

# A Química Medicinal

(Planejamento Racional de Novos Fármacos)

XXXVI Semana da Química “Ciência, tecnologia e sociedade: em busca do conhecimento”

**unesp** Instituto de Química, UNESP – Araraquara, 25-29 de setembro de 2006

**Eliezer J. Barreiro**

**UFRJ**

**Laboratório de Avaliação e Síntese de Substâncias Bioativas**

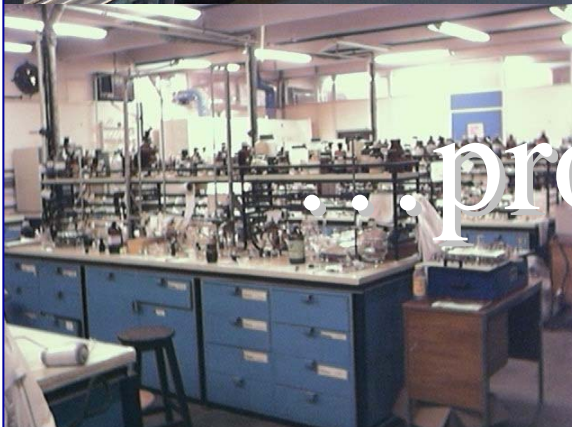


**Universidade Federal do Rio de Janeiro**

# Exemplos de casa.....



# ...protótipos descobertos no LASSBio



## 1. A Química (Farmacêutica) Medicinal: definição

## 2. Como se descobrem os fármacos?

## 3. A origem dos fármacos

3.1. O Papel dos produtos naturais na descoberta de fármacos

3.2 O Acaso e a descoberta de fármacos

3.3 Os fármacos sintéticos

## 4. O processo da descoberta

4.1. A abordagem fisiológica e a diversidade molecular

4.2 O paradigma do composto-protótipo: interações fármaco-biorreceptor

4.3 A importância dos fatores estruturais/conformacionais: grupos farmacofóricos/toxicofóricos

## 5. O planejamento racional

5.1 Fármacos inteligentes: Cimetidina; atovarstatina; celecoxib; me-too; imatinib

5.2 A diversidade molecular dos fármacos sintéticos

5.3 A diversidade molecular de novos protótipos descobertos no LASSBio, UFRJ

## 6. As estratégias de desenho estrutural da Química (Farmacêutica) Medicinal

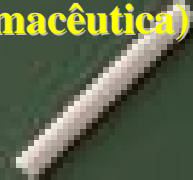
6.1 Bioisosterismo: LASSBio-346

6.3 Hibridação molecular: LASSBio-756

6.4 Simplificação molecular: LASSBio-294

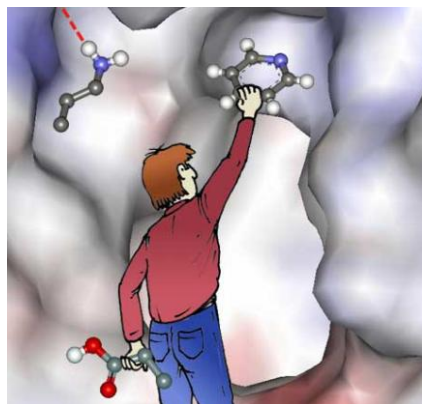
6.5 Desenho de protótipos simbióticos: LASSBio-468

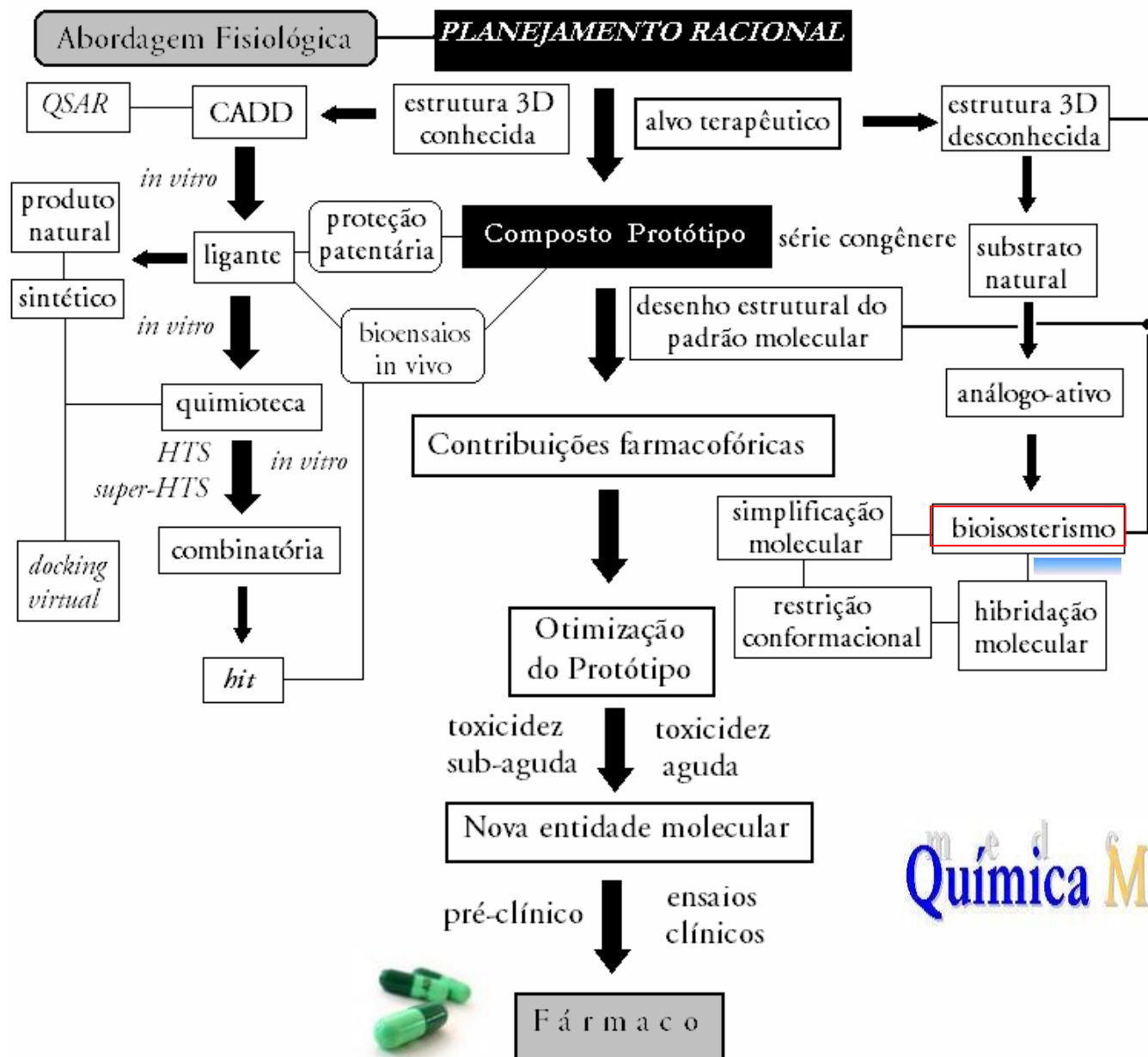
## 7. Conclusões





# *Estratégias de desenho molecular: bioisosterismo*





# Estratégias de desenho molecular

## Bioisosterismo



*Current Medicinal Chemistry*, 2005, 12, 23-49

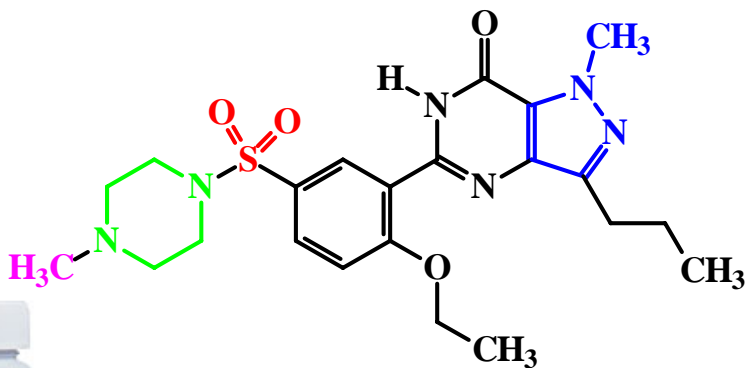
23

### Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

Lídia Moreira Lima and Eliezer J. Barreiro\*

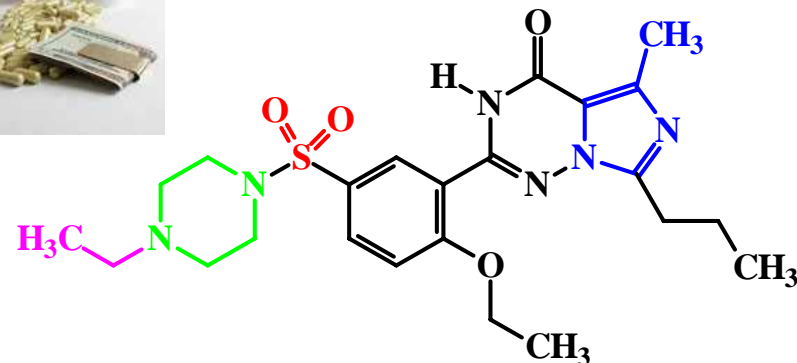
*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro. CCS, Cidade Universitária, CP 68.006, 21944-190, Rio de Janeiro, R.J., Brazil*

**Abstract:** This review aim to demonstrate the role of bioisosterism in rational drug design as well as in the molecular modification and optimization process aiming to improve pharmacodynamic and pharmacokinetic properties of lead compounds.

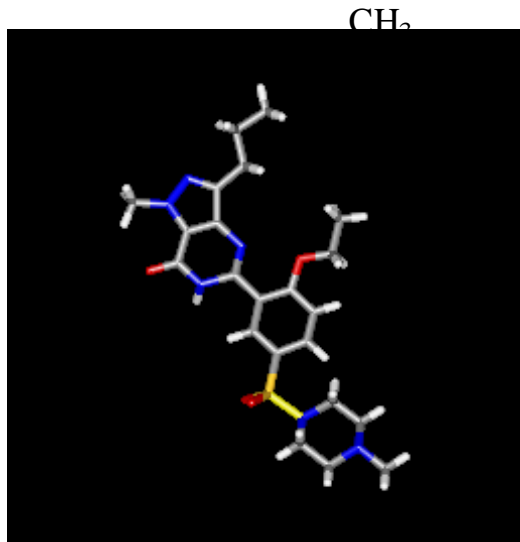


**Sildenafil (Viagra<sup>R</sup>)**  
**Pfizer**

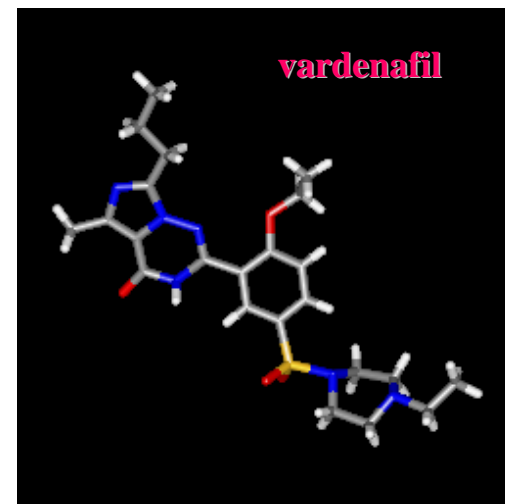
<http://pubs.acs.org/cen/coverstory/83/8325/8325viagra.html>  
<http://www.farmacia.ufrj.br/lassbio/index.htm>



**Vardenafil (Levitra<sup>R</sup>)**  
**Bayer-GSK**

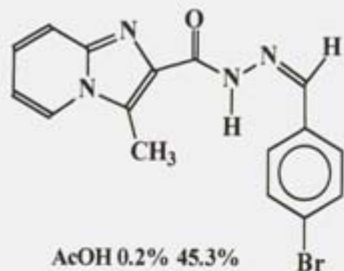


**Tadalafil (Cialis<sup>R</sup>)**  
**Lilly**

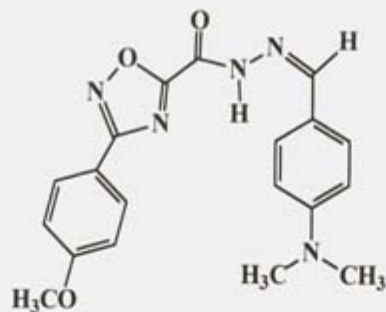




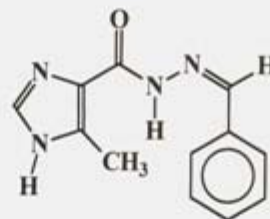
# Novos Protótipos Descobertos no LASSBio



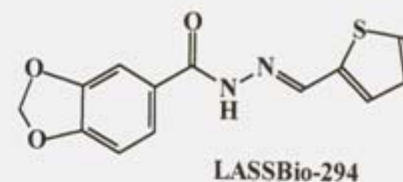
Eur. J. Med. Chem., 33, 225 (1998)



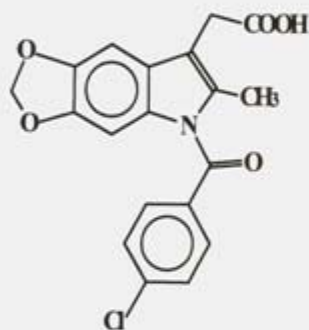
Il Farmaco, 54, 747-757 (1999)



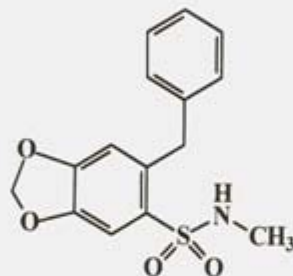
Bioorg. Med. Chem., 8, 2243 (2000)  
Química Nova, 25, 129 (2002)



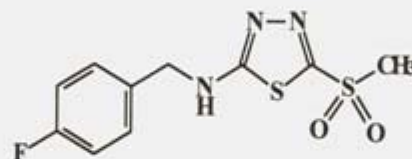
Química Nova, 25, 1172 (2002)  
J. Pharmacol. Exper. Therap., 299, 558 (2001)  
Br. J. Pharmacol., 134, 603 (2001)  
Br. J. Pharmacol., 135, 293 (2002)  
Eur. J. Pharmacol., 470, 79 (2003)



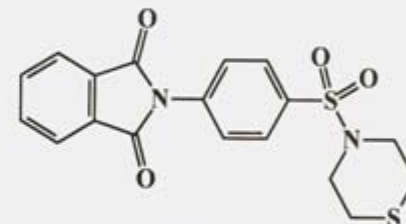
J. Chem. Res.(S), 102 (1982)  
Química Nova, 22, 744 (1999)



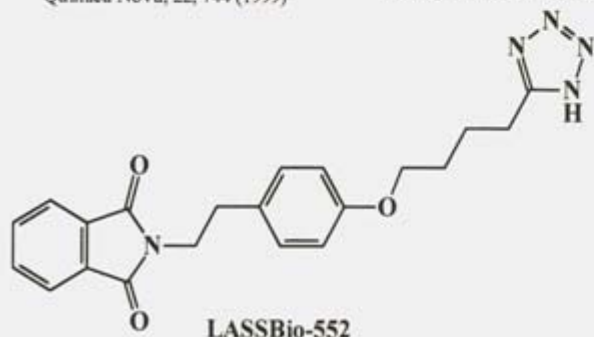
Bioorg. Med. Chem. Lett., 8, 183 (1998)



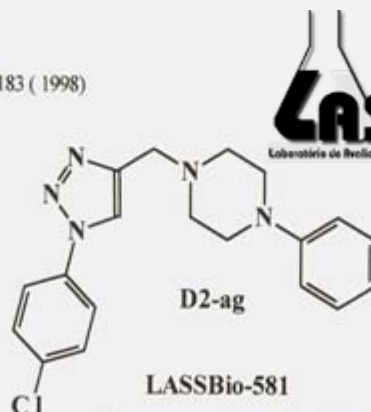
LS Varandas, MSc UFRJ, 2000



Bioorg. Med. Chem., 10, 3067 (2002)



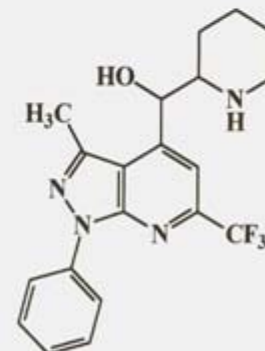
Bioorg. Med. Chem. Lett., 12, 1533 (2002)



Bioorg. Med. Chem., 11, 4807 (2003)  
Braz. J. Biol. Med. Res., 36, 625 (2003)  
J. Pharm. Biomed. Anal., 33, 1127 (2003)



Eur. J. Med. Chem., 37, 163 (2002)



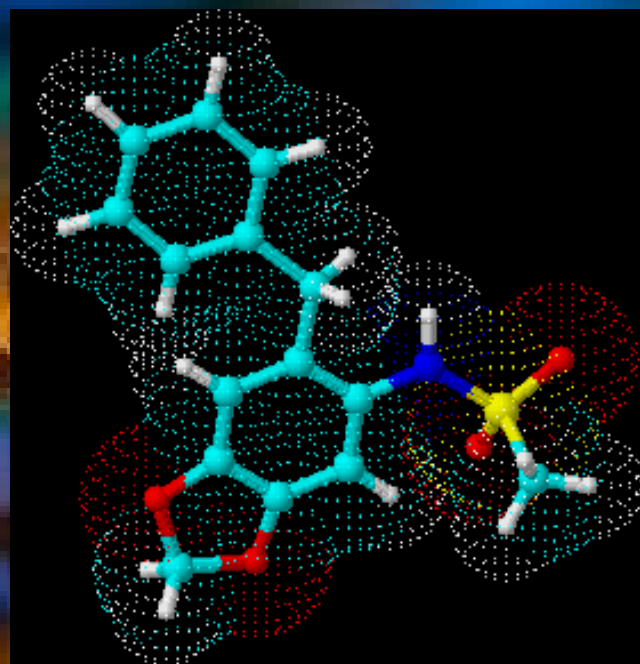
Boll. Chim. Farm., 139, 14 (2000)

**LASSBio**  
Laboratório de Desenvolvimento e Síntese de Substâncias Bioativas

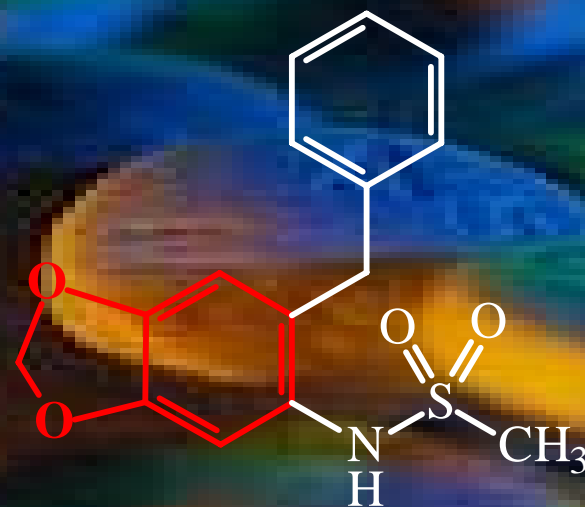
**Diversidade  
Molecular**



# Novos Protótipos de Fármacos Anti-inflamatórios

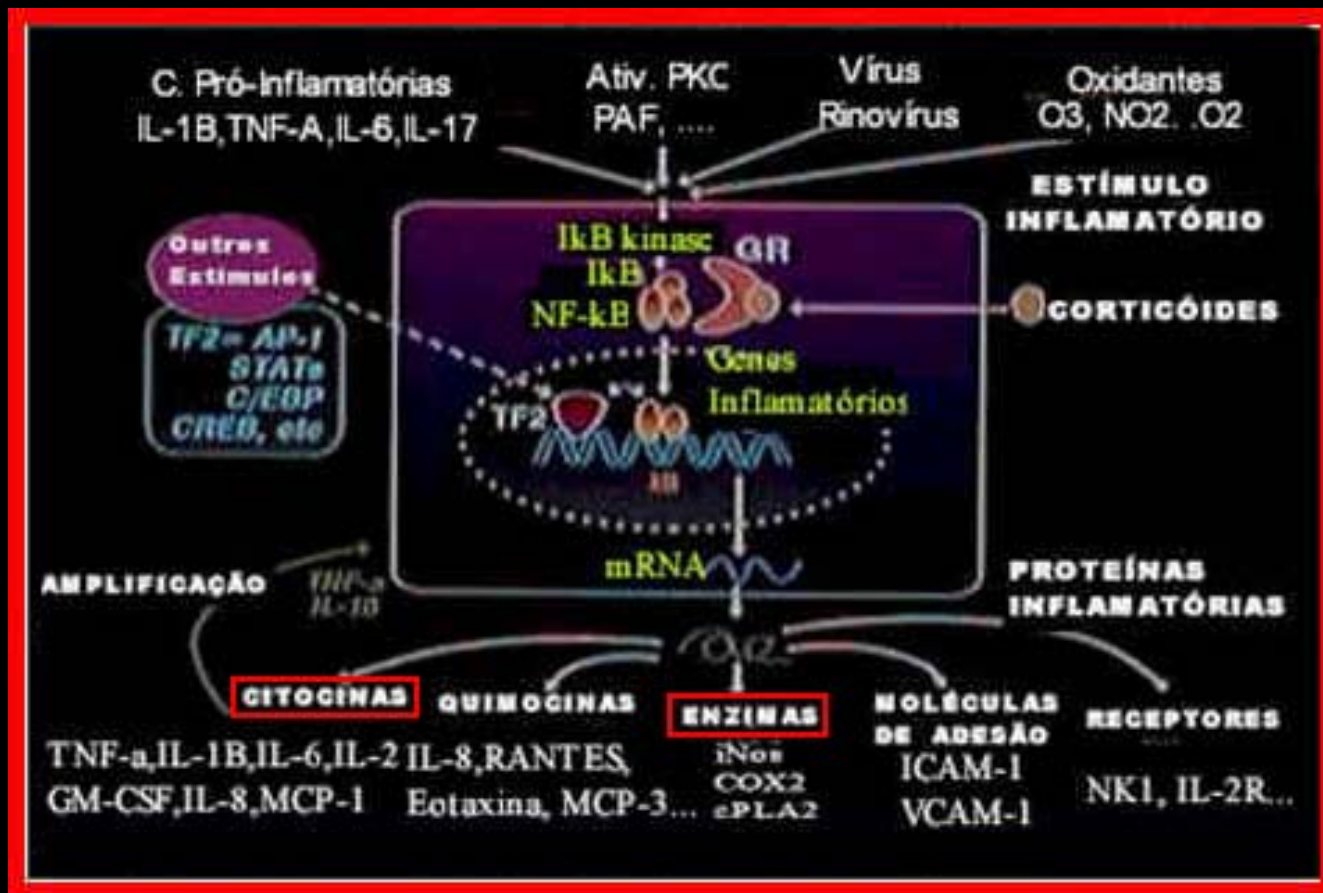


LASSBio-326



LASSBio-257

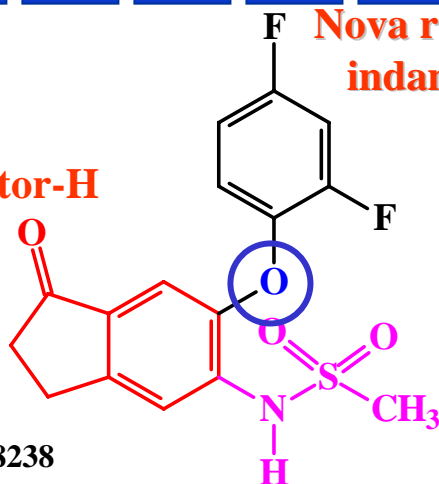
# Mediadores do Processo Inflamatório



*Nature Rev Drug Discov. 2004, 3, 401*

**Nova relação bioisostérica:  
indanona-benzodioxola**

**acceptor-H**



CGP 28238  
Futaki, 1995

**Flosulido**  
 $C_{16}H_{13}F_2NO_4S$   
353.34

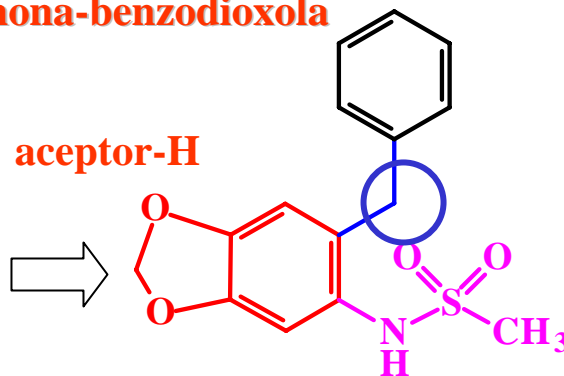
**IS COX-1/COX-2 = 5000**

*IS = índice de seletividade*

$IC_{50}$  (hPGHS-1) = 73,2  $\mu M$

$IC_{50}$  (rPGHS-2) = 0,015  $\mu M$

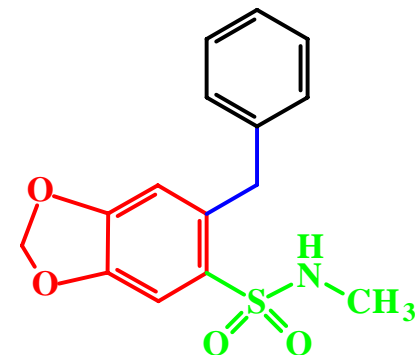
**acceptor-H**



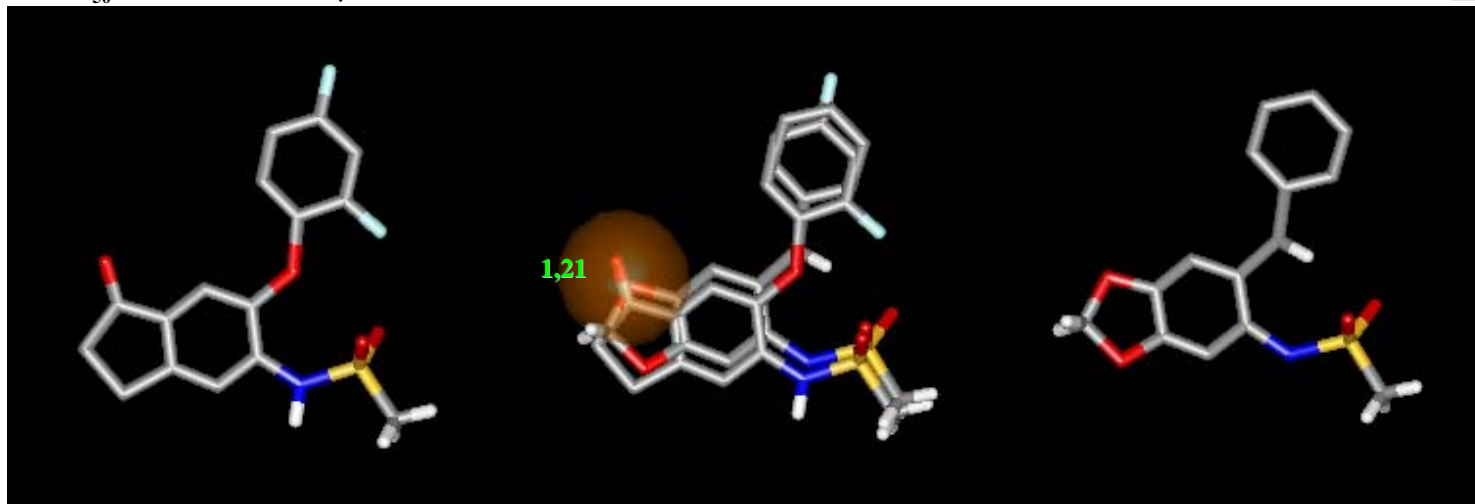
**safrulido**  
 $C_{15}H_{15}NO_4S$   
305.34

EJ Barreiro *et al.*, *Bioorg. Med. Chem. Lett.*, 8, 183 (1998)

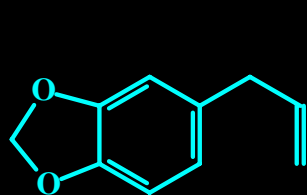
**retroisosterismo**



**safronamida**  
 $C_{15}H_{15}NO_4S$   
305.34



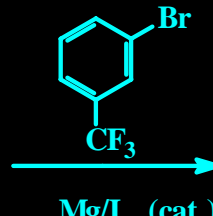
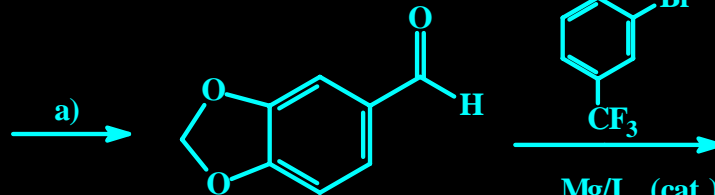




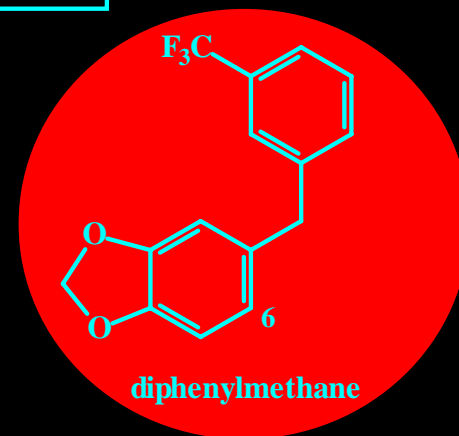
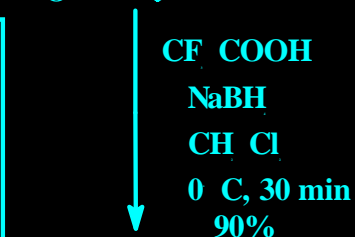
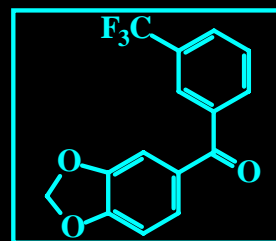
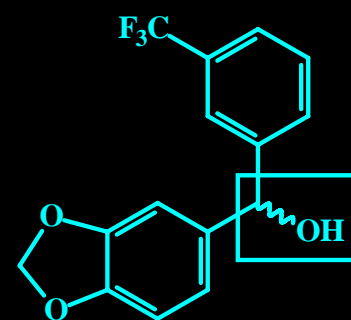
Safrole

a) EJ Barreiro *et al.*, 1982.

## Novo Sulido obtido a partir do safrol



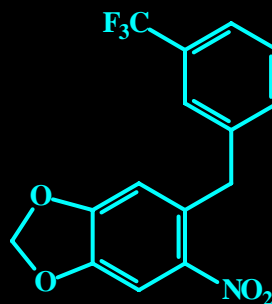
Mg/I (cat.)  
THF, rt  
30 min  
80%



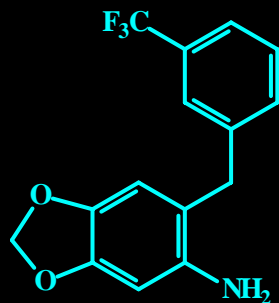
diphenylmethane



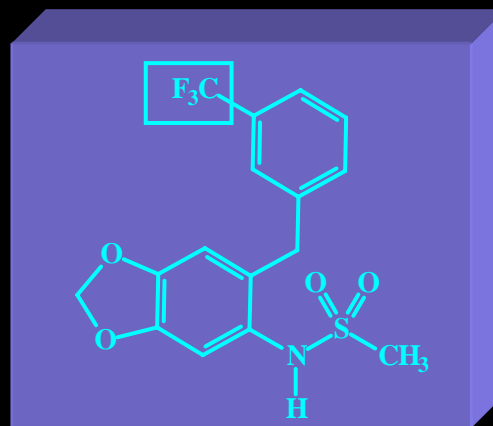
Fe, NH<sub>4</sub>Cl  
EtOH:HOH (2:1)  
reflux, 1h  
89%

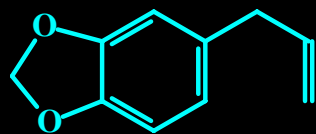


HNO<sub>3</sub> /CHCl<sub>3</sub>  
0 °C, 3h  
96%



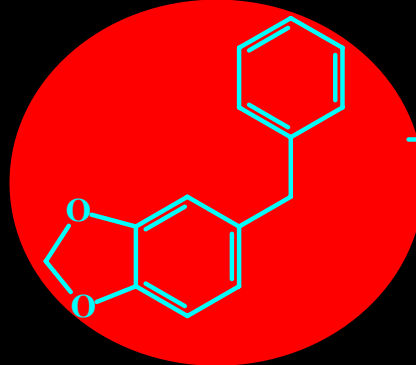
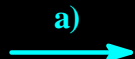
CH<sub>3</sub>SO<sub>2</sub>Cl  
Py, CH<sub>2</sub>Cl<sub>2</sub>  
rt, 40 min  
50%





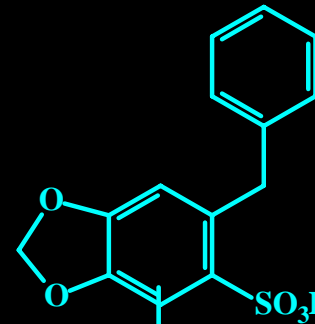
Safrole

a) AS Lages *et al.*, *Bioorg.Med.Chem.Lett.*8,183 (1998)



H<sub>2</sub>SO<sub>4</sub> / AcOH  
AcOEt, 0 °C  
rt, 4h

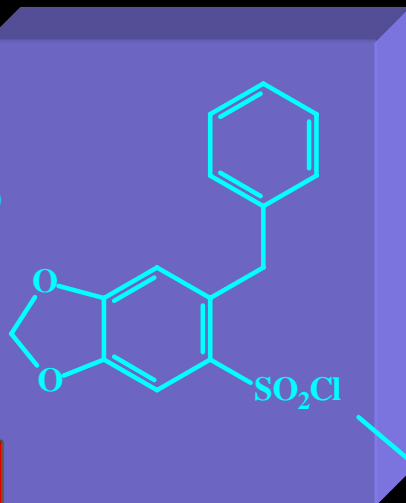
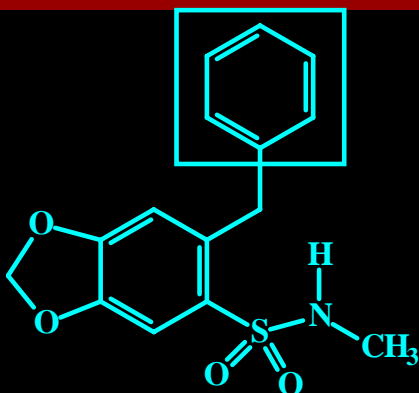
90%



KOAc/EtOH  
rt, 30 min  
90%

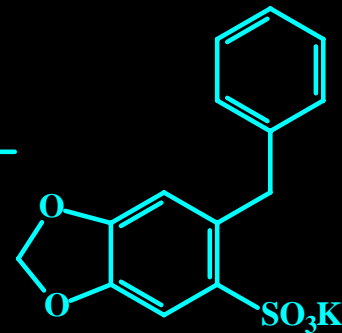
## Novo retroisômero a partir do safrol

40% CH<sub>3</sub>NH<sub>2</sub> (aq.)  
CHCl<sub>3</sub>  
0 °C, 4h  
95%

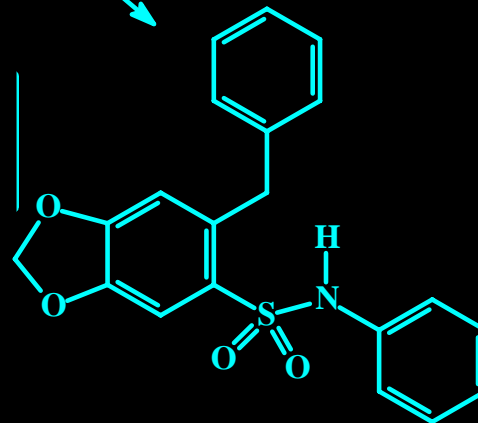


SO<sub>2</sub>Cl<sub>2</sub> / DMF (cat.)  
60 °C, 4h

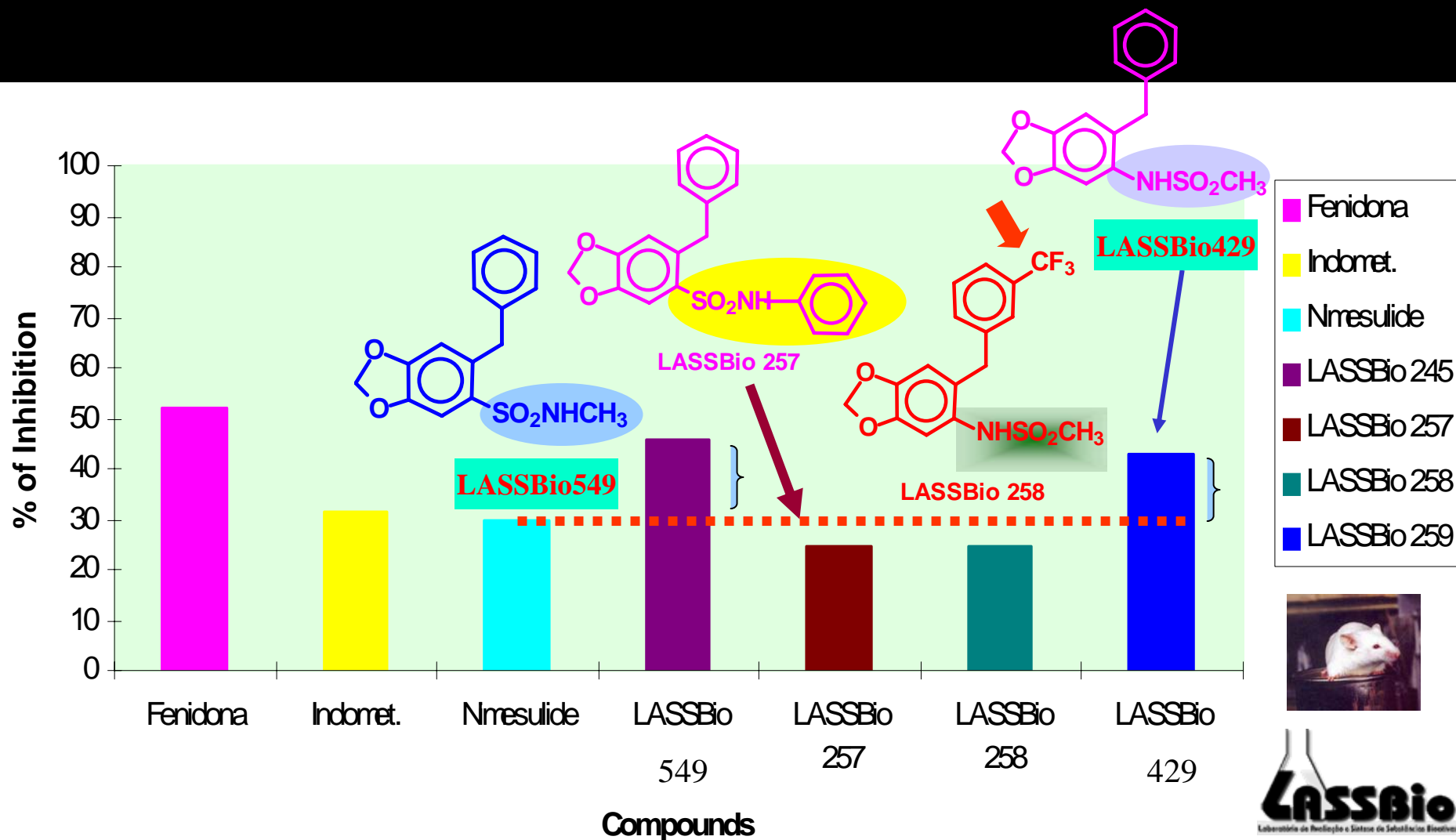
57%



PhNH<sub>2</sub> / CHCl<sub>3</sub>  
rt, 2h  
96%



# Effect of new candidates of PGHS-2 inhibitors in the carrageenan-induced rat paw edema (100 $\mu$ M, *po*)







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



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

Adriana S. Lages,<sup>a,b</sup> Kelli C. M. Silva,<sup>a</sup> Ana L. P. Miranda,<sup>a</sup> Carlos A. M. Fraga,<sup>a</sup> and Eliezer J. Barreiro,<sup>a</sup>

<sup>a</sup>*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*

<sup>b</sup>*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

**Abstract:** Four new aryl-sulfonamide derivatives (3a, 4a, 5a–b), having methylenedioxy group attached to phenyl ring, were prepared from natural safrole and evaluated as anti-inflammatory agents. The *N*-methylsulfonamide 3a and corresponding retrosulfonamide derivative 5a were more active than standards indomethacin and nimesulide, at the same molar concentration, in carrageenan-induced pleurisy assay.



# ENSAIO DE TOXICIDADE

(GAD & CHENGELIS, 1989)

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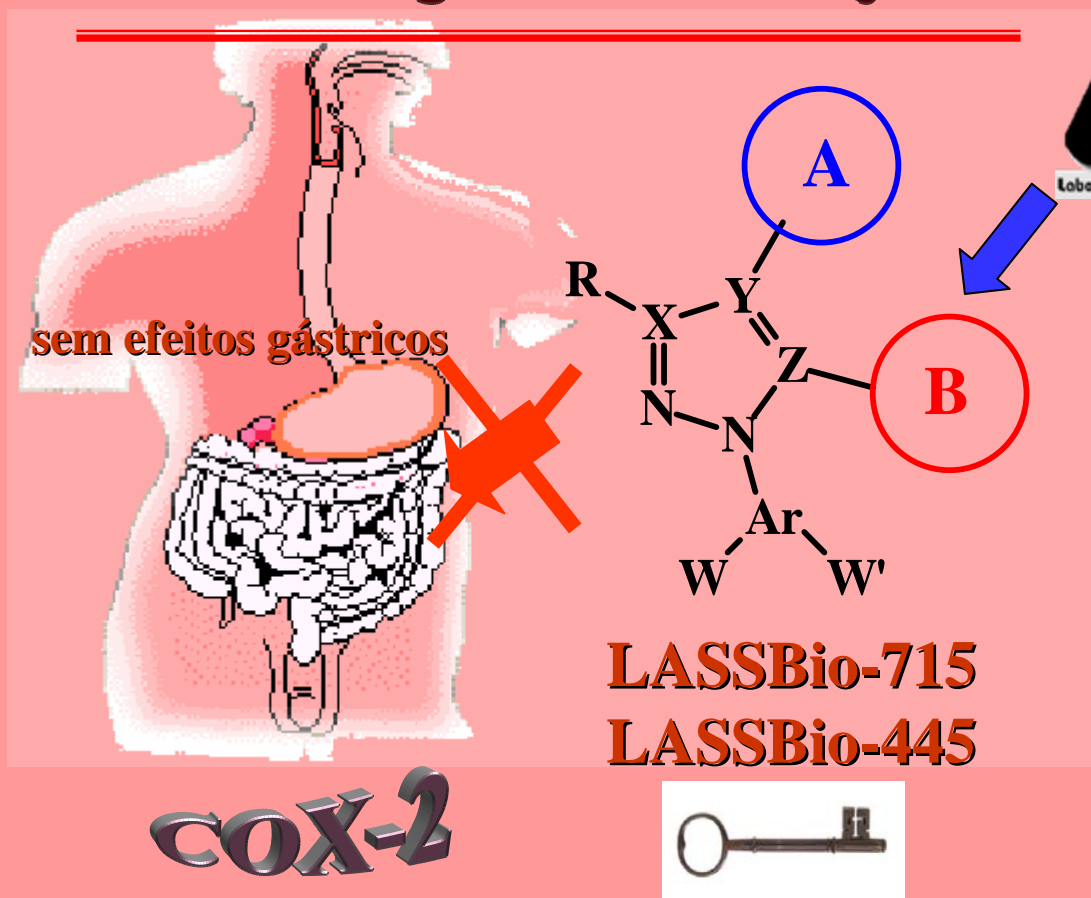
A incidência de óbitos foi verificada em ratos, após administração diária, durante período de sete dias, da mesma dose efetiva (p.o.)



Sinais de letargia, convulsões, perda de peso, considerados indícios de toxicidade aguda, não foram observados.



# Novo Protótipo de Fármaco Anti-inflamatório de Segunda Geração



E. J. Barreiro, M. P. Veloso, A. L. P. Miranda, C. A.M. Fraga, C. R. Rodrigues,  
"Novos Agentes Anti-inflamatórios Pirazólicos", Pedido de privilégio de invenção  
depositado em 29 de abril de 1999, INPI PI-38201866




# Nova Classe de Candidatos a Fármacos NSAID de Segunda Geração

LEAD COMPOUND  
Lead-optimization

CgIRPE\*

1999

**LASSBio**  
Laboratório de Reação e Síntese de Substâncias Bioativas

	DI <sub>50</sub>	Max. Eff.
<b>CELECOXIB</b> 	87,7 µmol/kg	35%
<b>LASSBio 715</b>	44,3 µmol/kg	39%
<b>LASSBio 445</b>	54,6 µmol/kg	37%

*Patent: PI 9902960-0 (29/04/99)*

Química Medicinal

E. J. Barreiro *et al.*, Selective PGHS-2 Inhibitors: A Rational Approach for Treatment of the Inflammation, *Current Medicinal Chemistry* 2002, **9**, 849



# Protocolos Farmacológicos

- ✱ Edema de pata de rato induzido por carragenina (FERREIRA, *et al.*, 1979)
- ✱ Potencial ulcerogênico (CHI-CHUNG CHAN *et al.*, 1995)
- ✱ Pleurisia induzida por carragenina em ratos: migração celular e permeabilidade (TOMLINSON *et al.*, 1994; HARADA *et al.*, 1996)
- ✱ Artrite induzida por adjuvante em ratos: inflamação crônica (NEWBOULD, 1963)
- ✱ Contorção abdominal induzida por ácido acético em camundongos: analgesia periférica (COOLIER *et al.*, 1968)
- ✱ Bioensaio da formalina: hiperalgesia/dor inflamatória (HUNSDAAR *et al.*, 1987)
- ✱ Agregação plaquetária em PRP citratado de coelhos: COX-1 (BORN & CROS, 1963)
- ✱ Dosagem de PGE<sub>2</sub>/EIA: Modelo de “Air Pouch” em ratos (SMITH *et al.*, 1998)
- ✱ Atividade sequestrante de radical livre: DPPH (TAIT *et al.*, 1996)
- ✱ Ensaios de toxicidade (GAD & CHENGELIS, 1989): histopatológico (fígado, SNC, pulmão), comportamental, sanguíneo ( *inter-alia*: TGO, TGP, glicose, uréia, creatinina, hematócrito)



# Ensaio de Toxicidade Aguda

## LASSBio 715 & LASSBio 455

**DOSE 600 e 1400  $\mu\text{g/Kg}$ , (Via oral, dose única)**

- ✱ Sem alterações comportamentais (e.g. catatonia, letargia, movimentação);
- ✱ Registro do peso diário: sem alteração;
- ✱ Aspecto do pelo: normal;
- ✱ Consumo de ração e água: normais;
- ✱ *LASSBio715 e 455 não apresentaram efeitos tóxicos em 1.400  $\mu\text{g/Kg}$ .*





**Novo NSAI  
de segunda geração**

$$ED_{50} = 75,0 \mu M/kg$$

**Sem toxicidade aguda em protocolos  
com roedores e cães;**

**Sem efeitos histopatológicos  
(fígado, pulmão, rins, SNC);**

**Sem efeito ulcerogênico (*p.o.* crônico);**

$$LD_{50}/ED_{50} > 45 \text{ vezes}$$

**Em fase de ensaios pré-clínicos finais**

**Primeiro candidato a ensaio clínico de Fase 1 descoberto no LASSBio**



Ministério da  
Ciência e Tecnologia

CARTA-CONVITE MCT/MS/FINEP – Ação Transversal – Cooperação ICTs - Empresas - INOVAÇÃO EM PRODUTOS  
TERAPÊUTICOS E DIAGNÓSTICOS – 08/2006

### PROJETOS APROVADOS

Prot. Elet.	Ref.	INTERVENIENTE CO-FINANCIADOR	Proponente/ Executor/ Projeto	Executor	
				Nome	UF Executor
1	2318/06	Laboratório Farmacotécnico Americano S/A	Pontifícia Universidade Católica do RS - PUCRS	Tecnopuc/BFR	RS
3	2303/06	Eurofarma Laboratórios S/A	FUJB	Faculdade de Farmácia	RJ

**20 kg → 30.000 comprimidos**



*PI 9902960-0 (1999)*

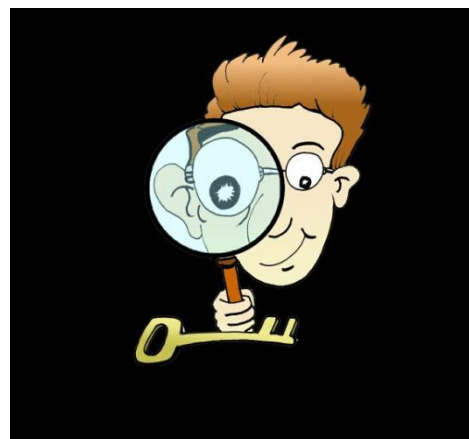


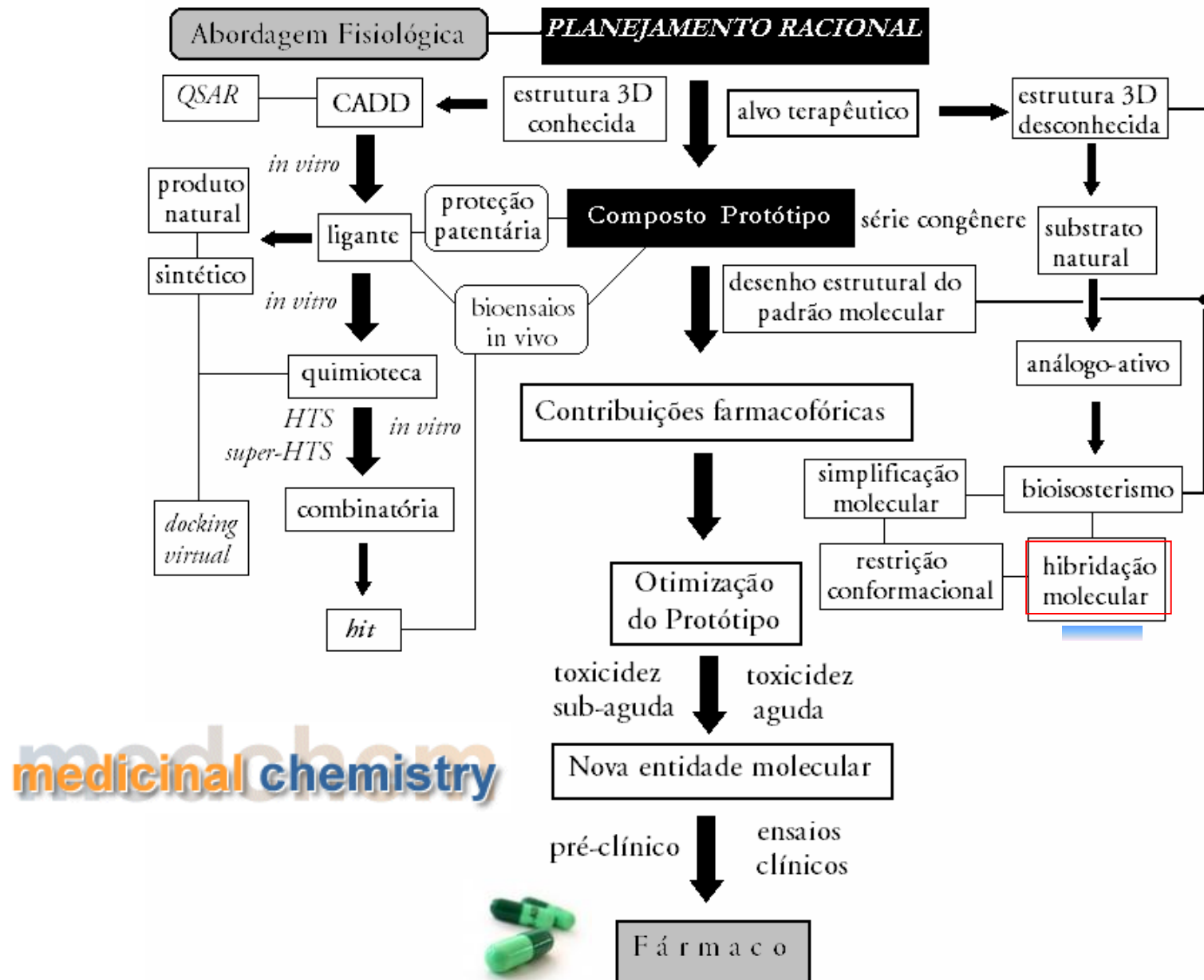
*NSAI de segunda geração\**



# *Estratégias de desenho molecular: hibridação*

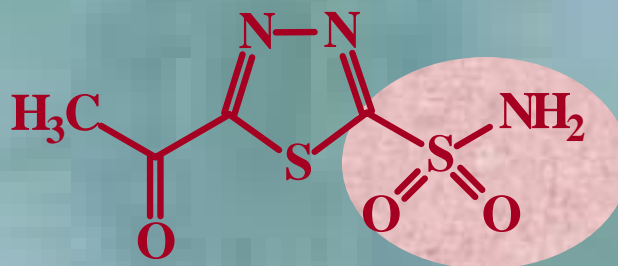
LASSBio-756



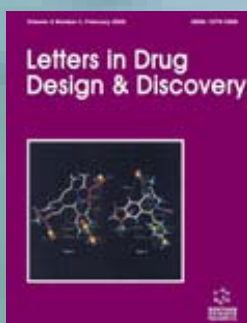


# Fármaco antigo & alvo novo

Acetazolamida:  
inibidor de anidrase carbônica



Hetero-arilsulfonamida



LASSBio-756

L. S. Varandas, C. A. M. Fraga, A. L. P. Miranda, E. J. Barreiro, "Design, Synthesis and Pharmacological Evaluation of New Nonsteroidal Antiinflammatory 1,3,4-Thiadiazole Derivatives", *Letters in Drug Design & Discovery*, **2**, 184-193 (2005)



# Design, Synthesis and Pharmacological Evaluation of New Nonsteroidal Antiinflammatory 1,3,4-Thiadiazole Derivatives

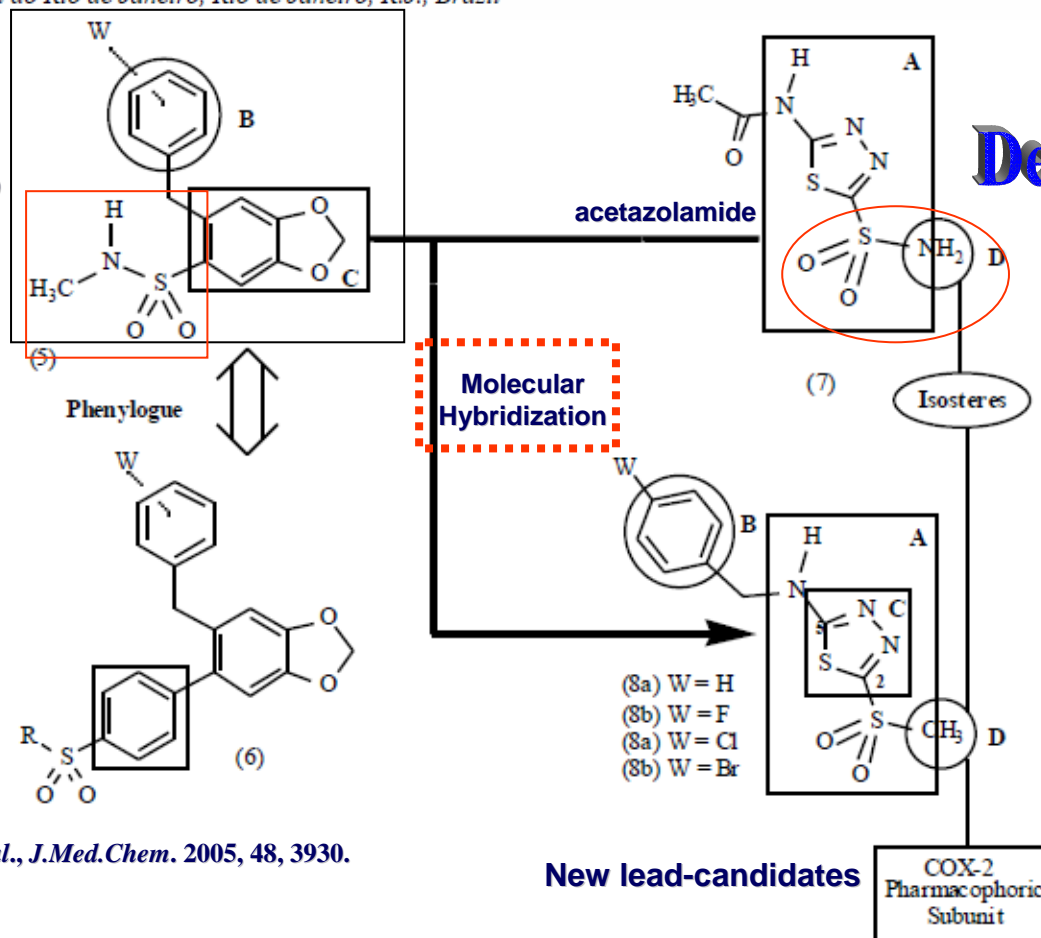
L.S. Varandas<sup>1,2</sup>, C.A.M. Fraga<sup>1,2</sup>, A.L.P. Miranda<sup>1</sup> and E.J. Barreiro<sup>1,2,\*</sup>

<sup>1</sup>Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, PO Box 68006, 21944971, Rio de Janeiro, R.J., Brazil; <sup>2</sup>Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, R.J., Brazil



LASSBio-349  
(1998)

AS Lages, KCM Silva, ALP Miranda, CAM Fraga, EJ Barreiro, "Synthesis and pharmacological evaluation of new flosulide analogues, synthesized from natural safrole", *Bioorg. Med. Chem. Lett.* 1998, 8, 183.

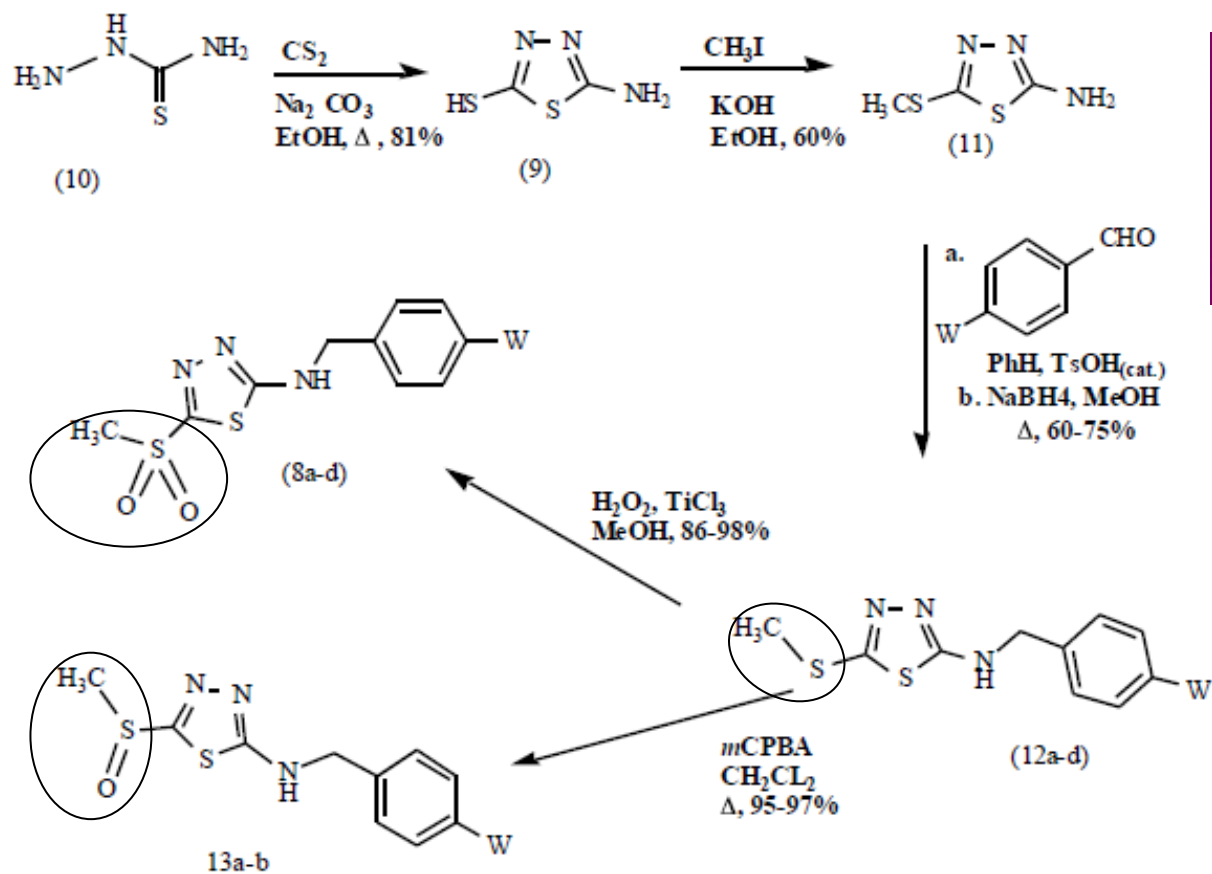


Design concept



SP Khanapure *et al.*, *J.Med.Chem.* 2005, 48, 3930.

Fig. (2). Design concept of new 1,3,4-thiadiazole COX-2 inhibitor candidates.



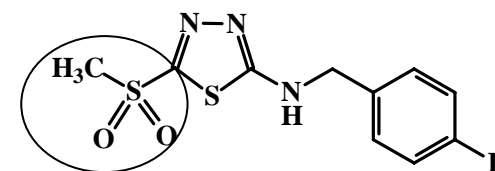
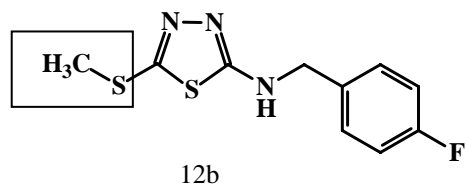
**Scheme 1.** Synthetic route for the preparation of new 1,3,4-thiadiazole derivatives (8a-d).

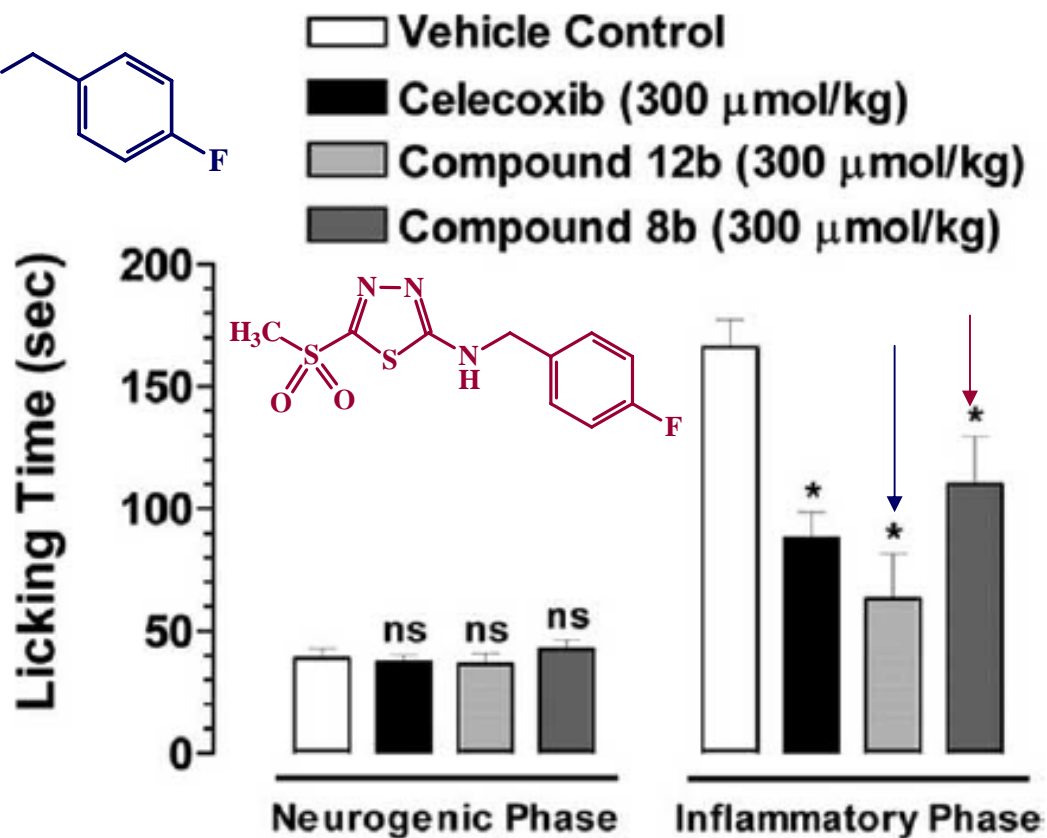
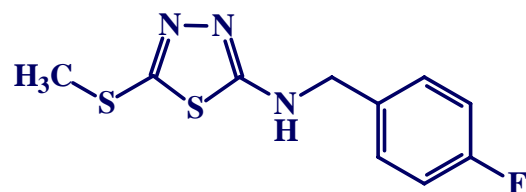


**Table 2. Effect of 1,3,4-thiadiazole Derivatives (12a-d), (8a-d), (13a-b) and Celecoxib (1) in the Carrageenan-Induced Rat Paw Edema (0.1mg/paw)**

Compound	Dose <sup>a</sup> (μmol/kg)	n <sup>b</sup>	Edema (μL) <sup>c</sup>	Inhibition (%) <sup>d</sup>
Vehicle Control	-	10	569.1 ± 45.1	-
Celecoxib	300	05	348.8 ± 25.9	38.7 *
12a	300	09	355.3 ± 32.3	37.6 *
12b	300	05	361.8 ± 17.6	36.4 *
12c	300	05	446.4 ± 40.4	21.6 *
12d	300	05	488.5 ± 31.4	14.2 n.s.
8a	300	05	514.6 ± 28.3	9.6 n.s.
8b	300	05	328.7 ± 51.0	42.2 *
8c	300	05	409.1 ± 24.9	28.1 *
8d	300	10	395.7 ± 21.2	30.5 *
13a	300	05	499.2 ± 20.2	12.3 n.s.
13b	300	05	366.0 ± 39.7	35.7 *

<sup>a</sup>all compounds were administered p.o. 60 min before carrageenan injection. <sup>b</sup>n = number of animals. <sup>c</sup>edema is the difference between the volumes of carrageenan treated paw and saline treated paw. <sup>d</sup>% of inhibition obtained by comparison with vehicle control group. \*  $p < 0.05$  (Student's t-test). n.s. – non significant. Results are expressed as mean ± SEM.

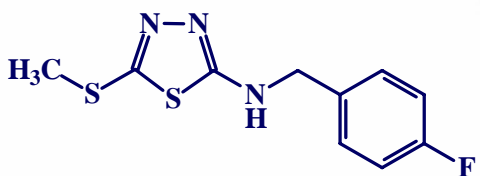
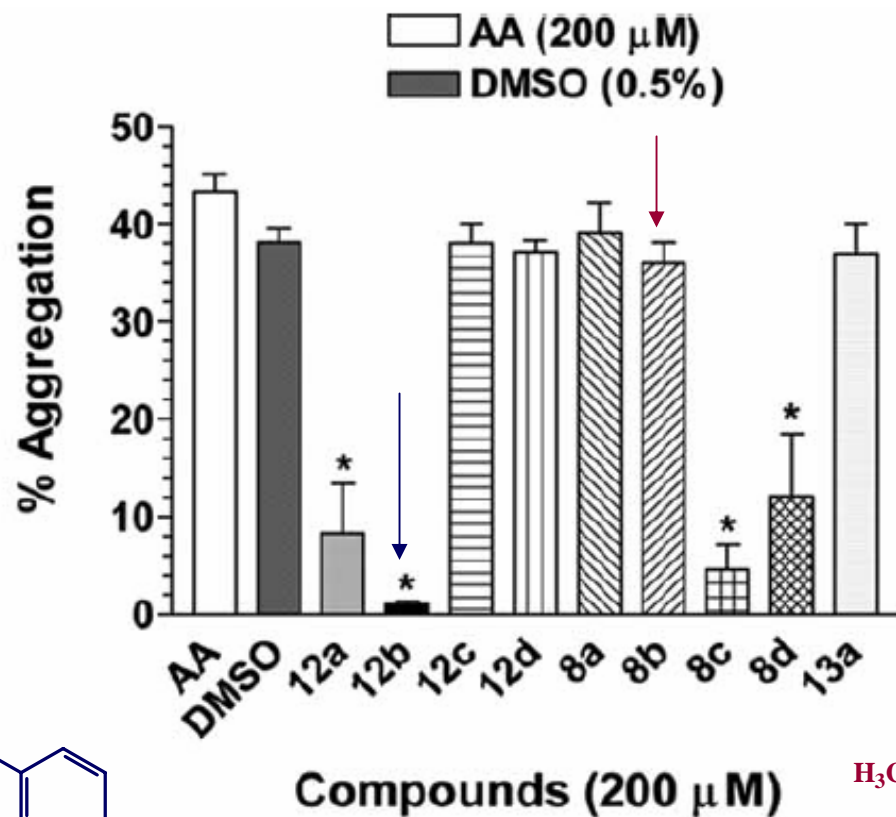




<sup>a</sup>all compounds were administered p.o. 60 min before formalin injection (2.5%; 2  $\mu\text{l/paw}$ ). \*  $p < 0.05$  (Student's t-test). n.s. – non significant. Results are expressed as mean  $\pm$  SEM and compared with vehicle control group.

Fig. (3). Effect of 1,3,4-thiadiazole derivatives (12b), (8b) and celecoxib (1) in the formalin induced pain test in mice.





COX-1



COX-2

Compounds were incubated with PRP 5 min before AA addition. \*  $p < 0.05$  (ANOVA oneway; Bonferroni's test). Results are expressed as mean  $\pm$  SEM of independent experiments carried out in triplicate and compared with AA control group.

**Fig. (4).** Effect of 1,3,4-thiadiazole derivatives (12a-d), (8a-d) and (13a) on in vitro platelet aggregation of citrated rabbit platelet-rich plasma induced by arachidonic acid (AA, 200  $\mu$ M).



## 1. A Química (Farmacêutica) Medicinal: definição

## 2. Como se descobrem os fármacos?

## 3. A origem dos fármacos

### 3.1. O Papel dos produtos naturais na descoberta de fármacos

### 3.2 O Acaso e a descoberta de fármacos

### 3.3 Os fármacos sintéticos

## 4. O processo da descoberta

### 4.1. A abordagem fisiológica e a diversidade molecular

### 4.2 O paradigma do composto-protótipo: interações fármaco-biorreceptor

### 4.3 A importância dos fatores estruturais/conformacionais: grupos farmacofóricos/toxicofóricos

## 5. O planejamento racional

### 5.1 Fármacos inteligentes: Cimetidina; atovarstatina; celecoxib; me-too; imatinib

### 5.2 A diversidade molecular dos fármacos sintéticos

### 5.3 A diversidade molecular de novos protótipos descobertos no LASSBio, UFRJ

## 6. As estratégias de desenho estrutural da Química (Farmacêutica) Medicinal

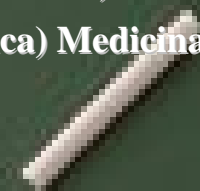
### 6.1 Bioisosterismo: LASSBio-326

### 6.3 Hibridação molecular: LASSBio-756

### 6.4 Simplificação molecular: LASSBio-294

### 6.5 Desenho de protótipos simbióticos: LASSBio-468

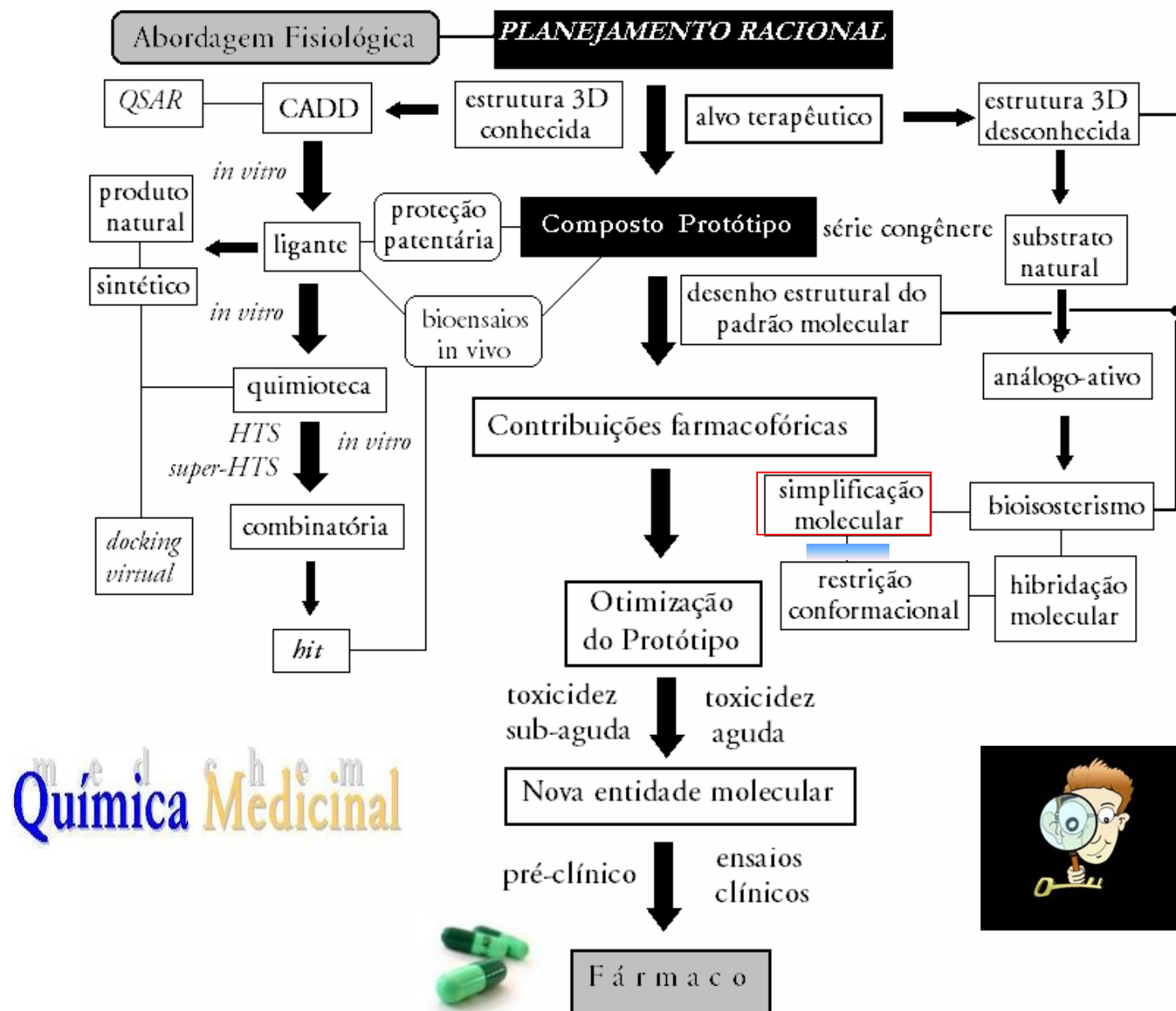
## 7. Conclusões



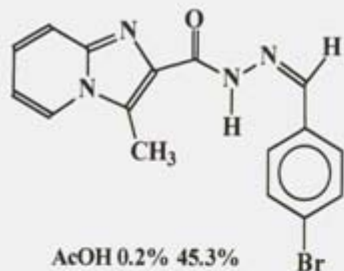


# *Estratégias de desenho molecular: simplificação*

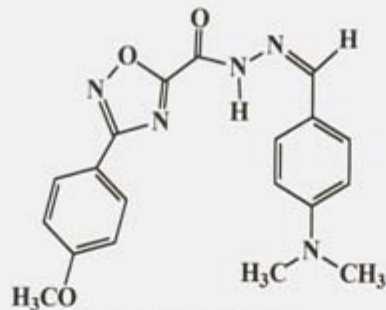
**LASSBio-294**



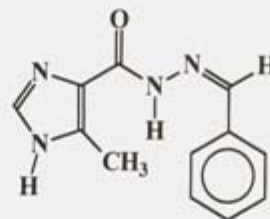
# Novos Protótipos Descobertos no LASSBio



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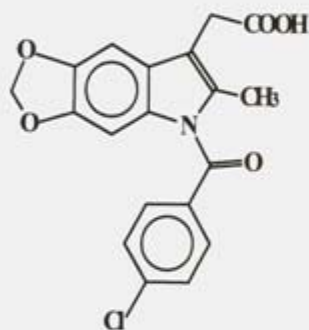
Il Farmaco, 54, 747-757 (1999)



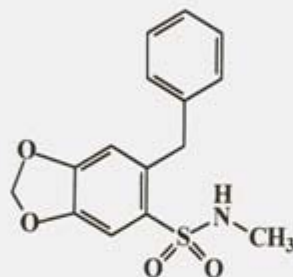
Bioorg. Med. Chem., 8, 2243 (2000)  
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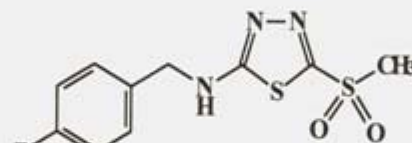
Química Nova, 25, 1172 (2002)  
J. Pharmacol. Exper. Therap., 299, 558 (2001)  
Br. J. Pharmacol., 134, 603 (2001)  
Br. J. Pharmacol., 135, 293 (2002)  
Eur. J. Pharmacol., 470, 79 (2003)



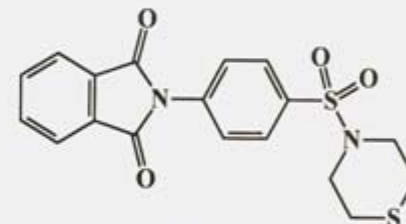
J. Chem. Res.(S), 102 (1982)  
Química Nova, 22, 744 (1999)



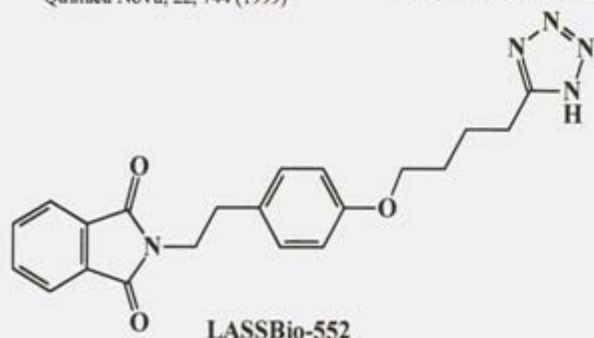
Bioorg. Med. Chem. Lett., 8, 183 (1998)



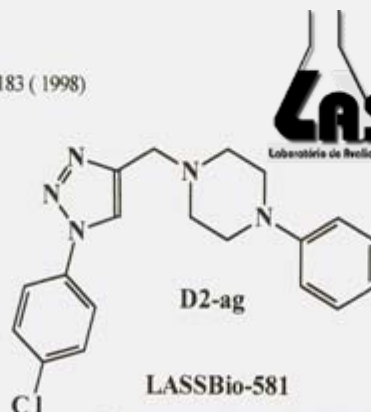
LS Varandas, MSc UFRJ, 2000



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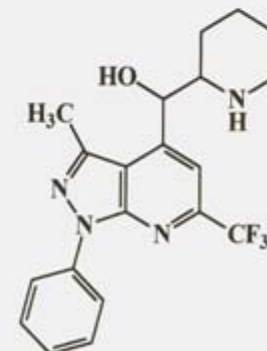
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Braz. J. Biol. Med. Res., 36, 625 (2003)  
J. Pharm. Biomed. Anal., 33, 1127 (2003)



Eur. J. Med. Chem., 37, 163 (2002)

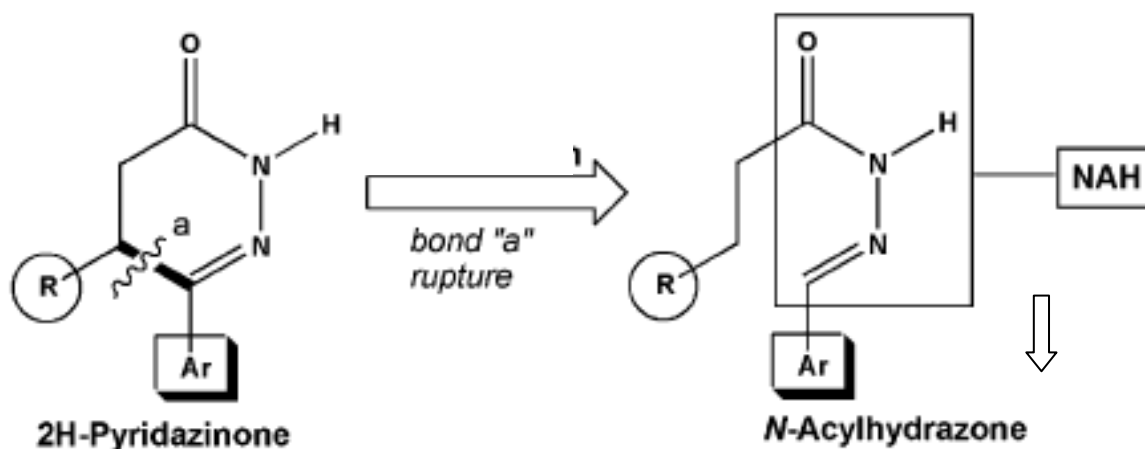


Boll. Chim. Farm., 139, 14 (2000)

**LASSBio**  
Laboratório de Pesquisa e Síntese de Substâncias Bioativas

**Diversidade  
Molecular**

## NAH-unit as isostere of pyridazinone moiety

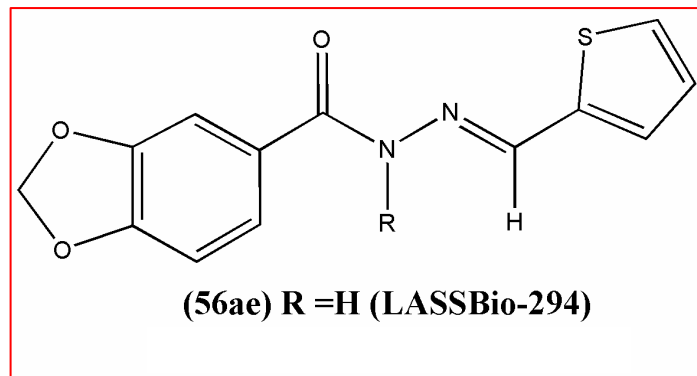


**Molecular simplification**

$C_{13}H_{10}N_2O_3S$

**PM 274**

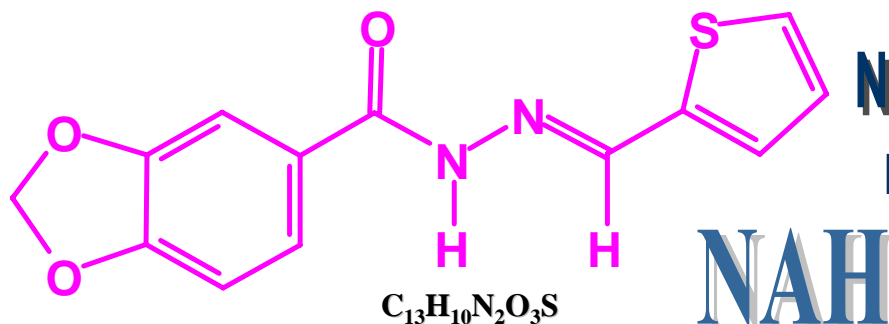
Lima, P. C. *et al.* (2000)  
*Eur. J. Med. Chem.* 35, 187.







# Novo Protótipo de Fármaco Cardioativo



**LASSBio-294**

**Estruturalmente simples;  
Sinteticamente acessível  
em ótimos rendimentos;  
Matéria-prima disponível  
(produto natural abundante).**

**Novo agente cardioativo, seletivo,  
não-digifálico, não-adrenérgico,  
com potentes propriedades  
inotrópicas & vasodilatadoras;  
Ativo por via oral;  
Sem toxicidade aguda.**

*P. hispidinervum*



**USPTO Prov. Number  
60-140,352 (1999)**

**“Novel, Non-toxic Chronotropic Stimulator of Cardiac  
and Skeletal Muscle”**

EX Albuquerque, EJ Barreiro, RT Sudo, "LASSBio 294 A Novel Digitalis-like Compound with Potential Antifatigue Activity", USPTO Provisional Number 60-140,352 (1999); WO Patent; Eur. Patent;



# ESTUDOS DE TOXICIDADE AGUDA E SUB-

## AGUDA

✓ A toxicidade sistêmica aguda e sub-aguda foi investigada em ratos, por duas vias de administração, *p.o.* e *i.p.*, nas doses de **1000  $\mu\text{M/kg}$**  e **73  $\mu\text{M/kg}$** , respectivamente (*i.p.*, administrando-se 2 vezes ao dia, durante 15 dias seguidos: ~ **100 vezes superior à  $\text{ED}_{50}$  *in vivo***).

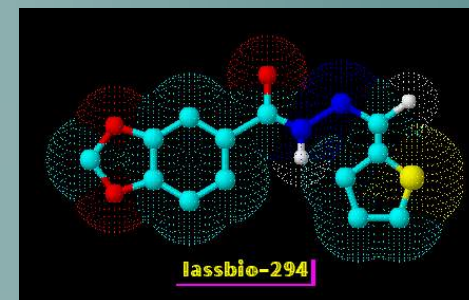
**LASSBio-294**



Não tem efeito letal, não provoca letargia, não reduz a motilidade, nem altera o peso dos animais.

Não provoca alterações na contagem de células sanguíneas, hematócrito, nem altera a taxa de glicose, uréia, TGO, TGP, creatinina.

Não altera histopatologicamente órgãos vitais, tais como fígado, pulmão, SNC.



Não se observaram efeitos neurotóxicos em culturas de neurônios hipocampus de ratos, tratadas com LASSBio-294 (500  $\mu\text{M}$ ).

Efeito neuroprotetor foi observado em < doses.

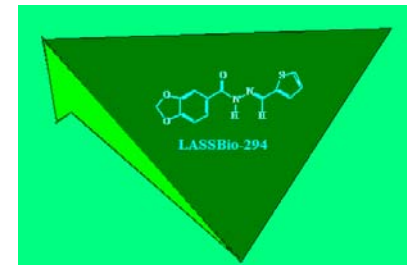
Novo protótipo de  
fármaco cardiovascular



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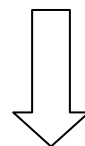


**USPTO 60-525,353 (1999) → Novo Protótipo Cardioativo\***

**USPTO 60-525,353 (1999) → WO 2000-078754 (64 países)**

**LASSBio 294:** a novel compound having digitalis-like  
cardiotonic properties and the potential to reduce  
muscle fatigue

Tech ID # 1558EA



otimização



**PI-0403363-9 20/08/2004 → Relaxantes musculares seletivos**

<http://www.inventabrasil.hpg.ig.com.br/ytabela.htm>

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10070128	08/15/2006	7091238	32390-178943	9691

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## ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

### Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 109 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

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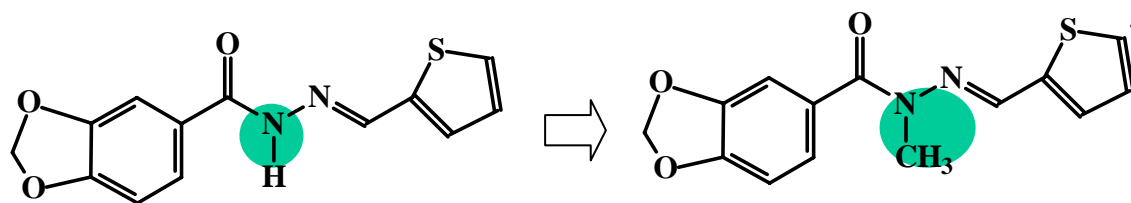
APPLICANT(s) (up to 18 names are included below, see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

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Francisco Germain Noel, Rio de Janeiro, BRAZIL;  
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Ana Luiza Palhares De Miranda, Petropolis, BRAZIL;





# Lead-optimization



**LASSBio-294**

**LASSBio-785**

**Table** - The concentration of compounds necessary to reduce 50% of maximal phenylephrine-induced contracture ( $IC_{50}$ ) in aorta with or without intact endothelium.

Compounds	$IC_{50}$ ( $\mu M$ )	
	With endothelium	Without endothelium
LASSBio-785 (N-Me)	10.2 $\pm$ 0.5	18.5 $\pm$ 3.6
LASSBio-788 (N-allyl)	67.9 $\pm$ 6.5	65.7 $\pm$ 8.0
LASSBio-786 (N-benzyl)	134.1 $\pm$ 31.0	141.6 $\pm$ 53.8
LASSBio-791 (NH, dihydro)	172.8 $\pm$ 26.7	ND
LASSBio-790 (NH, 5-Nitro)	216.0 $\pm$ 39.3	ND
LASSBio-787 (NH, 5-methyl)	293.0 $\pm$ 76.0	273.4 $\pm$ 22.0
LASSBio-789 (NH, 5-bromide)	ND	ND
LASSBio-294 (NH)	74.0	ND

ND = Not Determined.



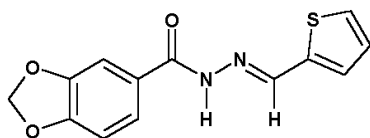
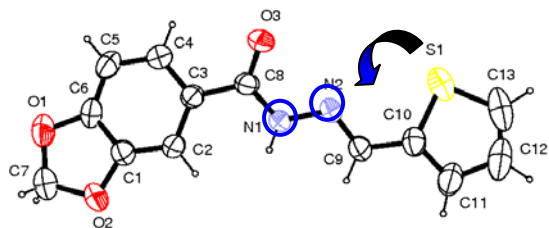
**PI-0403363-9 20/08/2004**

A G Silva, G Zapata-Sudo, AE Kummerle, CAM Fraga, EJ Barreiro, RT Sudo, "Synthesis and vasodilatory activity of new *N*-acylhydrazone derivatives, designed as LASSBio-294 analogues", *Bioorg. Med. Chem.* 2005, **13**, 3431.

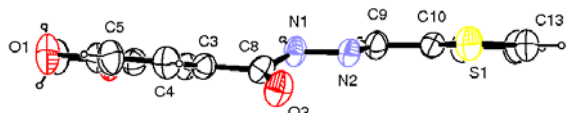


### LASSBio-294

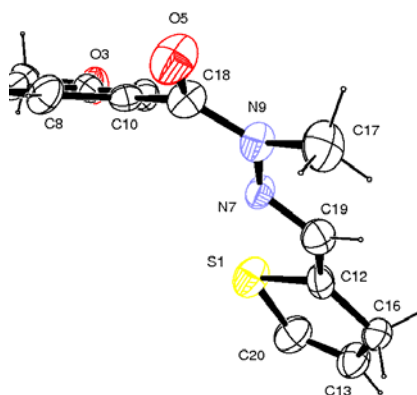
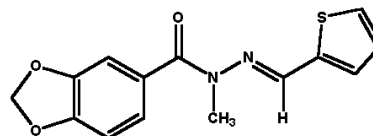
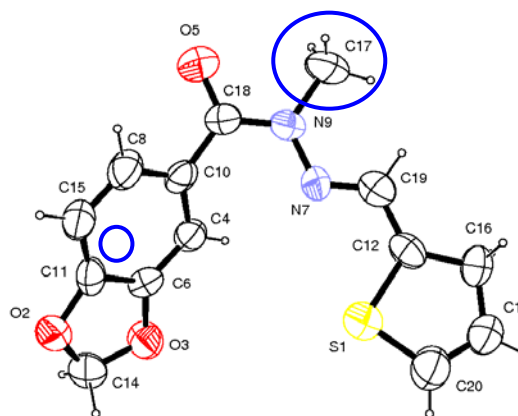
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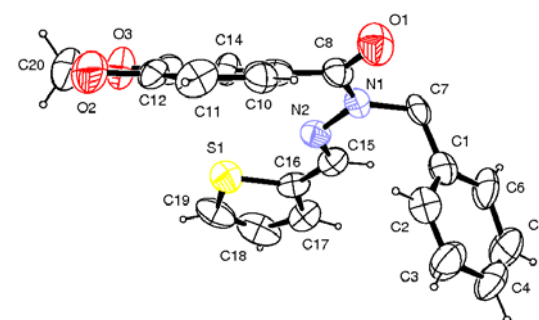
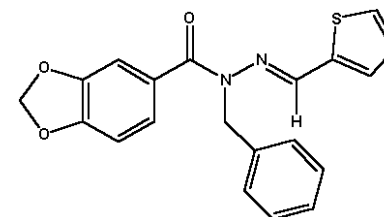
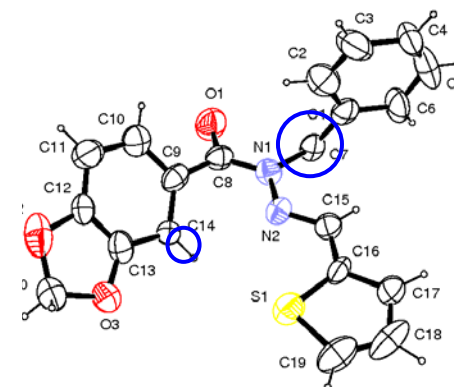
#### Vista Paralela



### LASSBio-785

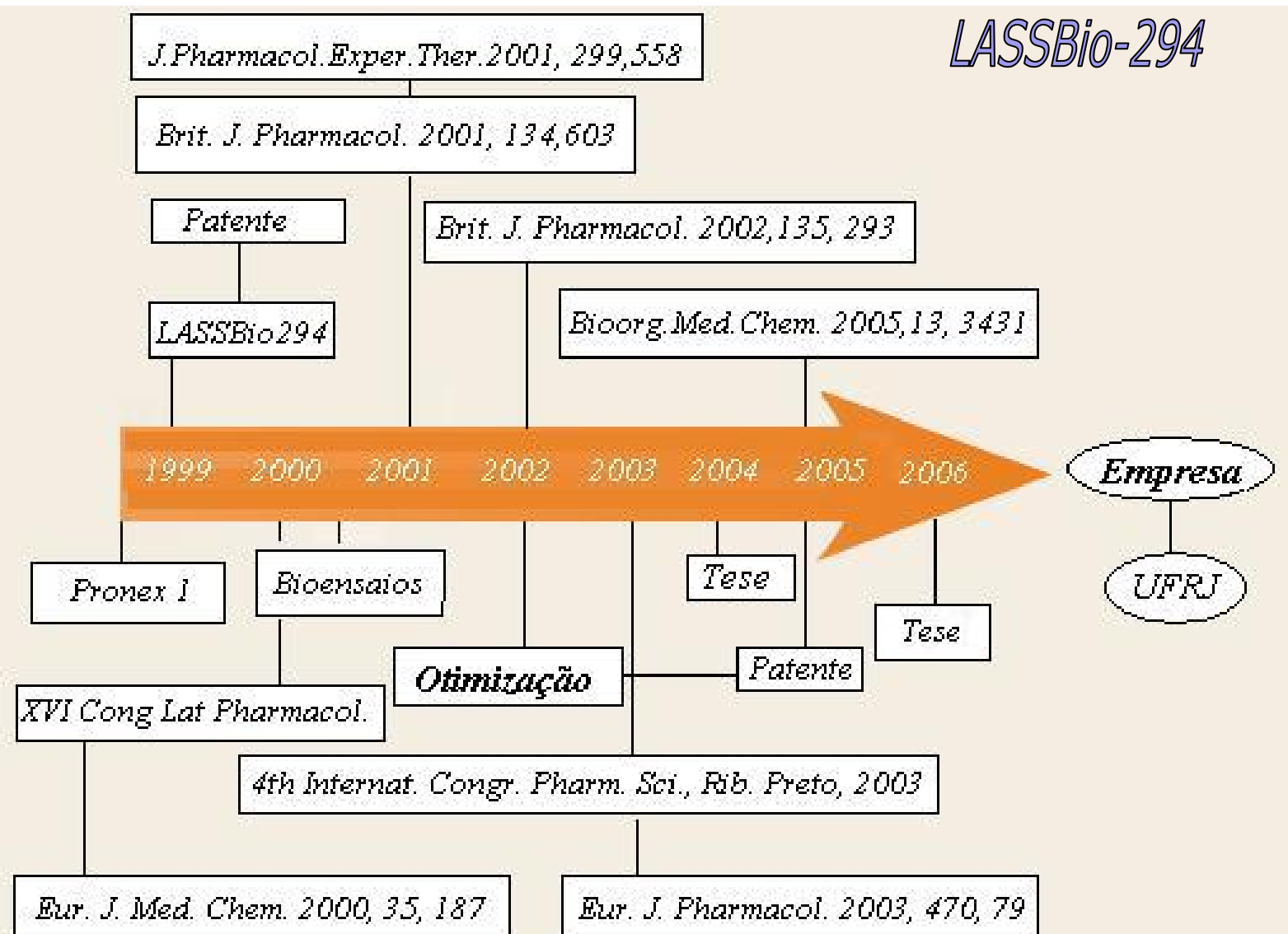


### LASSBio-786



# Cronologia da descoberta do novo candidato a fármaco cardioativo

*LASSBio-294*





• P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, “Synthesis and Non-addictive Analgesic Activity of Novel N--acylarylhydrazones and Isosters, Derived from Natural Safrole”, *Eur. J. Med. Chem.*, 35, 187-203 (2000);

H.Gonzalez-Serratos, R. Chang, E. F. R. Pereira, N. O. Castro, Y. Aracava, P. A. Melo, P. C. Lima, C. A. M. Fraga, E. J. Barreiro & E. X. Albuquerque, “A Novel Thienylhydrazone, (2-thienylilidene)-3,4-methylenedioxybenzoylhydrazone, Increases Inotropism and Decreases Fatigue of Skeletam Muscle”, *J. Pharmacol. Exper. Therap.*, 299, 558-566 (2001);



R.T. Sudo, G. Zapata-Sudo, E.J. Barreiro, “LASSBio-294, a Novel “Cardionotropic agent, Increases the Calcium Content in the Sarcoplasmatic Reticulum of Saponin-skinned Cardiac Fibres”, *Br. J. Pharmacol.*, 134, 603-613 (2001); C.L. Silva, F. Noël & E. J. Barreiro, “Vasodilatory Properties of LASSBio-294 and its dependence on cGMP increase”, *Br. J.Pharmacol.*, 135, 293-298 (2002);

G. Zapata-Sudo, R. T. Sudo, P. A. Maronas, G. L. M. Siilva, O. R. Moreira, M. I. S. Aguiar, E. J. Barreiro “ Thienylhydrazone Derivative Increases Sarcoplasmic Reticulum  $\text{Ca}^{+2}$  Release in Mammalian Skeletal Muscle”, *Eur. J. Pharmacol.*, 61, 79-85 (2003);

A. G. Silva, G. Zapata-Sudo, A.E. Kummerle, C.A.M. Fraga, E.J. Barreiro, R.T. Sudo, “Synthesis and vasodilatory activity of new N-acylhydrazone derivatives, designed as LASSBio-294 analogues “,*Bioorg. Med. Chem.*, 13, 3431-3437 (2005).



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LASSBio 294

Pesquisar

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Web

Resultados 1 - 10 de aproximadamente **451** para LASSBio 294 (0,11 segundos)

Dica: Ganhe tempo teclando Enter ao invés de clicar em "Pesquisar"

### [LASSBio-294](#)

Estamos falando do **LASSBio-294**, um fármaco desenvolvido pelo Laboratório de Avaliação ...

O próprio **LASSBio-294**, embora seja fruto da modelagem molecular, ...

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### [Inventores Brasileiros - Fármacos](#)

O **LASSBio-294** (que atua no aumento das contrações cardíacas), foi desenvolvido a partir de modelagem molecular e teve pedido de patente solicitado no INPI ...

[inventabrasilnet.t5.com.br/yfarmac.htm](http://inventabrasilnet.t5.com.br/yfarmac.htm) - 67k - [Em cache](#) - [Páginas Semelhantes](#)

### [\[PPT\] Apresentação do PowerPoint](#)

Formato do arquivo: Microsoft Powerpoint - [Ver em HTML](#)

Avaliar os perfis antiinflamatório e analgésico da série de derivados N-Acildrazônicos nitrados

(3) , análogos do composto **LASSBio 294**. 3. METODOLOGIAS ...

[acd.ufrj.br/~pharma/lassbio/download/painel1\\_SBFTE04.ppt](http://acd.ufrj.br/~pharma/lassbio/download/painel1_SBFTE04.ppt) - [Páginas Semelhantes](#)

### [Química Nova - Strategy of molecular simplification in rational ...](#)

Outrossim, o efeito de relaxamento observado com **LASSBio-294** (37) permaneceu inalterado quando os anéis de aorta isolados de ratos foram pré-tratados com K+ ...

[www.scielo.br/scielo.php?pid=S0100-40422002000700018&script=sci\\_arttext](http://www.scielo.br/scielo.php?pid=S0100-40422002000700018&script=sci_arttext) - 75k -

[Em cache](#) - [Páginas Semelhantes](#)

### [Química Nova - <B>Estratégia de simplificação molecular no ...](#)

A descoberta de novo protótipo cardiotônico **LASSBio-294** (37) ... De fato, a hipótese de inibição de PDE5 e 3 no mecanismo de ação de **LASSBio-294** foi ...

[www.scielo.br/scielo.php?script=sci\\_arttext&pid=S0100-](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-40422002000700018&lng=pt&nrm=iso)

[40422002000700018&lng=pt&nrm=iso](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-40422002000700018&lng=pt&nrm=iso) - 66k - [Em cache](#) - [Páginas Semelhantes](#)

## 1. A Química (Farmacêutica) Medicinal: definição

## 2. Como se descobrem os fármacos?

## 3. A origem dos fármacos

### 3.1. O Papel dos produtos naturais na descoberta de fármacos

### 3.2 O Acaso e a descoberta de fármacos

### 3.3 Os fármacos sintéticos

## 4. O processo da descoberta

### 4.1. A abordagem fisiológica e a diversidade molecular

### 4.2 O paradigma do composto-protótipo: interações fármaco-biorreceptor

### 4.3 A importância dos fatores estruturais/conformacionais: grupos farmacofóricos/toxicofóricos

## 5. O planejamento racional

### 5.1 Fármacos inteligentes: Cimetidina; atovarstatina; celecoxib; me-too; imatinib

### 5.2 A diversidade molecular dos fármacos sintéticos

### 5.3 A diversidade molecular de novos protótipos descobertos no LASSBio, UFRJ

## 6. As estratégias de desenho estrutural da Química (Farmacêutica) Medicinal

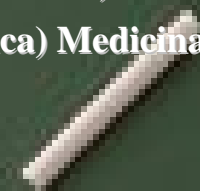
### 6.1 Bioisosterismo: LASSBio-326

### 6.3 Hibridação molecular: LASSBio-756

### 6.4 Simplificação molecular: LASSBio-294

### 6.5 Desenho de protótipos simbióticos: LASSBio-468

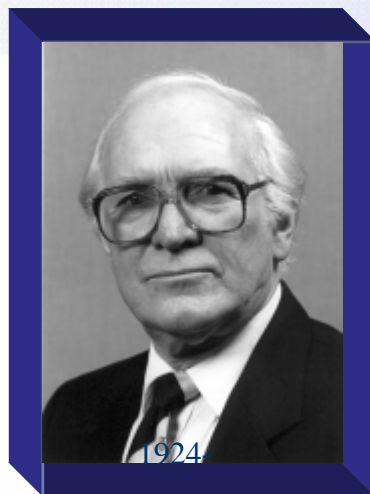
## 7. Conclusões







**“..the problem will not be  
our ability to do things.  
The terrible problem is,  
what will we choose  
to do next?”**

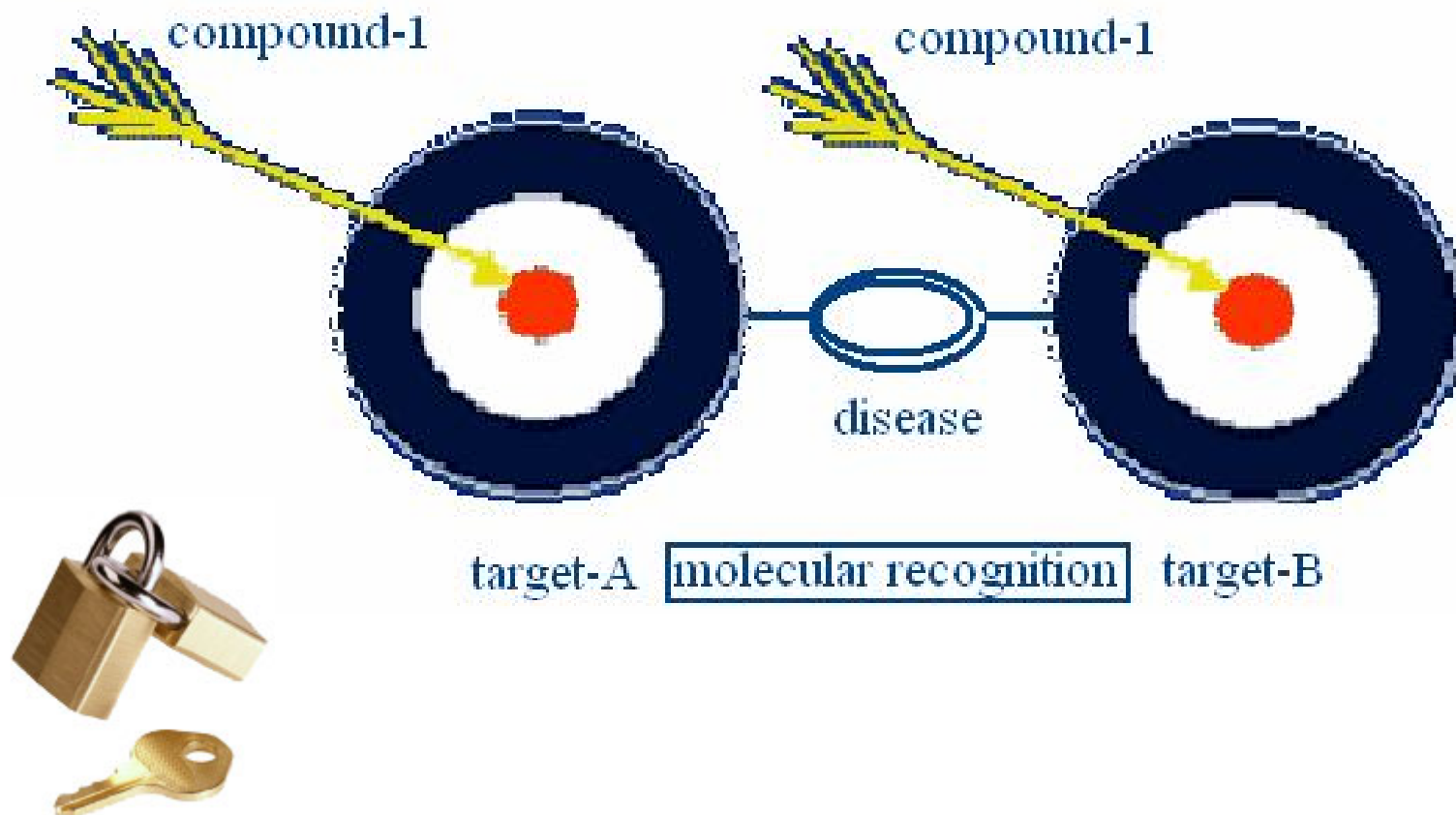


**Sir James W. Black**

1988, Nobel Winner



# The symbiotic lead-candidate design





# • Compostos-protótipos simbióticos:

*compostos-protótipos que possuam afinidade (Afi) por dois alvos terapêuticos distintos, simultaneamente, envolvidos na mesma fisiopatologia em estudo, mas pertencendo a diferentes cascatas bioquímicas;*

## *New Symbiotic lead-candidates*

*(Symbiotic multi-target lead-candidates)*

*a new compound able to be effective in **two** different targets, both relevant to disease, but belonging to distinct biochemical pathway;*

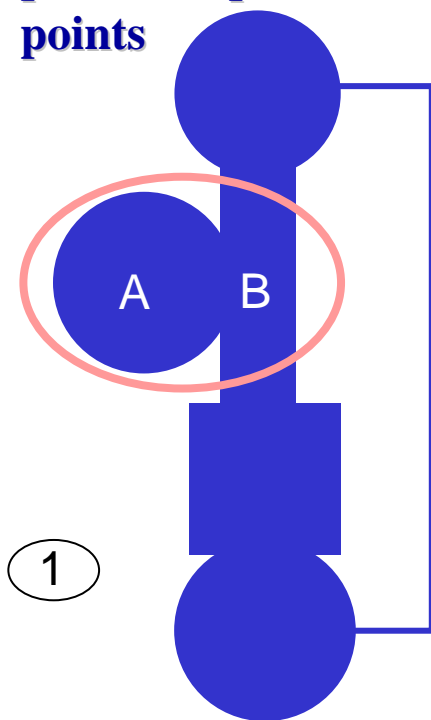


# Agentes simbióticos



# *Rational basis to symbiotic drug design*

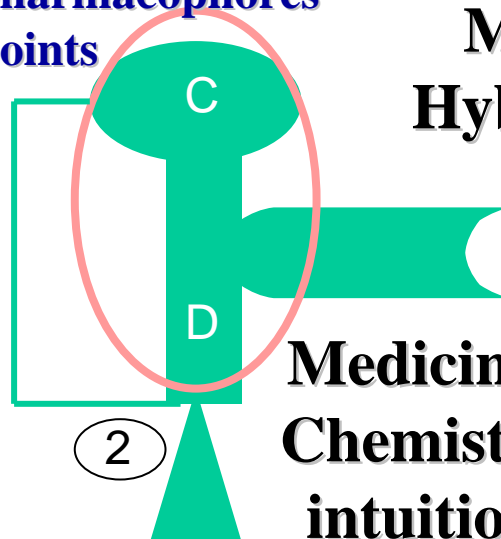
pharmacophores  
points



1

Receptor-a  
molecular  
recognition

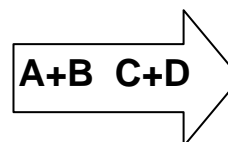
pharmacophores  
points



2

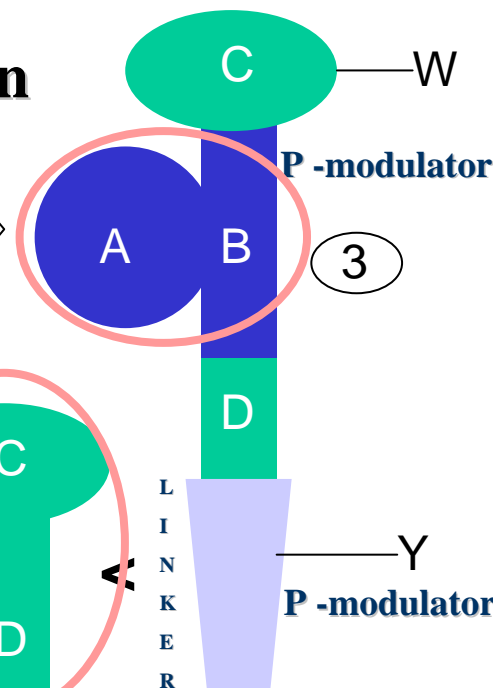
Receptor-b  
molecular  
recognition

Molecular  
Hybridization



Medicinal  
Chemistry  
intuition

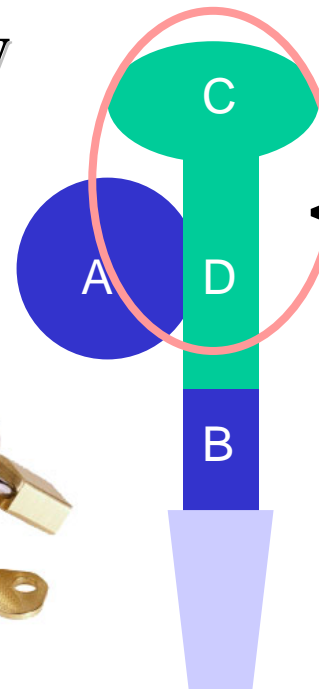
New  
Symbiotic  
Lead-candidate



3

Molecular  
recognition by  
both receptors

Congeneric  
Series

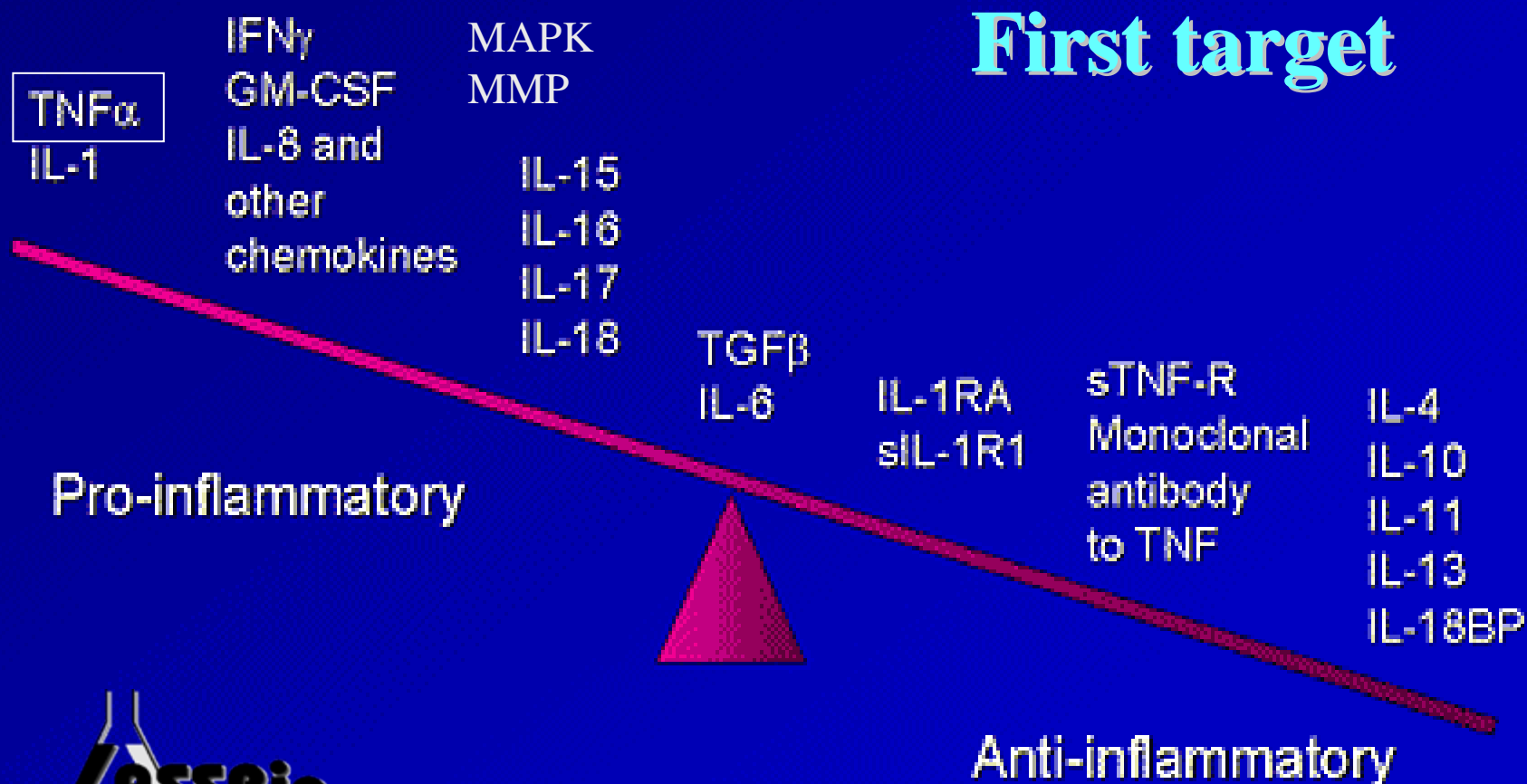


4

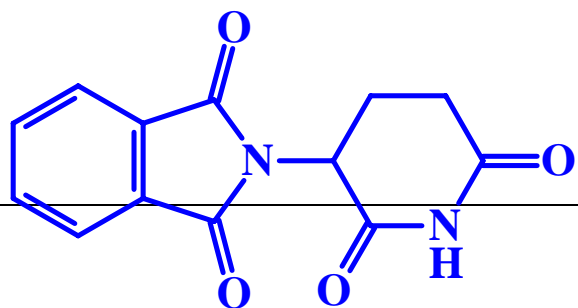
*integrate pharmacophores approach*



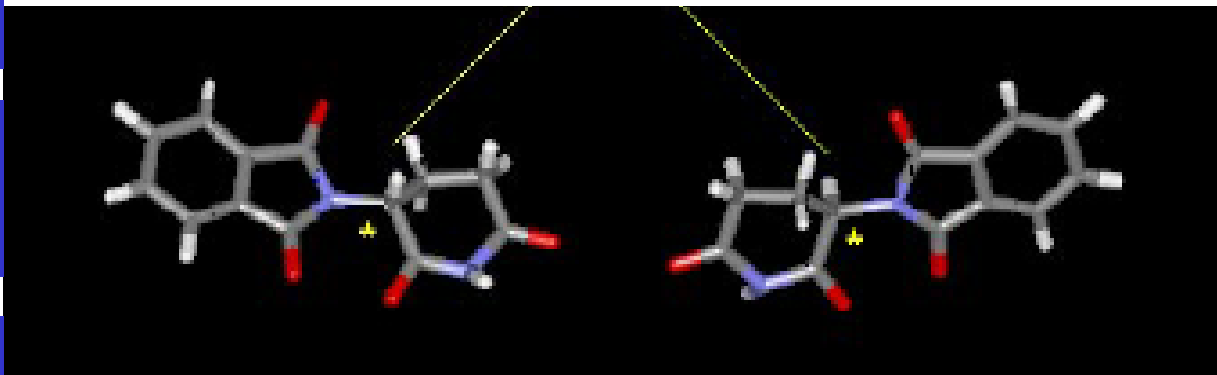
# Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation







2-(2,6-Dioxo-3-piperidiny)-1*H*-isoindole-1,3(2*H*)-dione



**THALIDOMIDE**

**TNF- $\alpha$  IC<sub>50</sub> = 200  $\mu$ M**

**Thalomid<sup>®</sup>, Phase III, Celgene**

Wilhelm Kunz, 1953  
Herbert Keller, 1953  
CNS, 1957  
Frances Kelsey, 1961  
Gilla Kaplan, 1991 (TNF- $\alpha$ )  
Elisabeth P. Sampaio, 1997

*L.M. Lima et al., O Renascimento de um Fármaco: Talidomida, Quim. Nova 2001, 24, 683; (www.scielo.br); E.P. Sampaio, D.S. Carvalho, J.A.C. Nery, U.G. Lopes, E.N. Sarno, "Thalidomide: An Overview of its Pharmacological Mechanisms of Action" Anti-inflammatory & Anti-allergy Agents in Medicinal Chemistry 2006, 5, 71; L.M. Lima, C.A.M. Fraga, V.L.G. Koatz, E.J. Barreiro, "Thalidomide and Analogs as Anti-inflammatory and Immunomodulator Drug Candidates", Anti-inflammatory & Anti-allergy Agents in Medicinal Chemistry 2006, 5, 79.*



## Phosphodiesterase-4 as a therapeutic target

Miles D Houslay, Peter Schefer & Kam Y J Zhang

Drug Discov Today 2005, 10, 1503,

## The p38 MAP kinase pathway as a therapeutic target in Inflammatory disease

Jeremy Saklatvala

Curr Op Pharmacol. 2004, 4, 372



## What next for rheumatoid asthritis therapy?

Simon M Blake & Barbara A Swift

Curr Op Pharmacol. 2004, 4, 276

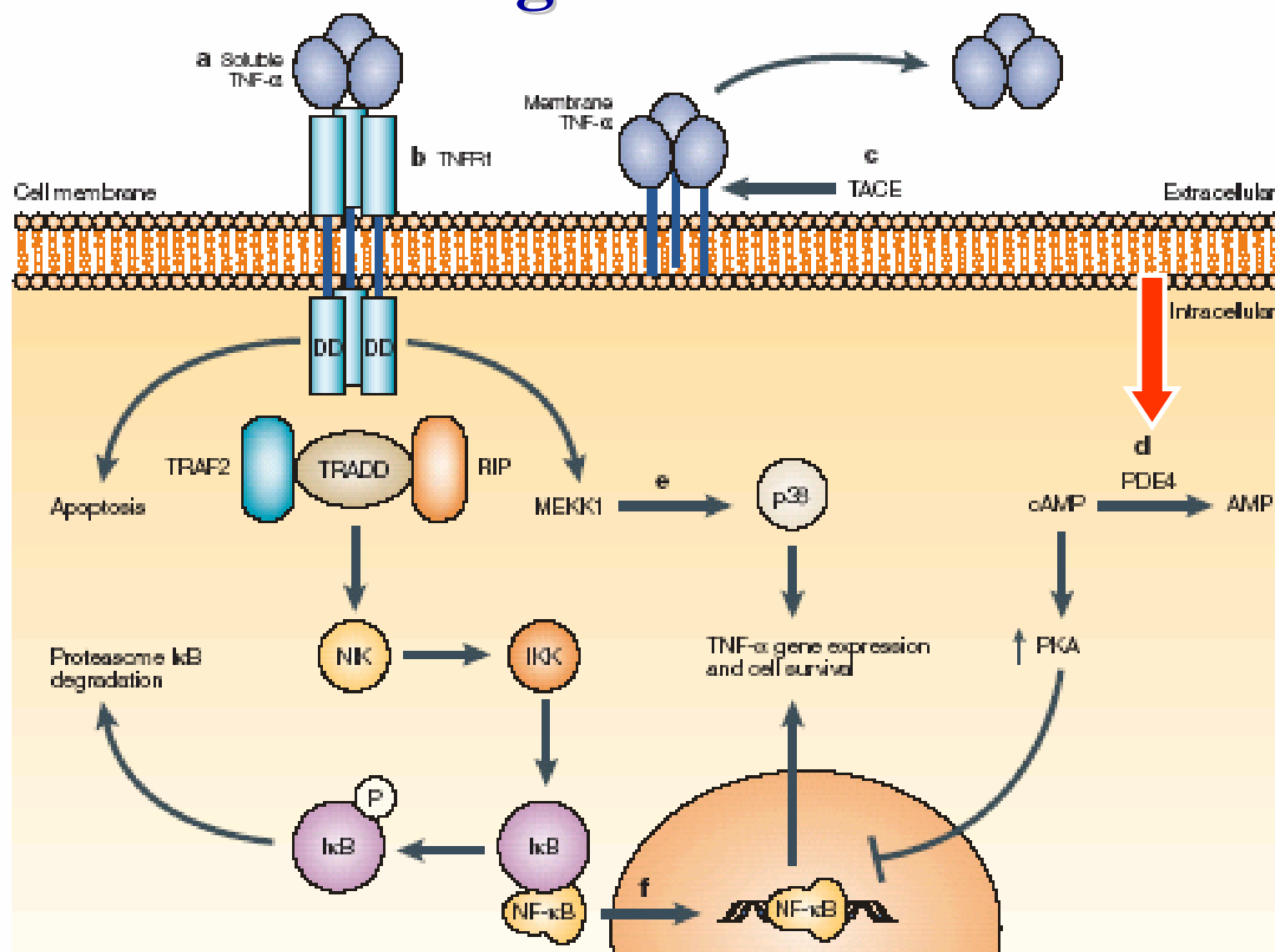
## Inflammatory resolution: New opportunities for drug discovery

Derek W. Gilroy, Toby Lawrence, Mauro Perretti & Adriano G. Rossi

Nature Rev Drug Discov. 2004, 3, 401



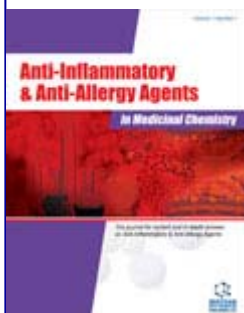
# The second target:



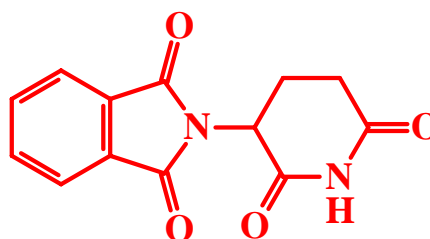
## Thalidomide and Analogs as Anti-Inflammatory and Immunomodulator Drug Candidates

Lídia Moreira Lima<sup>1</sup>, Carlos Alberto Manssour Fraga<sup>1</sup>, Vera Lucia Gonçalves Koatz<sup>2</sup>, and Eliezer J. Barreiro<sup>1,\*</sup>

<sup>1</sup>Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), CP 68.006, 21944-190, Rio de Janeiro, RJ, Brazil), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, RJ, Brazil; <sup>2</sup>Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro, RJ, Brazil.

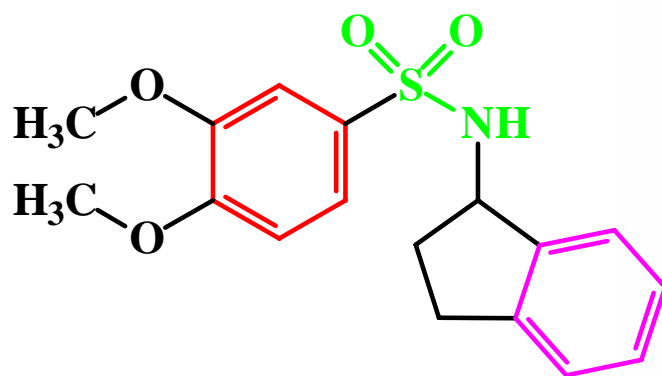


**Abstract:** Thalidomide ([2-(2,6-dioxo-hexahydro-3-(*R,S*)-pyridinyl)-1,3-isoindolinedione]), well known by its teratogenic effect, caused birth defects in up to 12,000 children in the 1960s. More recently, this drug was approved by the US Food and Drug Administration for the treatment of erythema nodosum leprosum, under restricted-use program, and a variety of new possible therapeutic applications have been described. This article will accomplish a review of medicinal chemistry aspects of thalidomide and state of the art in the development of new anti-inflammatory and immunomodulator drug candidates designed using thalidomide as lead-compound.

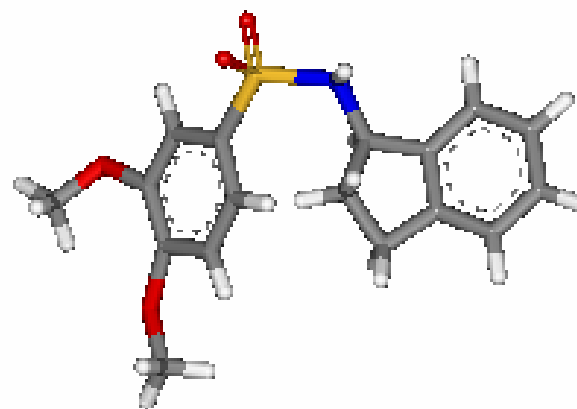




Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, UK  
(Celltech Chiroscience Ltd; UCB-Euronext )



**Aryl-sulfonamida**

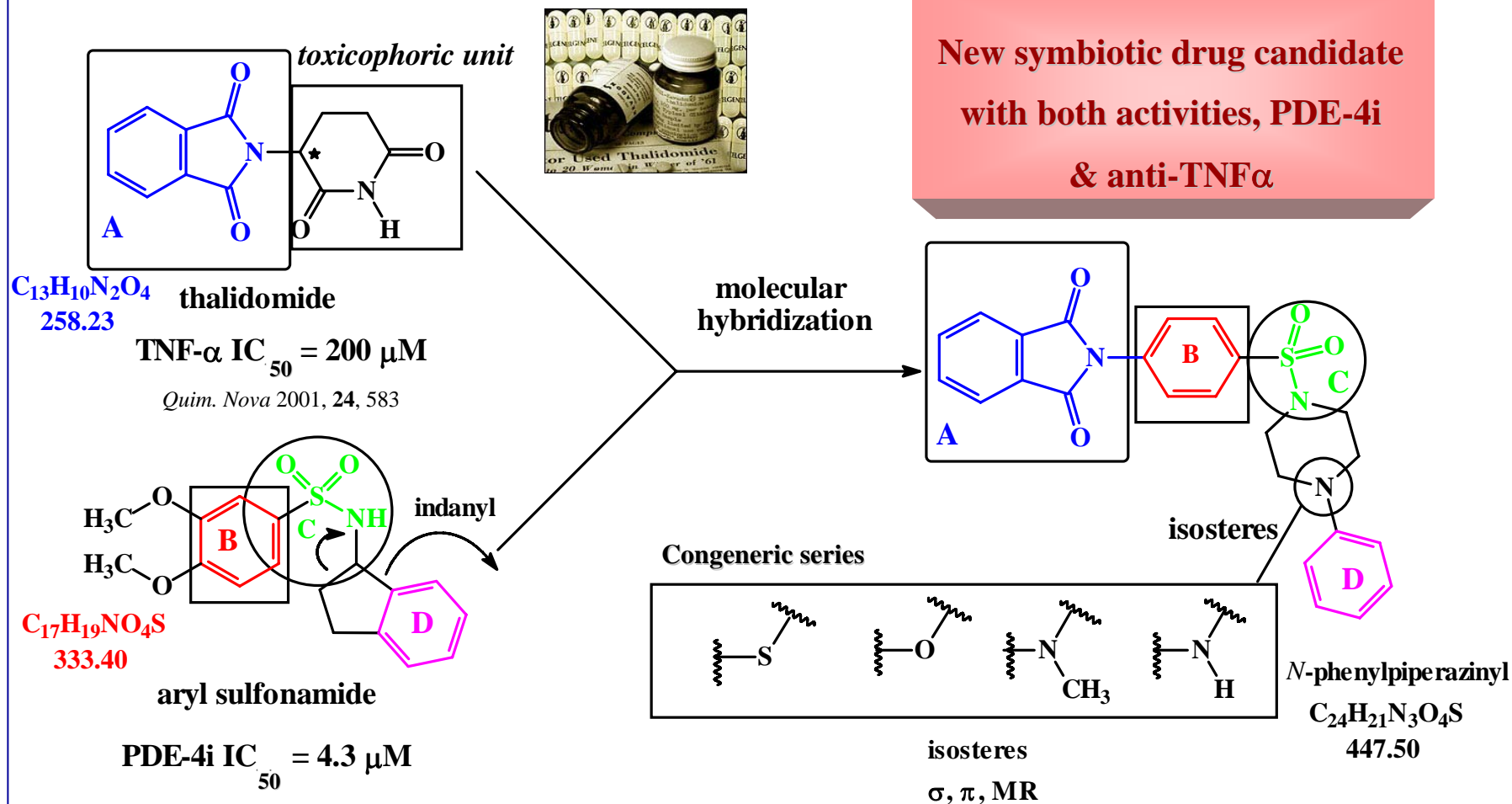


**PDE-4i IC<sub>50</sub> = 4.3 μM**

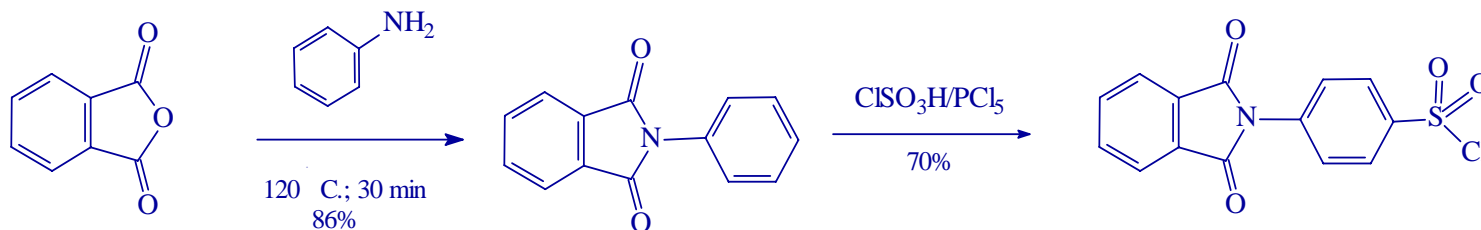
**J. G. Montana**, G. M. Buckley, N. Cooper, H. J. Dyke, L. Gowers,  
J. P. Gregory, P. G. Hellewell, H. J. Kendall, C. Lowe, R. Maxey,  
L. Miotla, R. J. Naylor, K. A. Runcie, B. Tuladhar, J. B. H. Warneck,  
“**Aryl sulfonamides as selective PDE-4 inhibitors**” , *Bioorg. Med. Chem. Lett.* 1998, **8**, 2635.



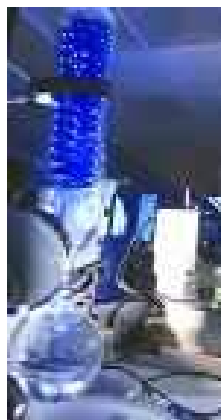
# Molecular Design of New Symbiotic Candidates



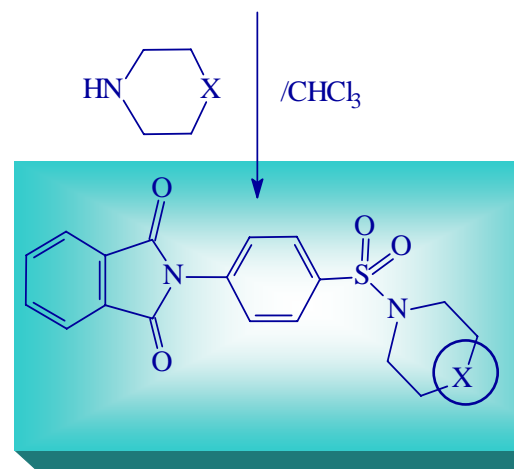
# Synthesis of LASSBio-468



anidrido ftálico

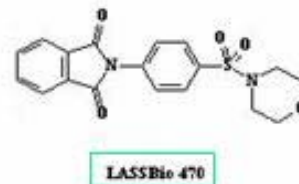
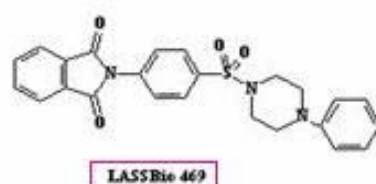
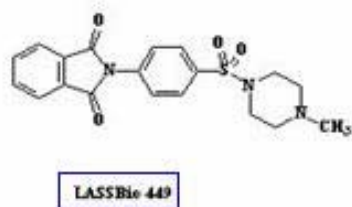
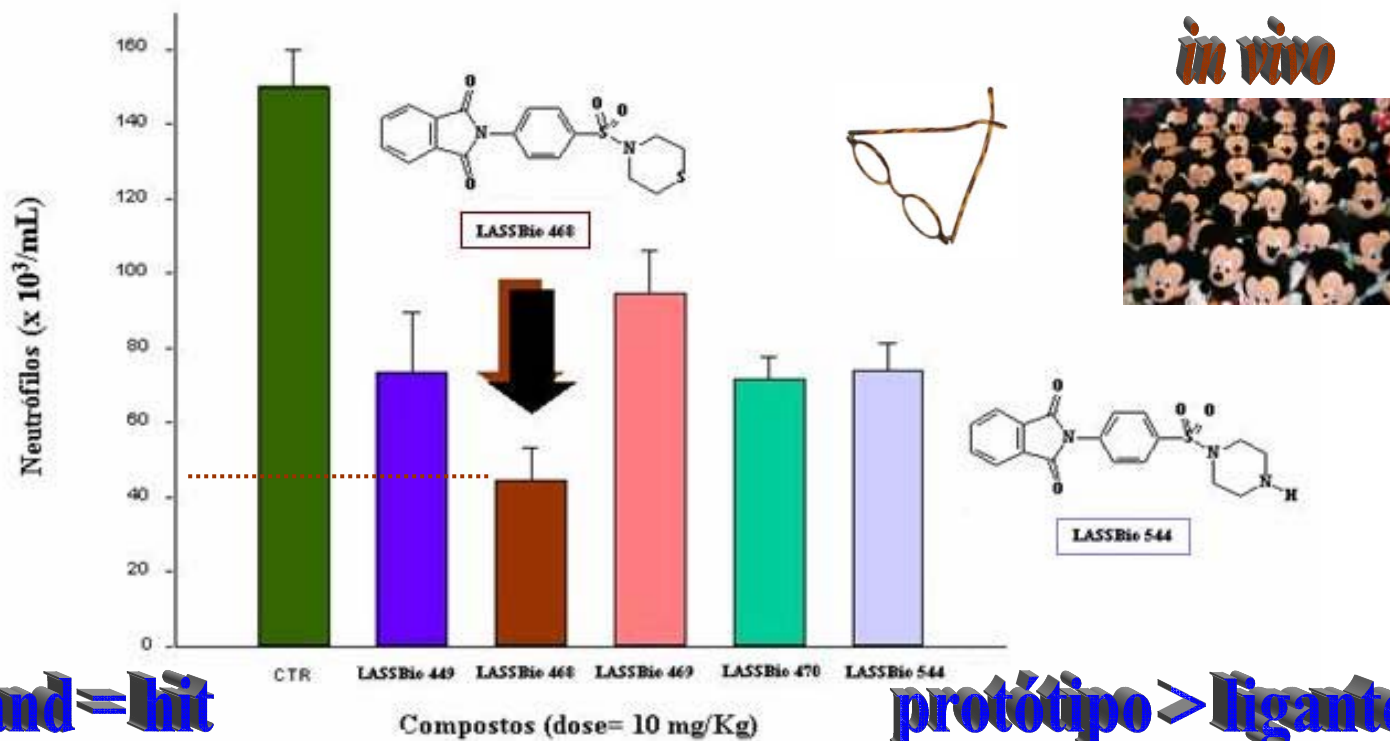


X = NMe 65%  
 X = NPh 67%  
 X = NH 58%  
 X = O 63%  
**X = S 67%**



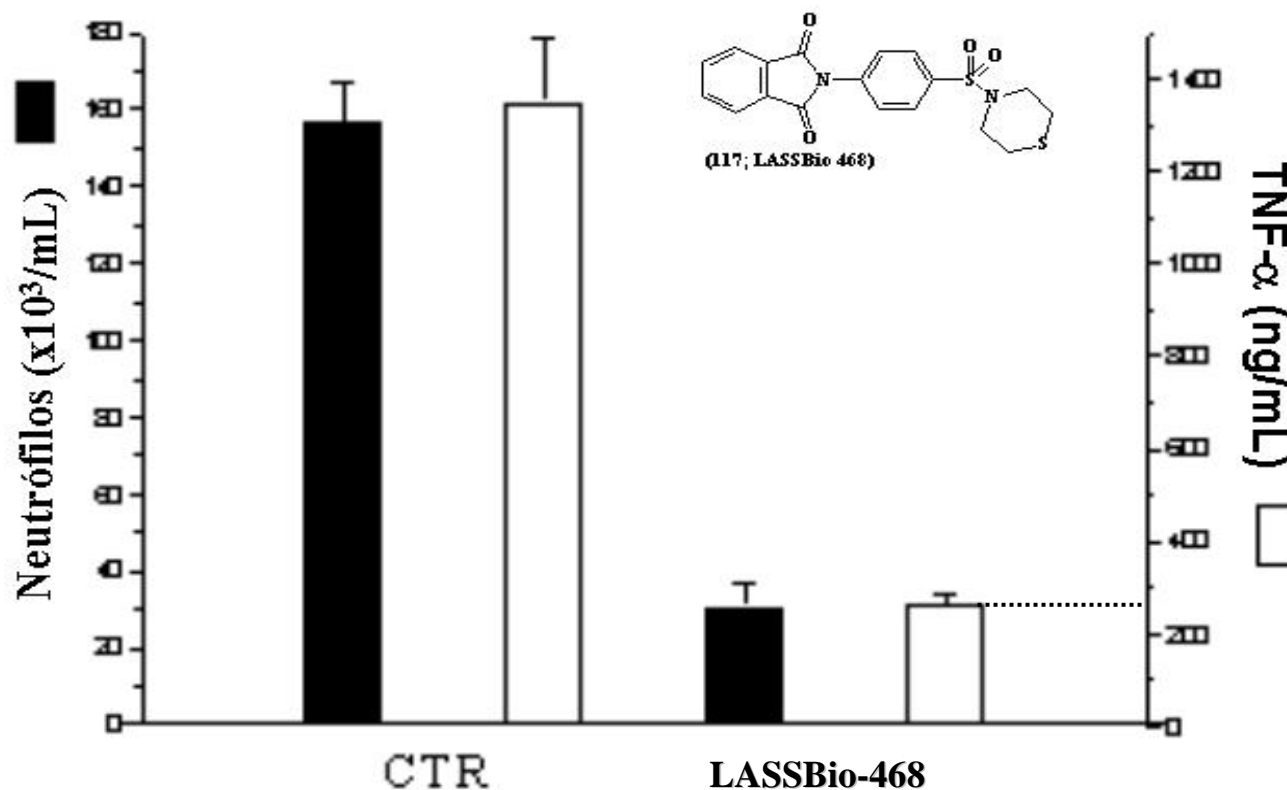
**Overall yield: *ca.* 20%**  
**(0.10 M *i.e.* *ca.* 40g)**

# Effect of new compounds and thalidomide on neutrophil influx induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; i.p.)

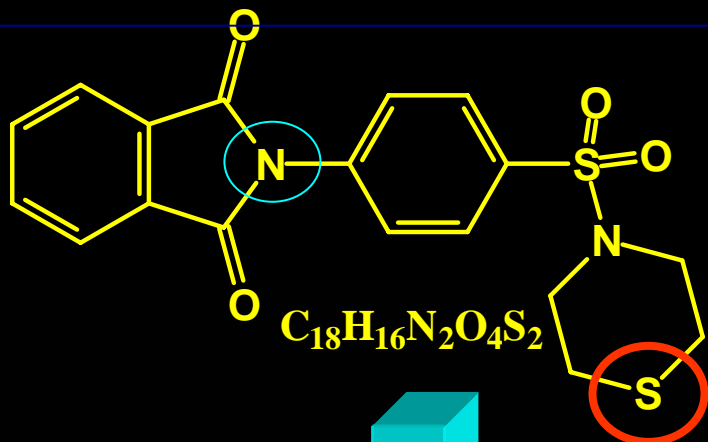




## Effect of compound LASSBio 468 on TNF- $\alpha$ levels and neutrophil influx into the BALB/c of mice lungs



50% more active than thalidomide



TNF- $\alpha$  ED<sub>50</sub> 2,5 mg/Kg

**LASSBio 468**

PDE-4 inibidor



Atividade PDE-4 de foi medida em aorta bovina:

IC<sub>50</sub> = 62,6  $\mu$ M

(cf. PDE-1, 2, 3, > 420  $\mu$ M; 5)

Dr Claire Lugnier (CAPES-COFECUB; LASSBio-Strasbourg)  
 Université Louis Pasteur de Strasbourg, FR.  
 Laboratoire de Pharmacologie et de Physicochimie des Interactions  
 Cellulaires et Moléculaires.

L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moraes, E. J. Barreiro, *Synthesis and Anti-inflammatory activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, Bioorg. Med. Chem.* 2002, 10, 3067.





# LASSBio-468

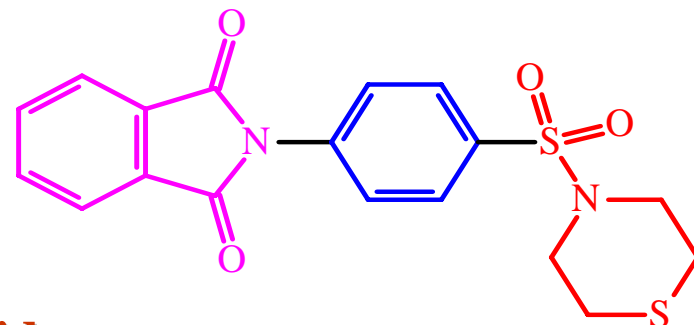
lead compound

## a new symbiotic drug candidate

LASSBio-468 is a new symbiotic lead-compound, designed as antiinflammatory agent acting at TNF- $\alpha$  and PDE-4 level.

LASSBio-468 was designed by molecular hybridization keeping pharmacophore points of thalidomide

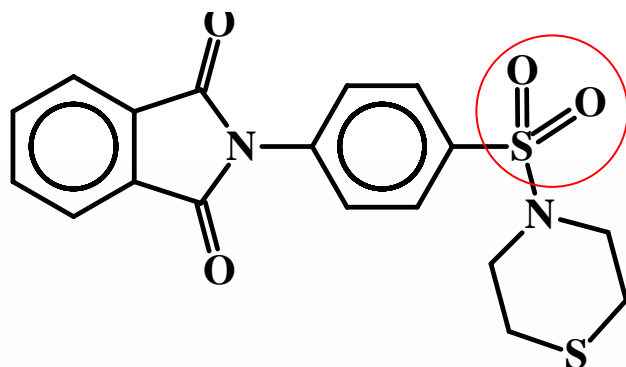
& arylsulfonamides, derivatives with anti-TNF- $\alpha$  & PDE-4 inhibitory activity, respectively. This new symbiotic-lead compound have a very simple structure, achiral, easy to obtained using classical synthetic methods, in high overall yield. This new NSAID drug candidate could be useful to treatment of rheumatic arthritis, Crohn disease and others chronical inflammatory state, without immunosupressor activity.



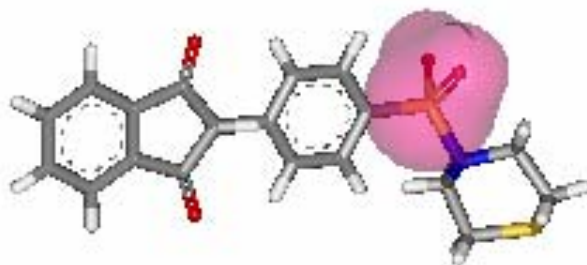
L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, **10**, 3067  
M. S. Alexandre-Moreira *et al.*, "LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF- $\alpha$  and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International*

# LASSBio-468 Optimization

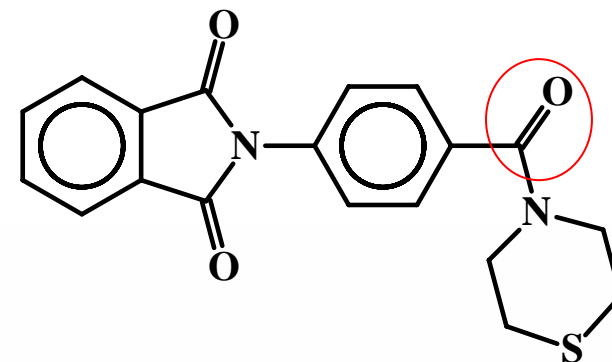
LEAD COMPOUND  
**Lead-optimization**



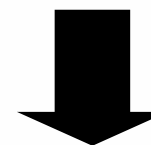
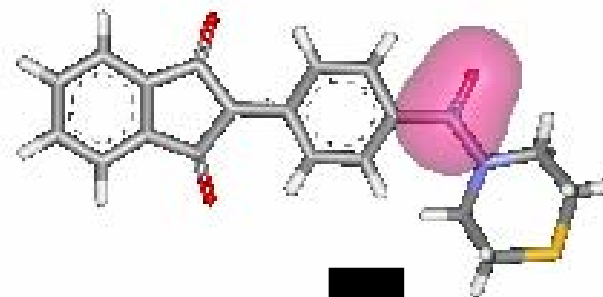
LASSBio-468



**Bioisosteres\***



LASSBio-595



**LASSBio-596**

**PI 041660-2**

\* L. M. Lima & E. J. Barreiro, "Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design", *Curr. Med.Chem.* 2005, 13, 23; [<http://www.bentham.org/cmc/samples/cmc12-1/0002C.pdf>]



e-mail of Eliezer J. Barreiro

---

De: Kyle Kuhn - Paramount BioCapital Investments, LLC  
Para: eliezer@pharma.ufrj.br  
Cc: eliezer@ufrj.br  
Data: 26/08/2006 11:01  
Assunto: Phthalimide derivative LASSBio-552



Dr. Barreiro,

My name is Kyle Kuhn, I represent a *biopharmaceutical investment firm called Paramount BioCapital Investments, LLC*. My job here at Paramount is to identify promising therapeutic technologies, and explore potential investment and/or licensing opportunities.

I recently saw a summary of some information you presented at the recent International Symposium on Nitric Oxide, Cytokines and Inflammation, in Malbourne, and I would like to learn more about compound LASSBio-552.

I would like to know the development status of this compound, as well as any plans for its continued development. *I would also like to know the IP status for this technology.* Any additional information you can provide would be very helpful.

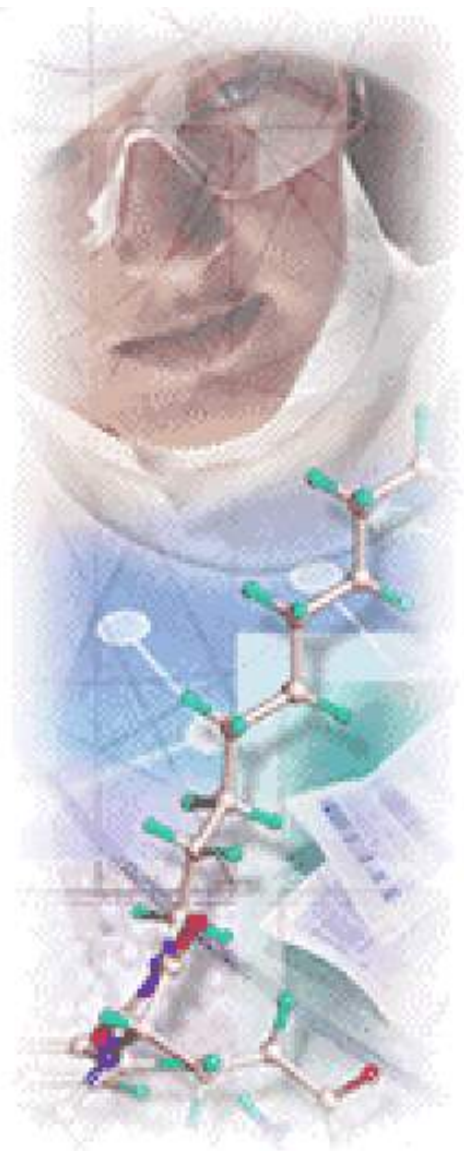
It may be more convenient to speak over the phone. If you would like to provide a number, and suggest a convenient time, I would be happy to give you a call. Alternatively, my contact information is provided below, please feel free to contact me at your convenience. I look forward to hearing from you.

Best regards,  
Kyle Kuhn



Biotechnology Venture Capital Analyst  
Paramount BioCapital Investments, LLC  
787 Seventh Avenue - New York, NY 10019 -Tel: 212.554.4315 -Fax: 212.554.4490  
e-mail: KKuhn@Paramountbio.com





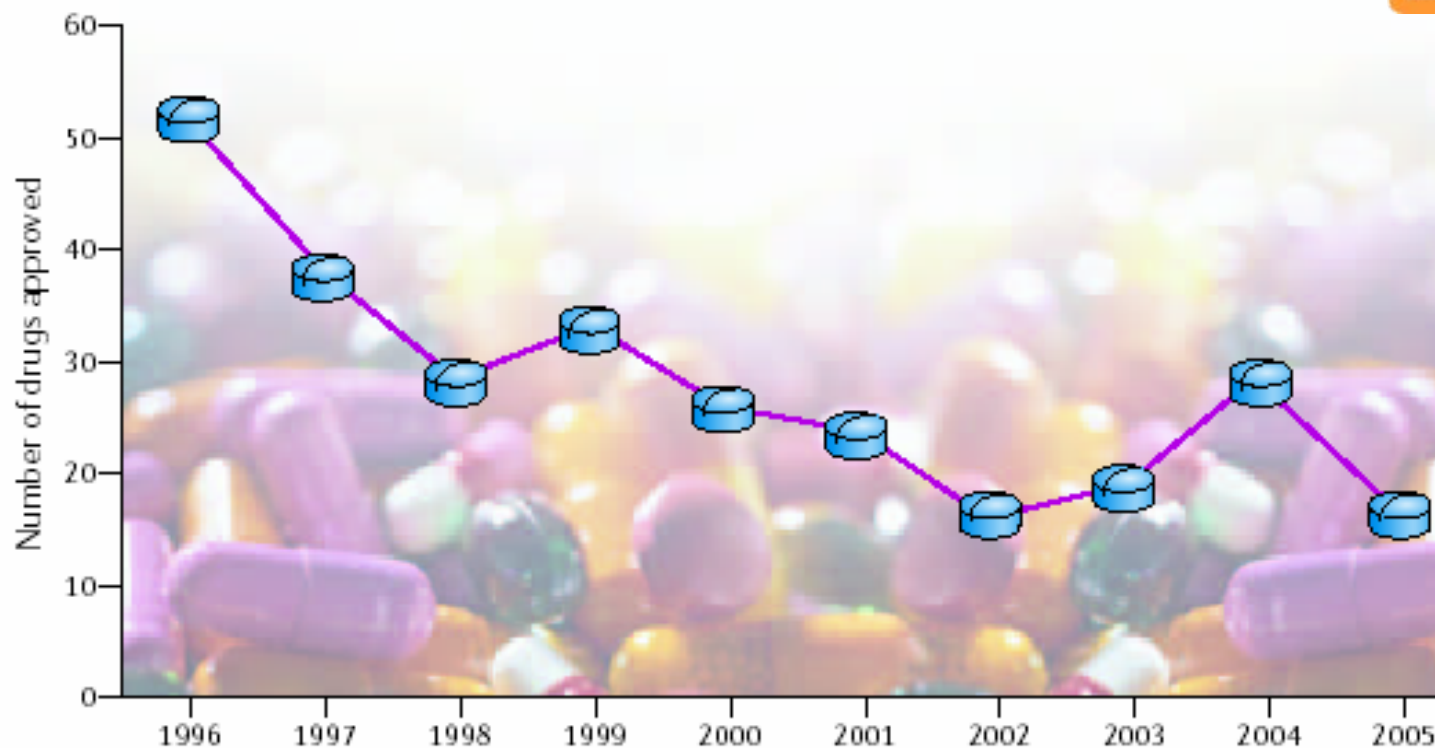
# *Conclusões*



# Academia given a helping hand in drug development

Malorye Allison Branca

*Nature Rev. Drug Disc.* 2006, 5, 177



The FDA hopes its new initiatives will help buck the recent downturn in innovative drugs approved.



*“...nobody in the world  
is condemned to work  
with as many variables  
as the medicinal chemist...”*

**Corwin Hansch, 1996.**



www.farmacia.ufrj.br/im-inofar

Endereço <http://www.farmacia.ufrj.br/im-inofar/>

Ir Links Norton AntiVirus



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REUNIÕES

Acesso Restrito

*im - inovação e desenvolvimento de fármacos e medicamentos*

#### INFORMES

- [Avaliação do I Workshop](#)
- [Conheça nossos Grupos de Pesquisa](#)
- [Acesse a Lei de Inovação](#)
- O Instituto do Milênio - Inovação e Desenvolvimento de Fármacos e Medicamentos é um Projeto apoiado pelo [CNPq](#) e coordenado pelo Prof. Eliezer J. Barreiro.
- O Im-Inofar disponibilizou alguns links interessantes na área de fármacos e medicamentos.



Apoio:



Processo nº 420015/05-1

Desenvolvida por:  
Cúpula Informática

Contatos:  
[ibelza@ccsdecania.ufrj.br](mailto:ibelza@ccsdecania.ufrj.br) e [nacoor@ccsdecania.ufrj.br](mailto:nacoor@ccsdecania.ufrj.br)

Projeto

Atualizada em  
Terça, 31 de Janeiro de 2006



# Departamento de Fármacos Faculdade de Farmácia Universidade Federal do Rio de Janeiro





LASSBio - Faculdade de Farmácia da UFRJ - Microsoft Internet Explorer fornecido por AOL Brasil

Arquivo Editar Exibir Favoritos Ferramentas Ajuda



Endereço <http://www.farmacia.ufrj.br/lassbio/>

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  - » 2004
- » Painéis Premiados
  - » 2004

<<< LASSBio cadastra candidatos a Pós-Doutoramento >>>



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

05 a 09 de fevereiro de 2007

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21:22



# Universidade Federal do Rio de Janeiro

## Laboratório de Avaliação e Síntese de Substâncias Bioativas



o b r i g a d o