

Química Medicinal



Mini-curso 17

62ª Reunião Anual SBPC - UFRN



27-30 julho de 2010



UFRJ

Eliezer j. Barreiro

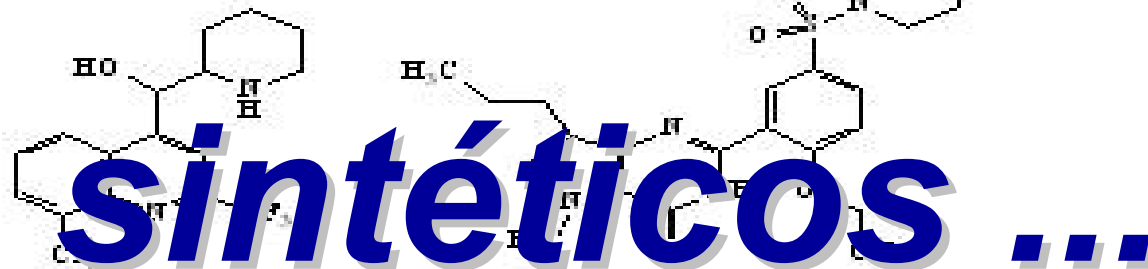
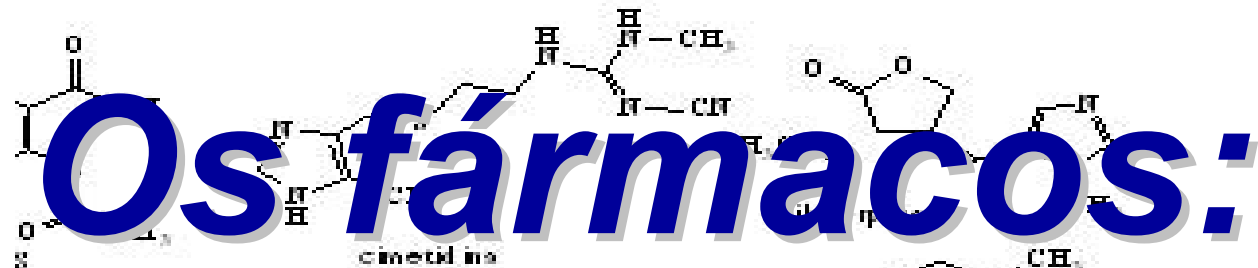
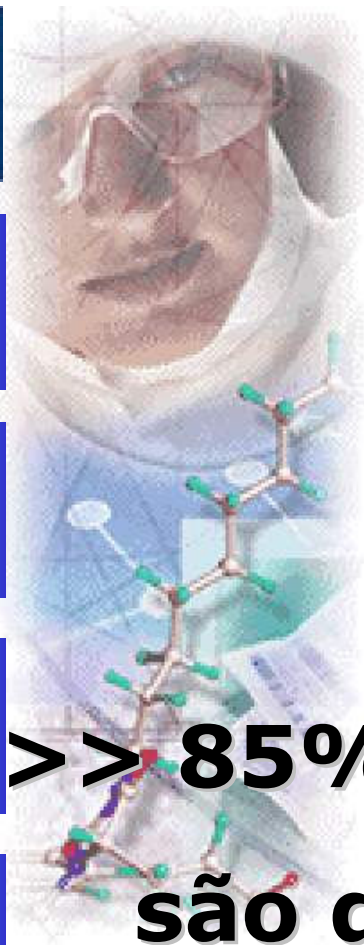
Professor Titular

Parte 4

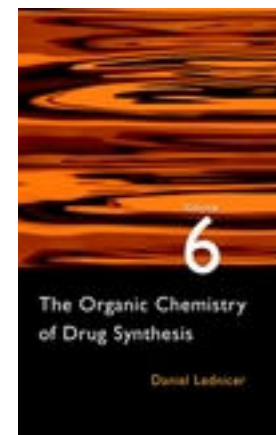
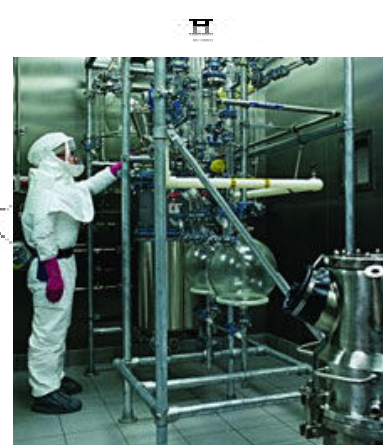
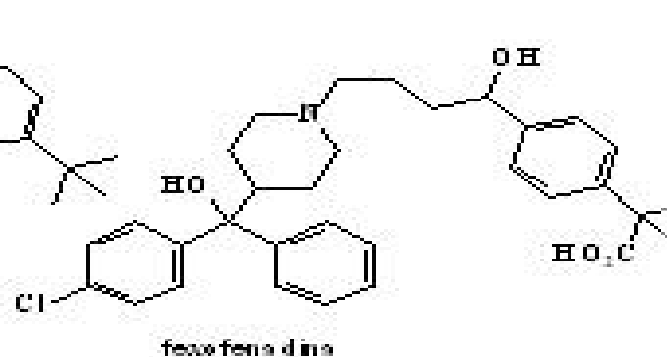
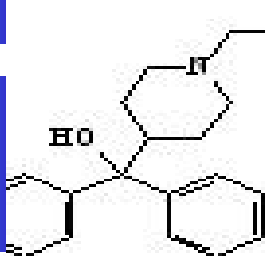
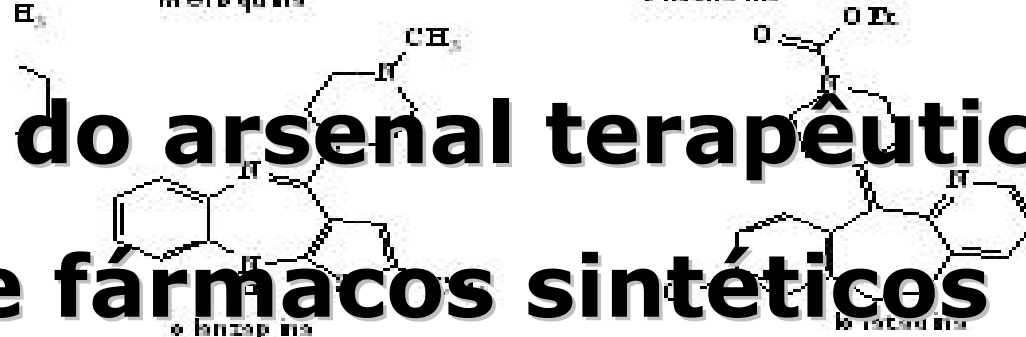




HC



>> **85% do arsenal terapêutico**
são de fármacos sintéticos





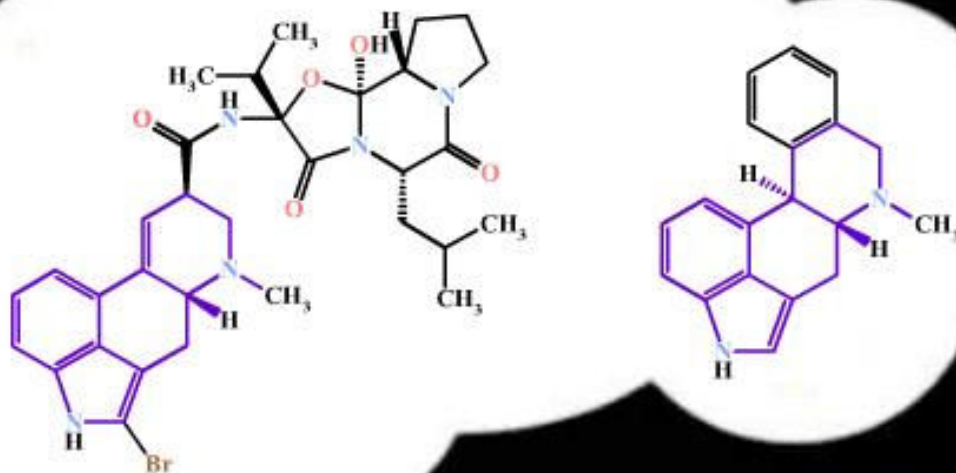
Química
Medicinal

Moléculas
inteligentes





Planejamento racional

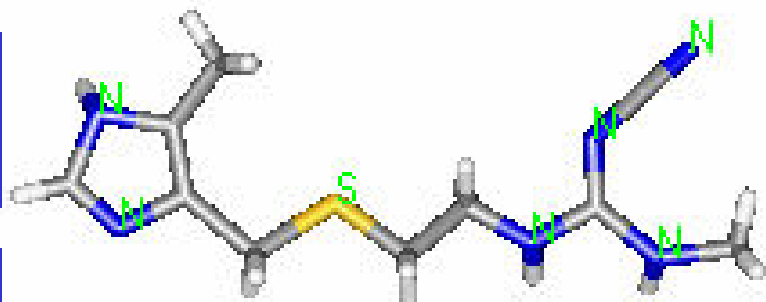
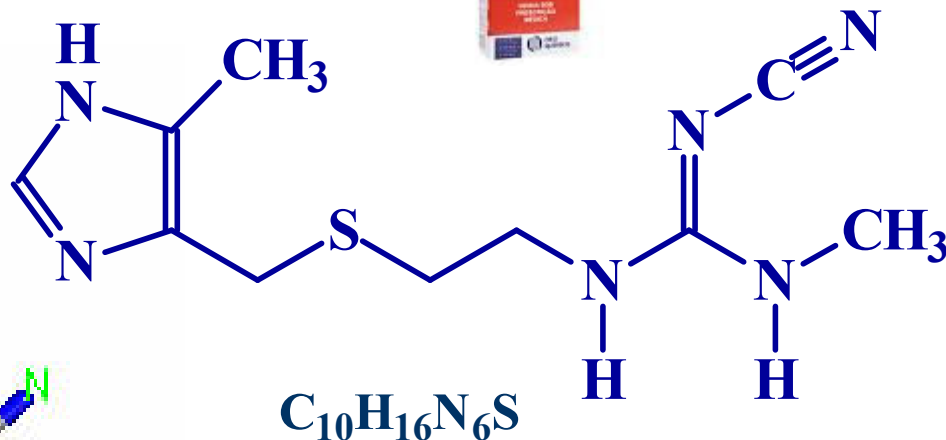


A descoberta da
cimetidina





Cimetidina



Inovação terapêutica



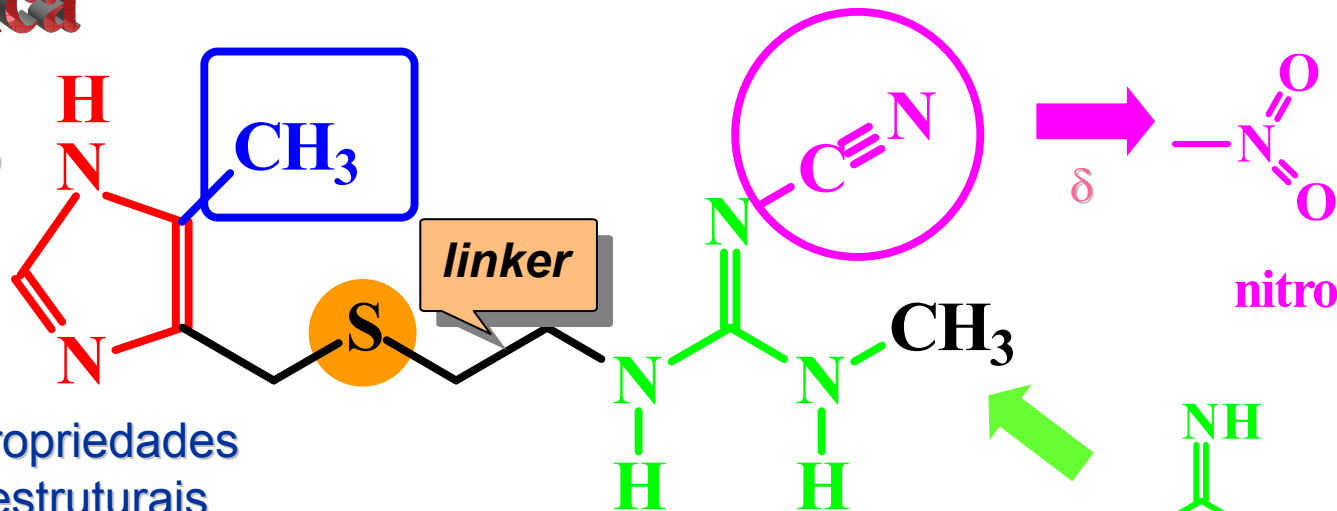
Os descobridores da cimetidina: Ganellim, Emmet, Durant & Black, da esquerda para a direita,



Inovação terapêutica

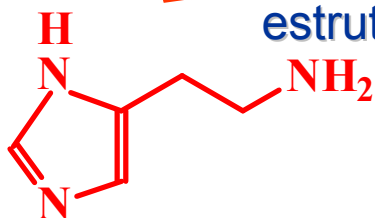
Abordagem Fisiológica

Análogo ativo

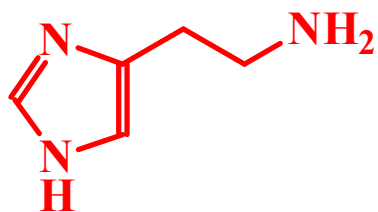


Ligações frágeis

Propriedades estruturais



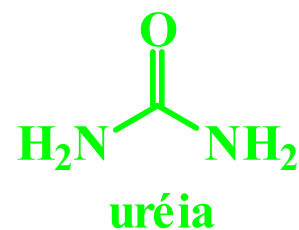
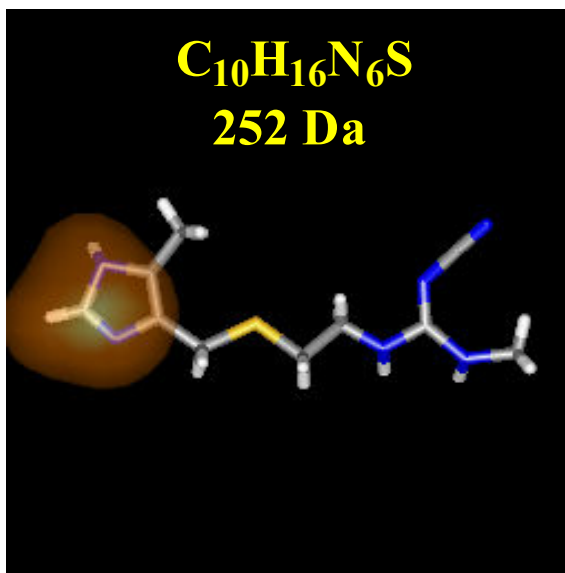
Agonista natural



histamina

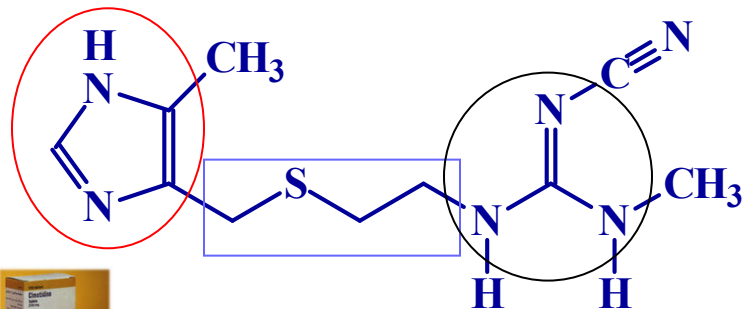
cimetidina

$C_{10}H_{16}N_6S$
252 Da



Retro-dissecação
molecular

Fragmentos moleculares



Cimetidina

Robin Ganellin *et al.*, 1974
 US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53**, 435 (1975).

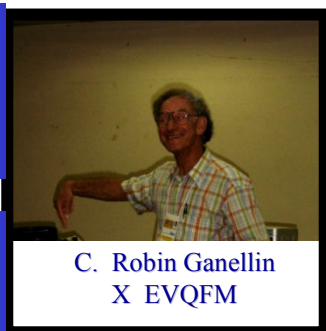
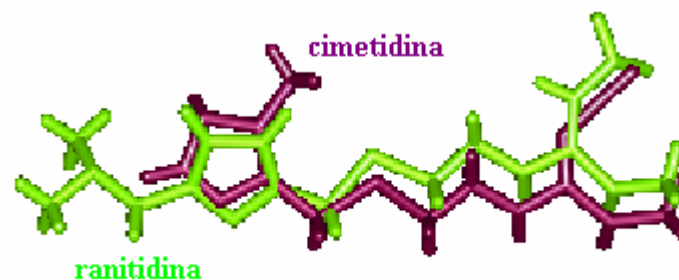
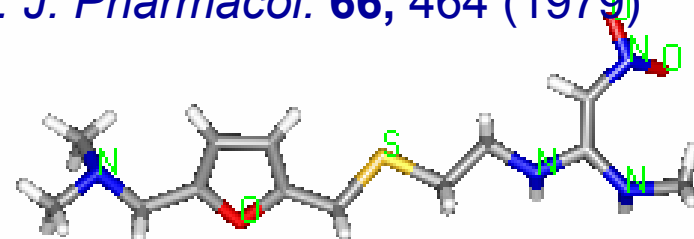
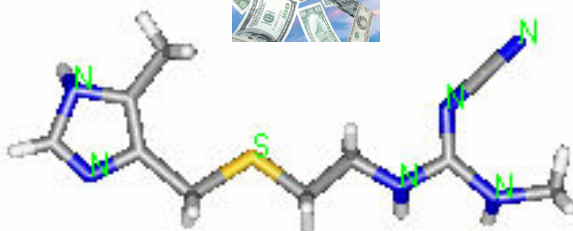


Ranitidina

Barry J. Price *et al.*, 1978
 US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66**, 464 (1979)

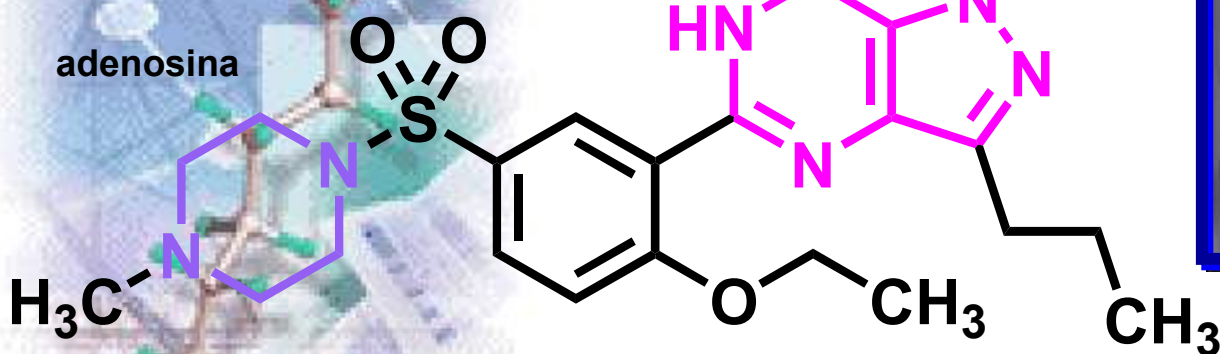
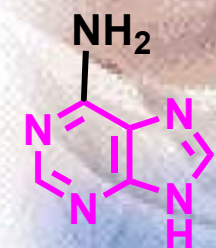
me-too

similaridade molecular





A descoberta do *sildenafil*



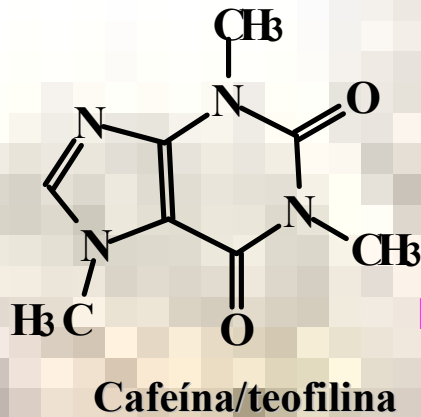
sildenafil



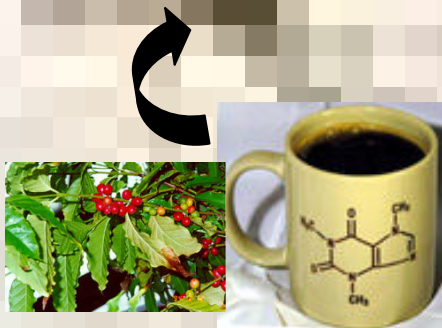
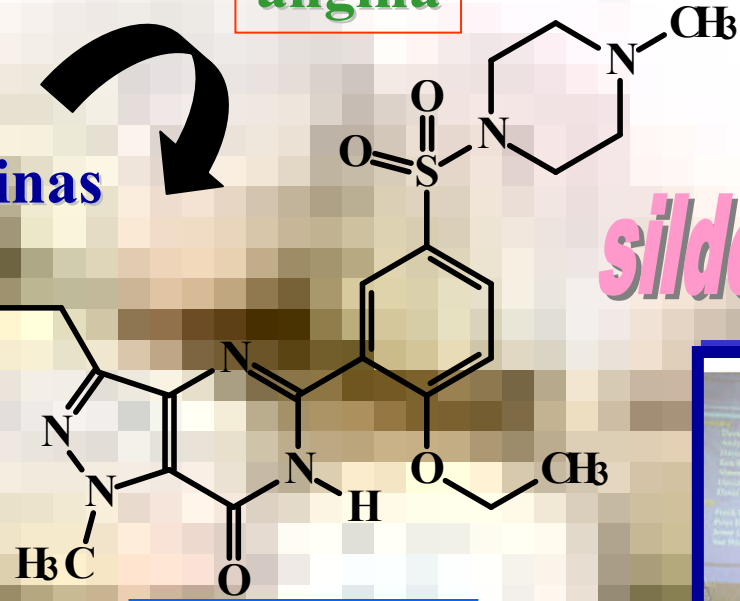
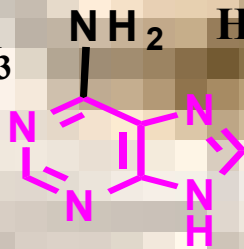


Disfunção erétil

angina



PDE-i
Metil-xantinas

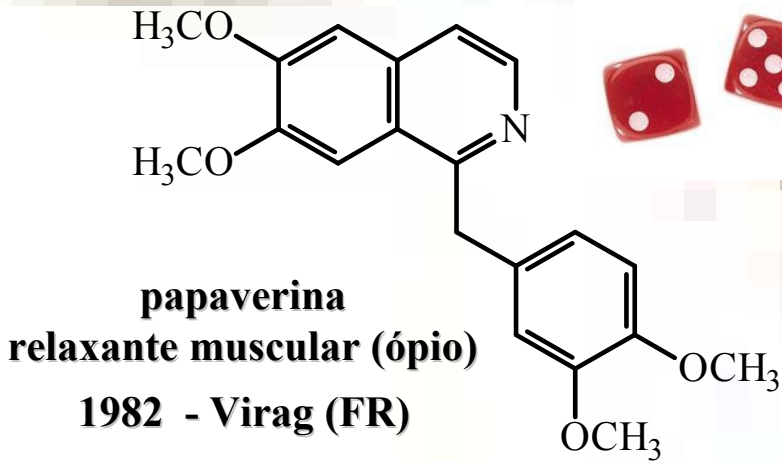


Fase 1
serendipidade

PDE-Vi

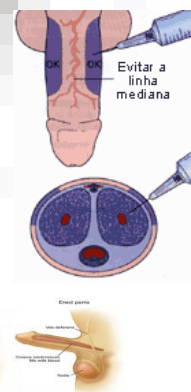


Simon Campbell



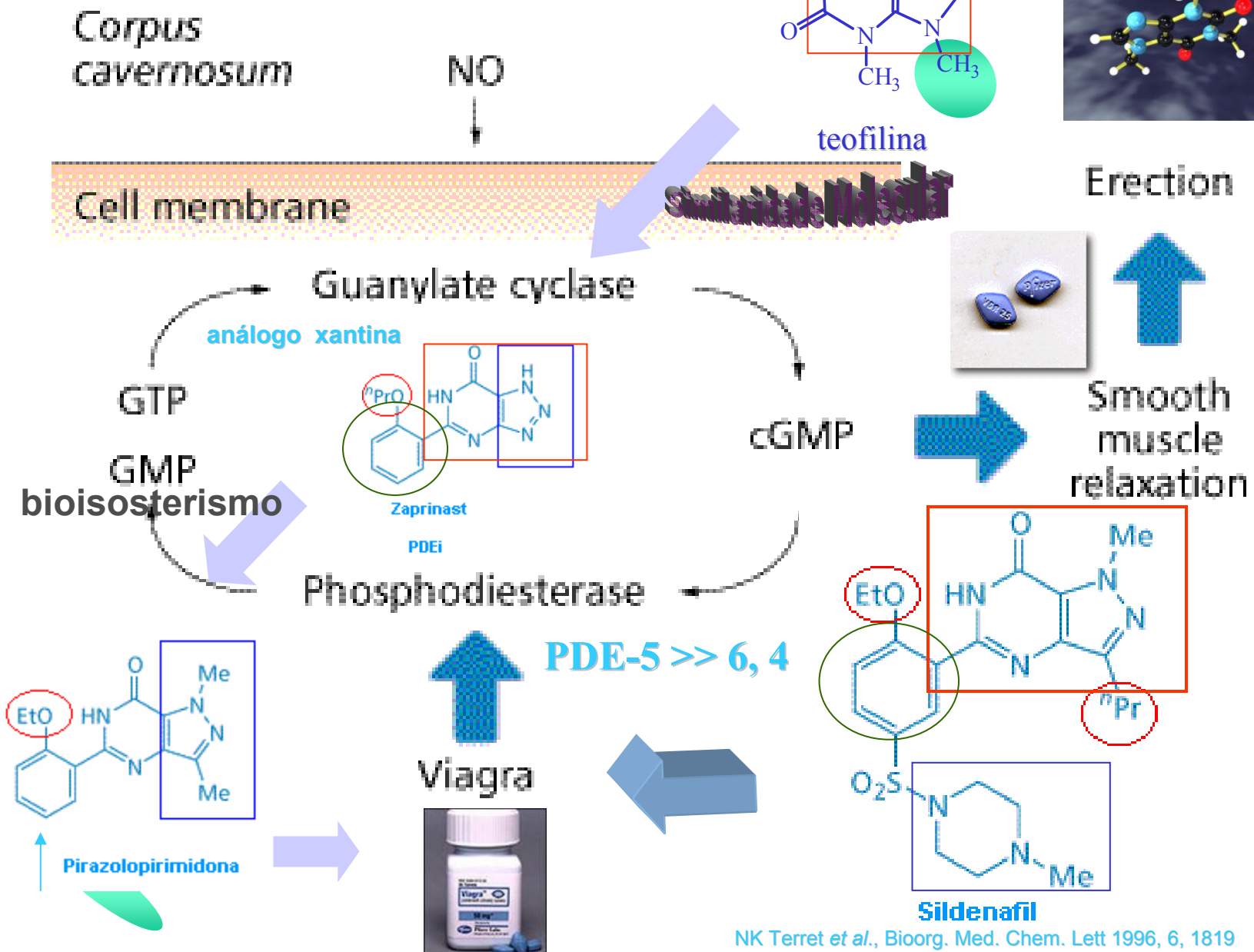
alprostadil
injetável

Caverject^R



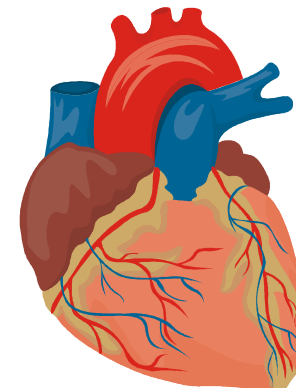


Disfunção erétil





A descoberta das estatinas

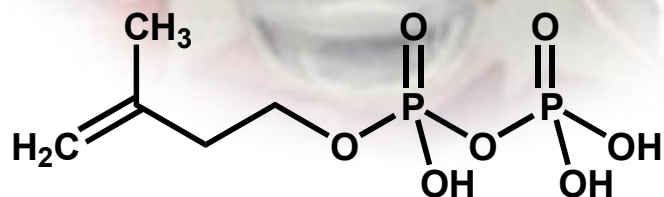
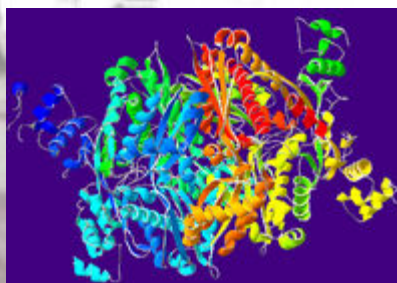
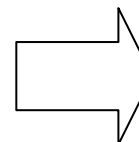
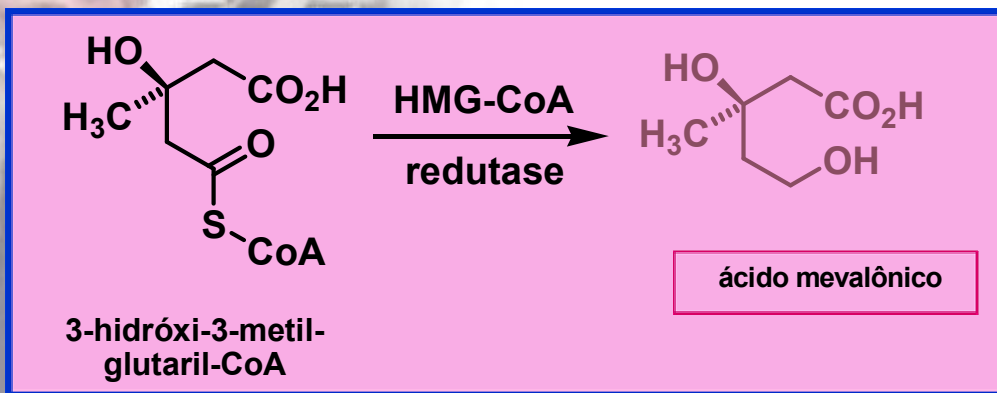


*Química
Medicinal*

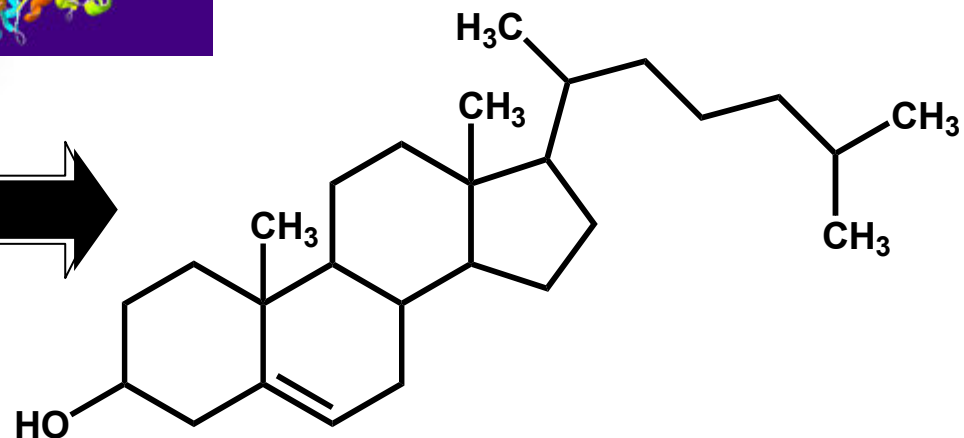
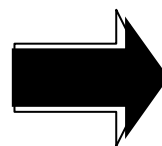




Biossíntese do colesterol



pirofosfato de isopentenila



colesterol



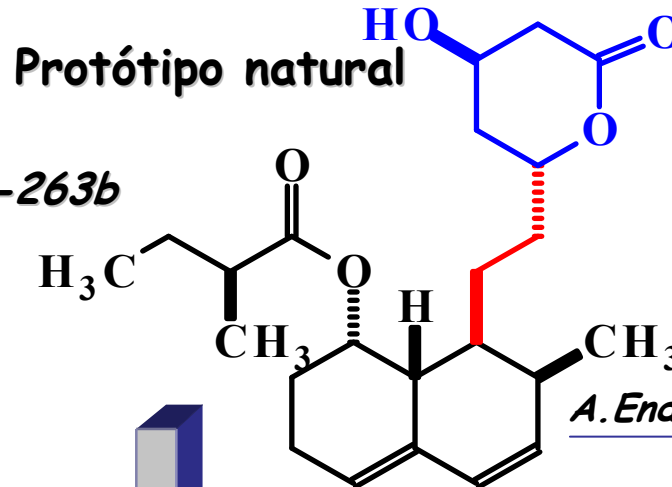
Akira Endo, Sankyo Co

1975 - Mevastatina (ML-263b)

Metabólito de Fungo



A.Endo, *J. Antibiot.*
1976, 29, 1346
Penicillium citrinum
Idem, *Ibid*, 1979, 32, 852
Monascus ruber
(*compactina*)

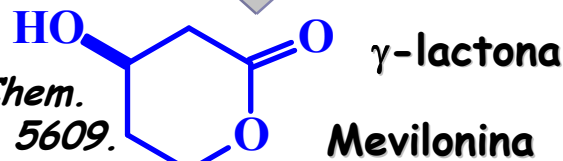


Similaridade molecular

Arthur A. Patchett

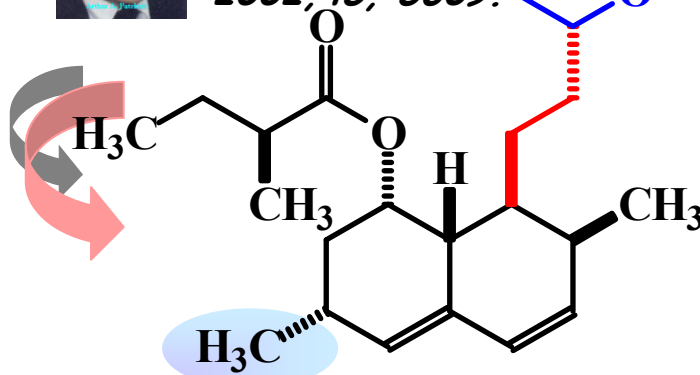


J. Med. Chem.
2002, 45, 5609.



US\$ 5,5 bi
(2007)

Pró-fármaco



Lovastatin (MK-803)

1980 - Merck & Co.

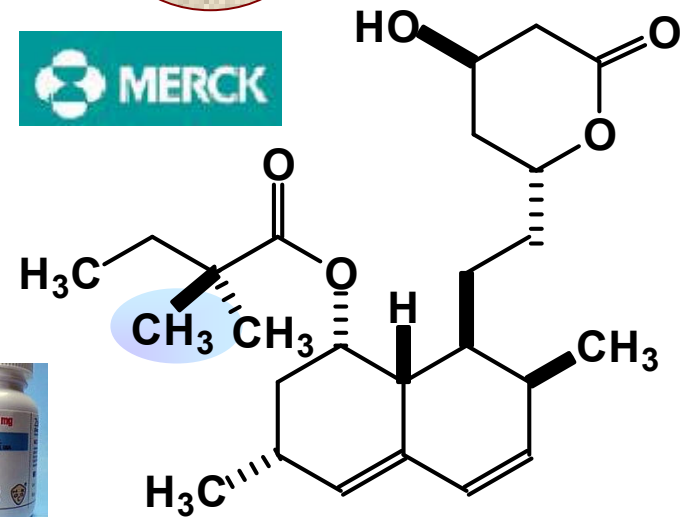
Aspergillus terreus

1987 - MS&D (Mevacor[®])

Simvastatin
(Zocor[®])
MK-733
1988



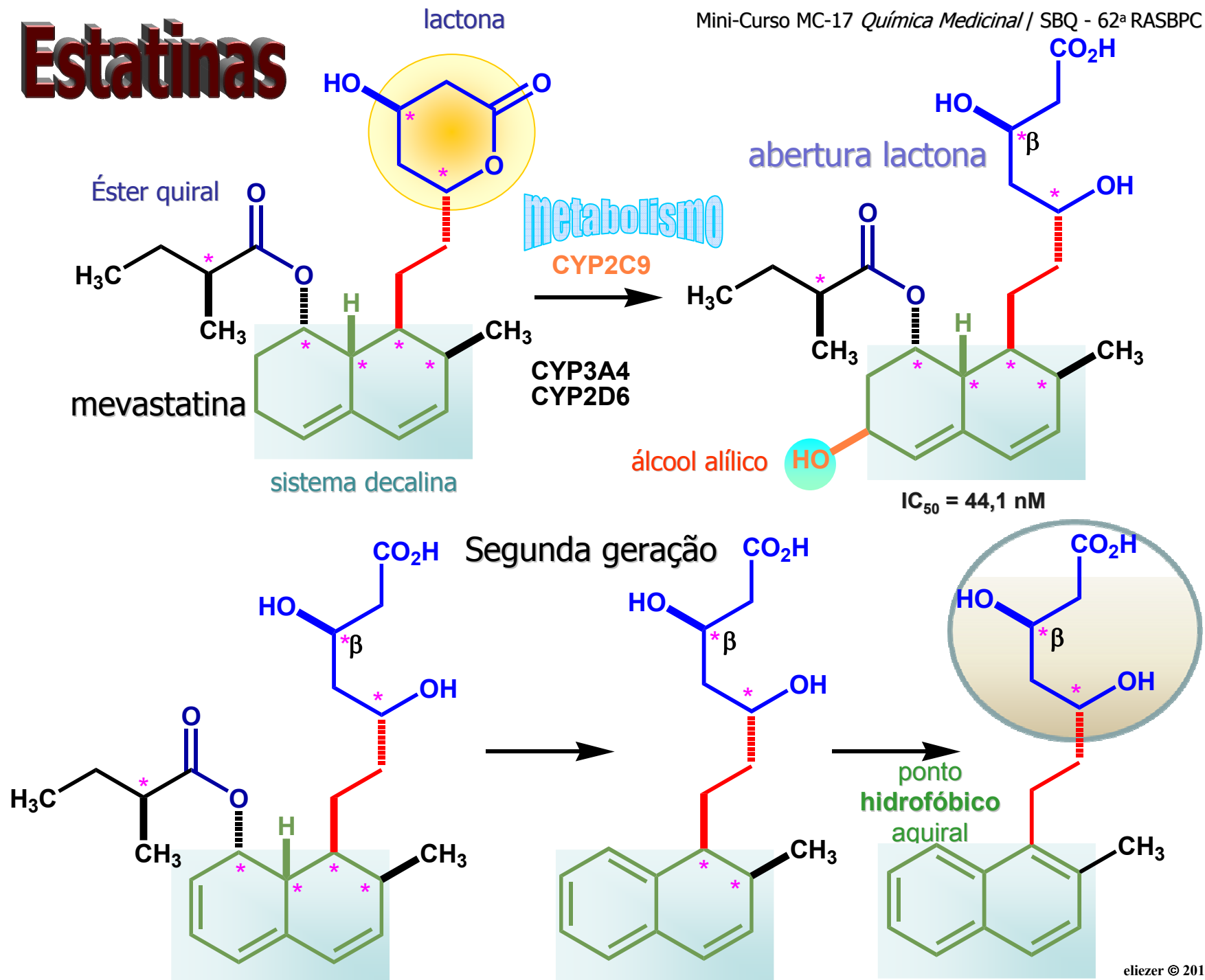
J. Med. Chem. 1986, 29, 849



IC₅₀ = 11,2 nM

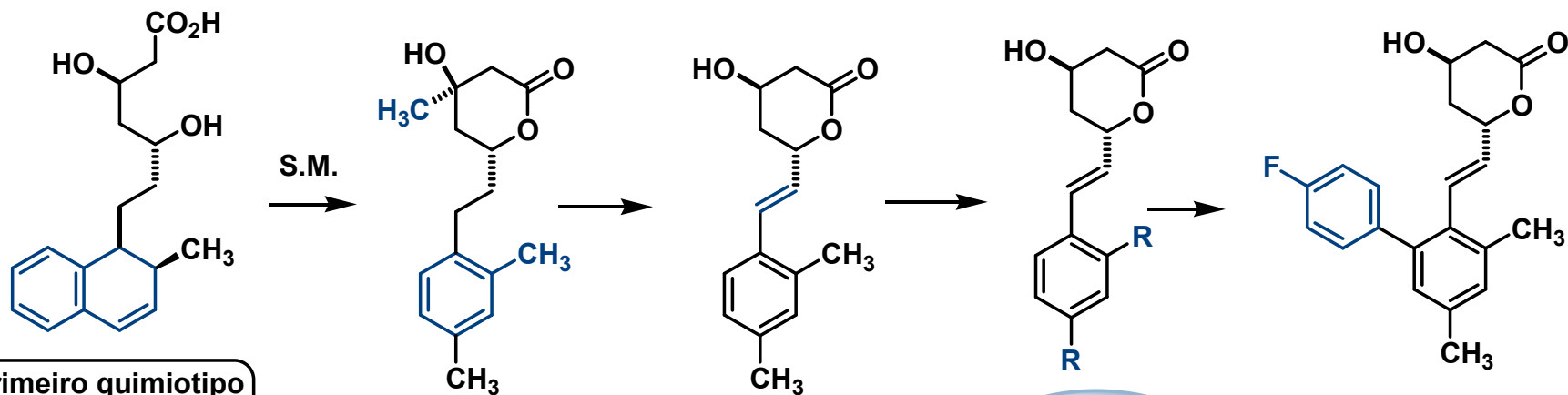


Estatinas





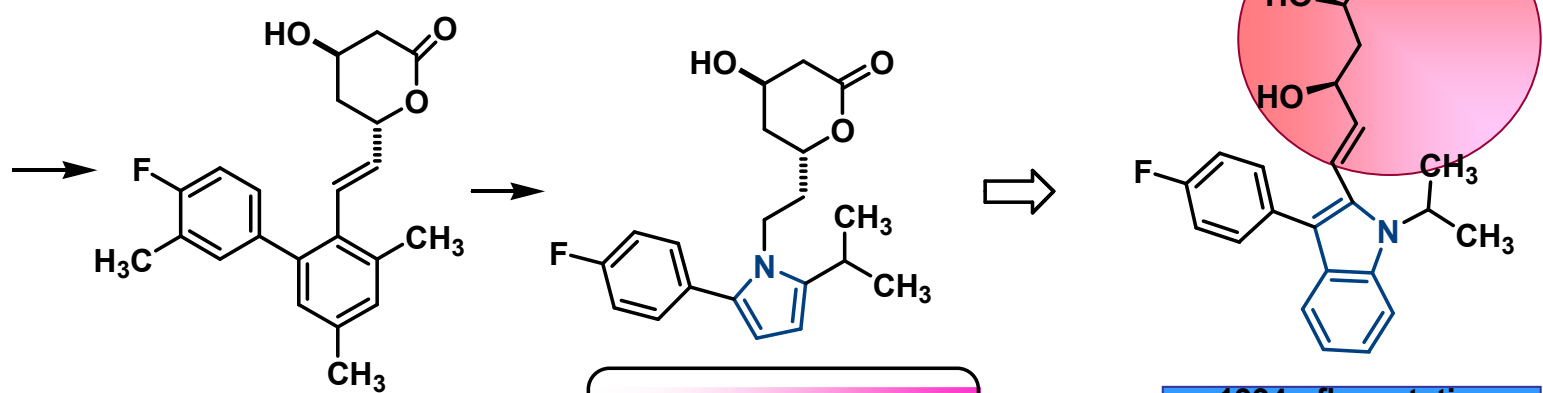
Gênese das estatinas de segunda geração (sm)



primeiro quimiotipo
aromático ativo

metabolismo

R = CH₃, Cl



primeiro quimiotipo
N-heterocíclico ativo
HMGC_oA-R

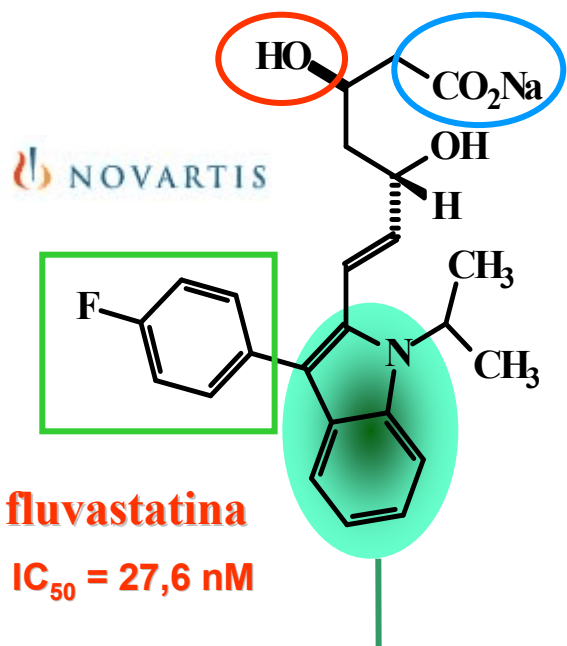
1994 - fluvastatina

IC₅₀ = 27,6 nM

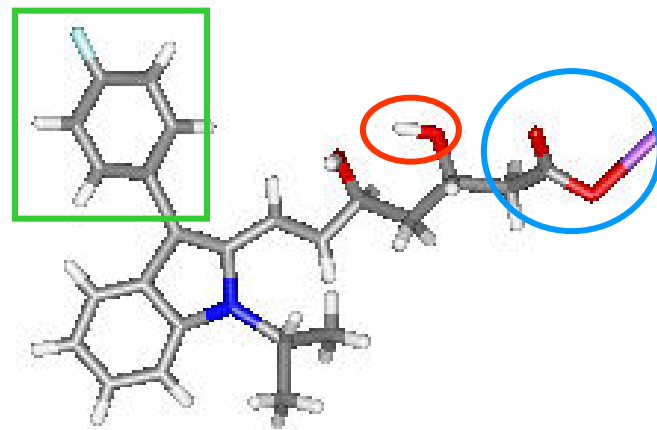




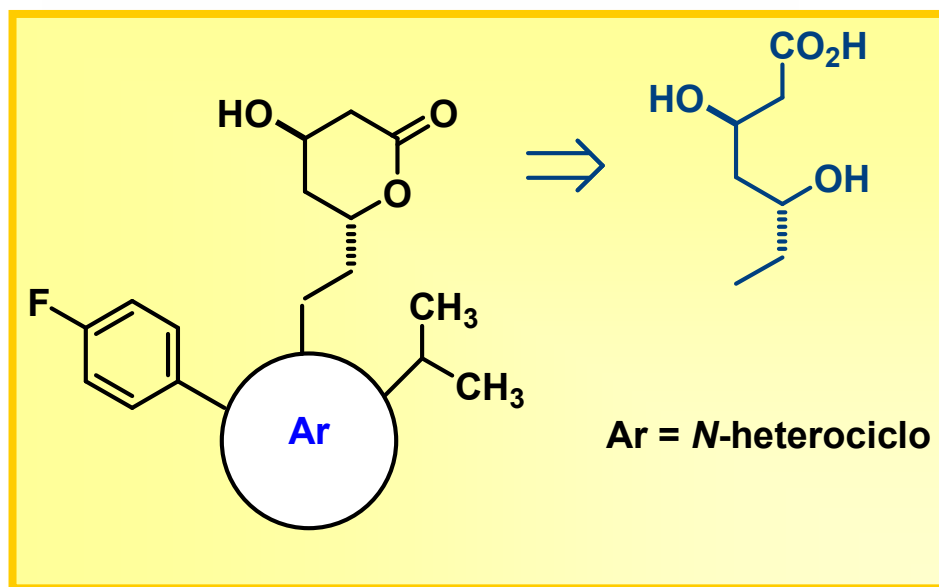
Gênese das estatinas de segunda geração (sm)



Sub-unidade hidrofóbica = aromática

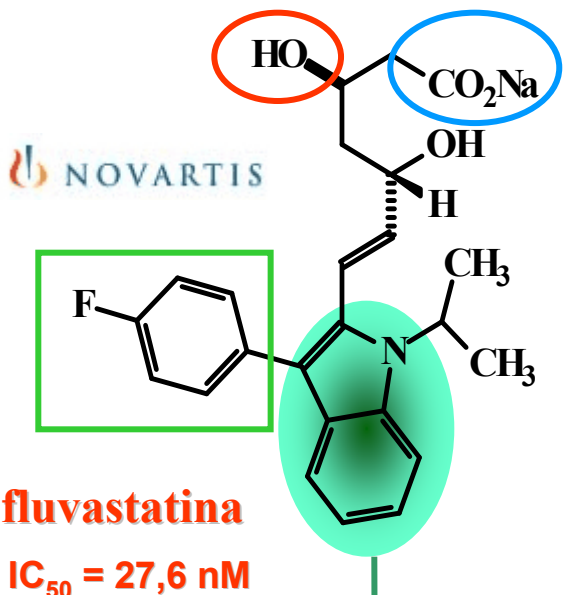


Quimiotipo das estatinas

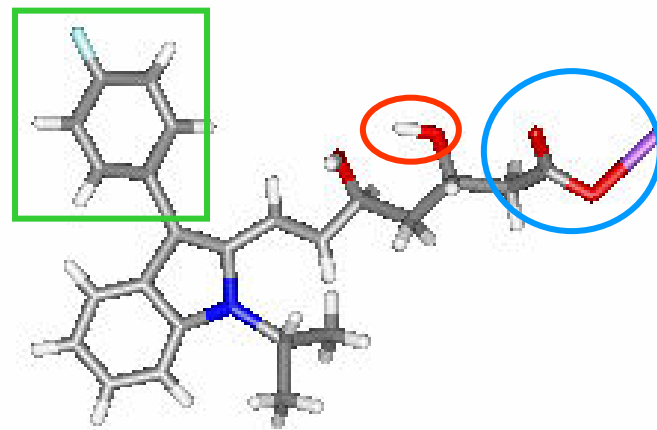




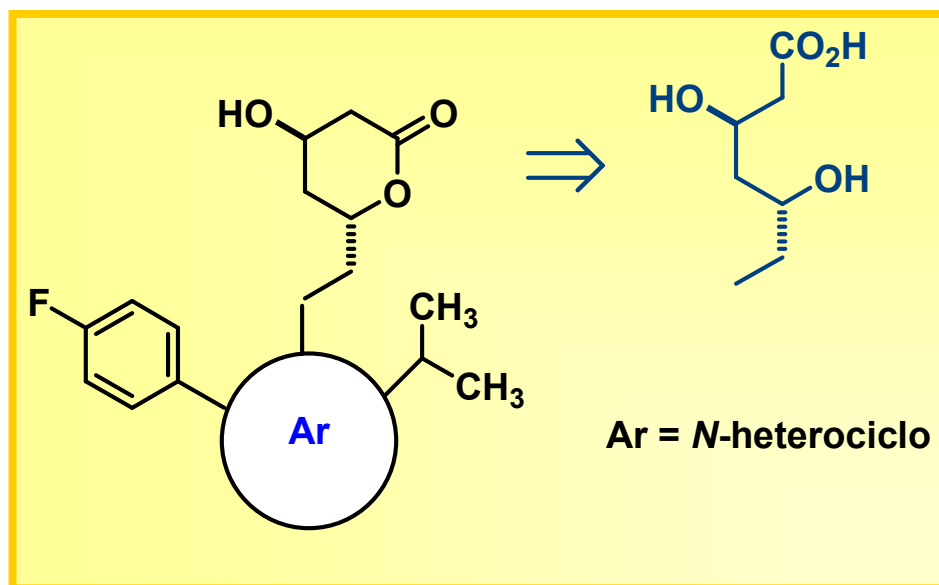
Gênese das estatinas de segunda geração (sm)



Sub-unidade hidrofóbica (aromática)



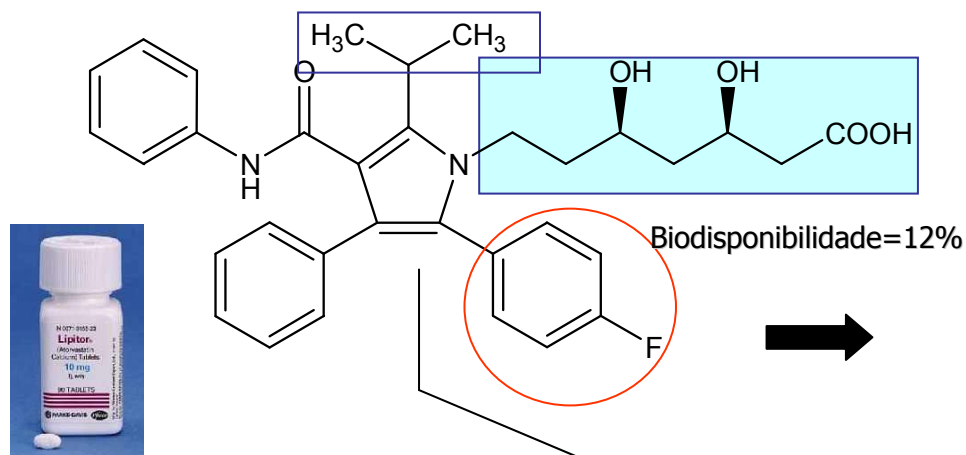
Quimiotipo das estatinas





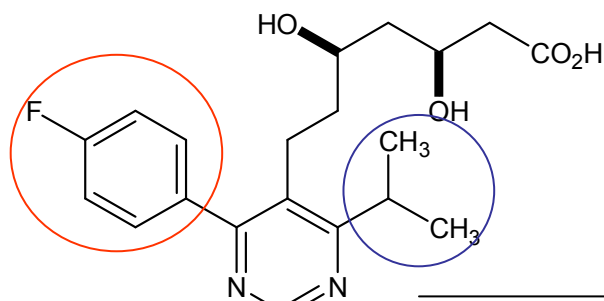
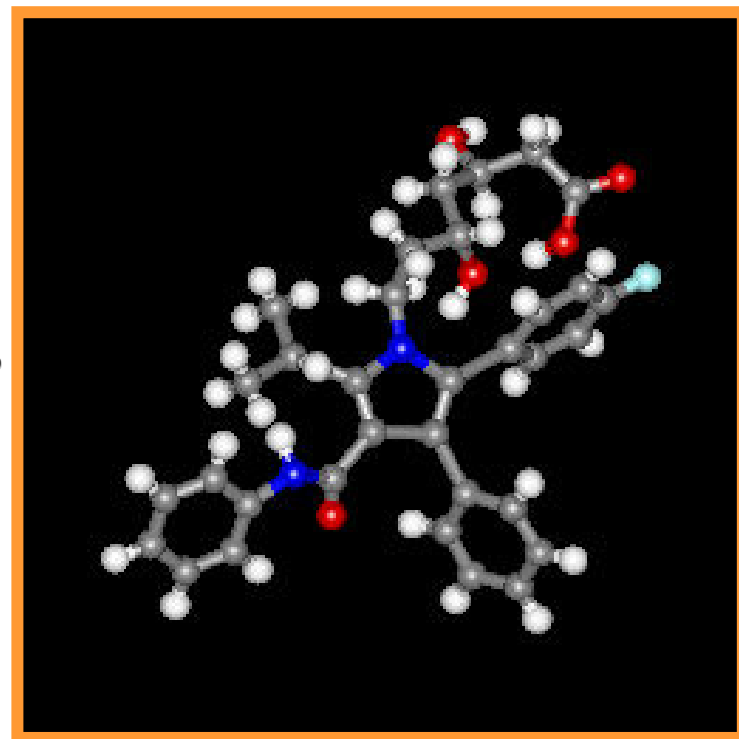
Estatinas

ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico

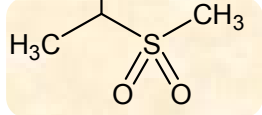


atorvastatina

IC₅₀ = 8,2 nM



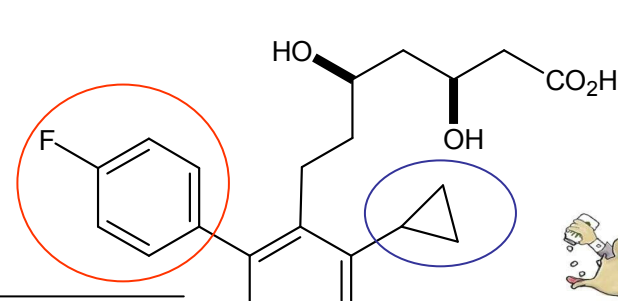
AstraZeneca



rosuvastatina

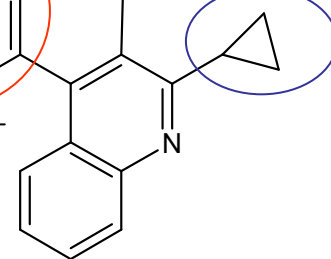
IC₅₀ = 5,4 nM

Biodisponibilidade = 20%



Livalo
(pitavastatin) tablets

Kowa Pharmaceuticals

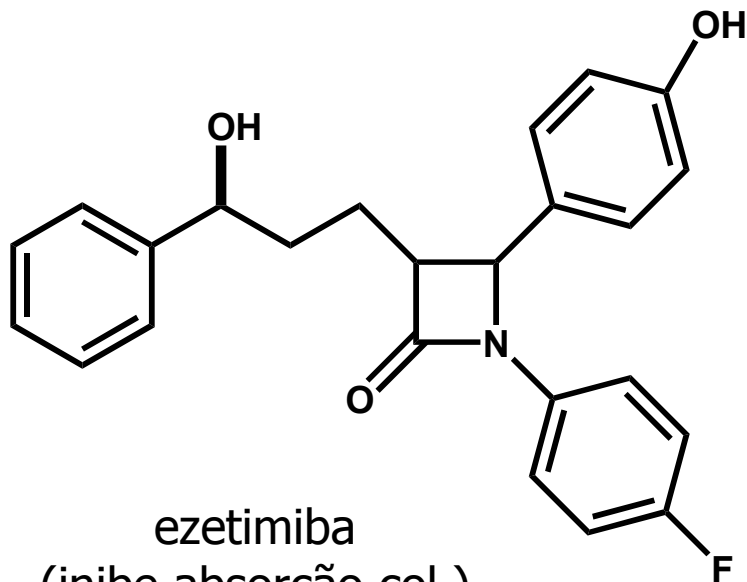


pitavastatina

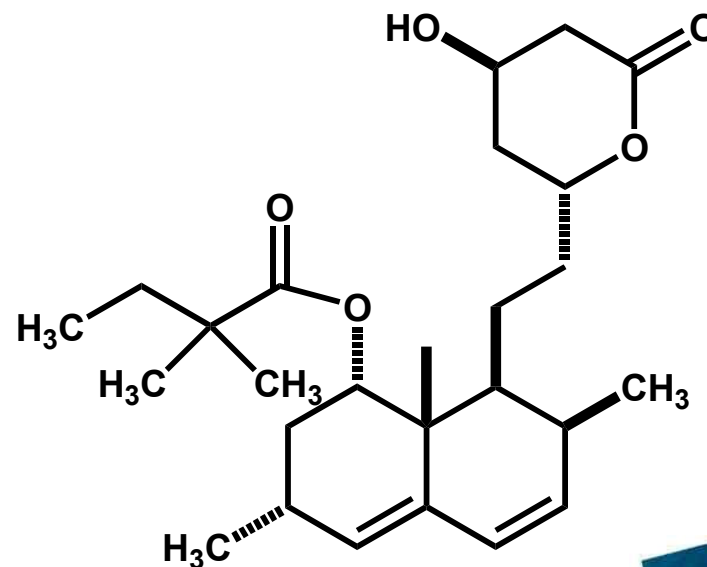
IC₅₀ = 3,4 nM

Biodisponibilidade=60%

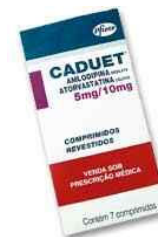




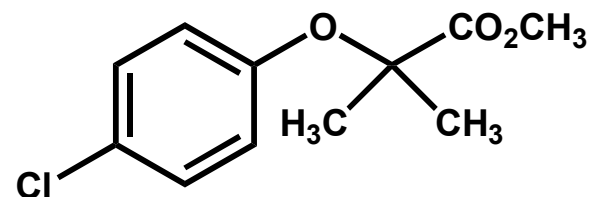
ezetimiba
(inibe absorção col.)



Simvastatina
(HMGCoARi)



American Academy of Cardiology's
57th Annual Scientific Session (2008)
Dislipidemia = hipercolesterolemia, LDL &
hipertrigliceridemia



clofibrato



Considerações

finais

*Química
Medicinal*



Laboratório de Avaliação e Síntese de Substâncias Bioativas

Faculdade de Farmácia
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a partir de
**01 DE SETEMBRO
2010**

24 a 28 de janeiro de 2011

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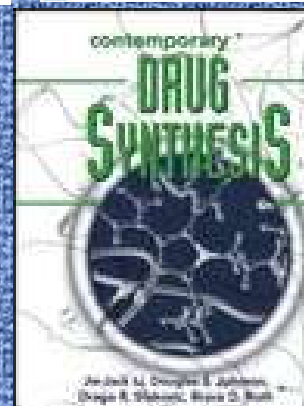
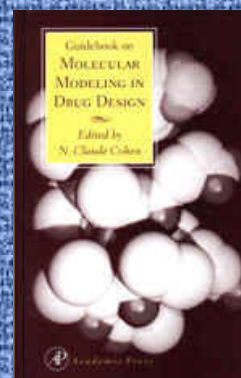
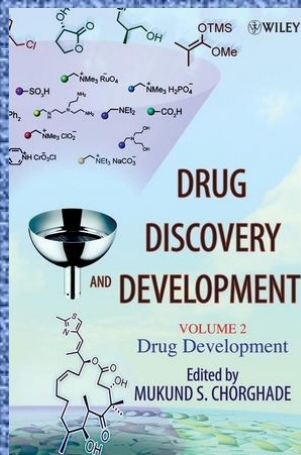
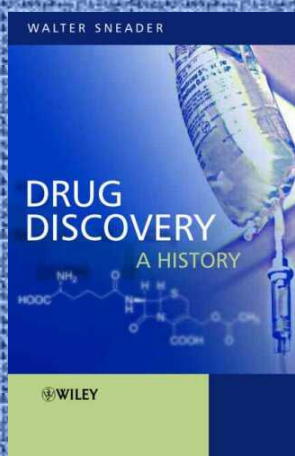
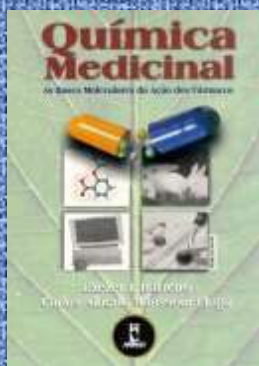
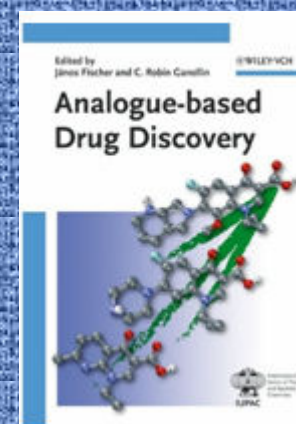
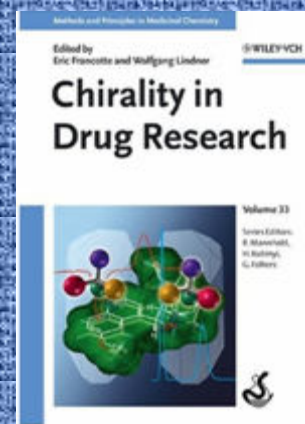
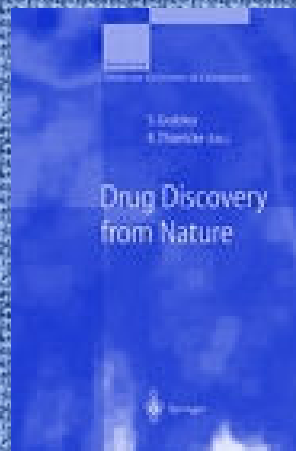
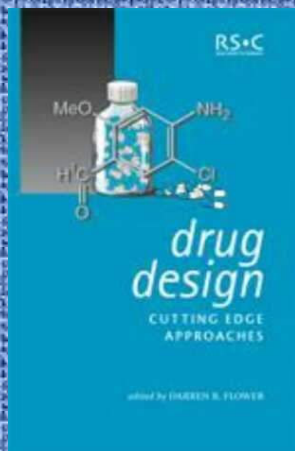
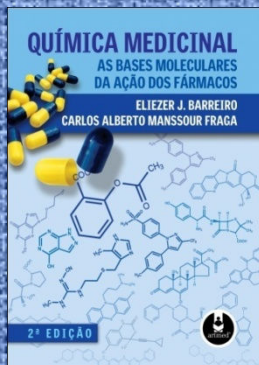
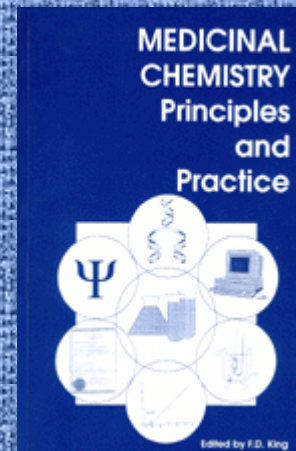
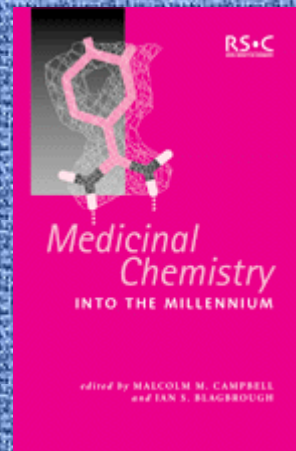
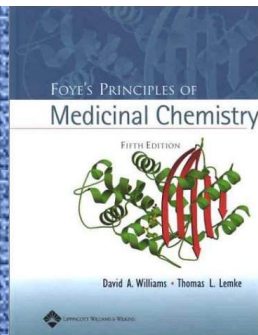
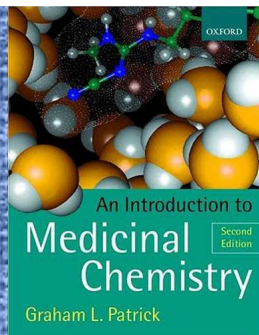
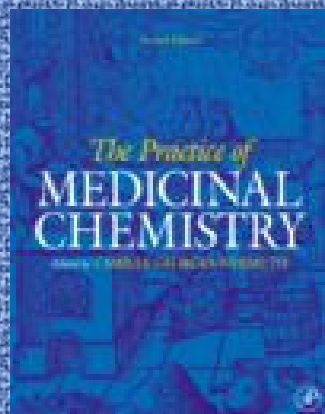
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co-authors

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The library is an integral part of a project being developed by FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo, in partnership with BIREME - the Latin American and Caribbean Center on Health Sciences Information. Since 2002, the Project is also supported by **CNPq** - Conselho Nacional de Desenvolvimento Científico e Tecnológico.

The Project envisages the development of a common methodology for the preparation, storage, dissemination and evaluation of scientific literature in electronic format.





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**“...Para achar água é preciso
descer terra adentro,
Encharcar-se no lodo.**

**Mas há os que preferem
olhar os céus,
E esperar pelas chuvas...”**

Oduvaldo Vianna Filho

*(em “Cúmplice da Paixão”, Dênis de Moraes
Ed. Nórdica, RJ, 1991).*



Obrigado.



Laboratório de Avaliação e Síntese de Substâncias Bioativas

