"Use of natural products as building blocks, leads or preferred scaffolds in drug design"

Drugs from natural sources: the potential of Brazilian plants used in tradiconal medicine

Ano Brasil-Alemanha da Ciência, Tecnologia & Inovação 2010/11

Club Transtlântico, São Paulo, S. P.
September 22nd, 2010

Eliezer J. Barreiro

Professor of Medicinal Chemistry

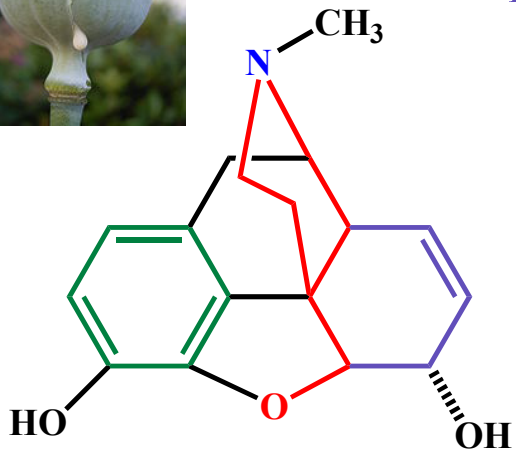
Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Programa de Desenvolvimento de Fármacos – ICB - UFRJ

http://www.farmacia.ufrj.br/lassbio

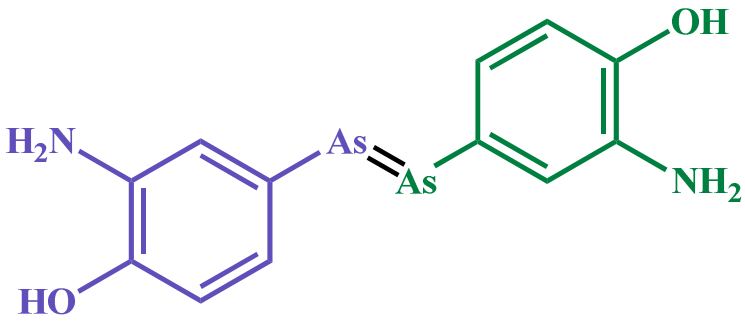
The first drug molecules…



morphine

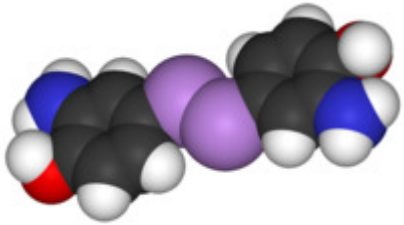
$C_{17}H_{19}NO_3$

Marco Polo
*ca.*1284- 1324

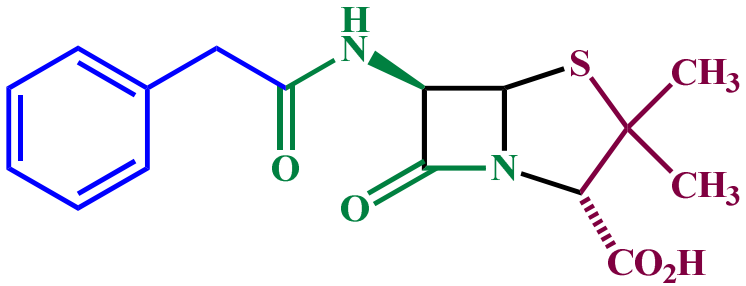


arsphenamine

$C_{29}H_{31}As_2N_3O_5$



Paul Ehrlich
1854-1915
Nobel 1908



penicillin

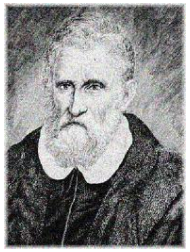
$C_{16}H_{18}N_2O_4S$

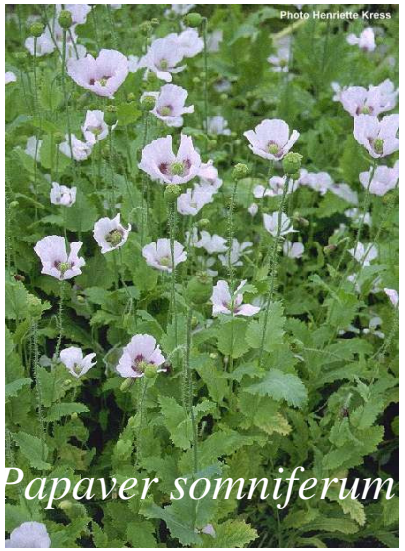
Alexander Fleming
1881-1955
Nobel 1945

Morphine

- 1493-1541 Marco Polo, Veneza, IT opium
- Friedrich WA Sertürner – 1806
- M Gates, synthesi 1952
- Beckett & Casey opiate effects were receptor mediate - 1954

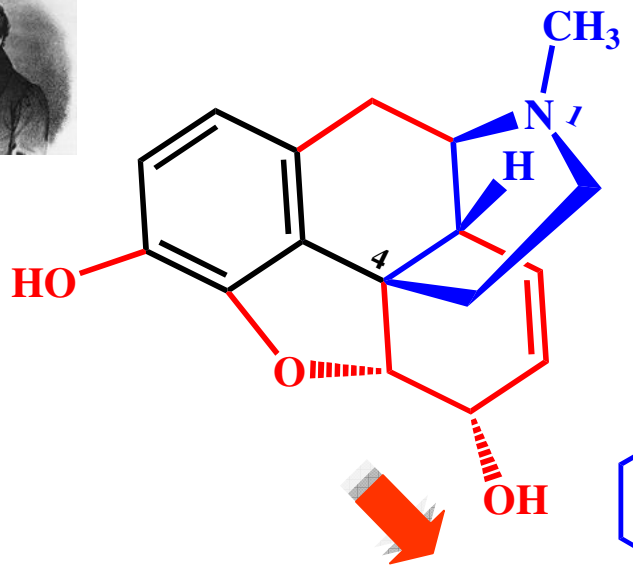
  δ, κ, μ - 1970



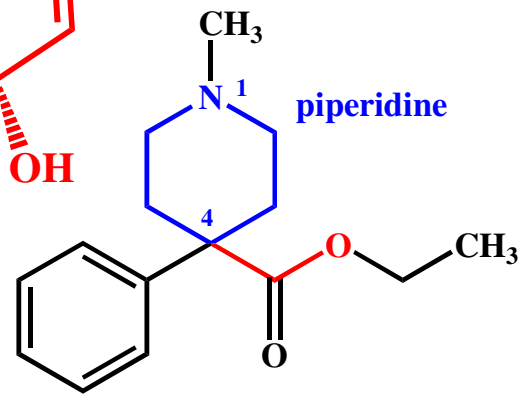


Phenantrene & benzylisoquinoline alkaloids (*e.g.* papaverine 0.2%)

***ca.* exists 21000 alkaloids (75% unknow)** [GA Cordell & MA Colvard, J. Ethnopharmacol., 100, 5 (2005)]



morfina



meperidine

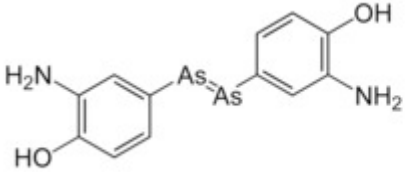
P. W. Schiller, *Progr. Med. Chem.* *1991*, **28**, 301

Paul Ehrlich
1854-1915

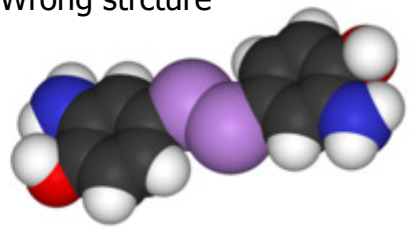
1908

Chemotherapeutics: scientific principles, methods and results. *Lancet* 1913, **2**, 445

medicinal chemistry

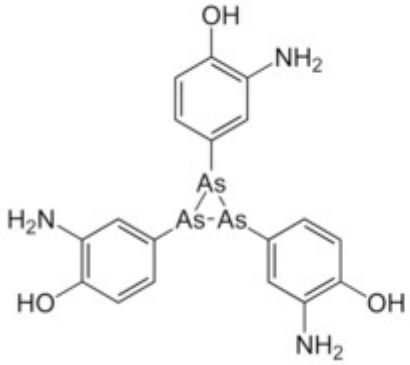


Wrong strcture

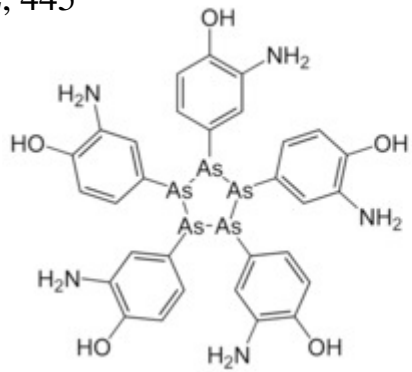


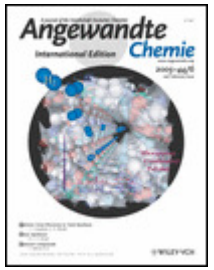
Arsphenamine

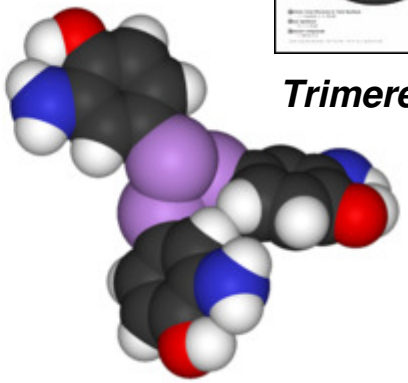
1908 - Anti-syphilitic activity



Correct strctures

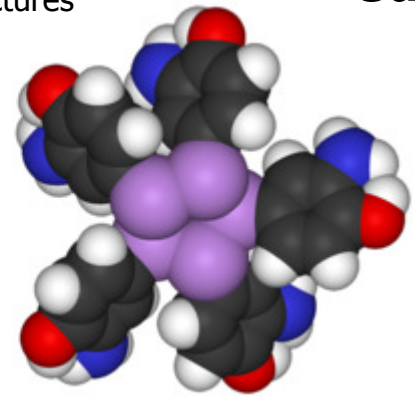






Trimere

Salvarsan^{R}

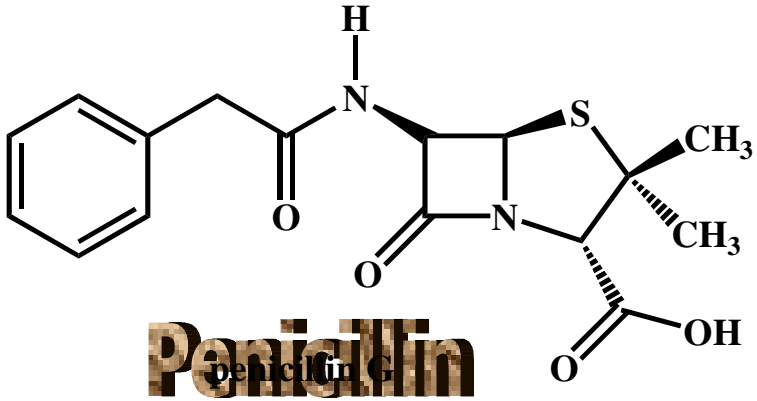


Pentamere

Lloyd NC, Morgan HW, Nicholson BK, Ronimus RS "The composition of Ehrlich's salvarsan: resolution of a century-old debate". Angew. Chem. Int. Ed. Engl. 2005, 44, 941.

Universidade Federal do Rio de Janeiro

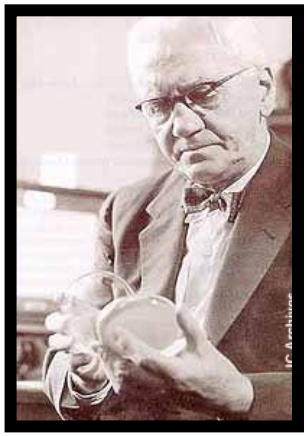
Antibiotic therapy



Penicillin

penicillin G

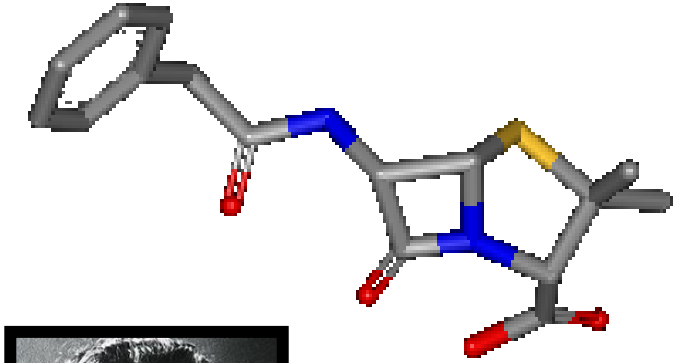
1929



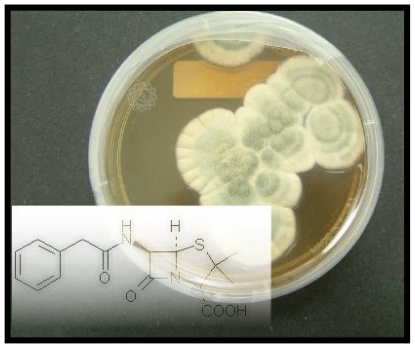
Alexander Fleming
1881-1955

A. Fleming, Br. J. Exp. Pathol., 10, 226 (1929)

http://nobelprize.org



Howard Walter Florey
1898-1968

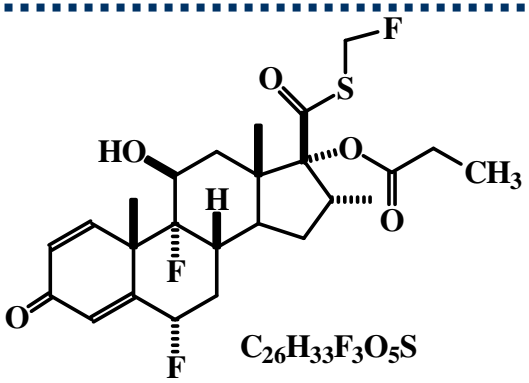


Ernst Boris Chain
1906-1999

1941

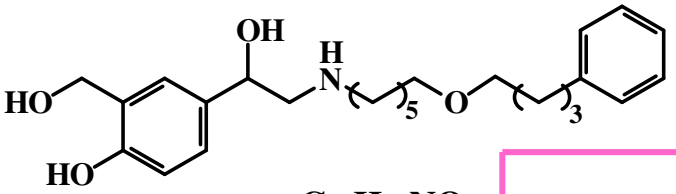
Nobel Prize of Medicine
1945

5 Top-selling drugs in WPh market 2009



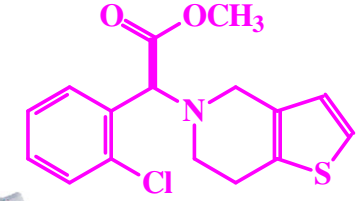
$C_{26}H_{33}F_3O_5S$

Seretide



$C_{25}H_{37}NO_4$

clopidogrel



$C_{16}H_{16}ClNO_2S$

1975:cimetidine

1 | 2,0 | 4,5-5,5 | 5,6 | 7,7 | 7,9 | 8,5 | 13,2 | 43,2

US$ bi

fluticazone
salmeterol

Etanercept
(biofármaco)

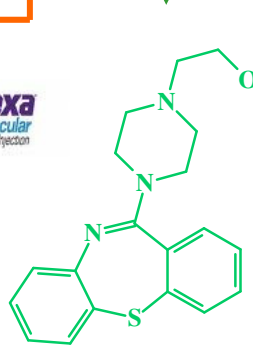
Olanzapine

Infliximab
(biofármaco)

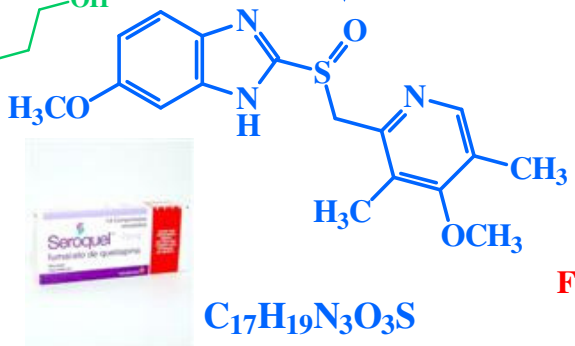
Montelukast

Rosuvastatin

68.1
(8,2%)

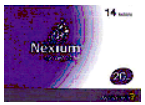


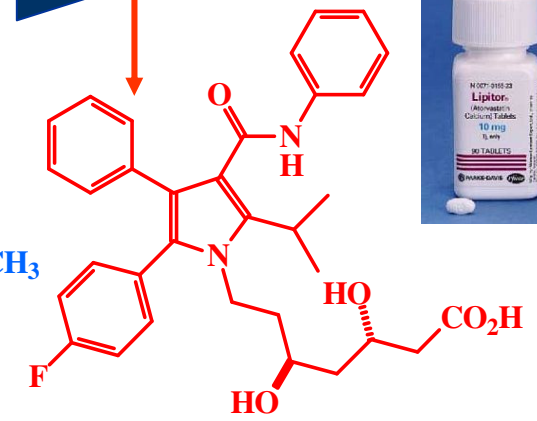
quetiapine



$C_{17}H_{19}N_3O_3S$

esomeprazole





$C_{33}H_{35}FN_2O_5$

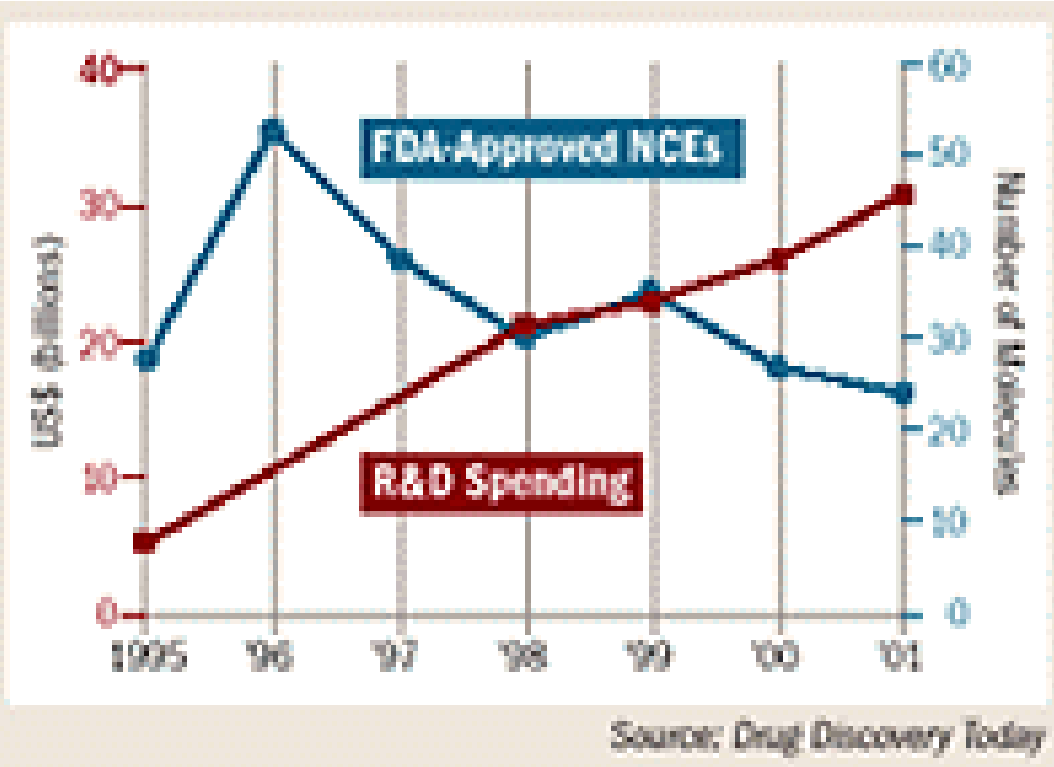
atorvastatin

"...The rate of introduction of new chemical entities has slowed despite the wealth of new technologies ...".

Donald Kennedy, ***Editor-in-Chief***

Drug Discovery – Editorial

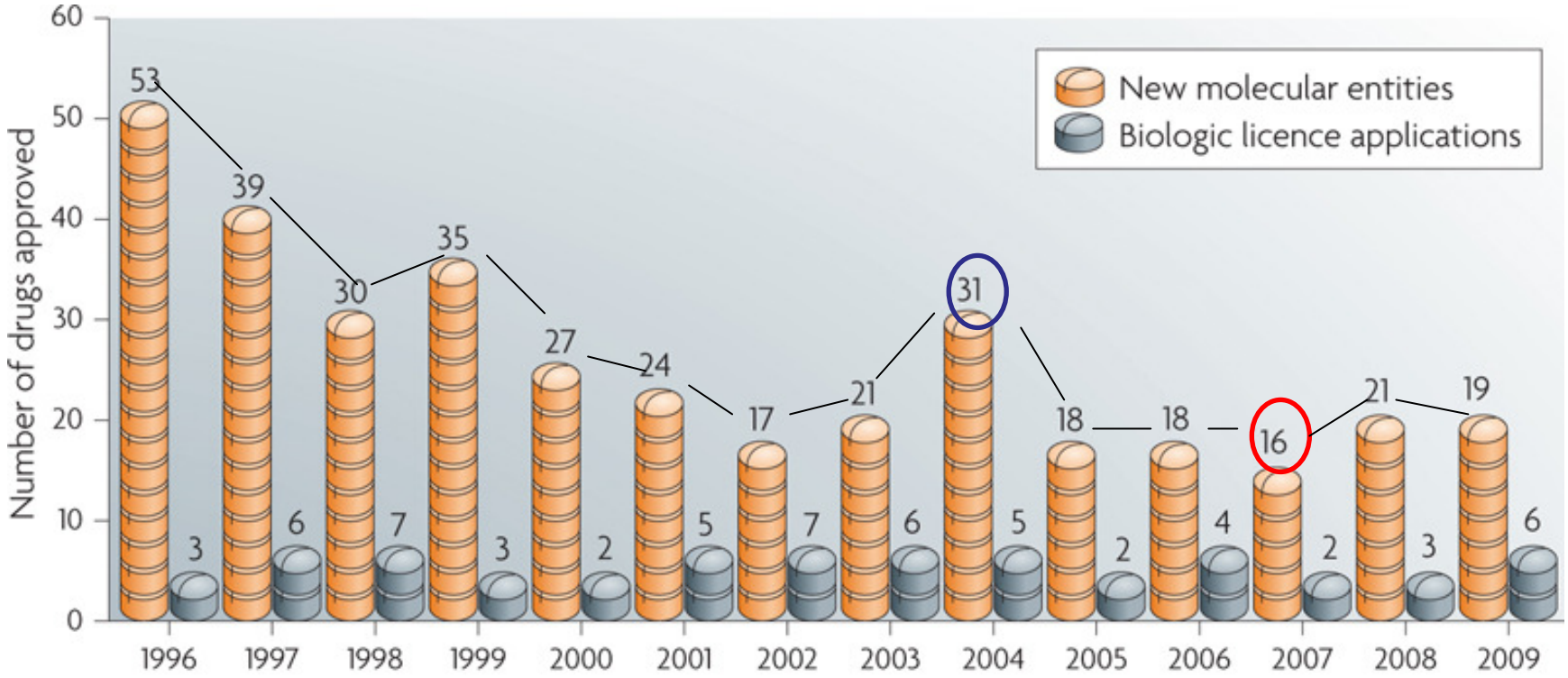
Science **2004**, *303*, 1717

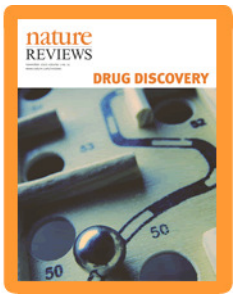


Fragment-based approach

M. Vieth *et al.*, **Characteristic Physical Properties and Structural Fragments of Marketed Oral Drugs,** *J. Med. Chem.* **2004,** *47,* 224

The Big-pharma criativity crisis





New molecular entities...

Nature Reviews | Drug Discovery

B. Hughes, 2009 FDA drug approvals, *Nature Rev. Drug Discov.* **2010,** *9*, 89-92 doi:10.1038/nrd3101

...or the *blockbuster syndrome*

Paclitaxel

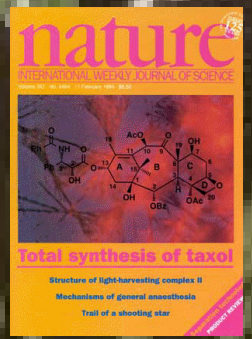
Cancer

M. E. Wall & M. C. Wani
Res. Triangle Park, 1967

1996 - National Cancer Institute
Award of Recognition

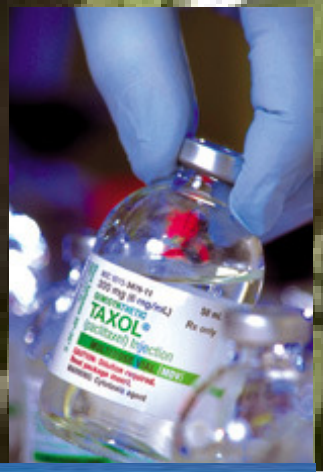
Taxol®

M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348

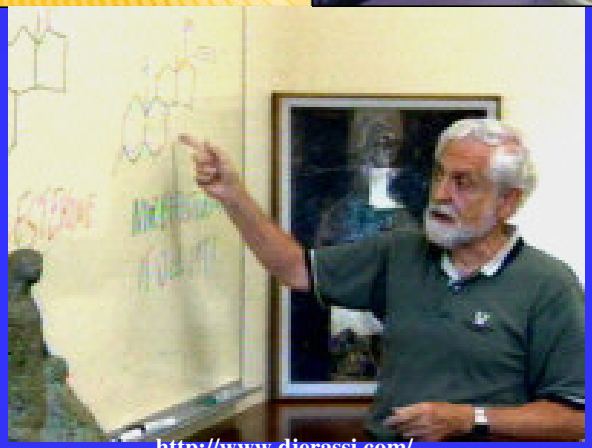


Terpenos

M. C. Wani *et al.*, J. Am. Chem. Soc. 93, 2325 (1971)

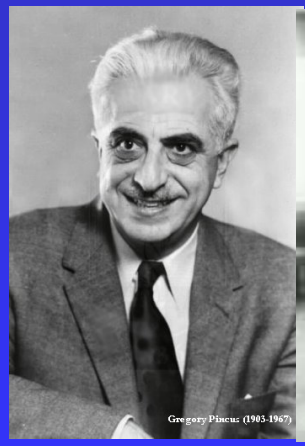


steroids



http://www.djerassi.com/

Carl Djerassi

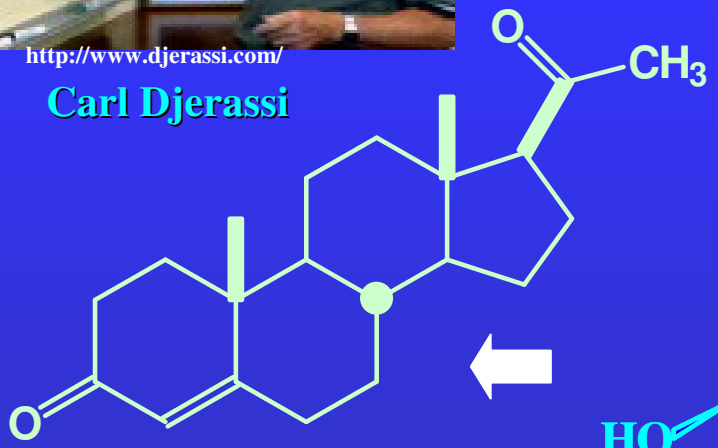


Russell E. Marker & Gregory Pincus

(*J. Chem. Educ.* 1973, *50*, 195).

The pill

In 1937 at Pond Laboratory, University of Pensilvanie, USA, Marker finished the first synthesis of progesterone using diosgenine as natural building block



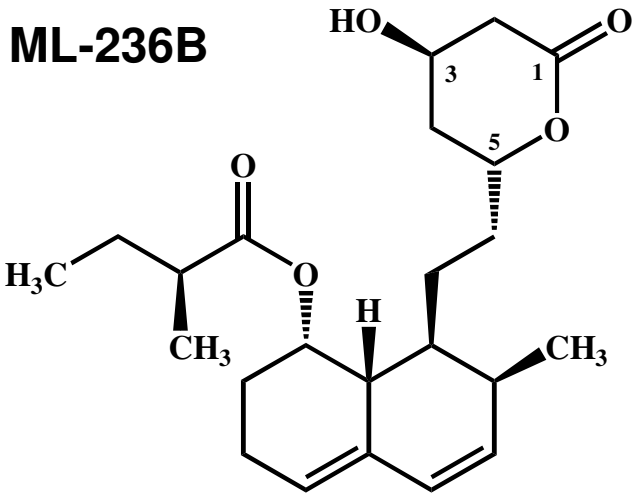
progesterona

diosgenina

Statins

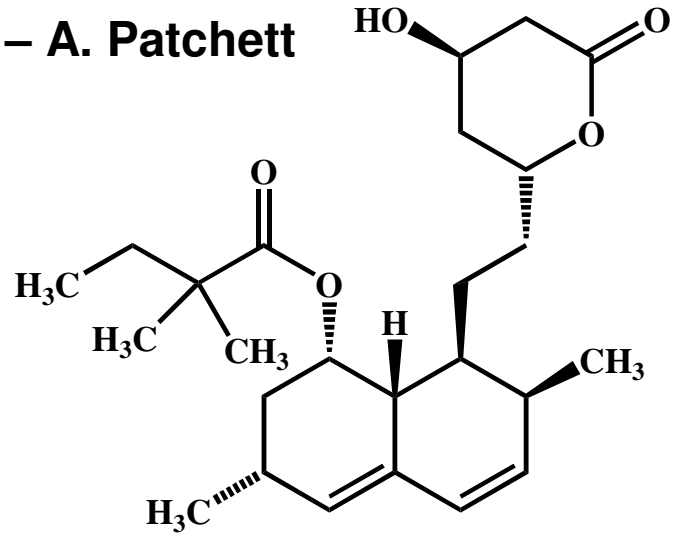
- **In 1976: ML-236A, ML-236B, ML-236C, metabolites isolated from a fungus (*Penicillium citrinum*) were found to reduce serum cholesterol levels in rats;**
- **This work was done by Akira Endo, Masao Kuroda and Yoshio Tsujita at the Fermentation Research Laboratories, Tokyo, Japan (Endo, A.; Kuroda, M.; Tsujita, Y., *J. Antibio.* 1976, *29*, 1346; A. Endo, Y. Tsujita, M. Kuroda, K. Tanzawa, *Eur. J. Biochem.*, 77, 31 (1977)).**

ML-236B



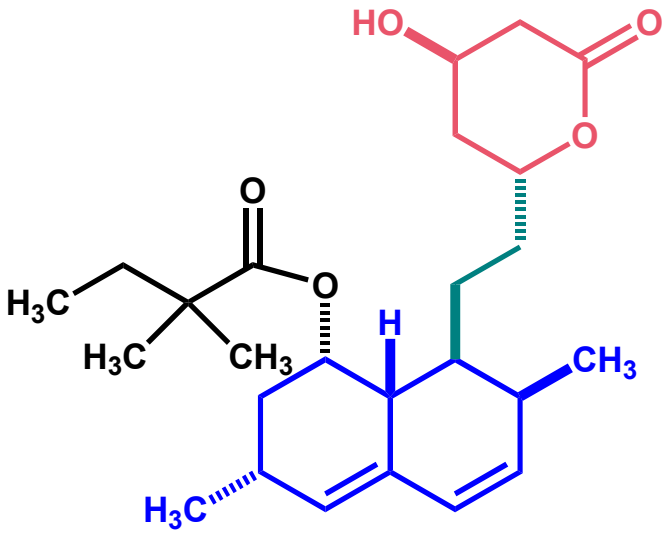
compactin or mevastatin

1986 – A. Patchett

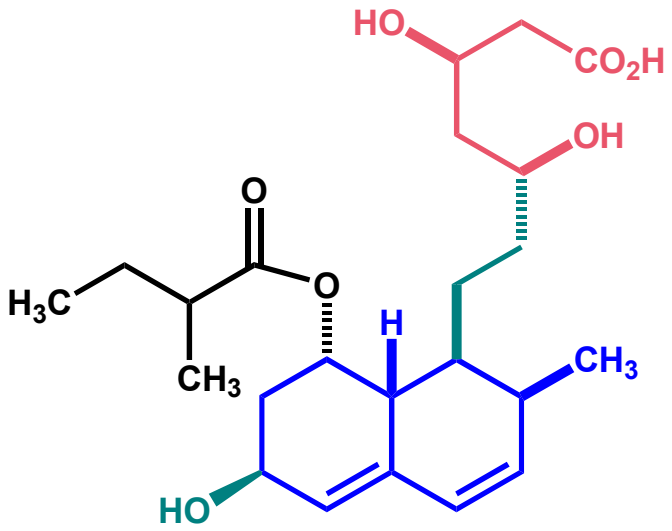


simvastatin

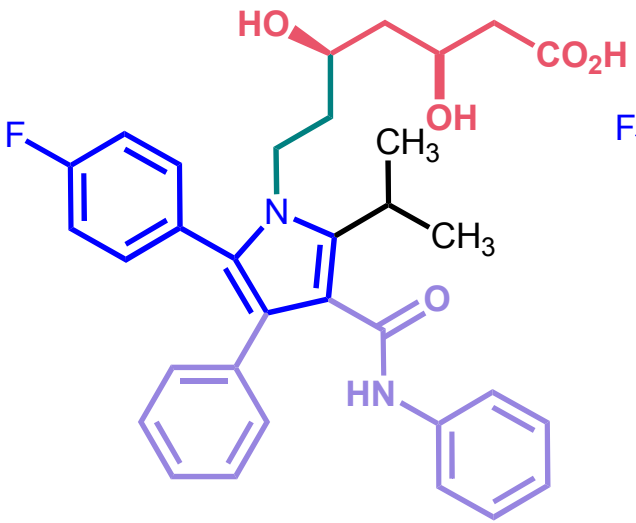
A. A. Patchett, *J. Med. Chem.*, **45**, 5609 (2002); J. A. Tobert, *Nature Rev. Drug Discov.*, **2**, 517-526 (2003); . C. A. S. Menezes, C. M. Avila, E. J. Barreiro, *Lett. Drug Des. Discov.*, **7**, 546-550 (2010).



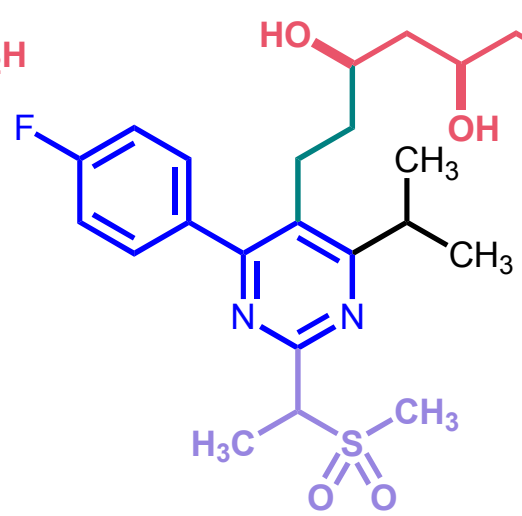
simvastatina
1986



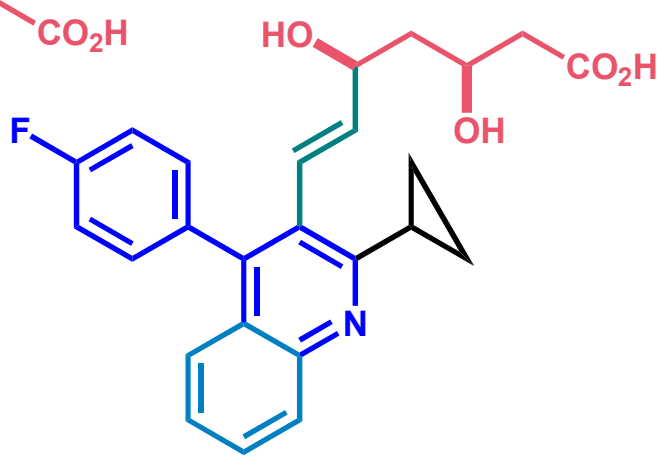
pravastatina
1988



atorvastatina
1991



rosuvastatina
2004



pitavastatina
2009

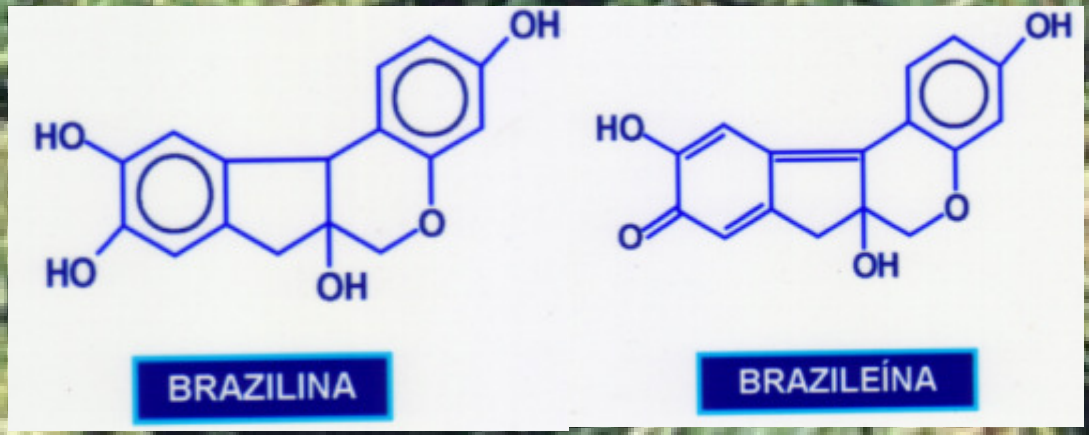
Drug development from marine natural products

Tadeusz F. Molinski, Doralyn S. Dalisay*, Sarah L. Lievens*‡ and Jonel P. Saludes*‡*

Abstract | Drug discovery from marine natural products has enjoyed a renaissance in the past few years. Ziconotide (Prialt; Elan Pharmaceuticals), a peptide originally discovered in a tropical cone snail, was the first marine-derived compound to be approved in the United States in December 2004 for the treatment of pain. Then, in October 2007, trabectedin (Yondelis; PharmaMar) became the first marine anticancer drug to be approved in the European Union. Here, we review the history of drug discovery from marine natural products, and by describing selected examples, we examine the factors that contribute to new discoveries and the difficulties associated with translating marine-derived compounds into clinical trials. Providing an outlook into the future, we also examine the advances that may further expand the promise of drugs from the sea.

Nat. Rev. Drug Discov. **2009**, *8*, 69

PAU-BRASIL
Caesalpinia echinata
IBIRAPITANGA



Red dye from the woods of *C. echinata*

The name of the country: Brasil

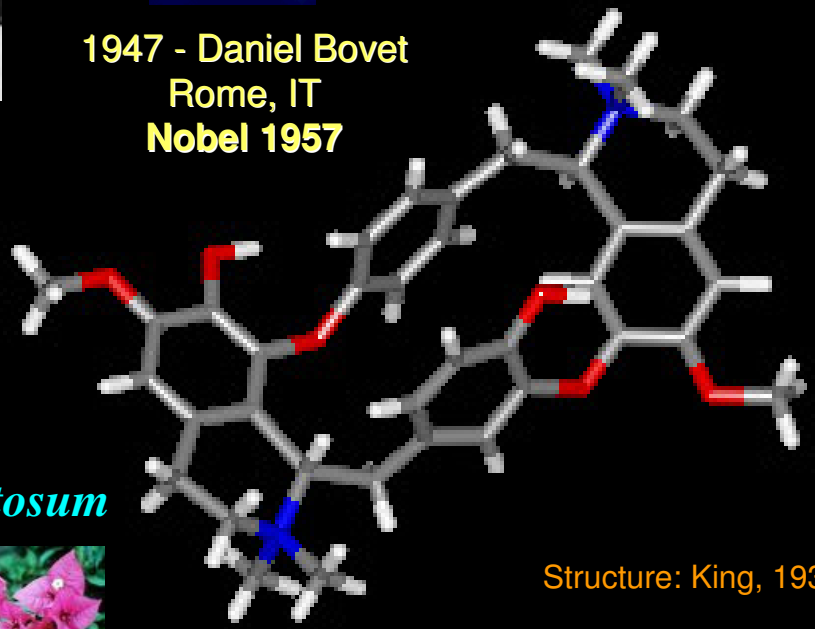
From 1128, in Italy, the bressil, bassily, bresilzy or bracilis ink was know.

Curare

The drug class of Amazon Natives

Institute Pasteur
Claude Bernard (1851)

1947 - Daniel Bovet
Rome, IT
Nobel 1957



Structure: King, 1935

Chondrodendron_tomentosum
Loganiaceae
(urari)

d-tubocurarine

From the Brazilian jararaca to ACE inhibitors

M. O. Rocha e Silva
1910-1983

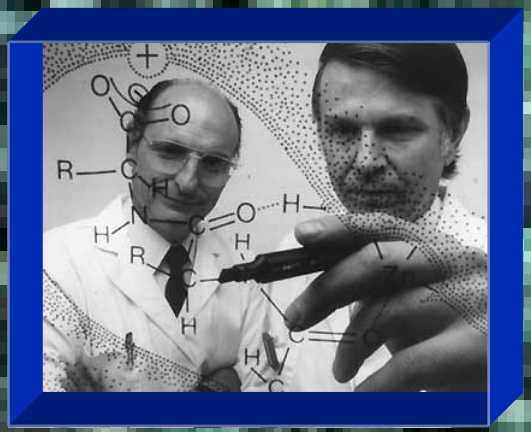
Bothrops jararaca

S. H. Ferreira
1934-

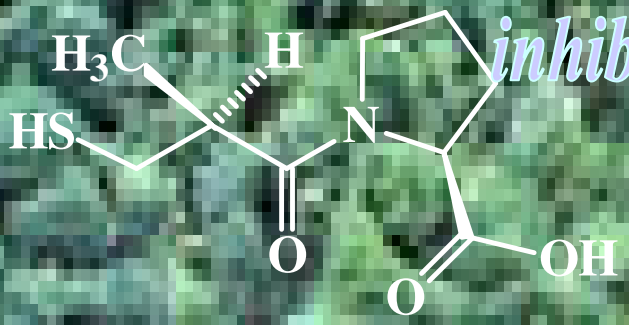
S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venon of *Bothrops jararaca, Brit. J. Pharmacol.* 1965, *24*, 163.

The renine-angiotensine system (RAS)

ACE inhibitor



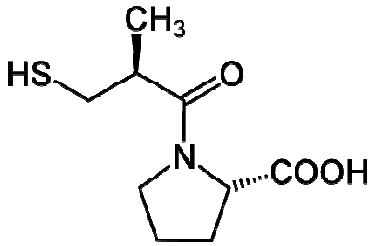
D. W. Cushman & M. A. Ondetti



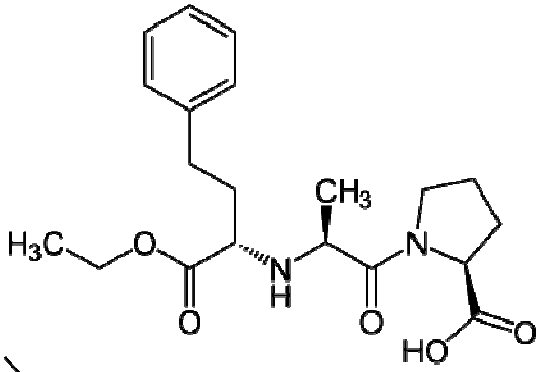
Captopril
(Capoten^{R})

M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

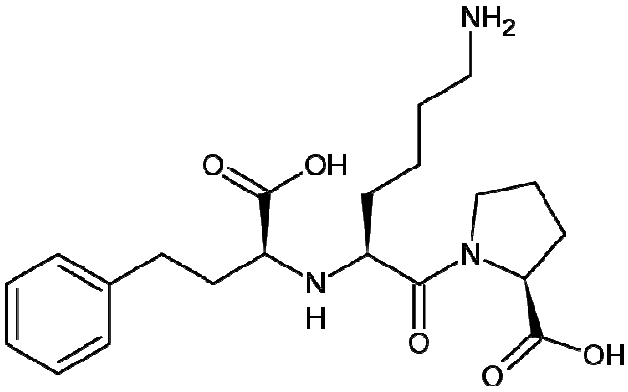
Inibidores da ECA



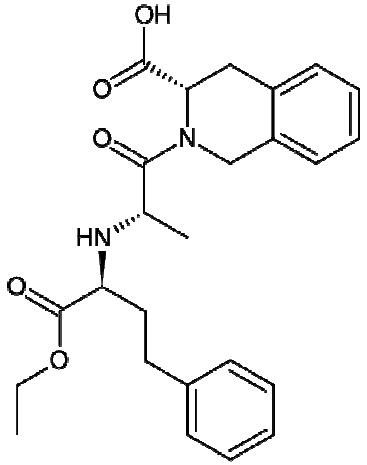
captopril



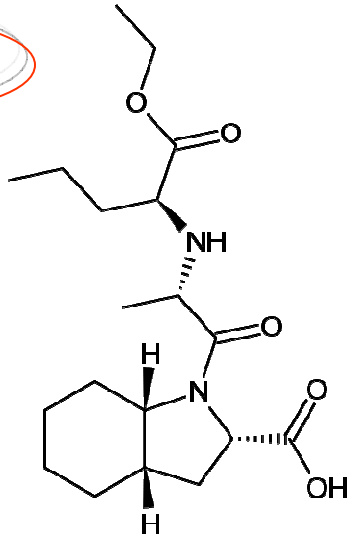
enalapril



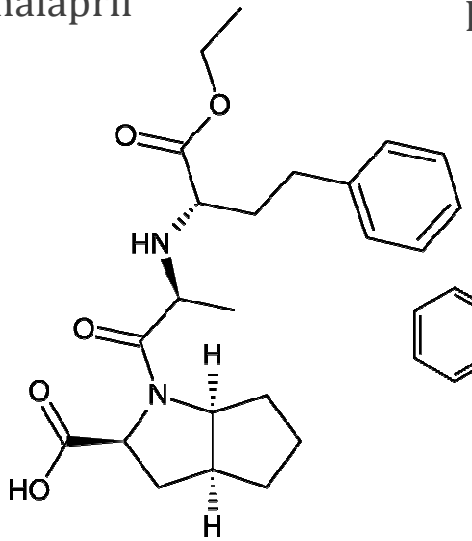
lisionopril



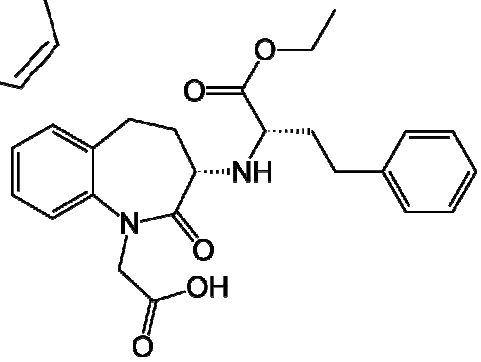
quinapril



perindopril



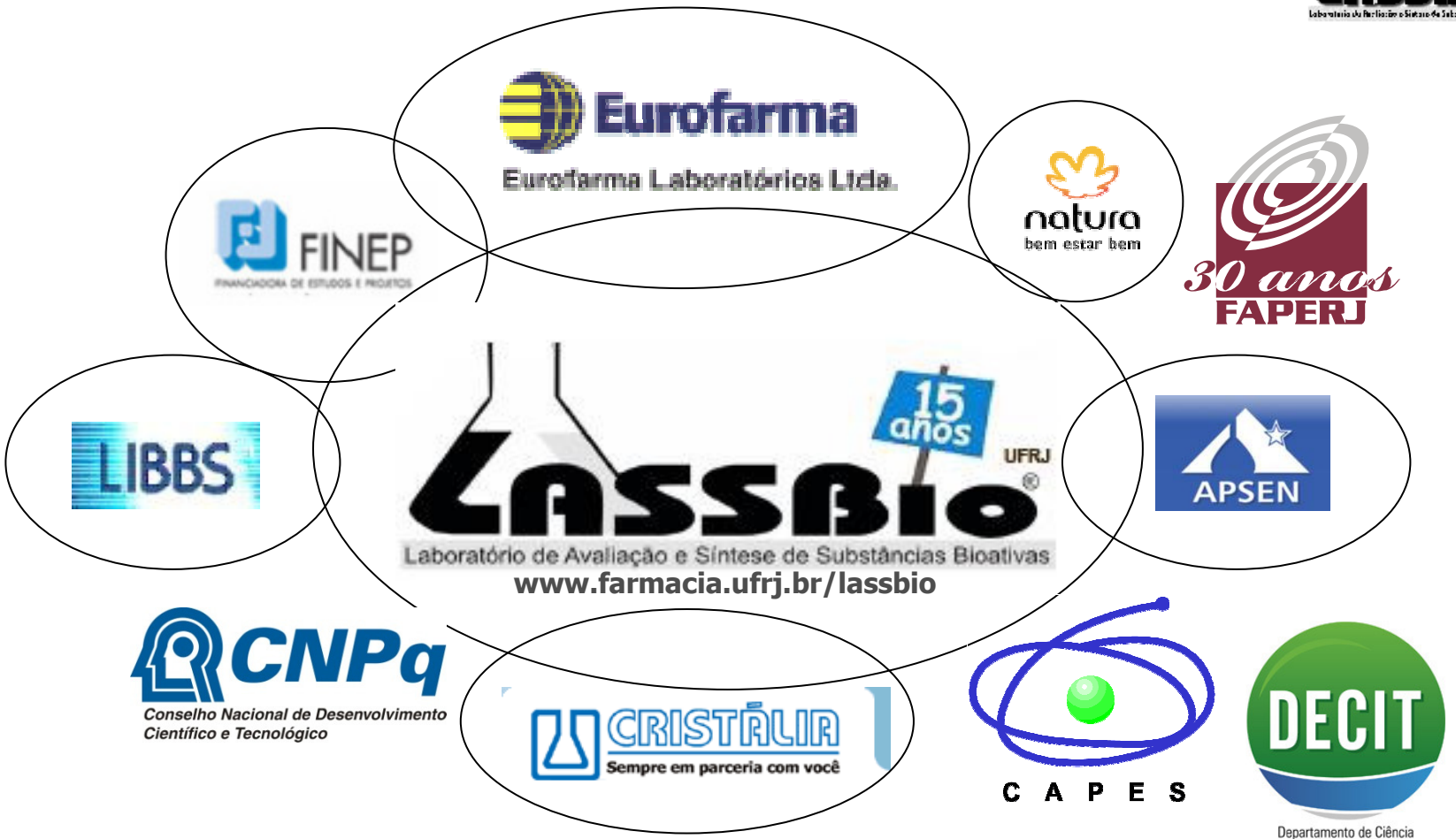
ramipril



benazepril

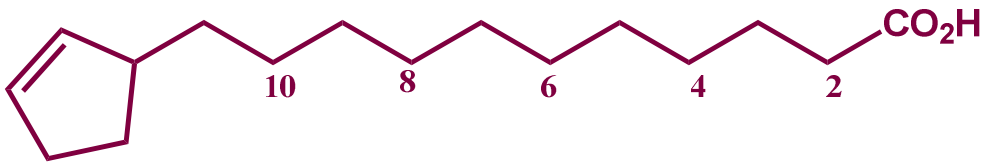
medicinal chemistry

Universidade Federal do Rio de Janeiro



E. J. Barreiro, V. S. Bolzani, Biodiversidade: Fonte potencial para a descoberta de fármacos, *Quim. Nova*, **32**, 679-688 (2009);

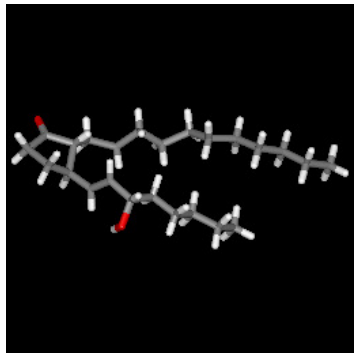
Natural product as synthetic building block



Hydnocarpic acid

$C_{16}H_{28}O_2$

Carpotroche brasiliensis, Endl
Flacourtiácea



The first Brazilian prostaglandins

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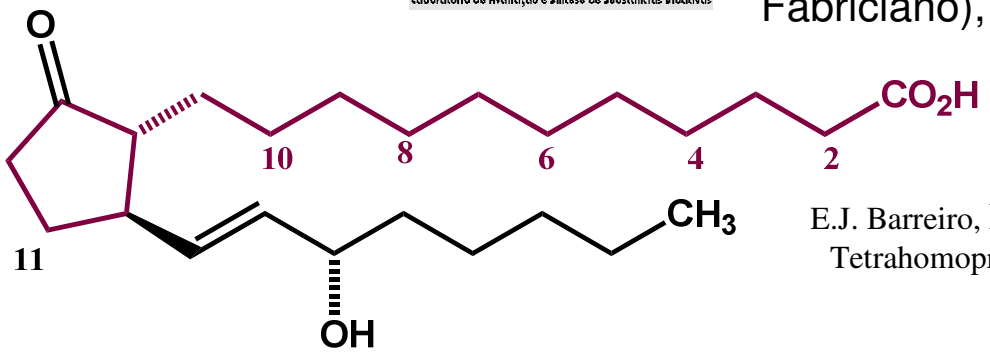
Obtained from **Sapucainha oil (BR)** (chaulmoogra oil, Inde);

Occurs: Rio de Janeiro, Minas Gerais (Coronel Fabriciano), Espírito Santo, Bahia



11-deoxy-1,1,1,1-tetrahomo PGE_1

E.J. Barreiro, L N LF Gomes, Prostaglandin Analogues. Synthesis of Tetrahomoprostaglandin Derivatives From Natural Hydnocarpic Acid Isolated From Sapucainha Oil..*J. Chem. Res*. **1983**, 2701
EJ Barreiro, LNLF Gomes, **PI/BR 38201866**, 02/04/1982
Chem. Abstr., 100, 17452lu (1984)].

Natural products as building blocks

Piperidine alkaloid

ethanolamine framework

(-)- Spectaline $C_{20}H_{39}NO_2$ PM 325.5

Principal alkaloid component of *Cassia leptophylla*

Instituto de Química, UNESP (Profa. Dra V. S. Bolzani & C. Viegas Jr)

M. S. Alexandre-Moreira, C. Viegas Jr., A. L. P. Miranda, ***V. S. Bolzani***, E. J. Barreiro, *Planta Medica*, 69, 795 (2003). C. Viegas Jr., V. S. Bolzani, L. S. B. Pimentel, N. G. Castro, R. F. Cabral, R. F. Cabral, R. S. Costa, C. Floyd, M. S. Rocha, M. C. M. Young, E. J. Barreiro, C A. M. Fraga, *Bioorg. Med. Chem.*, 13, 4184 (2005); V. S. Bolzani, A. A. L. Gunatilaka, C. Viegas-Jr.; A. C. Viegas-Jr., V. S. Bolzani, E. J. Barreiro, C. A. M. Fraga, *Mini Rev. Med. Chem.*, 5, 915-926 (2005); deRezende, D. H. S. Silva, I. Castro-Gâmboa, V. S. Bolzani, E. J. Barreiro, A. L. P. Miranda, M. S. Alexandre-Moreira, M. C. M. Young, *Quim. Nova,* 29, 1279-1286 (2006); D. H. S. Silva, C. Viegas-Jr, L. A. Santos, I. Castro-Gamboa, A. J. Cavalheiro, V. S. Bolzani, N. G. Castro, M. Pivatto, M. C. M. Young, M. S. Rocha, C. A. M. Fraga, E. J. Barreiro, *Rev. Virtual Quim.*, 2, 38-46 (2010).

Molecular modification

LASSBio-785

AChE-inhibitor

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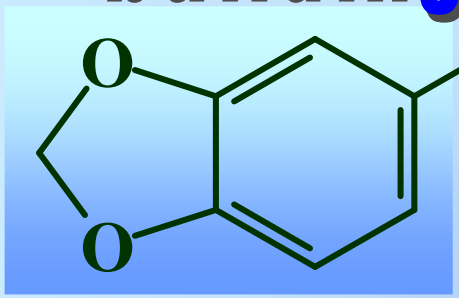
Natural products as building blocks



Alyl-benzene
$C_{10}H_{10}O_2$

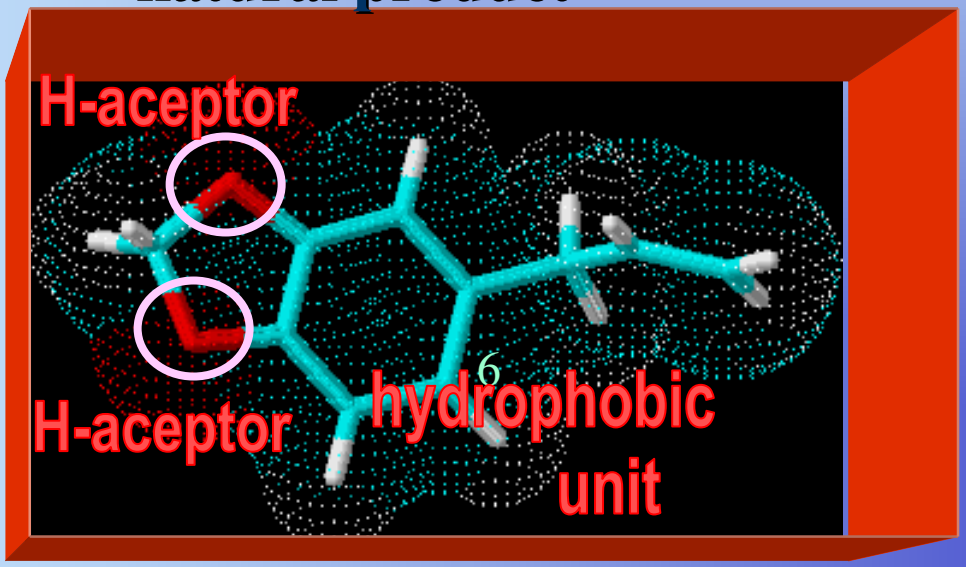
Piper sp

Brazilian abundant natural product

Sassafraz oil

Ocotea sp.

Natural biophore



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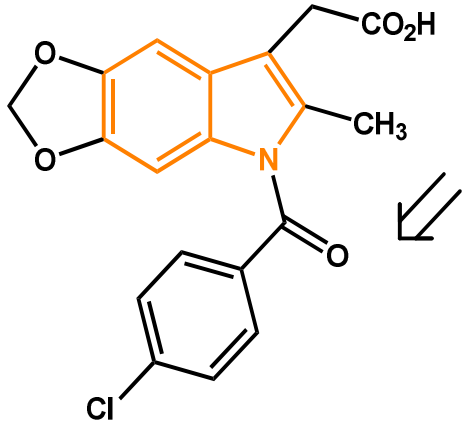
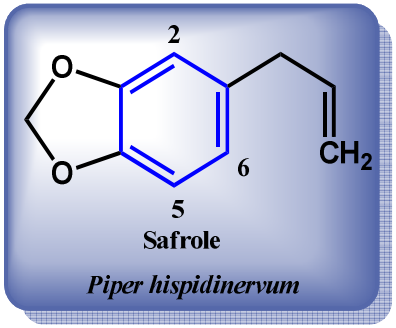
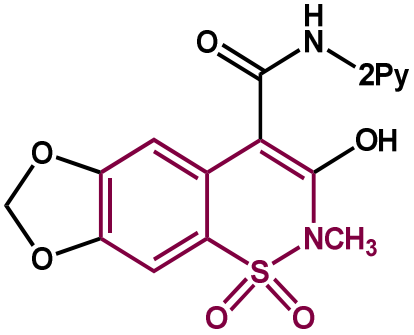
E. J. Barreiro & C. A. M. Fraga, "A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substancias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos". *Química Nova*, *22*, 744 (1999).

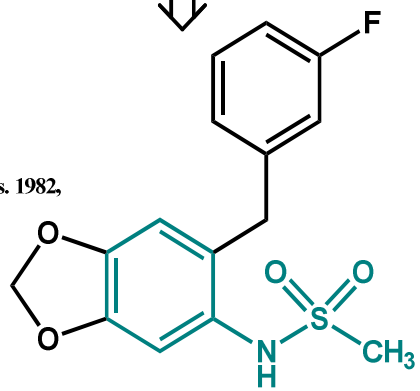


EJ Barreiro, PRR Costa, PRVR Barros, WM Queiroz, J. Chem. Res. 1982, (S) 102; (M) 1142

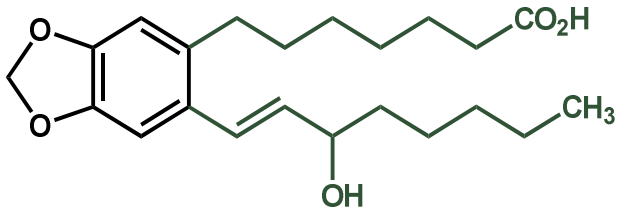




CAM Fraga, EJ Barreiro, J. Heterocyclic Chem. 1992, 29, 301



AS Lages, KCM Silva, ALP Miranda, CAM Fraga, EJ Barreiro, Bioorg. Med. Chem. Lett. 1998, 8, 183.



EJ Barreiro, PRR Costa, FAS Coelho, FMC Farias, J. Chem. Res. 1985, (S) 220, (M) 2301.

medicinal chemistry

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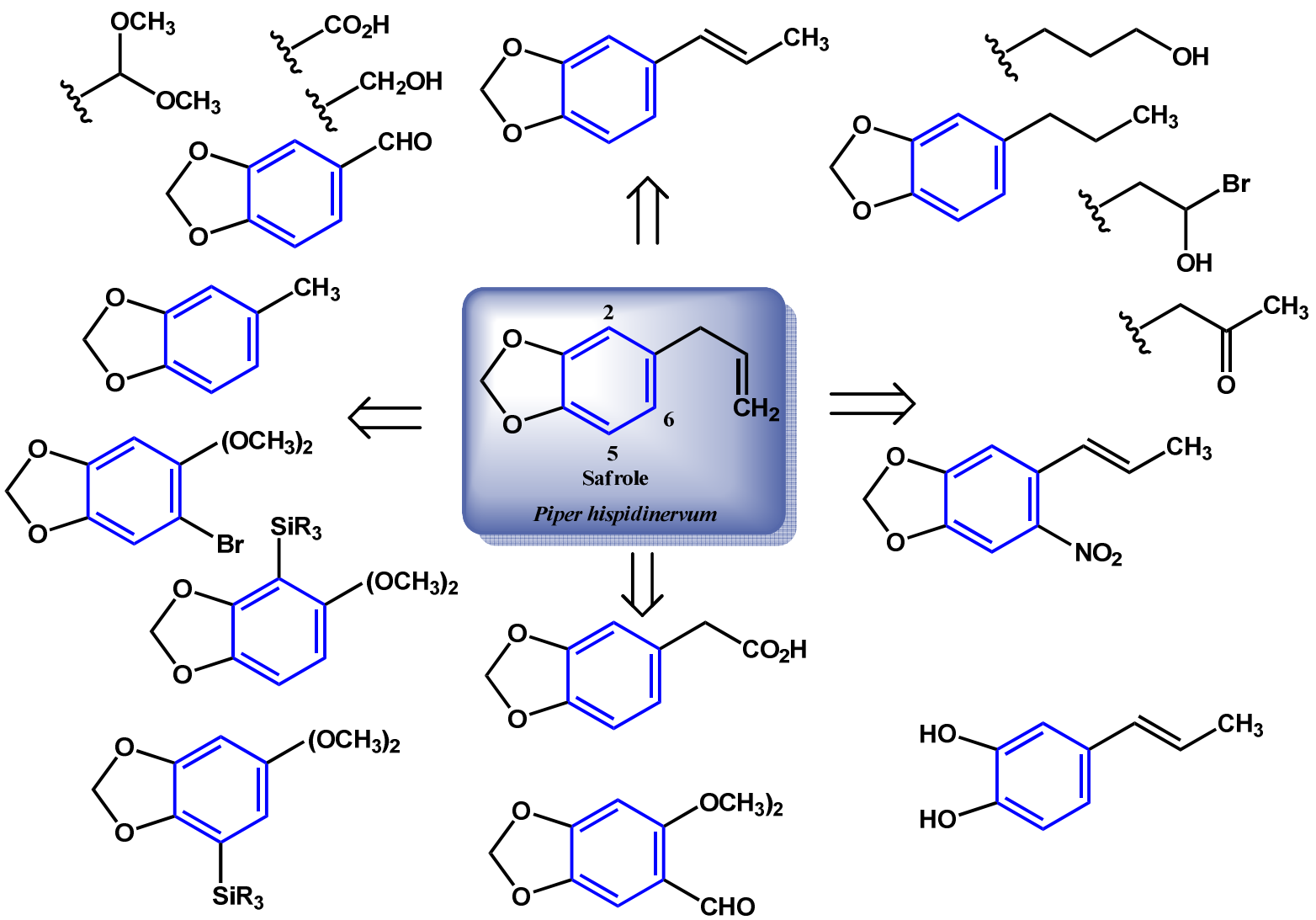
The safrole chemical reactivity



EJ Barreiro & CAM Fraga, *Quim. Nova* **1999**, *22*, 744; PRR Costa, *Quim. Nova* **2000**, *23*, 357

Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 183–188

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW FLOSULIDE ANALOGUES, SYNTHESIZED FROM NATURAL SAFROLE

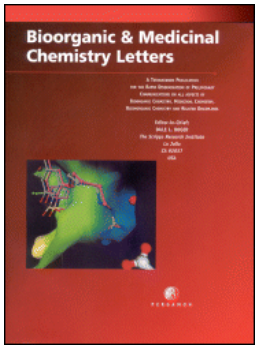
Adriana S. Lages,[a,b] Kelli C. M. Silva,[a] Ana L. P. Miranda,[a] Carlos A. M. Fraga,[a] and Eliezer J. Barreiro,[a]

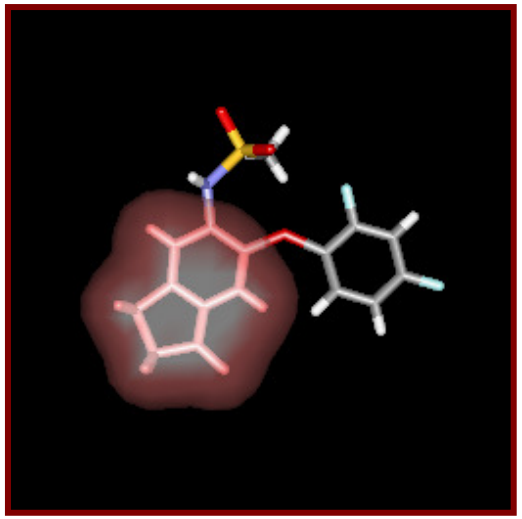
[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68006, ZIP 21944-970, Rio de Janeiro - RJ, Brazil*

[b]*Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, Brazil*

Received 27 October 1997; accepted 2 December 1997

COX - 2 Inhibitors





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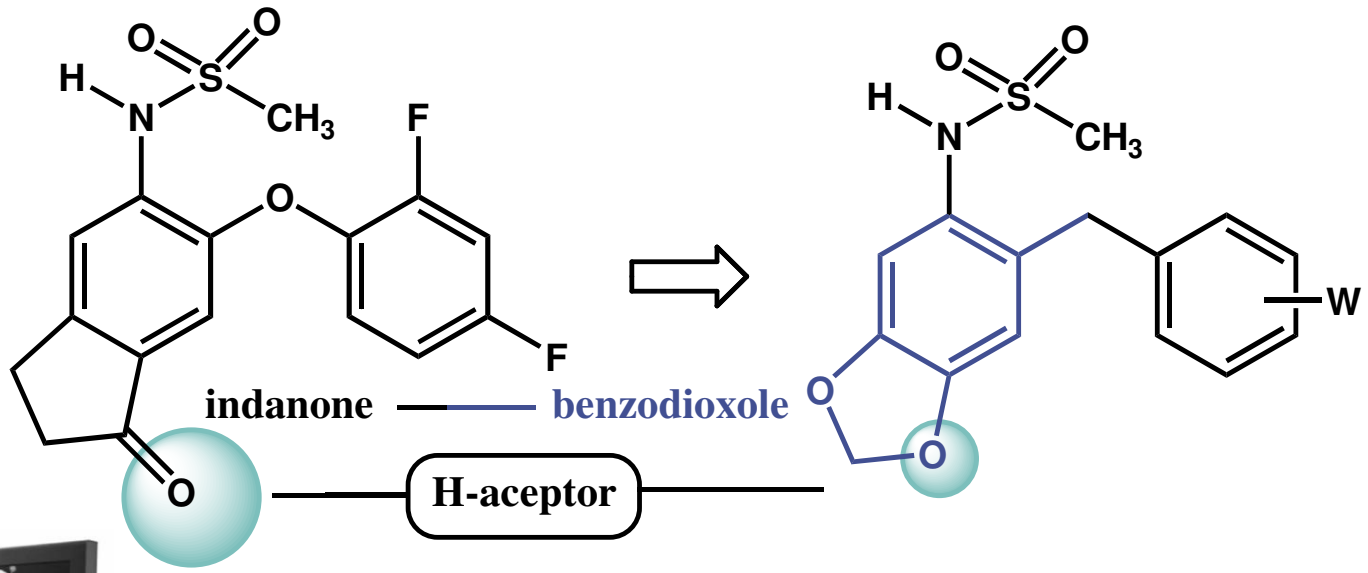
A. S. Lages, K. C. M. Silva, A.L.P. Miranda, C.A. M. Fraga, E. J. Barreiro, *Bioorg. Med. Chem.*, **8**, 183 (1998).

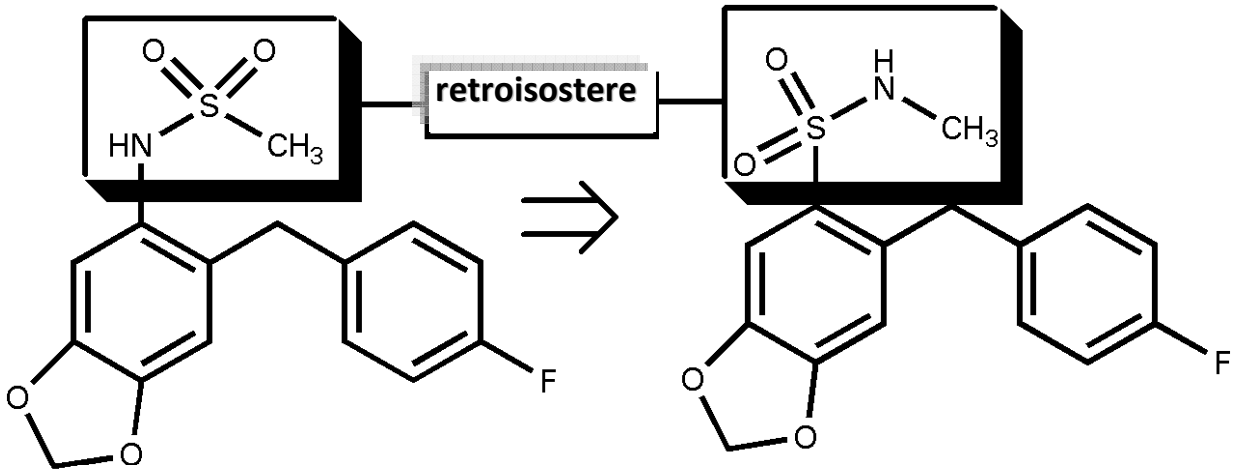
LASSBio-349: a new isostere relationship

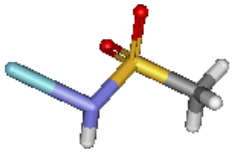


LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

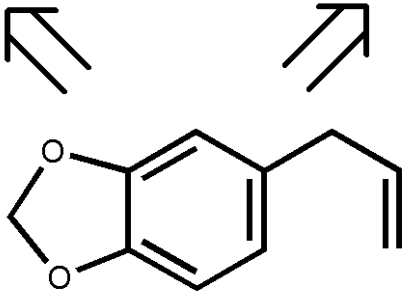
L. M. Lima, E. J. Barreiro, Bioisosterism: A useful strategy for molecular modification and drug design, Curr. Med. Chem., 12, 23-49 (2005).

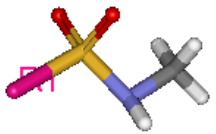
LASSBio-349: a new isostere relationship





sulfonylamine



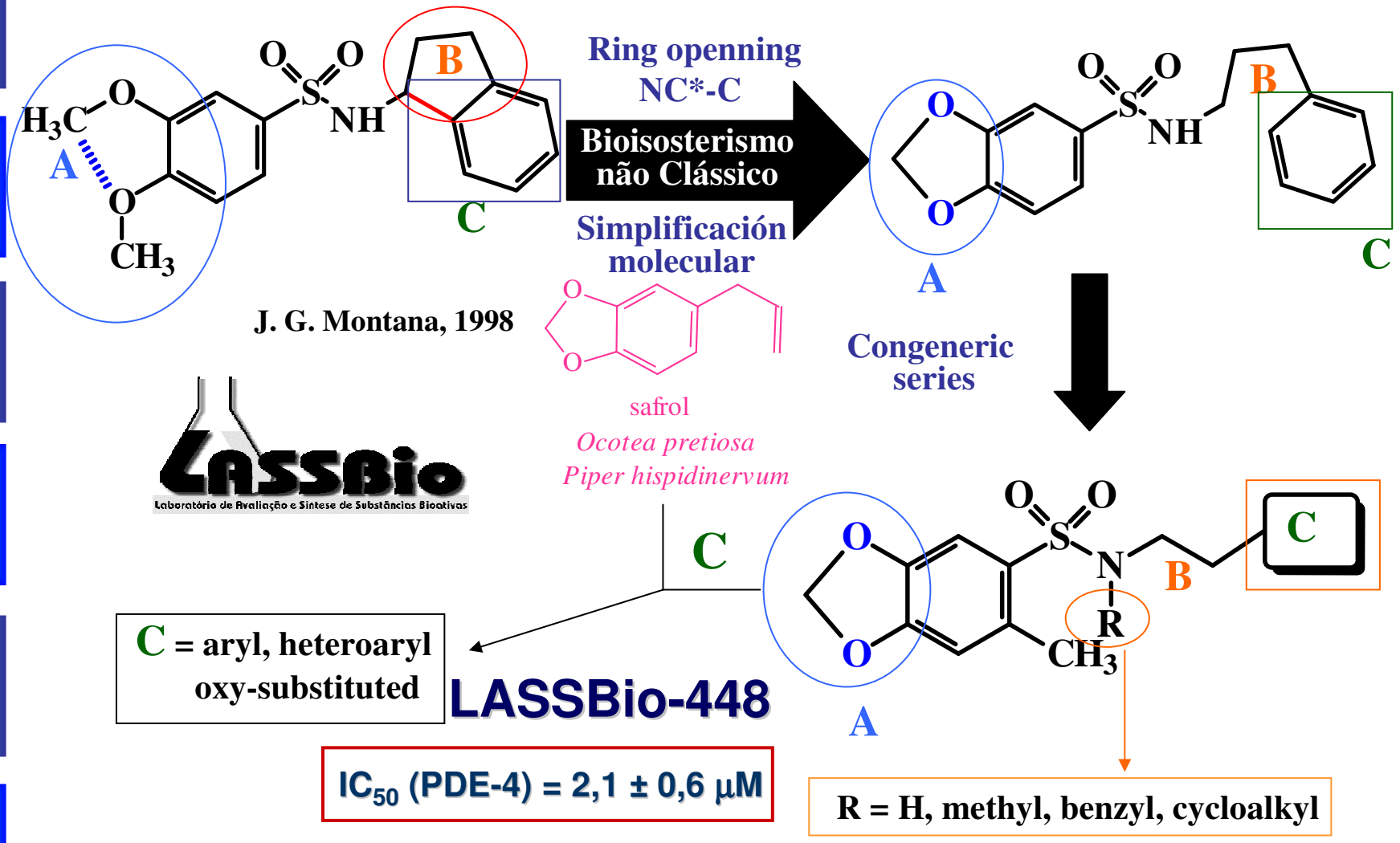


sulfonamide

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

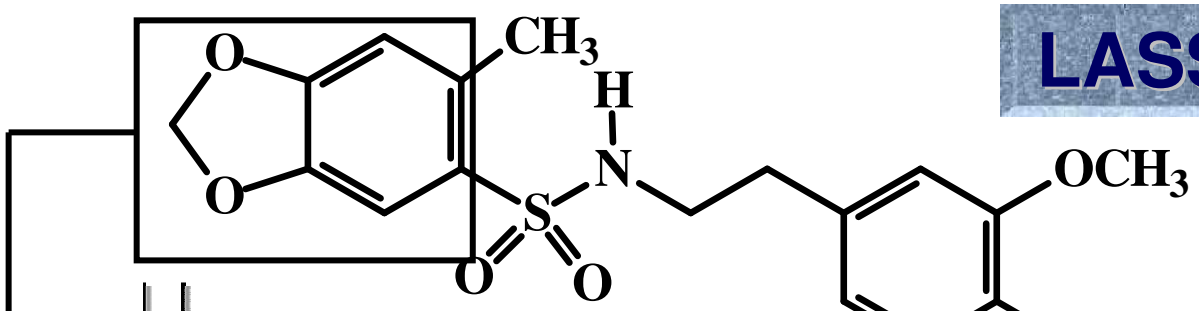
A. S. Lages, K. C. M. Silva, A.L.P. Miranda, C.A. M. Fraga, E. J. Barreiro, *Bioorg. Med. Chem.*, **8**, 183 (1998).

Design of novel PDE-4 inhibitors



E. J. Barreiro, C. Lugner & L. M. Lima, unpublished results

LASSBio-448 is a new anti-asthma multitarget lead-compound



LASSBio-448

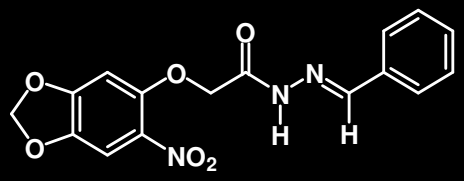
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

$C_{18}H_{21}NO_6S$

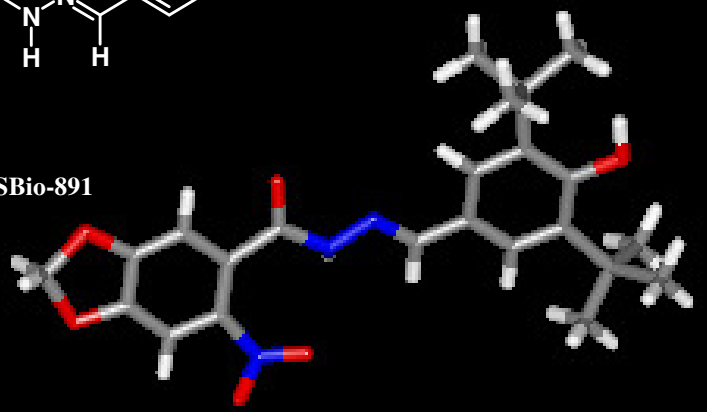
Natural Biophore

PDE-4 inhibitor IC_{50} = 9 µM;
Inhibit the TNF-α, IL-4 & IL-13 effect;
Powerful antiinflammatory properties with antispasmodic & broncho dilator effect (*p.o.*);
Promote the remodeling of lung tissue;
Easy to synthesize in M-scale employing classic reactions in good overall yield;

Safrole: EJ Barreiro, CAM Fraga, *Quím. Nova* **1999**, 22; PRR Costa, *Quím. Nova* **2000**, *23*, 357



LASSBio-891



LASSBio-881

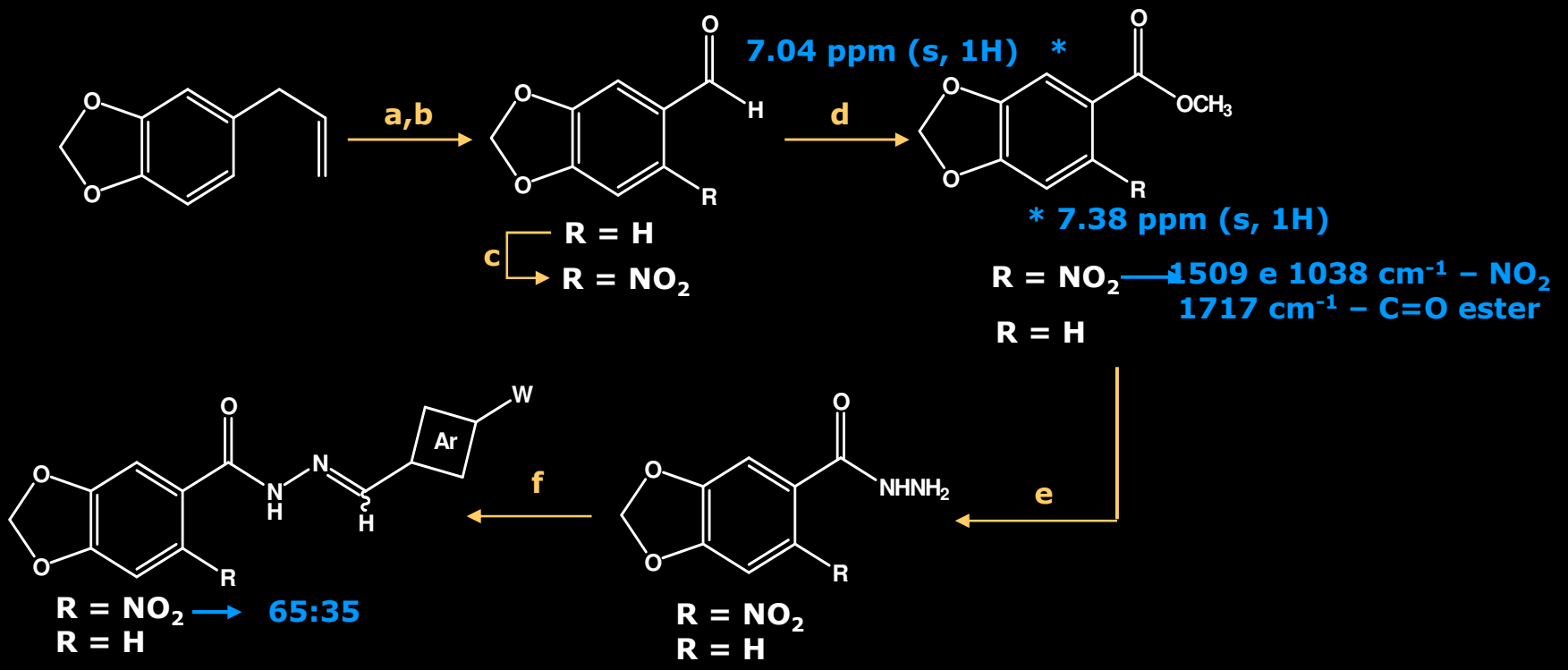
PI 0601885-8 (15/05/2006; PCT 14/05/2007) → *New analgesic /AI NAH derivatives*

LASSBio-881 represents a new analgesic **lead-compound**, with symbiotic profile, acting at **CB1** and **TRPV-1** receptor level with antagonistic properties, and without any hipnotic or dypirone profiles. This important new scaffold is being used, currently in LASSBio, to design more potent antagonistic – *lead-optimization* – in the discovery of new potent non-narcotic analgesic drugs, useful for the treatment of neuropathic pain.

medicinal chemistry

Bezerra Neto, H. J. C., Lacerda, D. I. *et al, Bioorg. Med. Chem.,* 14, 7924 (2006); Duarte, C. M., Tributino, J. L. M. *et al, Bioorg. Med. Chem.* 15, 2421 (2007); J. L. Tributino, M. L. Santos *et al.*, Br. J. Pharmacol., 159, 1716 (2010).

The synthetic route to LASSBio-881

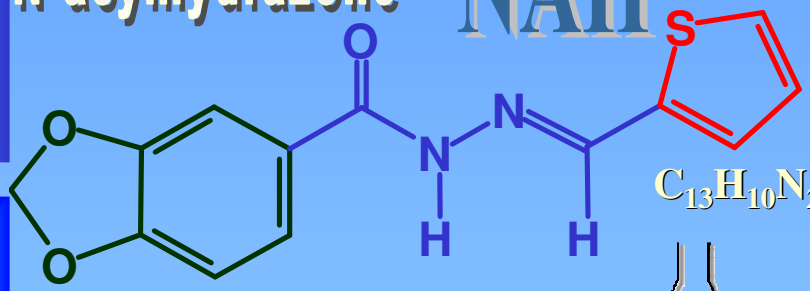


a) KOH aq. 3N, *n*-BuOH, t.a., 3h; b) *i* - O_3/O_2, AcOH, 0°C, 1h; *ii* - Zn°, AcOH (75%, 3 etapas); c) HNO_3 65%, 20-25°C, 0,5h, 95%; d) I_2, KOH, MeOH, 0°C, 1,5h, 88%; e) $NH_2NH_2.H_2O$ 80%, EtOH, t.a., 1h; 70-78%; f) ArCHO, EtOH, HCl_{cat}, t.a., 0,5h, 70-95%.

Barreiro, E.J. & Fraga, C.A.M. (1999) *Quím. Nova* 22, 744
Barreiro, E.J. & Lima, M.E.F. (1992) *J. Pharm. Sci.* 81, 1219
Barreiro, E.J. *et al.* (1985) *J. Chem. Res. (S)*, 220
Ekeley, J.B. & Klemme, M. (1928) *J. Am. Chem. Soc.* 50, 2711
Yamada, S.; Morizono, D.; Yamamoto, K. (1992) *Tetrahedron Lett.* 33, 4329
Lima, P.C. *et al.* (2000) *Eur. J. Med. Chem.* 35, 187

New lead-compound with cardioactive profile

N-acylhydrazone **NAH**



$C_{13}H_{10}N_2O_3S$

LASSBio-294

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Is a novel potent cardioinotropic lead-compound, no-digitalic, no-adrenergic, that could be beneficial in chronic heart failure; neuro & fadigue protector; Orally active (ED_{50} ~10 μM) Without acute toxicity (po 1000 μM/Kg ip 73 μM /Kg, 15 d., twice)

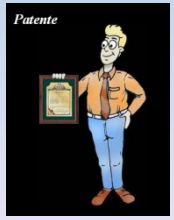
Is a structural simple compound (Barry Price's Principle); Synthetically accessible in >50% overall yield by classical methods (synthetic medicinal chemistry); Designed by classical *MedChem* strategies, *e.g.* molecular simplification & classical ring bioisosterism.

This new lead-compound is prepared from an abundant Brazilian natural product, that can be obtained in > 85% yield by simple distillation of the essential oil and represents an useful *MedChem* block due its biophore character.

Have a new mechanism of action

medicinal chemistry

E. J. Barreiro, *Quim. Nova*, **25**, 1172 (2002).



E. O. Carneiro *et al., Bioorg. Med. Chem. Lett.*, **20**, 3734 (2010); G. Zapata-Sudo *et al.*, *Am. J. Hypert.*, **23**, 135 (2010).

"Thienylhydrazon with digitalis-like properties (positive inotropic effects) - Patent 07091238 (USPTO), August, 2006;

WO 2000-078754 (65 countries)

Resultado da pequisa pelo c... | Tabelas em HTML - Extensões - T... | PHP: print_r - Manual

LASSBio LLDB
LIGAND DATA BANK

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DE SISTEMAS BIOLOGICOS
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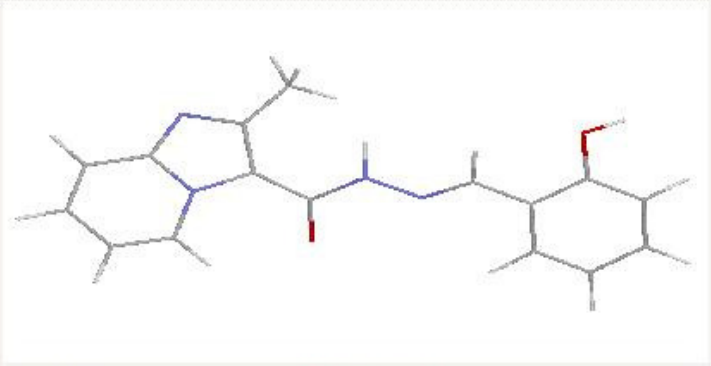
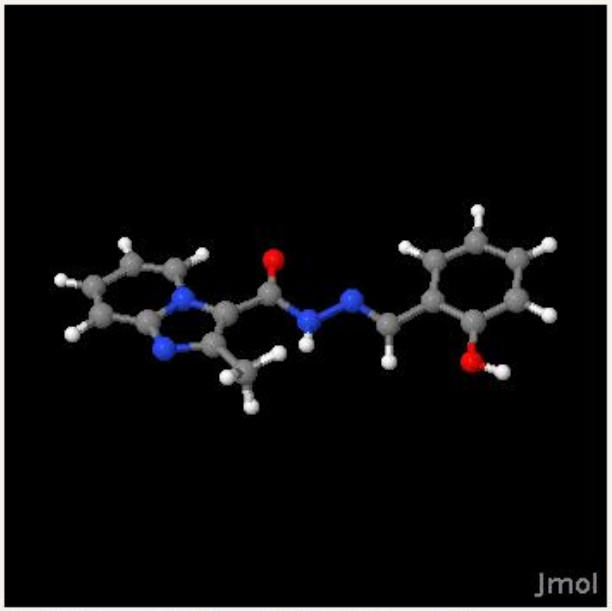
LASSBio964

The chemolibrary of LASSBio have 1565 bioactive original compounds



Molecular Form:	C16H14N4O2
IUPAC Nomenclature :	??????????????
Fantasy Name :	Teste
Number of Quiral Centers :	0
Number of H-Bond Donors	2
Number of H-Bond Acceptors	4
Number of Free Bonds	4
Log P	2.0
Fusion Point	100
Functional Group:	Acylhydrazone



Wireframe Ball-and-Stick Space Fill

To return for initial orientation

Rotacionar

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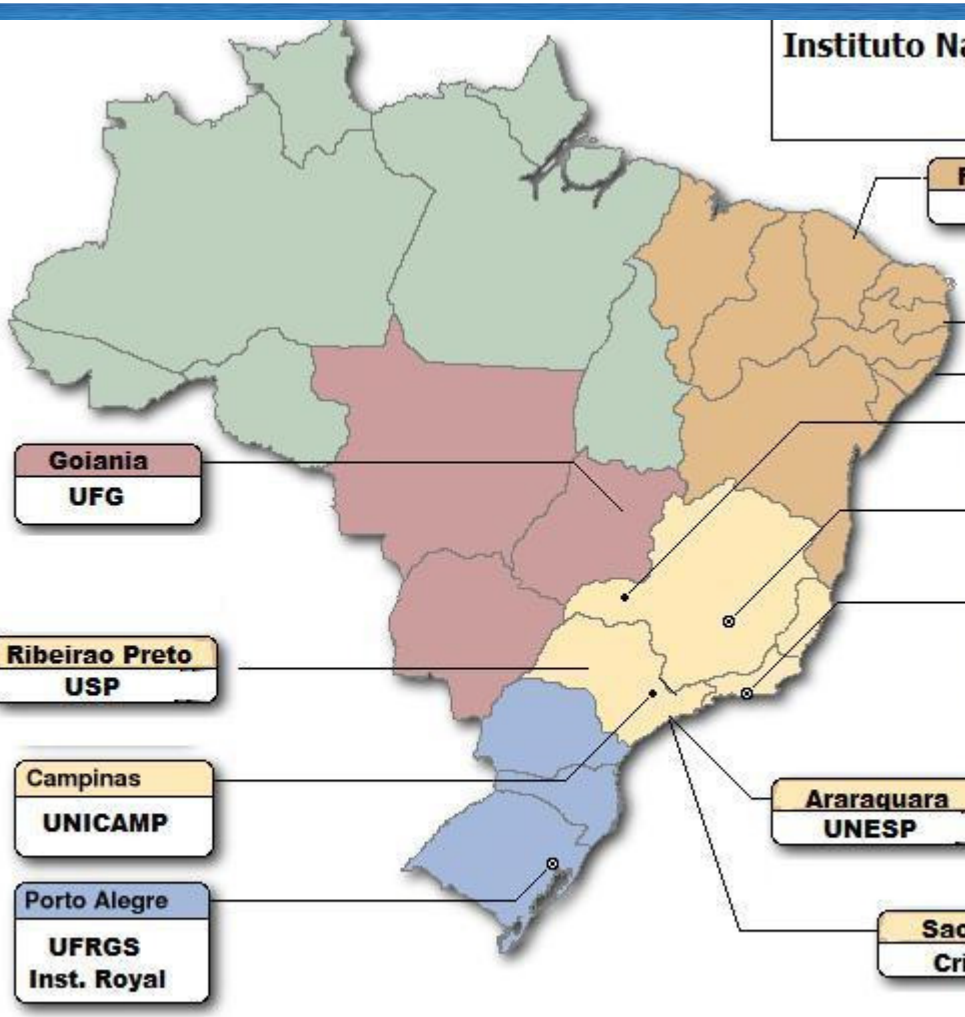

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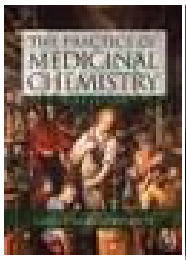
Foreign scientific consultants



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Eliezer J Barreiro; 2/5/2010

Conclusions & acknowledgments

Thanks for attention

Corcovado mountain with the statue of Cristo Redentor one of the new seven wonders of the world.