5.5-7.0



Propriedades moleculares



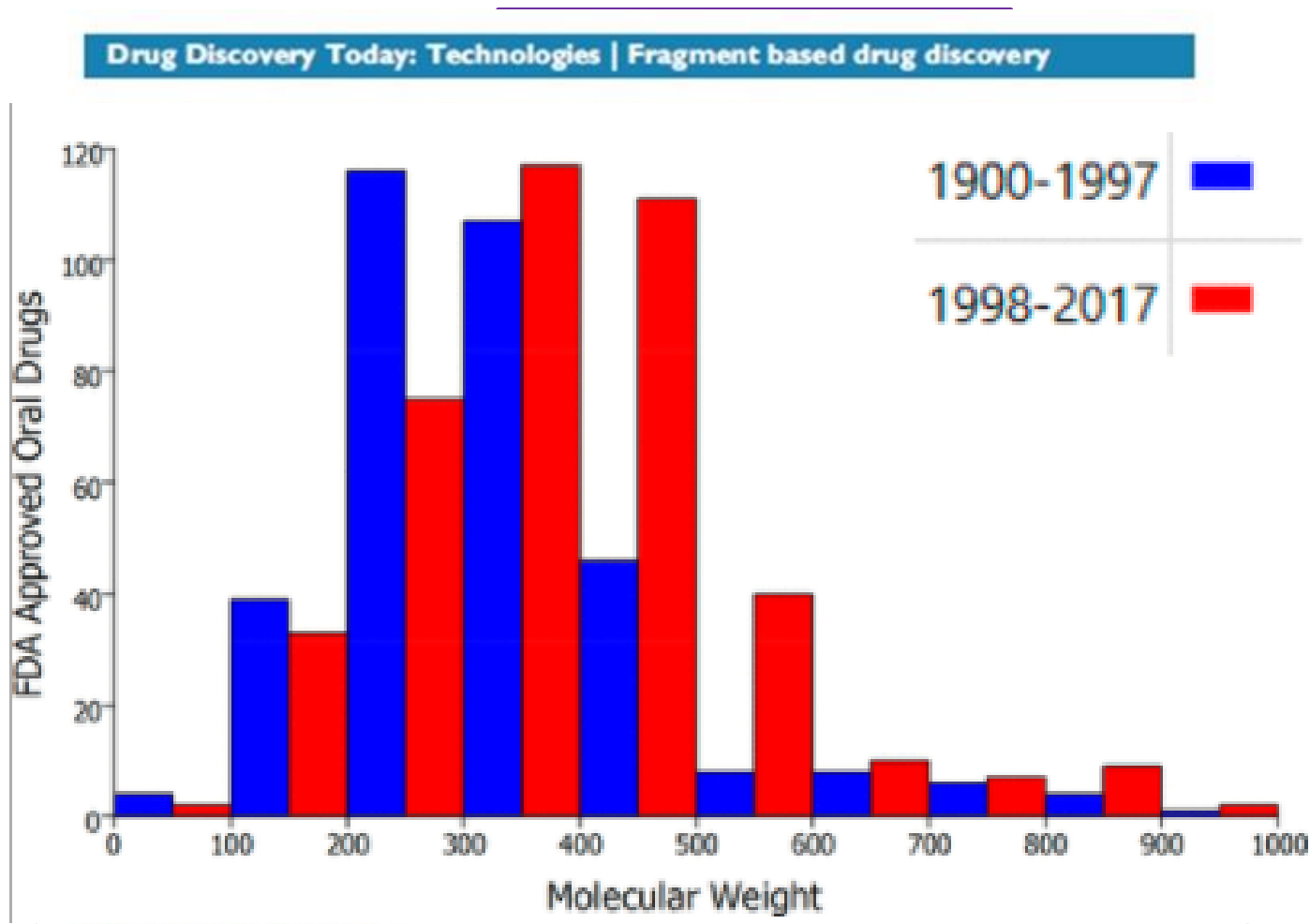
Aminas





Propriedades moleculares

Regras dos 5 de Lipinsky



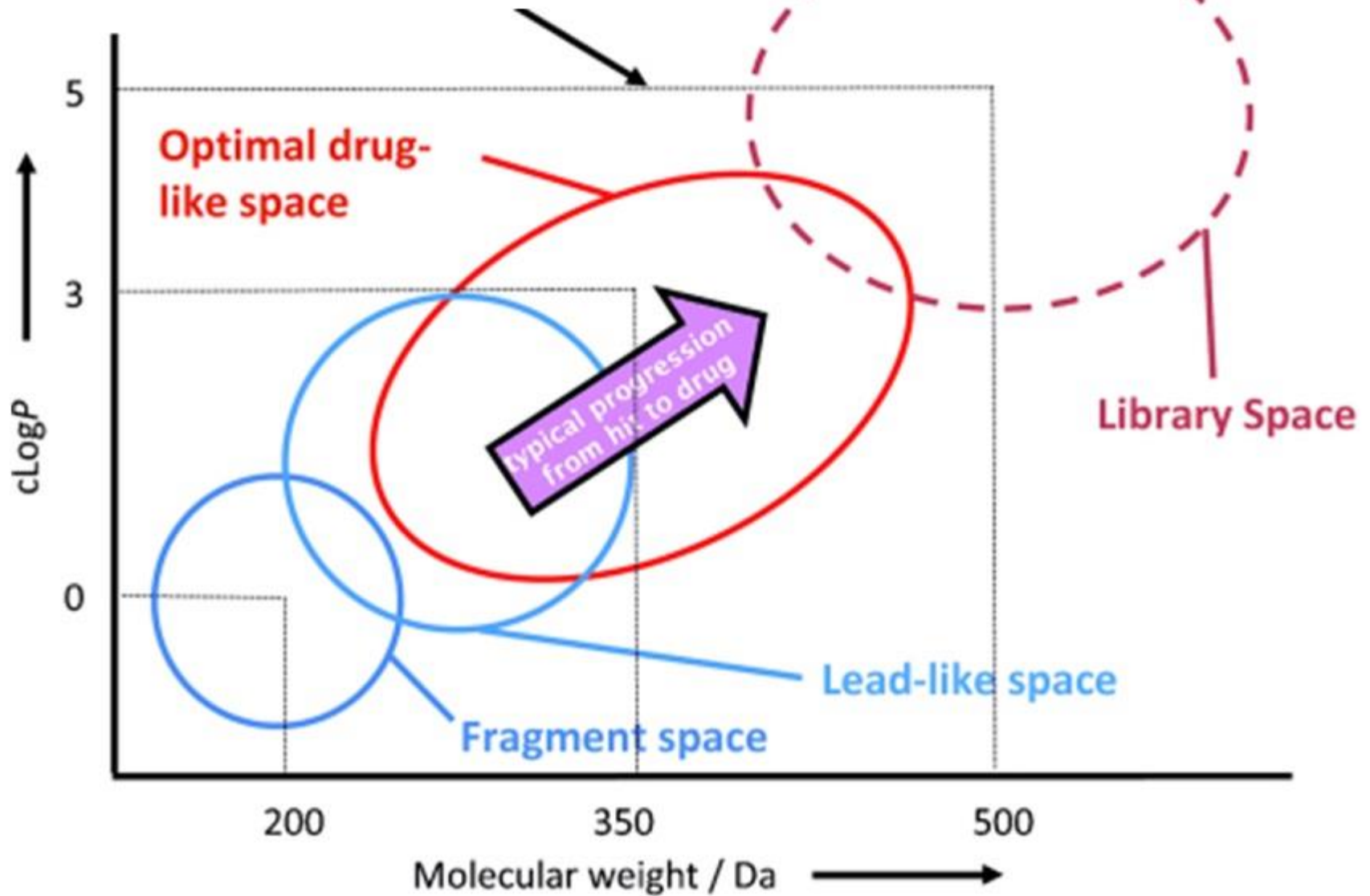
[Advanced Drug Delivery Reviews](#)

MD Shultz, Two Decades under the Influence of the Rule of Five and the Changing Properties of Approved Oral Drugs, *J. Med. Chem.* **2019**,62, 1701-1714.



Propriedades moleculares

“Lipinski Rule of 5” Space





Fármacos são sólidos >> líquidos



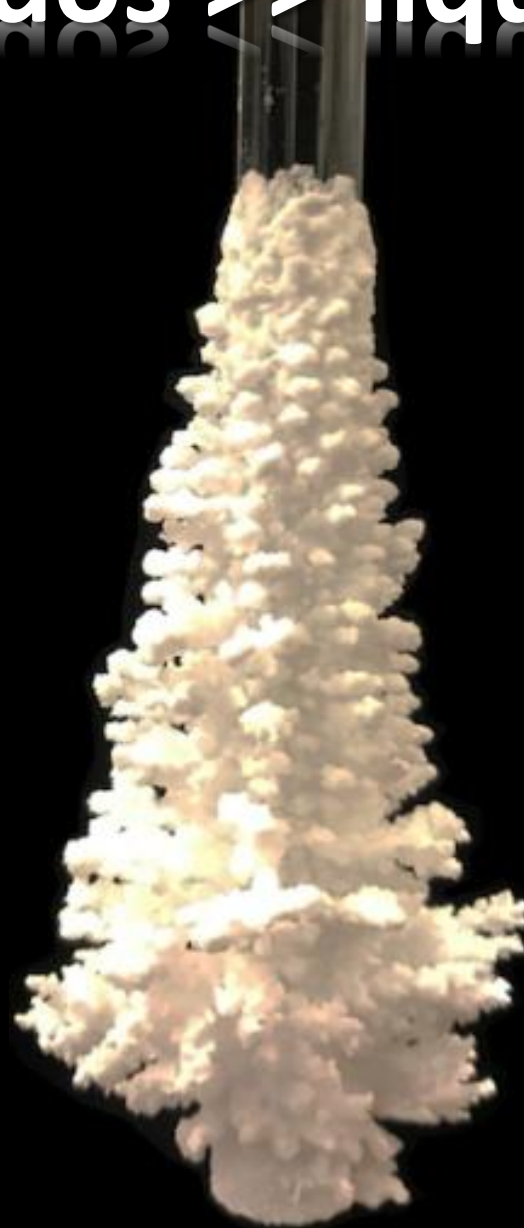
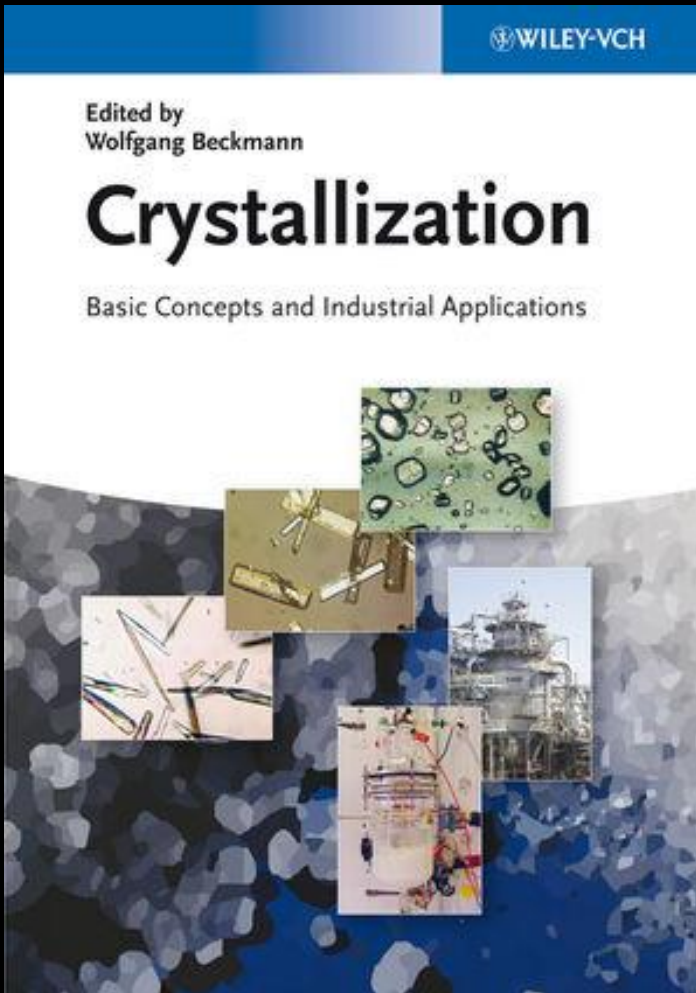


Fármacos são sólidos >> líquidos



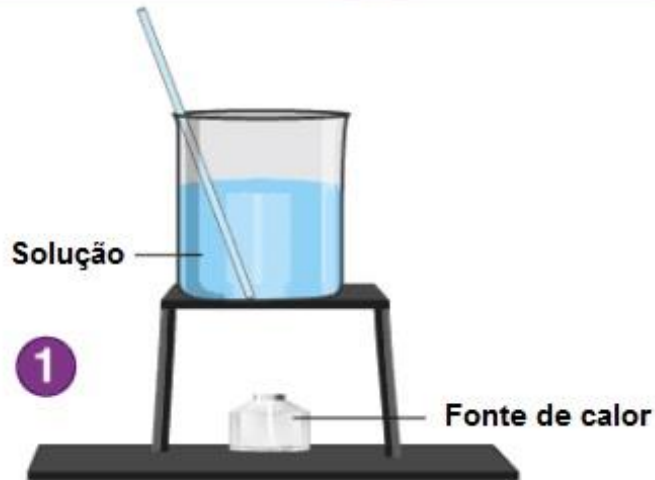


Fármacos são sólidos >> líquidos





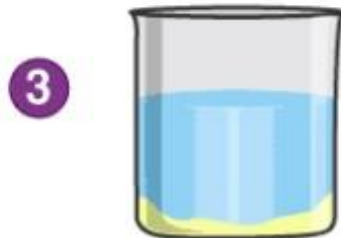
Cristalização



O sólido impuro é dissolvido (EtOH)



A solução é concentrada por aquecimento brando



A solução concentrada é deixada resfriar. Surgirão cristais iniciais.

À solução resfriada pode-se adicionar água destilada para >> a cristalização



A solução residual é colocada sobre papel de filtro, e os cristais são "secos" entre folhas de papel de filtro. Retira-se com espátula e seca-se sob vácuo em aparelho de secagem.



Propriedades moleculares

Fármacos & Polimorfismo

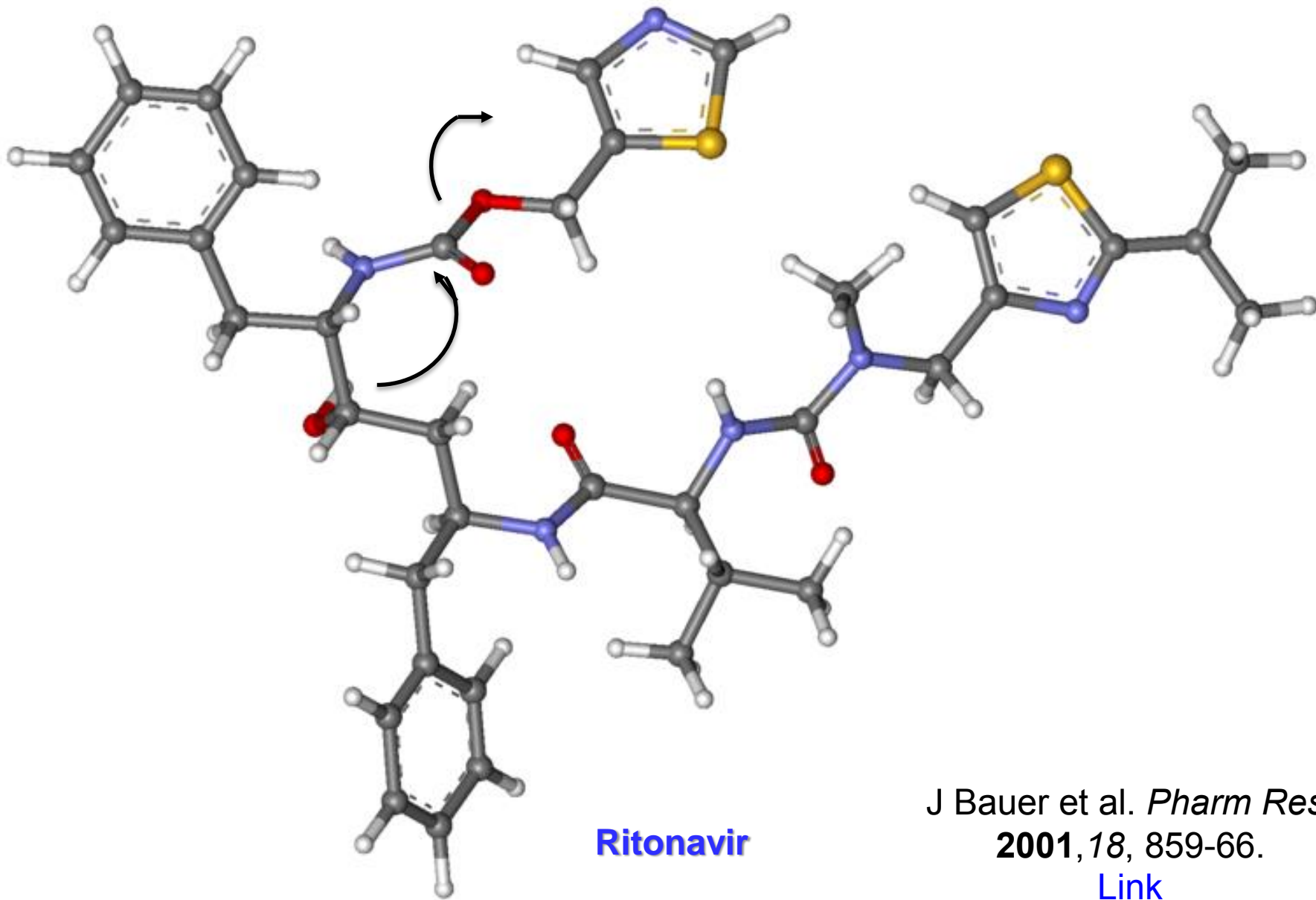


FN Costa, FF Ferreira, TF da Silva, EJ Barreiro, LM Lima, D Braza, RC Barroso, Structure Re-determination of LASSBio-294 – a cardioactive compound of the *N*-acylhydrazone class – using X-ray powder diffraction data, *Powder Diffraction* **2013**, 28, S491-S509

JR Azevedo, J-J Letourneau, F Espitalier, MI Ré, Solubility of a New Cardioactive Prototype Drug in Ionic Liquids, *J. Chem. Eng. Data* **2014**, 59, 1766–1773.



Ritonavir: an extraordinary example of conformational polymorphism



J Bauer et al. *Pharm Res*
2001, 18, 859-66.

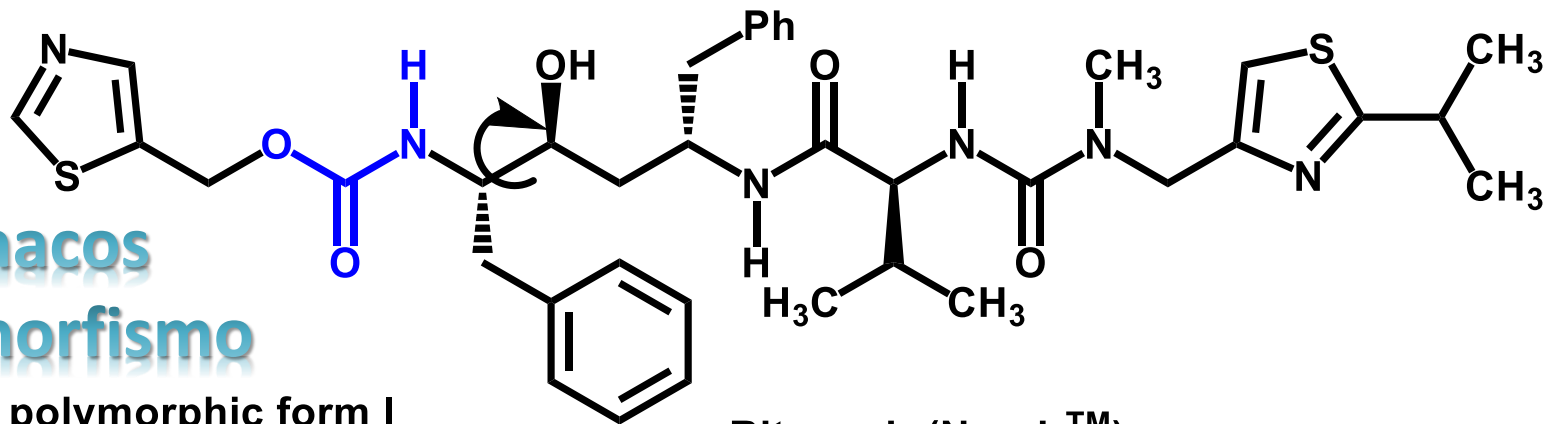
[Link](#)



Fármacos & Polimorfismo

polymorphic form I

J Bauer et al. *Pharm Res* 2001, 18, 859



Ritonavir (Norvir™)

Abbott

JD Dunitz & J Berstein, 1995

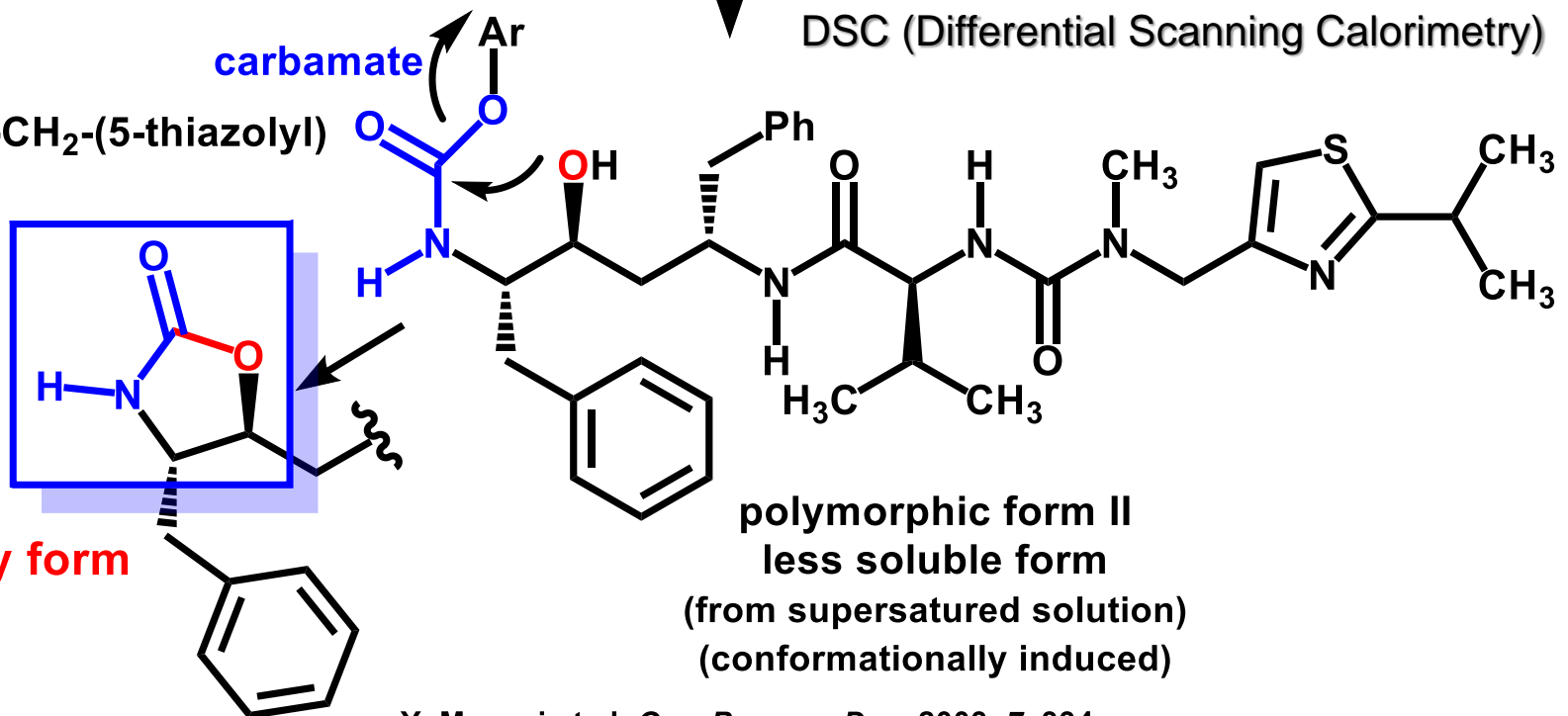
{after 240 batches production (2y after)}
DSC (Differential Scanning Calorimetry)

Ar = -CH₂-(5-thiazolyl)

carbamate

cyclic carbamate

impurity form



polymorphic form II

less soluble form

(from supersaturated solution)
(conformationally induced)

Y. Massui et al. *Org. Process Dev.* 2003, 7, 334