STRUCTURE and ACTIVITY of DRUGS - practical aspects IV.

György Domány

Scientific adviser
Gedeon Richter Plc.

Sir James Whyte Black (1924 – 2010) was a Scottish physician and pharmacologist. Black established a Veterinary Physiology department at the University of Glasgow, where he became interested in the effects of adrenaline on the human heart. He went to work for ICI Pharmaceuticals in 1958 and, while there, developed propranolol, a beta blocker used for the treatment of heart disease. Black was also responsible for the development of cimetidine, an H2 receptor antagonist, a drug used to treat stomach ulcers. He was awarded the Nobel Prize for Medicine in 1988 for work leading to the development of propranolol and cimetidine.

"The most fruitful basis of the discovery of a new drug is to start with an old drug."

Sir James Black

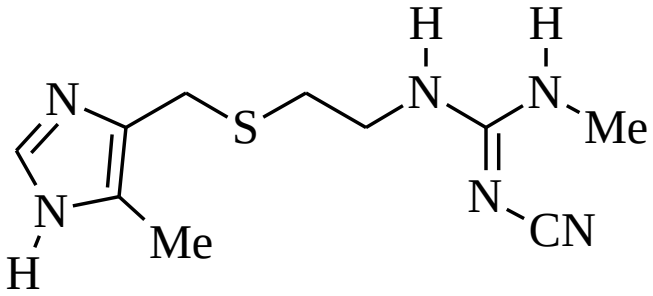
A chromophore is the part of a molecule responsible for its color.

A pharmacophore?

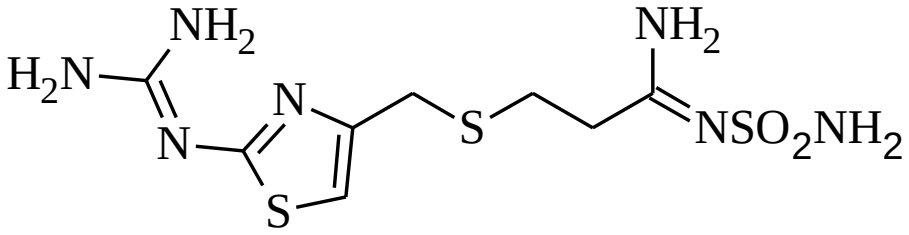
A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response.

C.-G. Wermuth et al., *Pure Appl. Chem.* 1998, 70: 1129-1143

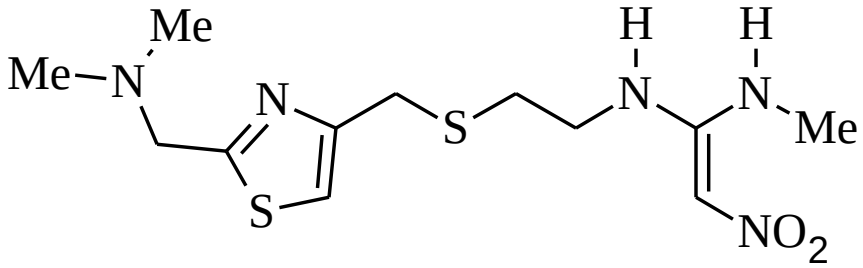
Histamine H_2 receptor antagonist anti-ulcer agents



cimetidine 1971
(Smith Kline & French)

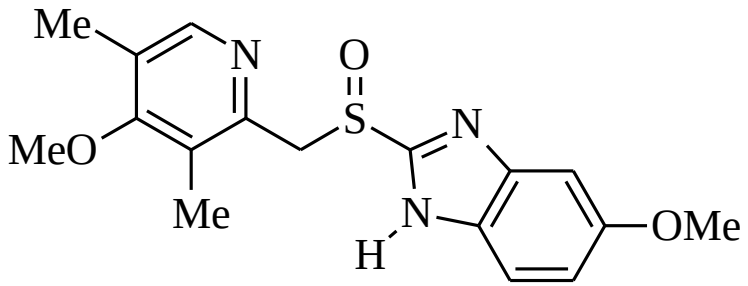


famotidine 1979
(Yamanouchi)

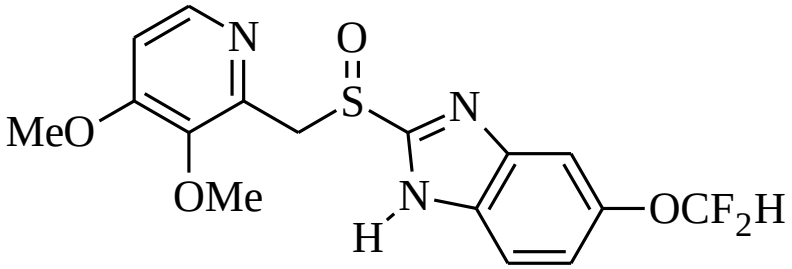


nizatidine 1980
(Eli Lilly)

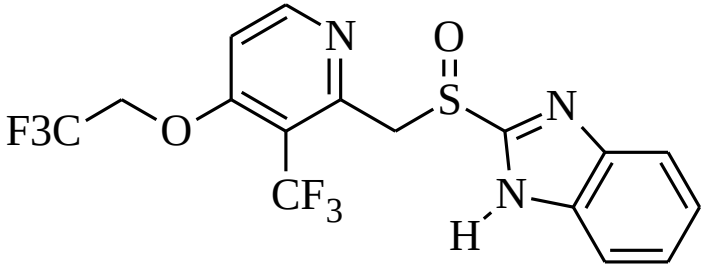
Proton pump inhibitor anti-ulcer agents



omeprazole 1978
(Hässle)

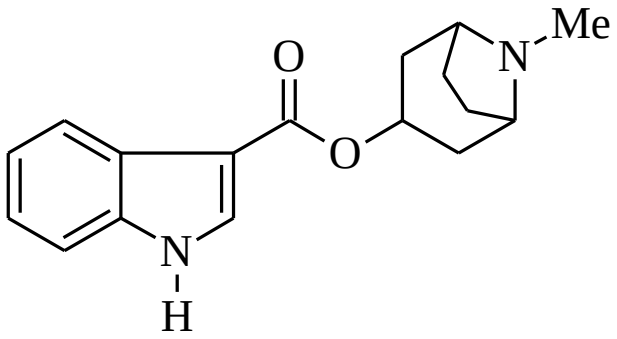


pantoprazol 1984
(Byk Gulden)

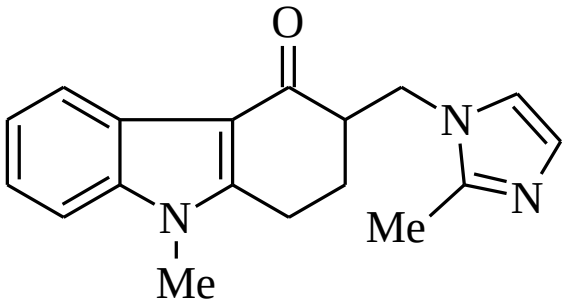


lansoprazole 1984
(Takeda)

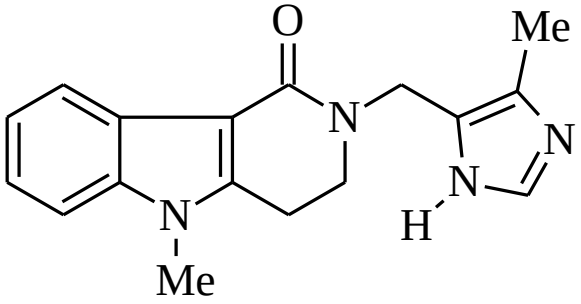
5-HT_3 antagonist anti-emetic agents



tropisetron 1982
(Sandoz)

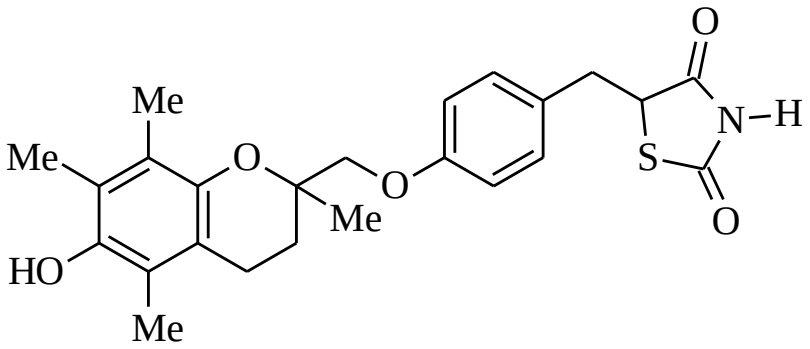


ondansetron 1984
(Glaxo)

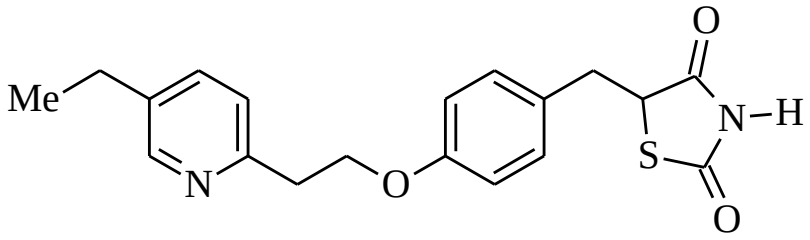


alosetron 1987 (IBS!)
(Glaxo)

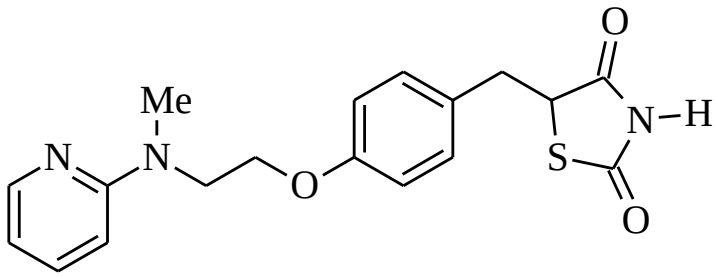
Peroxisome proliferator-activated receptor (PPAR) agonists anti-diabetics



troglitazone 1983
(Sankyo)

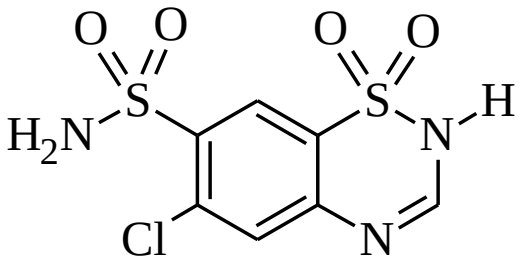


pioglitazone 1985
(Takeda)

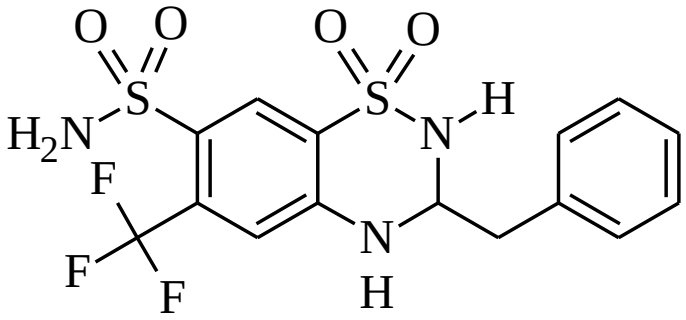


rosiglitazone 1987
(Sandoz)

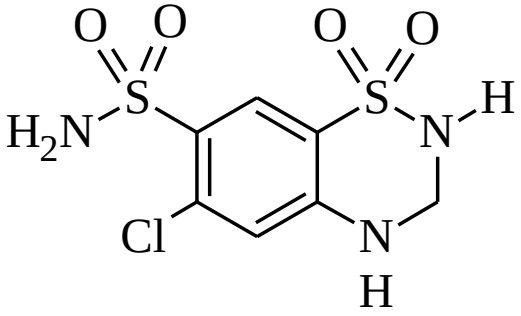
„Thiazide" diuretics



chlorothiazide 1956
(Merck & Co.)

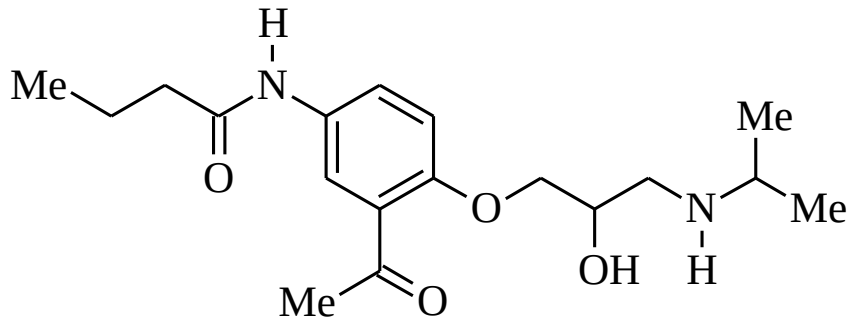


bendroflumethiazide 1958
(Lovens Kemiske Fabrik/BMS)

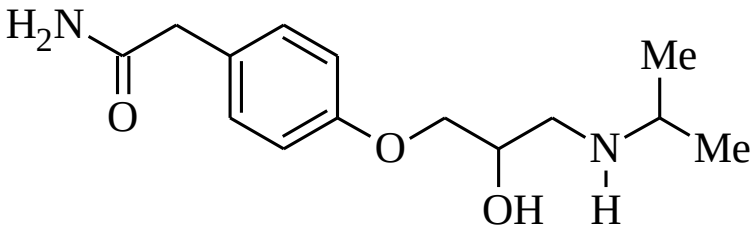


hydrochlorothiazide 1958
(Ciba)

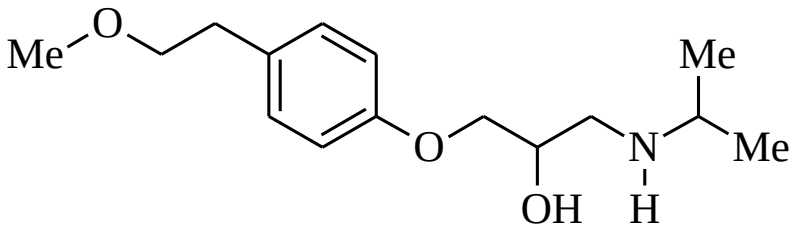
Cardioselective β-adrenoceptor blocking antihypertensive agents



acebutolol 1967
(May & Baker)

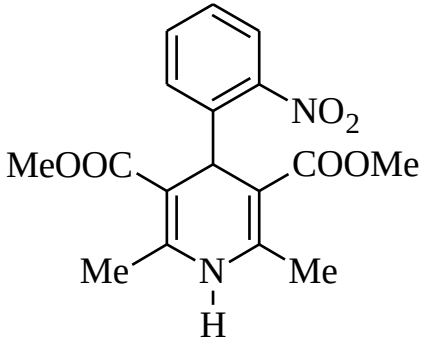


atenolol 1969
(ICI)

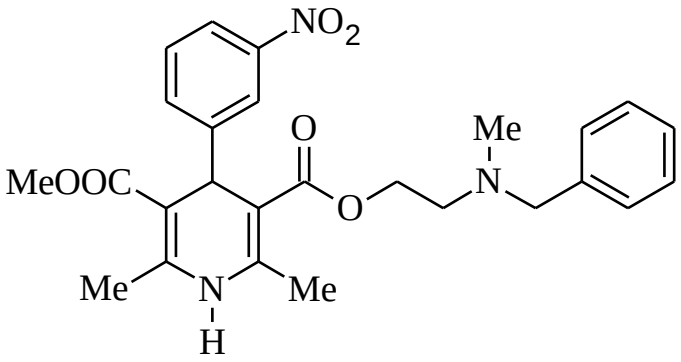


metoprolol 1970
(Hässle)

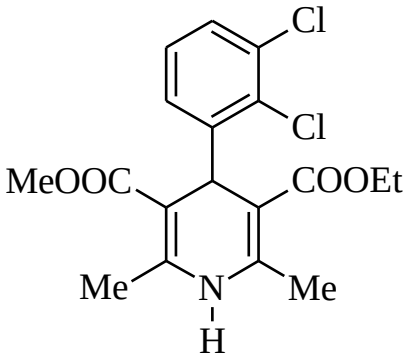
Ca^{2+}-channel blocking antihypertensive agents



nifedipine 1967
(Bayer)

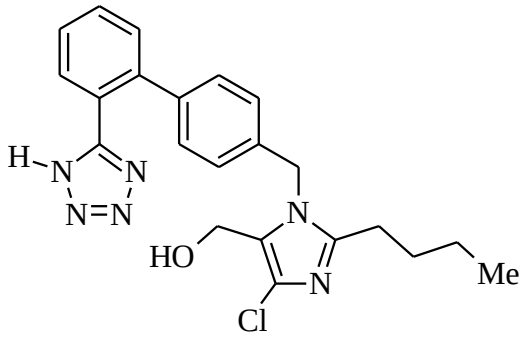


nicardipine 1973
(Yamanouchi)

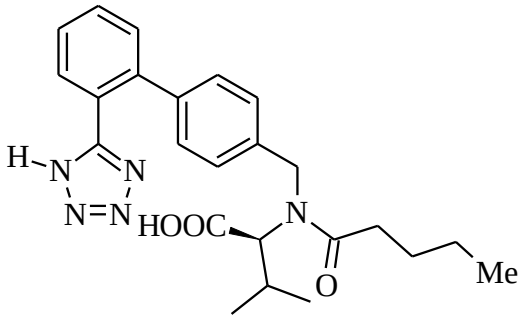


felodipine 1978
(Hässle)

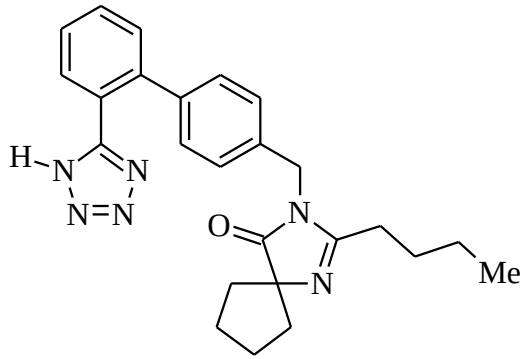
Angiotensin II receptor antagonist antihypertensive agents



losartan 1986
(Du Pont)

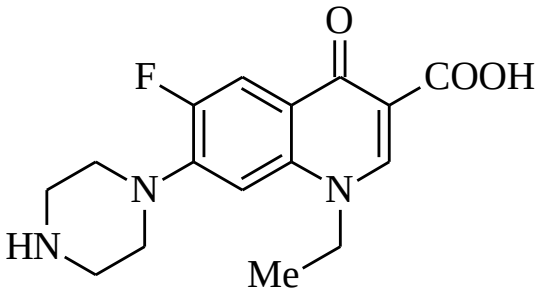


valsartan 1990
(Ciba-Geigy)

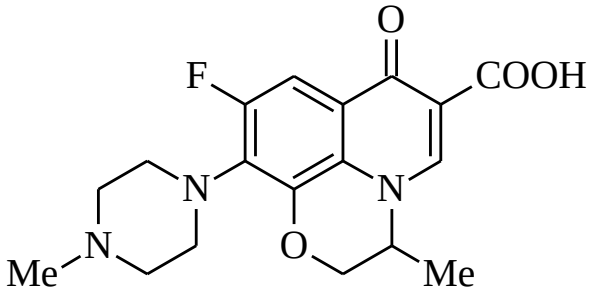


irbesartan 1990
(Sanofi)

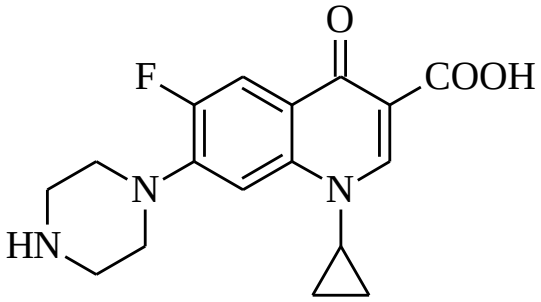
Quinolone antibacterials



norfloxacin 1977
(Kyorin)

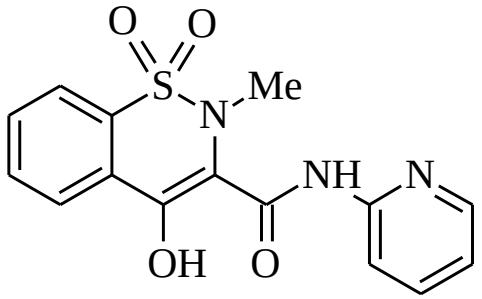


ofloxacin 1980
(Daichi Seiyaku)

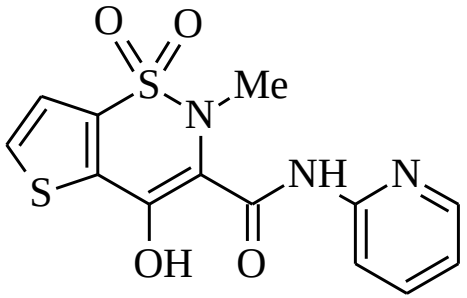


ciprofloxacin 1980
(Bayer)

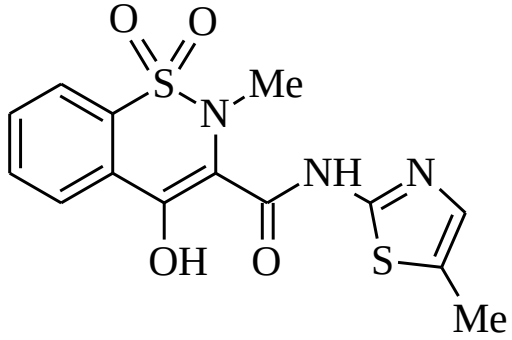
Nonsteroidal anti-inflammatory drugs (NSAID) –"oxicams"



piroxicam 1968
(Pfizer)

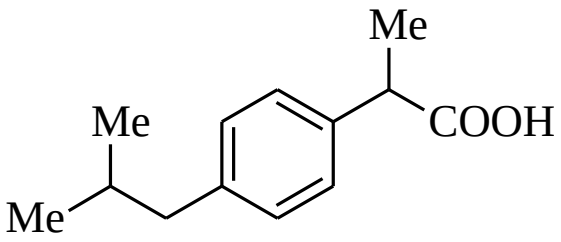


tenoxicam 1974
(Hoffmann-La Roche)

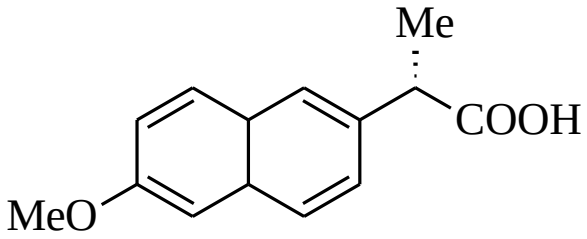


meloxicam 1977
(Dr. KarlThomae GmbH)

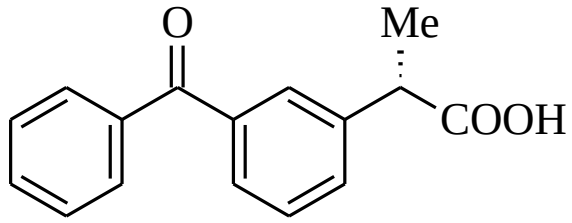
Nonsteroidal anti-inflammatory drugs (NSAID) –"propionic acids"



ibuprofen 1961
(Boots)

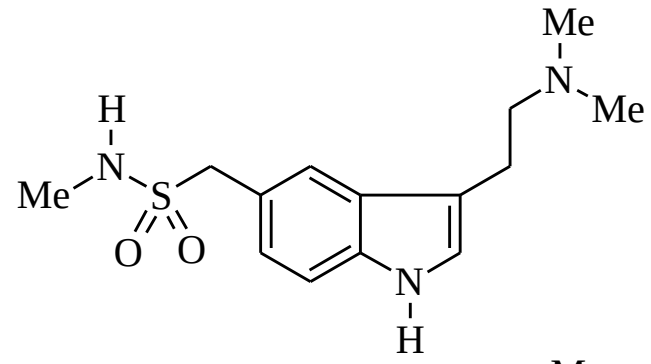


naproxen 1967
(Syntex)

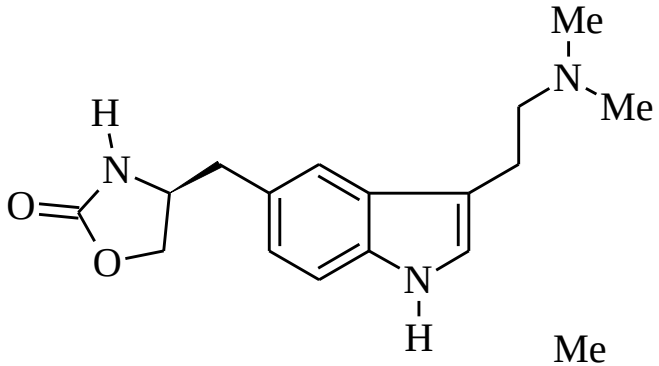


ketoprofen 1967
(Rhône-Poulenc)

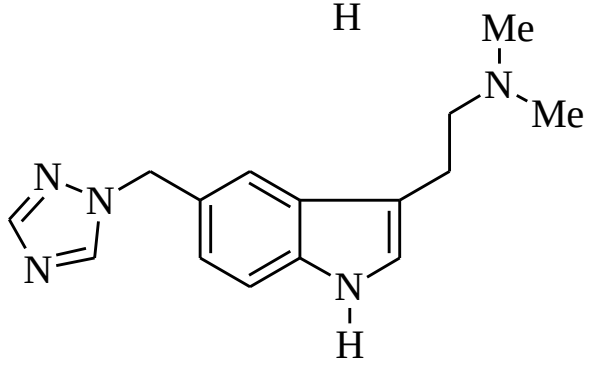
5-HT_1 agonist anti-migraine agents („triptanes")



sumatriptan 1982
(Glaxo)

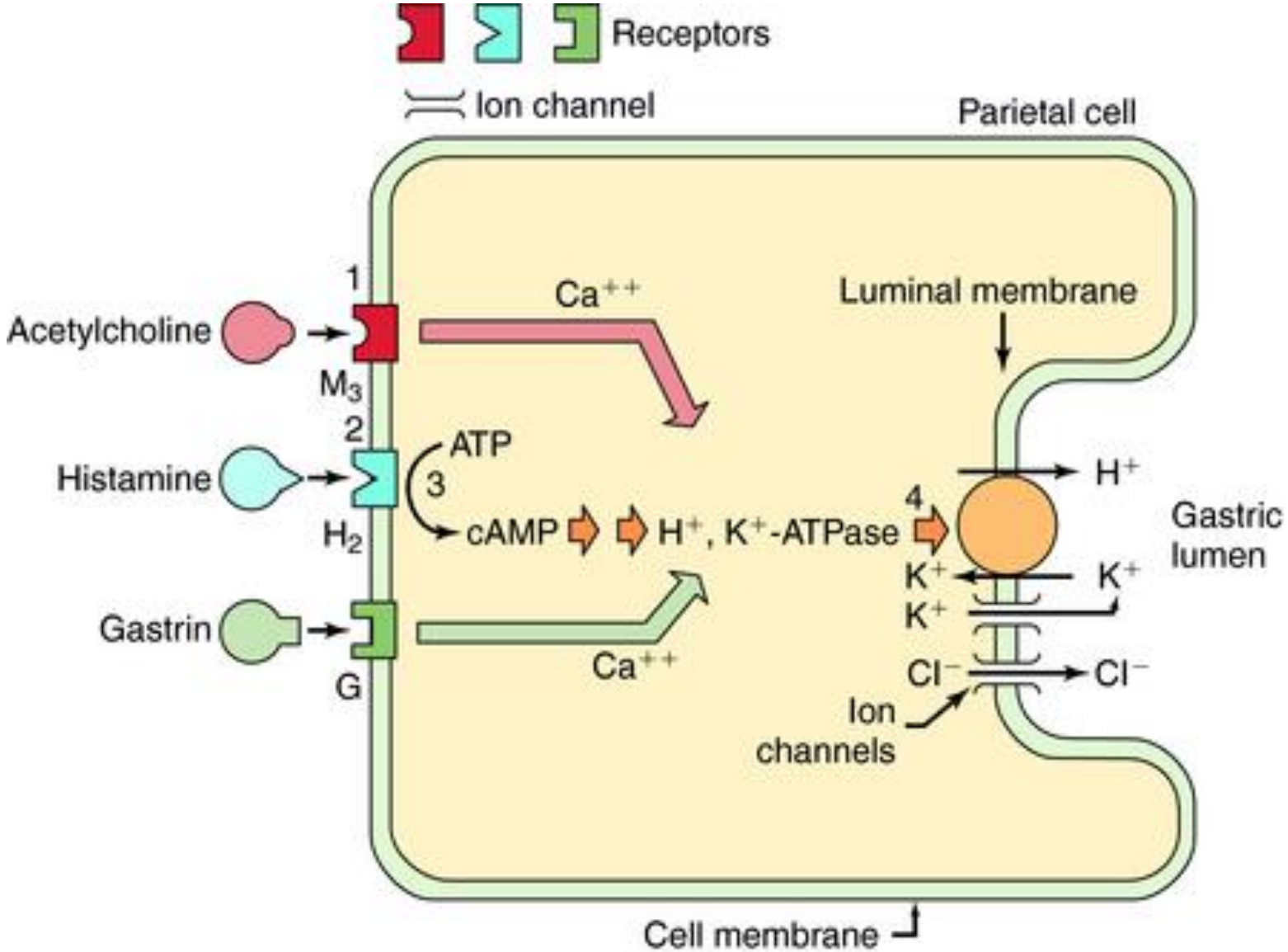


zolmitriptan 1990
(Wellcome Foundation)

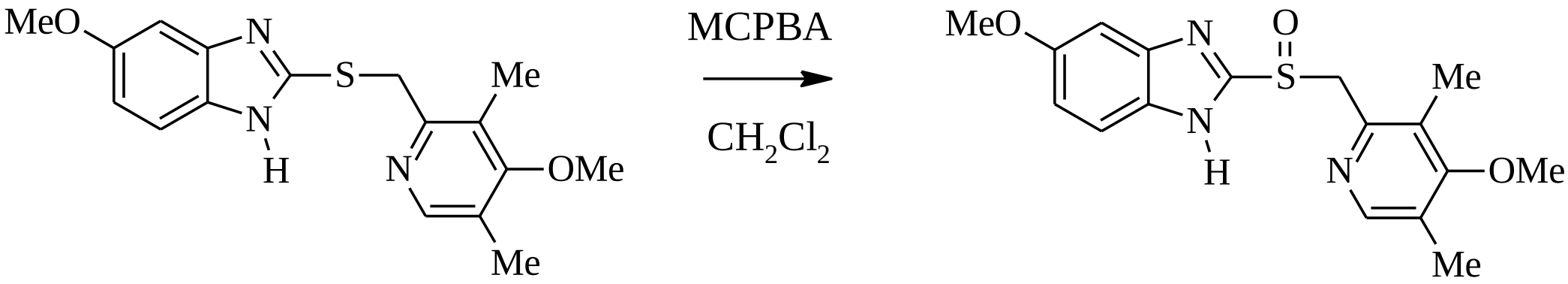


rizatriptan 1991
(Merck Sharp & Dohme)

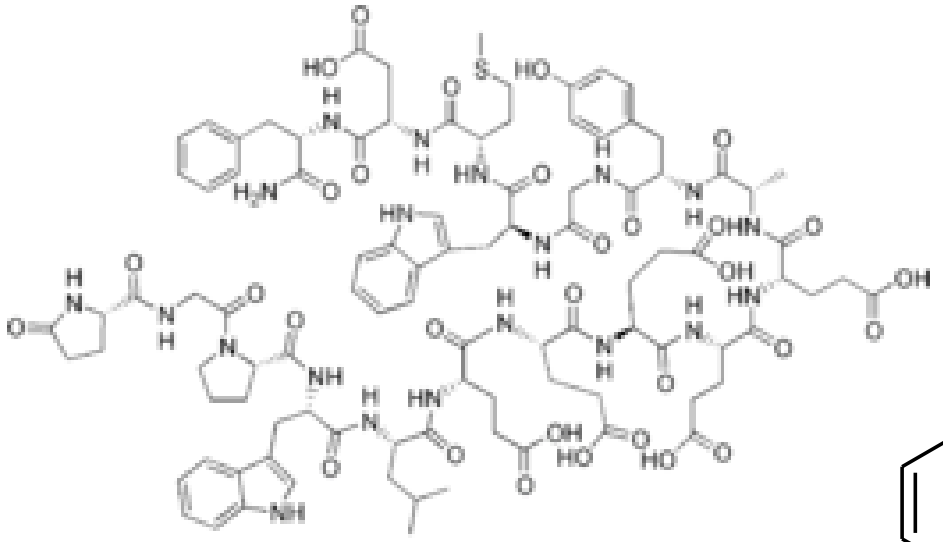
Discovery of omeprazole and esomeprazol

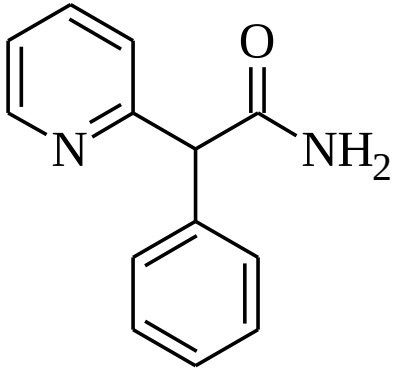

Receptors
Ion channel
Parietal cell
1
Acetylcholine
M3
Ca++
Luminal membrane
2
ATP
Histamine
3
H2
cAMP
H+, K+-ATPase
4
H+
Gastric lumen
K+
K+
K+
Gastrin
G
Ca++
Cl−
Cl−
Ion channels
Cell membrane

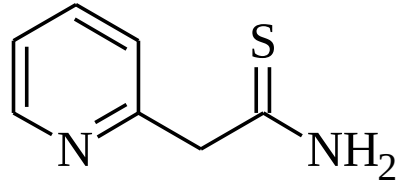
H 168/68 – January 1979



omeprazole - Losec® 1988, Prilosec® 1990

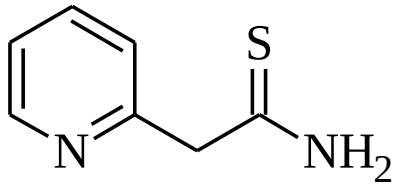




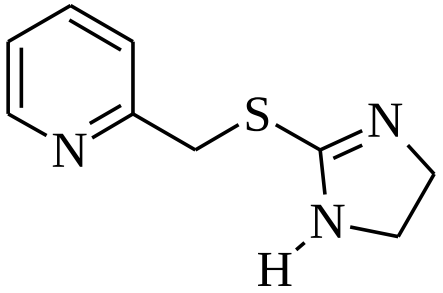


SC-15396 Antigastrin
Searle & Co.

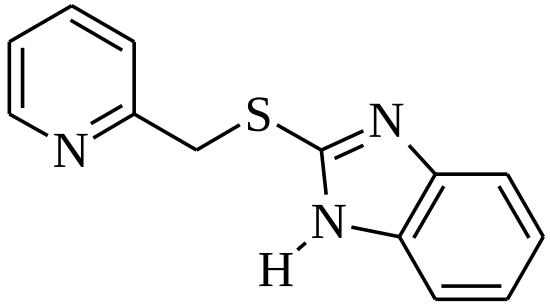
CMN 131
Servier



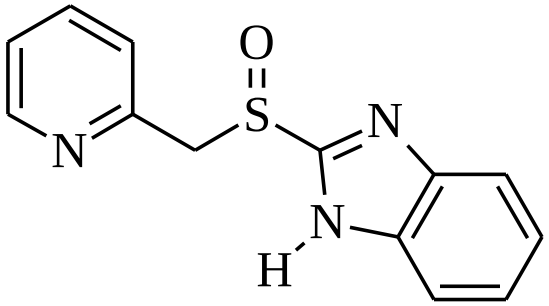
CMN 131



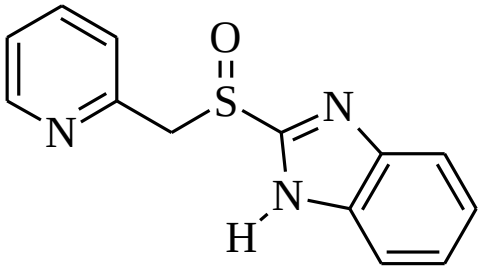
H 77/67



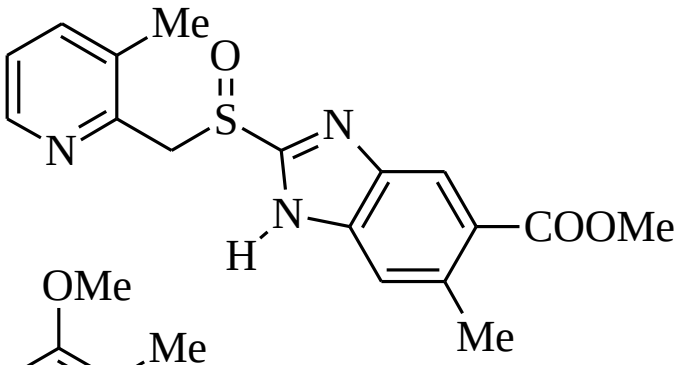
H 124/26



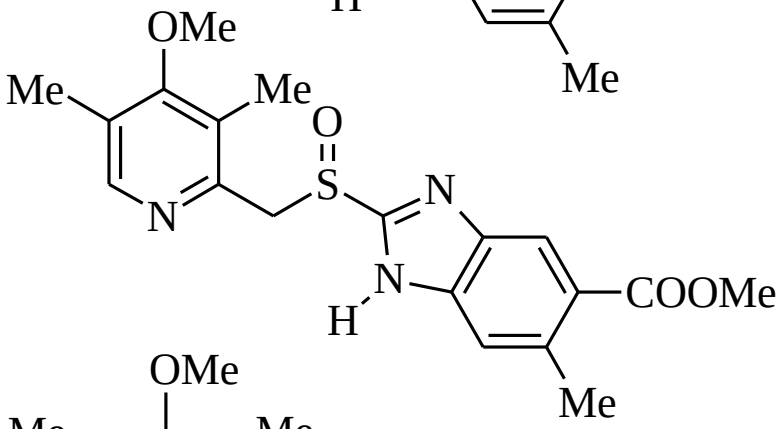
H83/69 timoprazole



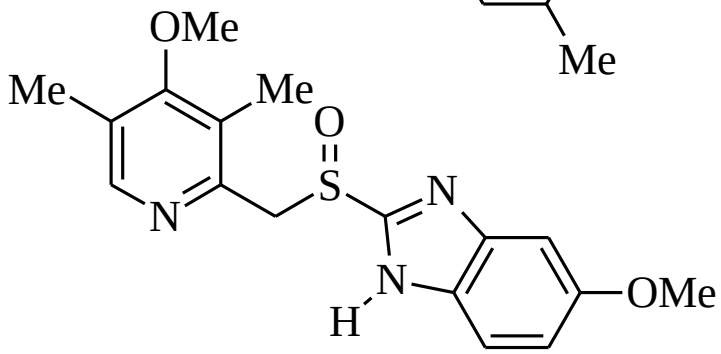
H 83/69 timoprazole



H 149/94 picoprazole

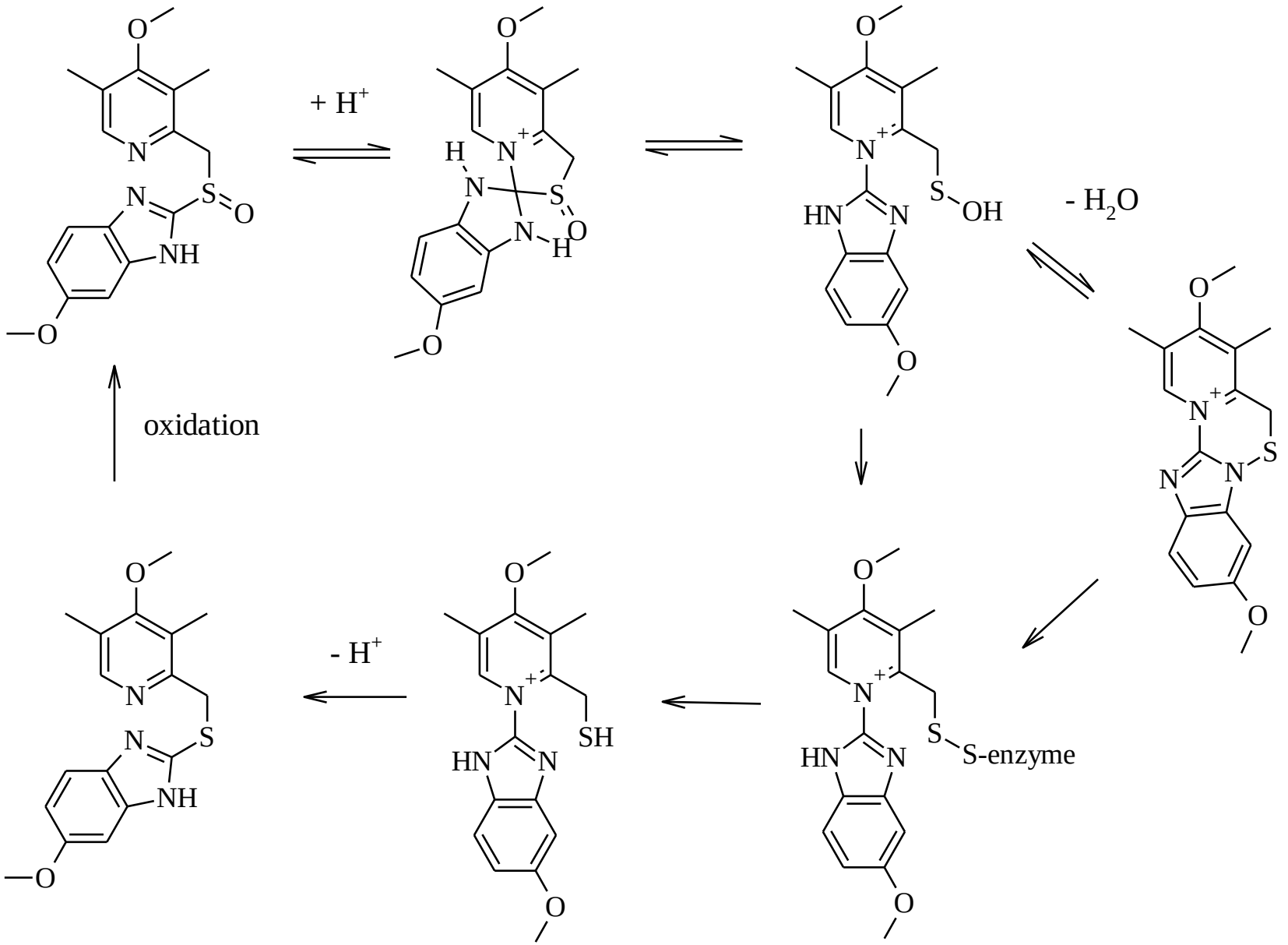


H 159/69

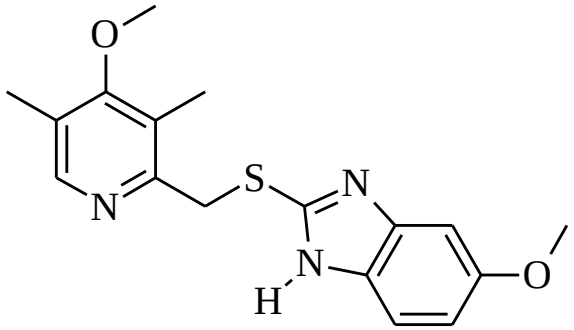


H 168/68 omeprazole

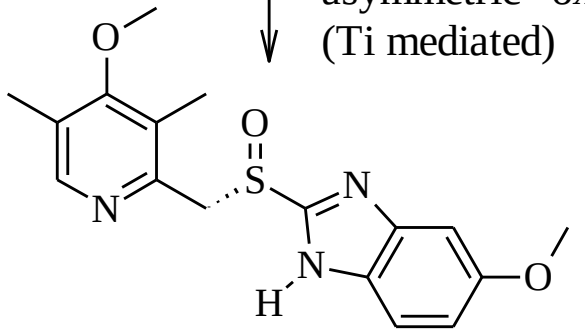
„The omeprazole cycle"



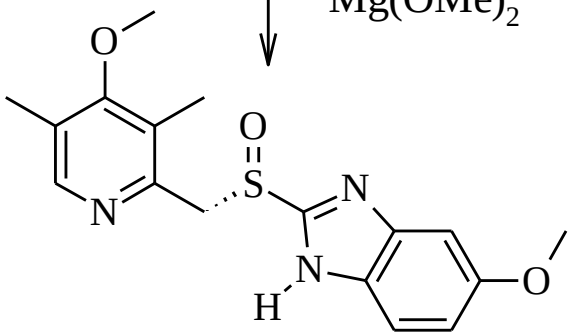
Esomeprazole



asymmetric oxidation
(Ti mediated)



$Mg(OMe)_2$

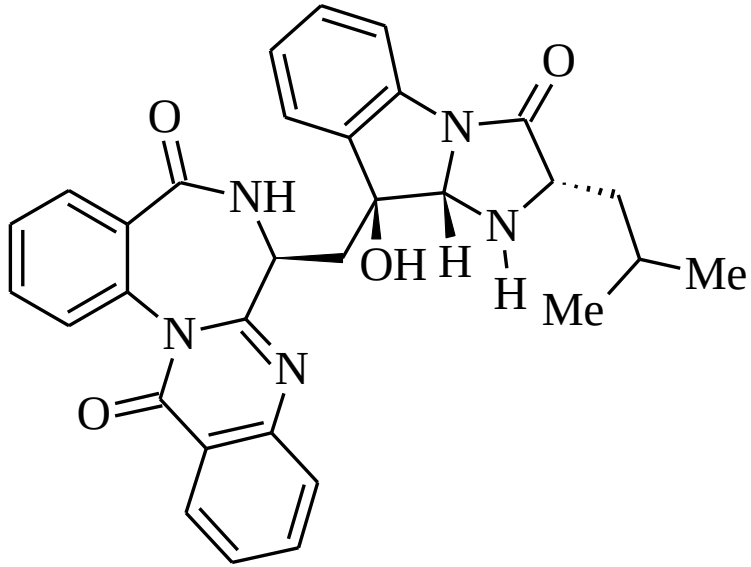


esomeprazole (94% ee)

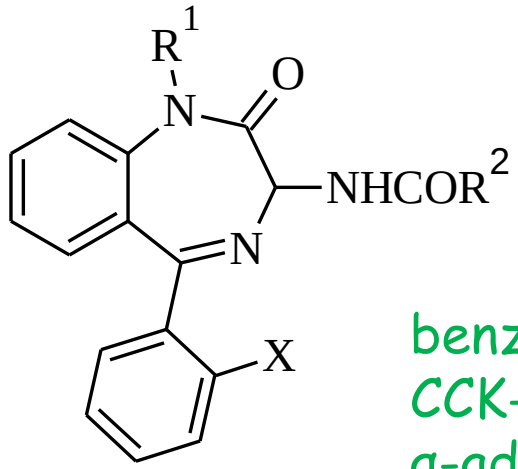
esomeprazole magnesium (100% ee)

Privileged structures

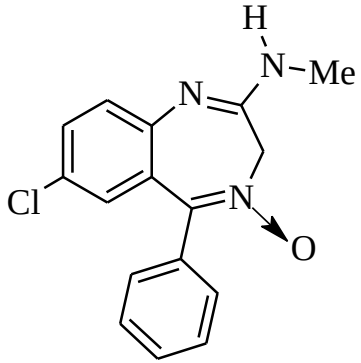
(Ben Evans, 1988)



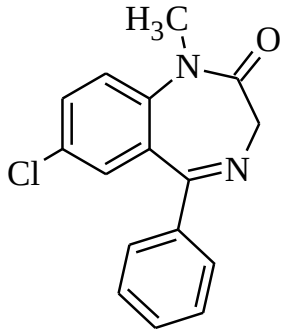
Asperlicin
mycotoxin, a selective CCK-A antagonist



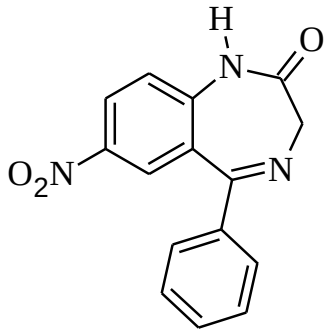
benzodiazepin,
CCK-A,
a-adrenergic,
serotonin,
muscarinic,
angiotensin I
receptors



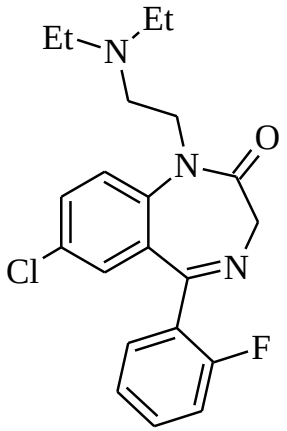
1960 chlordiazepoxide



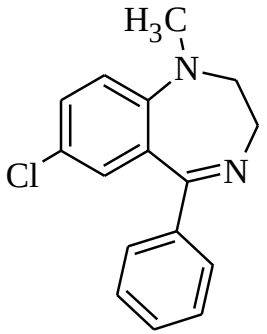
1963 diazepam



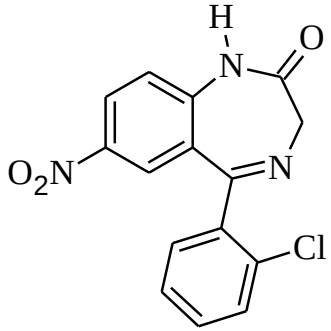
1965 nitrazepam



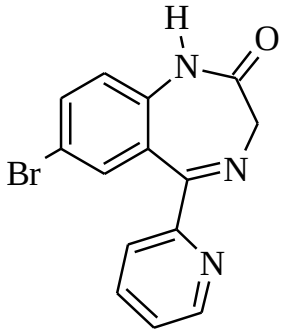
1968 flurazepam



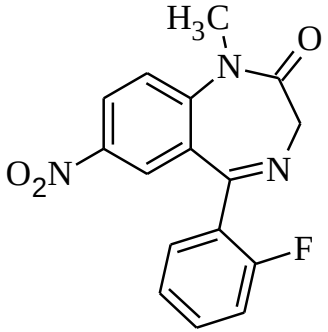
1968 medazepam



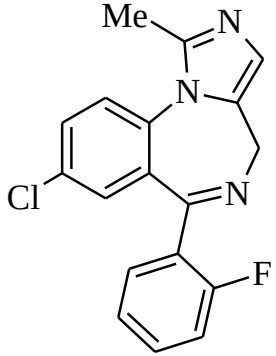
1973 clonazepam



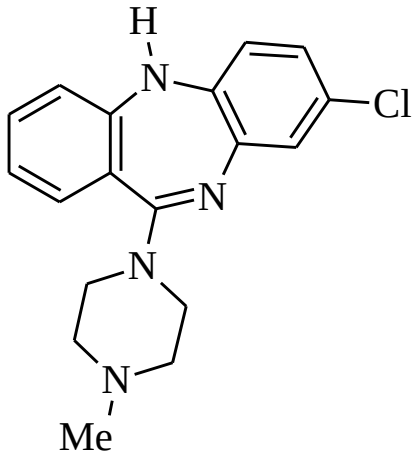
1974 bromazepam



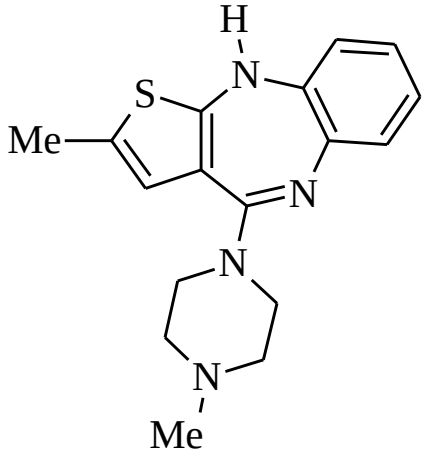
1974 flunitrazepam



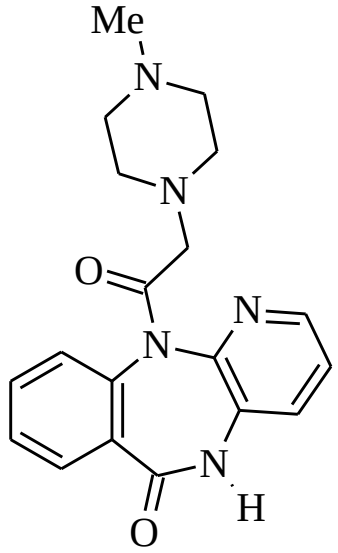
1982 midazolam



1989 clozapine
antipsychotic

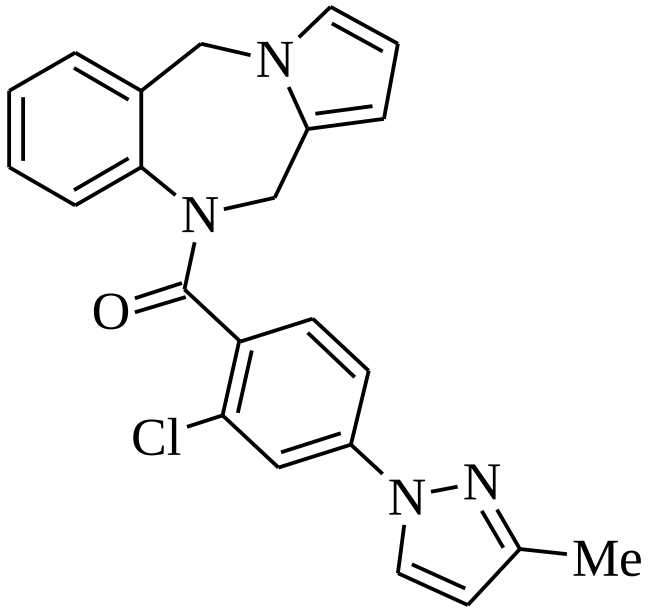


1996 olanzapine
antipsychotic



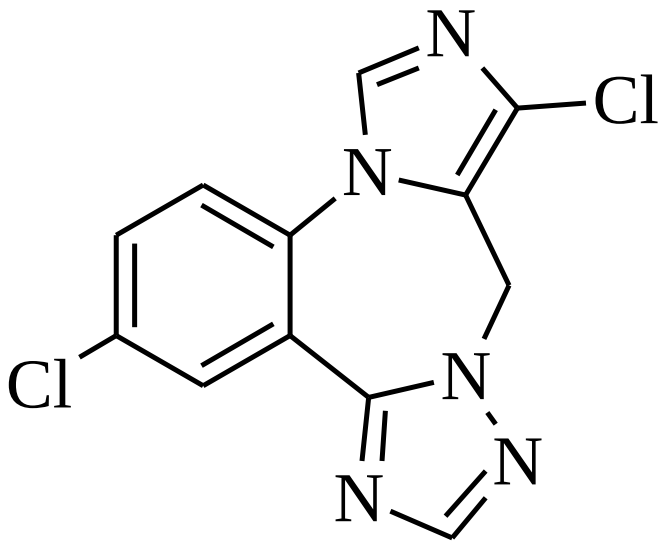
1980s pirenzepine
sel. muscarinic M_1 rec. antagonist
reduces gastric acid secretion

Cardiovascular application



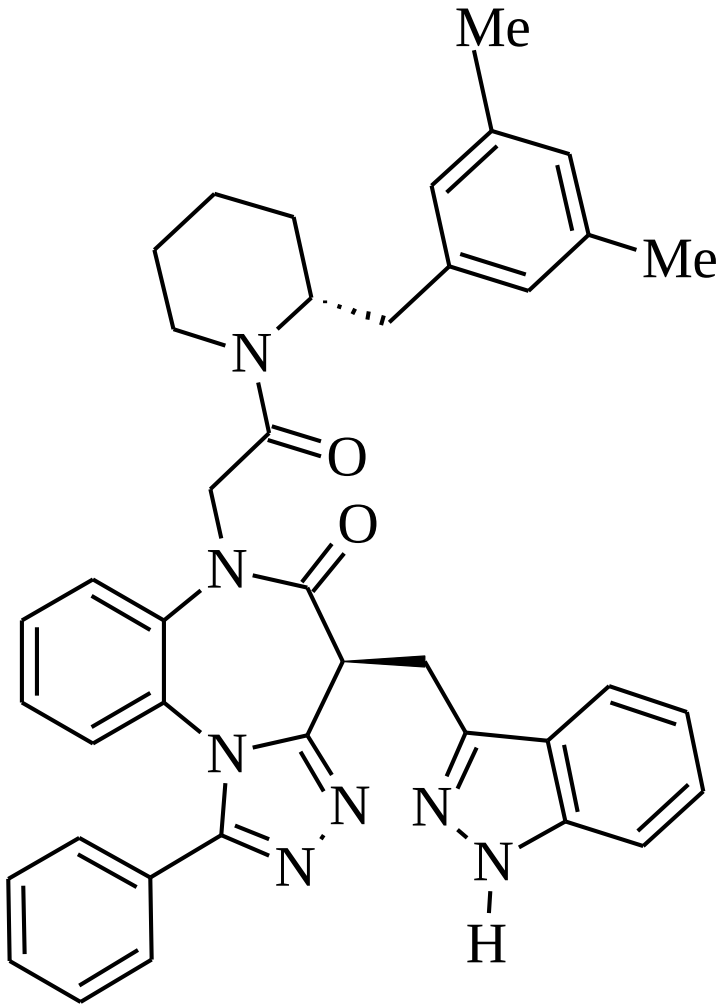
WAY-151932
antidiuretic
selective V2 receptor agonist

Central nervous system application



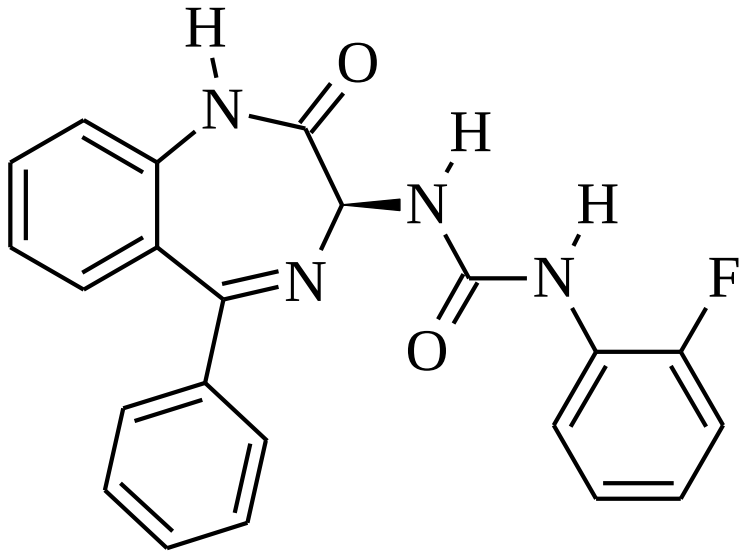
RO4882224
cognitive enhancer in
Alzheimer's disease
$GABA_A$ α5 inverse agonist

Gastrointestinal applications



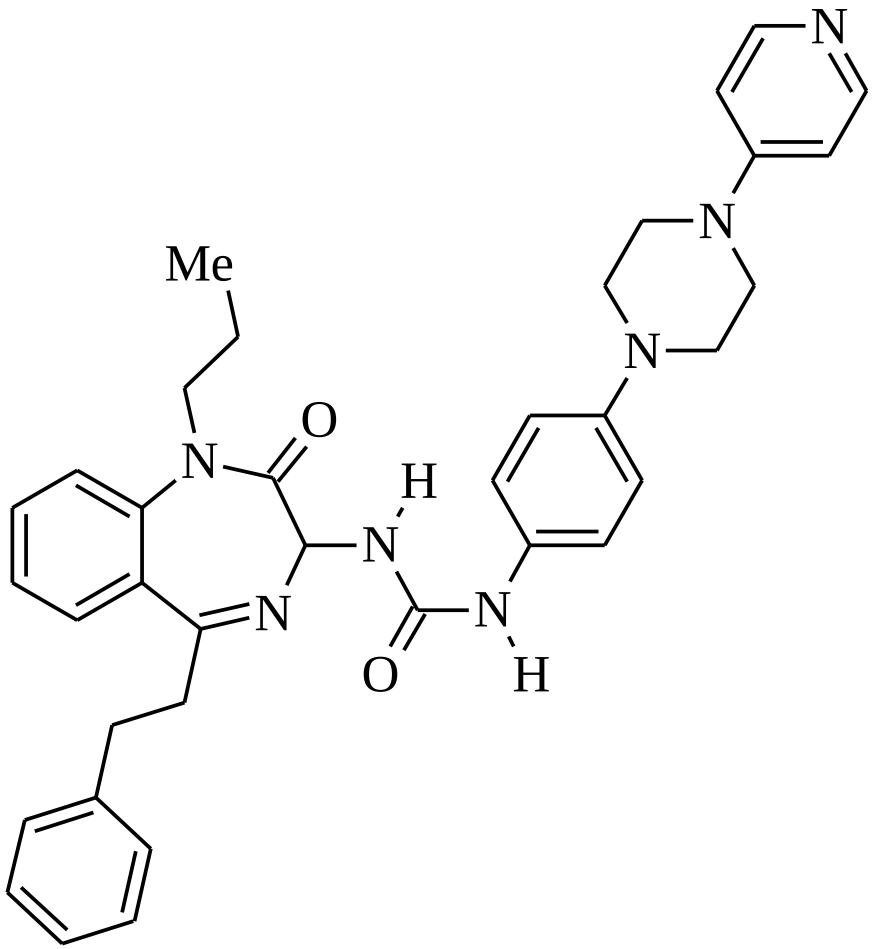
satiety agent in obesity
CCK-A selective agonist

Infectious diseases application



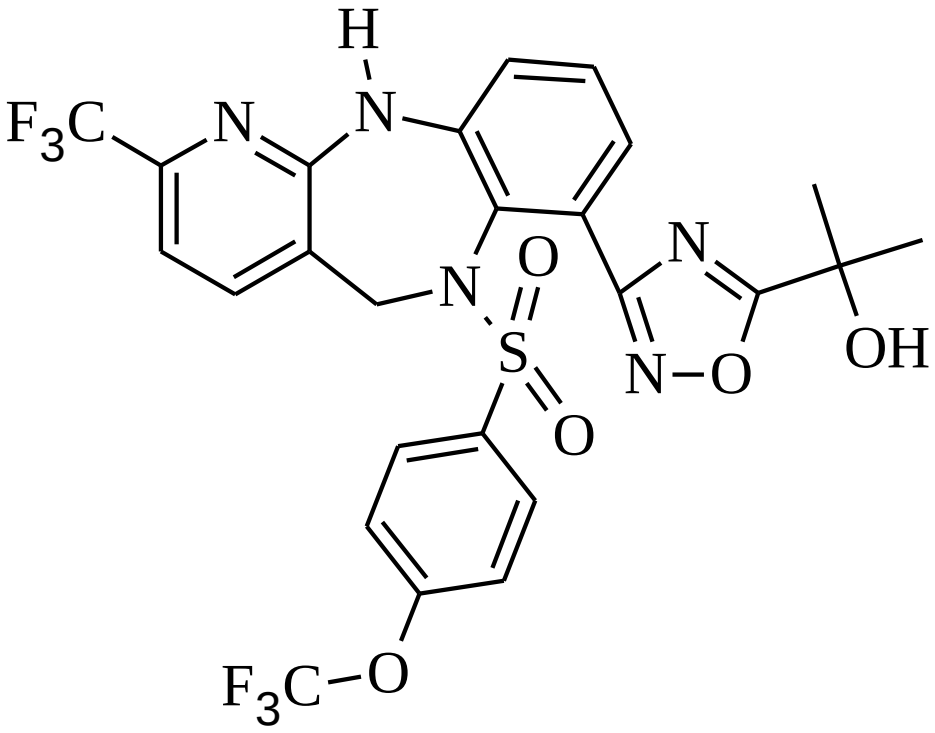
RSV-604
lower respiratory tract infections
antiviral agent against
respiratory syncytial virus

Inflammation application



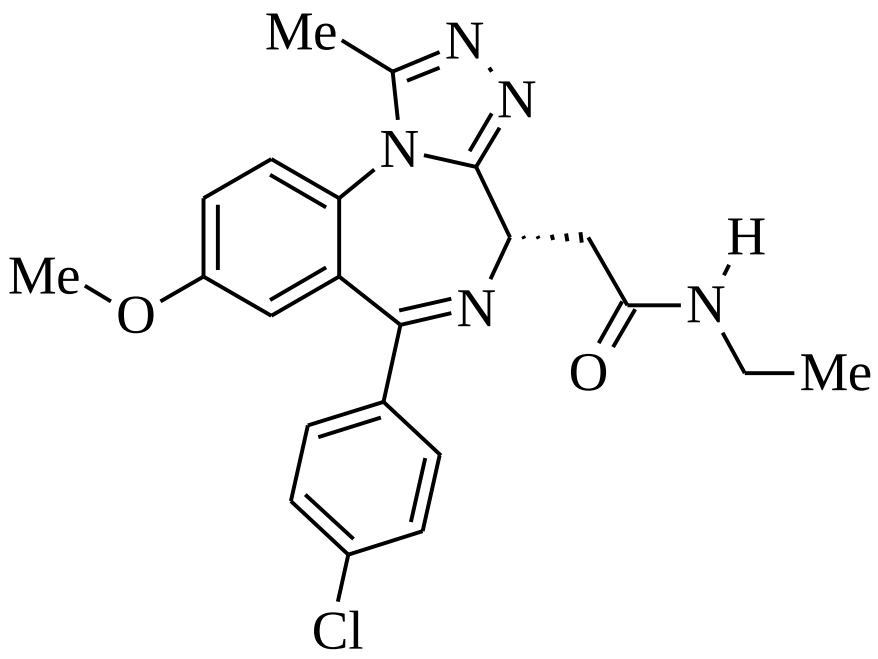
antiinflammatory, analgetic
bradykinin B_1 receptor antagonist

Metabolic diseases application



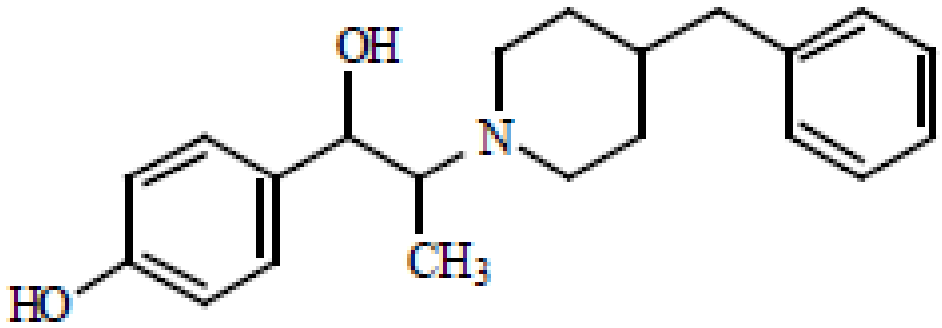
MK-7725
anti-obesity
bombesin receptor 3 agonist

Oncology application



I-BET762
anti-cancer activity
inhibitor of BET bromodomains

István Borza* and György Domány
NR2B Selective NMDA Antagonists: The Evolution of the Ifenprodil-Type Pharmacophore
Current Topics in Medicinal Chemistry, 2006, *6*, 687-695

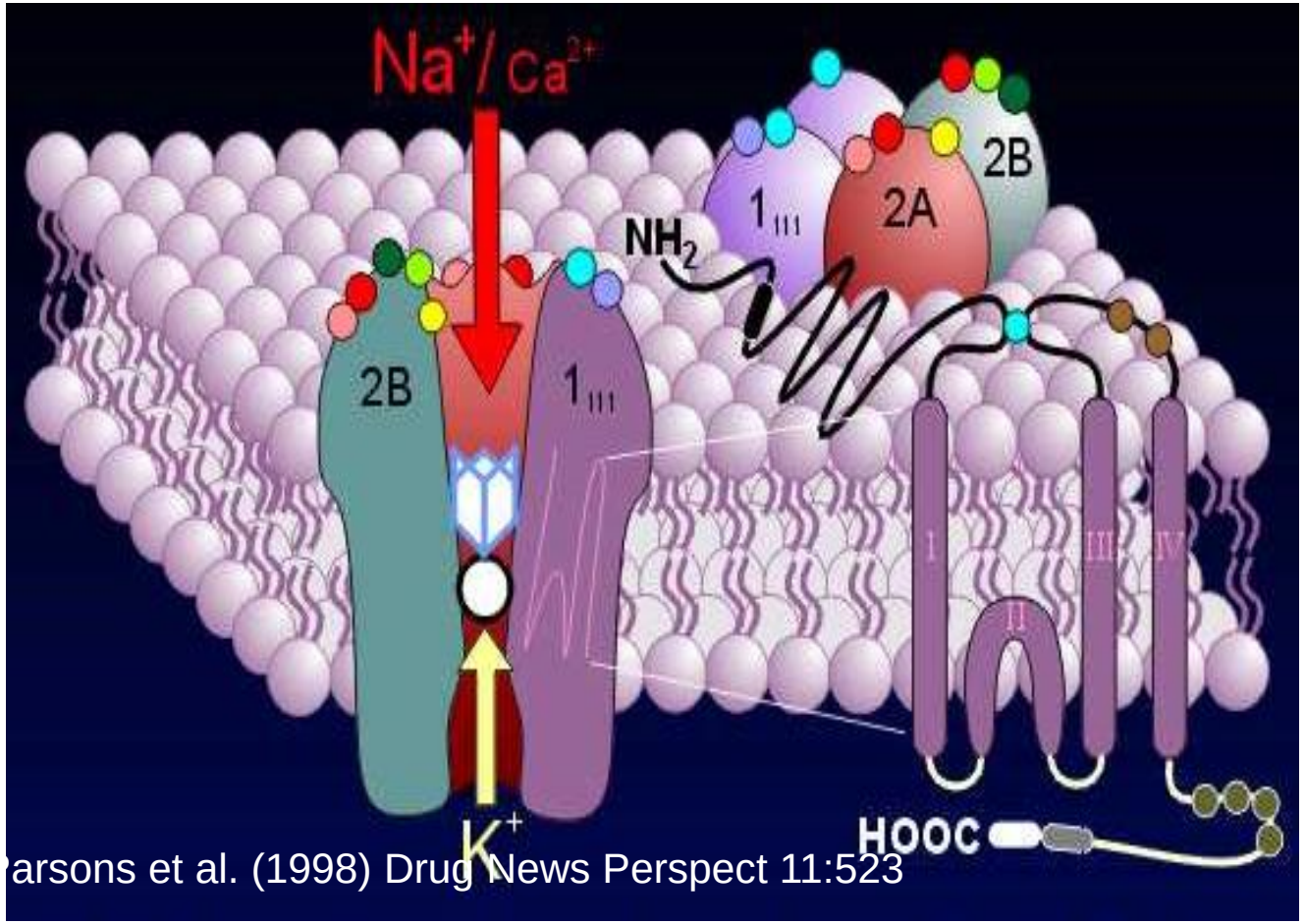


ifenprodil

Vasodilator α-1 adrenoceptor antagonist
(Cerocral, Dilvax, Vadilex)

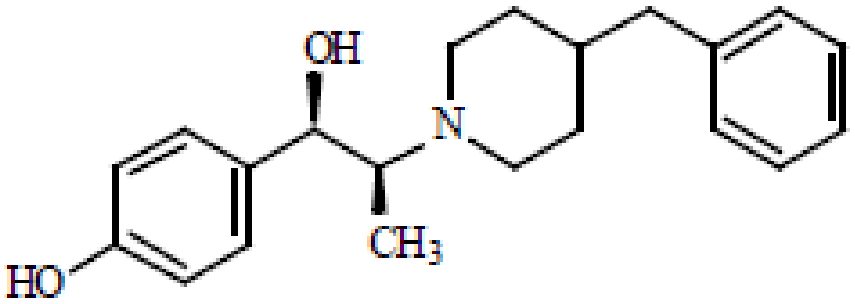
NMDA-receptor

One of numerous glutamate receptors. The functional receptor consists of 4 subunits. Heteromer composition, at least one NR1 subunit is necessary.

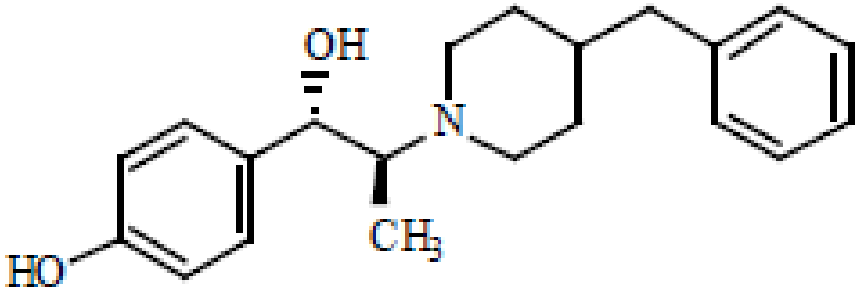


Parsons et al. (1998) Drug News Perspect 11:523

Pfizer



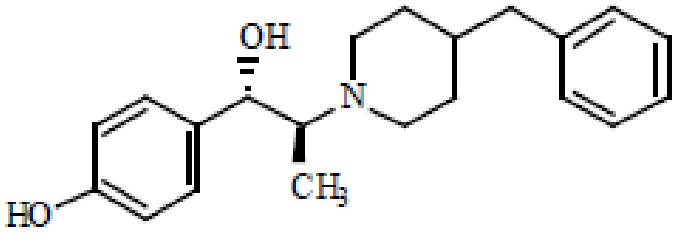
(+)-*erythro*-ifenprodil
CC-IC_{50}: 263 nM
α-1-IC_{50}: 100 nM



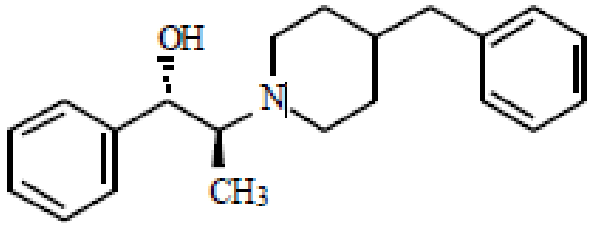
(+)-*threo*-ifenprodil
CC-IC_{50}: 55 nM
α-1-IC_{50}: 843 nM

CC-IC_{50}: a functional measure of NMDA antagonism, the potency for inhibition of glutamate-induced neuron death in primary cultures of rat hippocampal neurons

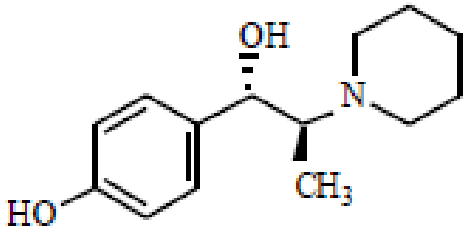
Pfizer



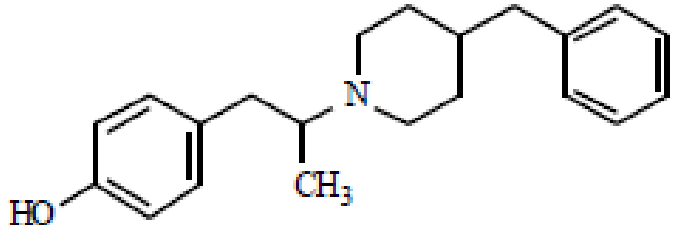
(+)-*threo*-ifenprodil
CC-IC_{50}: 55 nM
α-1-IC_{50}: 843 nM



1
CC-IC_{50}: 3700 nM
α-1-IC_{50}: 3400 nM

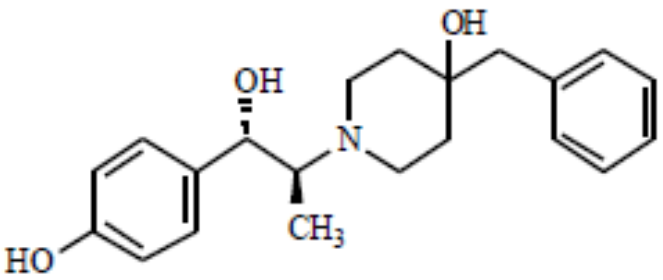


2
CC-IC_{50}: >10000 nM
α-1-IC_{50}: >10000 nM



3
CC-IC_{50}: 153 nM
α-1-IC_{50}: 130 nM

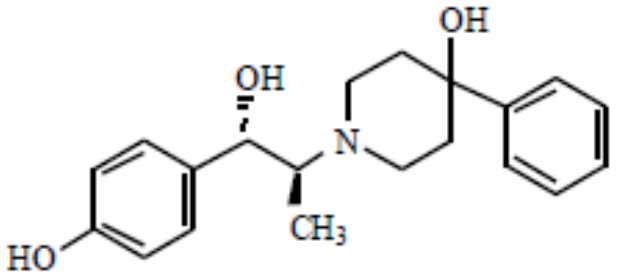
Pfizer



4

$CC\text{-}IC_{50}$: 58 nM

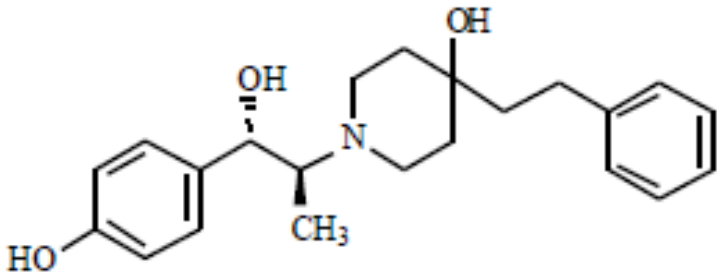
$\alpha\text{-}1\text{-}IC_{50}$: >10000 nM



5

$CC\text{-}IC_{50}$: 10.2 nM

$\alpha\text{-}1\text{-}IC_{50}$: 5700 nM

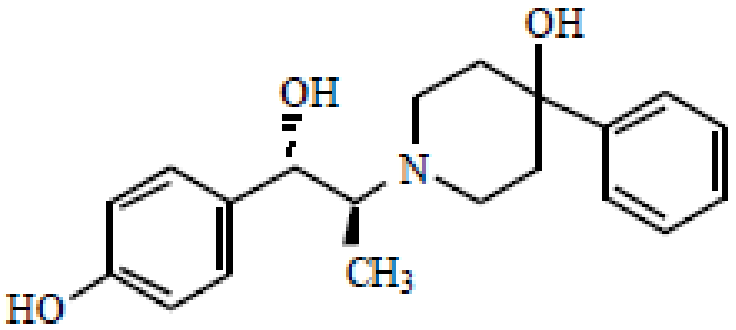


6

$CC\text{-}IC_{50}$: 1.3 nM

$\alpha\text{-}1\text{-}IC_{50}$: 137 nM

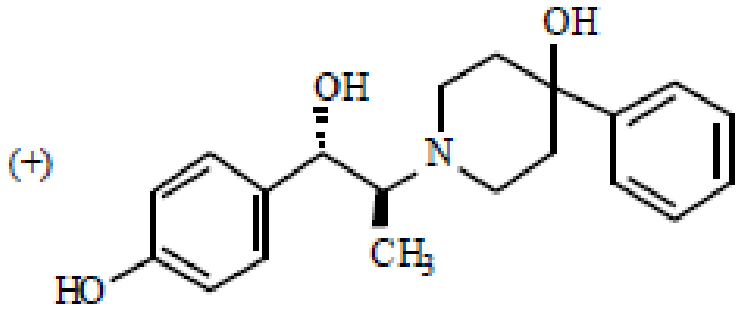
Pfizer



5

CC-IC_{50}: 10.2 nM

α-1-IC_{50}: 5700 nM

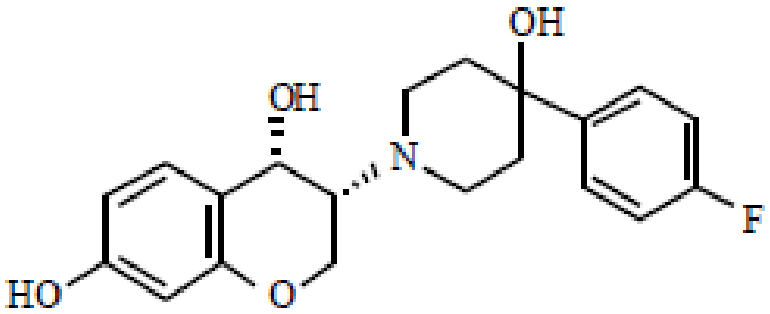


CP-101,606

CC-IC_{50}: 11 nM

α-1-IC_{50}: 19520 nM

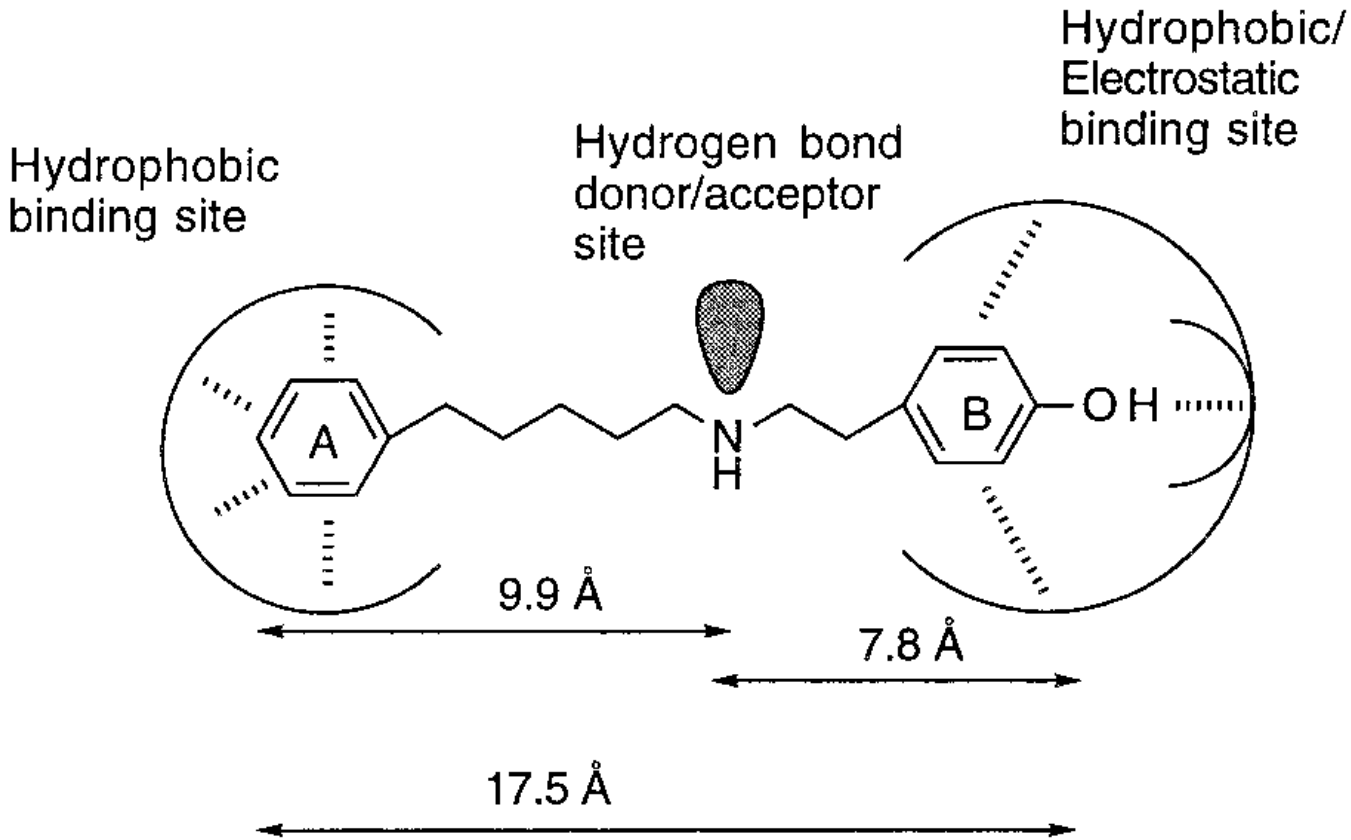
traxoprodil



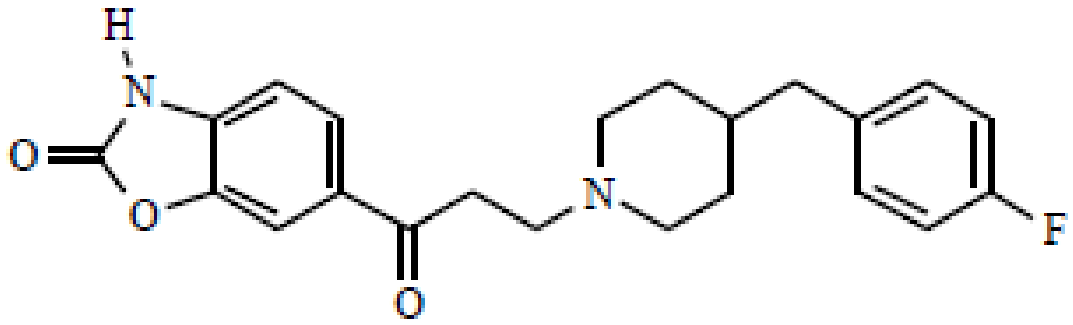
7

CC-IC_{50}: 58 nM

1. Two benzene rings connected by a spacer of a certain length seemed essential.
2. A hydroxyl group on one of these two benzenes was also found to be an important feature of the active compounds.
3. The nature of the spacer between the lipophilic benzenes and the stereochemistry of substituents on this spacer was also investigated but firm conclusions could not be drawn from the collected data.



Merck KGaA



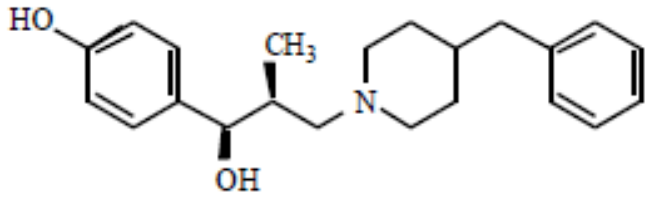
8

EMD 95885

IC_{50}: 3.9 nM (ifenprodil: IC_{50}: 23.3 nM)
in rat cortex using [^{3}H]-ifenprodil

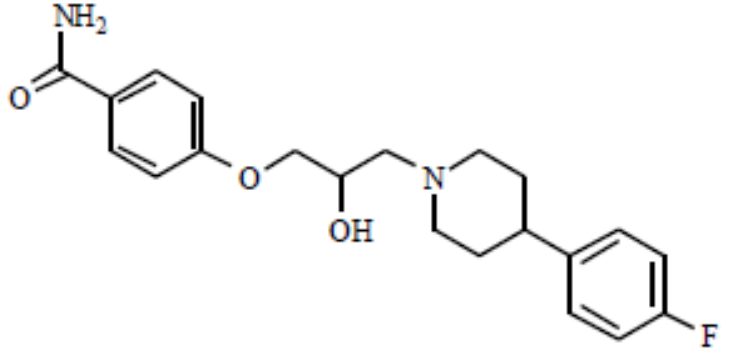
F. Hoffmann – La Roche Ltd.

([^{3}H]-Ro-25-6981 binding)



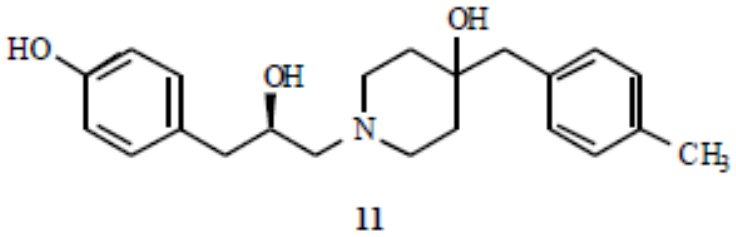
9

Ro-25-6981
K_i: 5.6 nM



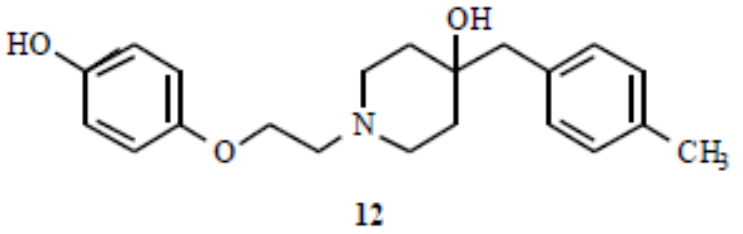
10

Ro-8-4304



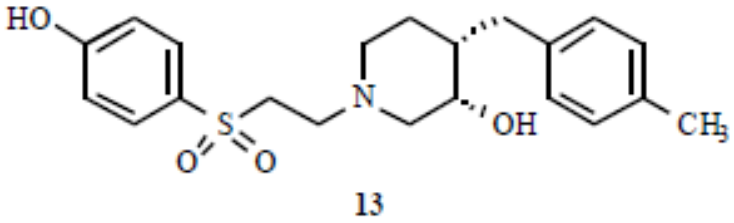
11

K_i: 4.9 nM



12

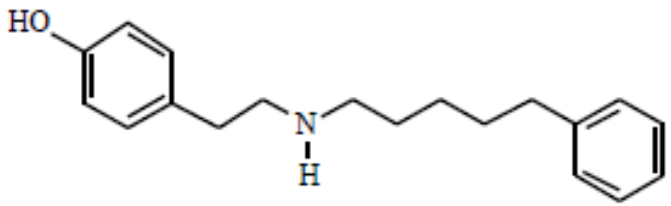
Ro-63-1908
IC_{50}: 5.6 nM (α-1 IC_{50}: 3.5 μM)



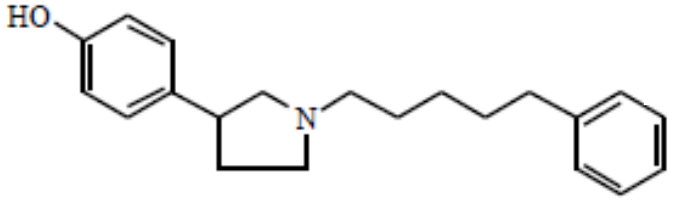
13

Ro-67-8867

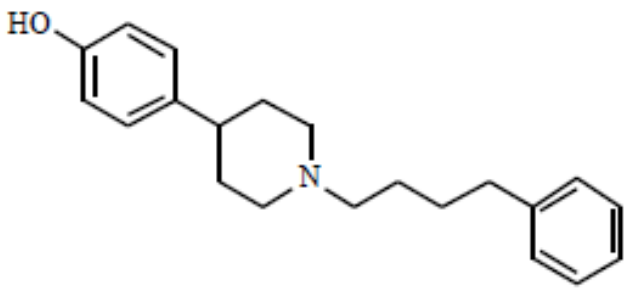
CoCensys/Parke-Davies Pharm.Res.



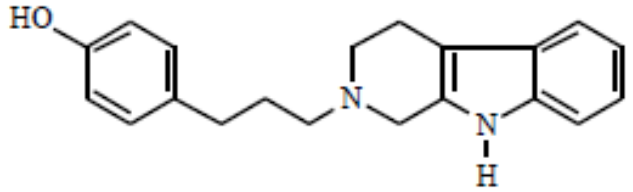
14
NR2B-IC_{50}: 8 nM



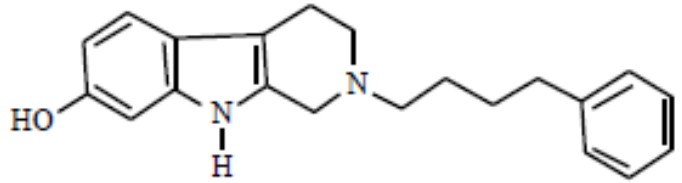
15
NR2B-IC_{50}: 17 nM



16
NR2B-IC_{50}: 22 nM



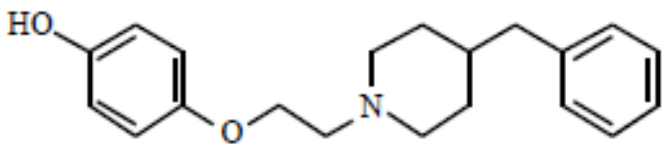
17
NR2B-IC_{50}: 87 nM



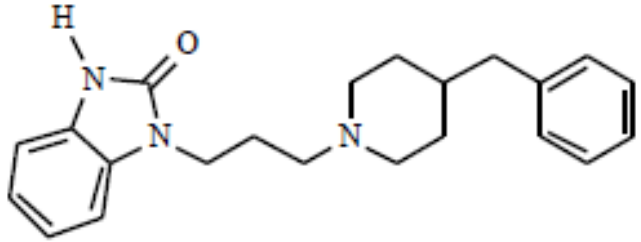
18
NR2B-IC_{50}: 50 nM

Potency and subunit selectivity were assayed by electrical recordings in *Xenopus* oocytes expressing the binary combinations of cloned rat NMDA receptor subunits: NR1A expressed in combination with either NR2A, NR2B NR2C.

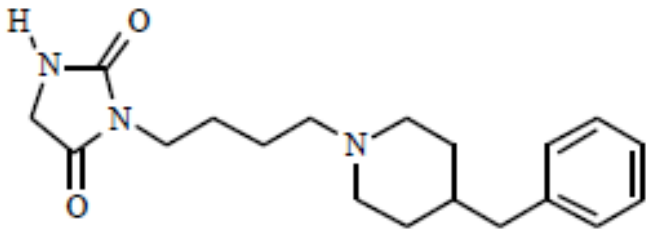
CoCensys/Parke-Davies Pharm.Res.



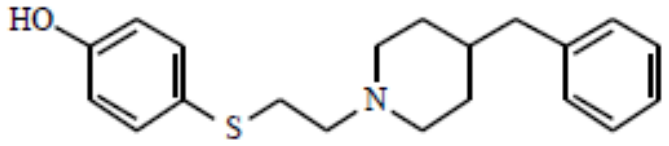
19
NR2B-IC_{50}: 25 nM



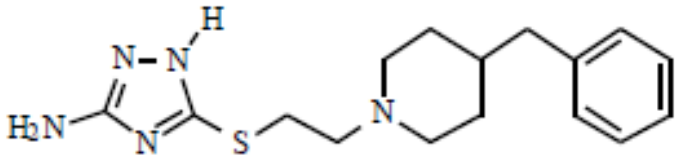
20
NR2B-IC_{50}: 95 nM



21
NR2B-IC_{50}: 1000 nM

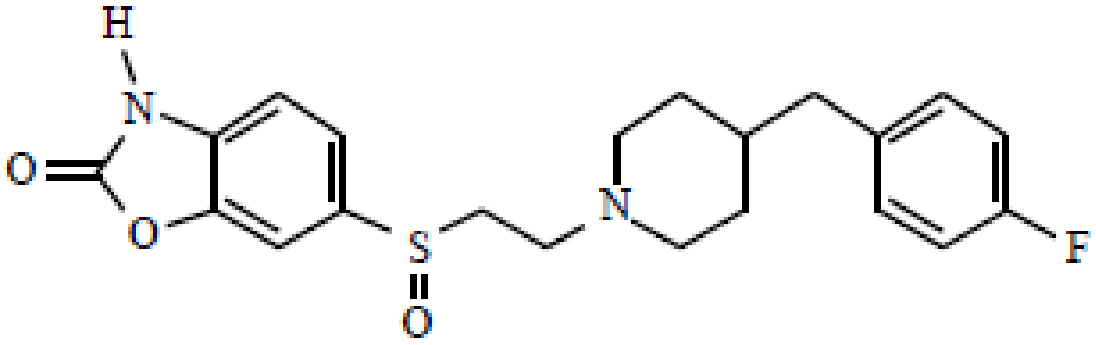


22
NR2B-IC_{50}: 100 nM



23
NR2B-IC_{50}: 35 nM

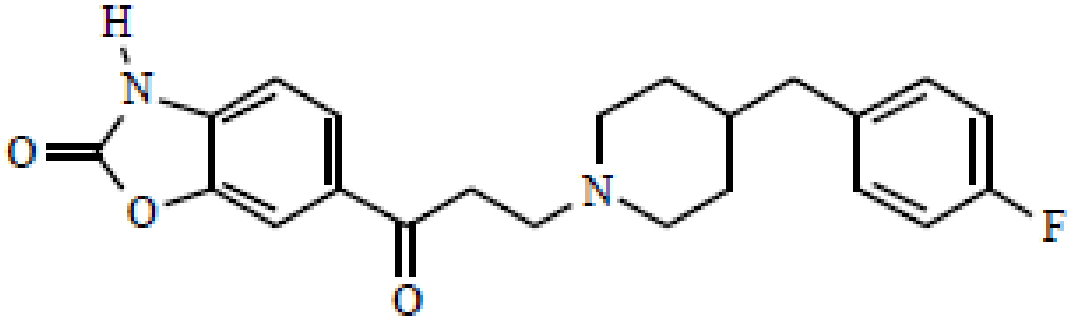
CoCensys/Parke-Davies Pharm.Res.



24

NR2B-IC_{50}: 30 nM

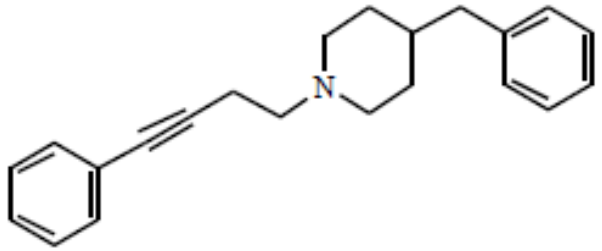
besonprodil



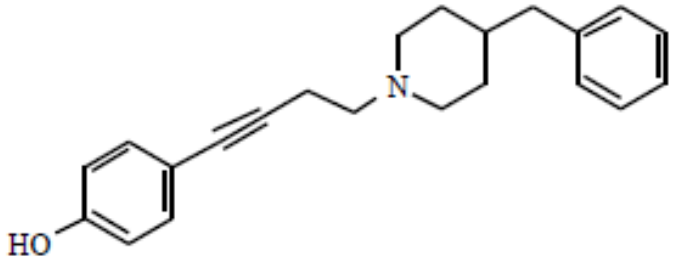
8

EMD 95885 (Merck KGaA)

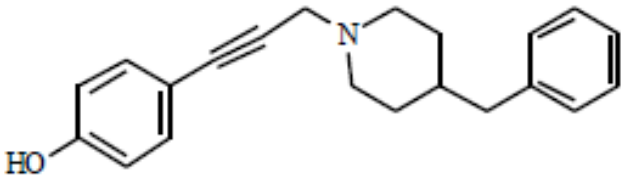
CoCensys/Parke-Davies Pharm.Res.



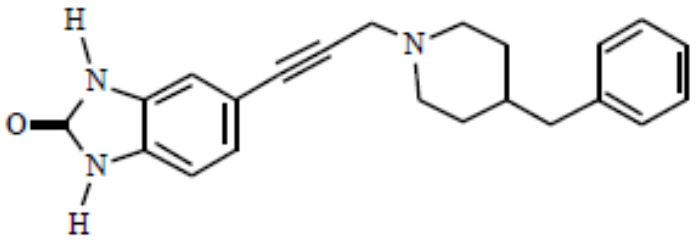
25
NR2B-IC_{50}: 4.7 μM



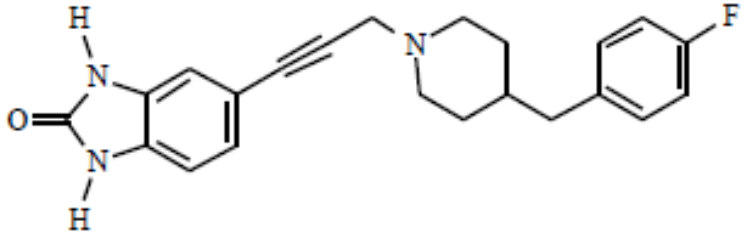
26
NR2B-IC_{50}: 0.17 μM
α-1-IC_{50}: 0.58 μM; D_2-IC_{50}: 0.29 μM



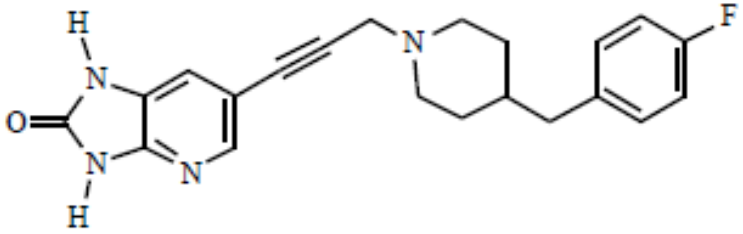
27
NR2B-IC_{50}: 0.10 μM
α-1-IC_{50}: 1.5 μM; D_2-IC_{50}: 1.7 μM



28
NR2B-IC_{50}: 0.0053 μM
α-1-IC_{50}: 0.5 μM; D_2-IC_{50}: 2.6 μM

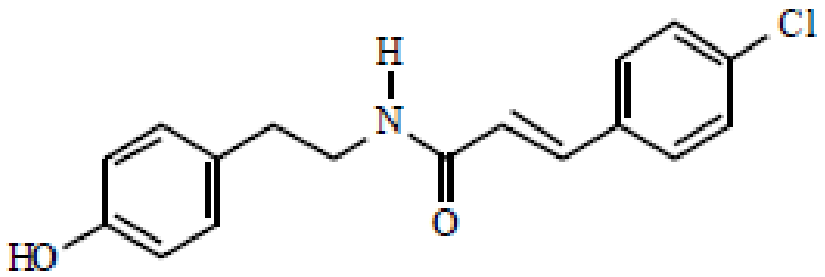


29
IC_{50}: 3 nM

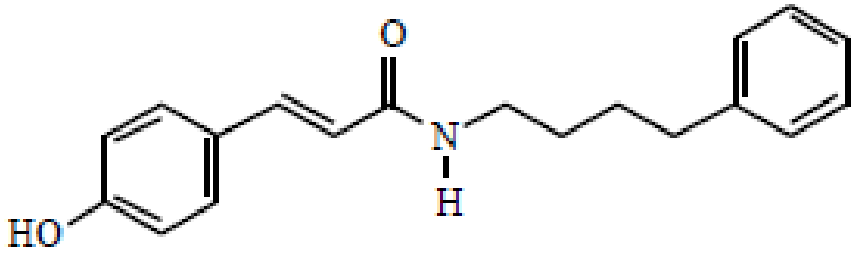


30
IC_{50}: 2 nM

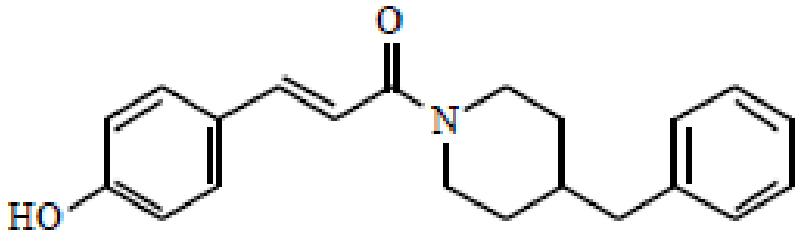
CoCensys/Parke-Davies Pharm.Res.



31
NR2B-IC_{50}: 170 nM

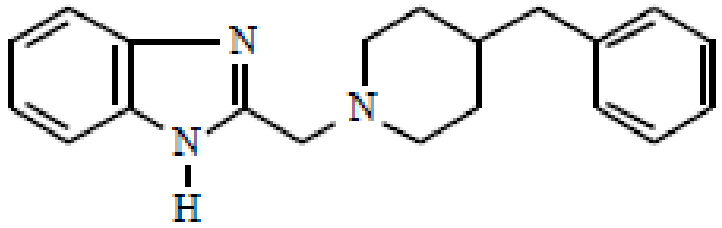


32
NR2B-IC_{50}: 77 nM



33
NR2B-IC_{50}: 120 nM

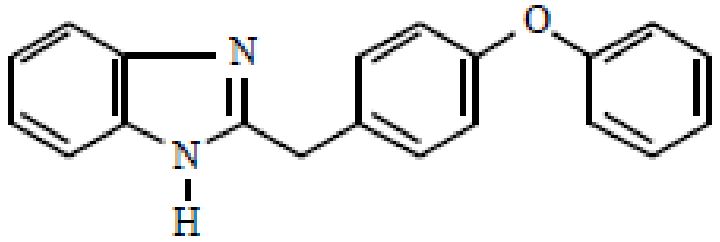
Merck Research Laboratories



34

NR2B bind. K_i: 420 nM; Ca^{2+}-IC_{50}: 710 nM

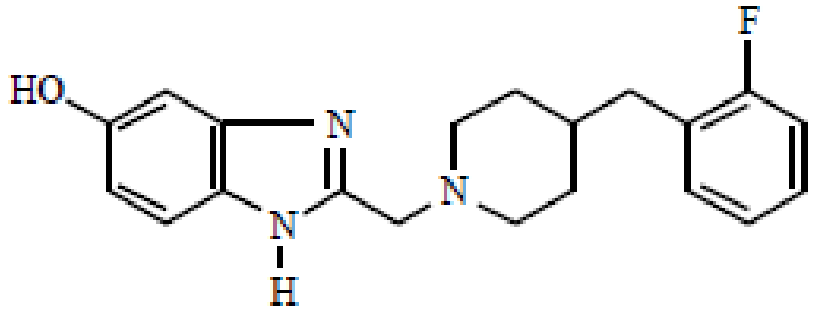
hERG-IP: 1400 nM; α-1-IC_{50}: 2800 nM



35

NR2B bind. K_i: 260 nM; Ca^{2+}-IC_{50}: 200 nM

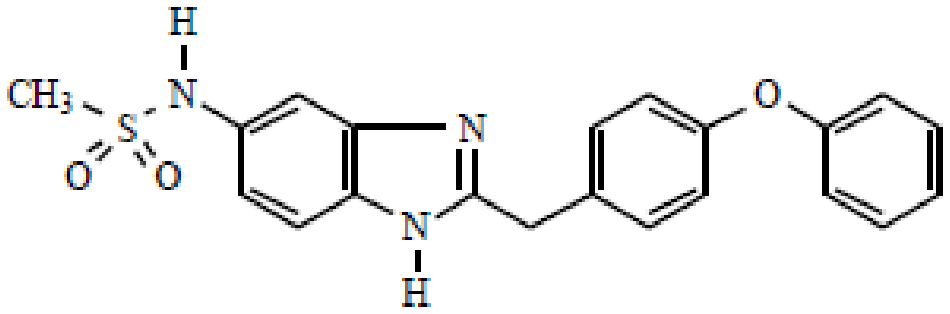
hERG-IP: 2000 nM; α-1-IC_{50}: 4200 nM



36

NR2B bind. K_i: 0.85 nM; Ca^{2+}-IC_{50}: 9.7 nM

hERG-IP: 2900 nM; α-1-IC_{50}: 730 nM

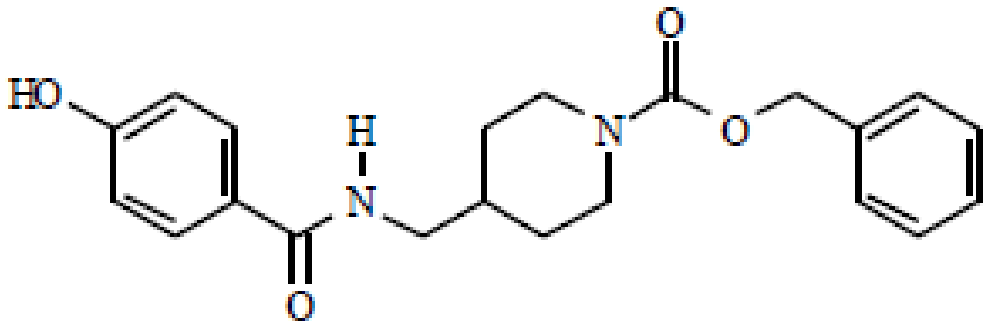


37

NR2B bind. K_i: 0.68 nM; Ca^{2+}-IC_{50}: 0.72 nM

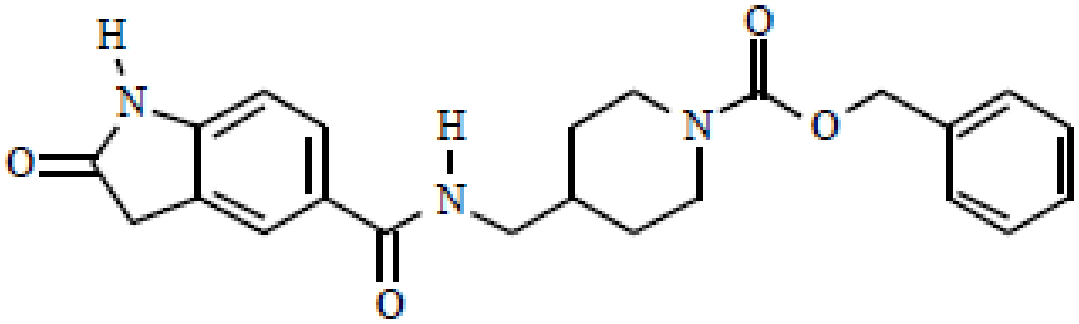
hERG-IP: 120 nM; α-1-IC_{50}: 4000 nM

Merck & Co. Inc.



42

Ca^{2+}-IC_{50}: 4.8 nM



43

Ca^{2+}-IC_{50}: 6.0 nM

NR2B subtype selective NMDA receptor antagonists for neuropathic pain at Gedeon Richter Plc.

Why neruopathic pain?

- The **unmet medical need** is high. „Classical" analgetics (opiates, NSAID-s) are not effective enough.
- Incidence: 2-8%.
- Causes: diabetes, viral infection (Herpes zoster, HIV), alcoholism, surgical interventions, vitamin deficiency etc.

Why NMDA receptor antagonists?

- NMDA-receptor antagonists (selective and non-selective) are effective in animal models
- With NMDA antagonists used in clinic analgetic activity was shown in acute hyperalgesia and in chronic pain syndromes

Why NR2B subtype?

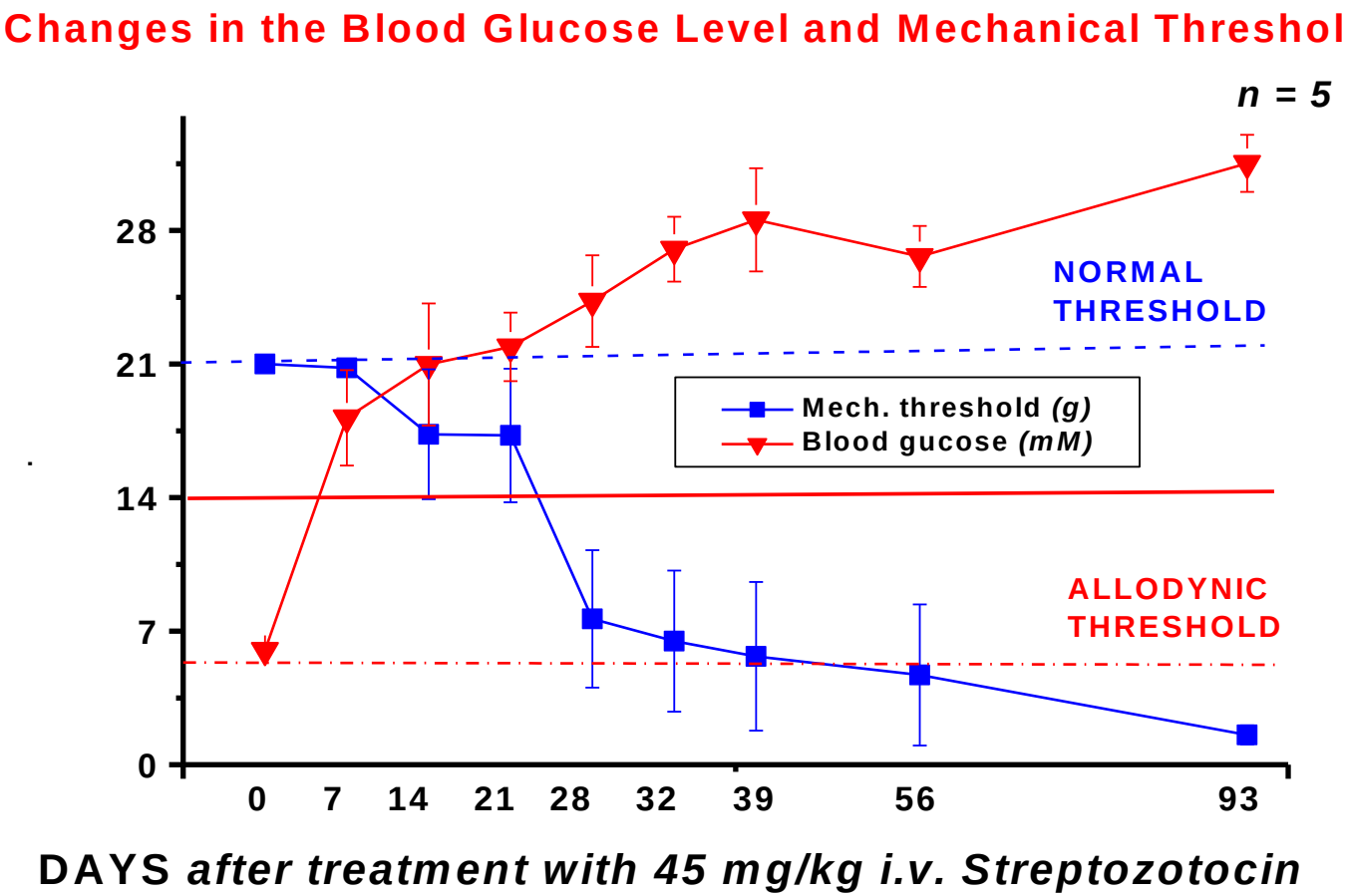
- Only a part of NMDA receptors are intended to block
- Normal pain sensation is not transmitted via these receptors
- Good side-effect profile is expected compared to non-selective NMDA antagonists

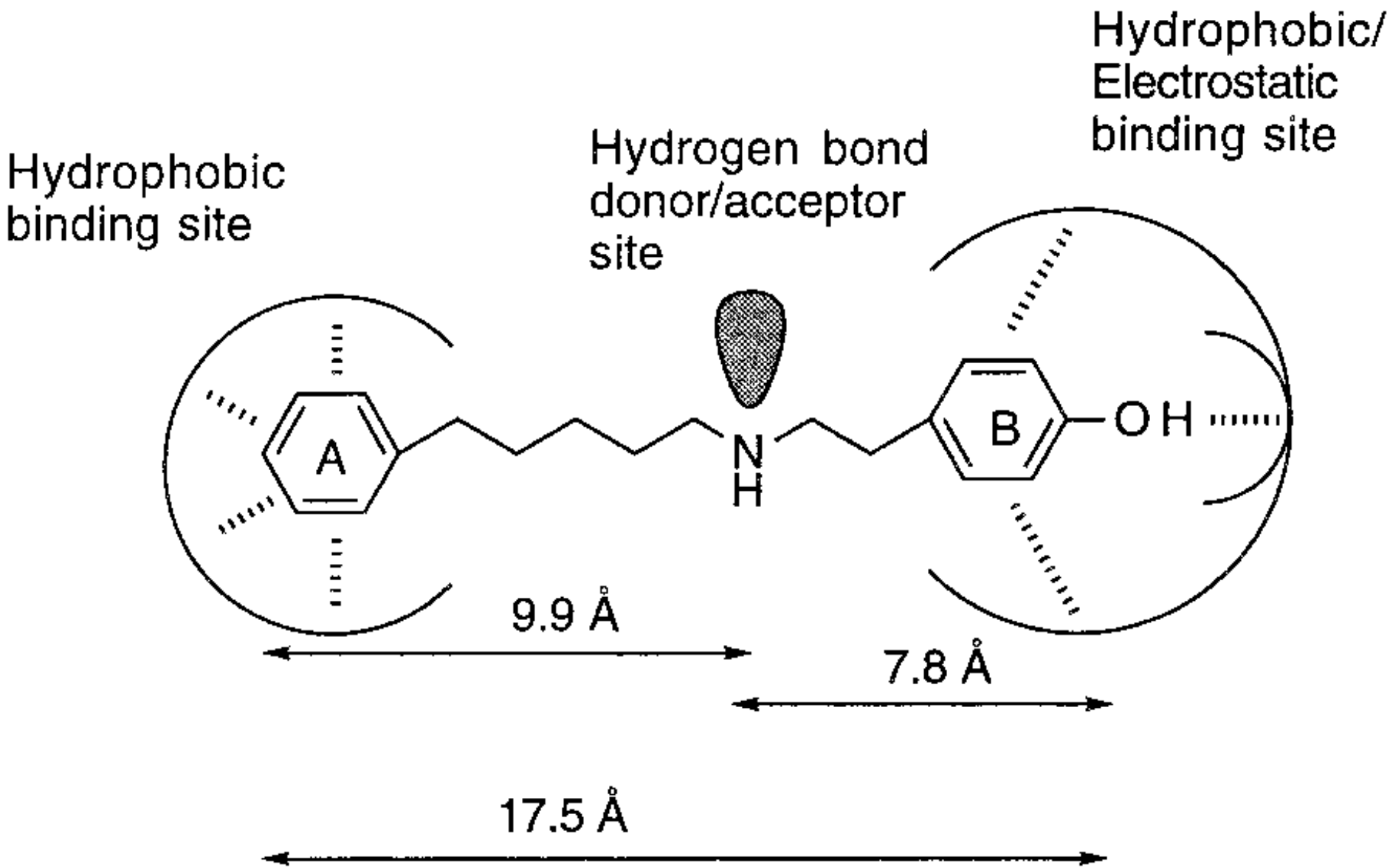
Primary in vitro test

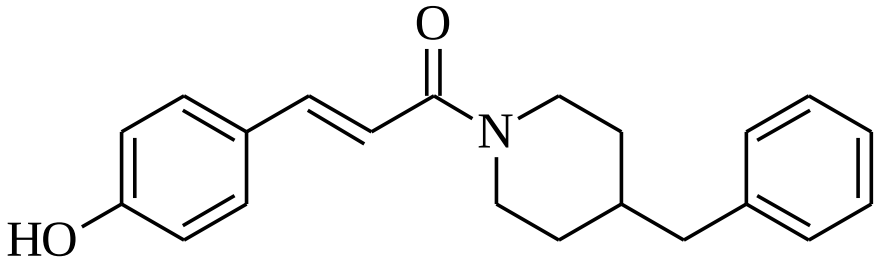
IC_{50}:

The measurement of the blockade of NMDA-induced increase of intracellular Ca^{2+}-level in rat cortical cells

Disease model

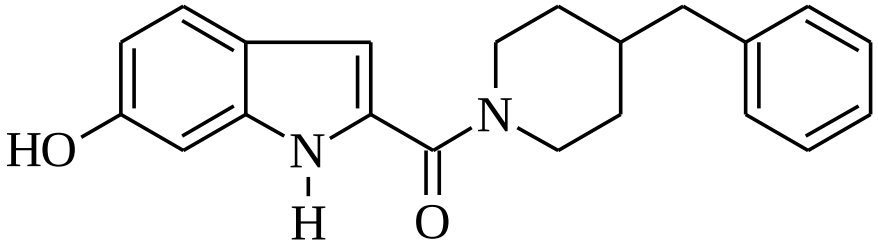



Hydrophobic/
Electrostatic
binding site
Hydrogen bond
donor/acceptor
site
Hydrophobic
binding site
A
N
H
B
O H
9.9 Å
7.8 Å
17.5 Å



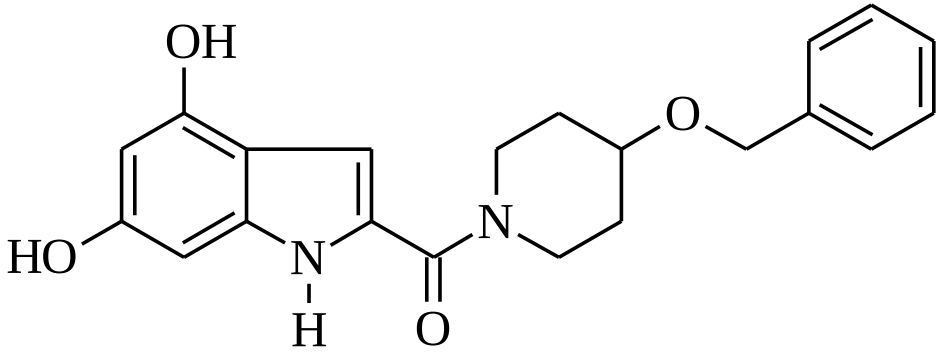
33

IC_{50}: 131 nM



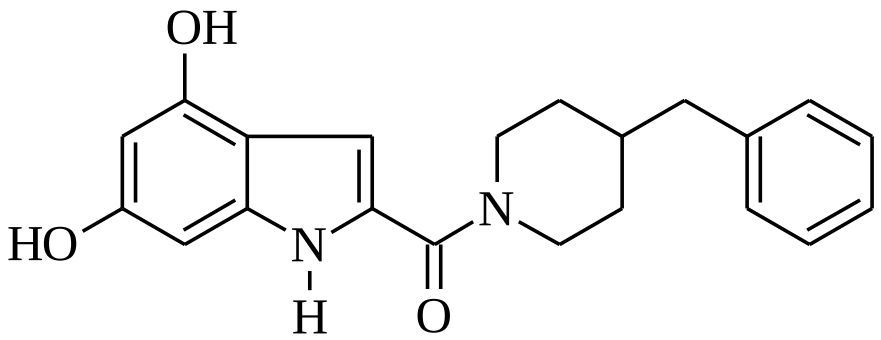
44

IC_{50}: 18 nM



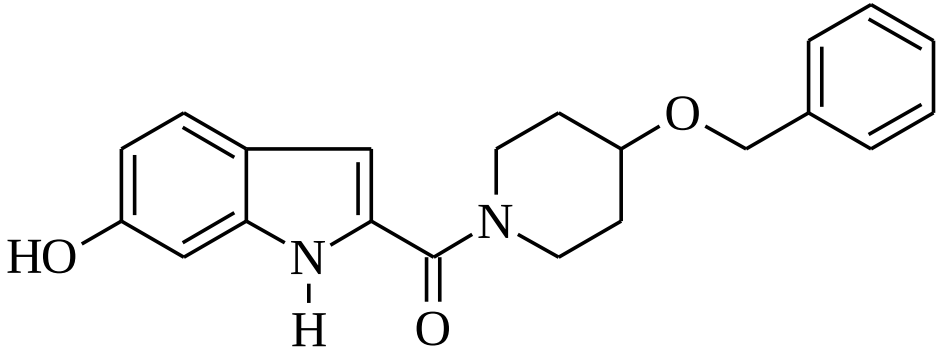
45

IC50: 4 nM



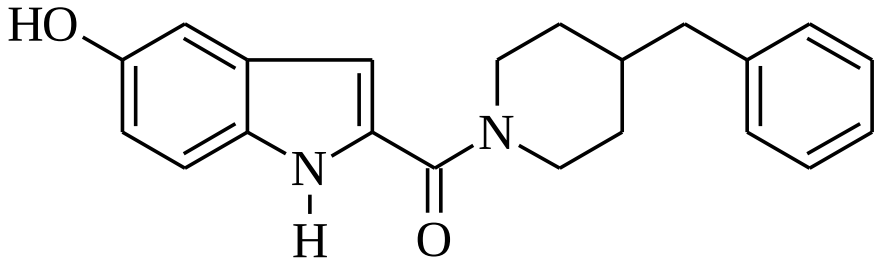
46

IC50: 7 nM



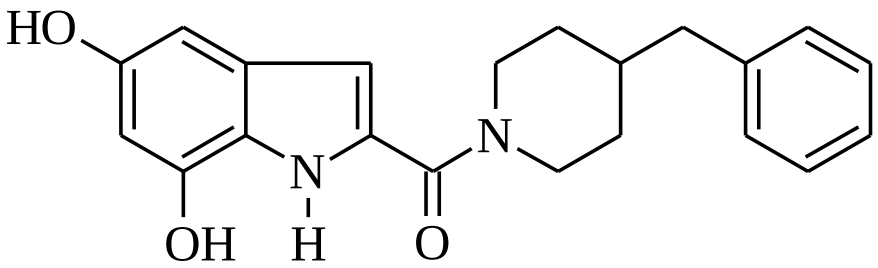
47

IC50: 16 nM



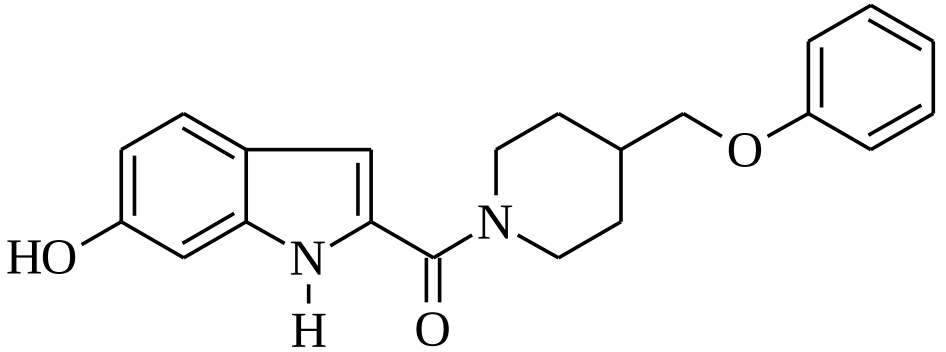
48

IC50: 24 nM



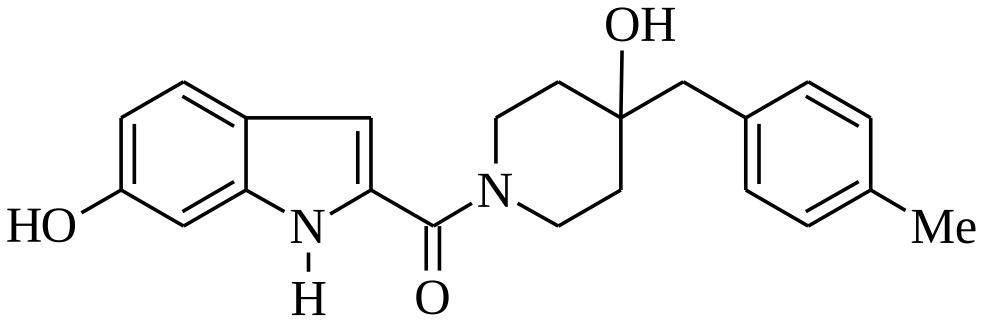
49

IC_{50}: 30 nM



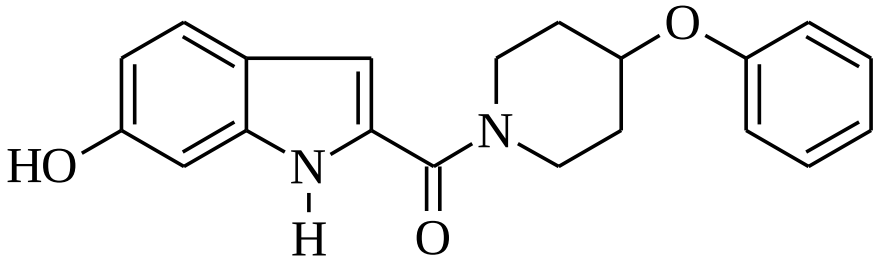
50

IC_{50}: 36 nM



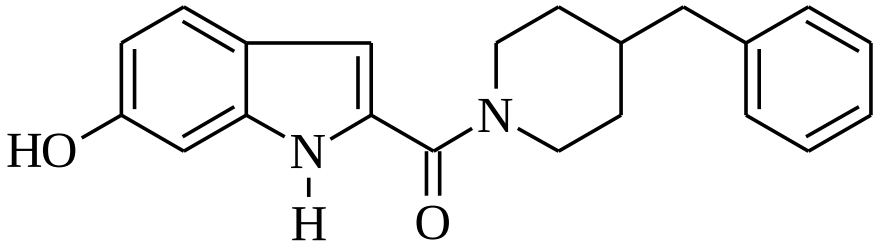
51

IC_{50}: 37 nM



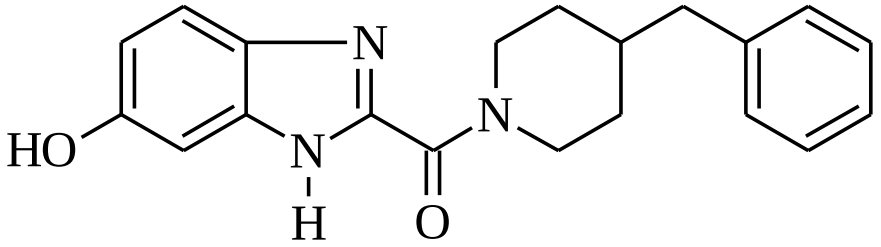
52

IC_{50}: 107 nM



44

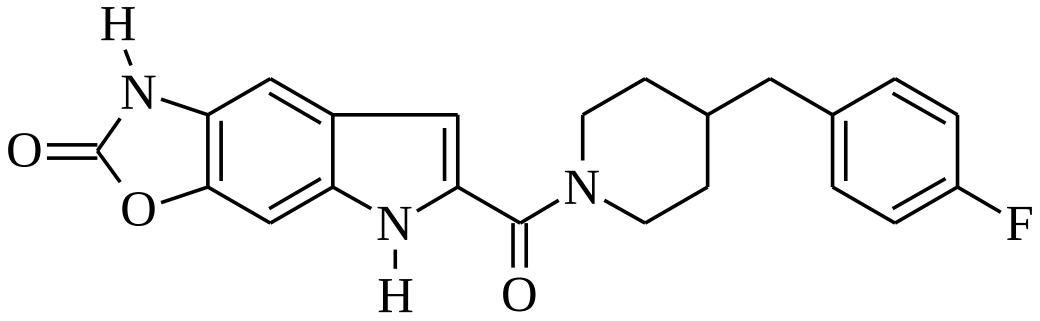
IC_{50}: 18 nM



53

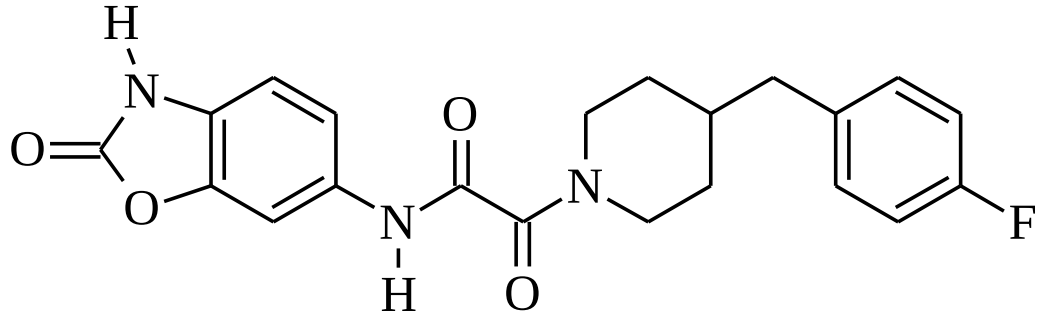
IC_{50}: 2.2 nM

s: 72µg/ml; rBA: 31%



54

IC_{50}: 41 nM

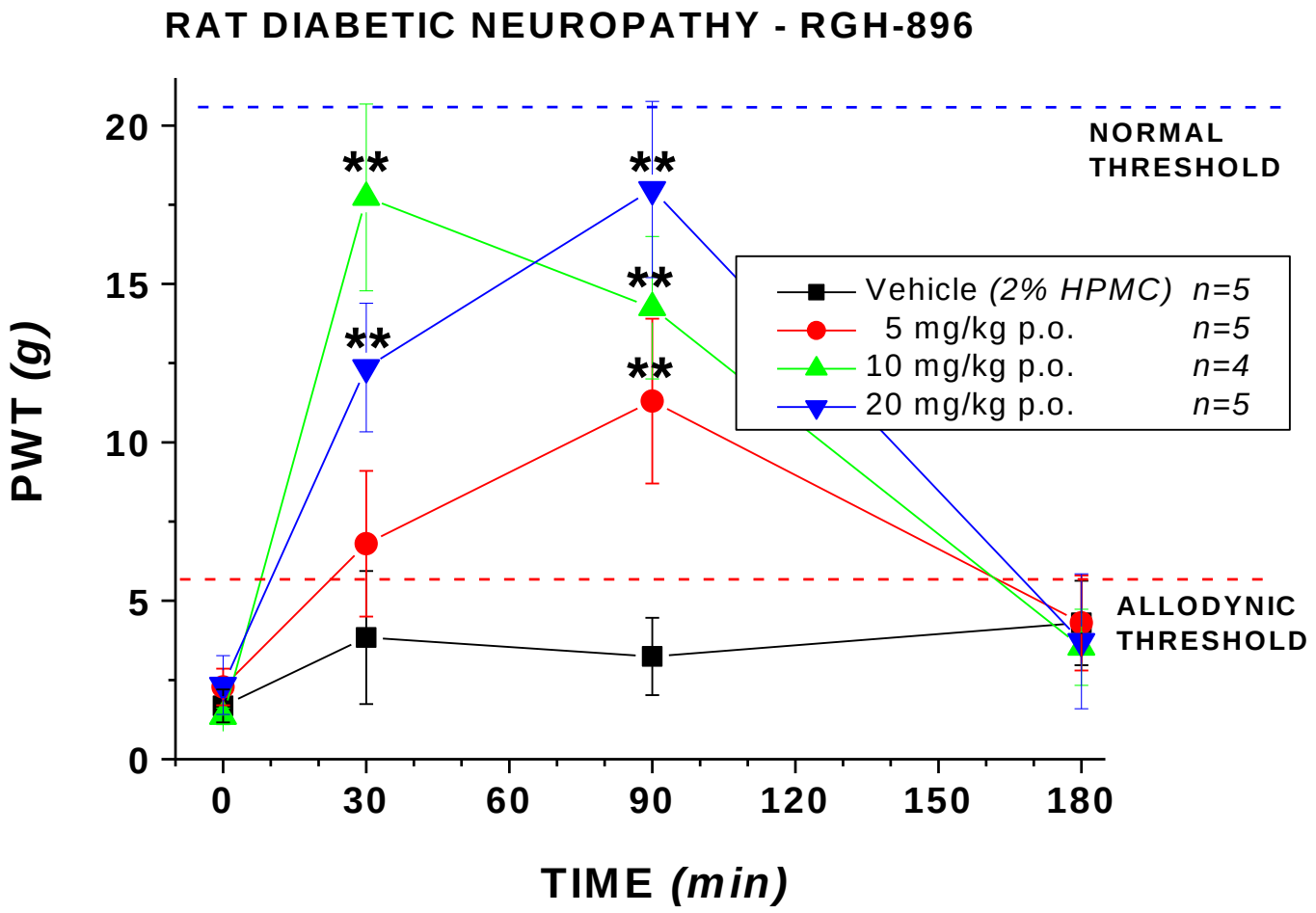


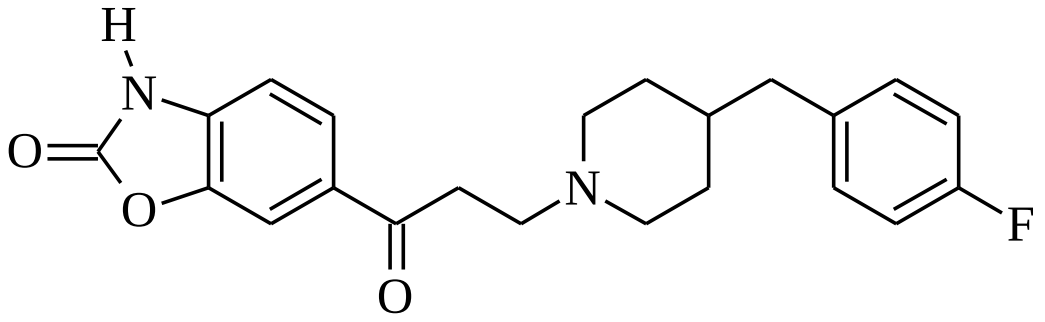
55

IC_{50}: 0.9 nM

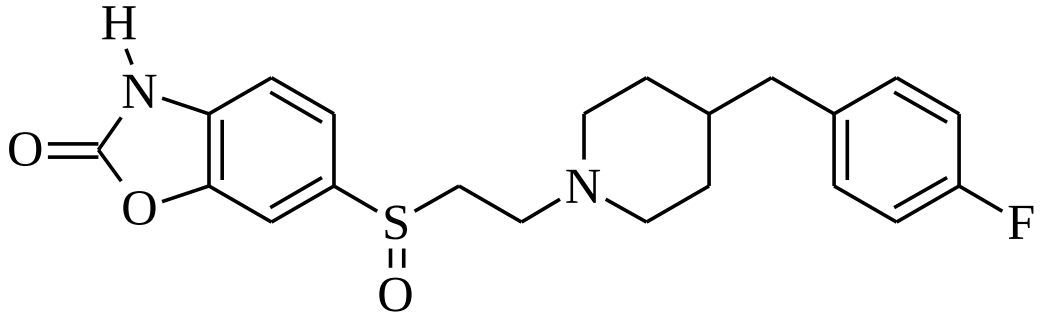
radiprodil

Activity in the disease model

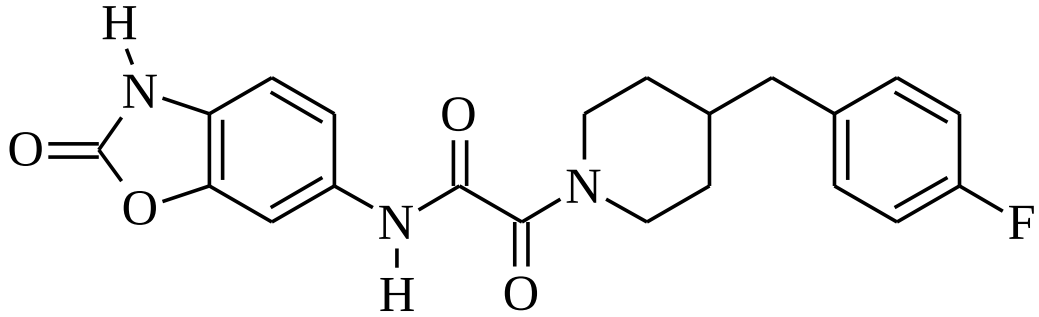




8
Merck KGaA



24
CoCensys/Parke Davies



55
Gedeon Richter

Pharmacophore hybridization, polypharmacology

Jens-Uwe Peters (F. Hoffmann-La Roche Ltd.)
J. Med. Chem. 2013, 56, 8955–8971

„Polypharmacology describes the activity of compounds at multiple targets. Current research focuses on two aspects of polypharmacology: (1) unintended polypharmacology can lead to adverse effects; (2) polypharmacology across several disease-relevant targets can improve therapeutic efficacy, prevent drug resistance, or reduce therapeutic-target-related adverse effects."

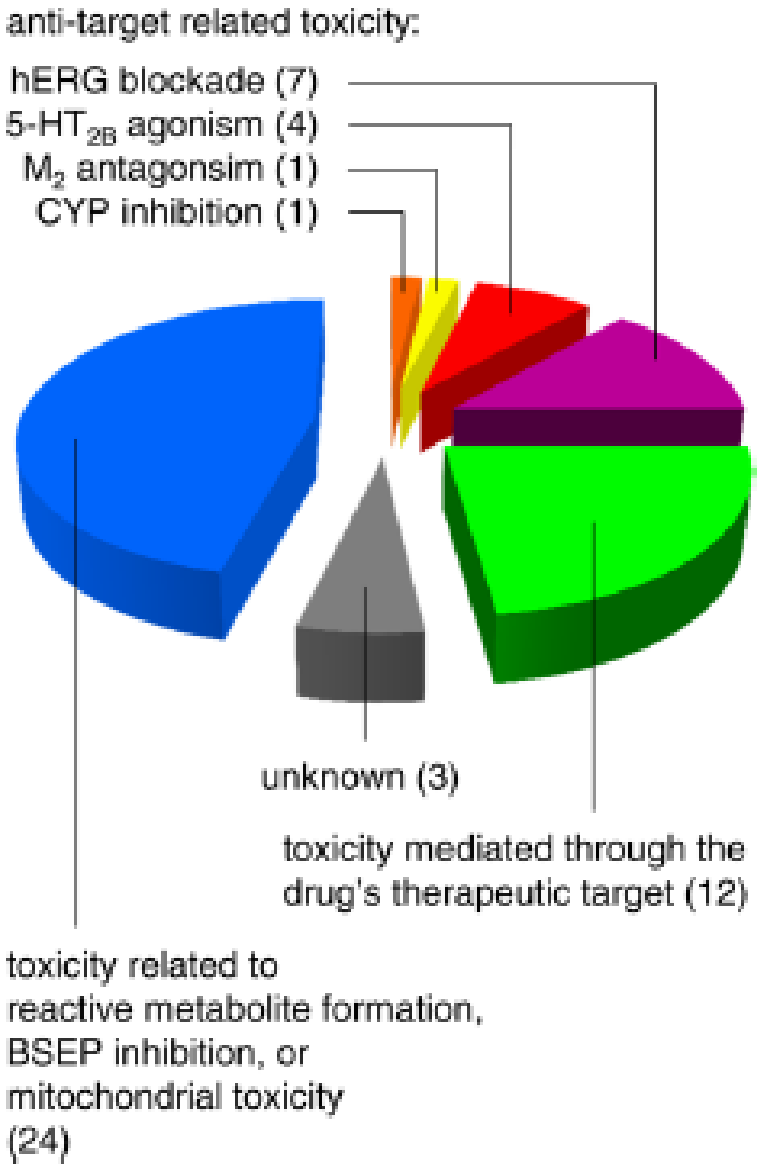
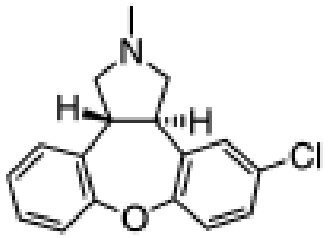
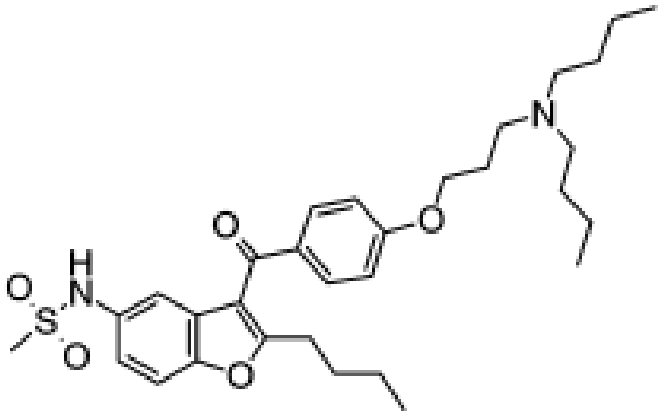


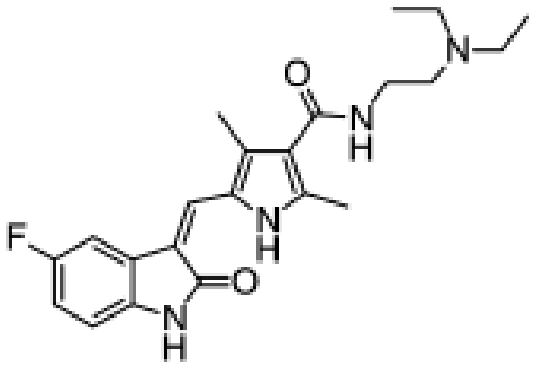
Figure 3. Mechanistic reasons for drug withdrawals since 1980. Withdrawn drugs were classified by the presumed mechanism of their main adverse effects: (a) hERG blockade: astemizole, cisapride, grepafloxacin, levomethadyl, terfenadine, terodiline, thioridazine; (b) serotonin 5-HT_{2B} receptor agonism: benfluorex, dexfenfluramine, fenfluramine, pergolide; (c) muscarinic M_2 receptor antagonism: rapacuronium; (d) CYP interaction: mibefradil; (e) therapeutic-target related: alosetron, cerivastatin, encainide, etretinate, flosequinan, hydromorphone extended-release (Palladone), methaqualone, phenylpropanolamine, rimonabant, rofecoxib, rosiglitazone, valdecoxib; (f) reactive metabolite formation, bile salt export pump (BSEP) inhibition, or mitochondrial toxicity: alpidem, amineptine, benoxaprofen, benzbromarone, bromfenac, chlormezanone, levamisole, lumiracoxib, nefazodone, nomifensine, pemoline, phenacetin, remoxipiride, sitaxentan, suprofen, temafloxacin, ticrynafen, tolcapone, tolrestat, troglitazone, trovafloxacin, ximelagatran, zimelidine, zomepirac; (g) unknown: gatifloxacin, sibutramine (likely therapeutic target related), tegaserod.



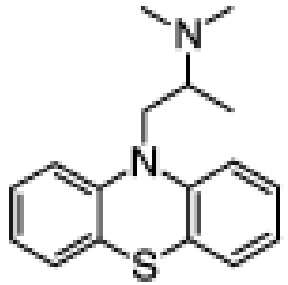
asenapine
Schering-Plough (2009)
antipsychotic
low nM affinity for at least 18 GPCRs



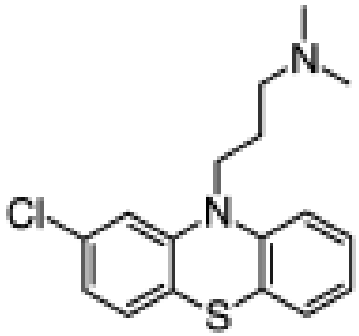
dronedarone
Sanofi-Aventis (2009)
anti-arrhythmic
blockade of multiple cardiac ion channels



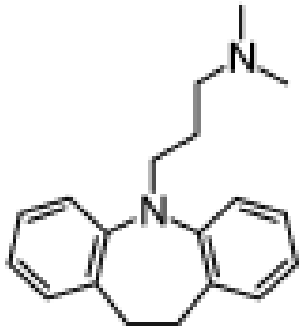
sunitinib
Pfizer (2006)
anti-cancer
inhibition of 79 kinases (K_D < 10 μM)



promethazine
~ 1949
antihistamine

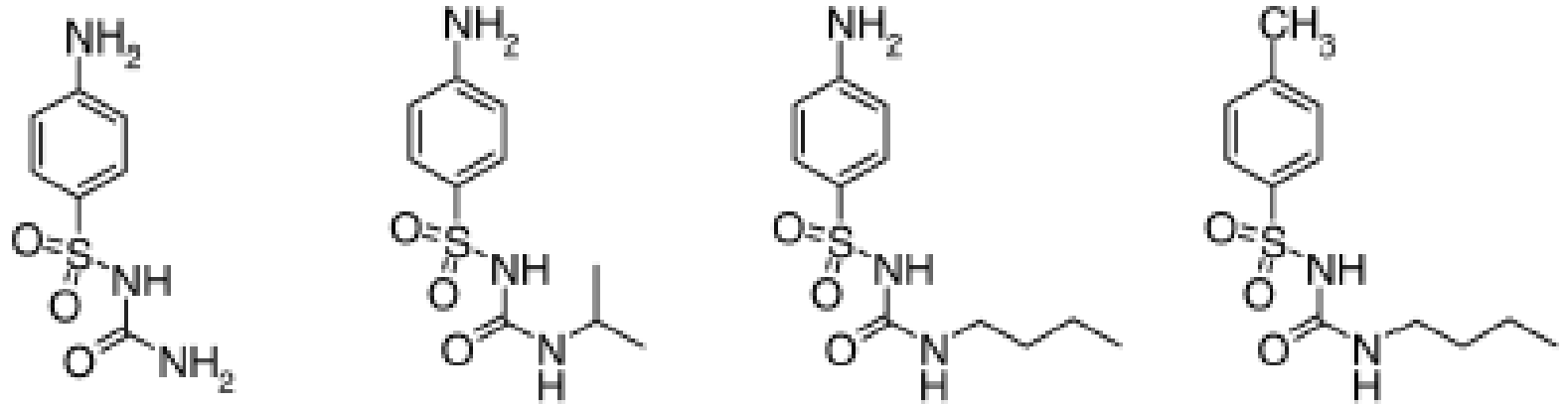


chlorpromazine
1952
antipsychotic

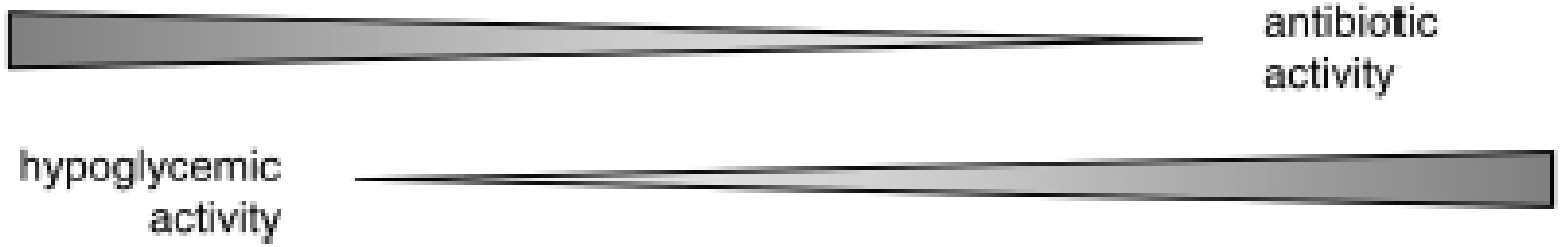


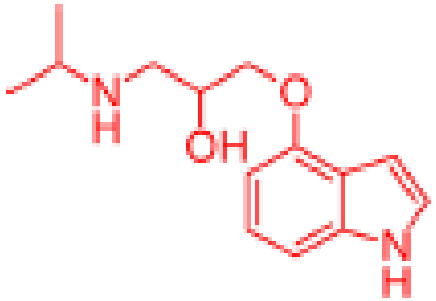
imipramine
1955
antidepressant

Receptor	Target for ...	IC_{50} (radioligand binding, µM)		
H_1	allergy	0.0054	0.012	0.027
D_2	schizophrenia	0.1	0.021	0.41
5-HT_{2A}	schizophrenia	0.023	0.0034	0.22
SERT	depression	7.59	0.12	0.0035

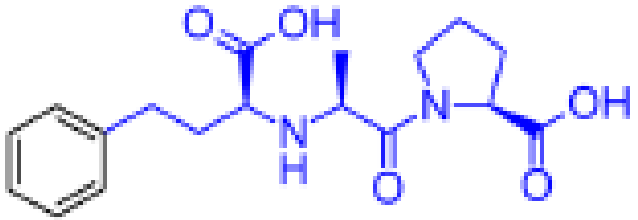


	sulfacarbamide	1	carbutamide	tolbutamide
	1943	1950	1954	1956
Indication:	bacterial infections			diabetes type 2
Therapeutic target:	likely: bacterial dihydropteroate synthetase	·····		pancreatic K_{ATP} channel

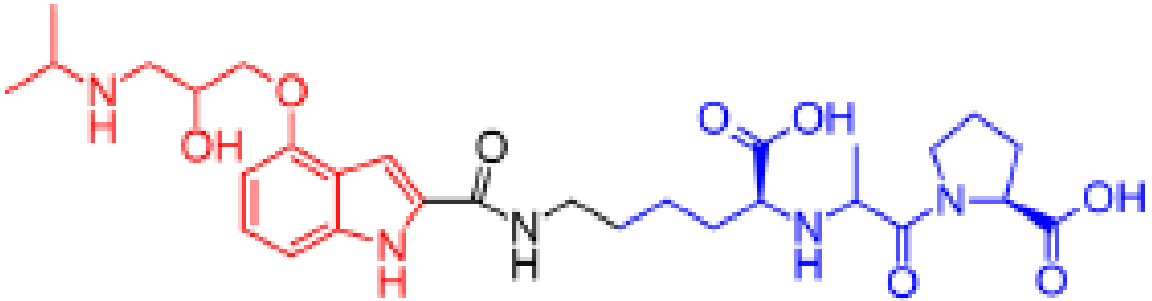




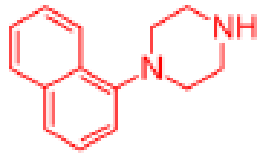
pindolol
beta blocker
MW = 248



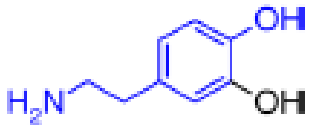
enalaprilat
ACE-inhibitor
MW = 348



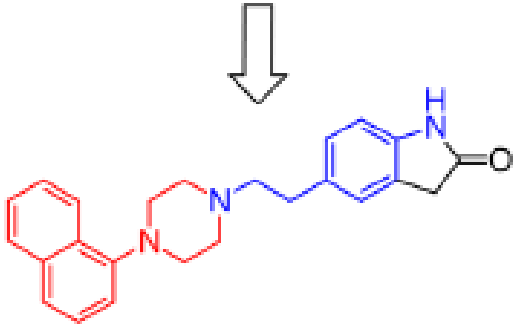
2 (BW-A575C)
dual beta blocker / ACE inhibitor
MW = 589



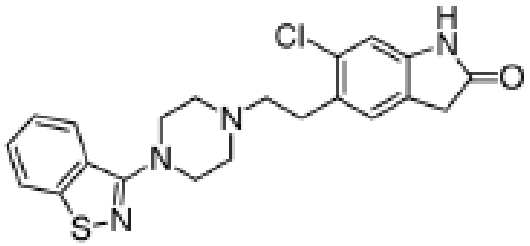
naphtylpiperazine
multiple 5-HT
receptor ligand



dopamine



3
multiple 5-HT and dopamine
receptor ligand



ziprasidone (Pfizer, 2001)

K_i (D_2 receptor) = 4.8 nM

K_i (D_3 receptor) = 7.2 nM

K_i (5-HT_{2A} receptor) = 0.4 nM

K_i (5-HT_{2C} receptor) = 1.3 nM

K_i (5-HT_6 receptor) = 61 nM

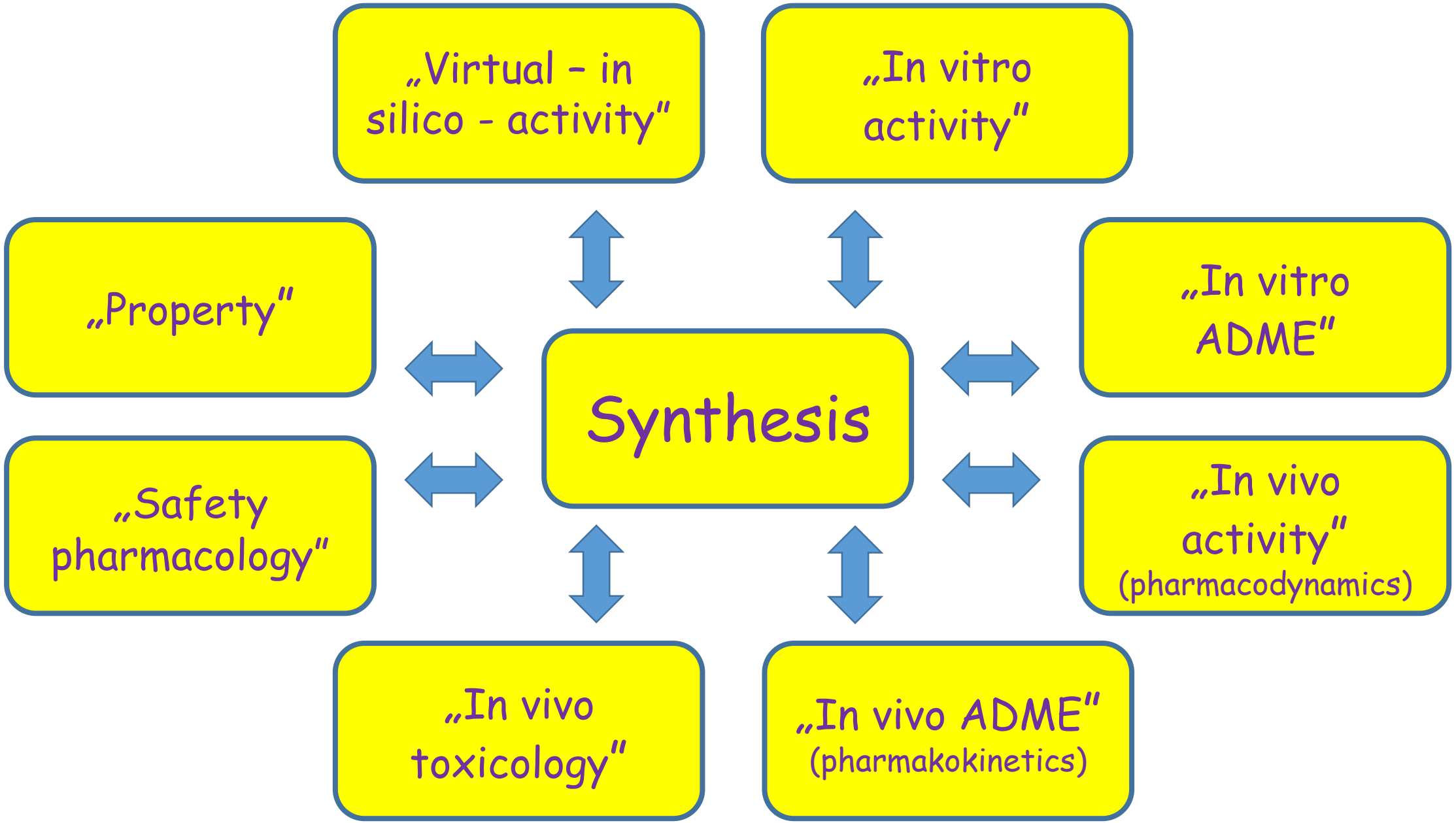
K_i (5-HT_7 receptor) = 6 nM

K_i (α_1 receptor) = 11 nM

„Since the 1990s, industrial drug discovery has been aiming for highly selective drugs to avoid adverse effects mediated through "antitargets". Lack of selectivity has usually been discovered late in a drug discovery project and has typically led to substantial delays or late-stage attrition. Major research organizations have therefore begun to screen early compounds against small panels of frequently hit antitargets and made selectivity a matter of early optimization."

„On the other hand, the opportunities of polypharmacological drug discovery are increasingly being appreciated. The FDA has approved numerous polypharmacological drugs for different target classes and indications in recent years. Many multigenic diseases do not succumb to single-target therapies but rather require a polypharmacological modulation of a network of targets. Some authors have even associated the "one disease – one target" philosophy with the productivity decline of the pharmaceutical industry and have advocated network pharmacology as the "next paradigm in drug discovery"."

pharmacophore
polypharmacology
pharmacophore hybridization


„Virtual – in silico - activity"
„In vitro activity"
„Property"
„In vitro ADME"
Synthesis
„Safety pharmacology"
„In vivo activity" (pharmacodynamics)
„In vivo toxicology"
„In vivo ADME" (pharmakokinetics)

Mark A. Murcko

What Makes a Great Medicinal Chemist?

A Personal Perspective

J. Med. Chem. 61 (17) 7419-7424 (2018)

General characteristics of great scientists

Intellectually curious and constantly learning
Tightly focused on important problems
Pragmatic
Obsessed with data

General characteristics of great scientists

Sweat the details
Sense of urgency
Recognize great science happens everywhere
Savvy about and open to new technologies

General characteristics of great scientists

Challenge assumptions
Passionate about their work
Aware of their own ignorance; they „know what they don't know"
Resilient

General characteristics of great scientists

Good communicator
Often have a very high emotional intelligence
Often selfless „unsung heros"
Seek out mentors, and become mentors

Discipline-specific characteristics of medicinal chemists

Always thinking about the target product profile
Creative drug designer
Manage the properties of the compounds
Think in three dimensions

Discipline-specific characteristics of medicinal chemists

Always want another scaffold
Don't panic over IP
Don't give up on validated targets
Care deeply about biology

Discipline-specific characteristics of medicinal chemists

Always have a good idea of what to make next
Aren't afraid of tough syntheses
Avoid unnecessary complexity
Re-use whatever they can
Know the history of drug discovery

„It is a wonderful privilege to have a career in scientific research with access to substantial resources working with incredibly smart colleagues searching for new medicines to benefit mankind."

(Ian B. Campbell, Simon J.F. Macdonald, Panayiotis, A. Procopiou
Medicinal chemistry in drug discovery in big pharma: past, present and future
Drug Discovery Today https://doi.org/10.1016/j.drudis.2017.10.007)

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