STRUCTURE and ACTIVITY of DRUGS - practical aspects II.

György Domány

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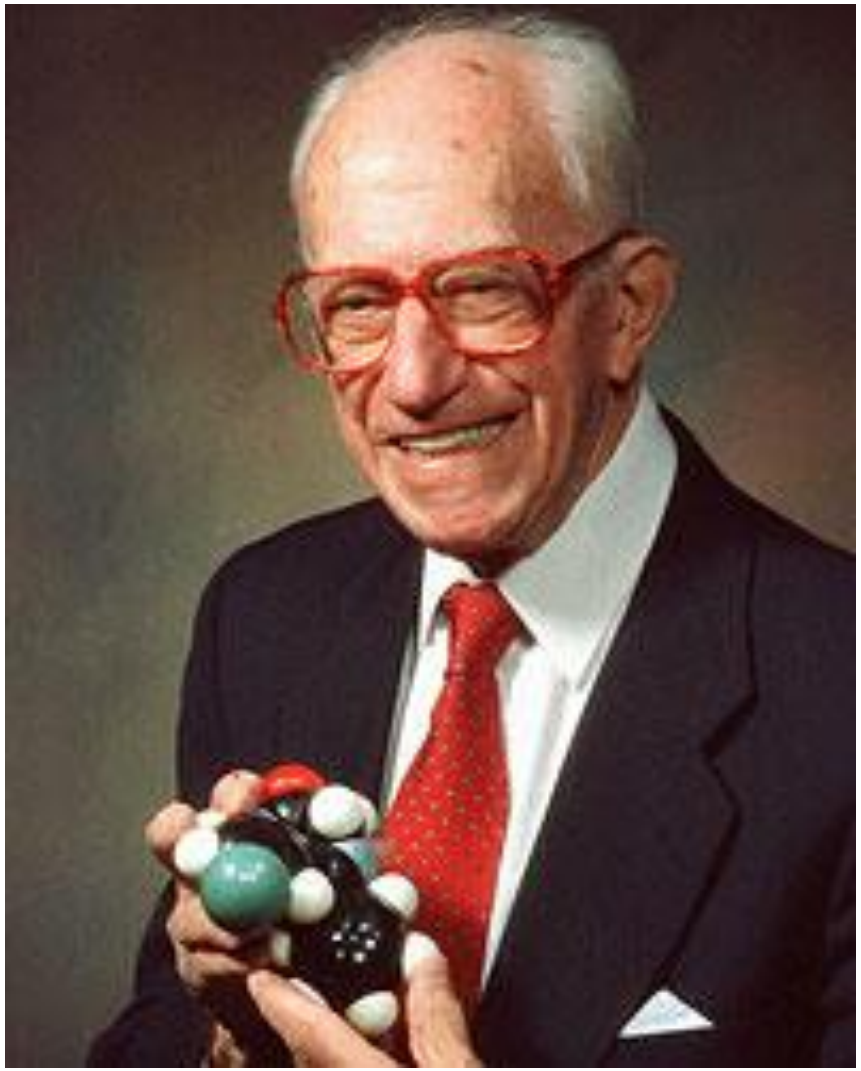
Leo H. Sternbach
(1908-2005)

The Benzodiazepine Story
J.Med.Chem. **22**, 1-7 (1979)

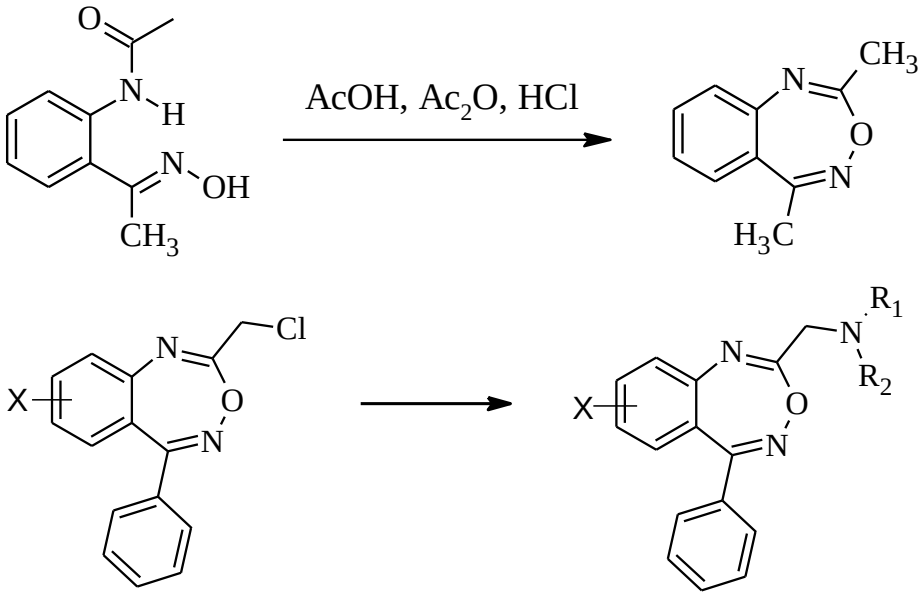


„The **pharmacological tests for the screening of sedatives and tranquilizers were well in hand**, and we chemists were asked to produce a new compound which would be superior to the then existing tranquilizers."

„Since **our main interest was chemical synthesis** we planned to select an approach which would be **chemically most attractive, challenging, and satisfying**. This left us essentially with two alternatives: to modify existing drugs or to search for a new class of tranquilizers."

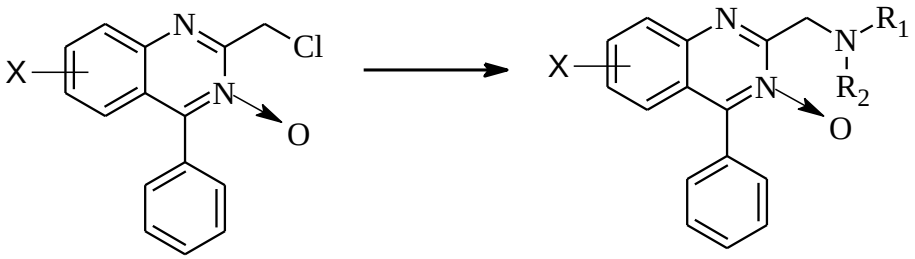
„The class of compounds we were seeking would be expected to fulfill the following criteria:
(1) be relatively unexplored,
(2) be readily accessible,
(3) give the possibility of a multitude of variations and transformations,
(4) **offer some challenging chemical problems**, and
(5) **„look" as if it could lead to biologically active products**."

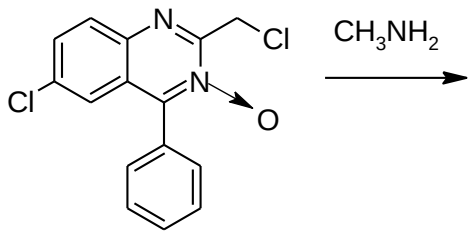
Benzheptoxdiazines



„The reaction products, we hoped, might have interesting properties, since it is known that basic groups frequently impart biological activity."

Quinazoline 3-oxides

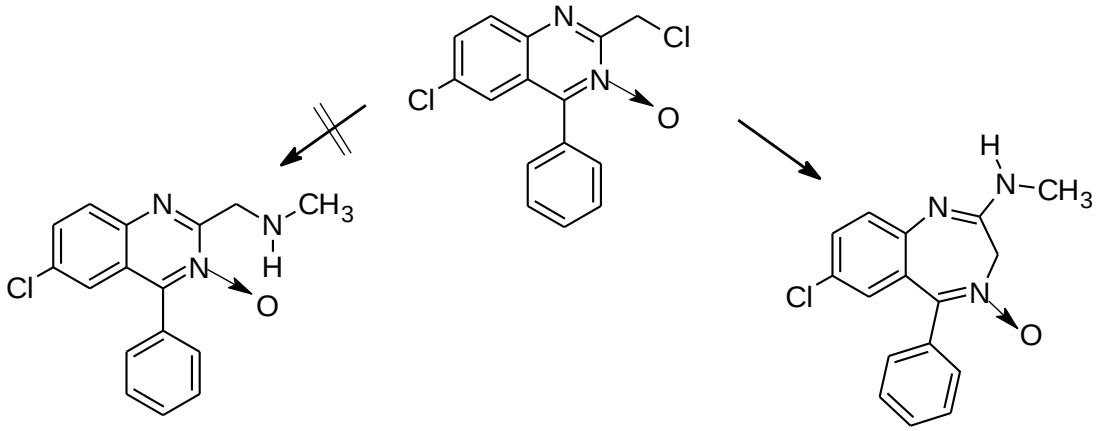




compound	Inclined screen	Foot shock	Cat	Anticonvulsant tests		
					electroshock	
				Pentylene tetrazole	max	min
New comp.	100	40	2	18	92	150
meprobamate	250	250	100	150	200	167
chlorpromazine	17	20	2.5	42	150	600
phenobarbital	120	80	10	75	18	90

Dose (mg/kg) of orally administered drug required to achieve the desired effect.

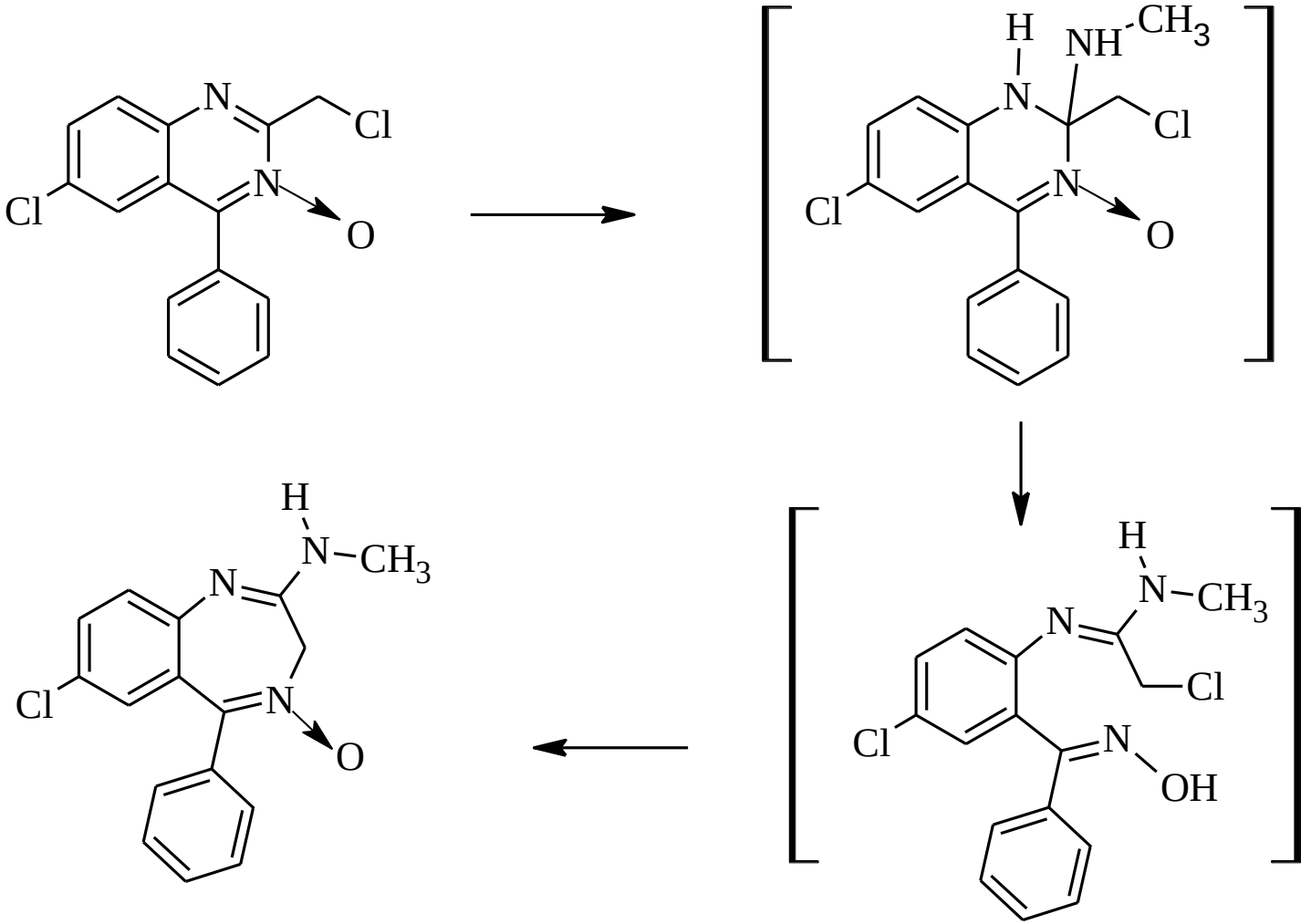
Benzodiazepines



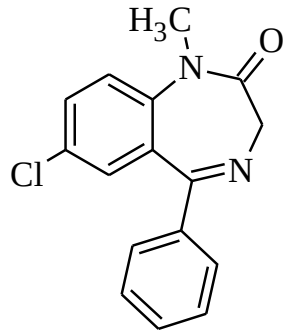
compound	Inclined screen	Foot shock	Cat	Anticonvulsant tests		
				Pentylene tetrazole	electroshock	
					max	min
New comp.	100	40	2	18	92	150
meprobamate	250	250	100	150	200	167
chlorpromazine	17	20	2.5	42	150	600
phenobarbital	120	80	10	75	18	90

Dose (mg/kg) of orally administered drug required to achieve the desired effect.

Prep.: 1955; test.: May 1957; patent application: May 1958; patent granted: July 1959; launch: 1960 (Librium – Elenium)

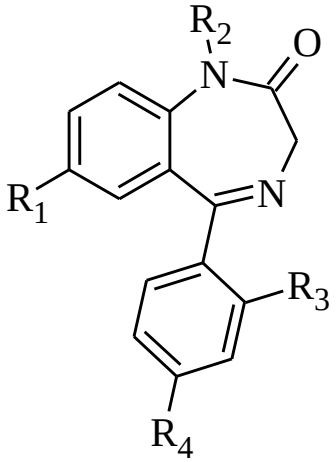

N
Cl
Cl
N
O
H
NH
CH3
Cl
N
Cl
O
H
N
CH3
N
Cl
N
O
H
N
CH3
N
Cl
Cl
N
OH

Benzodiazepines



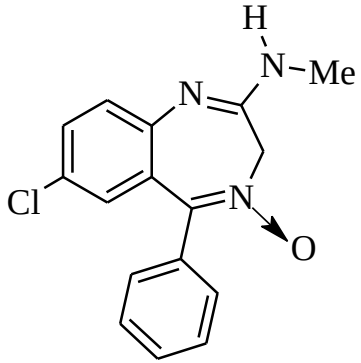
Prepared and tested: 1959; launch: 1963 Valium – Seduxen, „Mother's Little Helper" (1966 Rolling Stones)

				Anticonvulsant tests		
					electroshock	
compound	Inclined screen	Foot shock	cat	Pentylene tetrazole	max	min
Librium	100	40	2	18	92	150
Valium	30	10	0.2	1.4	6.4	64

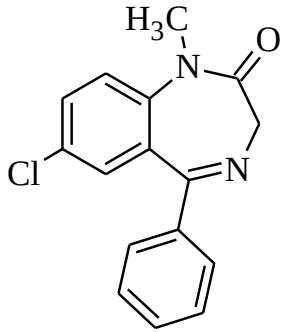


Over 3000 1,4-benzo- and heterodiazepinones by Roche

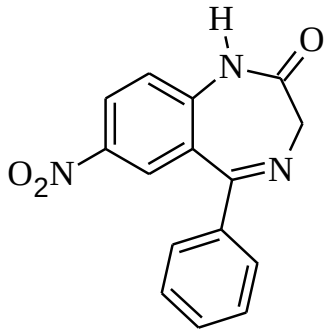
R_1: activity increased by electronwithdrowing groups (Hlg, NO_2, CF_3);
R_2: activity increased by Me (decreased by larger groups);
R_3: activity increased by halogens (F, Cl);
R_4: activity very strongly decreased by any substituents



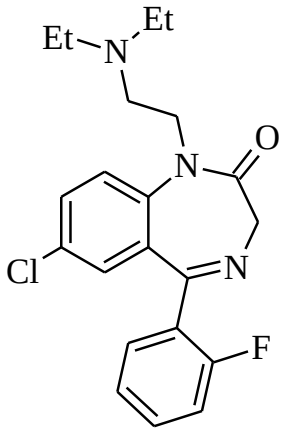
1960 chlordiazepoxide



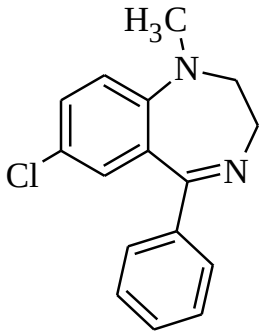
1963 diazepam



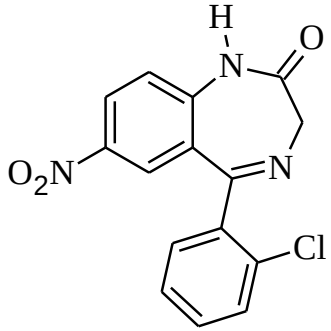
1965 nitrazepam



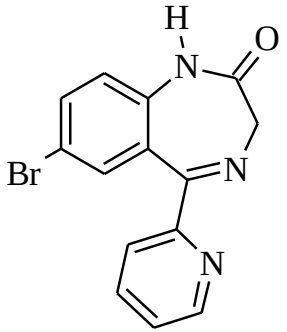
1968 flurazepam



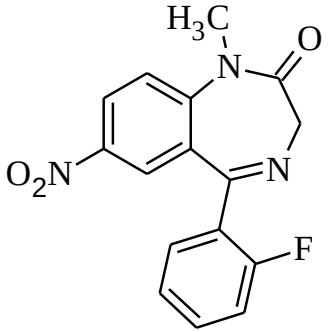
1968 medazepam



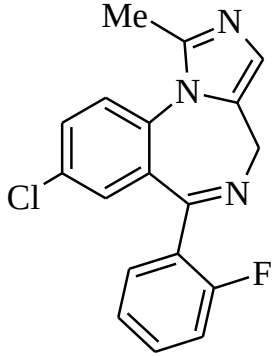
1973 clonazepam



1974 bromazepam



1974 flunitrazepam



1982 midazolam

1960 chlordiazepoxide (Roche)

1963 diazepam (Roche)

1964 oxazepam (Pfizer)

1965 nitrazepam (Roche)

1967 clorazapate (Sanofi)

1968 flurazepam (Roche)

1968 medazepam (Roche)

1969 temazepam (Pfizer)

1971 lorazepam (Pfizer)

1973 clonazepam (Roche)

1973 nordazepam (Midy)

1973 prazepam (Pfizer)

1974 bromazepam (Roche)

1974 flunitrazepam (Roche)

1974 tofizopam (Mochida)

1975 clomazam (Sanofi)

1975 estazolam (Abbott)

1978 triazolam (Pfizer)

1979 clotiazepam (Mitsubishi)

1980 ketazolam (Pfizer)

1980 lormetazepam (Pfizer)

1982 ethyl loflazepate (Sanofi)

1982 halazepam (Merck&Co.)

1982 midazolam (Roche)

1983 alprazolam (Pfizer)

1983 loprazolam (Sanofi)

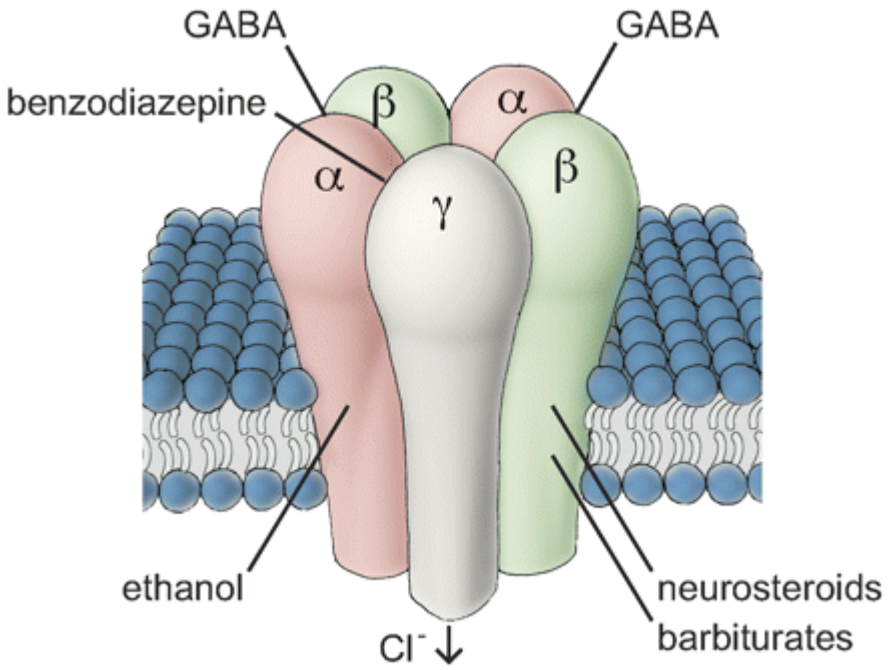
1984 brotizolam (Boehringer)

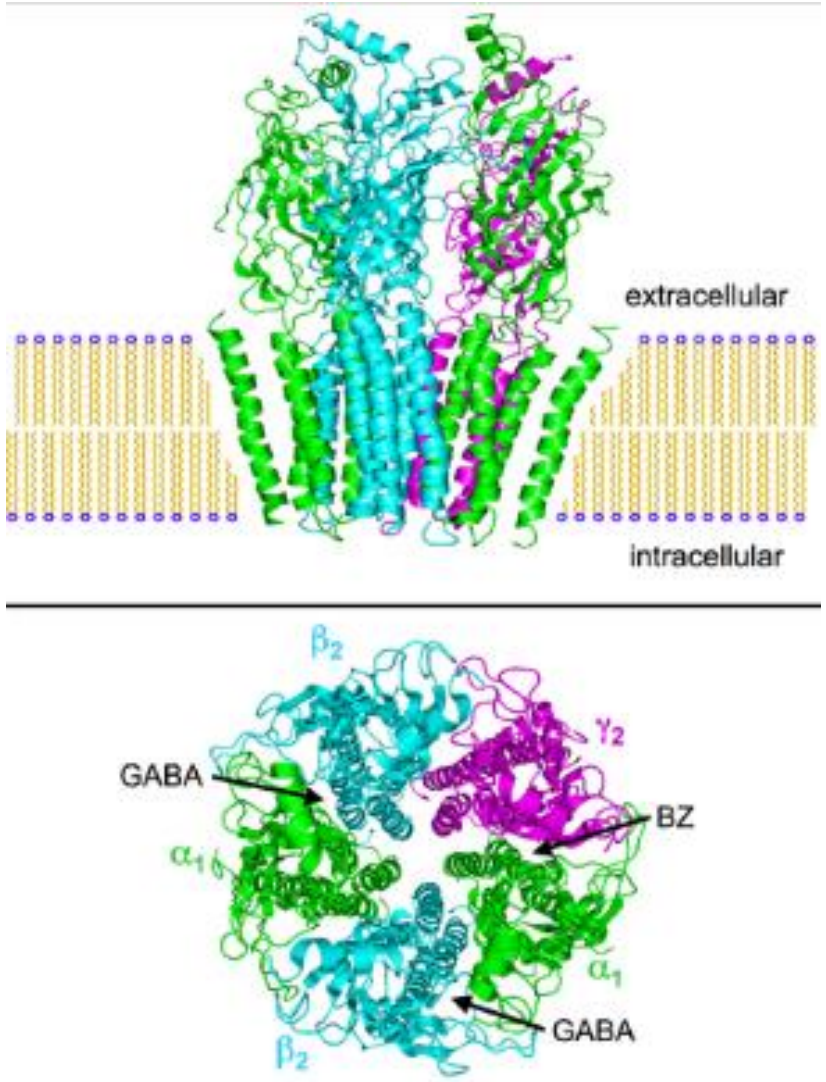
1984 doxefazepam (Schiapp.)

1985 quazepam (Merck&Co.)

1992 cinolazepam (GL Pharma.)

MoA: $GABA_A$ positive allosteric modulators

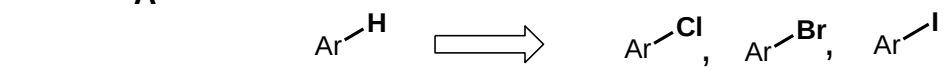


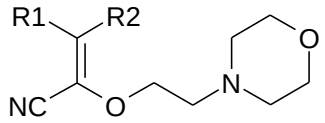


Bioisosterism: the relationship between bioisosteres, substituents or groups with similar physical or chemical properties that impart similar biological properties to a chemical compound.

Bioisosterism

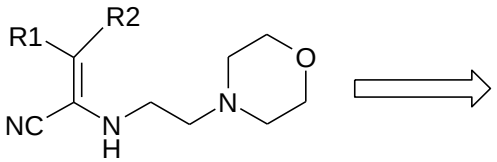
A



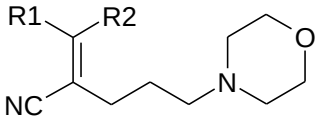


PDE4 IC_{50}: 3,8 nM

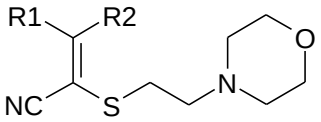
B



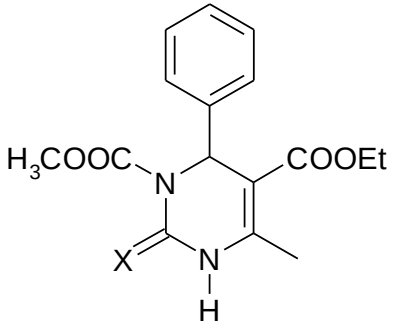
PDE4 IC_{50}: 8,2 nM



PDE4 IC_{50}: 1,4 nM



PDE4 IC_{50}: 0,6 nM



X	Van der Waal's rádiusz (Å)	IC_{50} (nM)*
O	1,40	140
NH	1,50	160
S	1,85	17

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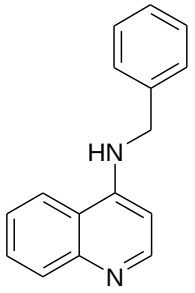
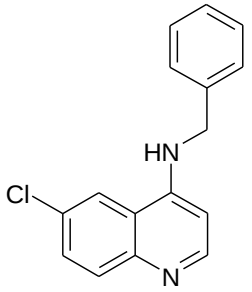
Bioisosterism

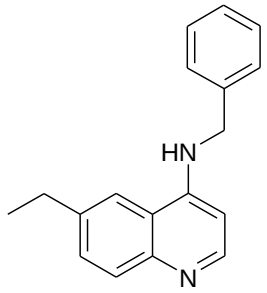
Adenosin A3 antagonists



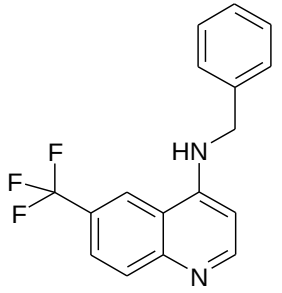
clogP: 3,41 (szám.)



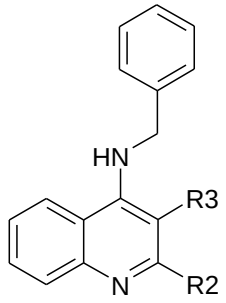
clogP: 4,07 (szám.)



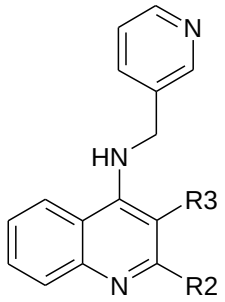
clogP: 4,35 (szám.)



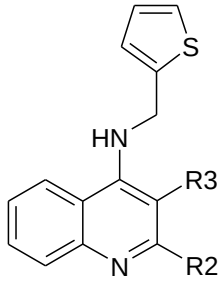
clogP: 4,35 (szám.)



A3 IC_{50}: 0,5 nM



A3 IC50: 1,7 nM



A3 IC50: 0,4 nM

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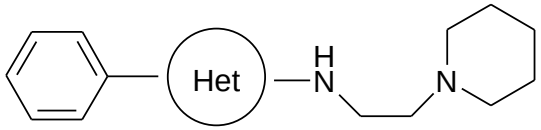
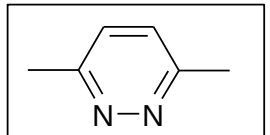
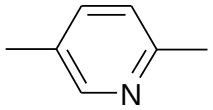
Bioisosterism

AChE inhibitors

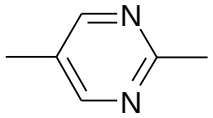




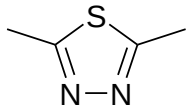
IC_{50}: 13μM



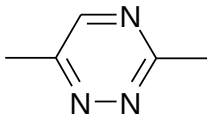
IC_{50}: 70μM



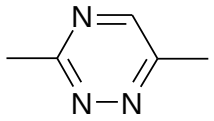
IC_{50}: >100μM



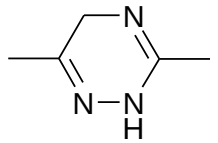
IC_{50}: 54μM



IC_{50}: 60μM



IC_{50}: 57μM



IC_{50}: 47μM

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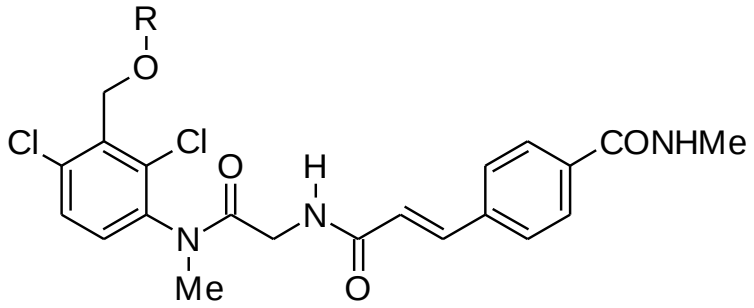
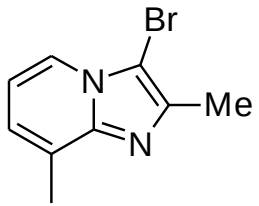
Bioisosterism

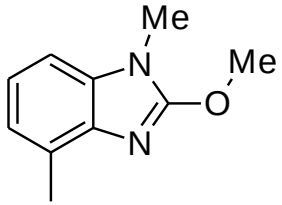
Bradykinin B2 antagonists



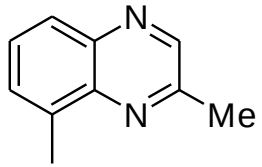
R:



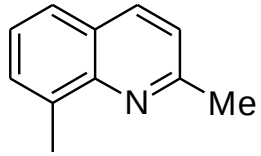
IC_{50}: 1,5 nM



IC_{50}: 2,2 nM



IC_{50}: 3,1 nM



IC_{50}: 1,3 nM

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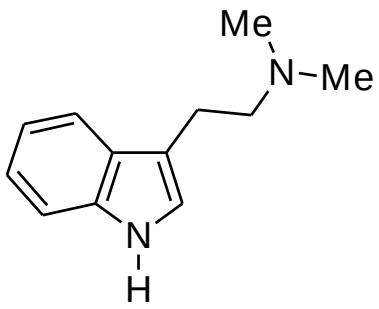
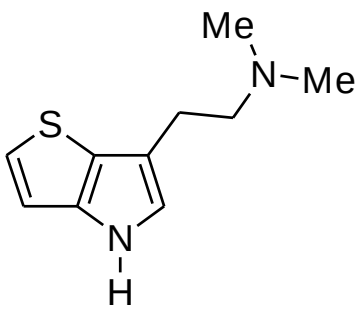
Bioisosterism

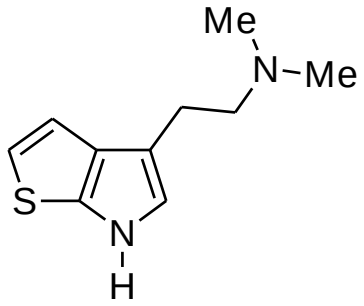
5HT receptor ligands



A



B



C

	$5HT_{1A}$ K_i (nM)	$5HT_{2A}$ K_i (nM)	$5HT_{2B}$ K_i (nM)	$5HT_{2C}$ K_i (nM)
A	259	65	101	33
B	76	276	214	64
C	184	106	483	102

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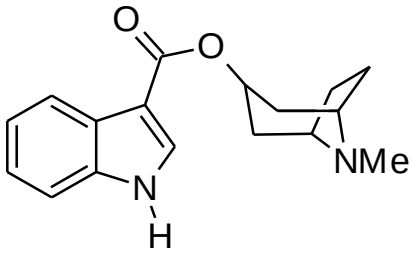
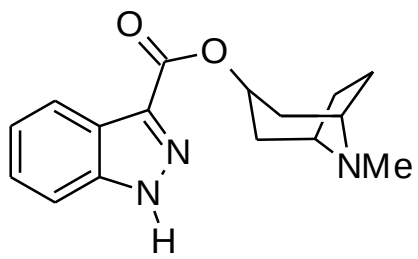
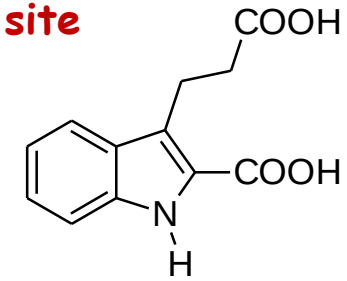
Bioisosterism

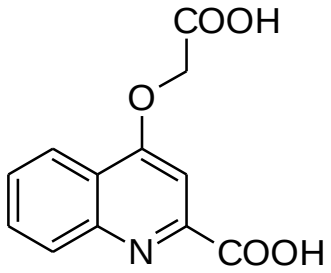
$5HT_3$ agonists





NMDA glicin site





Gly IC_{50}: 27 μM

Gly IC_{50}: 25 μM

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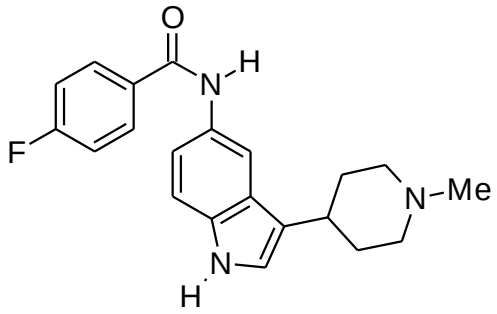
Bioisosterism

$5HT_{1F}$ receptor agonists



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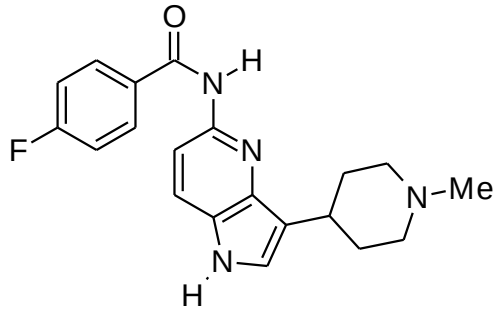

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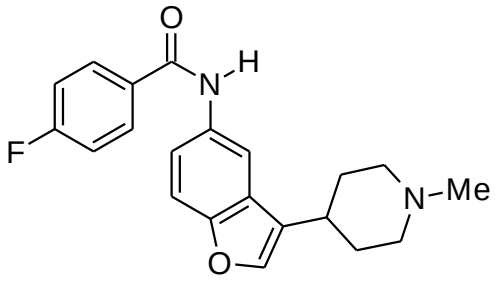

3

	$5HT_{1F}$ Ki (nM)	5HT szelektivitás 1A/1F	1B/1F	1D/1F
1	1,6	7	85	86
2	7,6	7,3	160	960
3	3,1	134	>1000	>1000

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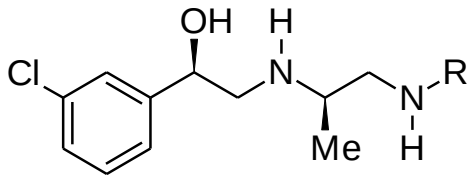
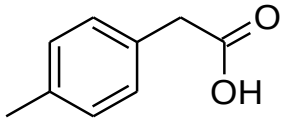
Bioisosterism

β3 adrenoceptor agonists

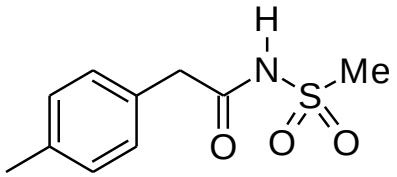


R:



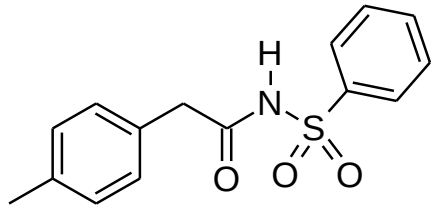
pEC_{50}: 7,8
E_{max}: 117%

R:



pEC_{50}: 8,3
E_{max}: 96%

R:



pEC_{50}: 9,1
E_{max}: 110%

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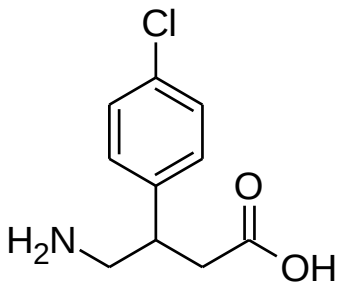
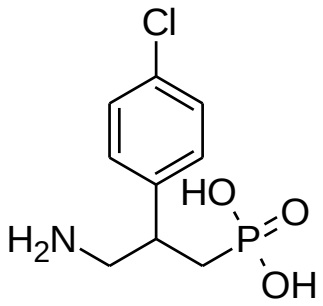
Bioisosterism

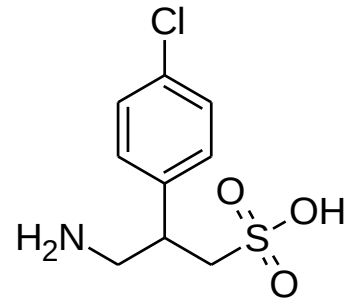
$GABA_B$ agonists



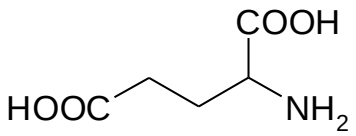
baclofen

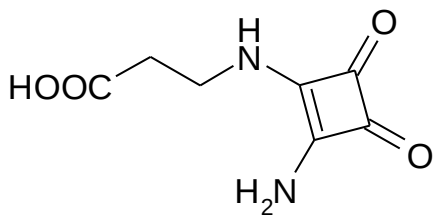


phaclofen



saclofen





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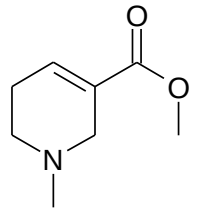
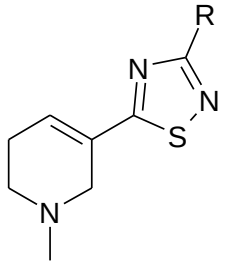
Bioisosterism

Muscarinic agonists



14
Arecoline



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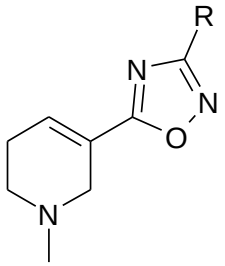

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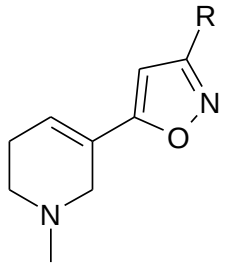

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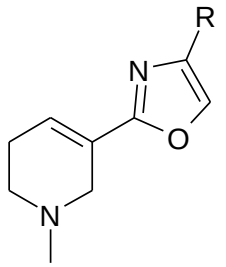

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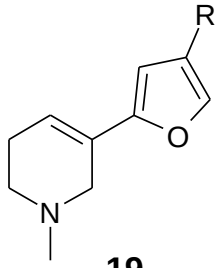

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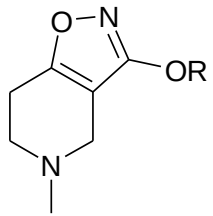

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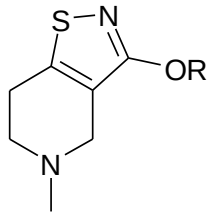

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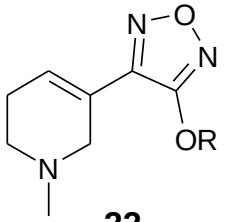

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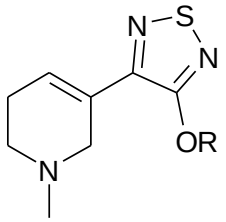

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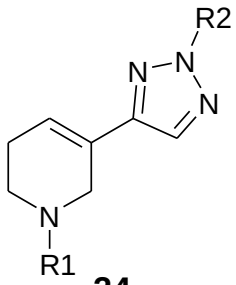

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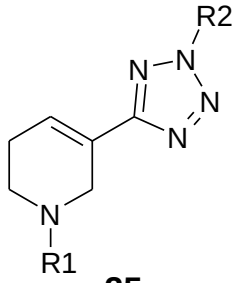

25

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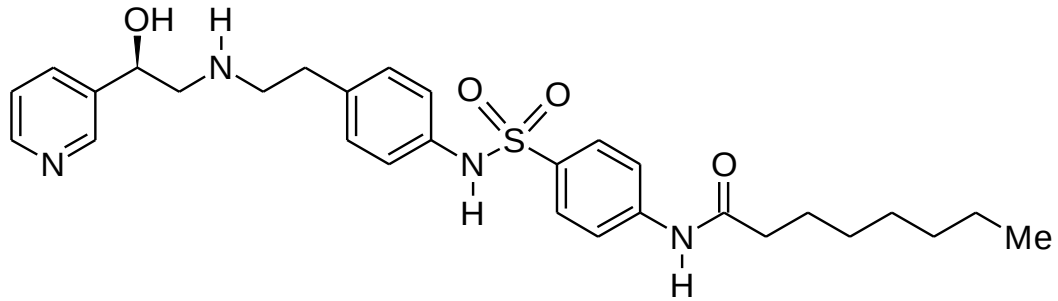
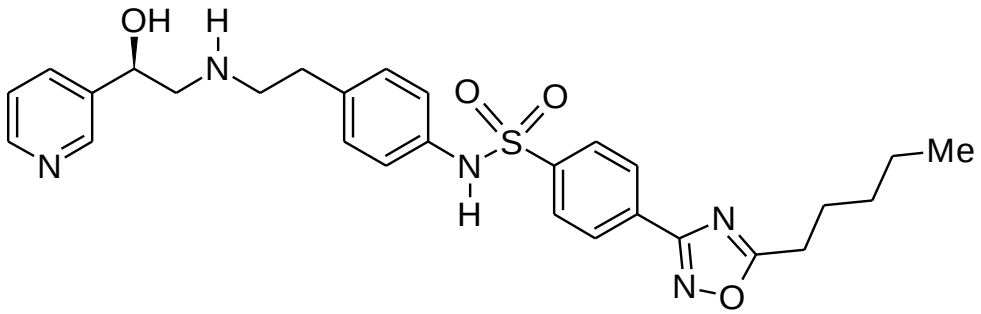
Bioisosterism

β3 adrenoceptor agonists



β_3 EC_{50}: 18 nM, E_{max}: 81%



β_3 EC_{50}: 23 nM, E_{max}: 53%

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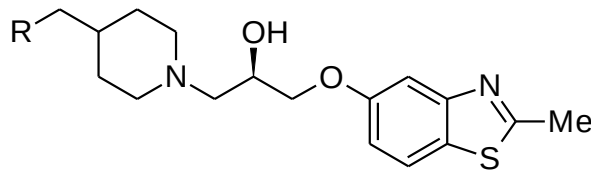
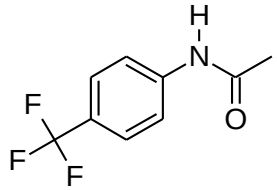
Bioisosterism

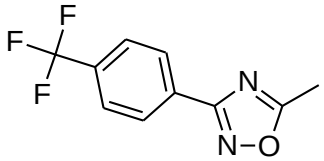
Fatty acid oxidation inhibitors



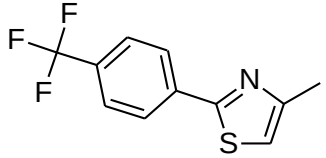
R:



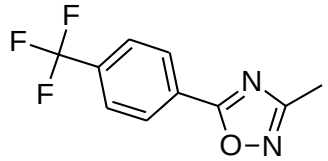
IC50: 7,6 μM
met.stab.: 28%



IC50: 3,6 μM
met.stab.: 72%



IC50: 1,3 μM
met.stab.: 40%



IC50: 0,38 μM
met.stab.: 74%

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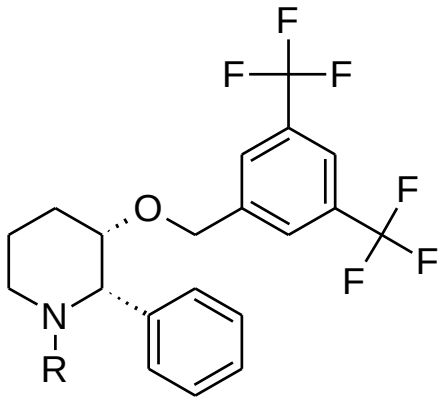
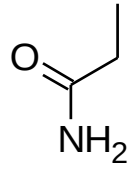
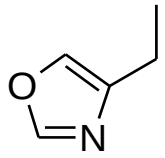
Bioisosterism

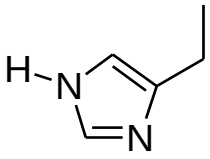
NK1 antagonists

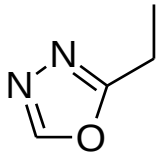


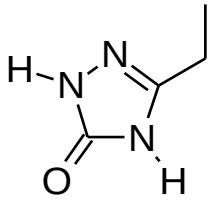
R:











IC_{50}: 1,3 nM

IC_{50}: 1,0 nM

IC_{50}: 0,90 nM

IC_{50}: 0,97 nM

IC_{50}: 0,05 nM

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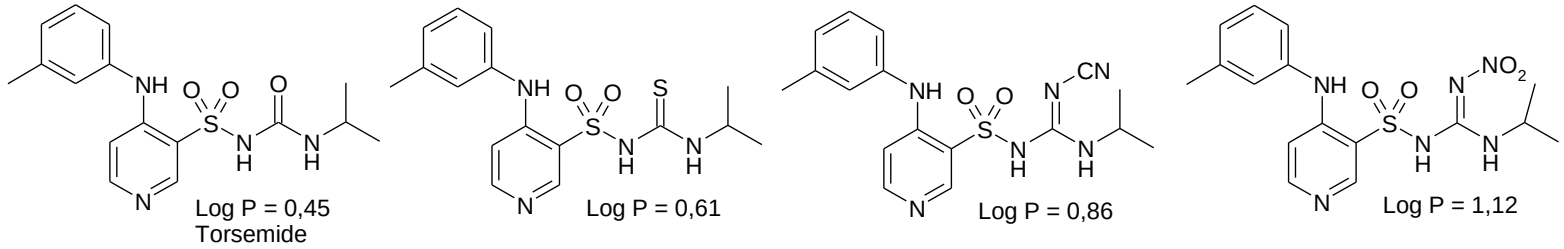
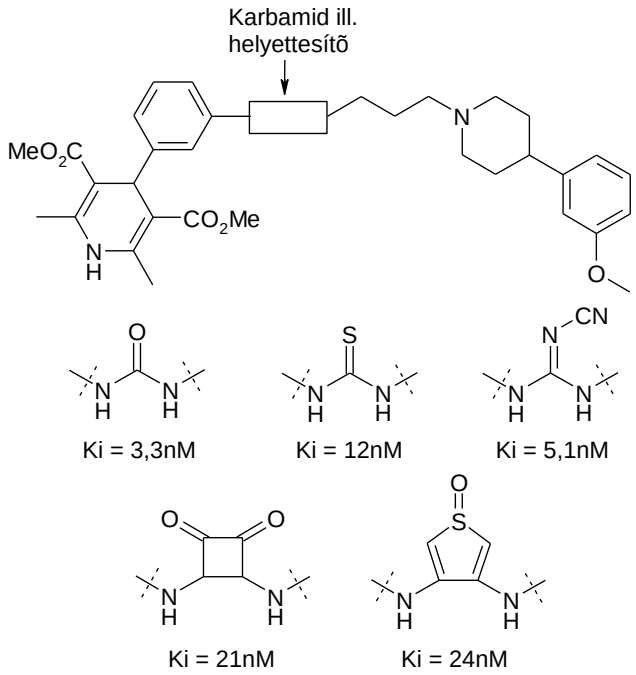
Bioisosterism

Diuretics



NPY Y1 antagonists



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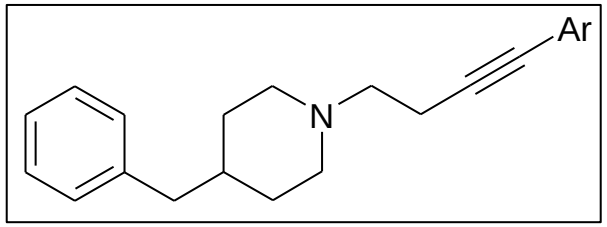
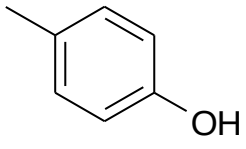
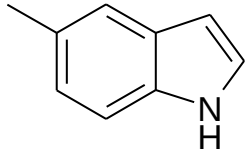
Bioisosterism

NMDA antagonists

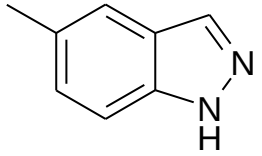




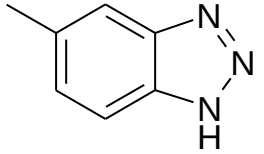
4-Fenol
IC_{50}: 0,17μM



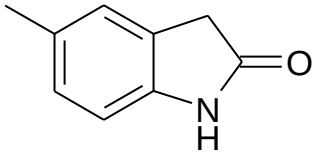
5-Indol
IC_{50}: 0,63μM



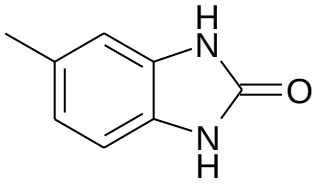
5-Indazol
IC_{50}: 0,25μM



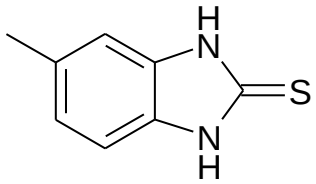
5-Benztriazol
IC_{50}: 0,22μM



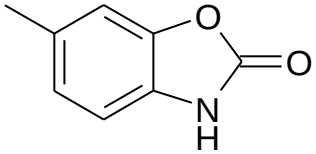
5-Indolon
IC_{50}: 0,32μM



5-Imidazolon
IC_{50}: 0,09μM



5-Imidazol-tion
IC_{50}: 0,18μM



5-Imidazolon
IC_{50}: 0,12μM

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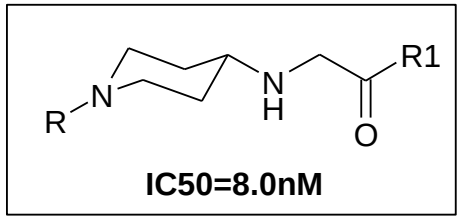
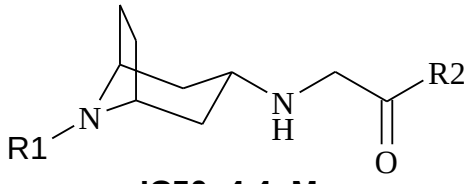
Bioisosterism

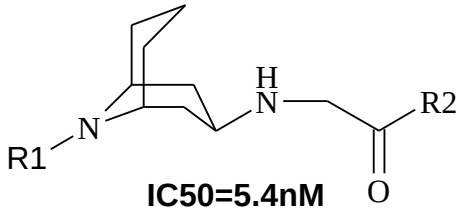
DPP IV inhibitors



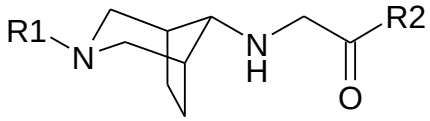
IC50=8.0nM



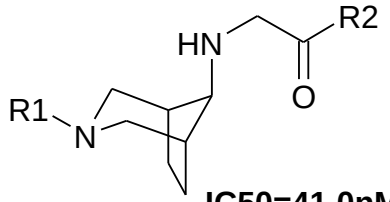
IC50=4.4nM



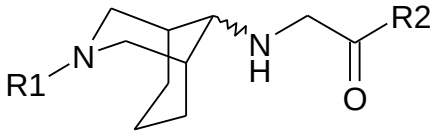
IC50=5.4nM



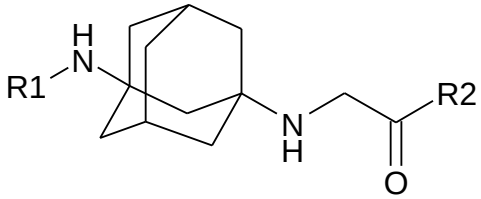
IC50=4.0nM



IC50=41.0nM



IC50=6.7nM



IC50=4.0nM

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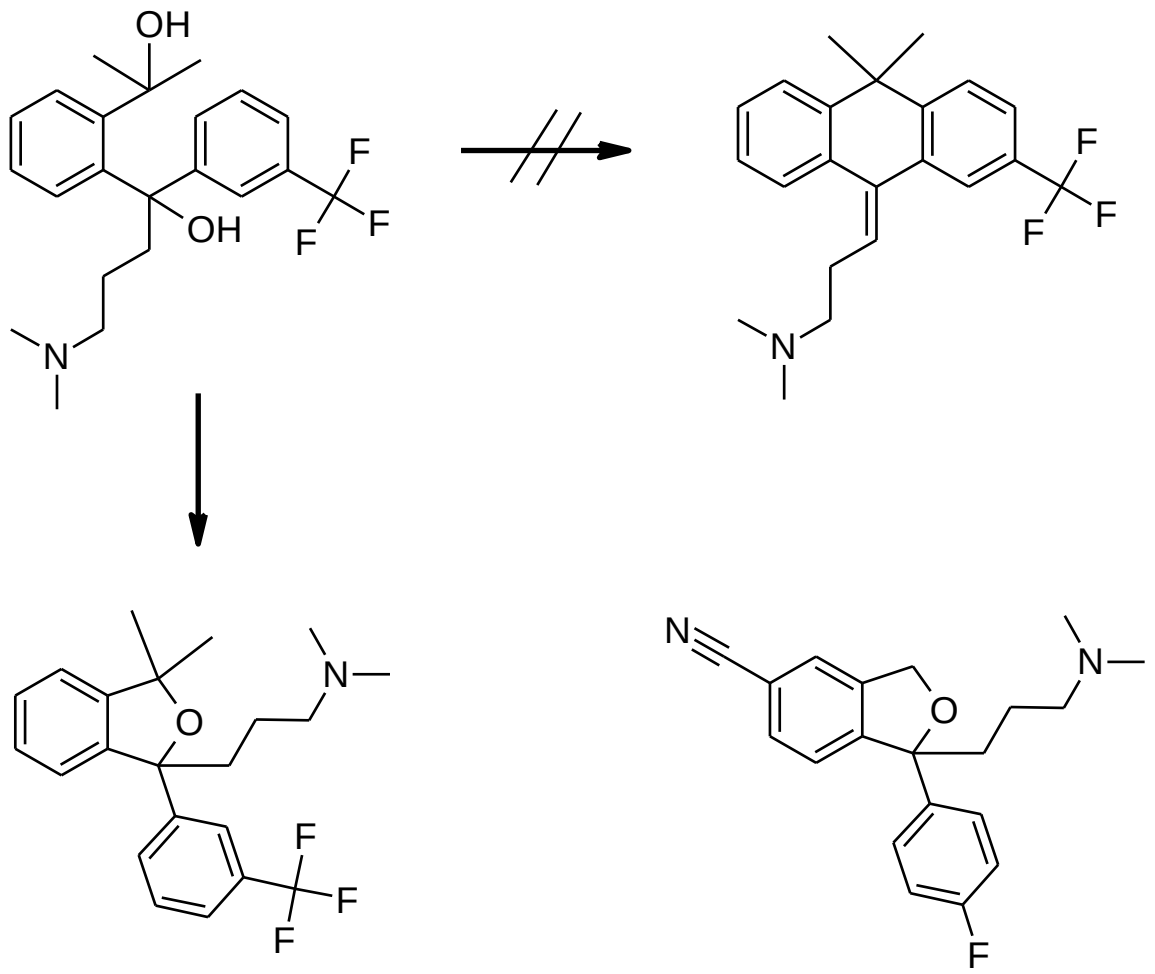
Scaffold hopping



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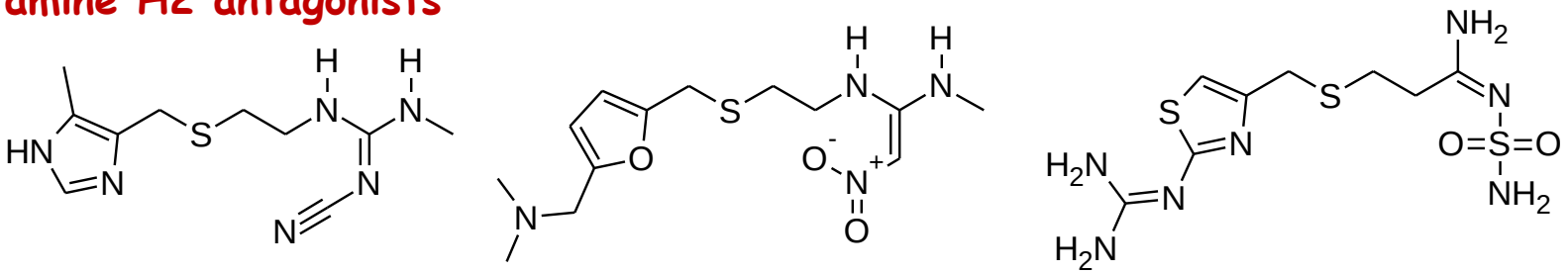
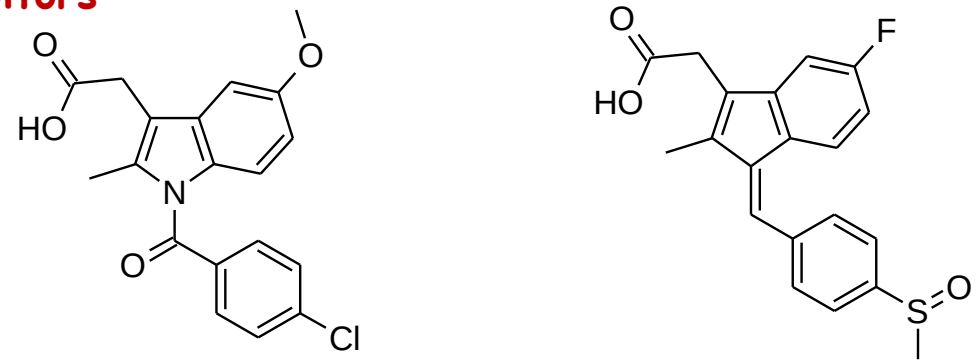
Scaffold hopping

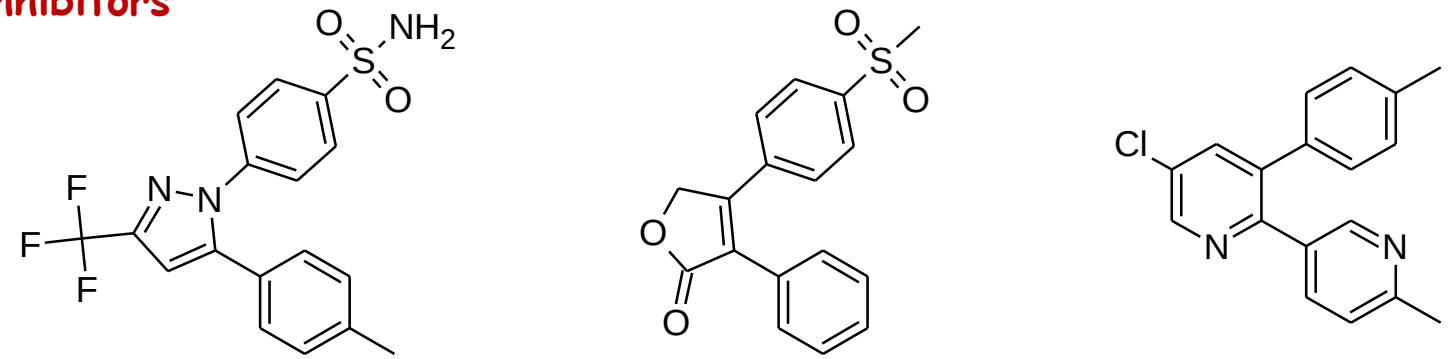
Histamine H2 antagonists



COX1/COX2 inhibitors



COX2 inhibitors



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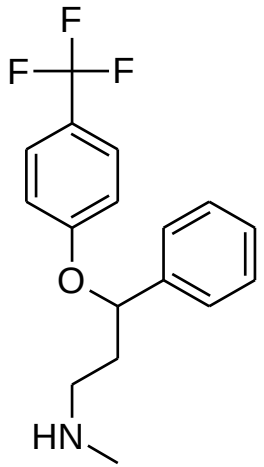
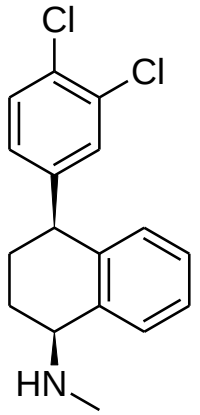
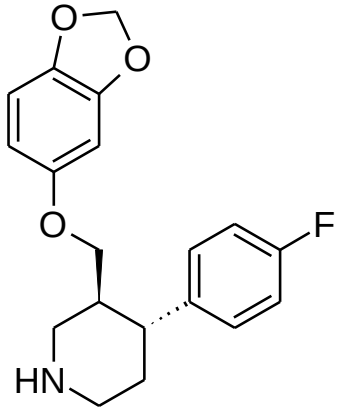
Scaffold hopping

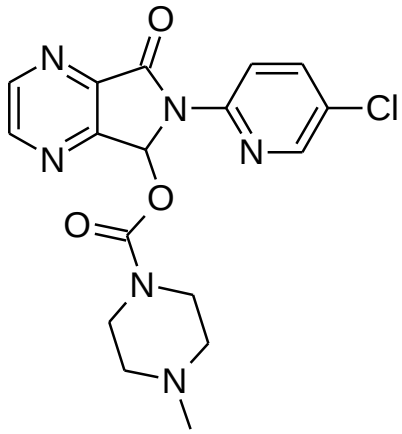
SSRIs

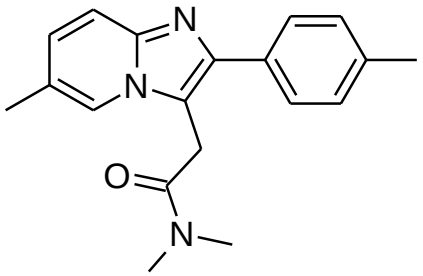


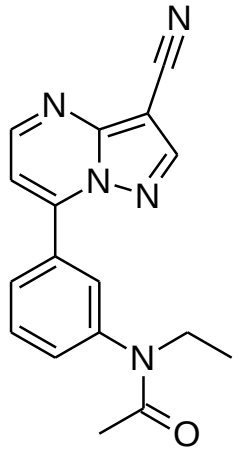




$GABA_A$ ligands



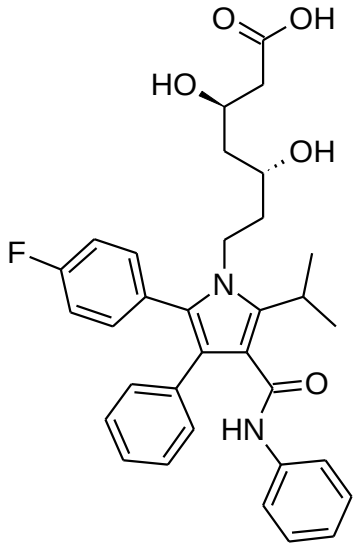


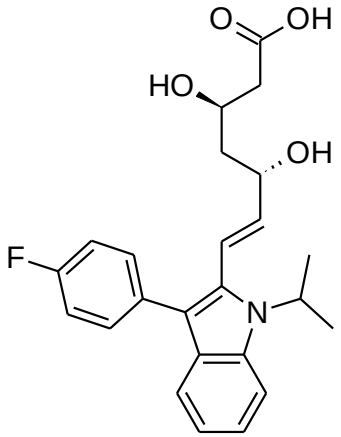


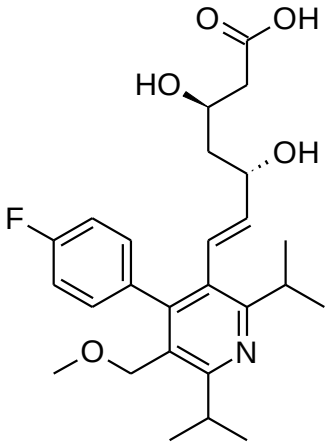
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

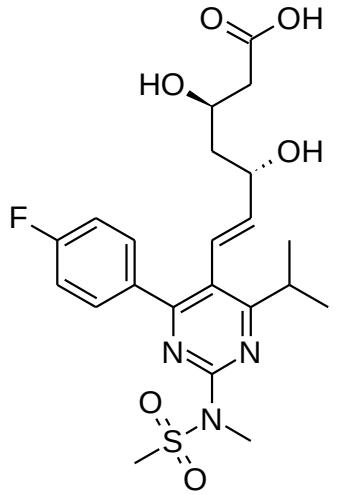
Scaffold hopping

HMG-CoA reductase inhibitors





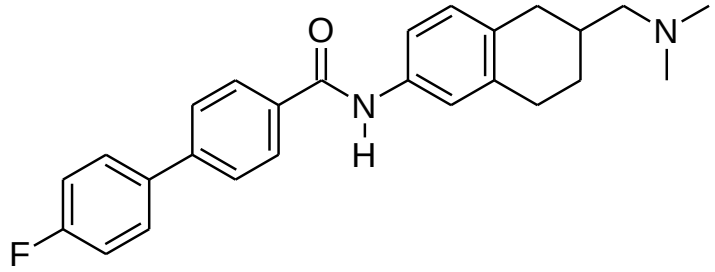




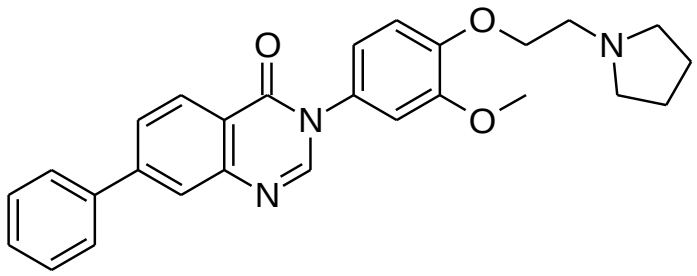
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Scaffold hopping

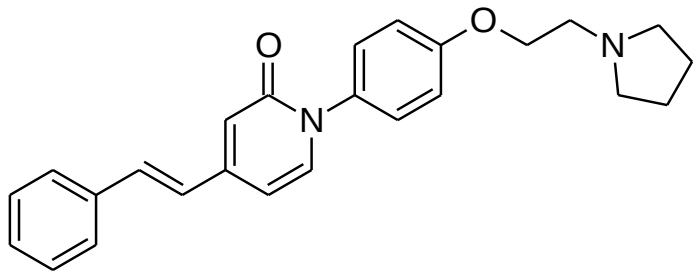
MCHR-1 antagonists



GTPγS IC_{50}: 19 nM



K_i: 2,1 nM (Boehringer)

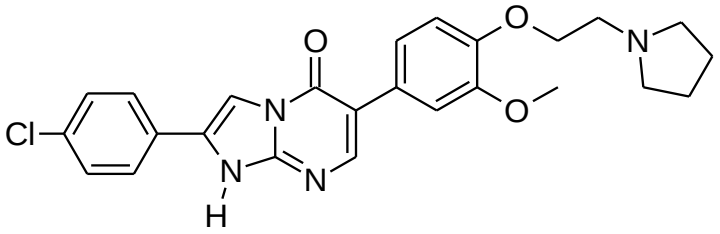


K_i: 1,5 nM (Banyu)

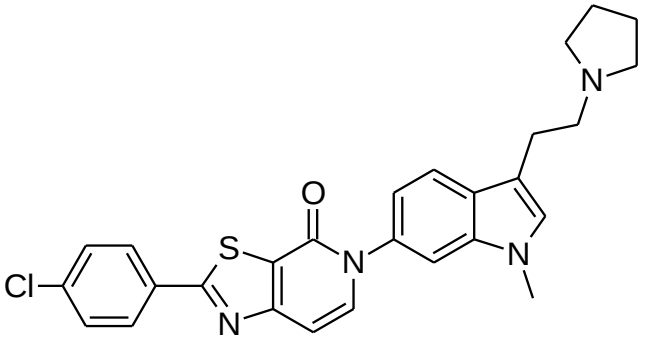
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Scaffold hopping

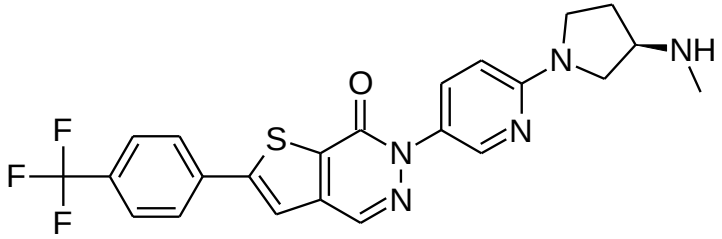
MCHR-1 antagonists



K_i: 77 nM (Pharmacopeia)



K_i: 3,16 nM (Eli Lilly)

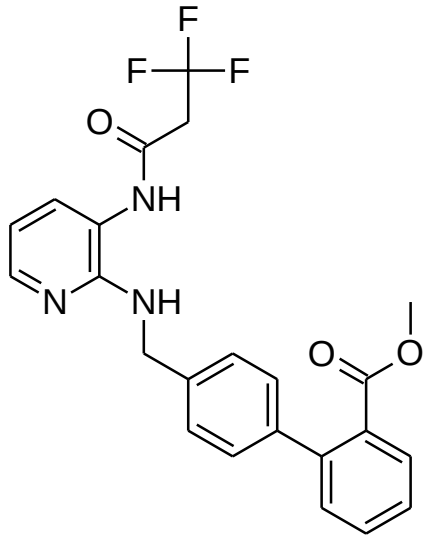


K_i: 3,3 nM (Neurocrine)

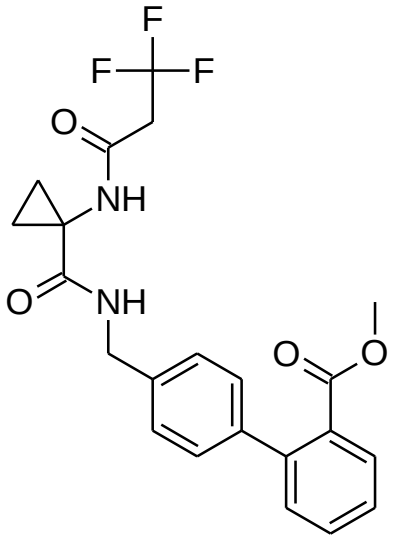
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Scaffold hopping

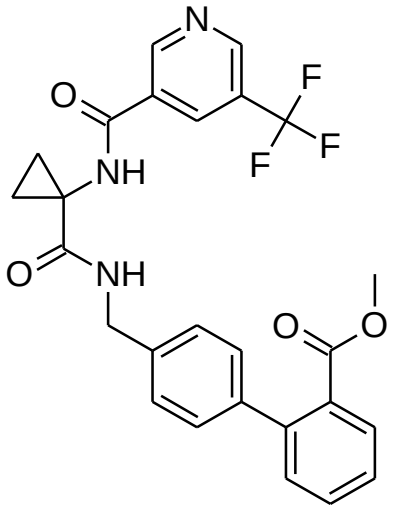
Bradykinin B1 antagonists



K_i: 11.8 nM



K_i: 63 nM

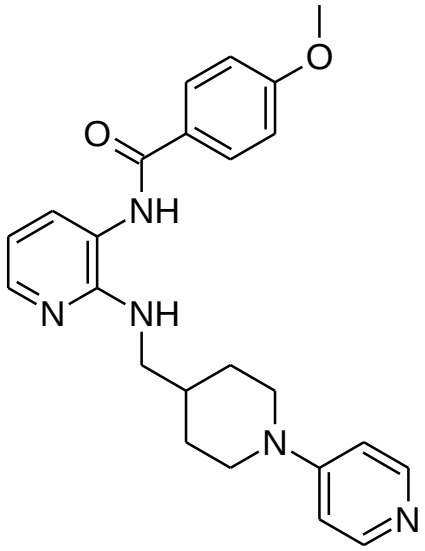


K_i: 1.8 nM

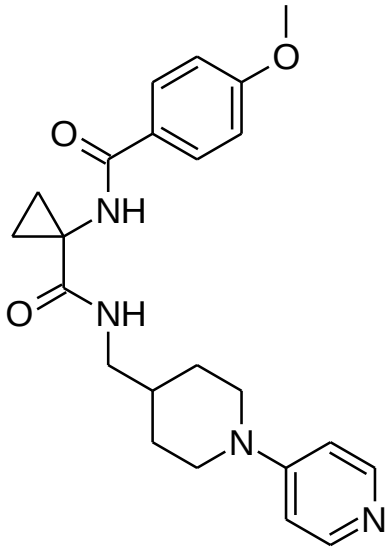
Keserű György Miklós *A gyógyszerkutatás kémiája* Akadémiai Kiadó, Budapest, 2011

Scaffold hopping

Factor Xa inhibitors



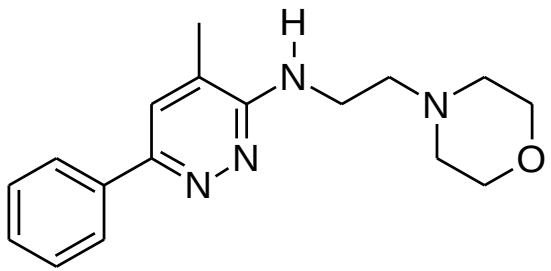
K_i: 39 nM



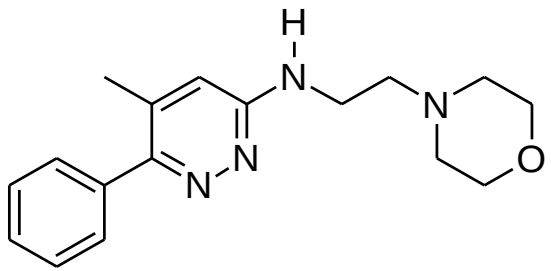
K_i: 175 nM

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

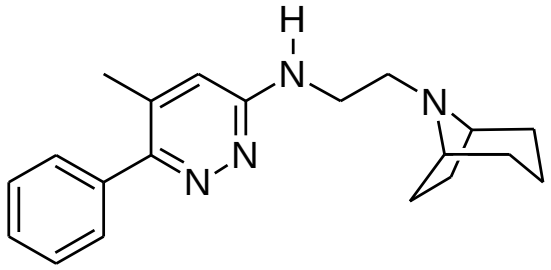
Selective Optimization of Side Activities (SOSA)



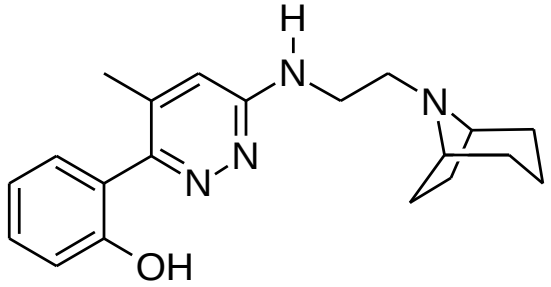
M_1 K_i: 17000 nM
Minaprine (*MAO-A*)



M_1 K_i: 550 nM



M_1 K_i: 50 nM



M_1 K_i: 3 nM

Camille G. Wermuth (1933-2015)

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

Scaffold hopping: practical application of bioisosterism

Druglikeness, structure/property relationships

Christopher A. Lipinski

Born: 1944 (?)
BSc: 1965
PhD: 1968
Pfizer: 1970-2002
„Rule of 5": 1995

Goal: to identify compounds that reached Phase II clinical trial

World Drug Index : 50427 compounds
Out of which United States Adopted Name: 7894
Out of which International Non-proprietary Name: 6320
The sum of the above two groups minus the identicals: 8548
„Indication and usage" suggesting clinical exposure: 3704
Minus 1176 „POLY", 87 „PEPTIDE", 101 „Quat", 53 O=P-O.
REMAINED 2245-MEMBERED COMPOUND LIBRARY CALLED „USAN"

Calculated properties influencing solubility/permeability

Molecular weight: 11% of „USAN" had >500;
Lipophilicity (octanol/water partition coefficient, LogP): 10% of „USAN" had > 5;
H-bond donors (OH+NH): 8% of „USAN" had > 5;
H-bond acceptors (O+N): 12% os „USAN" had > 10.

„The **'rule of 5'** states that: poor absorption or permeation are more likely when:

There are more than 5 H-bond donors (expressed as the sum of OHs and NHs);

The MWT is over 500;

The Log P is over 5 (or MLogP is over 4.15);

There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os)

Compound classes that are substrates for biological transporters are exceptions to the rule."

The **‚Rule of 5'** was implemented at Pfizer in 1995, and published in 1997.

Advanced Drug Delivery Reviews Volume 23, Issue 1-3, 15 January 1997, Pages 3-25

Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings (Review)

Lipinski, C.A. Email Author,
Lombardo, F.,
Dominy, B.W.,
Feeney, P.J.

Cited by: 5377

This paper was republished in a special issue dedicated to Dr. Eric Tomlinson, Advanced Drug Delivery Reviews, A Selection of the Most Highly Cited Articles, 1991-1998

Advanced Drug Delivery Reviews Volume 46, Issue 1-3, 1 March 2001, Pages 3-26

Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings (Article)

Lipinski, C.A. Email Author,
Lombardo, F.,
Dominy, B.W.,
Feeney, P.J.

Cited by: 4942

Christopher A. Lipinski

‚Rule of 5' paper
citations: 10319

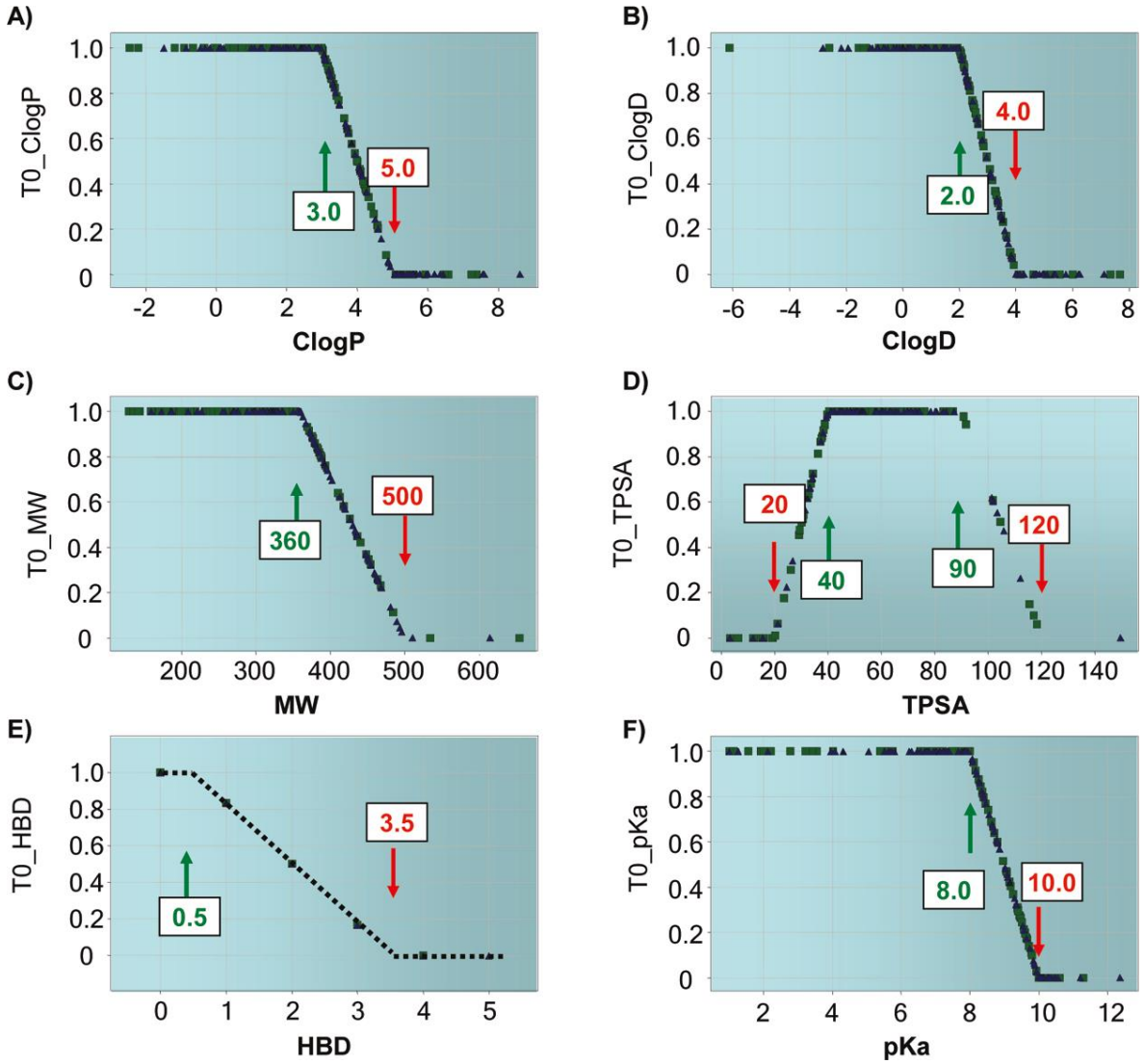
Total papers: 60
Total citations: 15974

Rules for Rapid Property Profiling from Structure

	MW	logP	HBD	HBA	TPSA
Rule of 5 drugs	< 500	< 5	< 5	< 10	< 140
Rule of 4 leads	< 400	< 4	< 4	< 8	< 120
Rule of 3 fragments	< 300	< 3	< 3	< 3	< 60

Graham F. Smith *Progress in Med. Chem.* **48**, 1-29 (2009)

Central Nervous System Multiparameter Optimization (CNS MPO) [1]

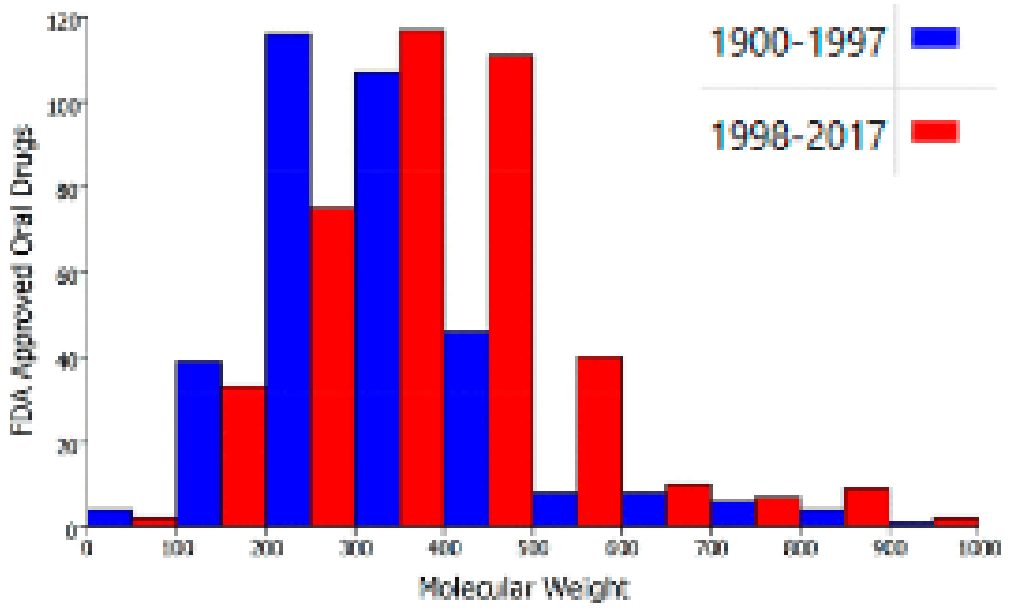


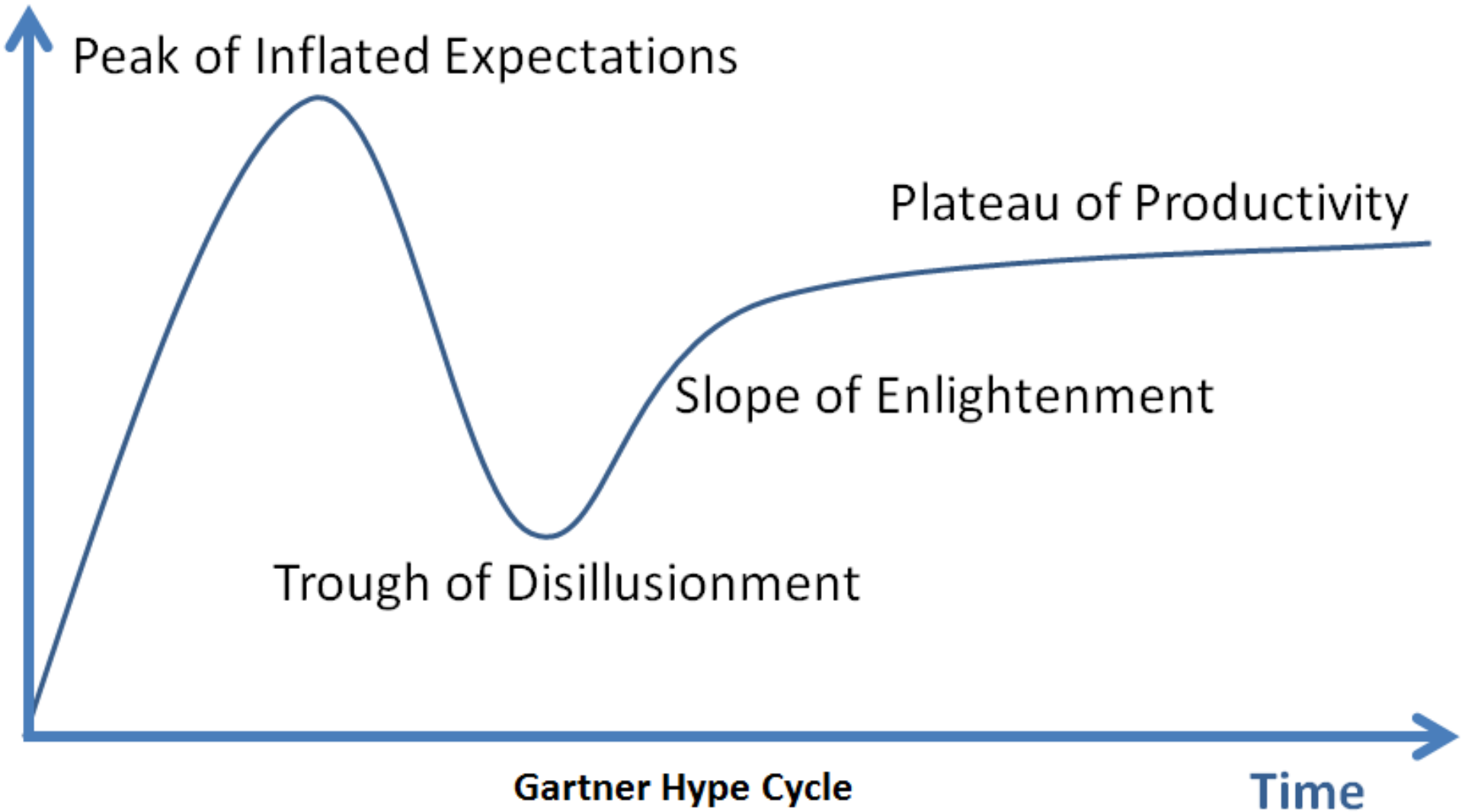
[1]Travis T. Wager et al. *ACS Chemical Neuroscience* **1**, 434-449 (2010)

Two Decades under the Influence of the Rule of Five and the Changing Properties of Approved Oral Drugs

Michael D. Shultz

Publication Date (Web): September 13, 2018 (Perspective)
DOI: 10.1021/acs.jmedchem.8b00686




Peak of Inflated Expectations
Plateau of Productivity
Slope of Enlightenment
Trough of Disillusionment
Gartner Hype Cycle
Time

„Rule of 5”, CNS MPO

Aqueous solubility

Aqueous solubility (s)

„Results indicated that the majority of CNS drugs are highly soluble. Greater than 85% of the drugs have solubility greater than 100 µM; greater than 90% of the drugs have solubility greater than 10 µM."

„ when the measured solubility is **less than 1 µM**, the compound is unlikely to become a CNS drug"

„when the measured solubility if **less than 10 µM**, there are high risks associated with the compound advancement"[1]

General Solubility Equation by Yalkowsky

$$\mathbf{logs = 0.5 - logP - 0.01(m.p. - 25\ ^{o}C)}$$

$$\mathbf{logs_{pH7.4} = 0.5 - logD_{pH7.4} - 0.01(m.p. - 25\ ^{o}C)}$$

[s] = M; [m.p.] = ^{o}C

Solubility decreases 10 fold as logP increases by 1 unit or melting point increases by 100 ^{o}C.

Bioavailability = f(solubility, permeability)
Solubility range: 0.1 µg/ml – 100 mg/ml; Permeability range: 0.001 min^{-1} – 0.05 min^{-1}

[1]Yun W. Alelyunas et al. *B.M.C.L.* **20**, 7312-7316 (2010)

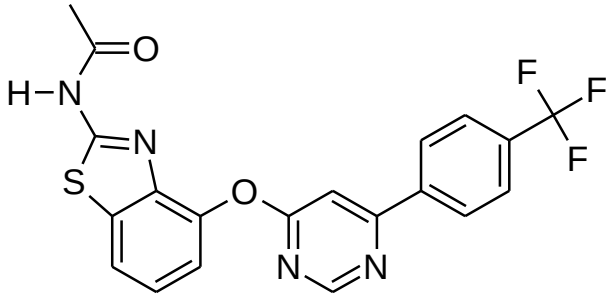
Structure Modification Strategies for Solubility Improvement

Add ionizable group
Reduce logP
Add hydrogen bonding
Add polar group
Reduce molecular weight
Out-of-plane substitution to reduce crystal packing
Construct prodrug

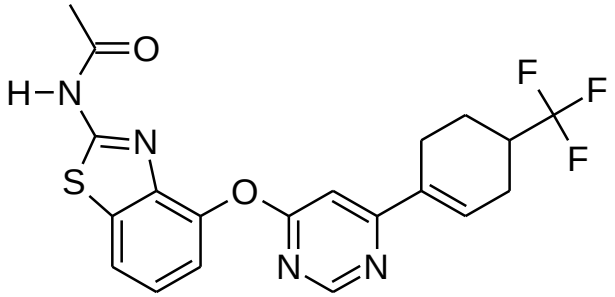
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Solubility

TRPV1 antagonists



rat TRPV1 (acid) IC_{50}: 0.5 nM
s (0.01 M HCl): < 1 µg/ml
clogP: 4.6
m.p.: 219-221 °C

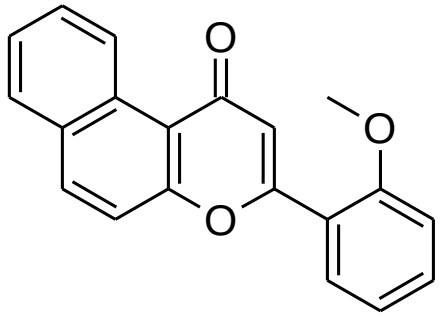


rat TRPV1 (acid) IC_{50}: 2.4 nM
s (0.01 M HCl): 13 µg/ml
clogP: 3.7
m.p.: 130-131 °C

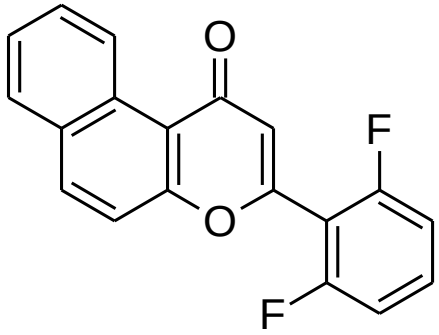
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

AhR agonists



EROD EC_{50}: 0.27 nM
s: 45.8 µg/ml
clogP: 4.1
m.p.: 192-193 °C

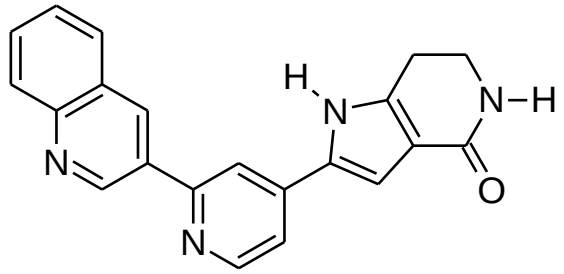


EROD EC_{50}: 0.20 nM
s: 248 µg/ml
clogP: 4.9
m.p.: 150 °C

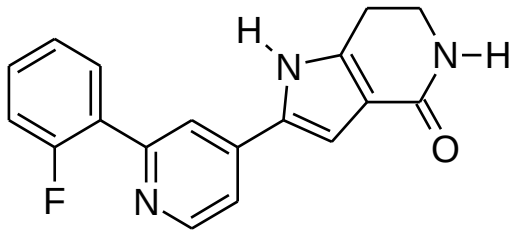
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

MK-2 inhibitors



MK-2 IC_{50}: 8.5 nM
s: < 0.4 µM
clogP: 2.7

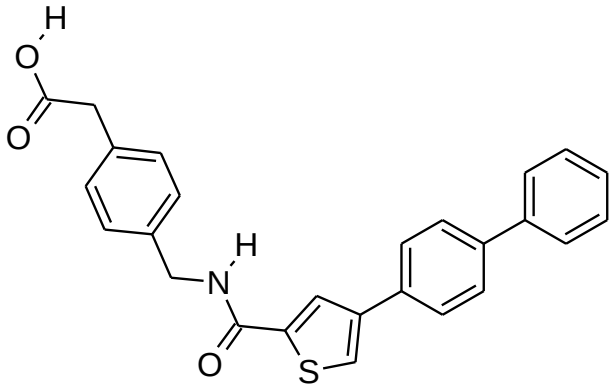


MK-2 IC_{50}: 126 nM
s: 160 µM
clogP: 2.9

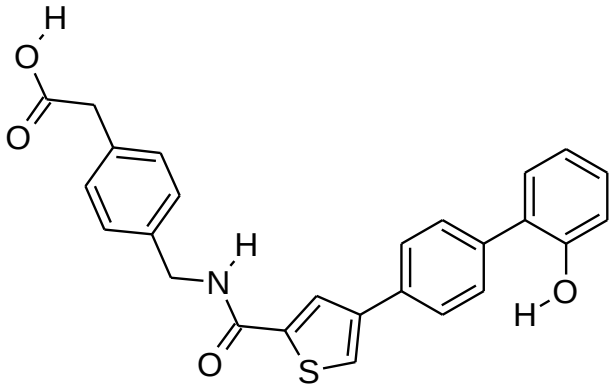
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

MMP-12 inhibitors



MMP-12 IC_{50}: 70 nM
s: < 1 µg/ml
clogP: 5.7

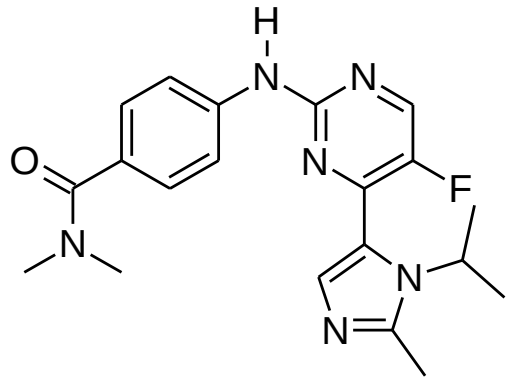


MMP-12 IC_{50}: 90 nM
s: 134 µg/ml
clogP: 4.6

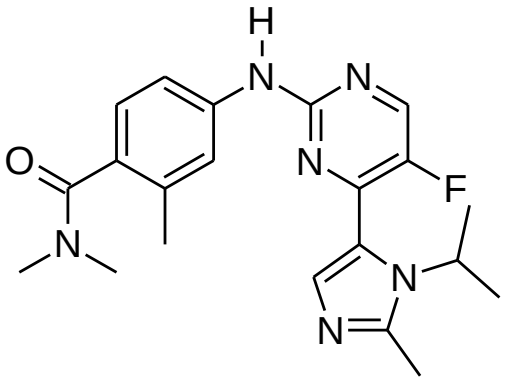
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

CDK2 inhibitors



CDK-2 IC_{50}: 2 nM
s: 11 µM
clogP: 2.5

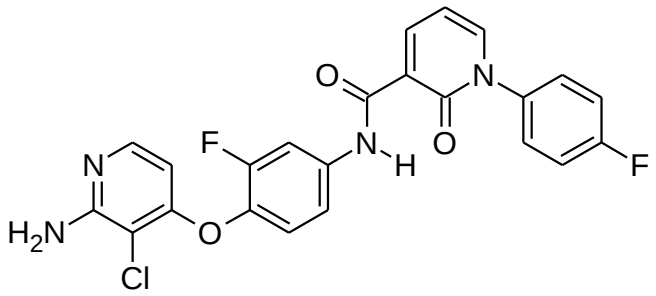


CDK-2 IC_{50}: 9 nM
s: > 2600 µM
clogP: 3.0

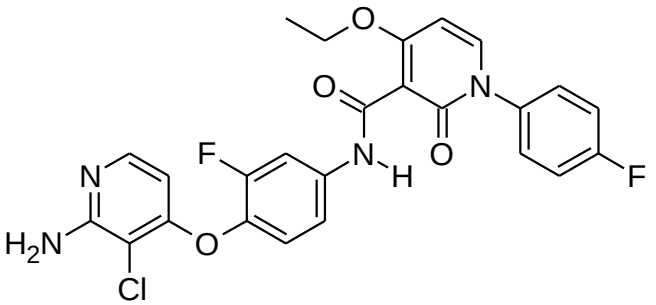
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

Met kinase inhibitors



Met IC_{50}: 1.0 nM
s at pH 1: < 10 µg/ml
clogP: 4.0

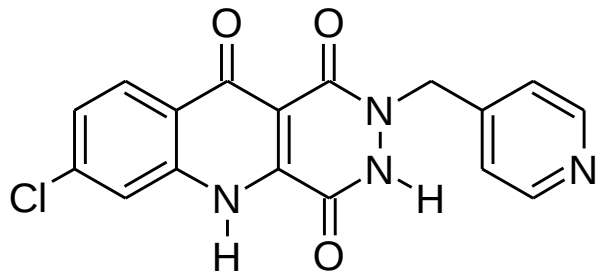


Met IC_{50}: 3.9 nM
s at pH 1: 400 µg/ml
clogP: 4.4

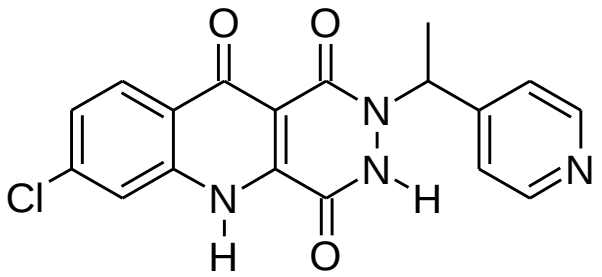
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

NMDA antagonists



[^{3}H]MDL 105519 K_i: 115 nM
s at pH 7.4: 0.05 mg/ml
Rat F: 5%
m.p.: 277-278 °C
clogP: 0.98

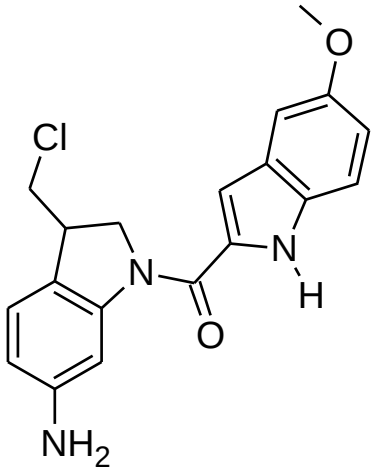


[^{3}H]MDL 105519 K_i: 248 nM
s at pH 7.4: > 0.29 mg/ml
Rat F: 30%
m.p.: 245-247 °C
clogP: 1.3

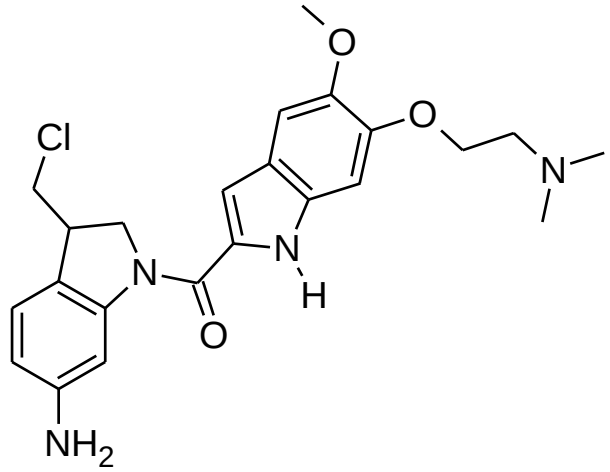
Minoru Ishikawa and Yuichi Hashimoto *J. Med. Chem.* **54**, 1539-1554 (2011)

Solubility

Antitumor agents



AA8 IC_{50}: 0.31 μM
s: 23 μM

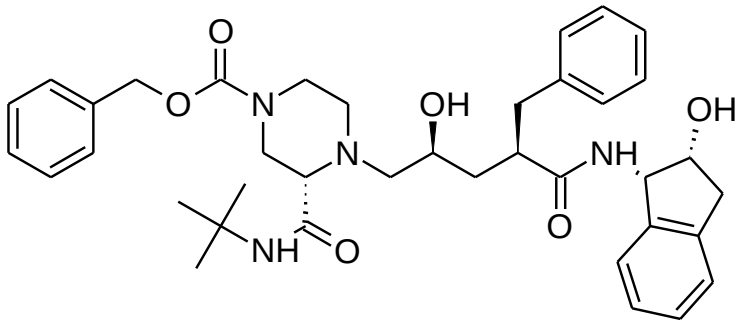


AA8 IC_{50}: 0.22 μM
s: > 1200 μM

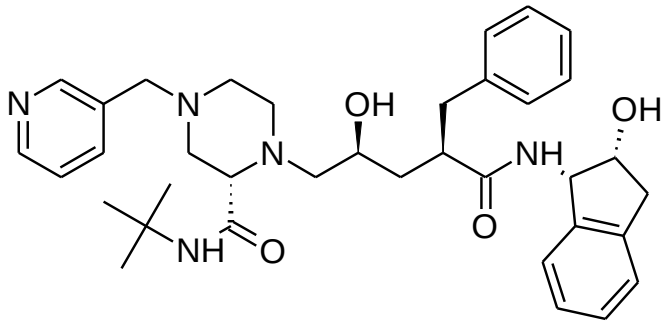
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Solubility

Protease inhibitors (indinavir)



logP: 4.67
s: < 0.001 mg/ml
Cmax: < 0.10 µM

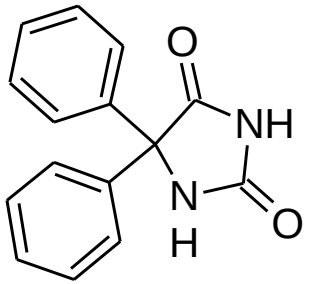


logP: 2.92
s: < 0.07 mg/ml
Cmax: 11.4 µM

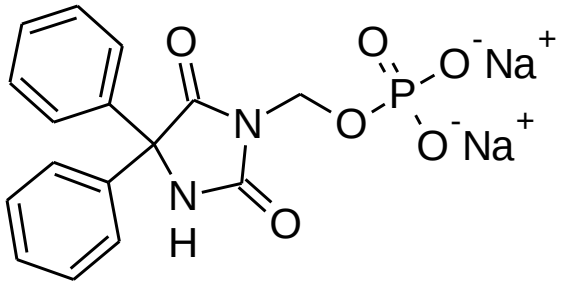
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Solubility

Prodrug for increasing solubility



Phenytoin
s: 20-25 µg/ml
Problematic formulation



Fosphenytoin
s: 142 mg/ml (4400 fold!)
Cerebryx™

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

Metabolism, metabolic stability, prodrugs

Metabolism describes the chemical reactions that change drugs into compounds which are easier to eliminate. The products of these chemical reactions are called metabolites.

Phase 1 metabolism involves chemical reactions such as oxidation (most common), reduction and hydrolysis. There are three possible results of phase 1 metabolism. The drug becomes completely inactive. In other words, the metabolites are pharmacologically inactive. One or more of the metabolites are pharmacologically active, but less so than the original drug. The original substance is not pharmacologically active, but one of its metabolites is. The original substance is called a prodrug.

Phase 2 metabolism involves reactions that chemically change the drug or phase 1 metabolites into compounds that are soluble enough to be excreted in urine. In these reactions, the molecule (drug or metabolite) is attached to an ionisable grouping. This is called conjugation and the product is called a conjugate. Metabolites formed in phase 2 are unlikely to be pharmacologically active.

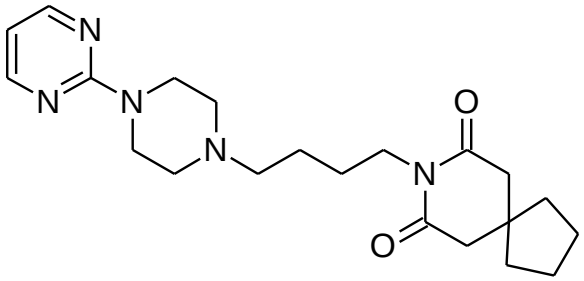
Structure Modification Strategies for Phase I Metabolic Stability Improvement

Block metabolic site by adding fluorine
Block metabolic site by adding other groups
Remove labile functional group
Cyclization
Change the ring size
Change chirality
Reduce lipophilicity

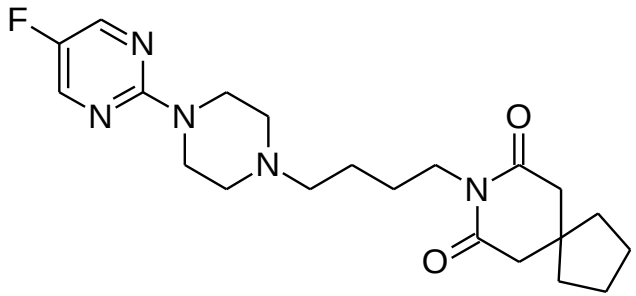
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

$5HT_{1A}$ partial agonists (Buspiron/anxiolytic)



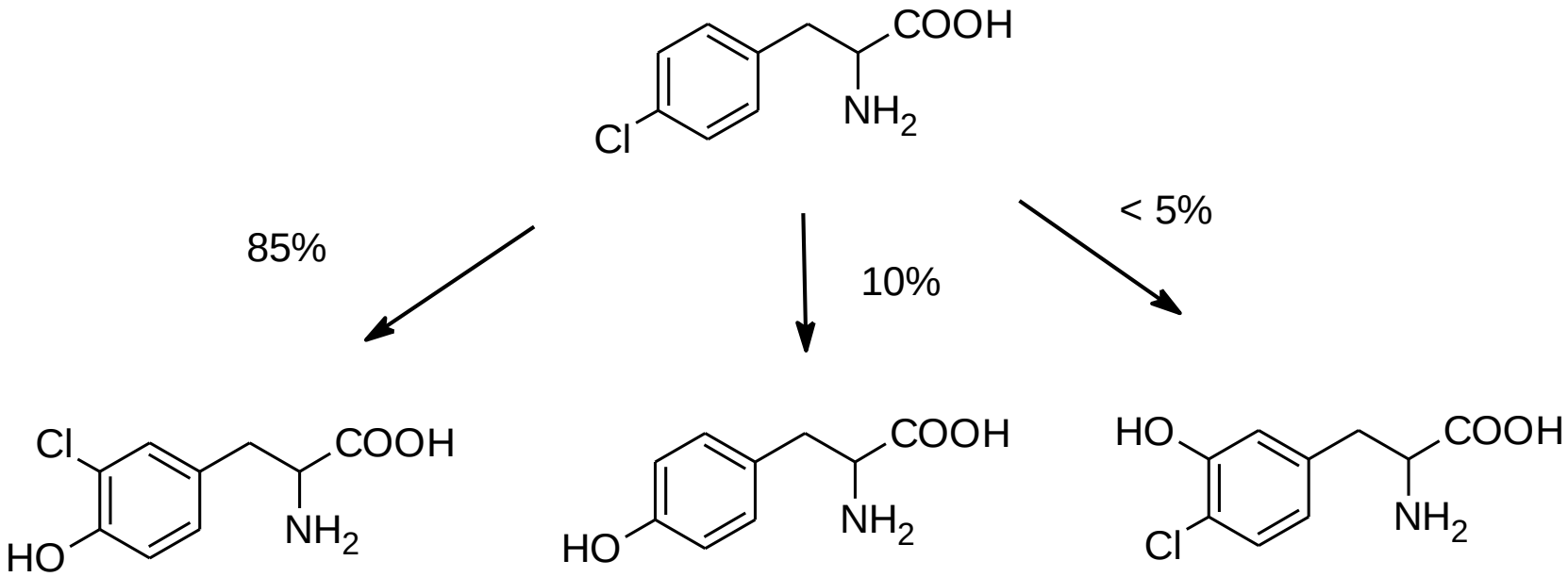
$5HT_{1A}$ IC_{50}: 25 nM
CYP3A4 $t_{1/2}$: 4.6 min



$5HT_{1A}$ IC_{50}: 63 nM
CYP3A4 $t_{1/2}$: 52.3 min

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

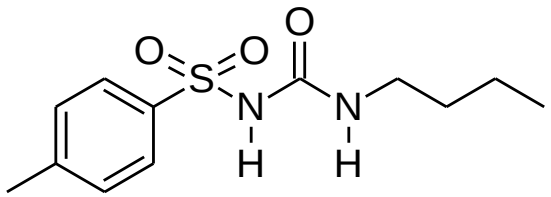
Phase I Metabolic Stability

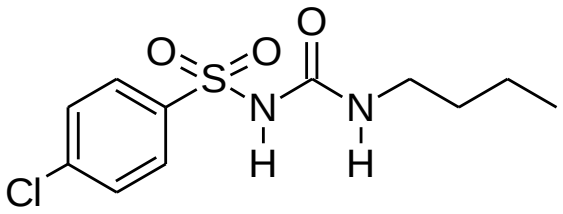


Gordon Guroff et al. *Science* **158**, 1524-1530 (1967)

Phase I Metabolic Stability

Hypoglycemics (Tolbutamide-Chlorpropamide)





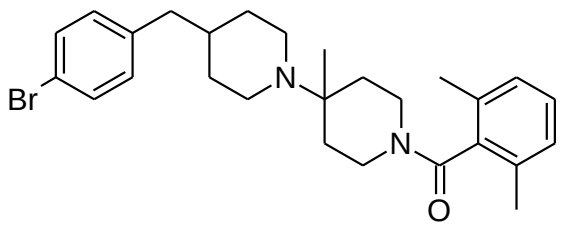
Clearance: 0.22 ml/min/kg
$t_{1/2}$: 5.9 hr

Clearance: 0.03 ml/min/kg
$t_{1/2}$: 33 hr

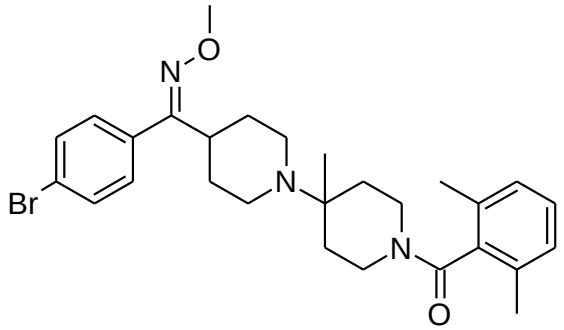
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

CCR5 receptor antagonists (anti-HIV avtivity)



CCR5 IC_{50}: 10.0 nM
AUC (p.o.): 0.04 h.μg/ml

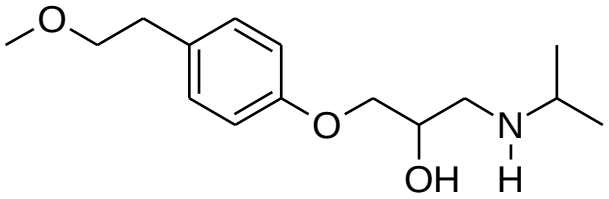


CCR5 IC_{50}: 1.3 nM
AUC (p.o.): 1.2 h.μg/ml

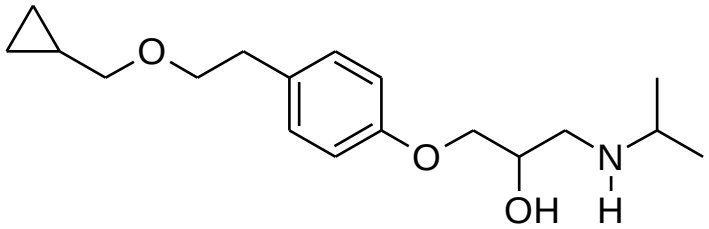
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

β-blockers (metoprolol - betaxolol)



First Pass Elimination: 50%
Human $t_{1/2}$: 3.5 – 6 hr

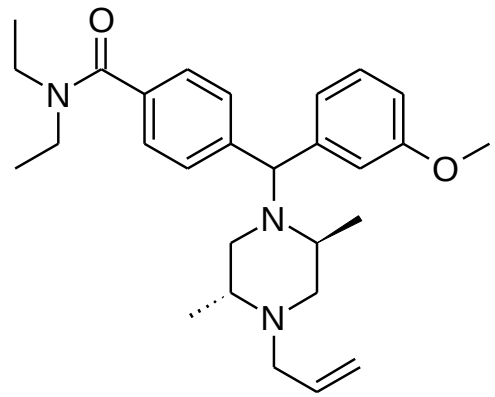


First Pass Elimination: 15%
Human $t_{1/2}$: 16 – 22 hr

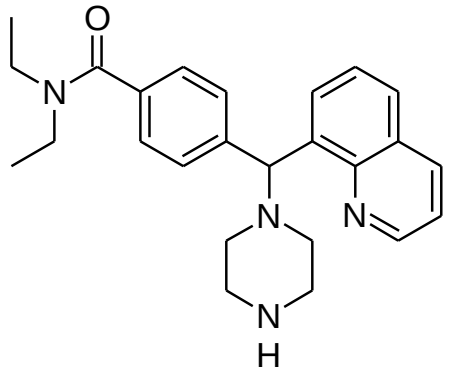
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

δ-opioid agonists



IC_{50}: 1.3 nM
Stability (rat): 1%

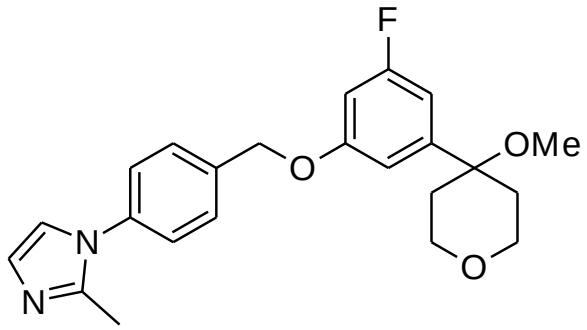


IC_{50}: 0.51 nM
Stability (rat): 52%

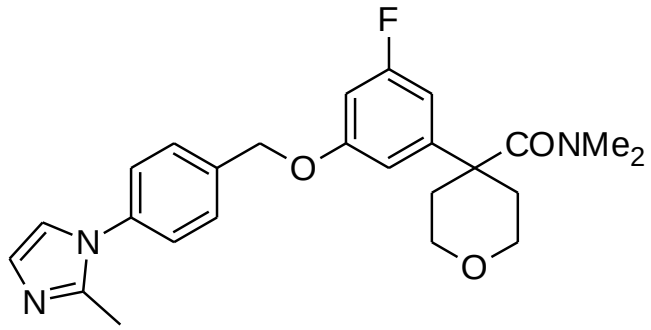
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

5-lipoxygenase inhibitors



IC_{50}: 60 nM
C_{max}: 0.24 µg/ml

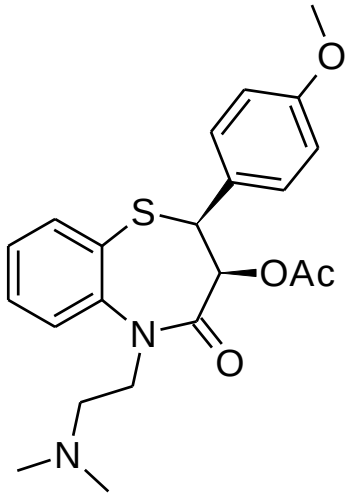


IC_{50}: 340 nM
C_{max}: 1.57 µg/ml

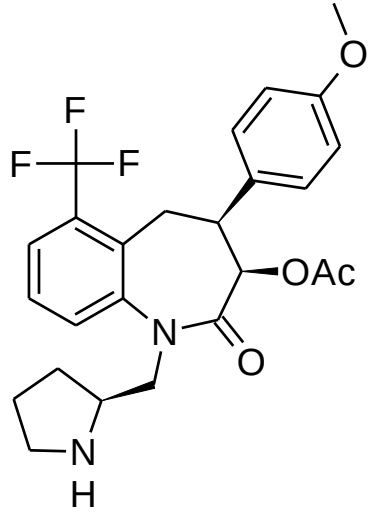
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase I Metabolic Stability

Calcium channel blockers



IC_{50}: 210 nM
Decrease in BP (0-6 h): 23%



IC_{50}: 91 nM
Decrease in BP (0-6 h): 45%

David M. Floyd et al. *J. Med. Chem.* **35**, 756-772 (1992)

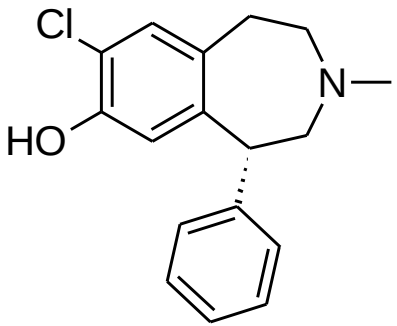
Structure Modification Strategies for Phase II Metabolic Stability Improvement

Introduce electron-withdrawing groups and/or steric hindrance
Change phenolic hydroxyl to cyclic urea or thiourea
Change phenolic hydroxyl to prodrug

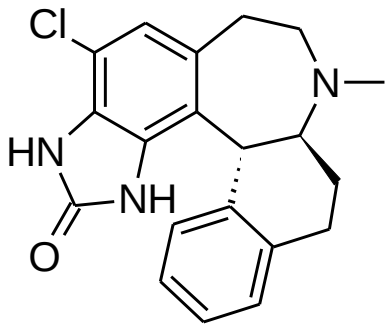
Edward H. Kerns and Li Di *Drug-like Properties: Concepts, Structure, Design and Methods* Academic Press/Elsevier (2008)

Phase II Metabolic Stability

Dopamine D_1/D_5 antagonists



D_1 Ki: 1.2 nM
D_5 Ki: 2.0 nM
F: 0.6 %

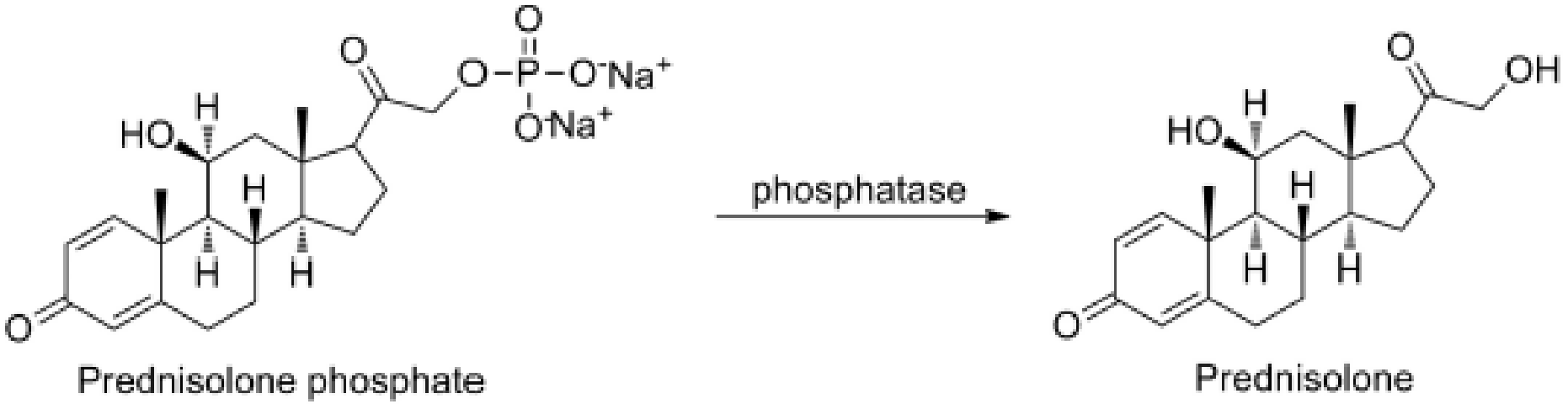


D_1 Ki: 7 nM
D_5 Ki: 4.2 nM
F: 87 %

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

Prodrugs

Immunosuppressant, antiinflammatory (s>30 times greater)

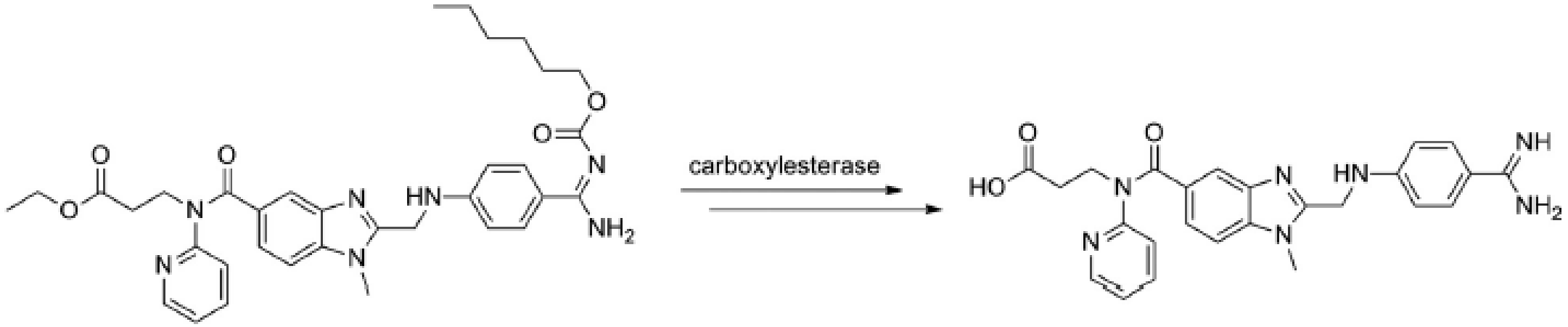


Prednisolone phosphate

Prednisolone

Prodrugs

Direct thrombin inhibitor for stroke prevention (BA: from 0% to 7%)



Dabigatran etexilate

Dabigatran

Prodrugs

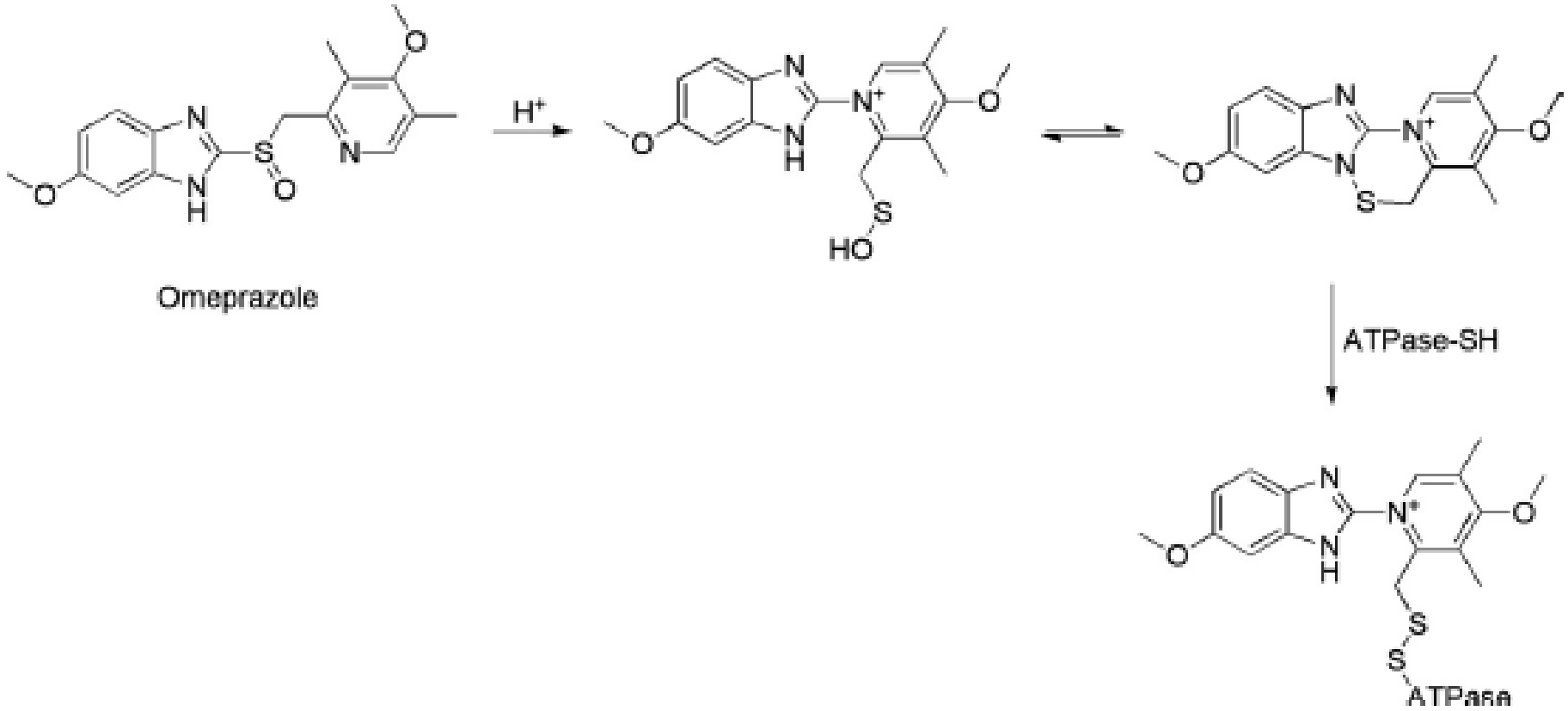
β2-agonist bronchodilator (once daily vs. three times daily)

Bambuterol

Terbutaline

Prodrugs

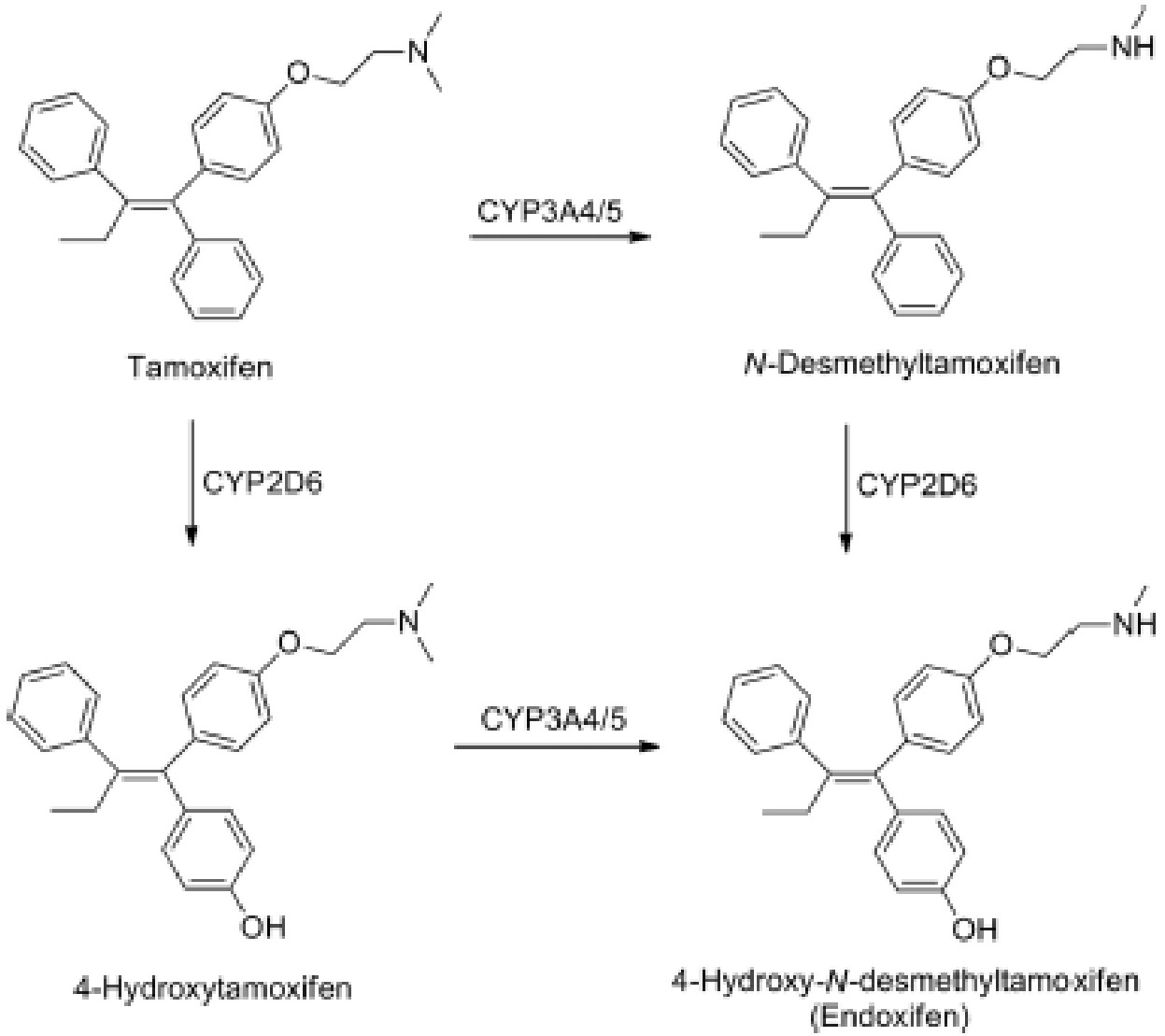
Proton pump inhibitor (PPI) blocks H^+/K^+ ATPase



Omeprazole

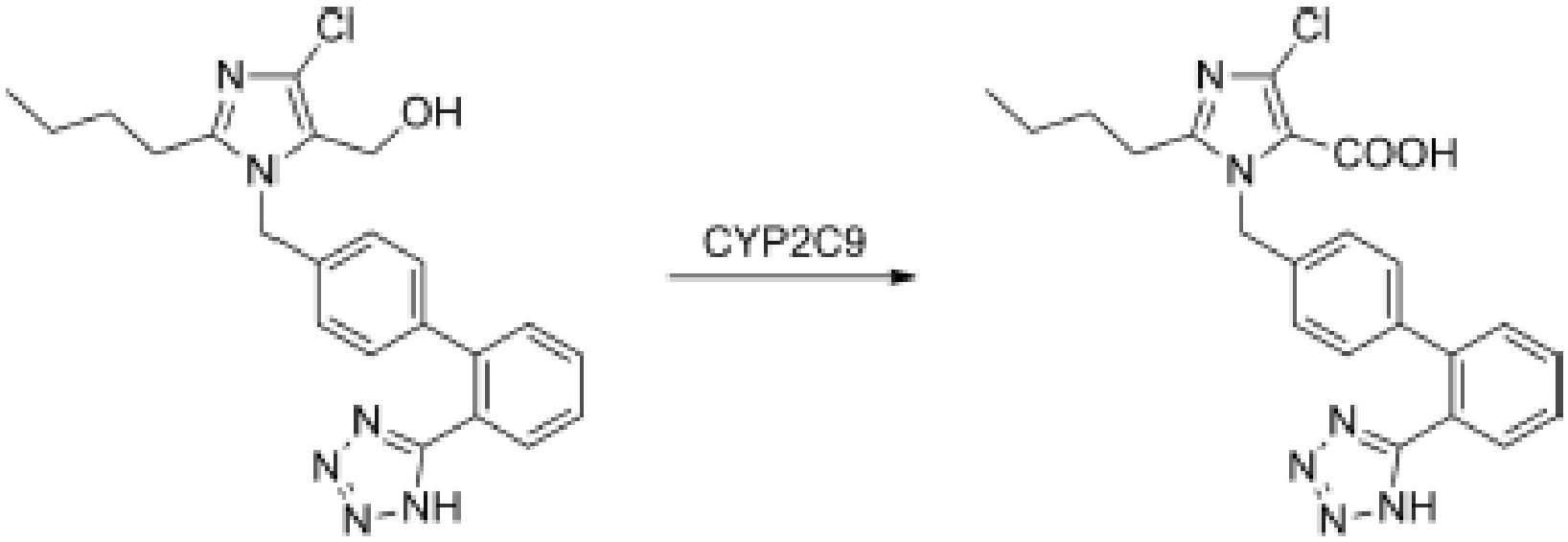
Prodrugs

Synthetic antiestrogen in breast cancer therapy



Prodrugs

Angiotensin II type 1 receptor antagonist (14% converted to EXP3174, 10-40 fold more potent)

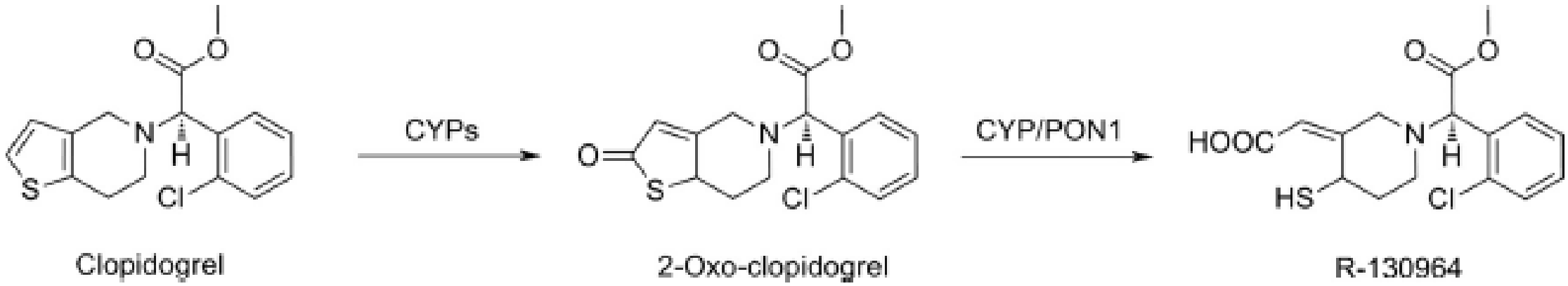


Losartan

EXP3174

Prodrugs

Antithrombotic (only 15% is transformed to the active R-130964 the rest turns to inactive acid)



Scaffold hopping: practical application of bioisosterism

Druglikeness, structure/property relationships

„Rule of 5”, CNS MPO

Aqueous solubility

Metabolism, metabolic stability, prodrugs