

Aula 7 – 08/07

Tópicos Especiais em Química Medicinal

**Tópicos Especiais
em Química Medicinal**

Código: **BMF-777**

Carga Horária: 45 horas

Créditos: 3 créditos



Fenol

OH

Cetona

HO

Éter

O

Grupos Funcionais

OH

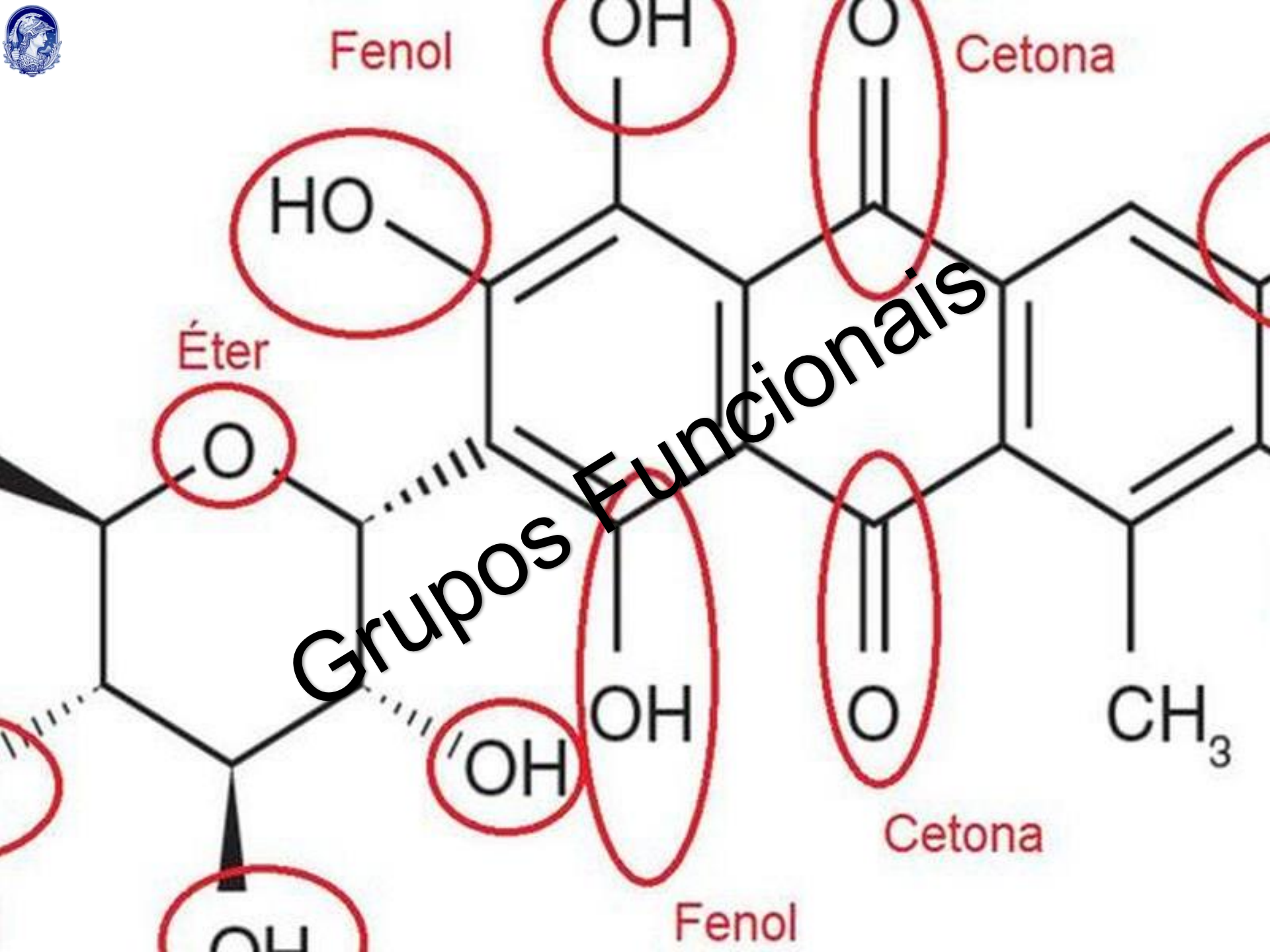
Cetona

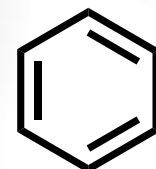
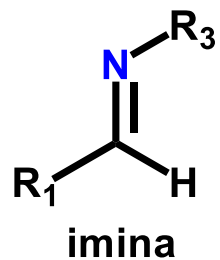
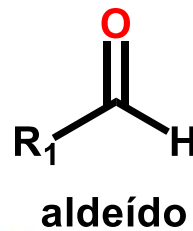
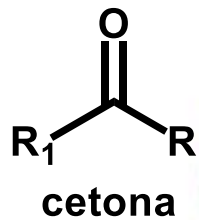
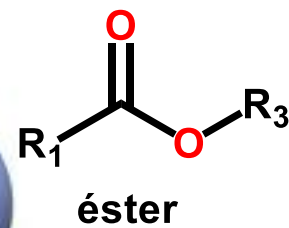
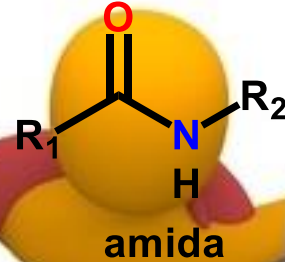
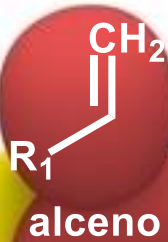
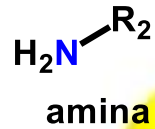
OH

Fenol

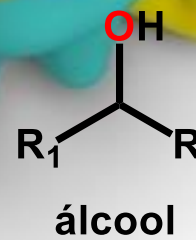
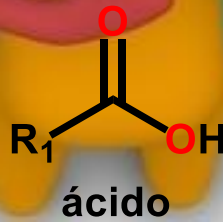
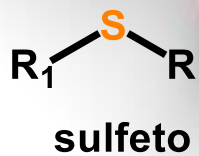
OH

CH₃



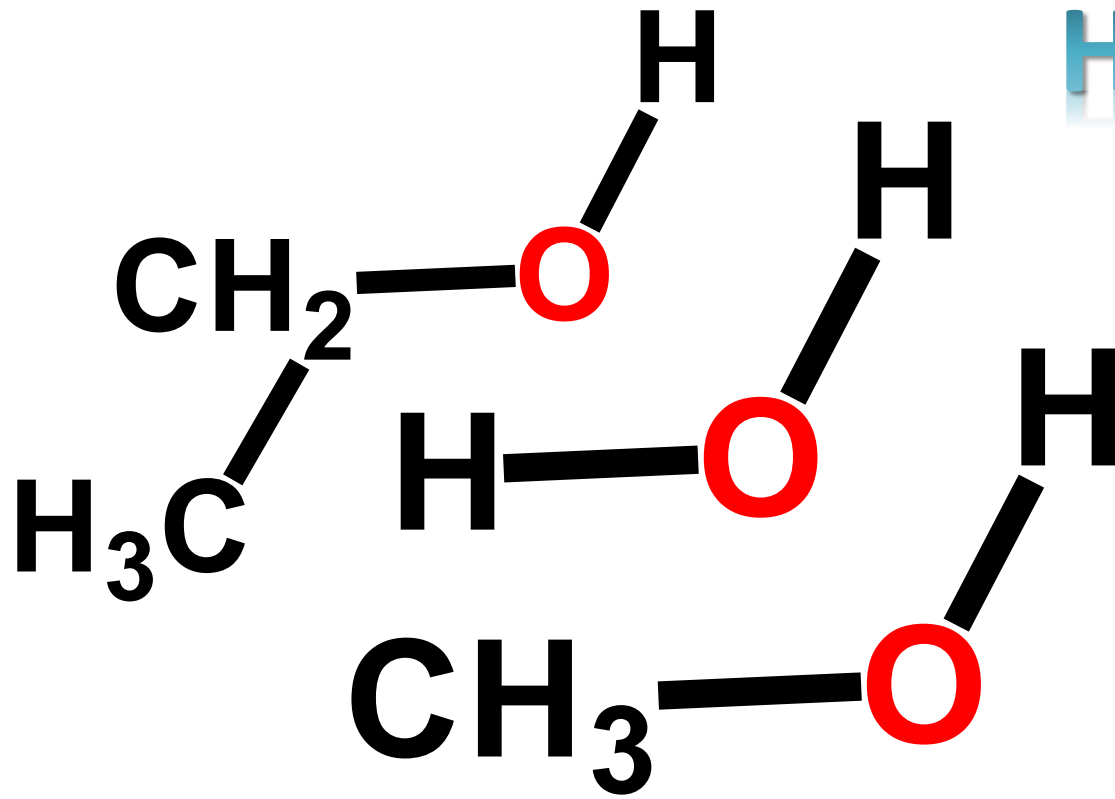


arila

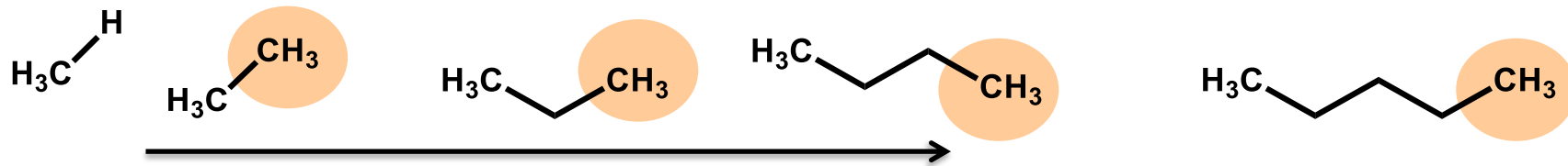




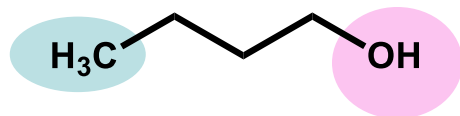
Homólogos



As séries homólogas

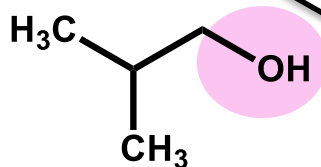


Lipofilicidade



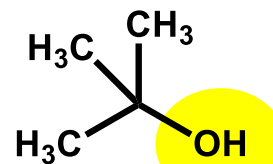
n-butanol

solubility in water
8.2g/100g



isobutanol

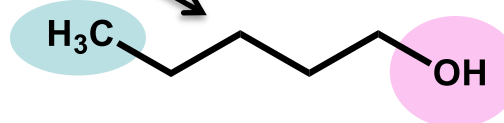
solubility in water
12,5 g/100g



tert-butanol

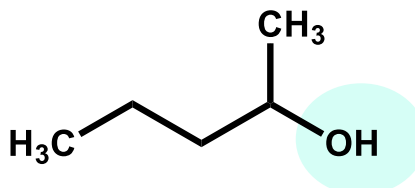
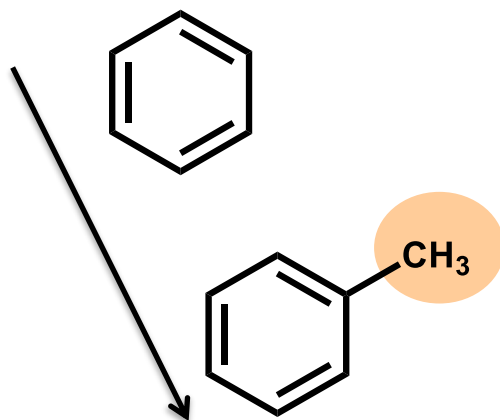
solubility in water
miscible

G Némethy, *Angew Chem
Int Ed Engl* 1967, 6, 195



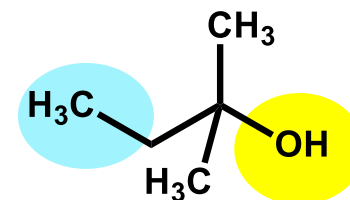
n-pentanol

solubility in water
2.4g/100g



2-pentanol

solubility in water
4.9g/100g

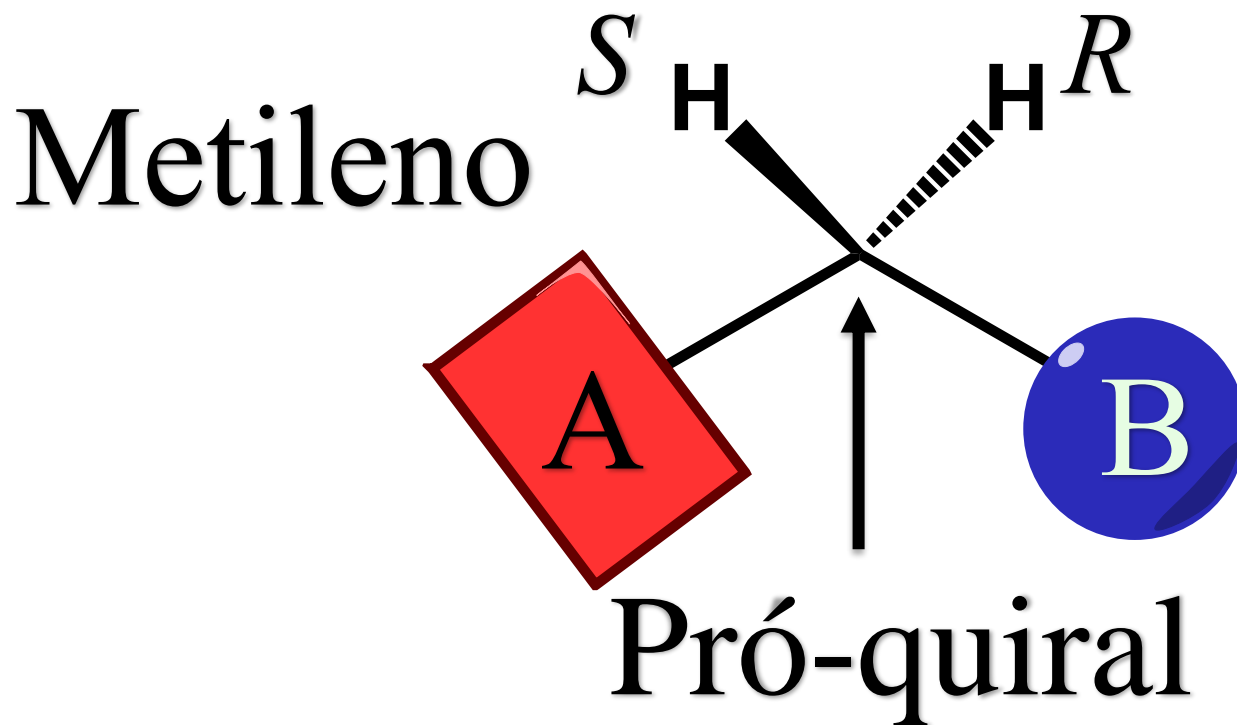


neopentanol

solubility in water
12.2g/100g



Homólogos



Eutômero / Distômero

Homólogo superior

Homólogo superior

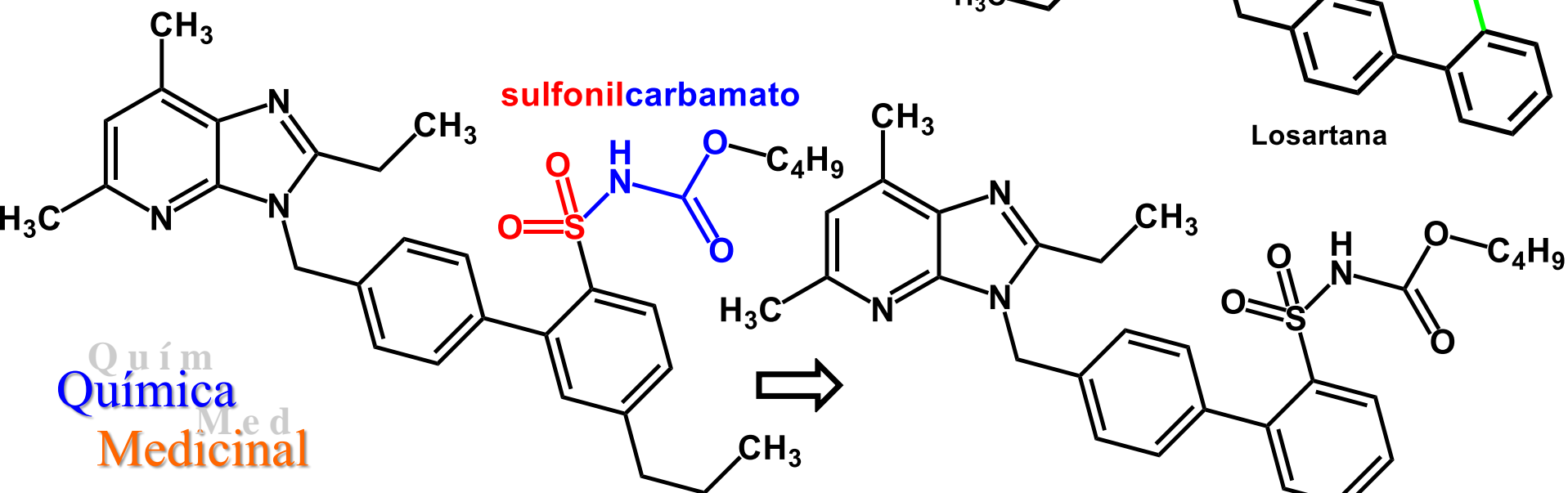
primeiro agonista não-peptídico de AT

Os sutis efeitos da estrutura química na atividade

HOMOLOGIA



tetrazola



Quím
Química
Med
Medicinal

L-162.389

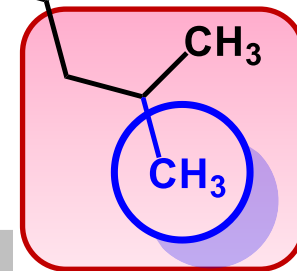
$IC_{50} h-AT_1 = 4 \text{ nM}$
 $K_i = 8 \text{ nM}$

Ef. max. 64% (ag. parcial)

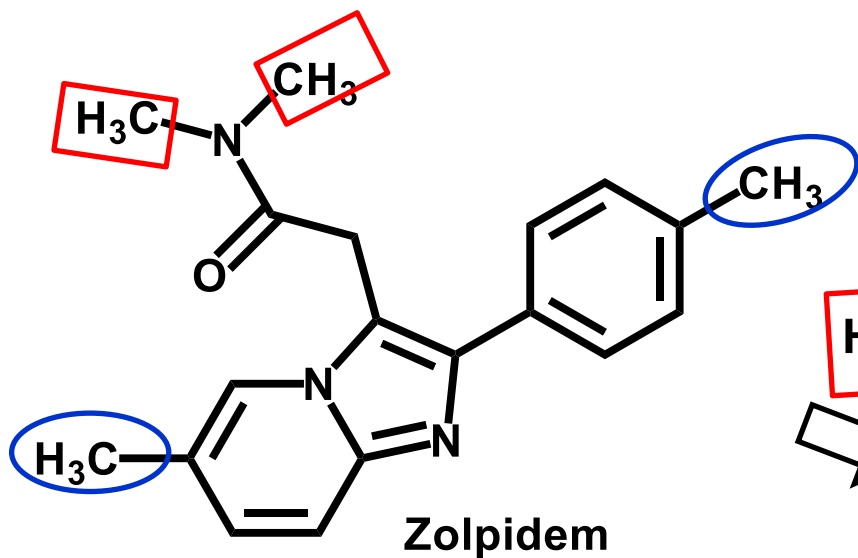
L-162.782

$IC_{50} h-AT_1 = 25 \text{ nM}$
 $K_i = 28 \text{ nM}$

Ef. max. 6% (ant)



Homólogos

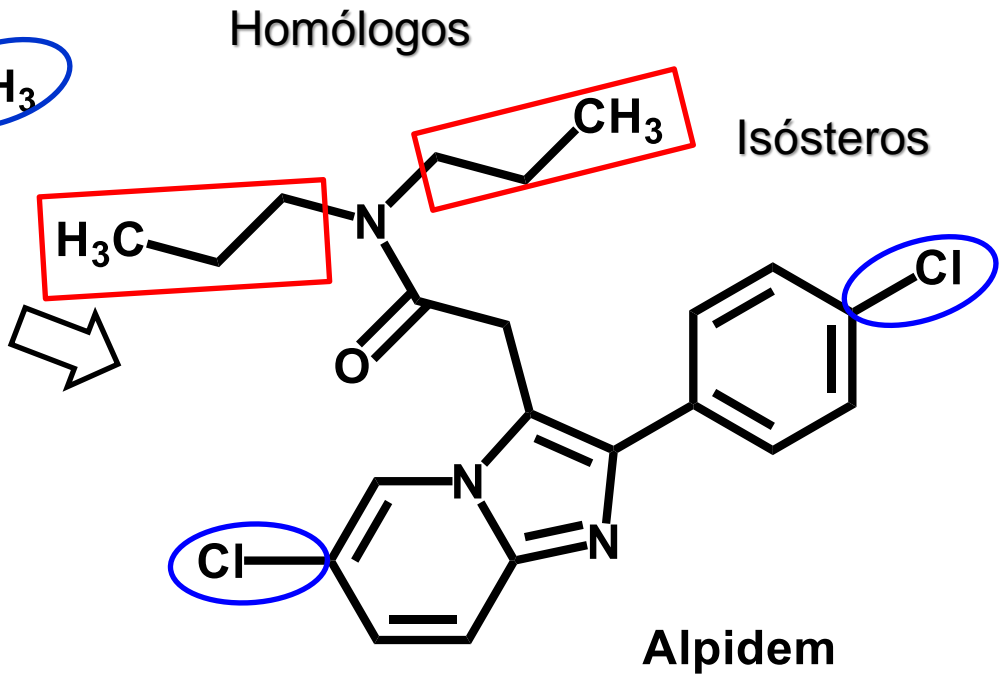


$T_{1/2} = 2,5h$

F 67%

Log P = 3,07

Melhor absorção oral



$T_{1/2} = 18-20h$

F 13%

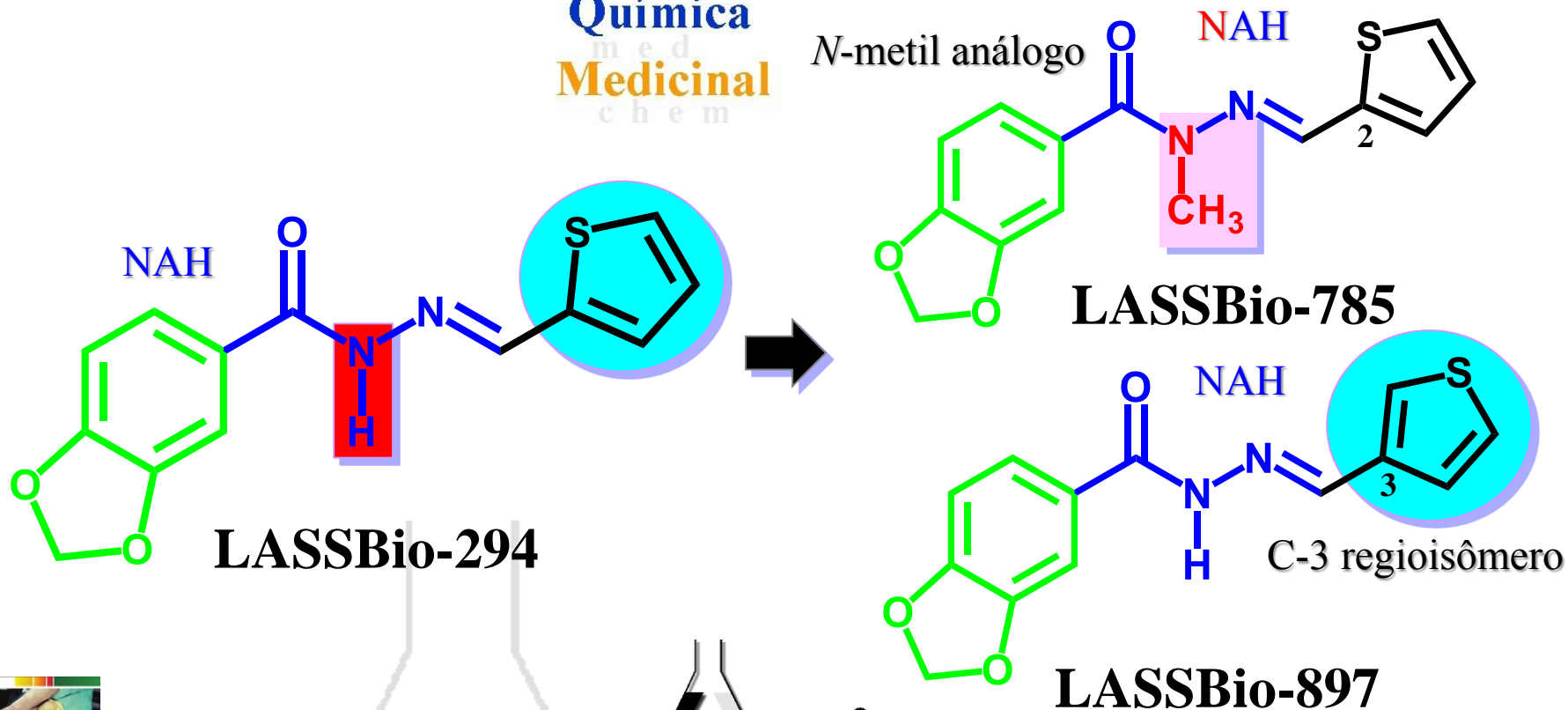
Log P = 5,49

PD/PK



Efeito conformacional

Química
med
Medicinal
chem



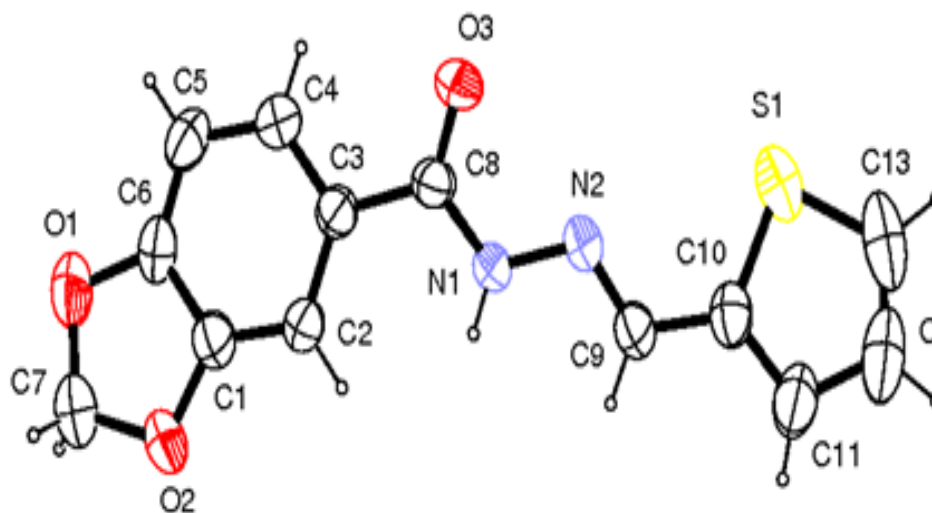
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



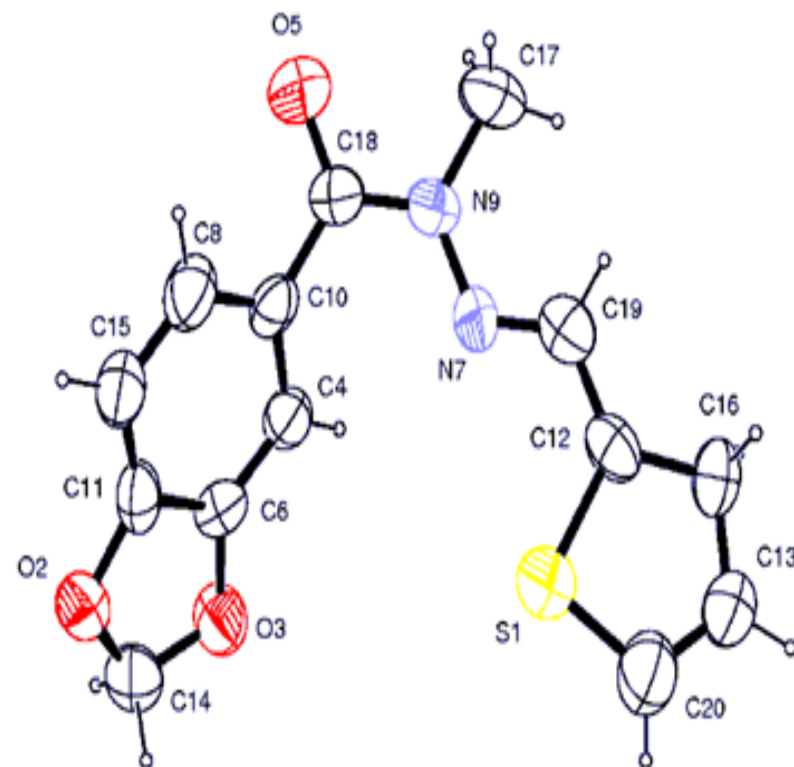
- *D. D. Viveiros, Efeito do derivado *N*-acilidrazônico LASSBio-897 sobre a resposta inflamatória pulmonar na asma e silicose experimentais, Tese Doutor (Biologia Celular e Molecular) – FIOCRUZ, IOC, Rio de Janeiro, RJ, **2014**;
- *P R Nasciutti, R Oliveira, E J Barreiro, Efeitos do LASSBio-897 sobre o sistema cardiovascular de cães hígdos da raça Beagle, Novas Edições Acadêmicas, **2016**, ISBN 978-3-330-73277-3.
- &G Zapata-Sudo et al., *Am J. Hypertens.* **2010**, 23, 135; GAP Silva et al., *Braz. J. Med. Biol. Res.* **2013**, 46, 263;
- EB Marques et al., *Int. J. Cardiol.* **2015**, 201, 282.

Efeito conformacional

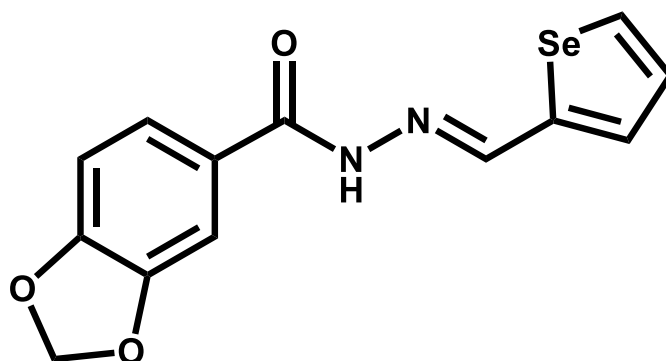
Difração de raios-X



LASSBio-294



LASSBio-785



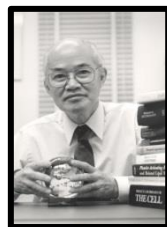
LASSBio-2202

JGB Pedreira, PhD Thesis,
IQ-UFRJ, 2020

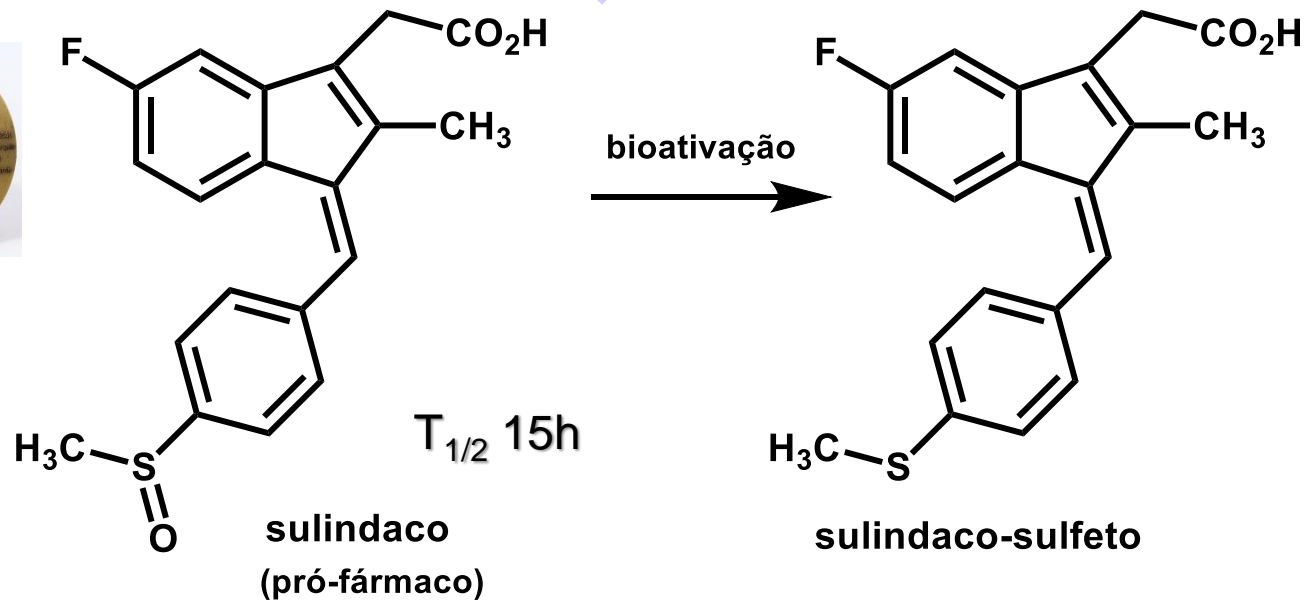
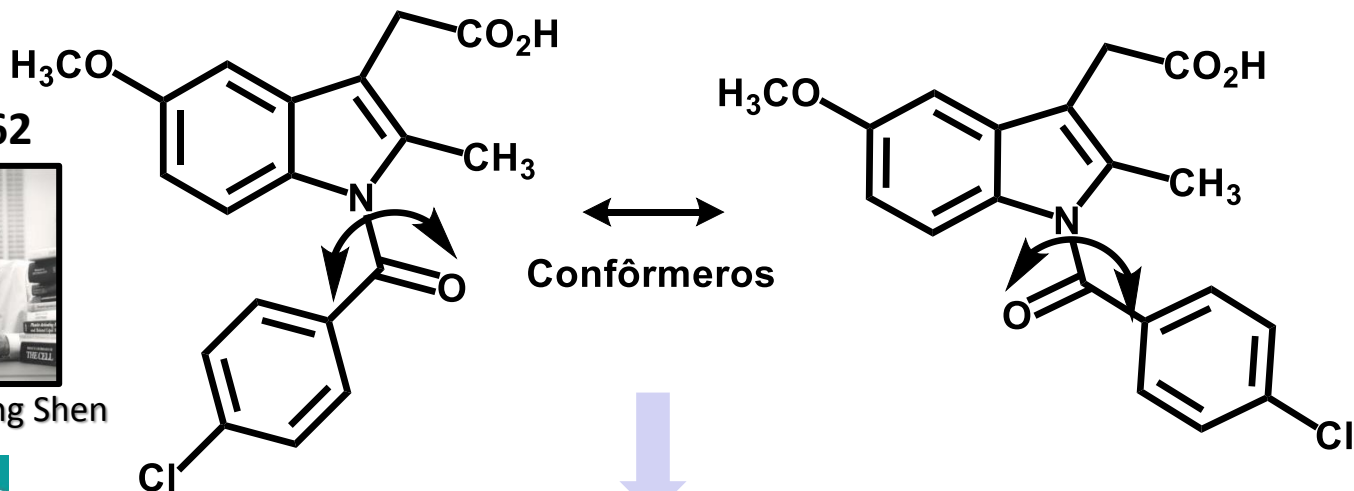
Efeitos conformacionais

Conformação bioativa

1962

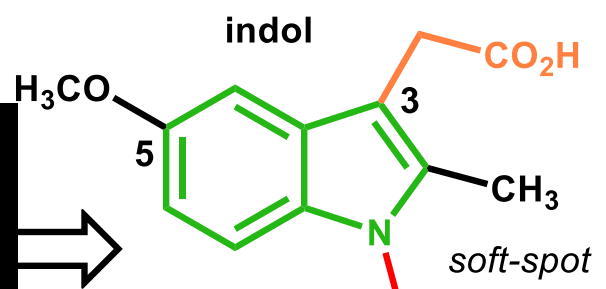
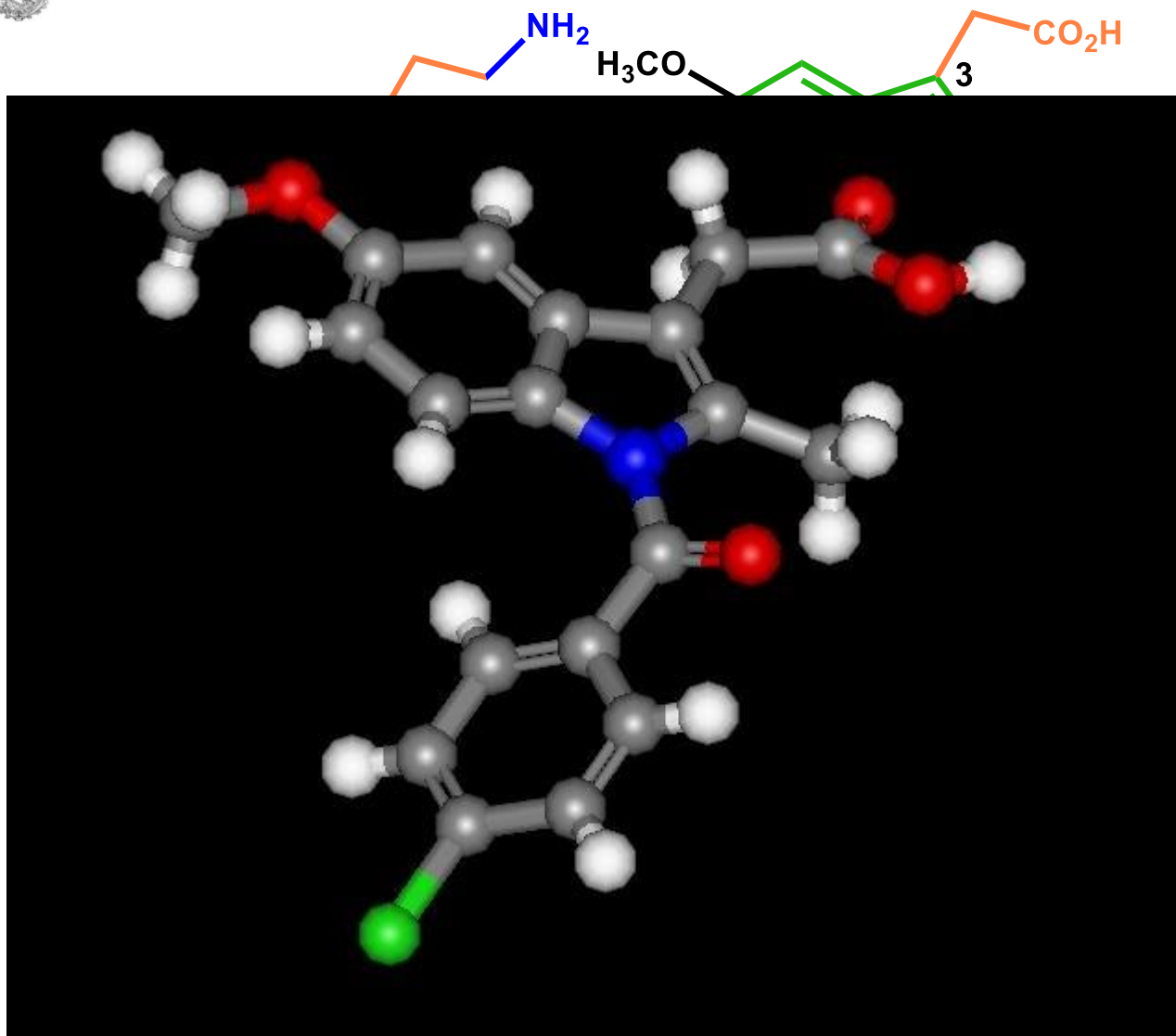


Tsung Ying Shen

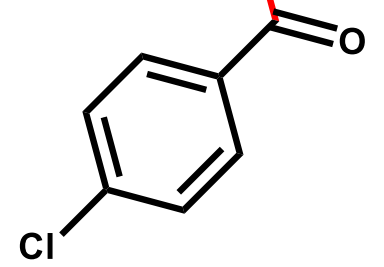


T. Y. Shen et al., *J. Am. Chem. Soc.* **1963**, *85*, 488

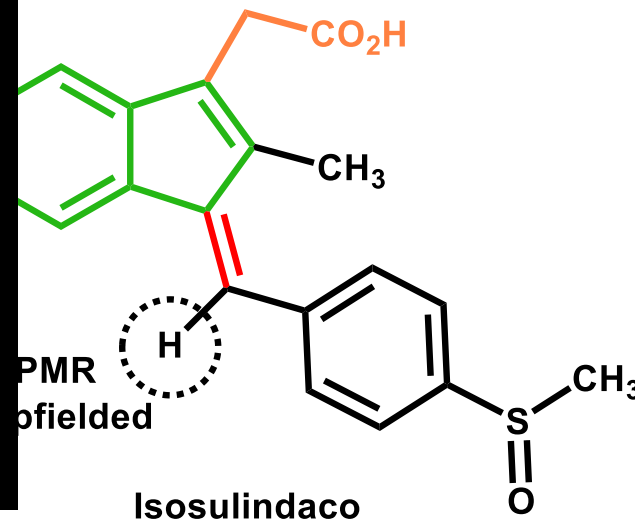
T. Y. Shen, Toward more selective antiarthritic therapy, *J. Med. Chem.*, **1981**, *24*, 1



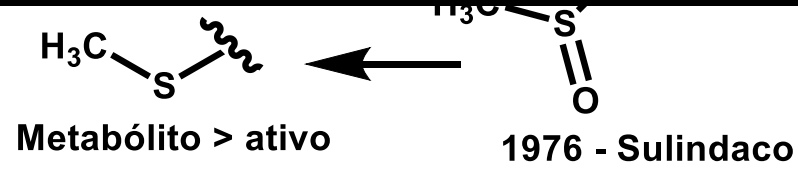
Shen



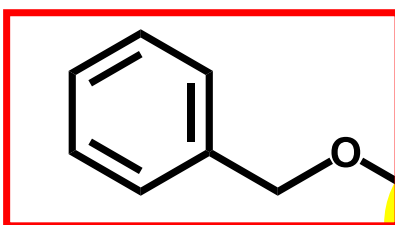
1963 - Indometacina



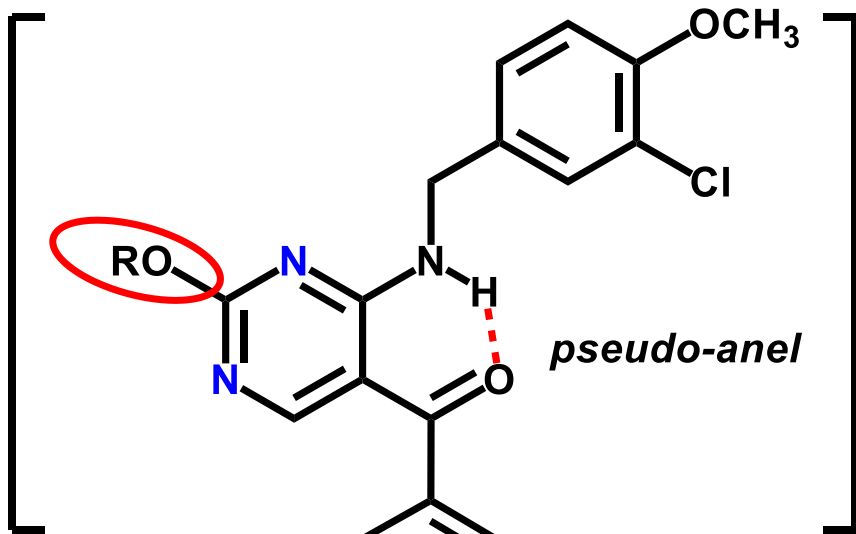
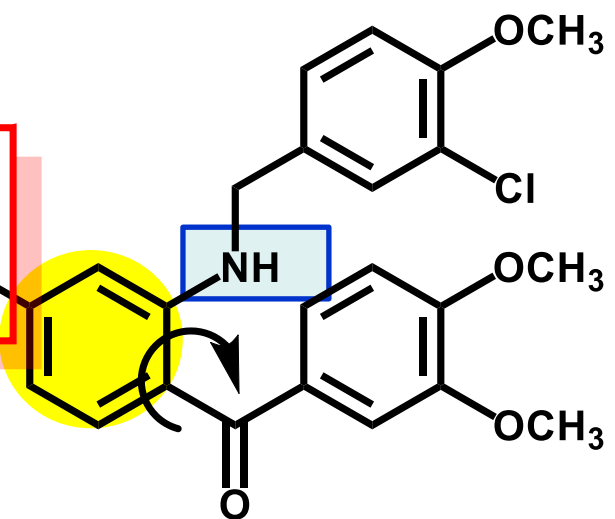
Isosulindaco
1/4 da atividade



PDE-5



benzil-éter

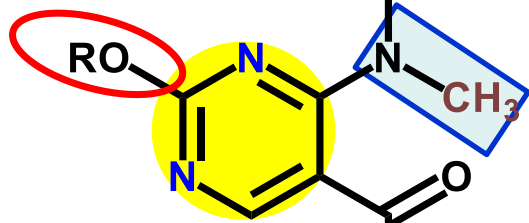


pseudo-anel

$IC_{50} = 0,126 \text{ nM}$

\ll

$IC_{50} = 5,01 \text{ nM}$



N-metila

Ligação-H
intramolecular

Efeitos conformacionais

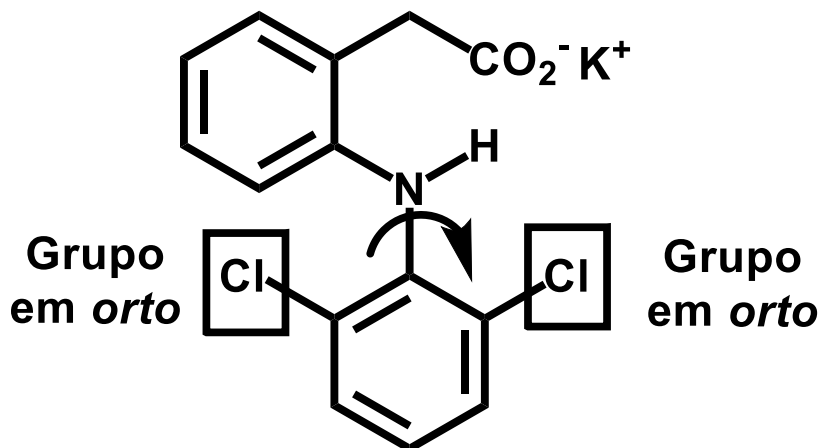
Quím
Química
Med
Medicinal

Efeitos conformacionais

Efeito *orto*-

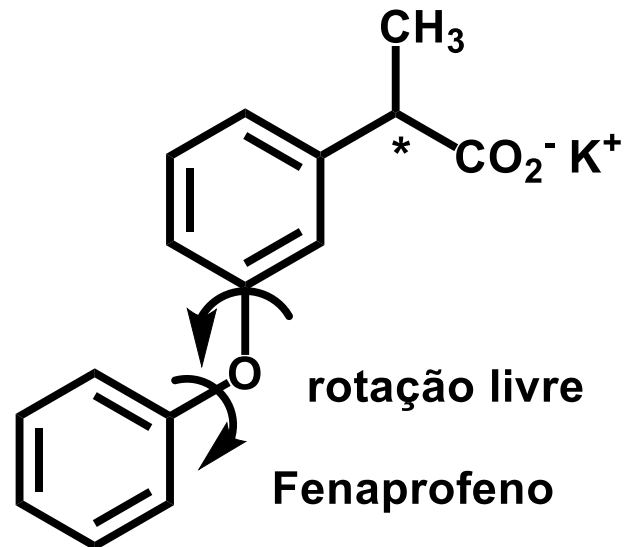
$-\text{CO}_2\text{H}$ $\text{pK}_a = 4,45$

$-\text{CO}_2\text{H}$ $\text{pK}_a = 4,5$

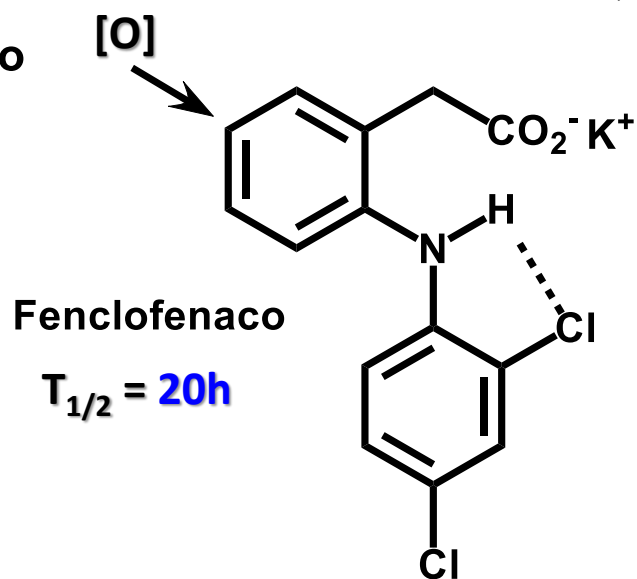


Diclofenaco

$T_{1/2} = 1,5\text{h}$

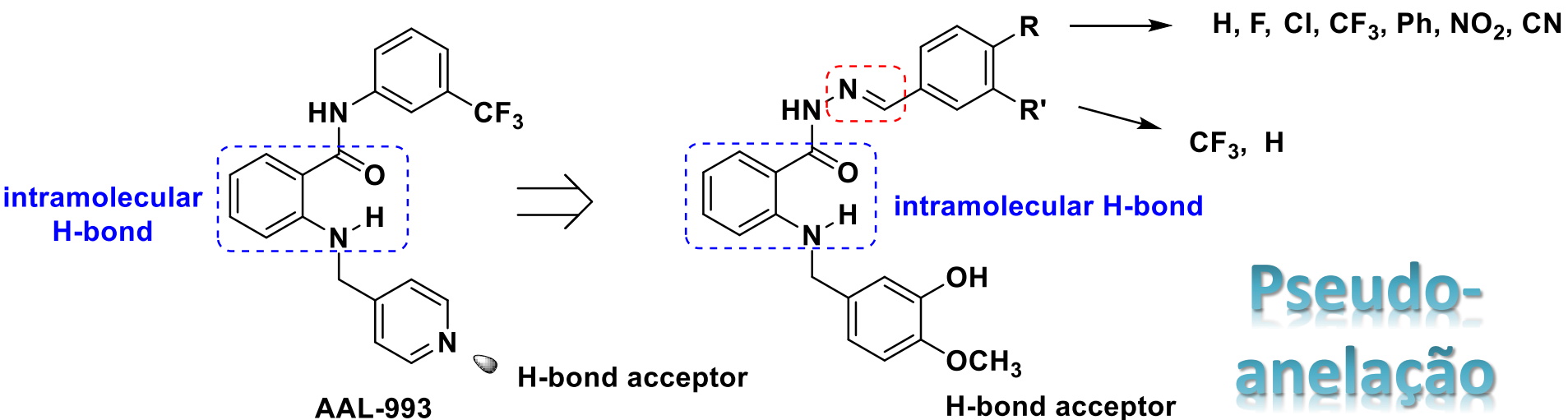


$T_{1/2} = 3,0\text{h}$



Interação-H intramolecular

Efeitos conformacionais



AAL-993

H-bond acceptor

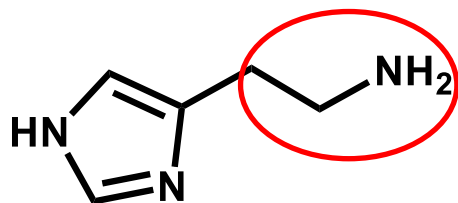
H-bond acceptor

- | |
|---|
| R = H; R' = CF ₃ (LASSBio-2026) |
| R = H; R' = H (LASSBio-2027) |
| R = F; R' = H (LASSBio-2028) |
| R = Cl; R' = H (LASSBio-2029) |
| R = C ₆ H ₅ ; R' = H (LASSBio-2051) |
| R = CF ₃ ; R' = H (LASSBio-2052) |
| R = NO ₂ ; R' = H (LASSBio-2053) |
| R = CN; R' = H (LASSBio-2054) |

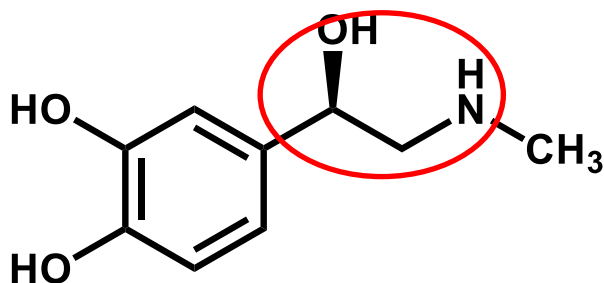
Fernanda P. Pauli, Dissertação de Mestrado, PGQU/UFRJ, 2018.

FP Pauli, J Martins, T Paschoalin, M Ionta, MLC Barbosa, EJ Barreiro, Novel VEGFR-2 inhibitors with a N-acylhydrazone (NAH) Scaffold, *Archiv der Pharmazie* **2020**, 353, e2000130..

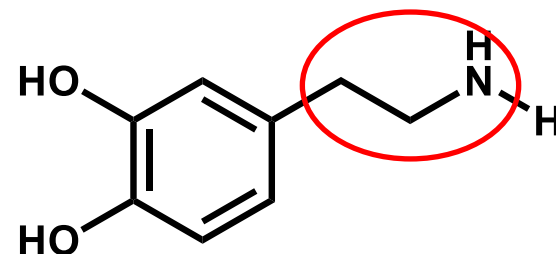
Efeitos conformacionais



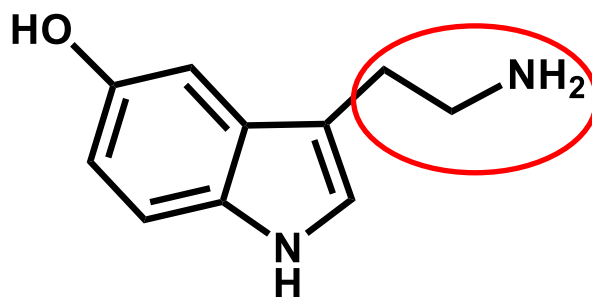
histamina



adrenalina



dopamina

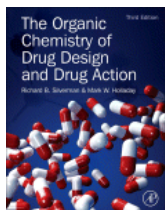


serotonina

Cap. 4, p. 292



Aminas biogênicas

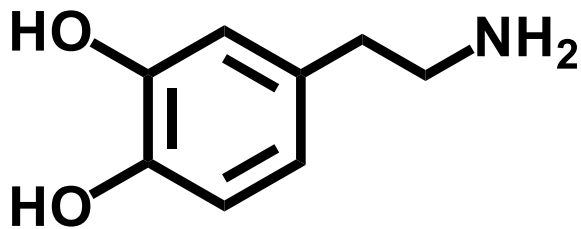
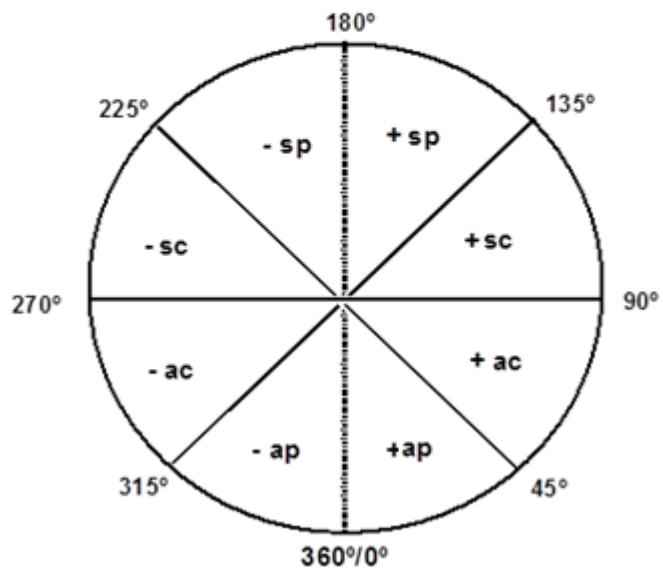


R. B. Silverman, M. W. Holladay, The Organic Chemistry of Drug Design and Drug Action, 3rd Edition, Academic Press, 2014

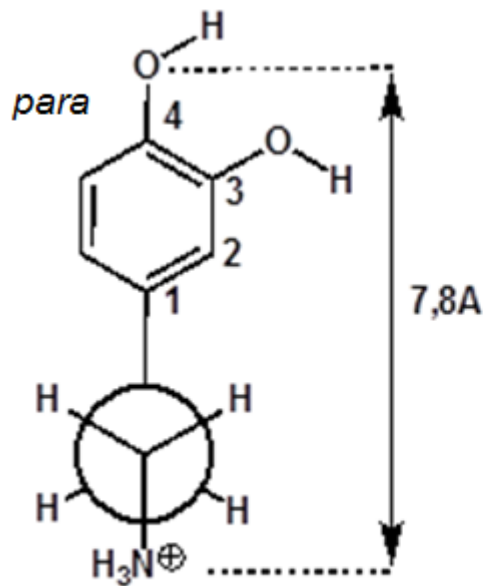
Confôrmeros

Projeção de Newman

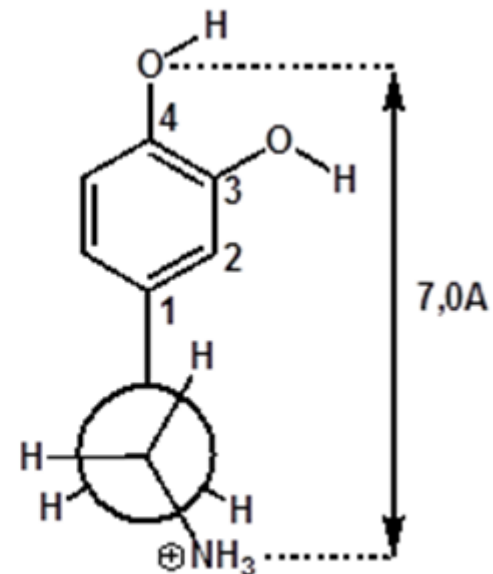
Ângulos de Torção



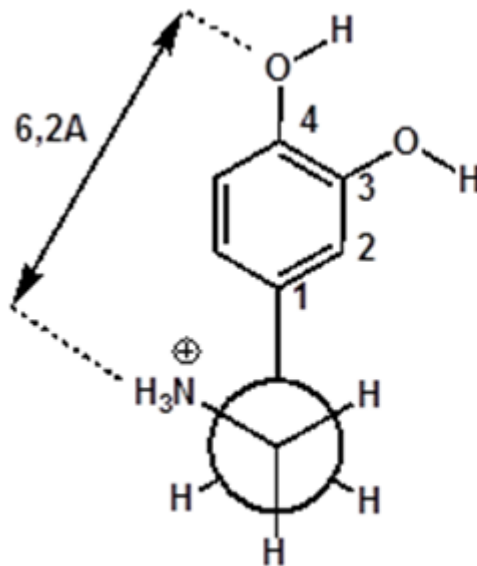
dopamina



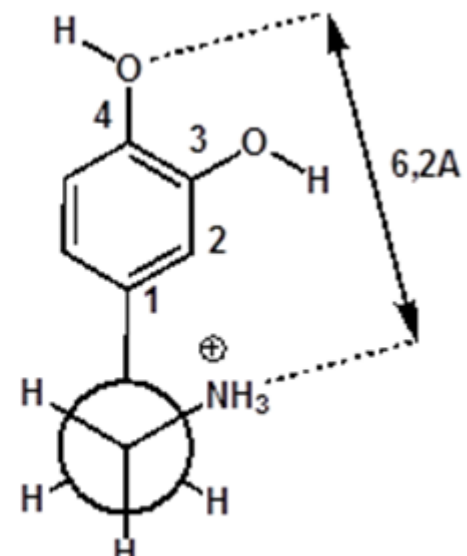
anti



+ap



-sc



+sc