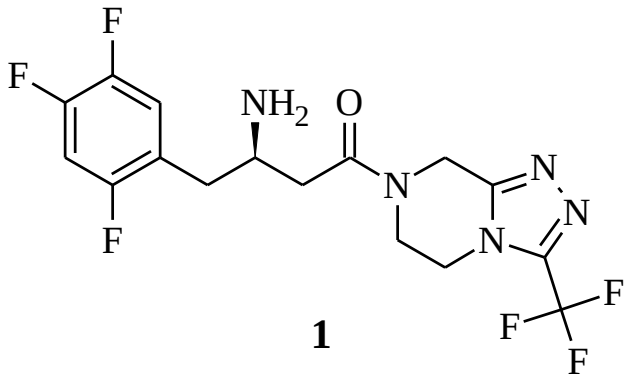
STRUCTURE and ACTIVITY of DRUGS - practical aspects III.

György Domány

Scientific adviser
Gedeon Richter Plc.

OPTIMIZATION OF THE LEAD COMPOUND
Case studies

Sitagliptin (Januvia® - Merck)



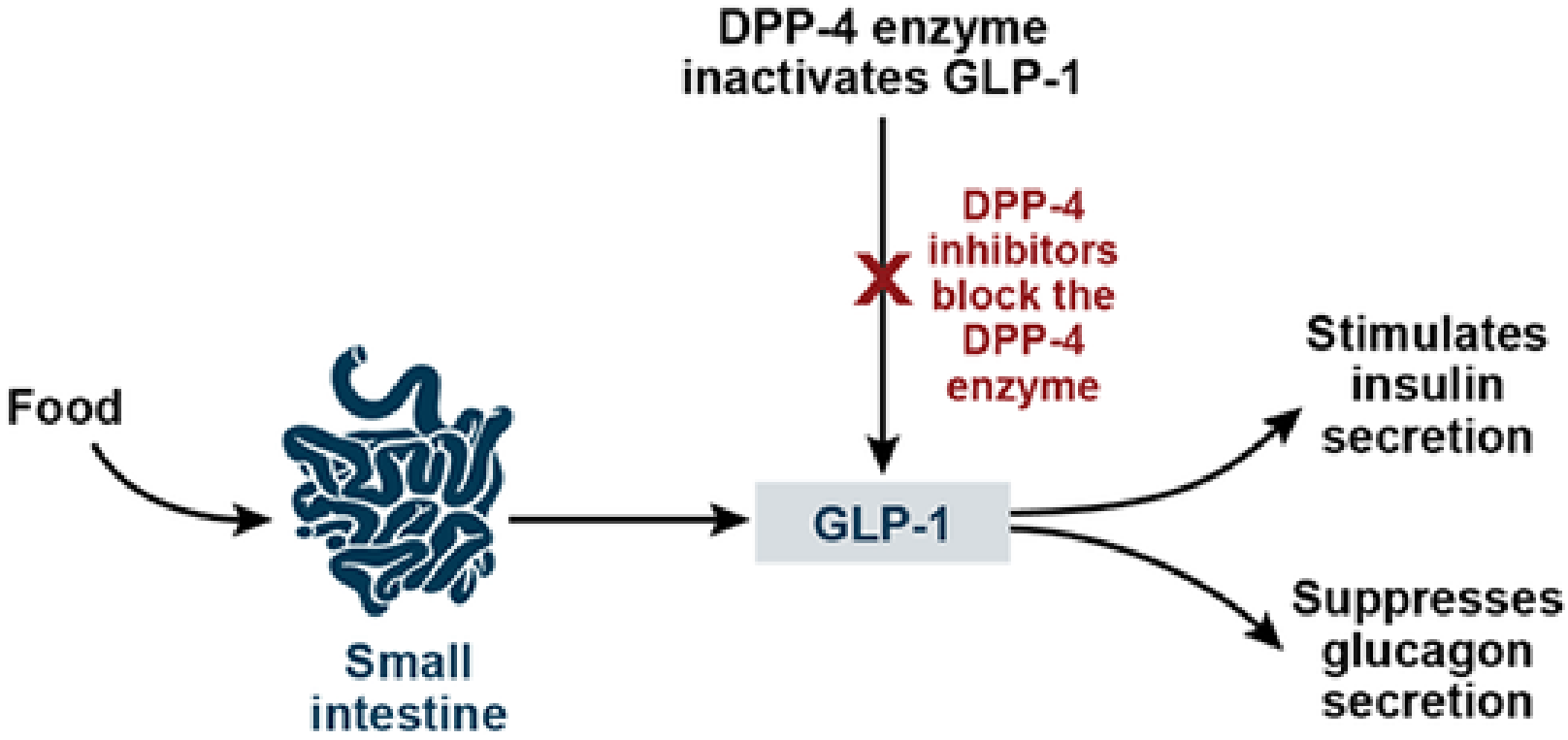
1

Selective dipeptidyl peptidase IV inhibitor for the treatment of type II diabetes

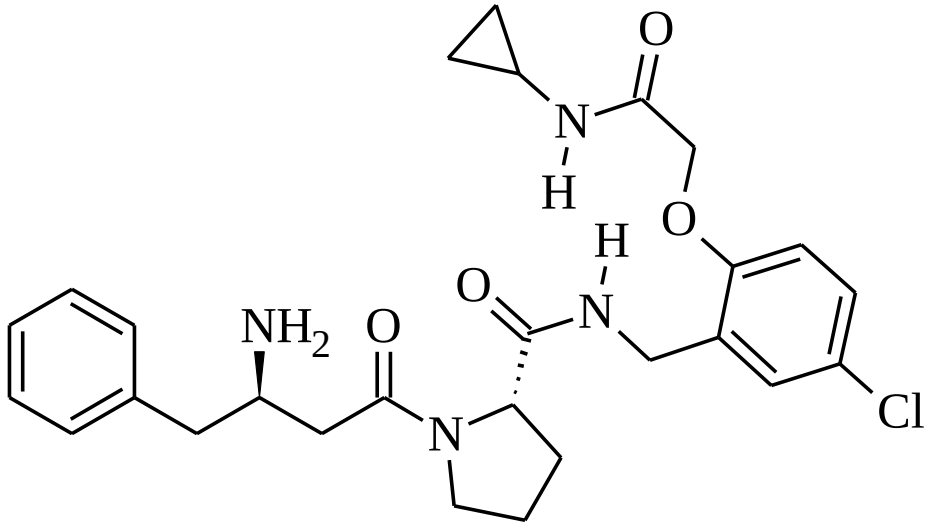
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

DPP-4 Inhibitors

Mechanism of Action

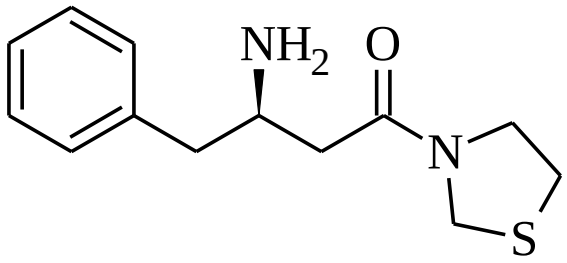


Drucker DJ. *Diabetes Care*. 2007;30:1335-1343.



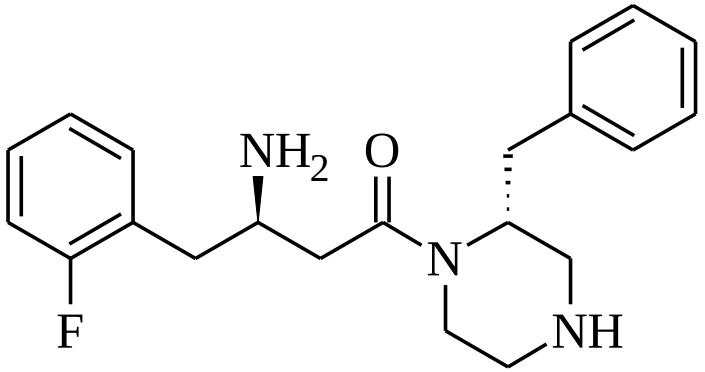
2a

DPP-IV IC_{50}: 1900 nM



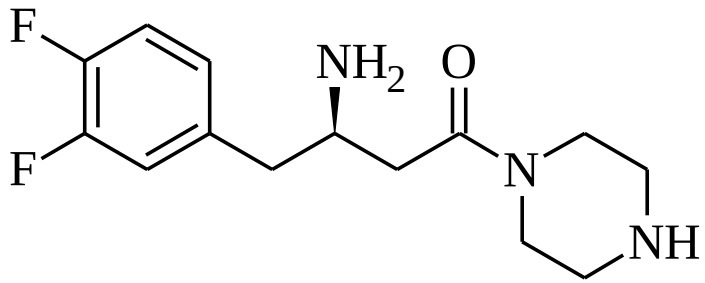
2b

DPP-IV IC_{50}: 3000 nM



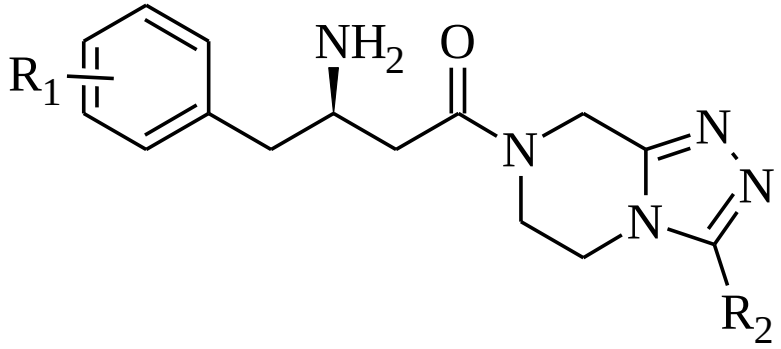
2c

DPP-IV IC_{50}: 139 nM



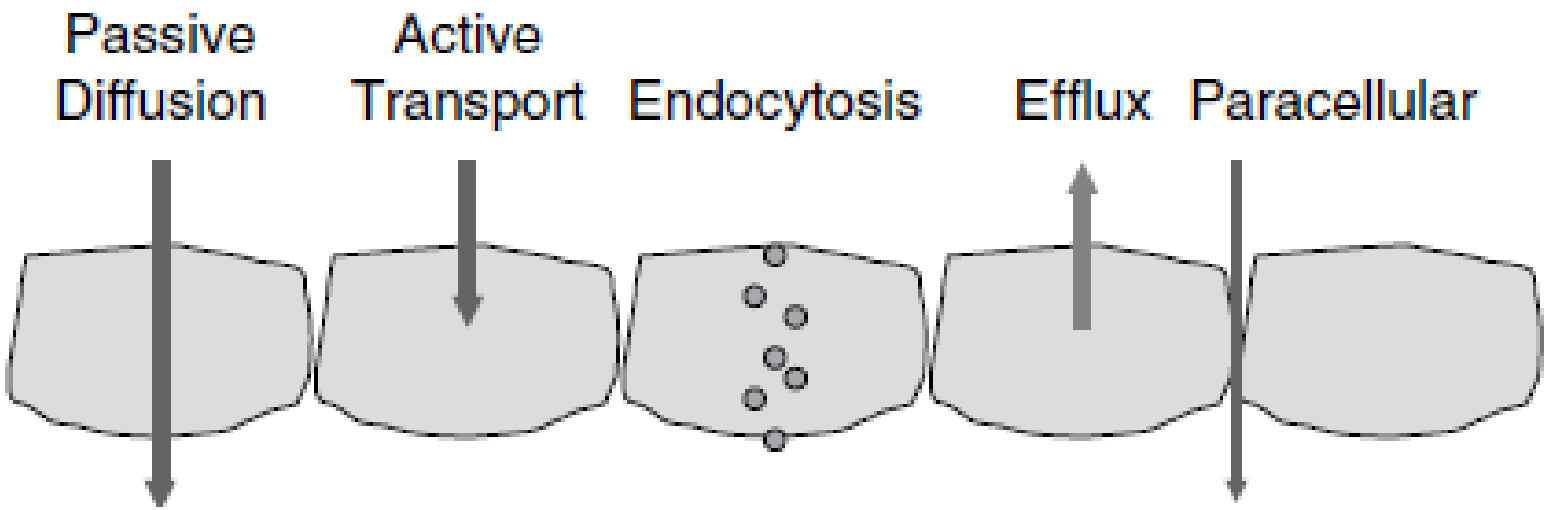
2d

DPP-IV IC_{50}: 3100 nM



	R_1	R_2	DPP-IV IC_{50} (nM)	$T_{1/2}$ (h)	F (%)
3	3,4-di-F	H	455		
4	3,4-di-F	Et	231	2,7	2
5	3,4-di-F	CF_3	128	1,8	44
6	2,5-di-F	CF_3	27	1,6	51
1	2,4,5-tri-F	CF_3	18	1,7	76
7	2,4,5-tri-F	H	68	1,0	3
8	2,4,5-tri-F	CF_2CF_3	71	2,3	61
9	2,5-di-F	CF_2CF_3	103	1,5	1

Intestinal permeability



„It has been estimated that 95% of commercial drugs are predominantly absorbed in the GI tract by passive diffusion."

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

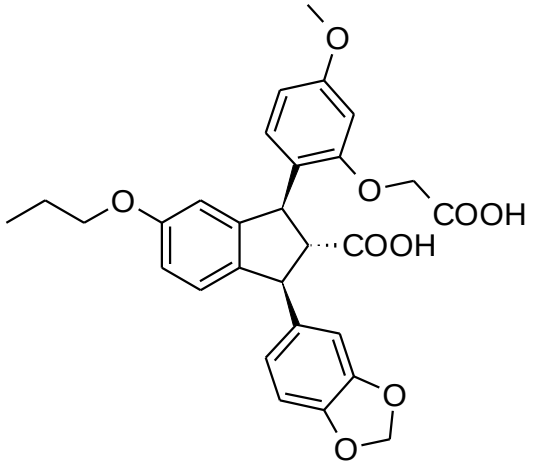
Structure Modification Strategies for Permeability Improvement

Ionizable group to non-ionizable group
Add lipophilicity
Isosteric replacement of polar groups
Esterify carboxylic acid
Reduce hydrogen bonding and polarity
Reduce size
Add nonpolar side chain
Construct prodrug

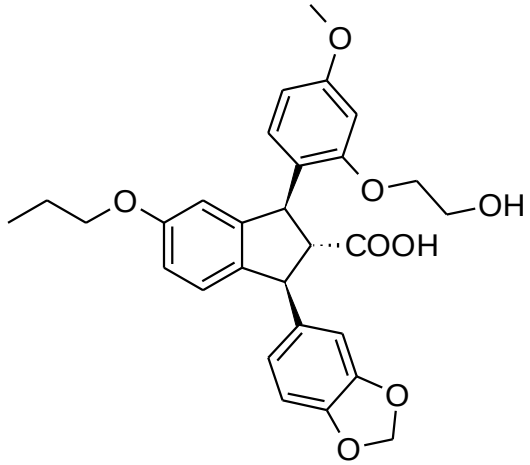
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Permeability

Endothelin recpetor antagonists



ETA Ki: 0.43 nM
Caco-2: 0.0075 cm/h
F(rat): 4 %



ETA Ki: 1.1 nM
Caco-2: 0.2045 cm/h
F(rat): 66 %

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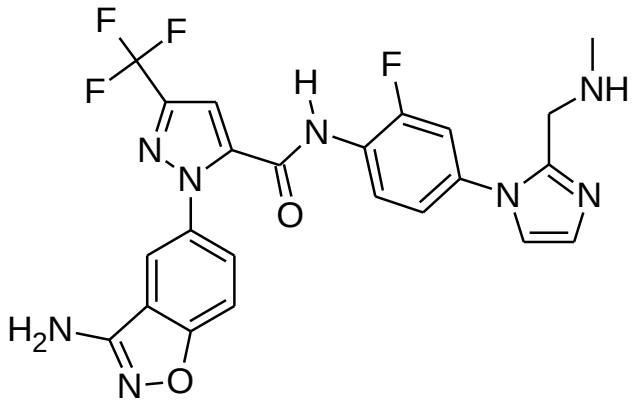
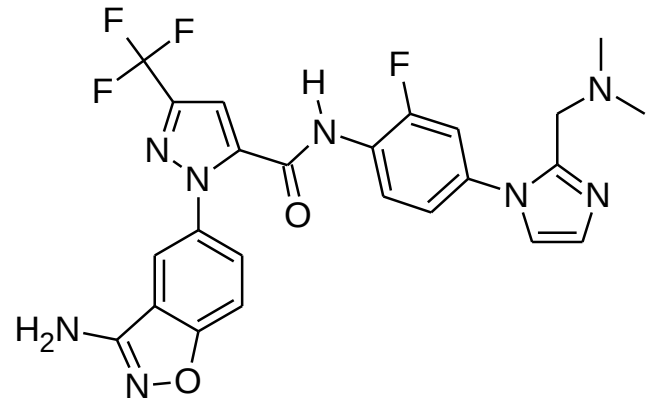
Permeability

Factor Xa inhibitors



FXa Ki: 0.12 nM
Caco-2 Papp: 0.2×10^{-6} cm/s
F(rat): 24%

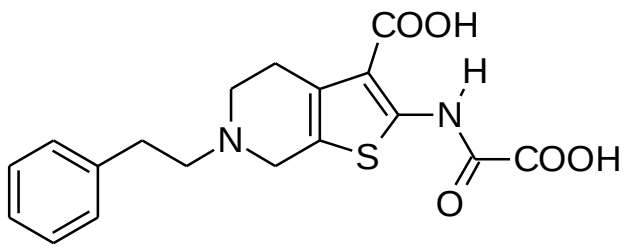


FXa Ki: 0.19 nM
Caco-2 Papp: 5.6×10^{-6} cm/s
F(rat): 84%

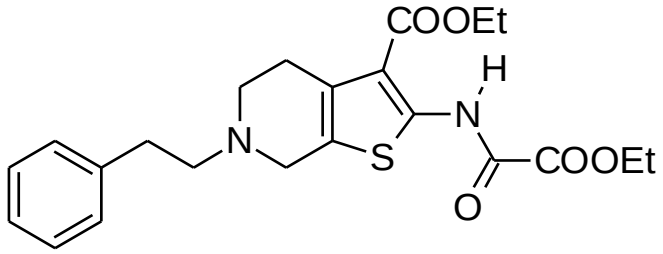
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Permeability

Protein Tyrosin Phosphatase inhibitors



Permeability (MDCK): low
2-DOG uptake in C2C14 cells: inactive

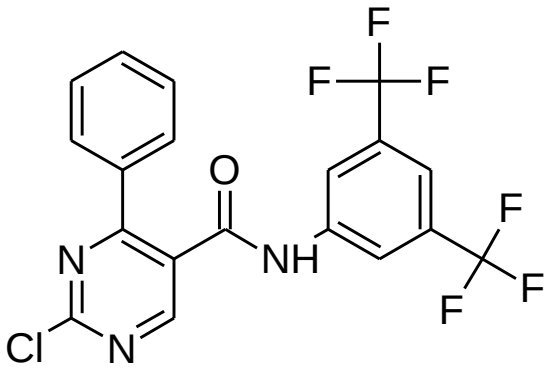


Permeability (MDCK): high
2-DOG uptake in C2C14 cells: 70%

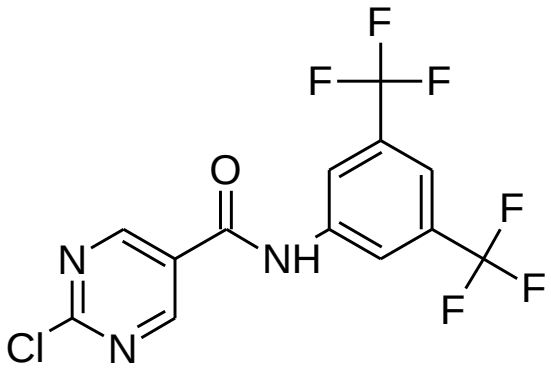
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods*
Academic Press/Elsevier (2008)

Permeability

NF-κB inhibitors



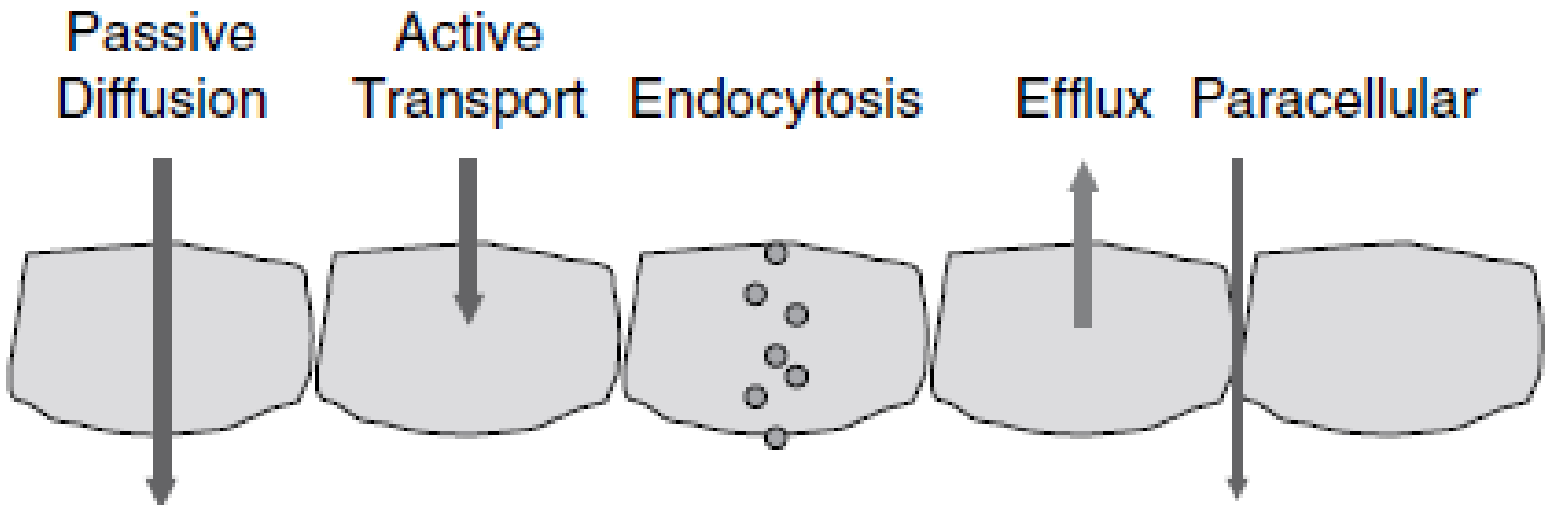
Caco-2 permeability: 9×10^{-7} cm/s



Caco-2 permeability: 61×10^{-7} cm/s

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Efflux transport (P-glycoprotein)



Structure Modification Strategies to Reduce Pgp efflux

„**Passive diffusion is the predominant mechanism** for the permeation of drugs throughout the body." [1]

„There is considerable and increasing evidence that drugs get into cells **more or less solely by hitchhiking on carriers** normally used for the transport of nutrients and intermediary metabolites [1-38]."[2]

„Pgp substrate"	„Pgp non-substrate"
N + O ≥ 8	N + O ≤ 4
MW > 400	MW < 400
Acid with pKa > 4	Base with pKa < 8

[1]Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

[2] Douglas B. Kell et al. *Drug Discovery Today* **16**, 704-714 (2011)

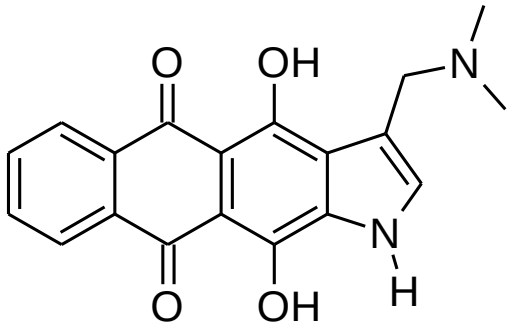
Pgp efflux

Introduce steric hindrance to the H-bond donating atoms by: attach bulky group; methylate the N.
Decrease H-bond acceptor potential by: add an adjacent electron withdrawing group; replace/remove the H-bonding group.
Modify other structural features e.g. add a strong acid.
Modify the overall structures logP to reduce penetration into the lipid bilayer

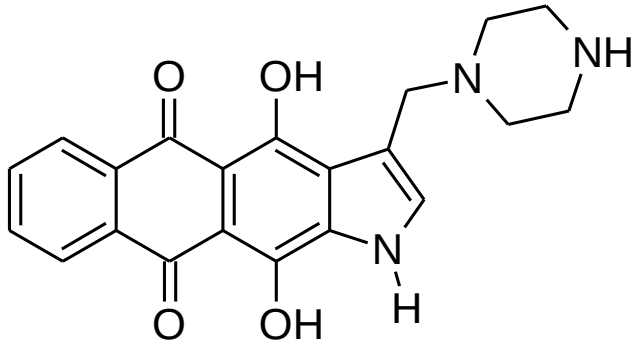
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Pgp efflux

Anticancer



Pgp/non Pgp: 10

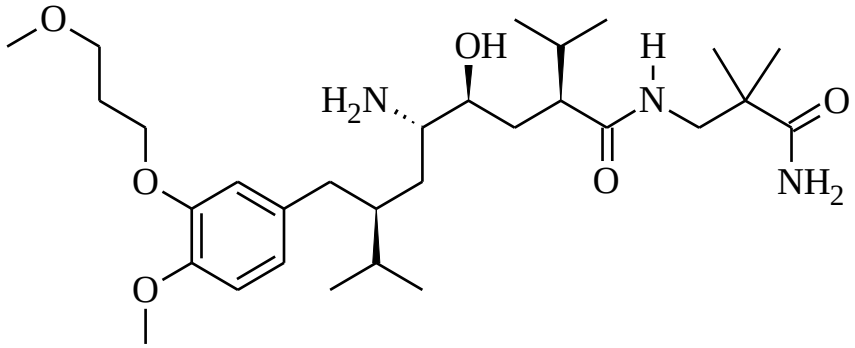


Pgp/non Pgp: 1

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

OPTIMIZATION OF THE LEAD COMPOUND
Case studies

Aliskiren (Tekturna®/Rasilez® - Novartis)

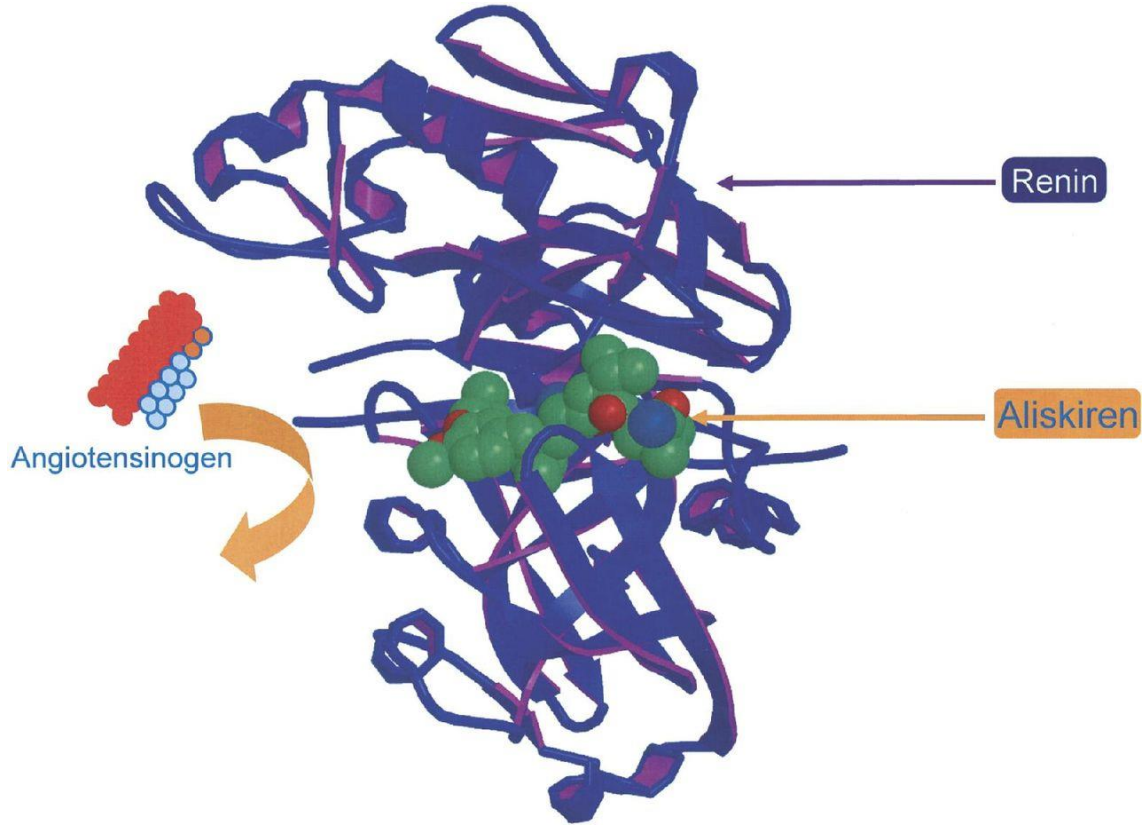


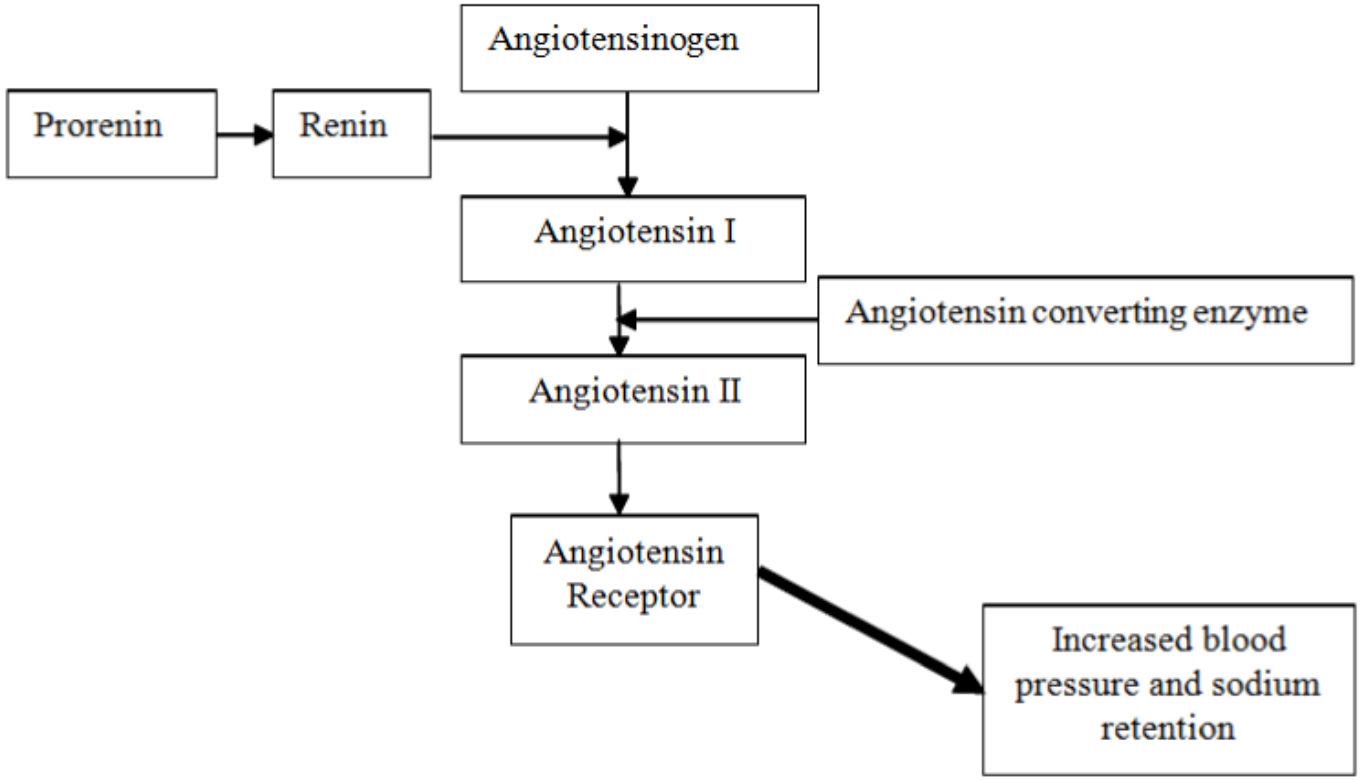
1

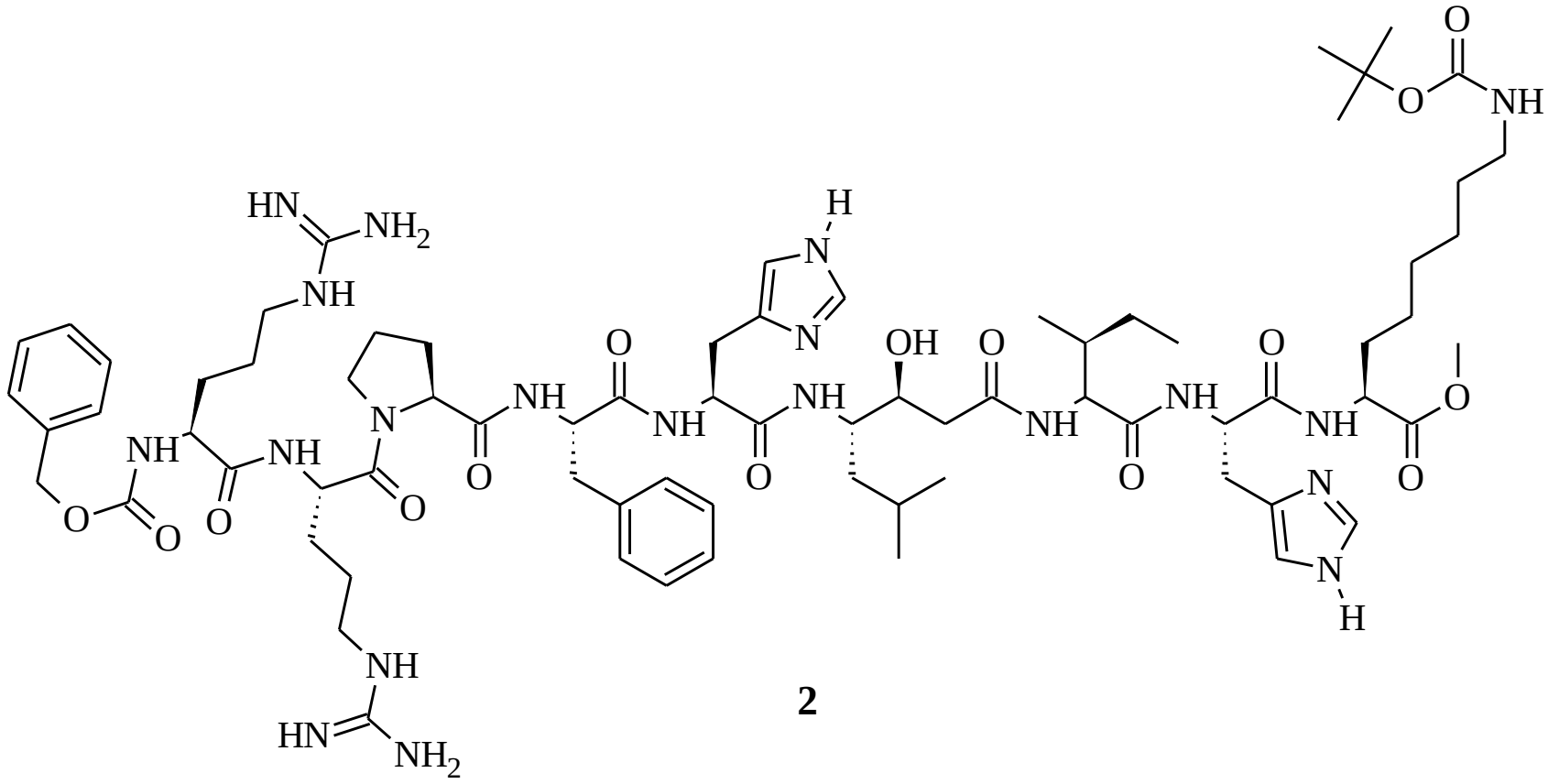
Direct renin inhibitor for the treatment of hypertension

Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

The renin-angiotensin system



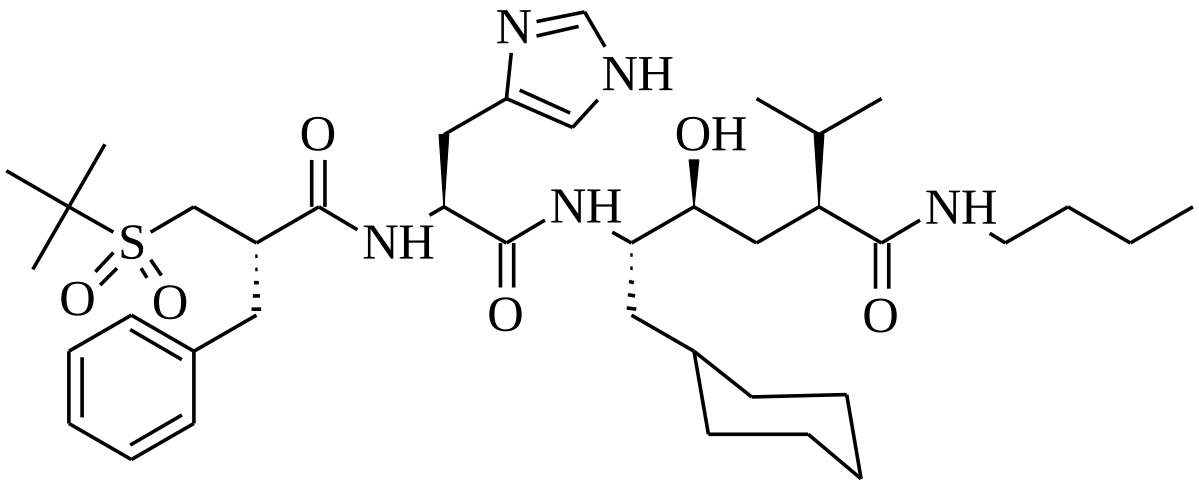




2

CGP29287 - p.o. active in monkeys

Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011



CGP38560 – IC_{50}: 0.7 nM
p.o. active in man, but F: < 1%

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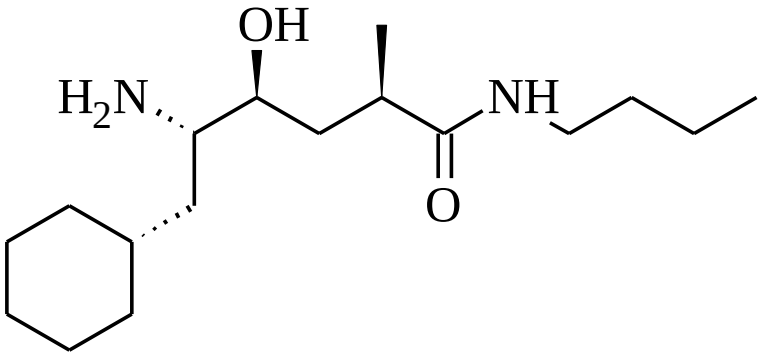
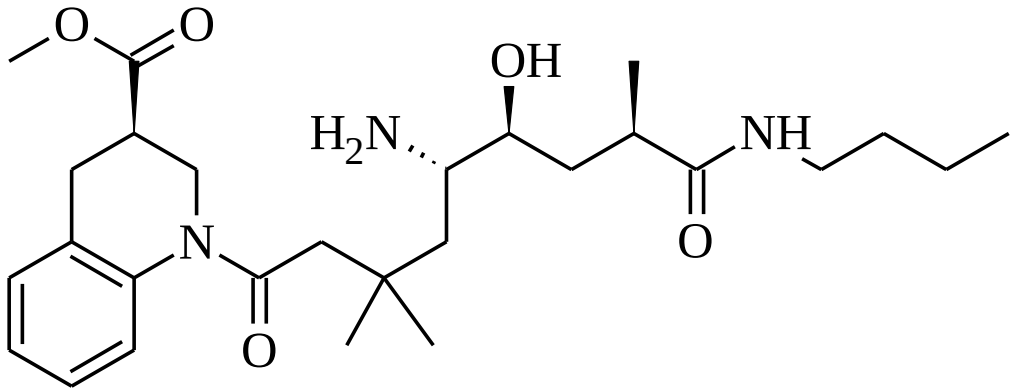


4

IC_{50}: 30 μM



5

IC_{50}: 0.8 nM

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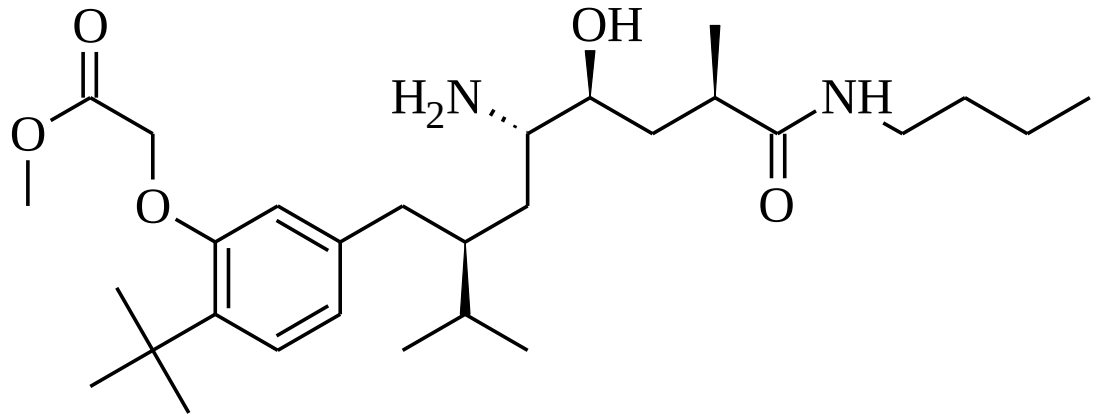

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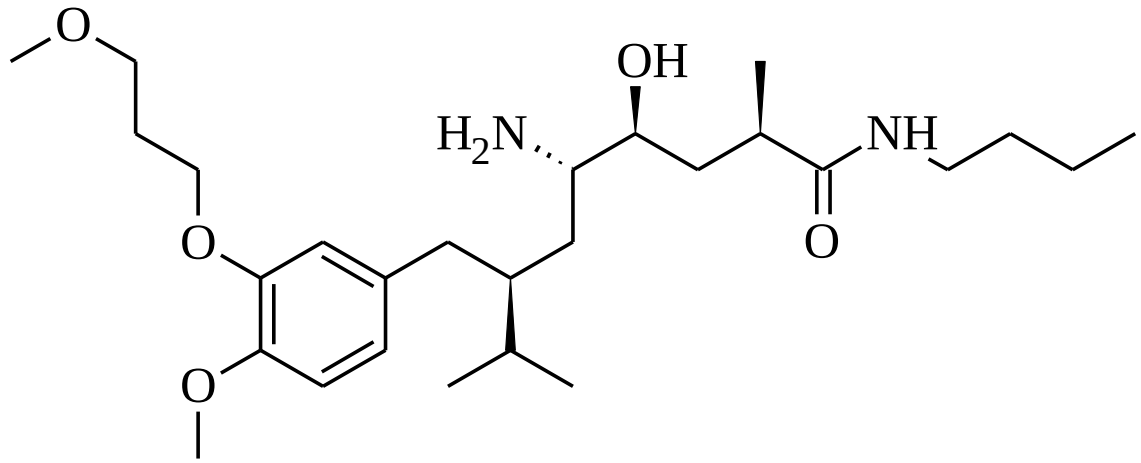

7

IC_{50}: 1 nM

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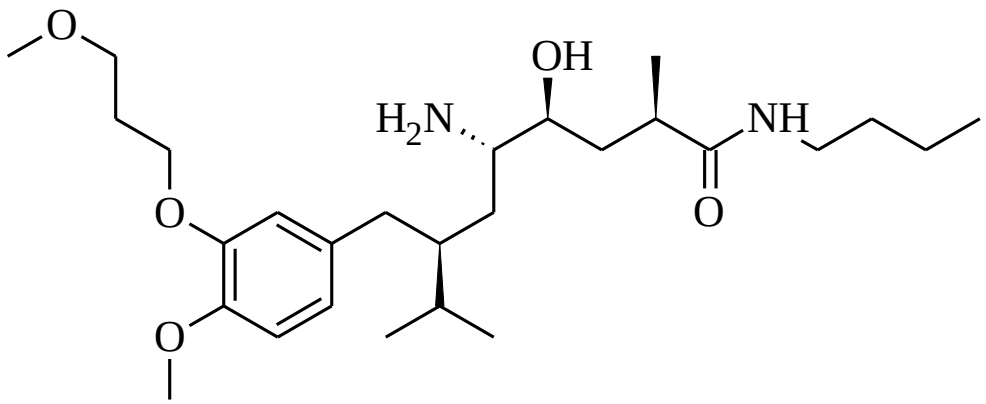
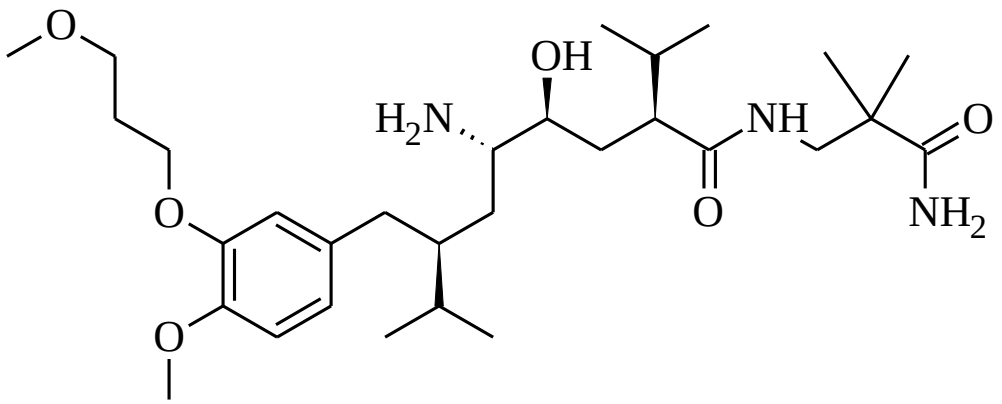


7



1

$T_{1/2}$: 40 h

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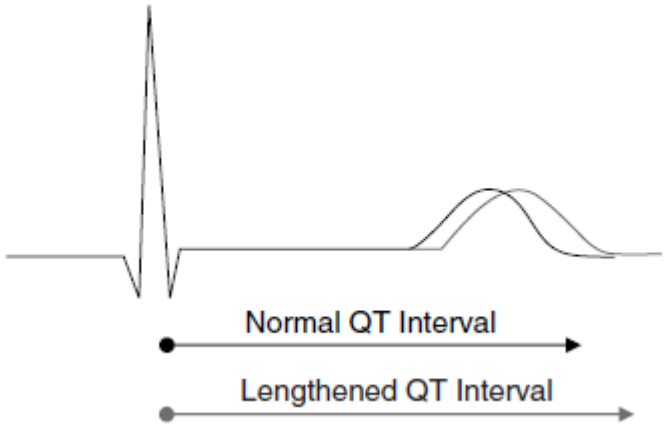
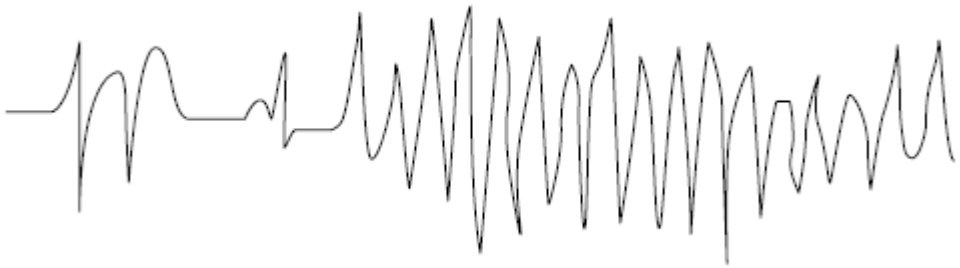
hERG blocking effects

„If a compound binds within the hERG K^+ channel, it can obstruct the flow of K^+ ions out of the cell. This causes a slower outflow of K^+ ions, thus lengthening the time required to repolarize the cell. From the ECG, it can be seen that the T event is delayed, thus lengthening the QT interval (long QT [LQT]). LQT may trigger life-threatening torsades de pointes (TdP) arrhythmia."





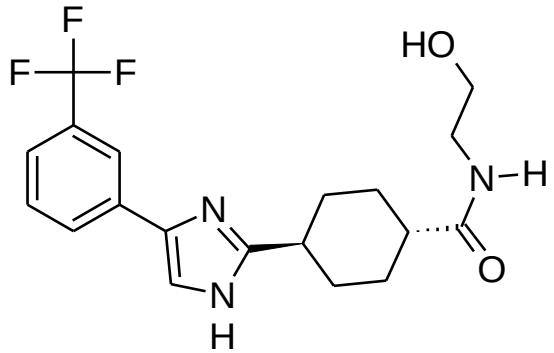
Structure Modification Strategies to Reduce hERG Activity

Reduce the pK_a of the amine
Reduce lipophilicity
Reduce the number of substructures in the binding region
Add acid moiety
Add oxygen H-bond acceptors
Rigidify linkers

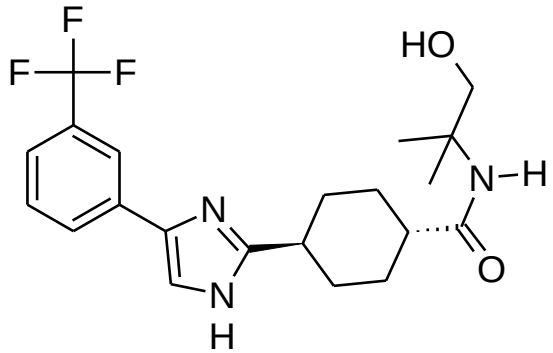
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

hERG activity

Neuropeptide Y5 antagonists



hERG: 87% @ 3μM
IC_{50}: 11 nM
clogP: 2,65
pK_a: 5,66



hERG: 6% @ 3μM
IC_{50}: 2,8 nM
clogP: 3,36
pK_a: 5,67

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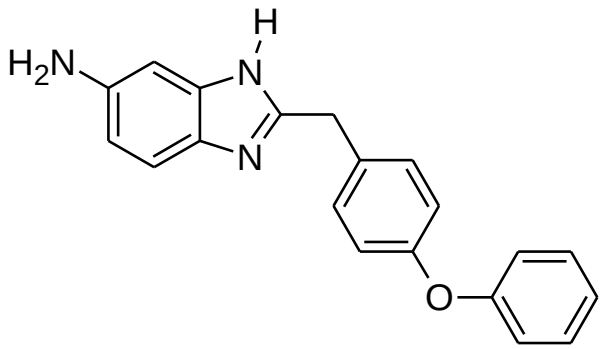
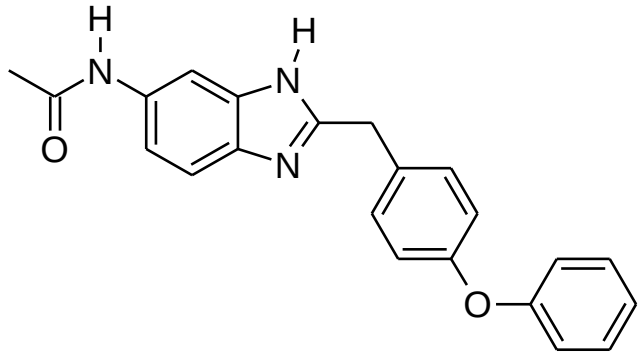
hERG activity

NR2B selective NMDA antagonists



hERG-IC_{50}: 0,12 μM
IC_{50}: 180 nM
clogP: 4,95
pK_a: 6,79



hERG-IC_{50}: 2,6 μM
IC_{50}: 93 nM
clogP: 5,14
pK_a: 5,49

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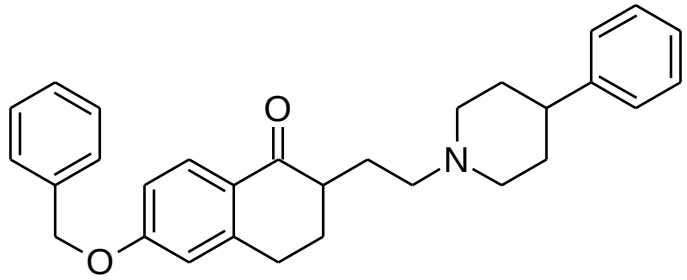
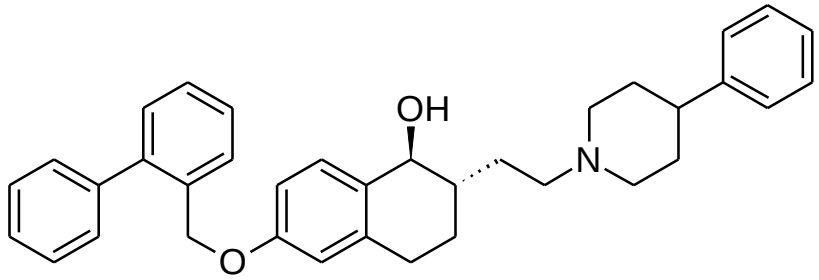
hERG activity

I_{Ks} potassium channel antagonists



hERG-IC_{50}: 0,17 μM
főhatás-IC_{50}: 69 nM
clogP: 7,06
pK_a: 9,14



hERG-IC_{50}: 1,5 μM
főhatás-IC_{50}: 37 nM
clogP: 7,97
pK_a: 9,34

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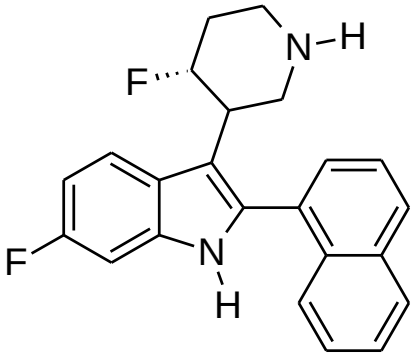
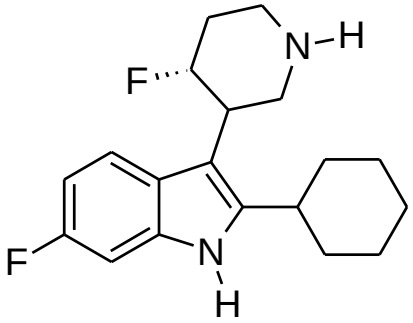
hERG activity

$5HT_{2A}$ receptor antagonists



hERG-IC_{50}: 0,11 μM
IC_{50}: 0,34 nM
clogP: 5,46
pK_a: 9,00



hERG-IC_{50}: 5,4 μM
IC_{50}: 0,25 nM
clogP: 5,06
pK_a: 9,11

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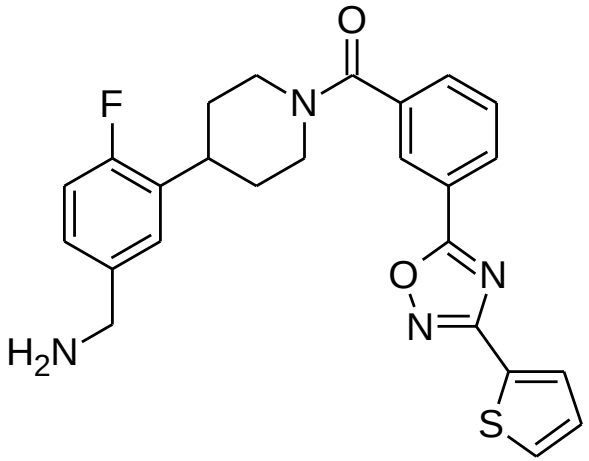
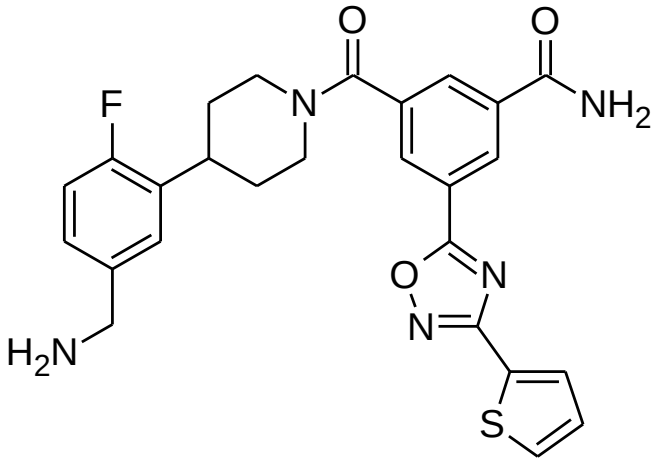
hERG activity

β-triptase inhibitors



hERG-IC_{50}: 0,8 μM
IC_{50}: 4,3 nM
clogP: 3,82

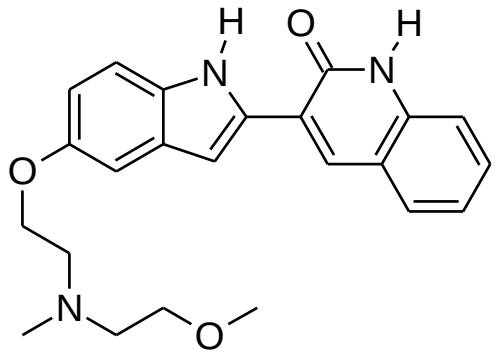


hERG-IC_{50}: 17,1 μM
IC_{50}: 1,3 nM
clogP: 2,73

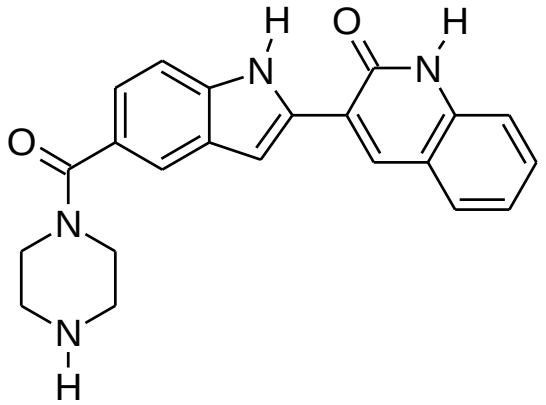
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

hERG activity

VEGFR-2 tirosine kinase inhibitors



hERG-IC_{50}: 1,9 μM
IC_{50}: 7 nM
clogP: 3,47
pK_a: 7,86

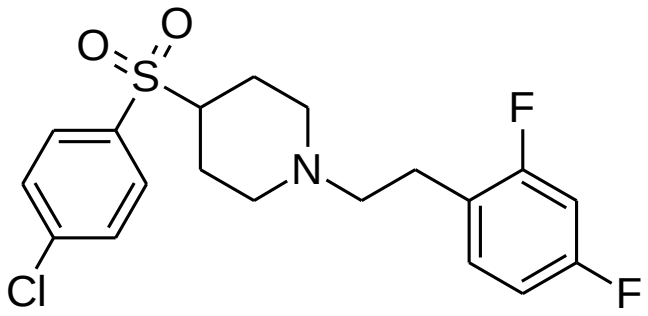


hERG-IC_{50}: >10 μM
IC_{50}: 5 nM
clogP: 2,06
pK_a: 7,71

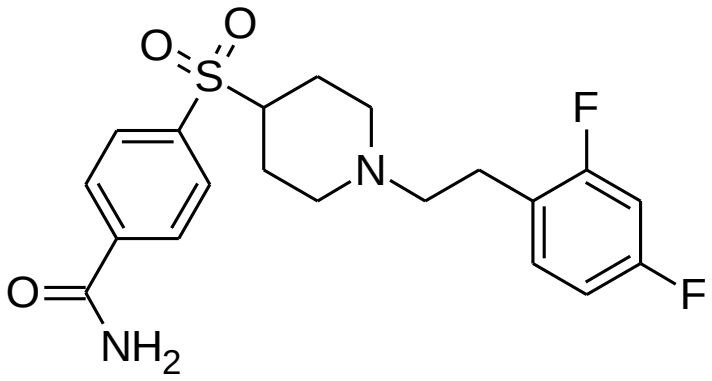
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

hERG activity

$5HT_{2A}$ receptor antagonists



hERG-IC_{50}: 0,15 μM
IC_{50}: 1,4 nM
clogP: 3,78
pK_a: 7,38

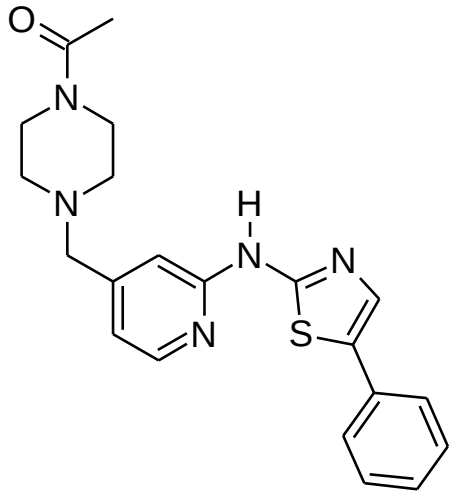


hERG-IC_{50}: 7,1 μM
IC_{50}: 0,52 nM
clogP: 1,85
pK_a: 7,33

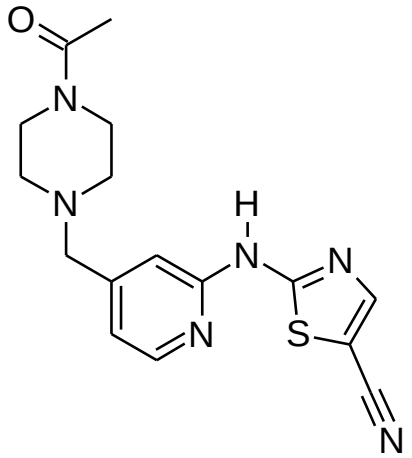
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

hERG activity

VEGFR-2 tirosine kinase inhibitors



hERG-IC_{50}: 0,24 μM
IC_{50}: 8 nM
clogP: 3,23
pK_a: 4,80

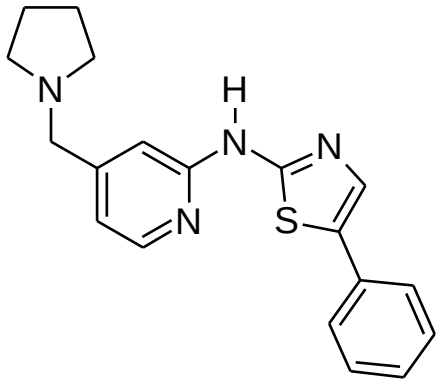


hERG-IC_{50}: 10,6 μM
IC_{50}: 13 nM
clogP: 0,66
pK_a: 4,40

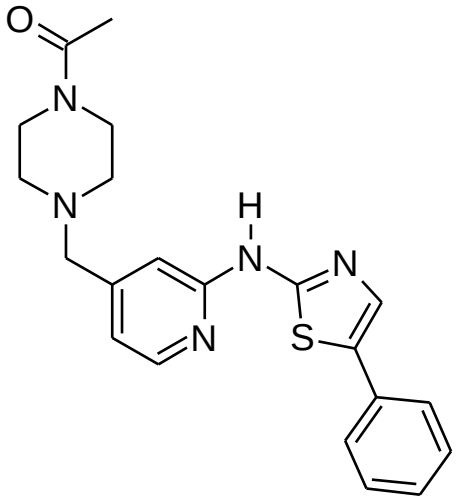
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

hERG activity

VEGFR-2 tirosine kinase inhibitors



hERG-IC_{50}: 0,022 μM
főhatás-IC_{50}: 3 nM
clogP: 4,37
pK_a: 8,87

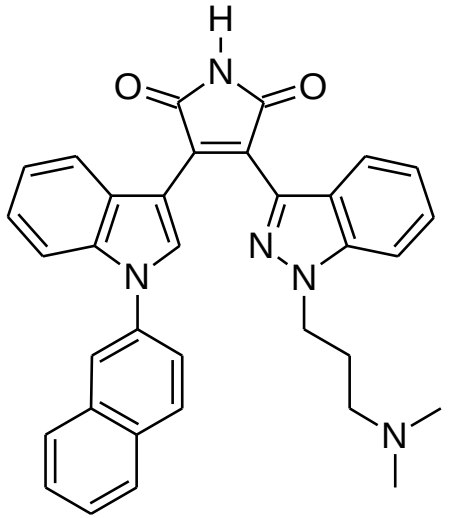


hERG-IC_{50}: 0,24 μM
főhatás-IC_{50}: 8 nM
clogP: 3,23
pK_a: 4,80

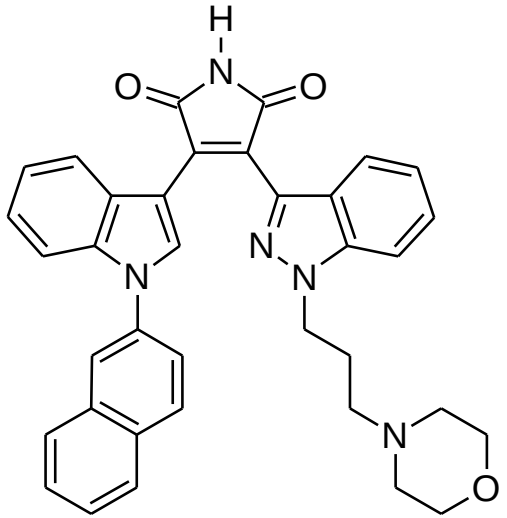
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

hERG activity

Protein kinase C-β inhibitors



hERG-IC_{50}: 0,025 μM
IC_{50}: 5 nM
clogP: 6,61
pK_a: 9,41

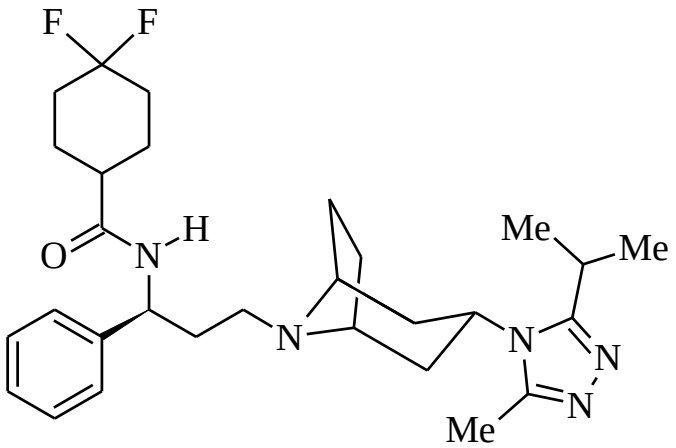


hERG-IC_{50}: 0,85 μM
IC_{50}: 18 nM
clogP: 6,54
pK_a: 7,45

Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

OPTIMIZATION OF THE LEAD COMPOUND
Case studies

Maraviroc (Selzentry®/Celsentri® - Pfizer)

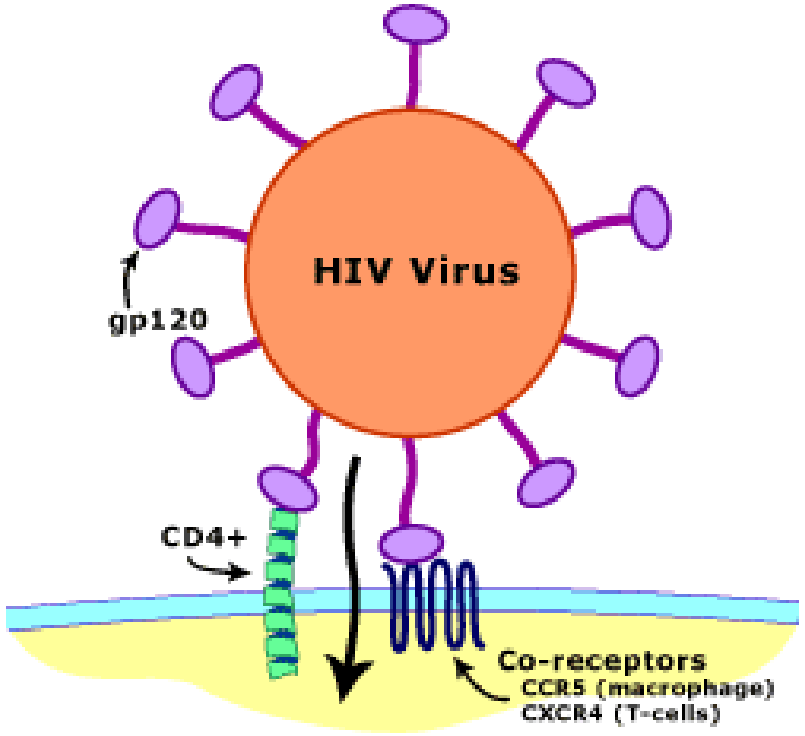


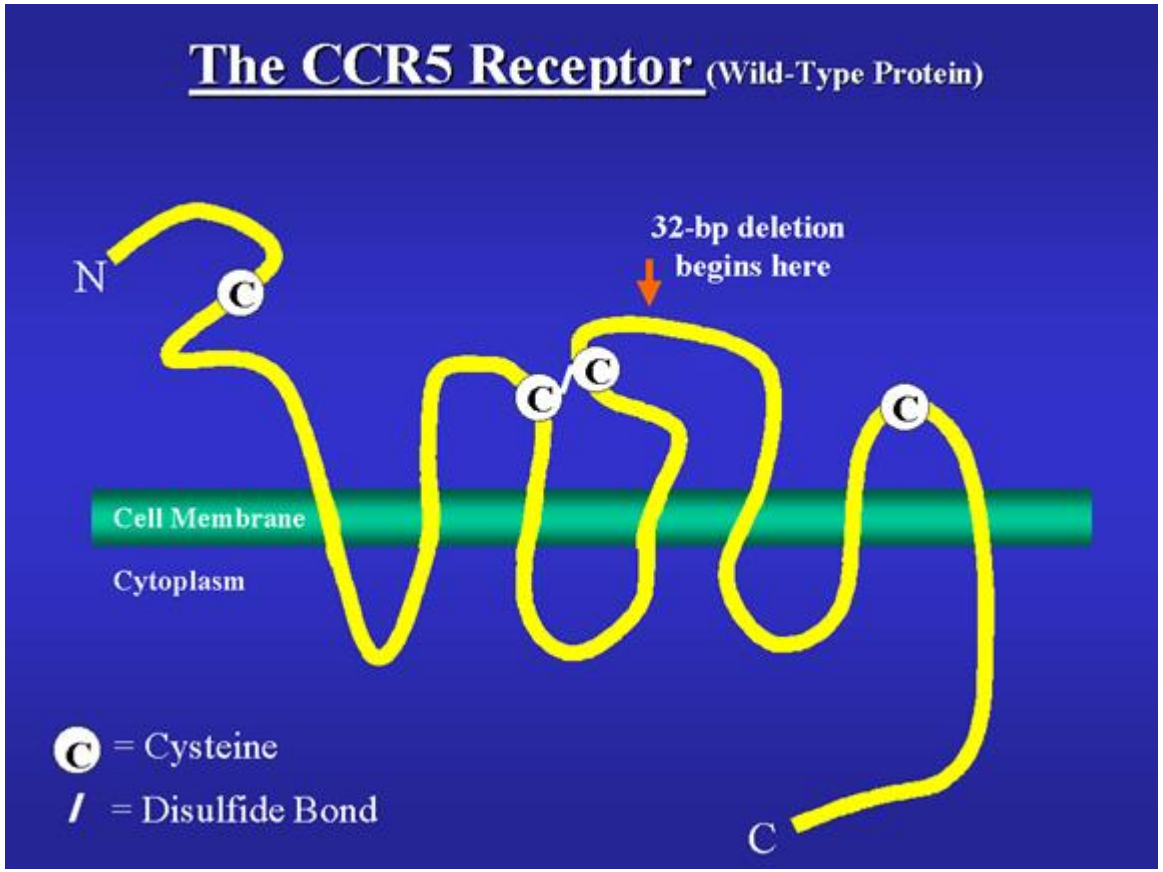
1

CCR5 receptor antagonist for the treatment of HIV infection and AIDS

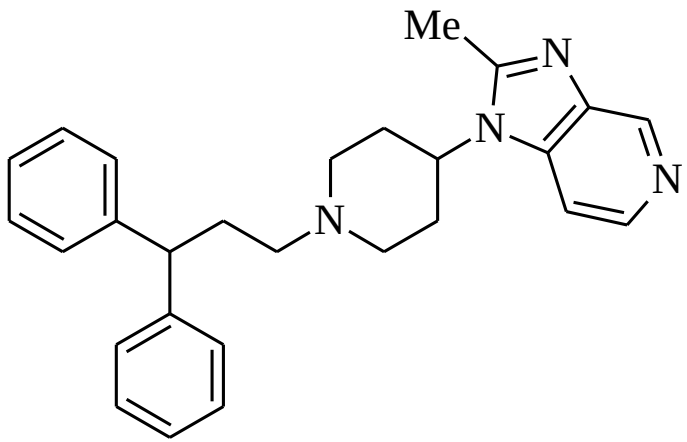
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

HIV virus and the CCR5 receptor



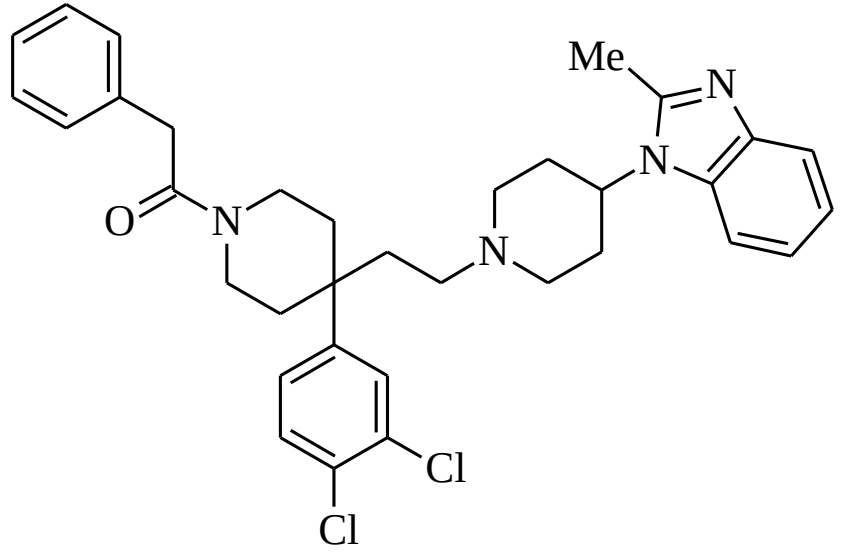


HTS hits



2

MIP-1β IC_{50}: 0.4 μM

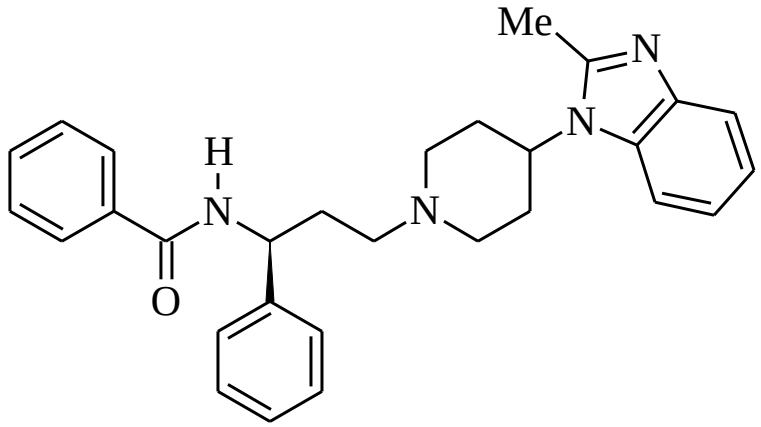


3

MIP-1β IC_{50}: 1.1 μM

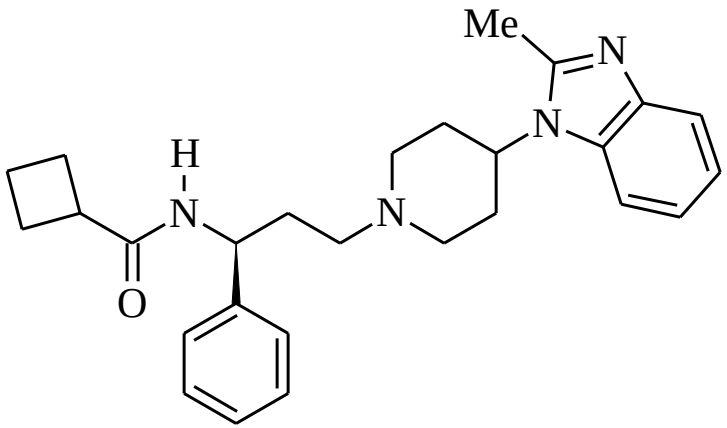
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Hit-to-lead (H2L)



4

MIP-1β IC_{50}: 13 nM
AV IC_{50}: 190 nM

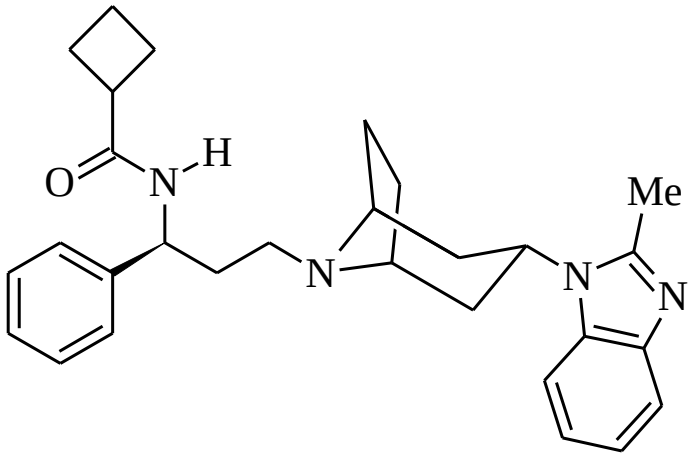


5

MIP-1β IC_{50}: 20 nM
AV IC_{50}: 73 nM

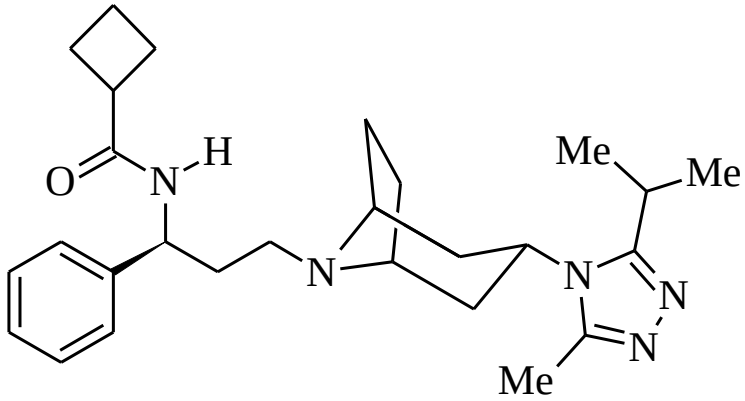
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Lead optimization (965 compounds in 2.5 years)



6

MIP-1β IC_{50}: 2 nM
AV IC_{50}: 13 nM
hERG: 80%@300 nM

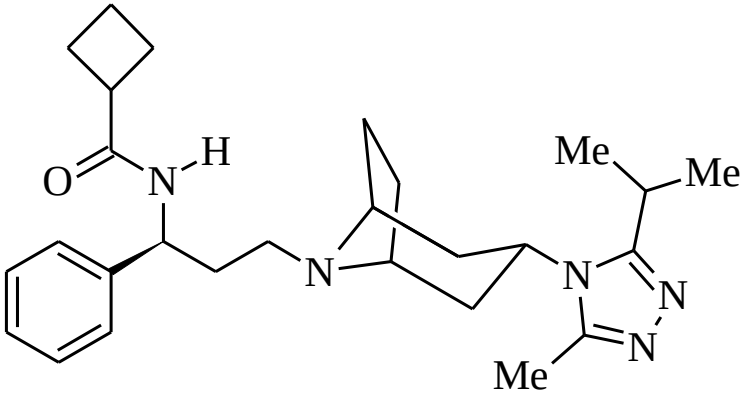


7

AV IC_{50}: 8 nM
hERG: 30%@300 nM

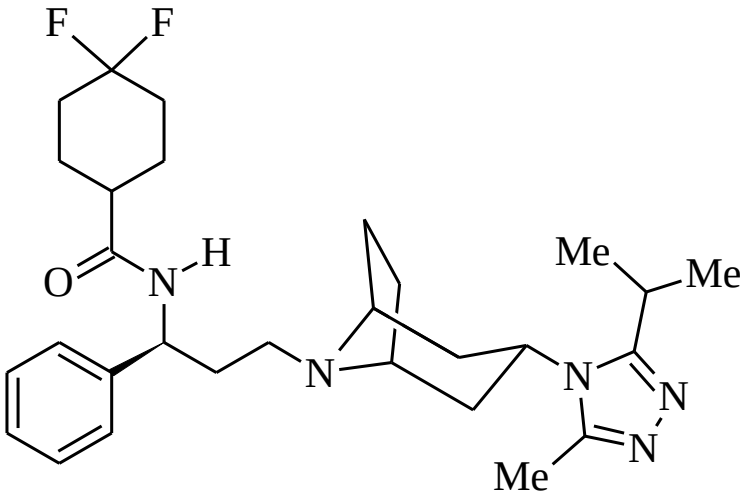
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

The clinical candidate



7

AV IC_{50}: 8 nM
hERG: 30%@300 nM



1

MIP-1β IC_{50}: 2 nM
AV IC_{50}: 1 nM
hERG: 0%@300 nM

Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Drug–drug interactions can occur when two drugs are coadministered and compete for the same enzyme.
In cytochrome P450 (CYP) inhibition, one drug ("perpetrator") binds to the isozyme and the other drug ("victim") is excluded from metabolism, thus increasing to a toxic concentration.

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods*
Academic Press/Elsevier (2008)

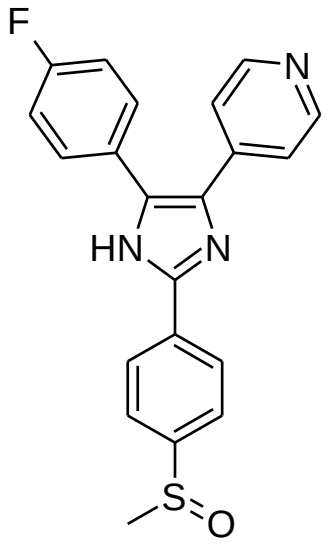
Structure Modification Strategies to Reduce CYP Inhibition

Decrease lipophilicity
Add steric hindrance para to nitrogen
Reduce pK_a of the nitrogen

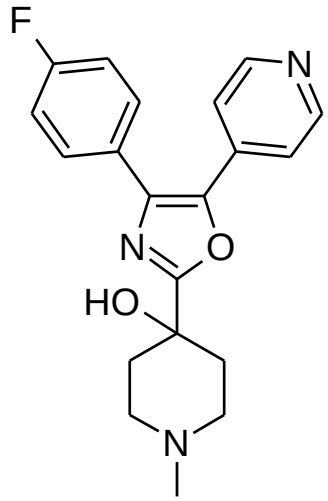
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

CYP interaction

p38 Map kinase inhibitors



p38a IC_{50}: 0.45 μM
COX-1 IC_{50}: 5 μM
3A4 IC_{50}: < 2 μM
2D6 IC_{50}: > 100 μM
2C9 IC_{50}: < 2 μM
1A2 IC_{50}: 4 μM

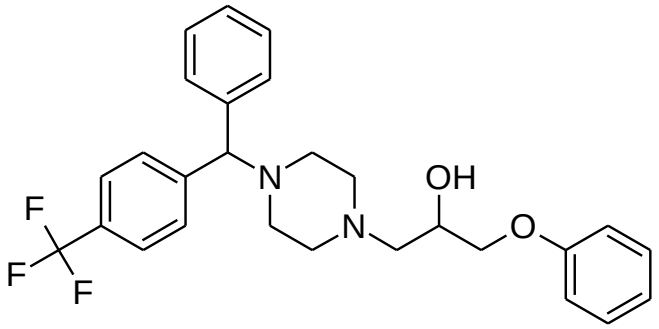


p38a IC_{50}: 0.35 μM
COX-1 IC_{50}: > 100 μM
3A4 IC_{50}: 100 μM
2D6 IC_{50}: 22 μM
2C9 IC_{50}: > 100 μM
1A2 IC_{50}: > 100 μM

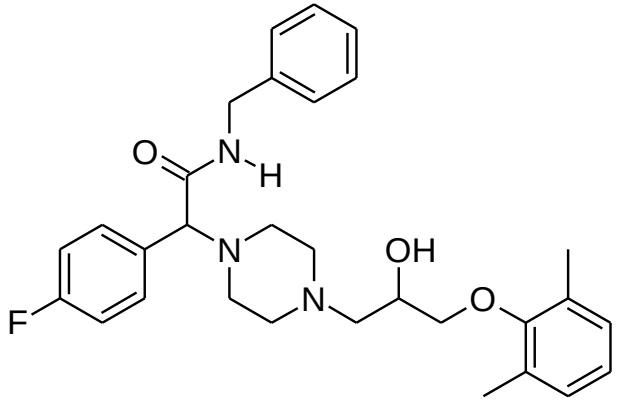
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

CYP interaction

Sodium channel blockers



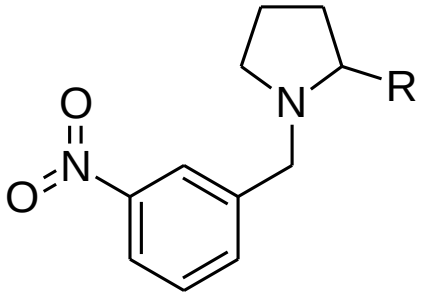
IC_{50}: 893 nM
2D6: 86% @ 2μM



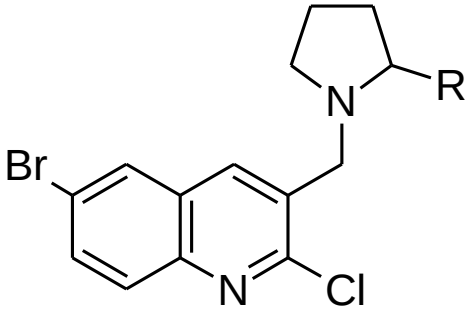
IC_{50}: 149 nM
2D6: 20% @ 2 μM

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

CYP interaction



GPCR IC_{50}: 0,33 μM
2D6 IC_{50}: < 0.05 μM



GPCR IC_{50}: 0,19 μM
2D6 IC_{50}: 22 μM

Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Drug-induced phospholipidosis is characterized by intracellular accumulation of phospholipids with lamellar bodies, most likely from an impaired phospholipid metabolism of the lysosome. Organs affected by phospholipidosis exhibit inflammatory reactions and histopathological changes. Despite significant advances in the understanding of drug-altered lipid metabolism, the relationship between impaired phospholipid metabolism and drug-induced toxicity remains enigmatic.

Structure Modification Strategies to Reduce Phospholipidosis Liability

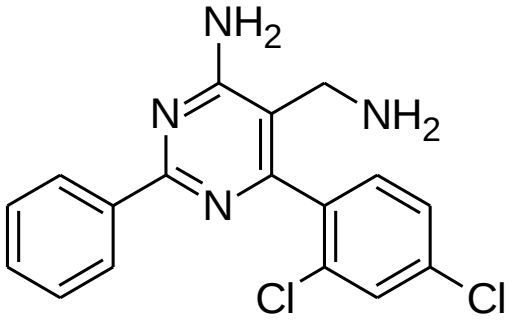
$(clogP)^2 + (cpK_a)^2 < 50$ (providing $pK_a > 6$; $clogP > 2$)

$pK_a < 6$, $clogP < 2$, net charge (NC) < 1

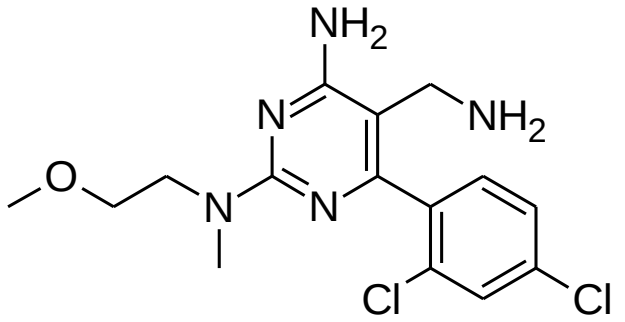
Andrew J. Ratcliffe *Current Medicinal Chemistry* **16**, 2816-2823 (2009)

Phospholipidosis

DPP-IV inhibitors



phospholipidosis at 2.5 μM
in cultured fibroblasts

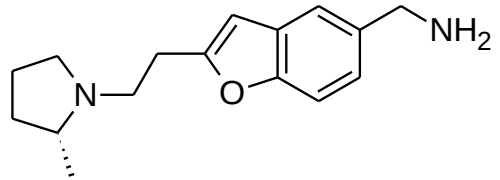


no phospholipidosis at 20 μM

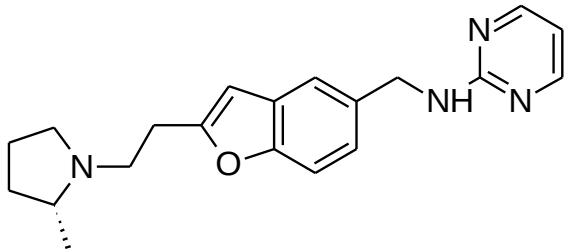
Andrew J. Ratcliffe *Current Medicinal Chemistry* **16**, 2816-2823 (2009)

Phospholipidosis

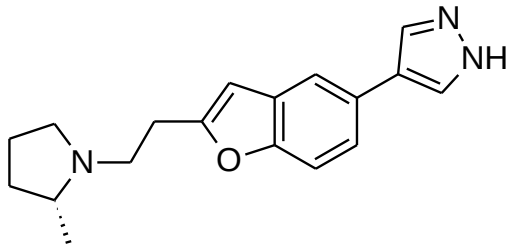
Histamine H3 inverse agonists



Amiodarone index: 1.22
in primary rat hepatocyte culture



Amiodarone index: 0.42

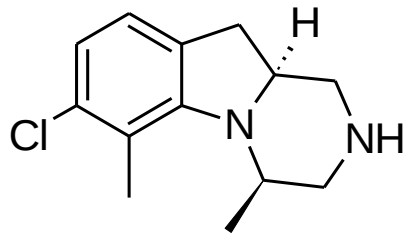


no phospholipidosis at 200 μM

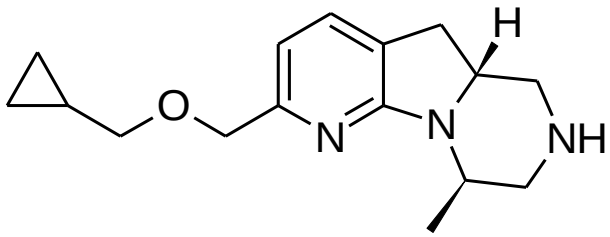
Andrew J. Ratcliffe *Current Medicinal Chemistry* **16**, 2816-2823 (2009)

Phospholipidosis

$5HT_{2C}$ agonists



phospholipidosis at 7.5 μM
in cultured fibroblasts

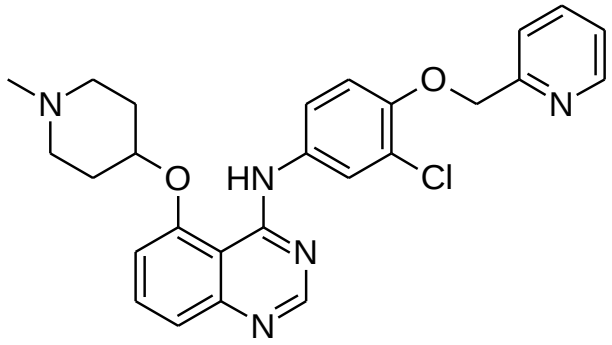


no phospholipidosis at 20 μM

Andrew J. Ratcliffe *Current Medicinal Chemistry* **16**, 2816-2823 (2009)

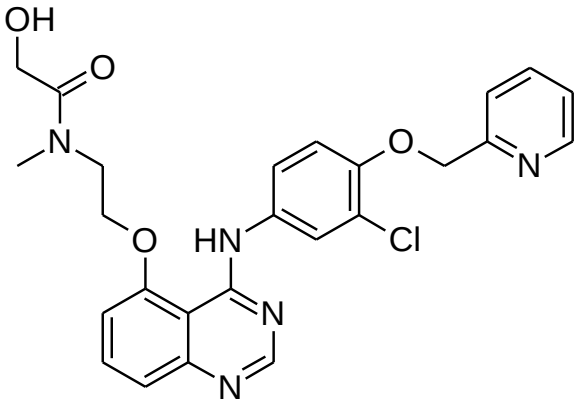
Phospholipidosis

erbB2 receptor tyrosine kinase inhibitors



logD: > 3.5; pK_a: 8.1

in vivo phospholipidosis in rats

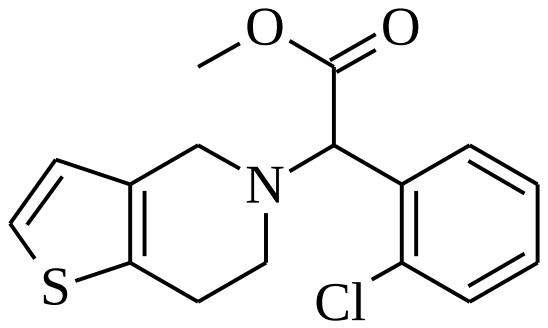


no phospholipidosis in 14 day rat tox. study

Andrew J. Ratcliffe *Current Medicinal Chemistry* **16**, 2816-2823 (2009)

OPTIMIZATION OF THE LEAD COMPOUND
Case studies

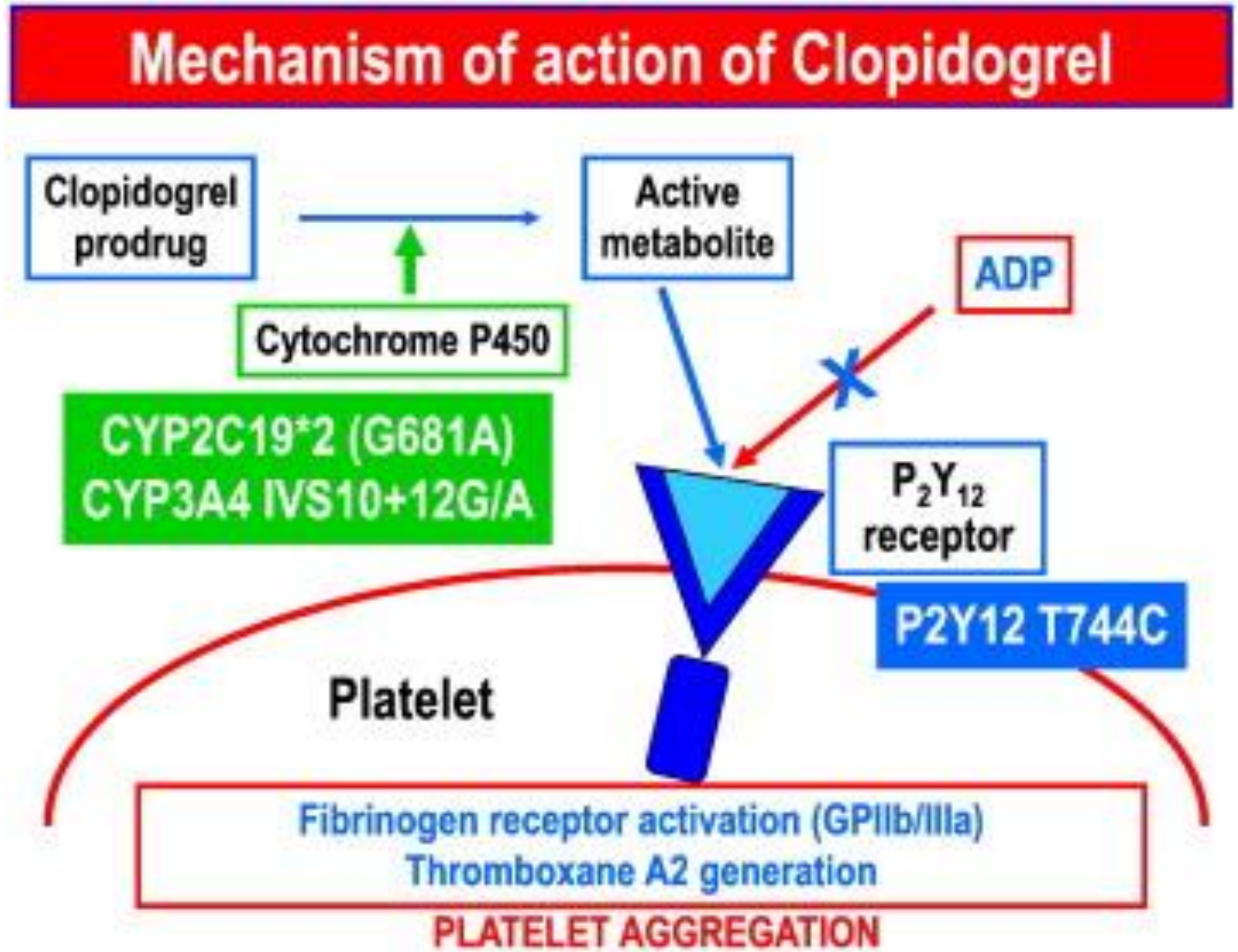
Clopidogrel (Plavix® - Sanofi)

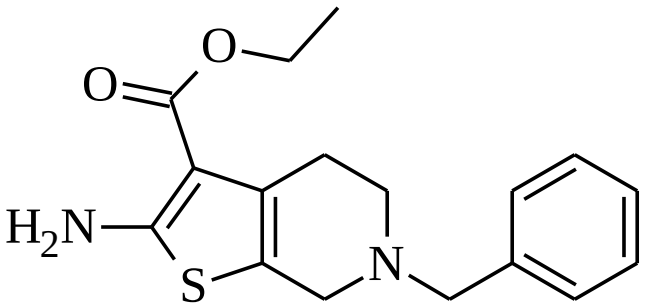


1

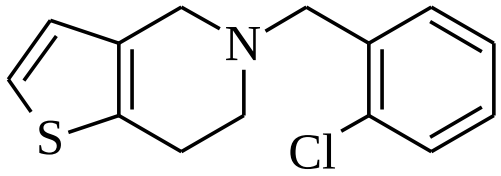
Inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation for the treatment of atherothrombosis

Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

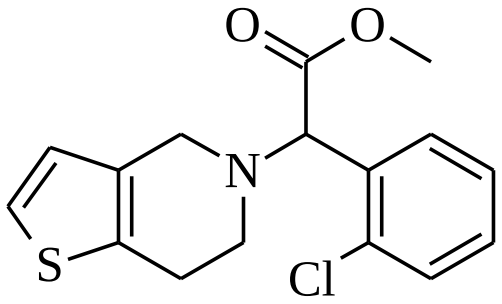

Mechanism of action of Clopidogrel
Clopidogrel prodrug
Active metabolite
ADP
Cytochrome P450
CYP2C19*2 (G681A)
CYP3A4 IVS10+12G/A
P2Y12 receptor
P2Y12 T744C
Platelet
Fibrinogen receptor activation (GPIIb/IIIa)
Thromboxane A2 generation
PLATELET AGGREGATION



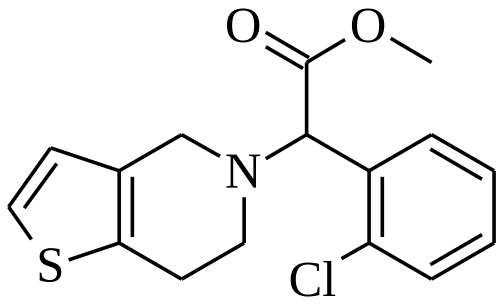
Tinoridine (1970)
gyulladásgátló



Ticlopidine (1972)
gátolja az ADP által kiváltott vérlemezke aggregációt

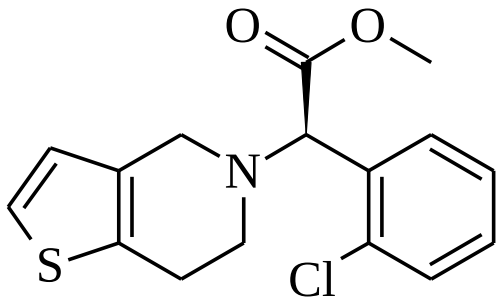


(1980)



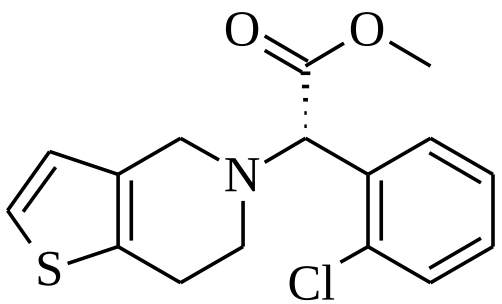
.HCl

solid
development stopped
in 1987



.H_2SO_4

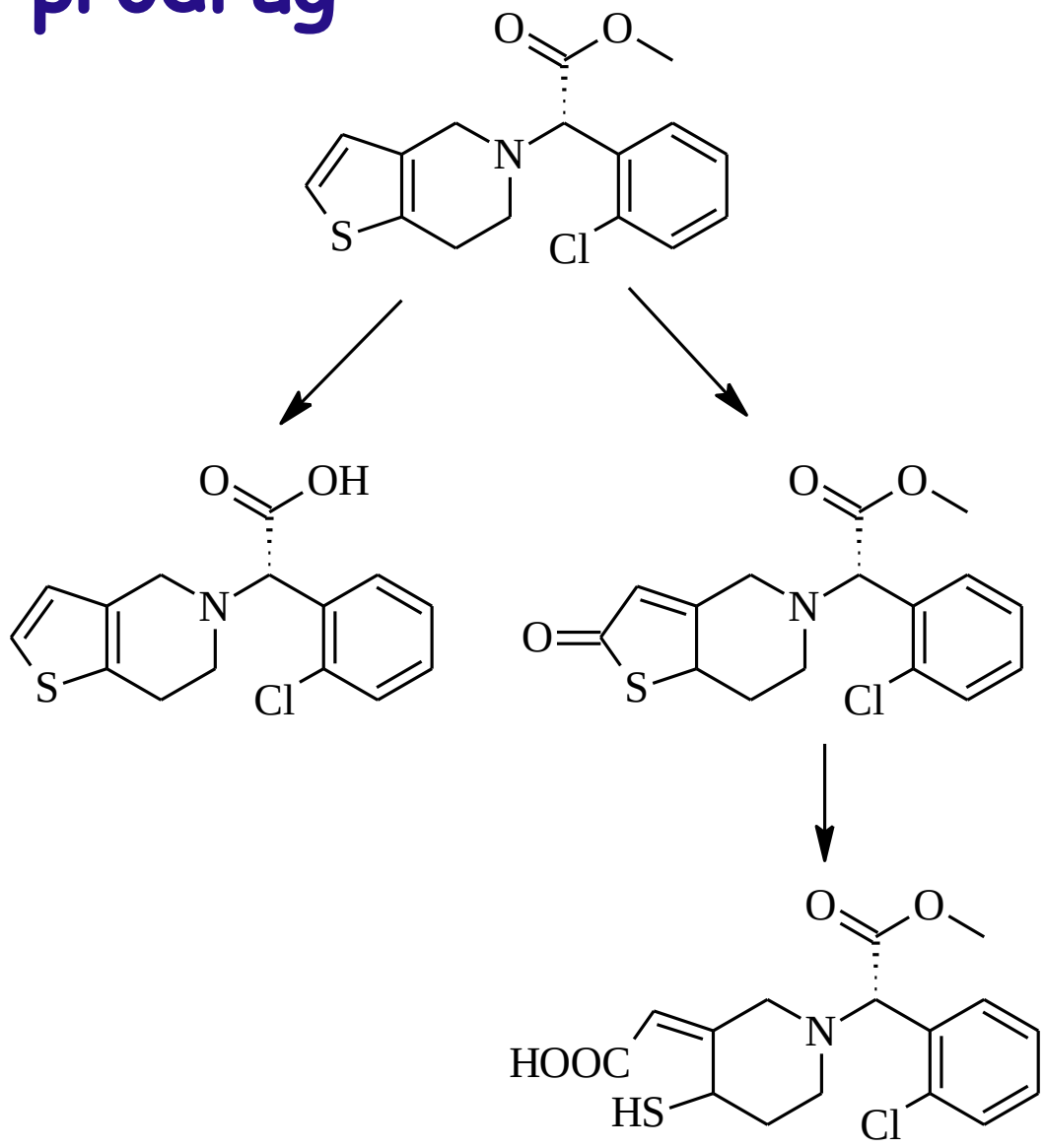
inactive, but toxic



.H_2SO_4

clopidogrel

Clopidogrel - a prodrug



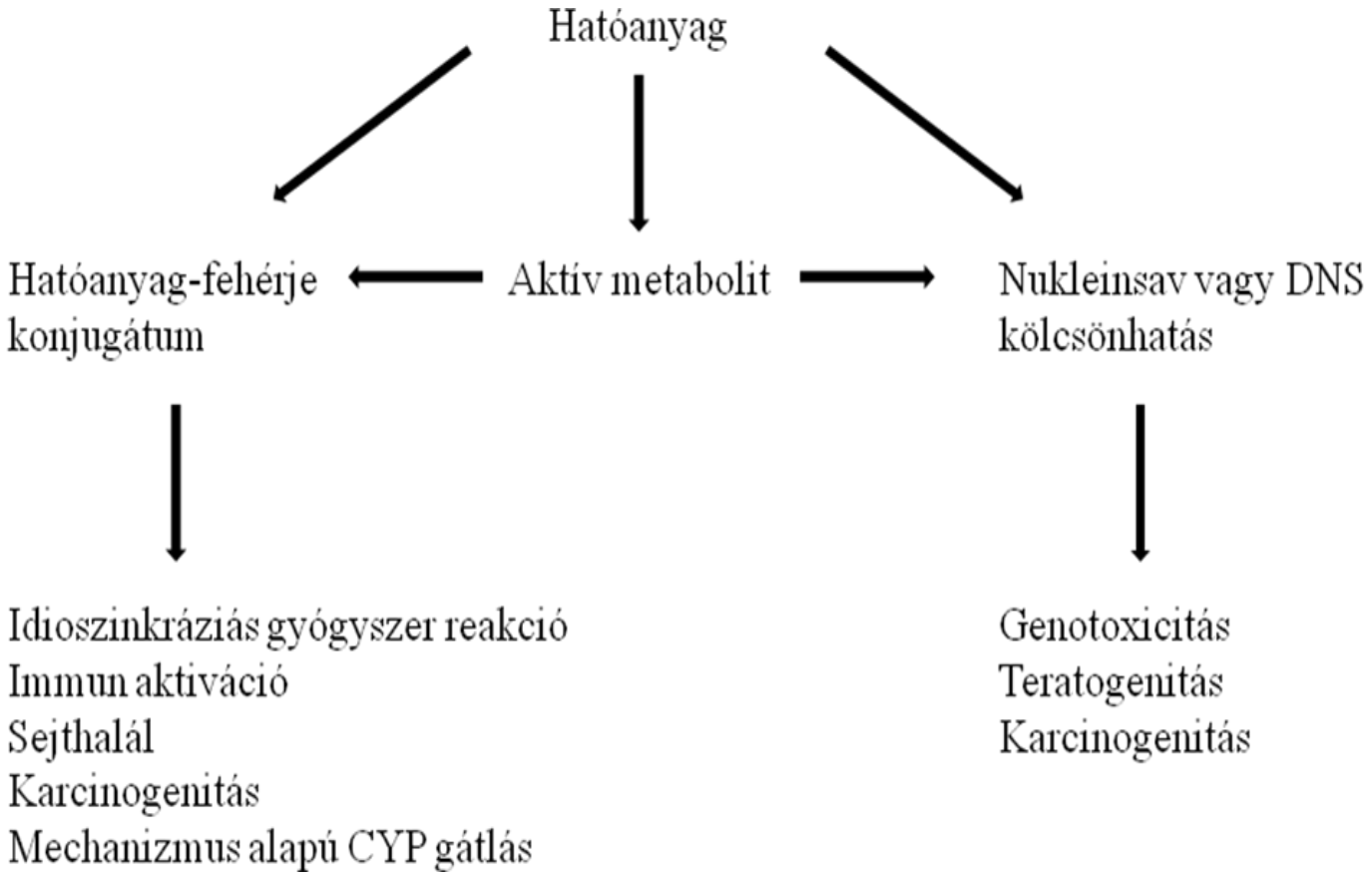
Toxicity

The degree to which a substance (a toxin or poison) can harm humans or animals.
Acute toxicity involves harmful effects in an organism through a single or short-term exposure.
Sub-chronic toxicity is the ability of a toxic substance to cause effects for more than one year but less than the lifetime of the exposed organism.
Chronic toxicity is the ability of a substance or mixture of substances to cause harmful effects over an extended period, usually upon repeated or continuous exposure, sometimes lasting for the entire life of the exposed organism.

Toxicity

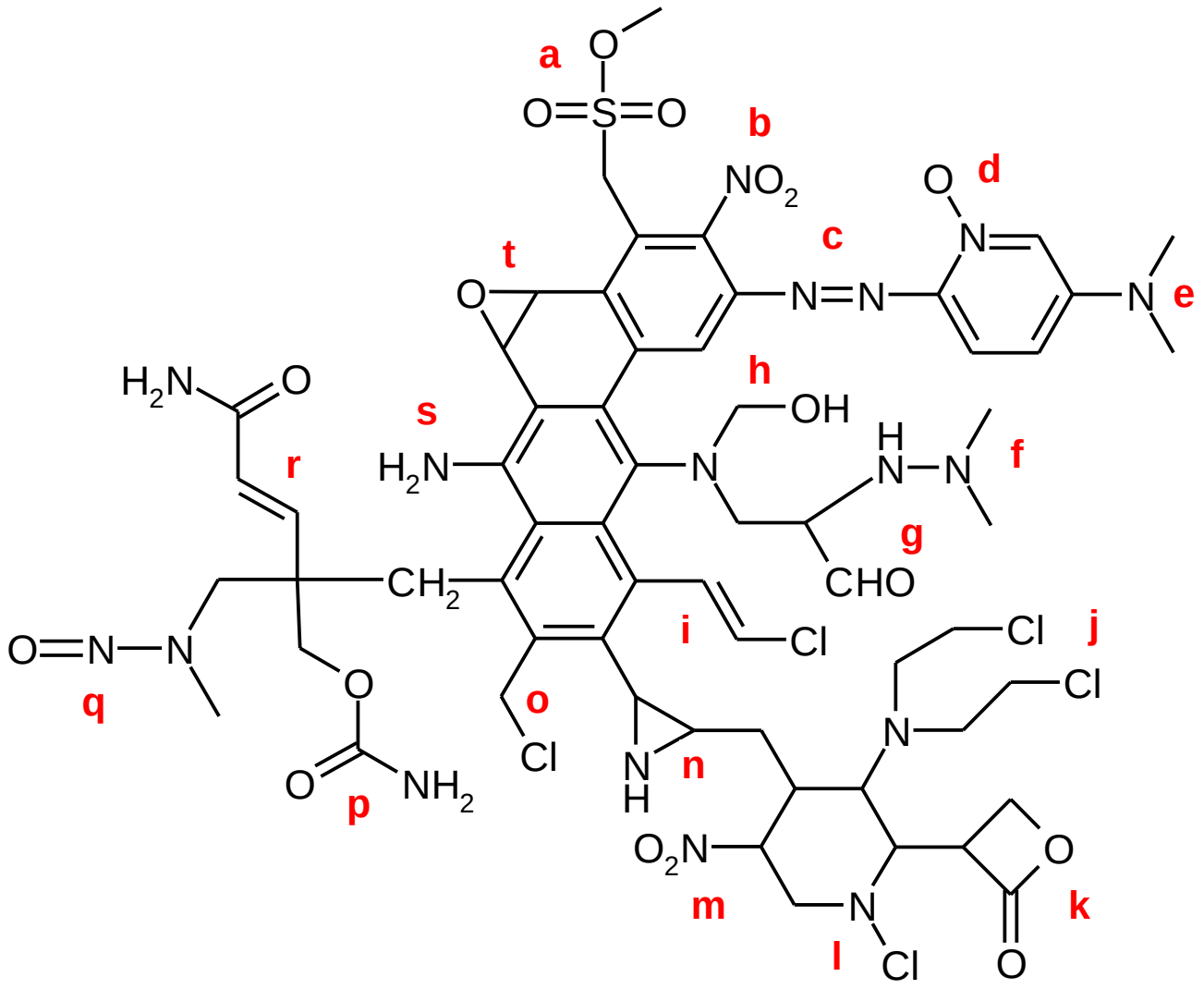
Almost 500 years ago, Paracelsus acknowledged that the subtle distinction between whether a given compound acts as a drug or poison is often determined by the dose at which it is given.

Toxicity

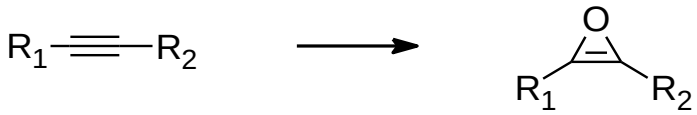


Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

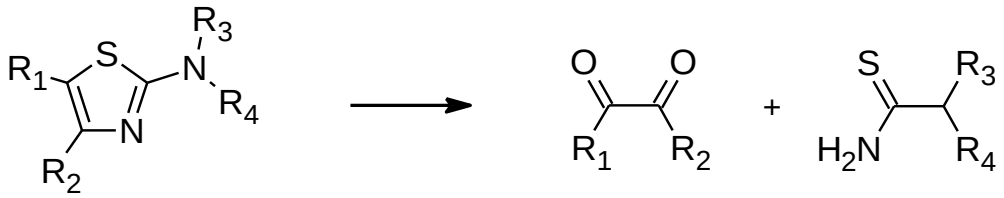
Toxicity


a
O
O=S=O
b
NO2
O
d
N
c
t
O
N=N
N
e
h
OH
H2N
s
N
H
N
N
f
g
r
H2N
O
CHO
CH2
i
Cl
O=N
N
q
O
o
Cl
Cl
j
Cl
N
O
p
NH2
N
H
n
O2N
m
N
O
k
l
Cl
O

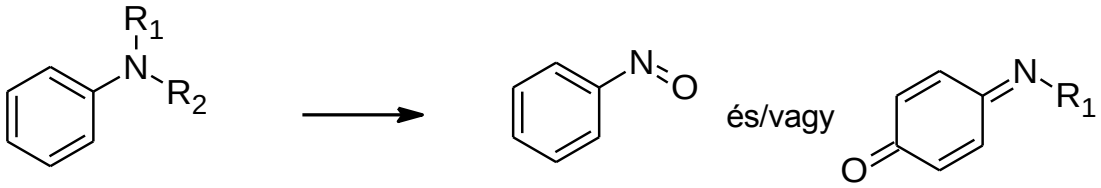
Toxicity



ahol R_1 = alkil vagy aril; R_2 = H, alkil vagy aril

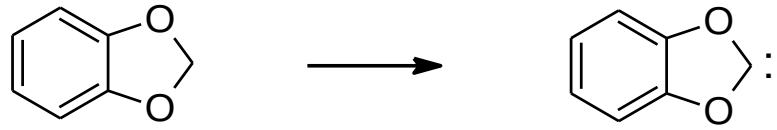


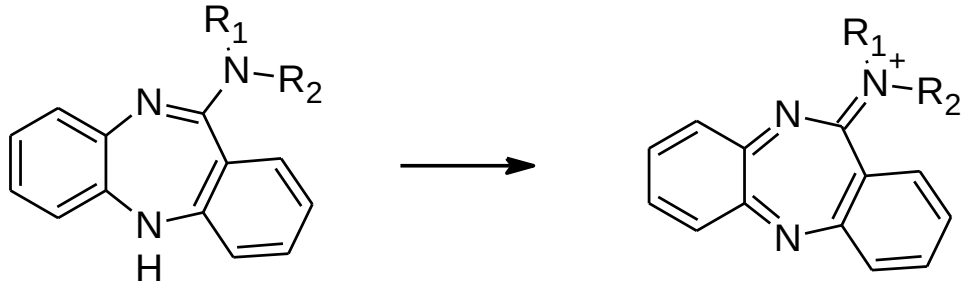
ahol R_1-R_4 = H vagy alkil



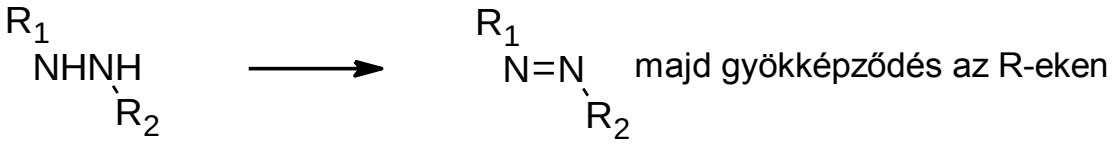
ahol R_1, R_2 = H, alkil, acil, aril stb.

Toxicity



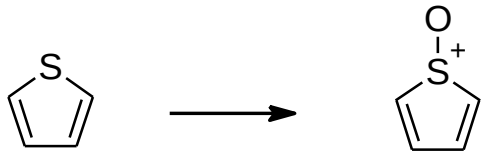


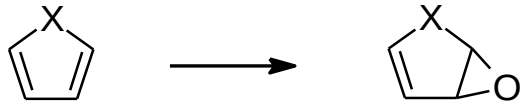
ahol R_1, R_2 = H, cikloalkil



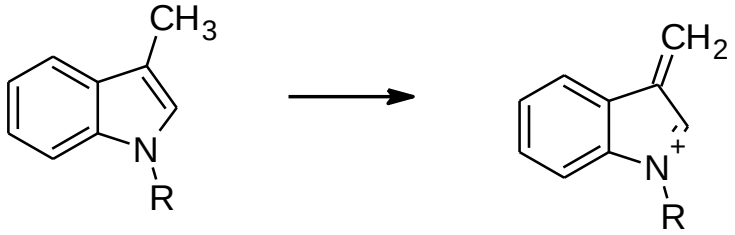
ahol R_1, R_2 = alkil, aril

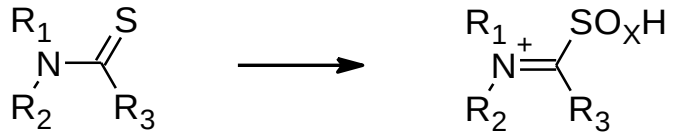
Toxicity



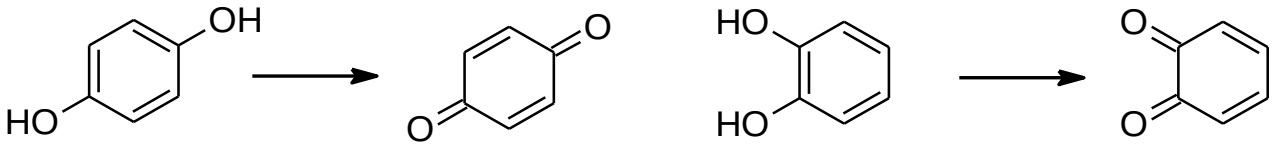


X = O vagy S





R1, R2 = H, alkil, aril; R3 = N vagy C; x = 1-3



Aromaticity and Druglikeness

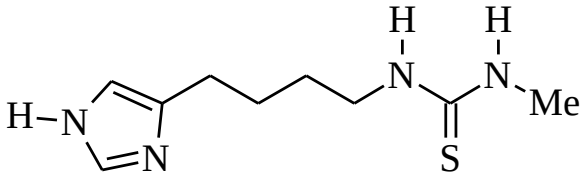
Number of aromatic rings	1	2	3	4	5
clogP	1.9	2.9	3.7	4.4	5.1
$LogD_{7.4}$	1.3	2.1	2.4	2.7	2.9
Serum albumin binding (%)	78	88	93	96	96
Aqueous solubility (ug/ml)	100	79	57	36	28
P450 3A4 inhibition (pIC_{50})	4.7	4.9	5.2	5.4	5.6
hERG inhibition (pIC_{50})	5.2	5.6	5.7	5.7	5.5

Timothy J. Ritchie and Simon J.F. MacDonald *Drug Discovery Today* **14**, (21/22) 1011-1020 (2009)

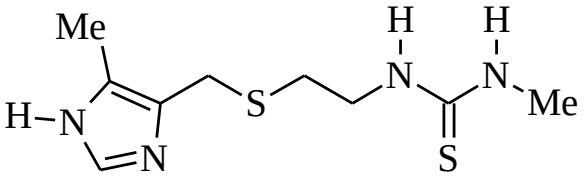
Discovery of anti-ulcer histamine H_2 receptor antagonists

Fischer, J. ; Ganellin, C.R. *Analogue-based Drug Discovery*, Viley-VCH, Weinheim, 2006

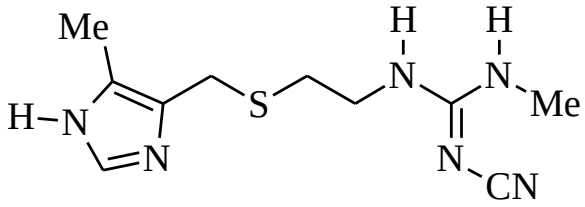
Smith Kline & French



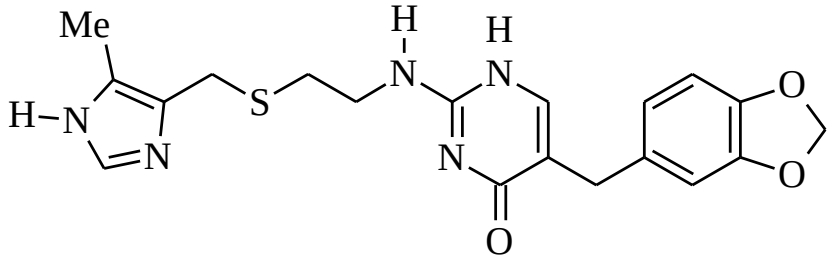
burimamide



metiamide

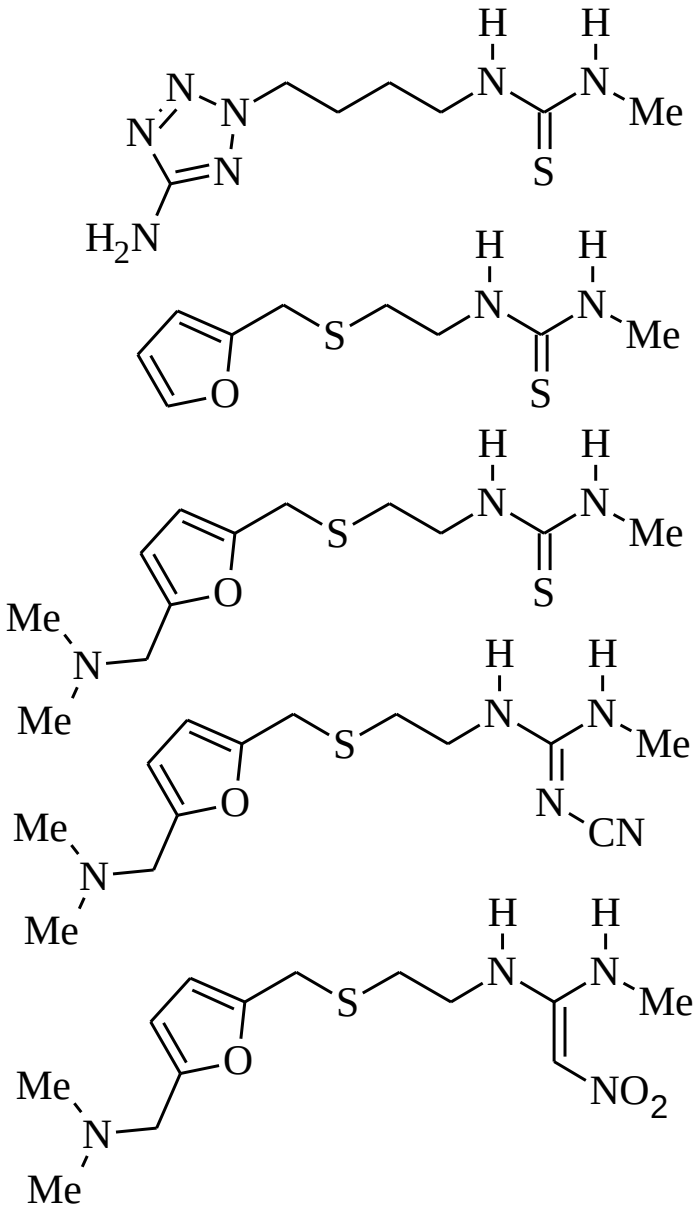


cimetidine
(Tagamet® 1976)



oxmetidine

Allen and Hanburies (Glaxo Group)



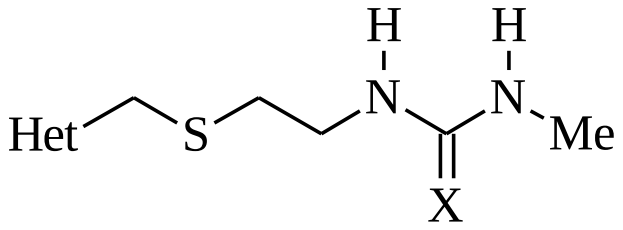
AH 15475

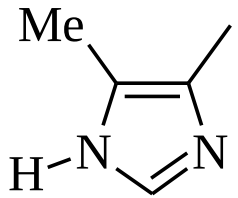
AH 18166

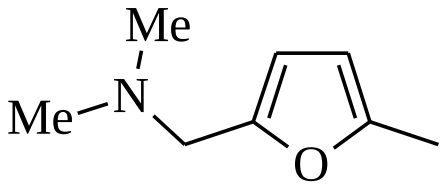
AH 18665

AH 18801

AH 19065 - ranitidine
(Zantac® 1981)

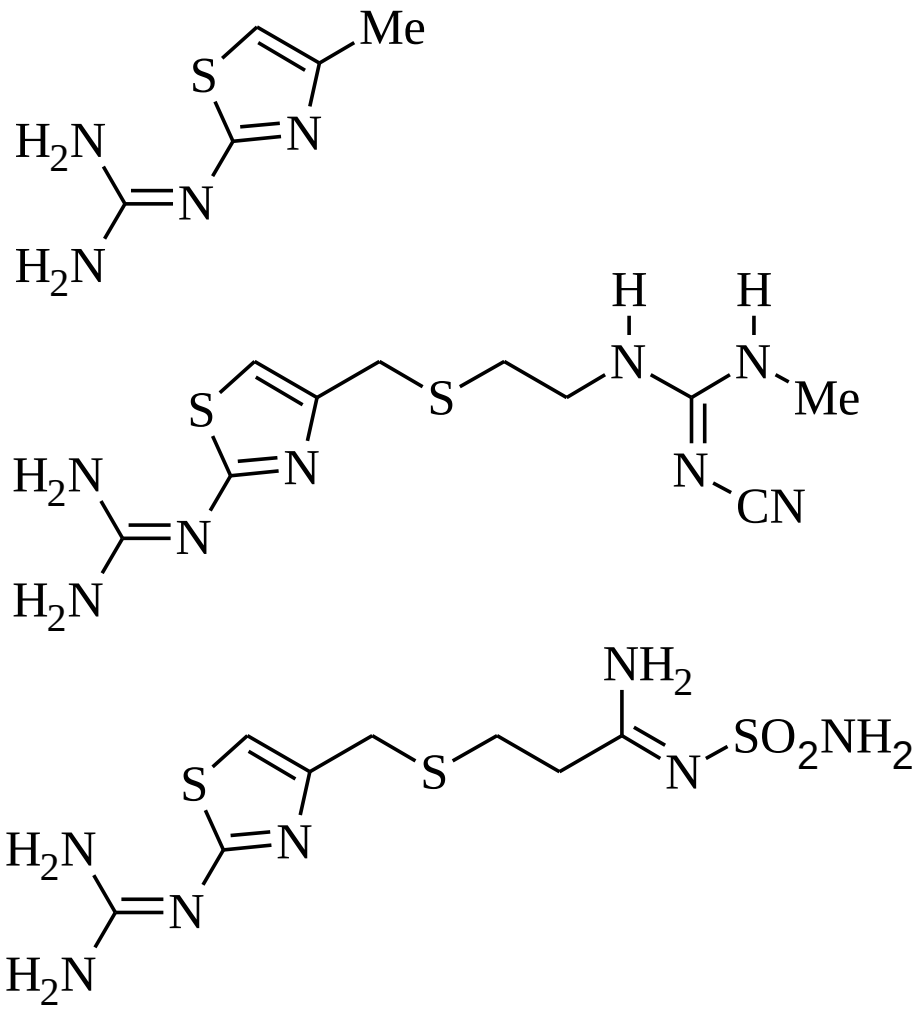






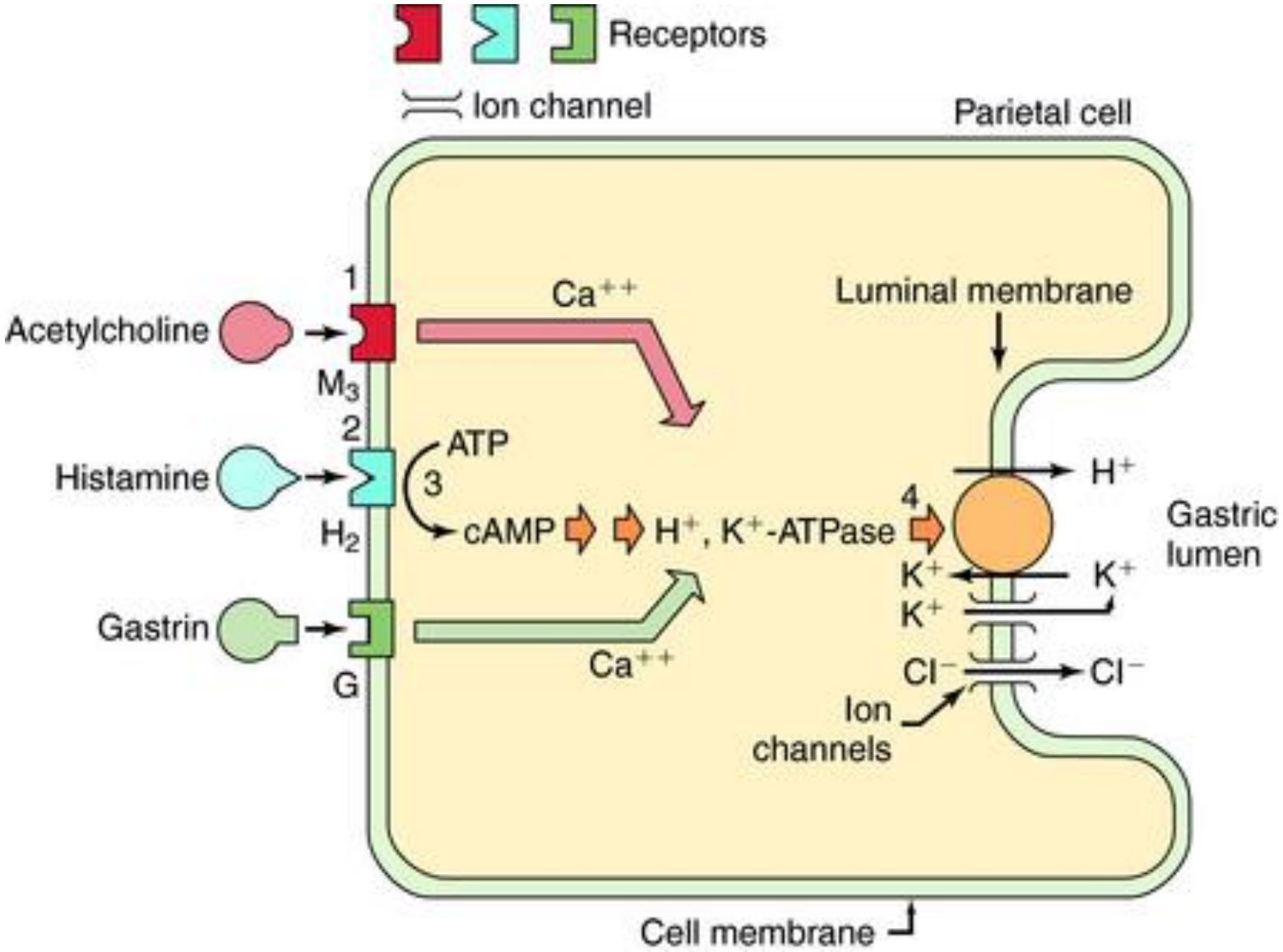
X	imidazole ED_{50} (mg/kg)	furan ED_{50} (mg/kg)
S	0.52	2.32
NCN	1.12 (c)	1.39
$CHNO_2$	1.75	0.18 (r)

Yamanouchi



tiotidine

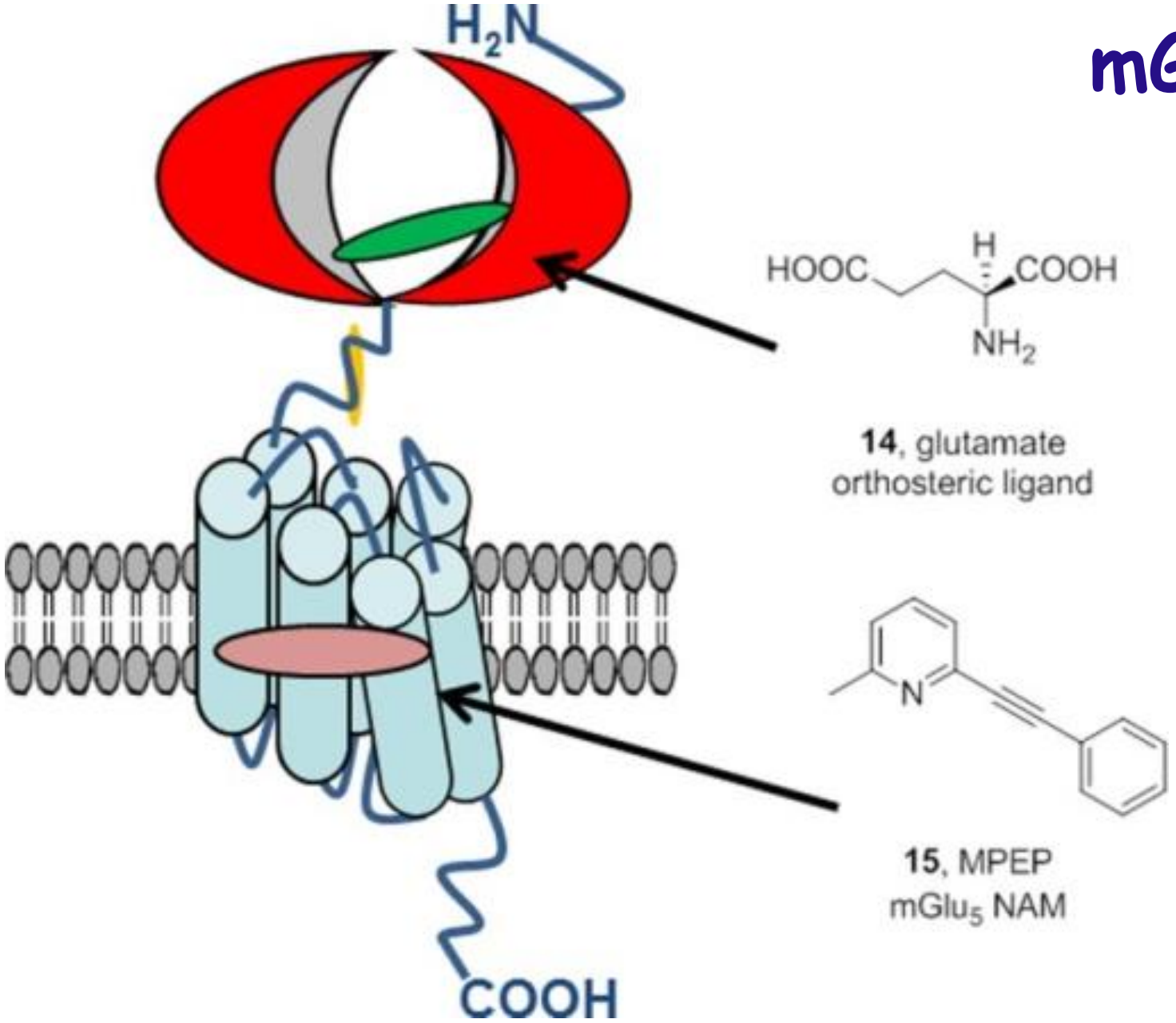
famotidine
(Gaster® 1985)



Drug	daily dose (mg)	MW
Cimetidine	800	252
Ranitidine	300	314
Famotidine	40	337

Domány, Gy., Galambos, J., Gál, K.
A metabotróp glutaminsav receptor 5 negatív allosztérikus modulátorainak kutatása
Magyar Kémiai Folyóirat **122** (2-4), 95-103 (2016)

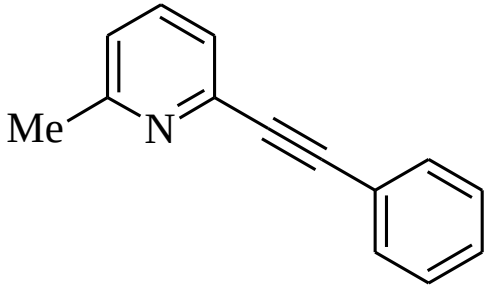
mGluR5 receptor



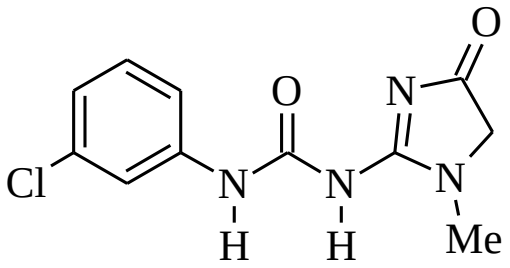
14, glutamate
orthosteric ligand

15, MPEP
$mGlu_5$ NAM

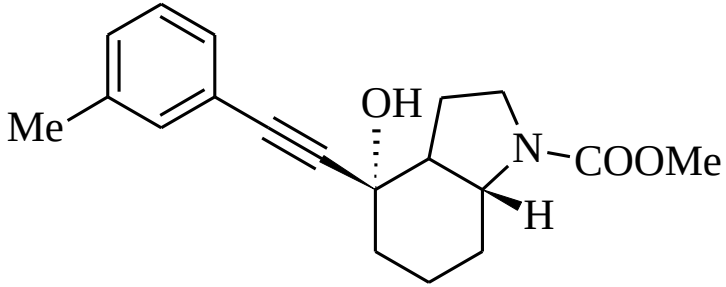
mGluR5 NAMs



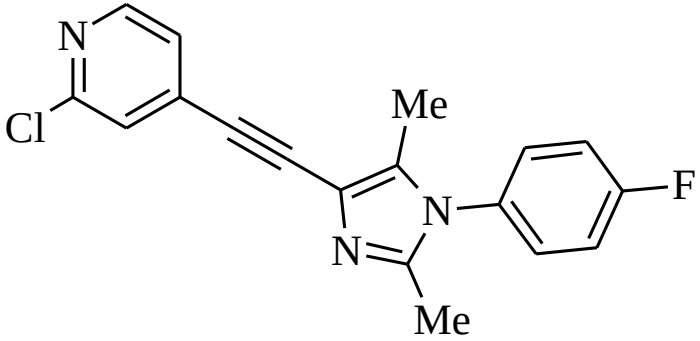
MPEP



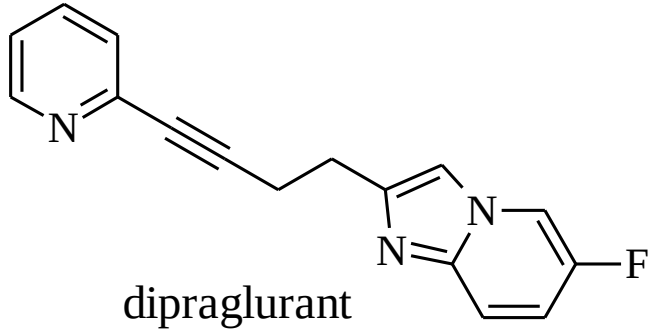
fenobam



mavoglurant

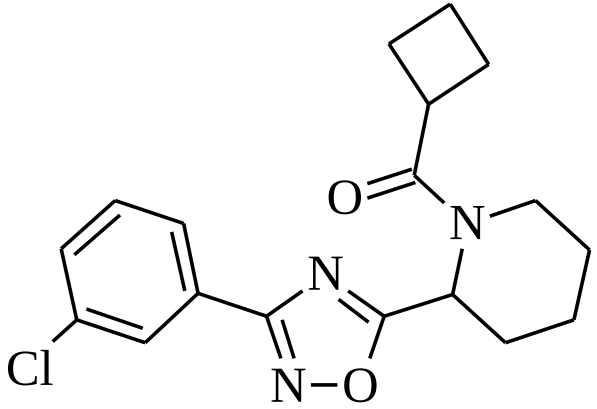


basimglurant



dipraglurant

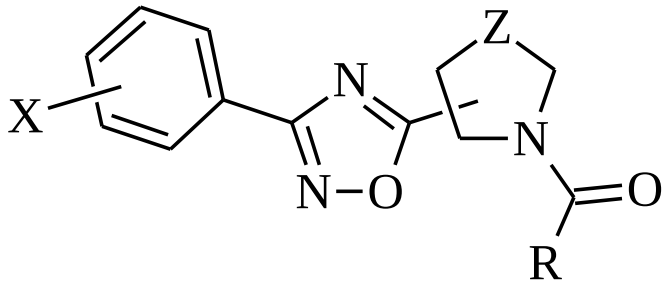
HTS hit No. 1



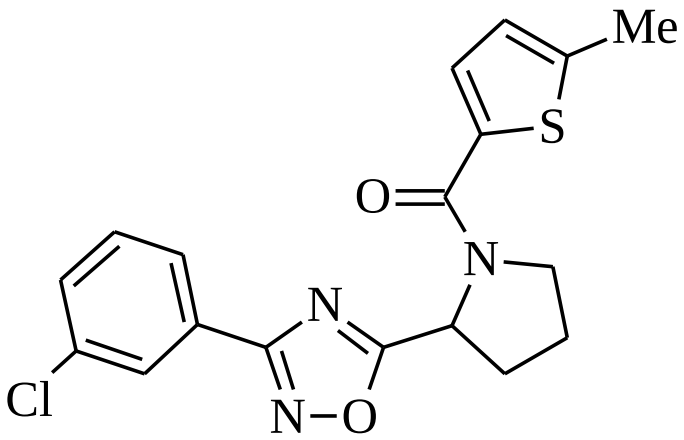
6

rmGluR5 pK_i: 6,69

Oxadiazoles

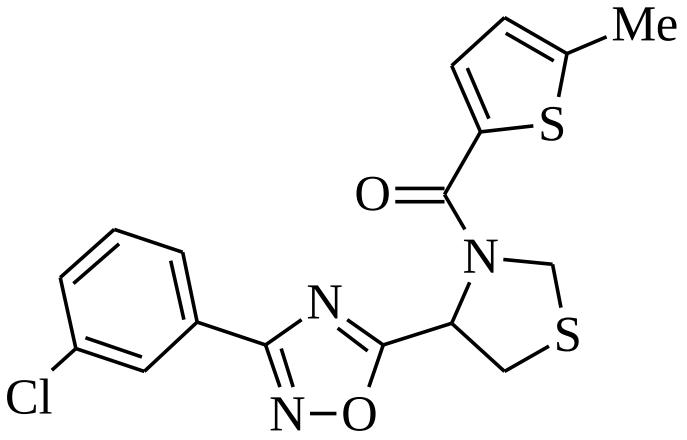


11



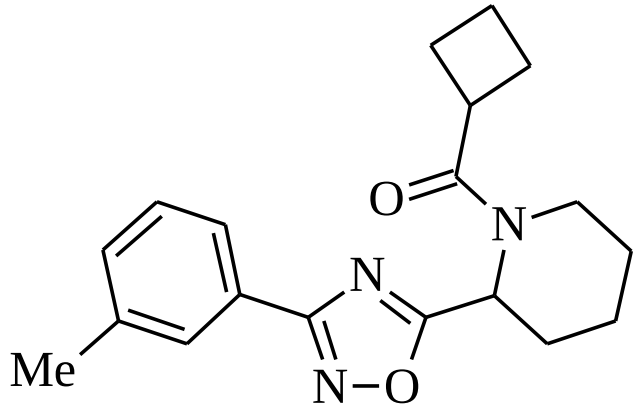
11a

rmGluR5 pK_i: 7,08



11b

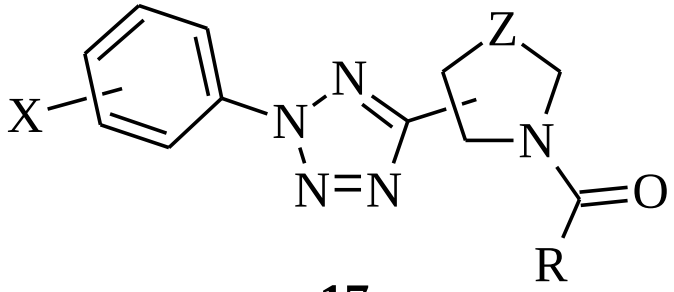
rmGluR5 pK_i: 6,91



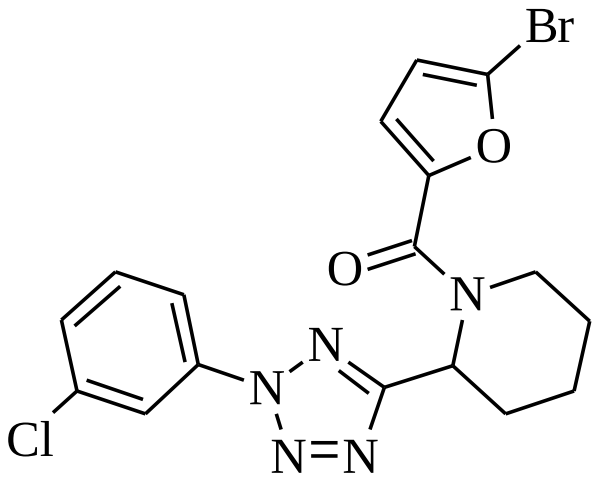
11c

rmGluR5 pK_i: 6,90

Tetrazoles

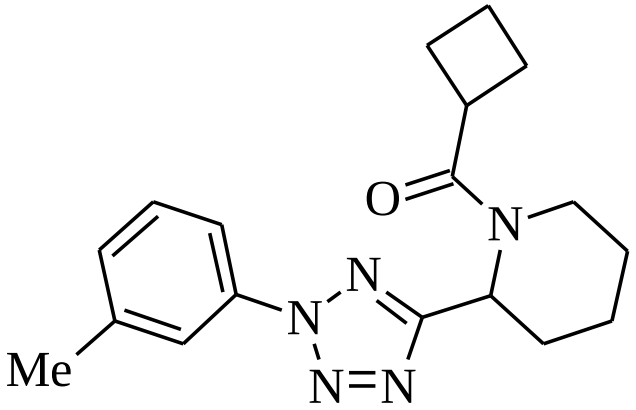


17



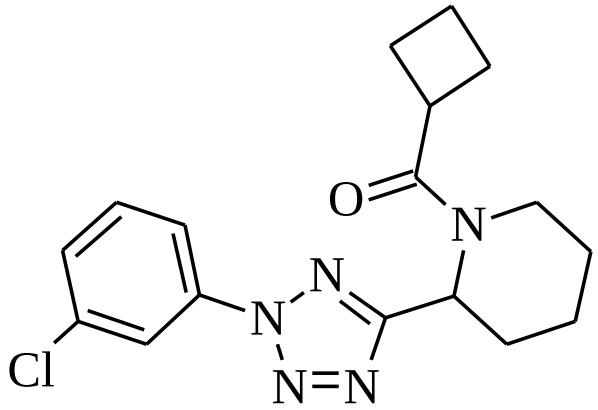
17a

rmGluR5 pK_i: 7,31



17b

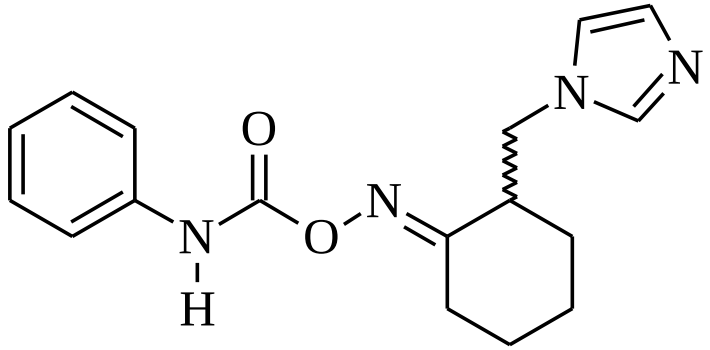
rmGluR5 pK_i: 7,14

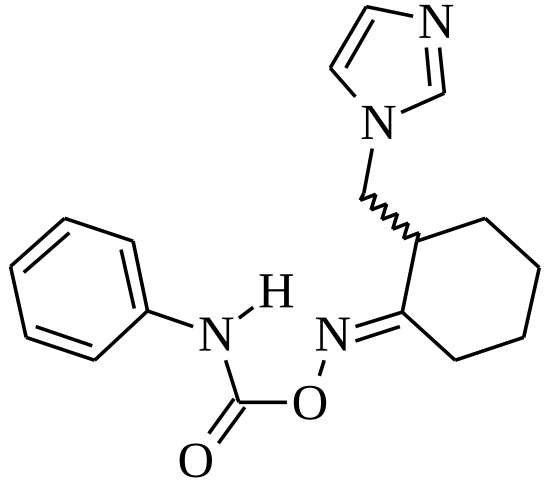


17c

rmGluR5 pK_i: 7,11

HTS hit No. 2

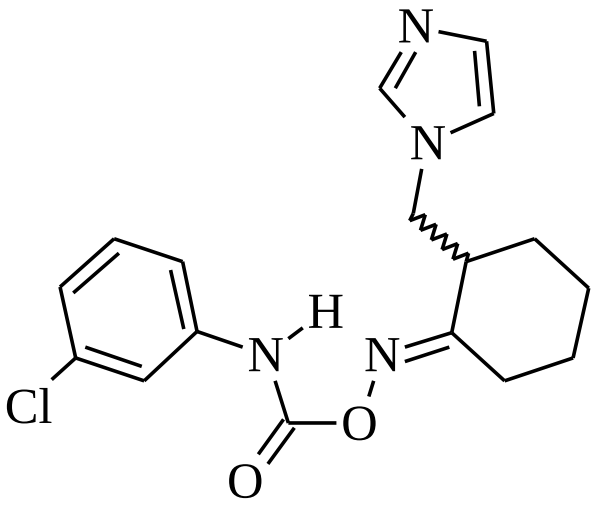




18

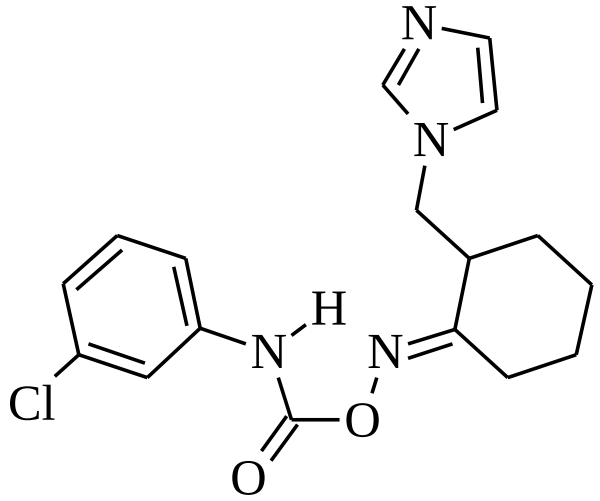
rmGluR5 pK_i: 6,98

Carbamoyl oximes



22a

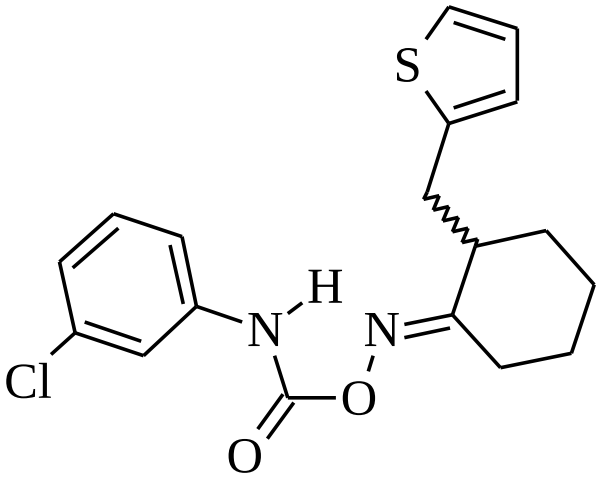
rmGluR5 pK_i: 7,97



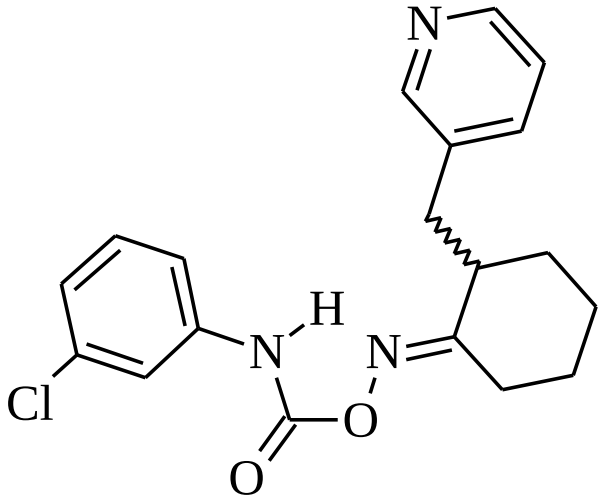
(+)-22a

rmGluR5 pK_i: 8,05

Carbamoyl oximes

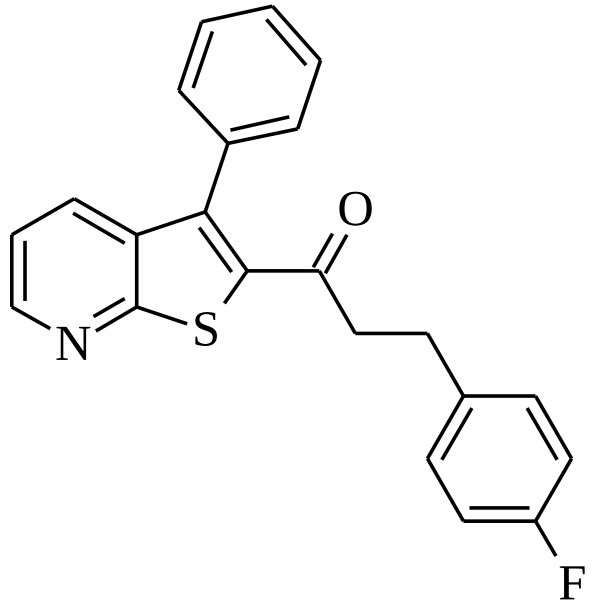


22b
rmGluR5 pK_i: 8,04



22c
rmGluR5 pK_i: 8,47

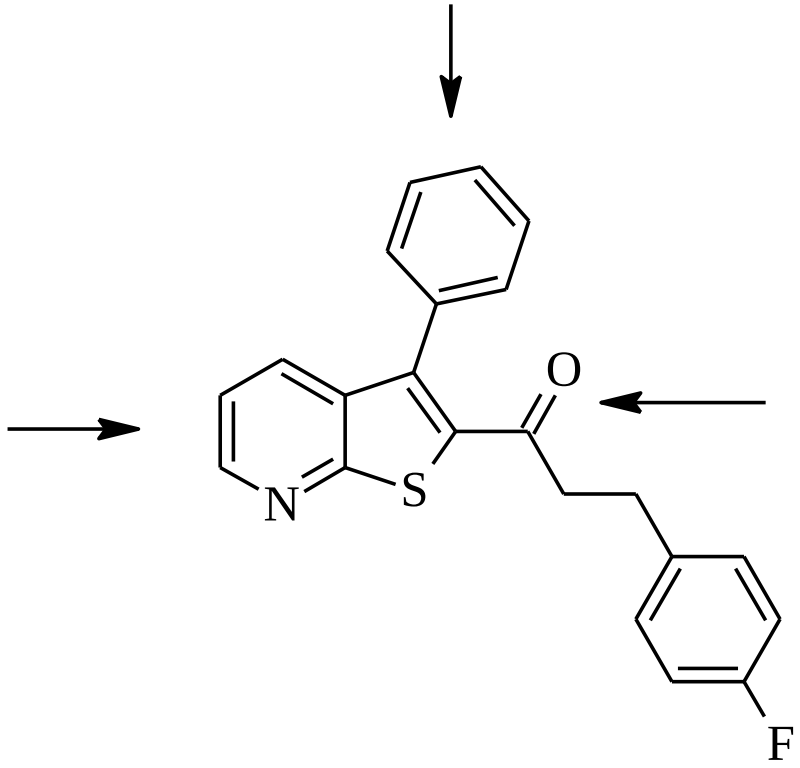
HTS hit No. 3



23

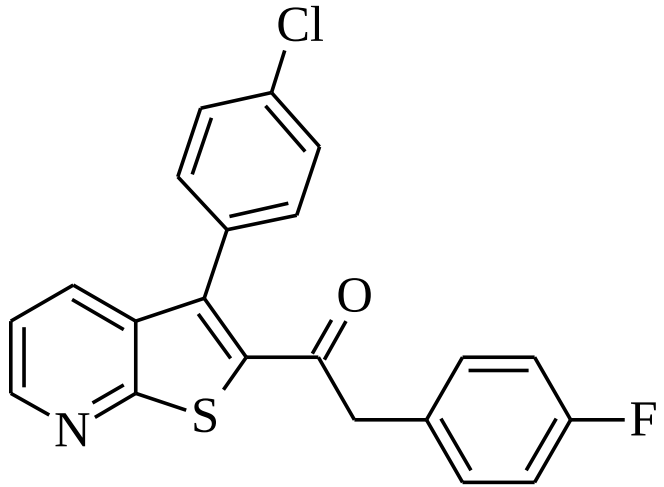
rmGluR5 pK_i: 6,46

Thienopyridines



23

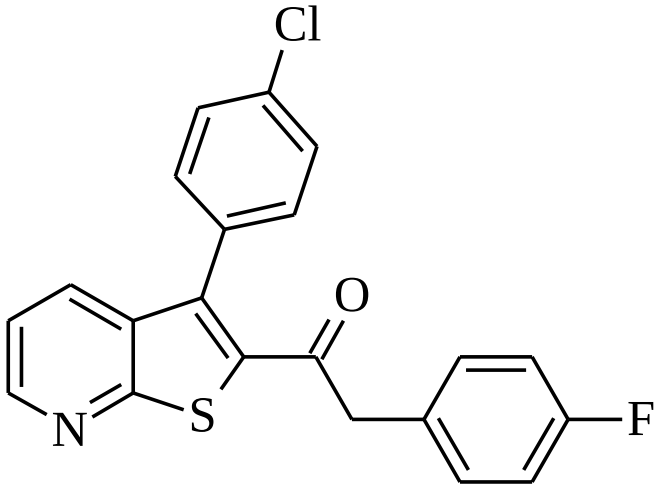
rmGluR5 pK_i: 6,46



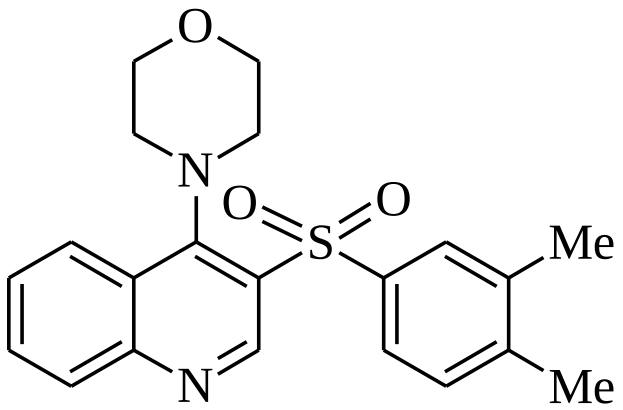
24

rmGluR5 pK_i: 7,08

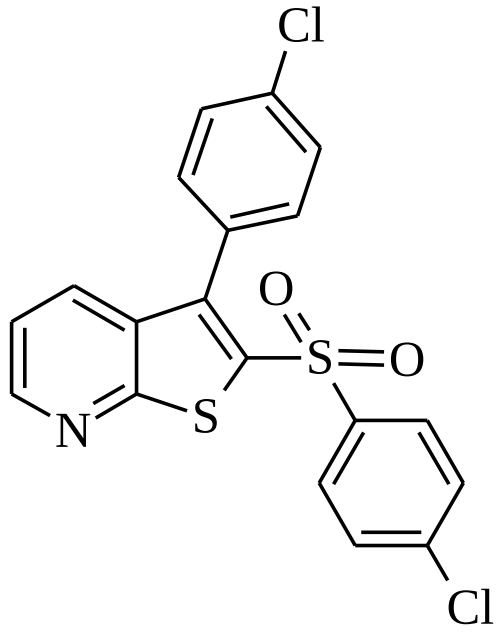
Thienopyridines



24
rmGluR5 pK_i: 7,08

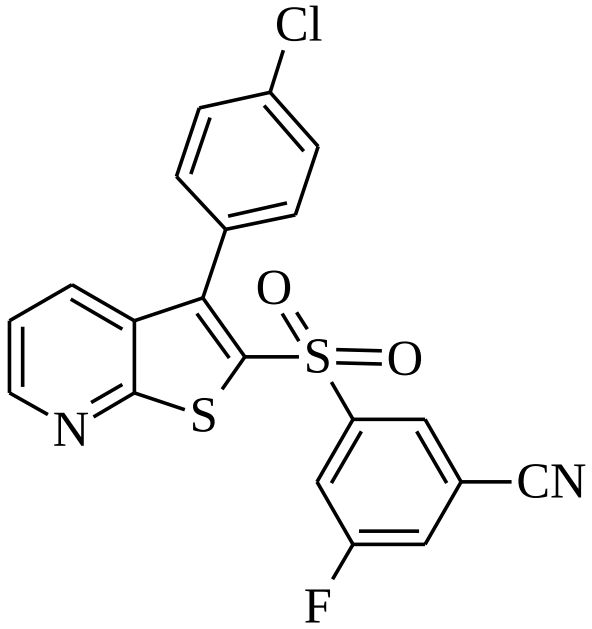


25
rmGluR5 pK_i: 7,17

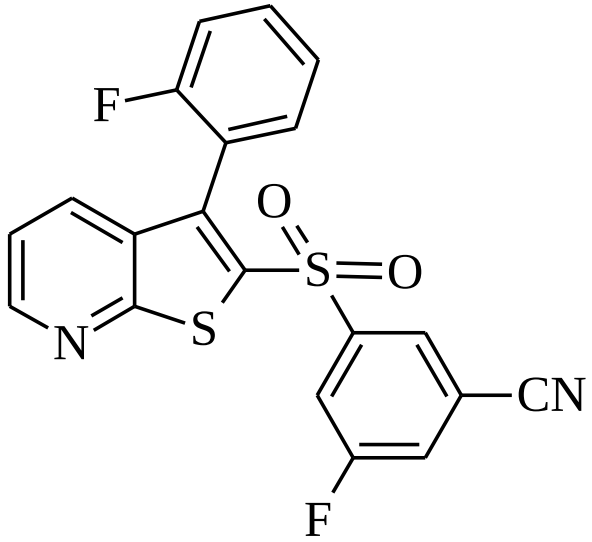


26a
rmGluR5 pK_i: 7,91

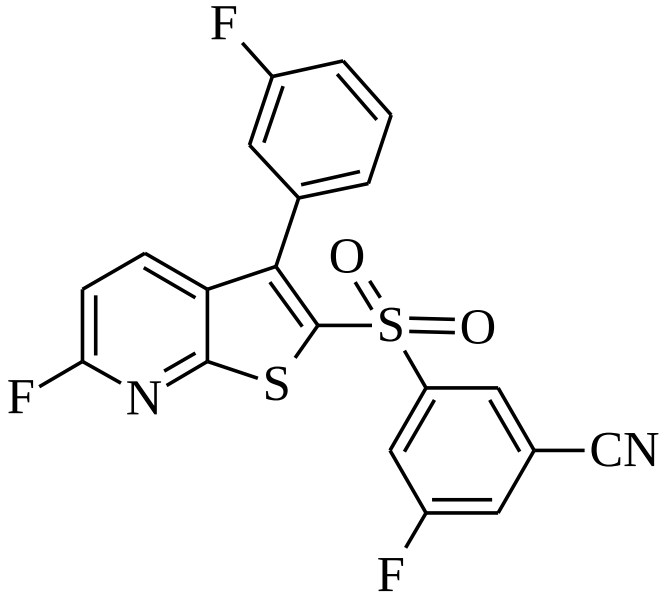
Thienopyridines



31a
rmGluR5 pK_i: 8,70

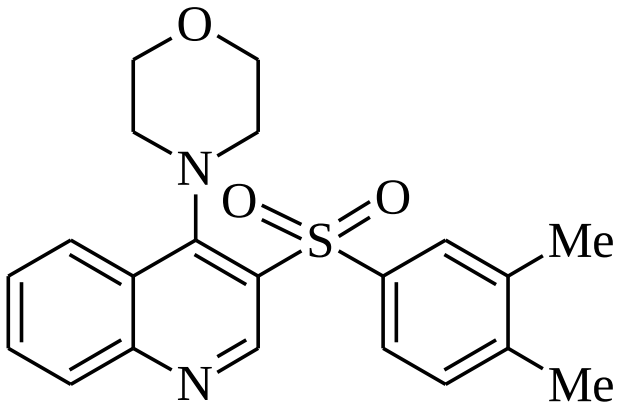


31d
rmGluR5 pK_i: 8,96

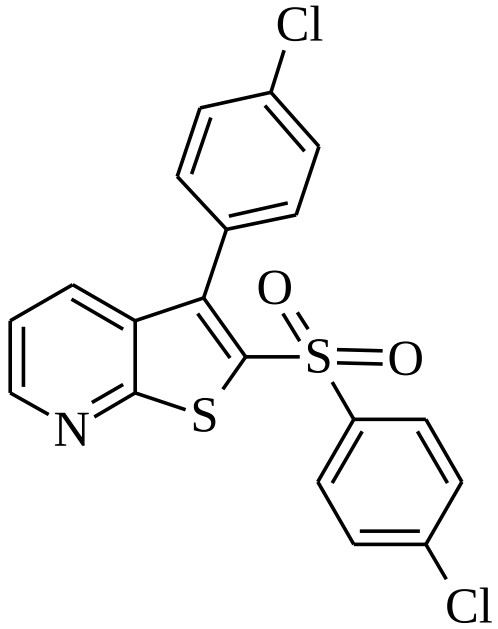


41a
rmGluR5 pK_i: 8,60

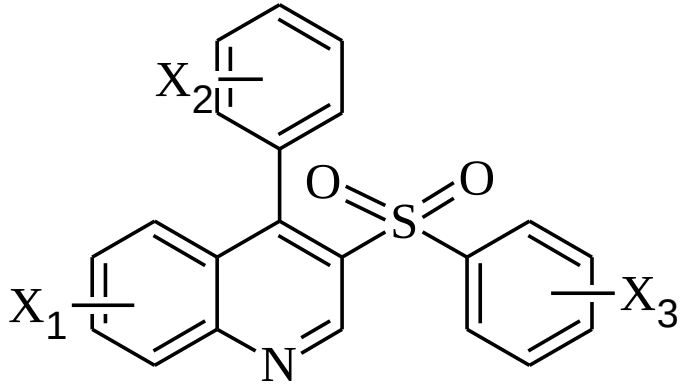
3-Arylsulfonyl-quinolines



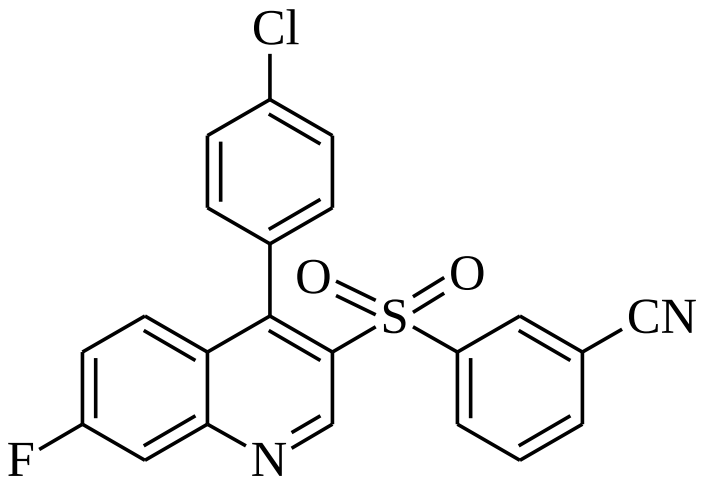
25
rmGluR5 pK_i: 7,17



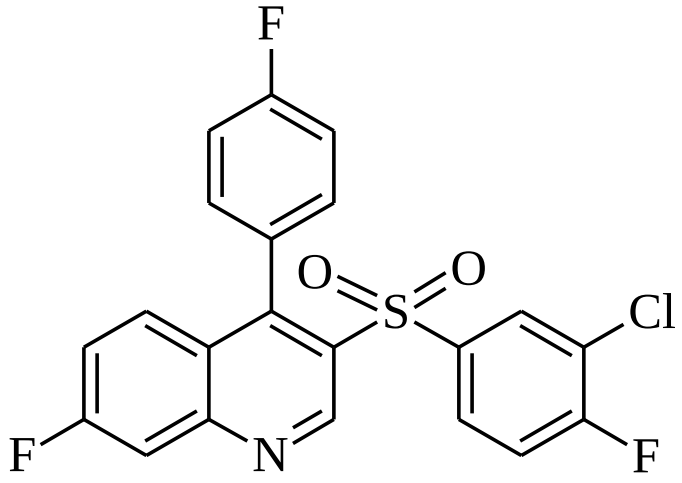
24
rmGluR5 pK_i: 7,08



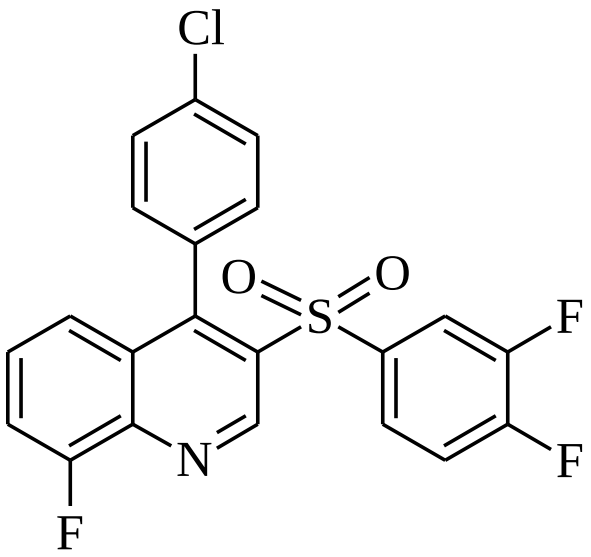
3-Arylsulfonyl-quinolines



42a
rmGluR5 pK_i: 8,28



42b
rmGluR5 pK_i: 8,28



42c
rmGluR5 pK_i: 8,08

structure - permeability
structure - hERG activity
structure - CYP activity
structure - phospholipidosis
structure - toxicity

Lead optimization:

sitagliptin

aliskiren

maraviroc

clopidogrel

Discovery of the histamine H_2 antagonists

The mGluR5 NAM story in Richter