Chemical Similarity and Biological Activities

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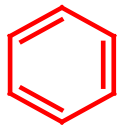
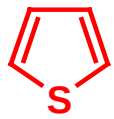
Similarity in Nature (Mimicry)

Monarch, *Danaus plexippus*

The Serendipitous Discovery of Thiophene

MW = 78.11
mp. = 5.5°C
bp. = 80.15°C
Log P = 2.13
MR = 26.4
d = 0.879





MW = 84.14
mp. = -38°C
bp. = 84°C
Log P = 1.81
MR = 25.0
d = 1.057

1825, Michael Faraday
"bicarburet of hydrogen", Fp. 42°F = 5.5°C

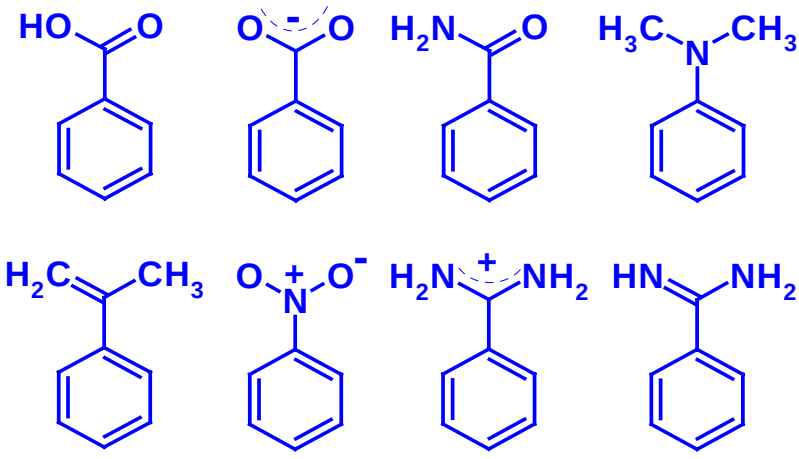
1879, Adolf v. Baeyer, Indigblau reaction

1882, Victor Meyer and Traugott Sandmeyer
Discovery of thiophene

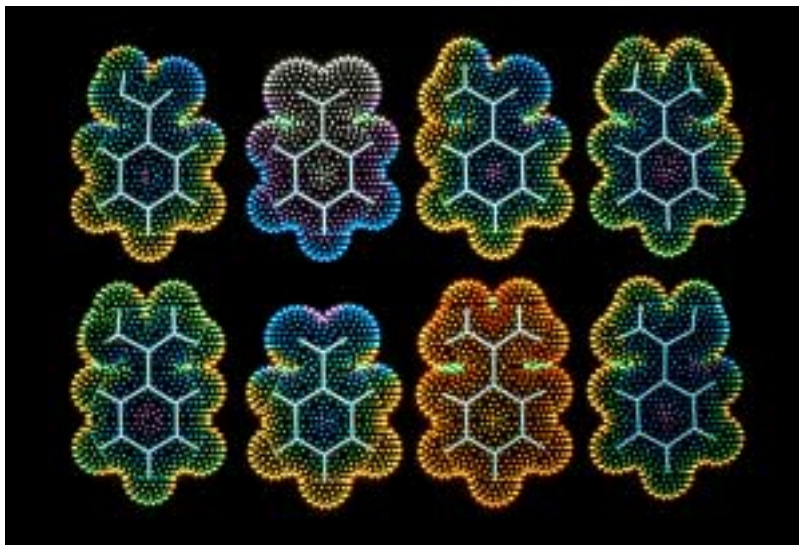
The Similarity Principle in Drug Design - Lead Optimization is an Evolutionary Procedure

Medicinal chemists, all the time, used the similarity of chemical compounds to design new analogs of active leads. Whenever they discovered compounds with improved activity, selectivity, pharmacokinetics, etc., they used these compounds to search analogs with even further improved properties. However, ...

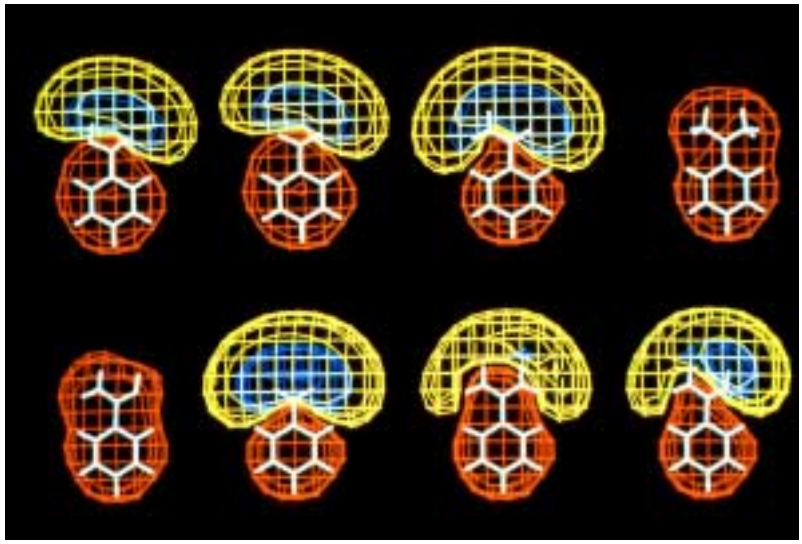
Similarity and Diversity



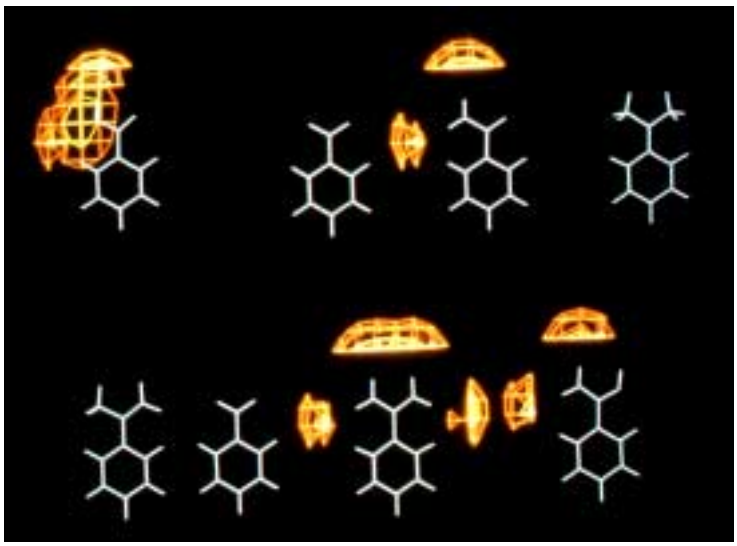
Volumes and Surface Potentials



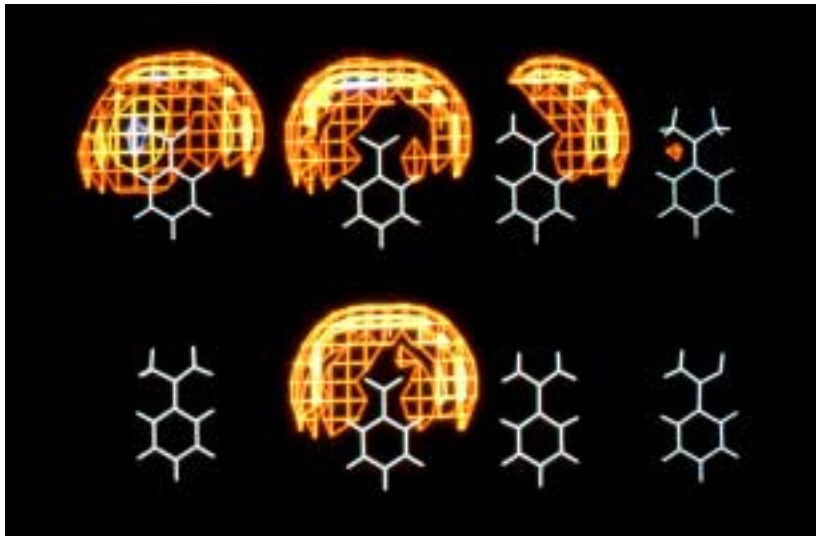
Hydrophobic and Polar Regions



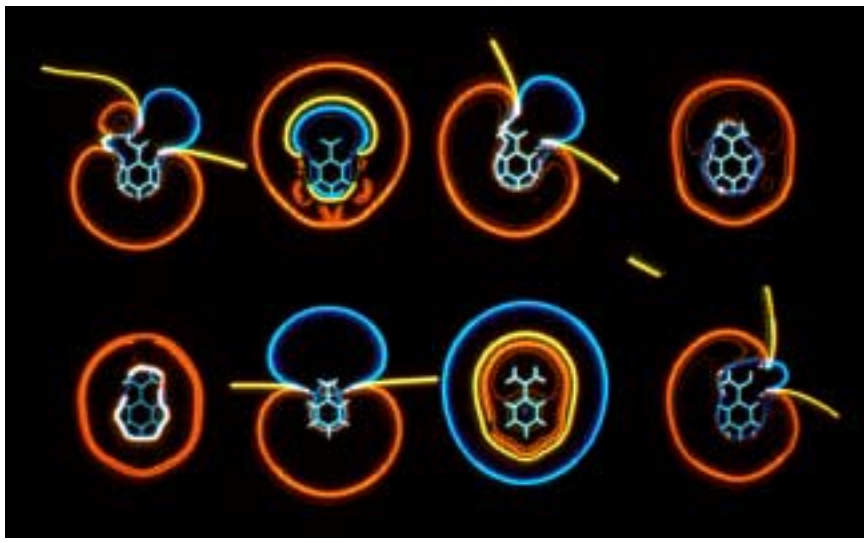
Hydrogen Bond Donor Potentials



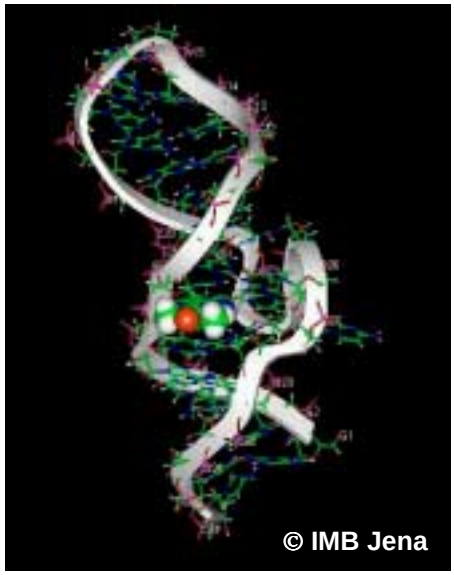
Hydrogen Bond Acceptor Potentials

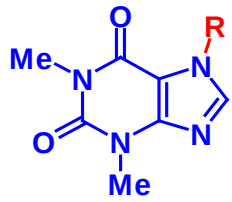


Molecular Electrostatic Potentials (MEP)



Selective Recognition of Theophylline by RNA



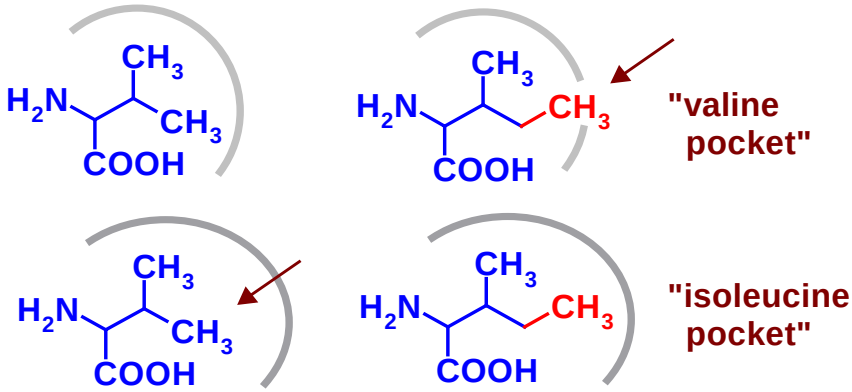


A theophyllin-binding aptamer binds theophylline (R = H)

10,000-times better than caffeine (R = Me)

G. R. Zimmermann et al., Nat. Struct. Biol. 4, 644-649 (1997)

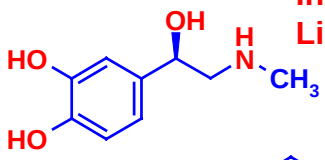
Recognition of Valine and Isoleucine



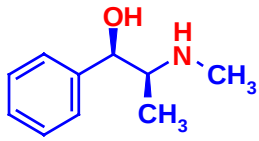
A „suspicious“ check by isoleucine tRNA synthase rejects valines (1:200,000) but also 80% of all isoleucines. Correspondingly, the error rate is about 1:40,000.

Lipophilicity and Blood-Brain Barrier

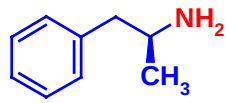
Polar Compounds — **Intermediate Lipophilicity** — **Lipophilic Compounds**



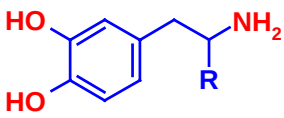
epinephrine



ephedrine

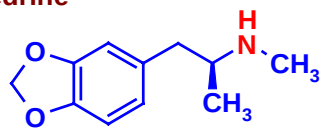


amphetamine
(speed)



a, dopamine, R = H

b, L-Dopa, R = COOH



MDMA (Ecstasy, XTC)

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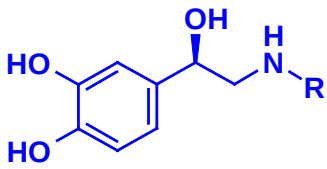
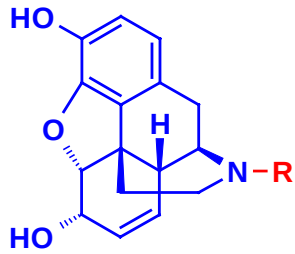
Agonists and Antagonists

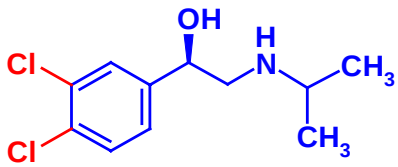


R = H , norepinephrine
R = CH_3, epinephrine
R = $CH(CH_3)_2$, isoproterenol



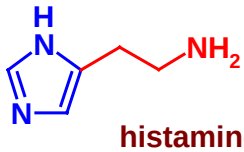
morphine
R = CH_3
(agonist)

nalorphine
R = CH_2-CH=CH_2
(antagonist)

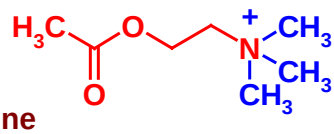


dichloroisoproterenol, DCI

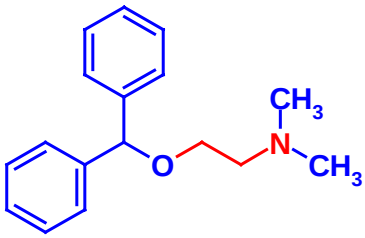
Agonists and Antagonists



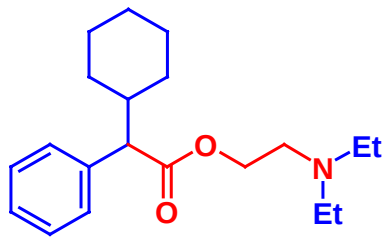
histamine
(agonist)



acetylcholine
(agonist)



diphenhydramine (antagonist)



drofenine (antagonist)

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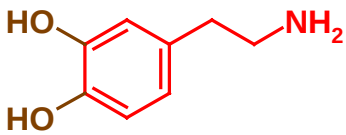
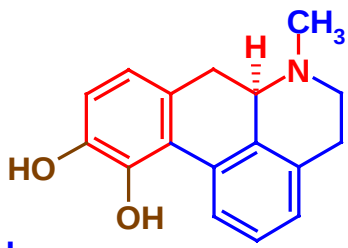
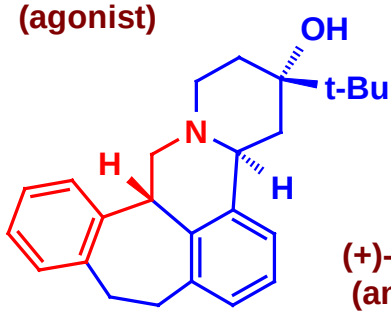
Agonists and Antagonists



dopamine
(agonist)

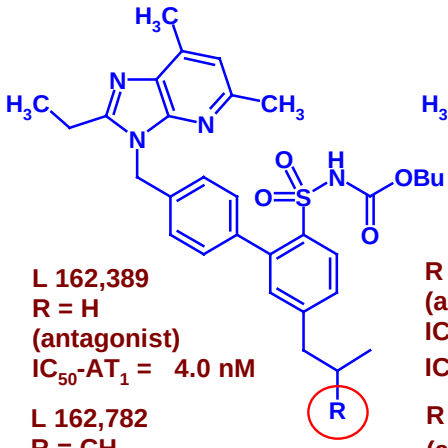


apomorphine
(agonist)



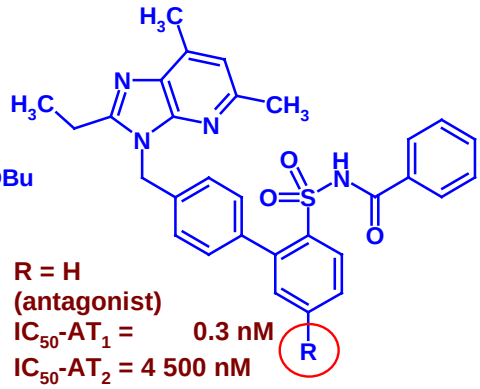
(+)-butaclamol
(antagonist)

Unexpected Effects of Alkyl Group Variation



L 162,389
R = H
(antagonist)
IC_{50}-AT_1 = 4.0 nM

L 162,782
R = CH_3
(agonist)
IC_{50}-AT_1 = 25 nM



R = H
(antagonist)
IC_{50}-AT_1 = 0.3 nM
IC_{50}-AT_2 = 4 500 nM

R = $CH_2CH(CH_3)_2$
(agonist)
IC_{50}-AT_1 = 13 nM
IC_{50}-AT_2 = 10 nM

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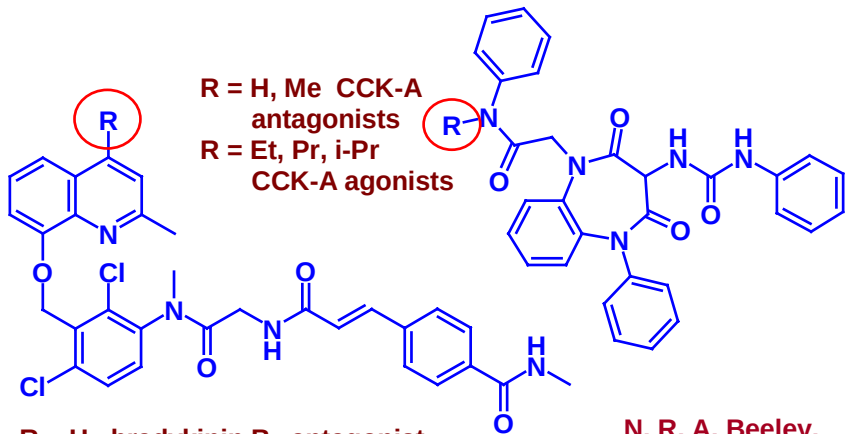
Unexpected Effects of Alkyl Group Variation



R = H, Me CCK-A antagonists
R = Et, Pr, i-Pr CCK-A agonists

R = H bradykinin B_2 antagonist

R =  **bradykinin B_2 agonist**

N. R. A. Beeley, Drug Discov. today 5, 354-363 (2000)

Isosteric Replacement of Atoms and Groups

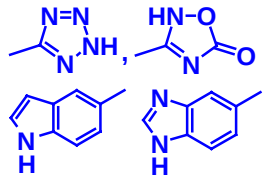
Substituents: F, Cl, Br, I, CF_3 , NO_2
Methyl, Ethyl, Isopropyl, Cyclopropyl, t.-Butyl,
-OH, -SH, $-NH_2$, -OMe, $-N(Me)_2$

Linkers: $-CH_2-$, -NH-, -O-
$-COCH_2-$, -CONH-, -COO-
>C=O, >C=S, >C=NH, >C=NOH, >C=NOAlkyl

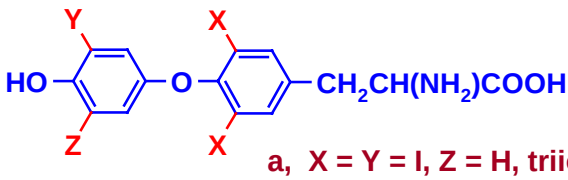
Atoms and Groups in Rings: -CH=, -N=
$-CH_2-$, -NH-, -O-, -S-,
$-CH_2CH_2-$, $-CH_2-O-$, -CH=CH-, -CH=N-

Large Groups: $-NHCOCH_3$, $-SO_2CH_3$

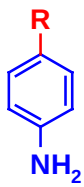
-COOH, -CONHOH, $-SO_2NH_2$,



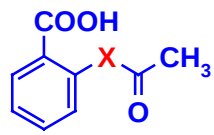
Consequences of Isosteric Replacement



a, X = Y = I, Z = H, triiodothyronine, T3
b, X = Y = Z = I, thyroxine, T4
c, X = I, Y = i-propyl, Z = H
d, X = CH_3, Y = i-propyl, Z = H



p-aminobenzoic acid,
R = COOH
sulfanilamide, R = SO_2NH_2



X = -O-
acetylsalicylic acid

Consequences of Isosteric Replacement

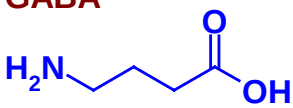
Inhibition of Carbonic Anhydrase by Sulfonamides

$CH_3SO_2NH_2$, K_i = 100 µM, pK_a = 10.5

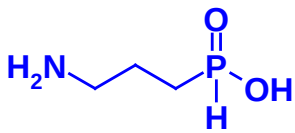
$CF_3SO_2NH_2$, K_i = 2 nM, pK_a = 5.8

Specificity of GABA Receptor Ligands

GABA

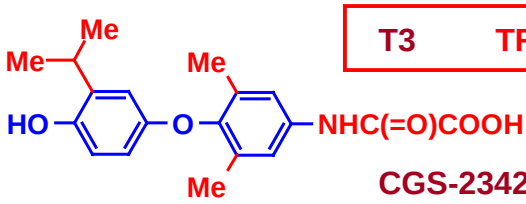


	$GABA_A$ receptor affinity	$GABA_B$
IC_{50} =	20 nM	20 nM



IC_{50} =	4,500 nM	1 nM

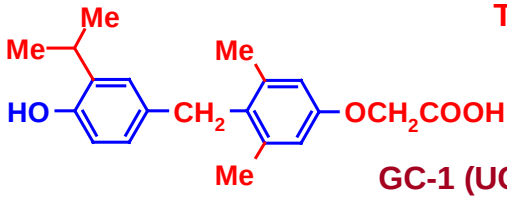
TRß1-Selective Thyromimetics Have No Cardiotoxic Side Effects



T3 TRα > TRß

CGS-23425 (Ciba-Geigy)

TRα < TRß

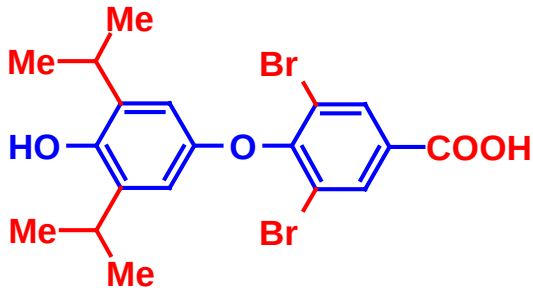


GC-1 (UCSF)

TRα < TRß

T. S. Scanlan et al., Curr. Opin. Drug Disc. Dev. 4, 614-622 (2001)

A Diisopropyl,dibromo Analog of T_4 Acts as Thyroid Hormone Receptor Antagonist



TRα no agonistic activity

TRß weak partial agonist

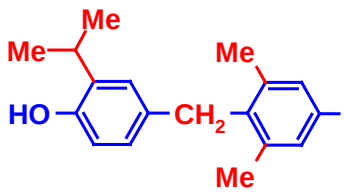
blocks T3 and T4 binding to the thyroid hormone receptor

J. D. Baxter et al., Endocrinology 143, 517-524 (2002)

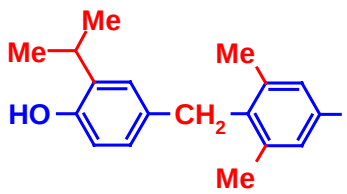
A Neutral TRß-Selective Thyromimetic Binds to a TRß R320C Mutant

H. F. Ye et al., J. Am. Chem. Soc. 123, 1521-1522 (2001)

	activity in nM TRα wild type	TRß wild type	TRß mutant
T3	0.14	0.66	4.3

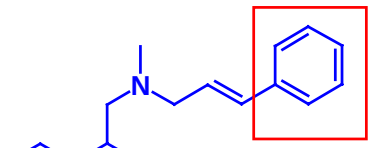


GC-1	6.6	3.7	38

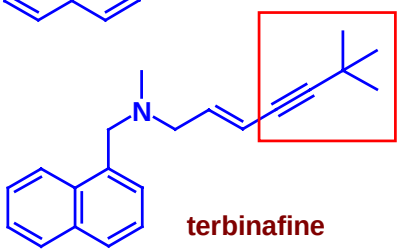


HY1	38	32	7.0

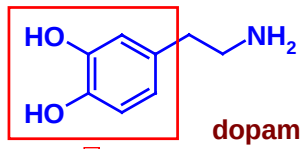
Isosteric Replacement of Aromatic Rings



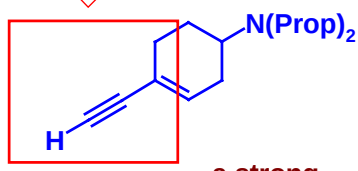
naftifine



terbinafine



dopamine

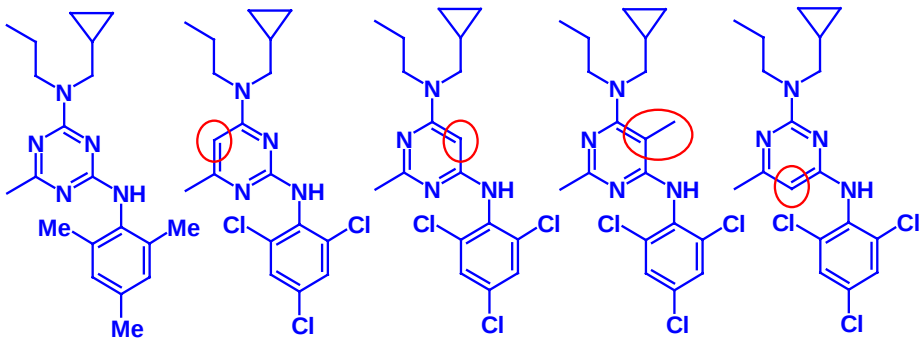


a strong dopamine D3 agonist

A. Stütz, Angew. Chem. Int. Ed. Engl. 26, 320-328 (1987)

H. Hübner et al., J. Med. Chem. 43, 756-762 (2000)

Isosteric Replacement in Corticotropin-Releasing Factor-1 (CRF1) Receptor Antagonists



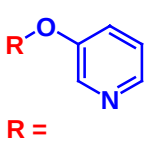
K_i CRF1 =

57 nM | 70 nM | 30 nM | 2 nM | >10,000 nM

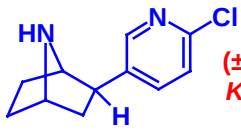
C. Chen et al., J. Med. Chem. 39, 4358-4360 (1996)

SAR of Epibatidine and its Structural Analogs

(displacement of cytisine at neuronal nACh receptors)

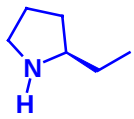


R =

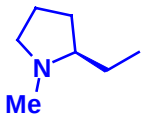


(±)-epibatidine
K_i = 0.043 nM

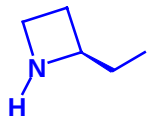
cf.
nicotine
K_i = 1 nM



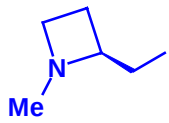
K_i = 0.16 nM



0.15 nM

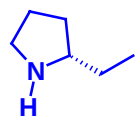


0.052 nM

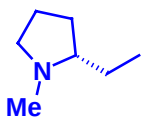


0.45 nM

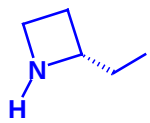
(S) series



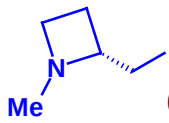
K_i = 0.14 nM



19.7 nM



0.05 nM



3.5 nM

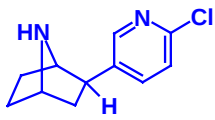
(R) series

M. A. Abreo et al., J. Med. Chem. 39, 817-835 (1996)

Hugo Kubinyi, www.kubinyi.de

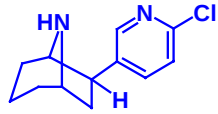
SAR of Epibatidine and its Structural Analogs

(affinity to the $\alpha_2\beta_4$ nACh receptor)

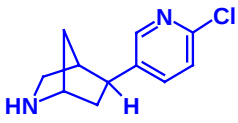


(+)-epibatidine
K_i = 19 pM

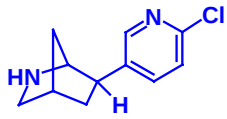
(-)-epibatidine
K_i = 20 pM



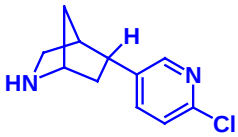
(±)-homoepibatidine
K_i = 230 pM



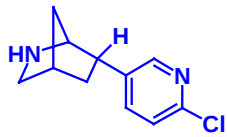
(±)-5-exo-aryl-aza-bicycloheptane
inactive



(±)-6-exo-aryl-aza-bicycloheptane
inactive



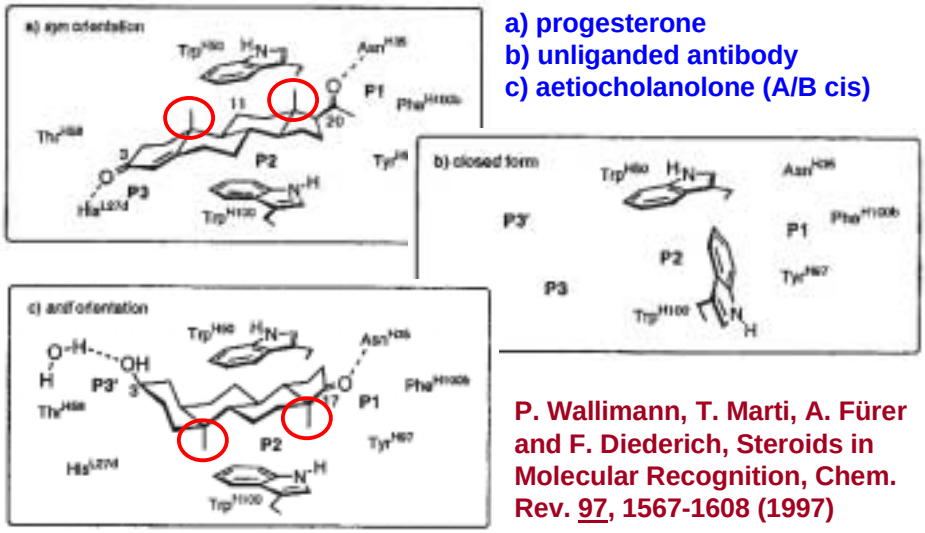
(±)-5-endo-aryl-aza-bicycloheptane
K_i = 56 pM



(±)-6-endo-aryl-aza-bicycloheptane
K_i = 45 pM

C. D. Cox et al., J. Chem. Soc. Perkin Trans. 1, 2001 (19), 2372-2379

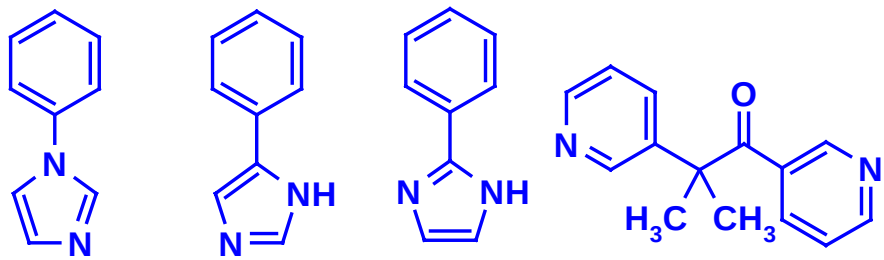
Binding Modes of Steroids to an Antibody



a) progesterone
b) unliganded antibody
c) aetiocholanolone (A/B cis)

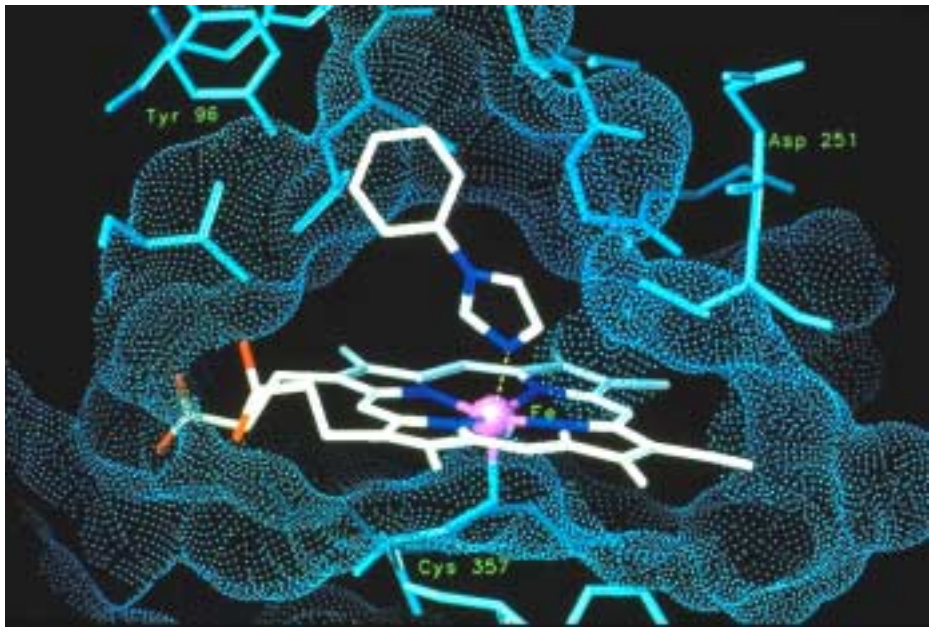
P. Wallimann, T. Marti, A. Fürer and F. Diederich, Steroids in Molecular Recognition, Chem. Rev. 97, 1567-1608 (1997)

Cytochrome P450 Inhibitors

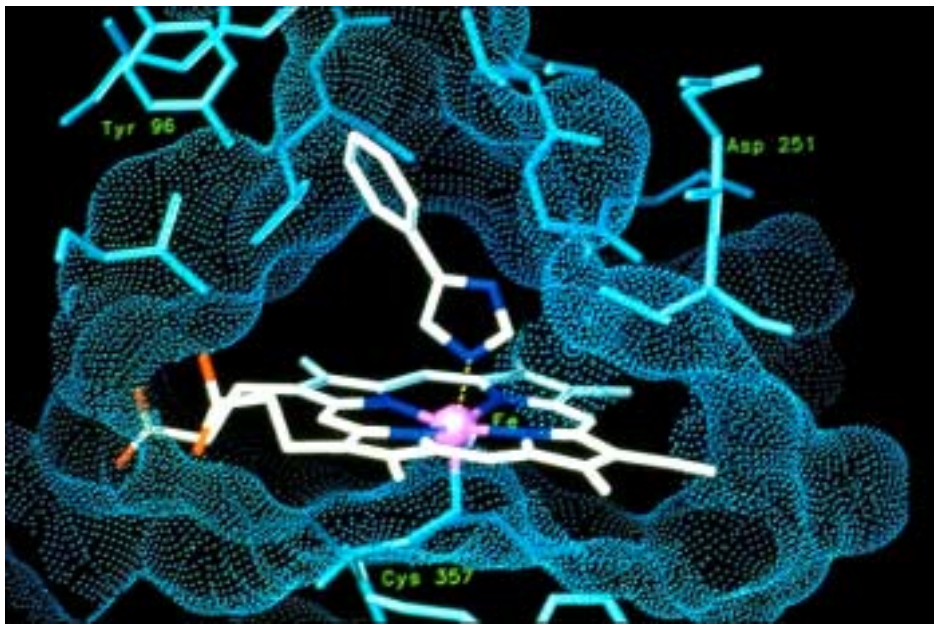


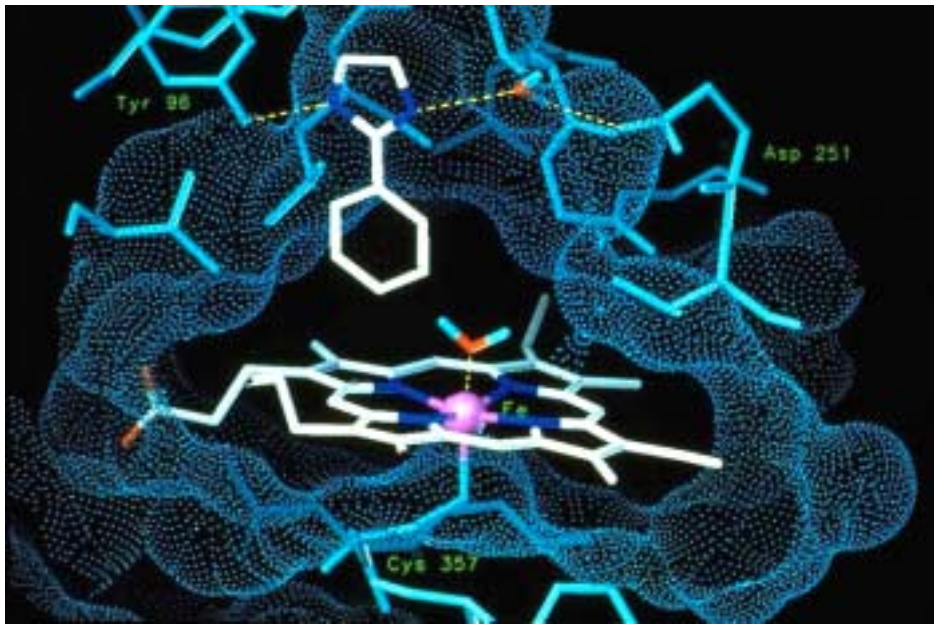
1-Phenyl-imidazole	4-Phenyl-imidazole	2-Phenyl-imidazole	Metyrapone
$1.0 \cdot 10^{-7}$ M	$4.0 \cdot 10^{-5}$ M	$7.0 \cdot 10^{-6}$ M	$2.2 \cdot 10^{-9}$ M

T. L. Poulos and A. J. Howard, Biochemistry 26, 8165-8174 (1987)

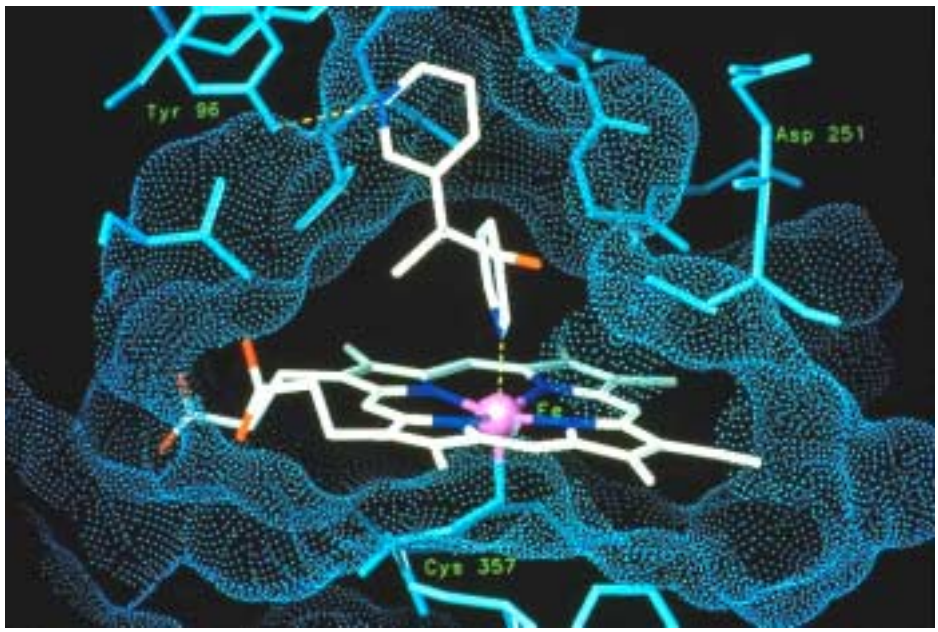


Hugo Kubinyi, www.kubinyi.de

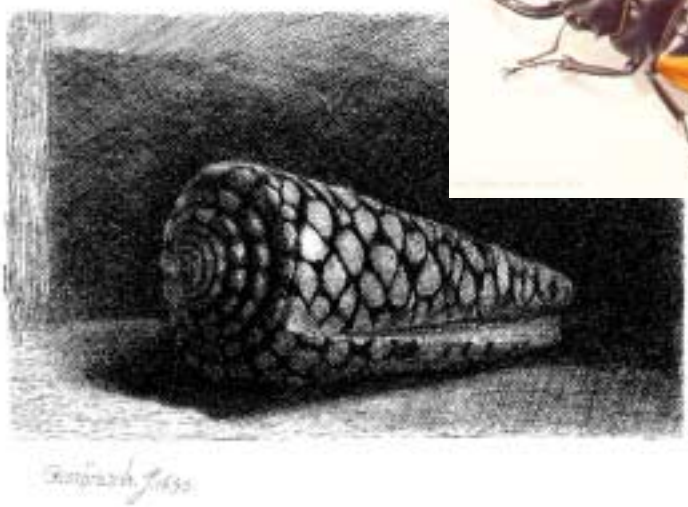




Hugo Kubinyi, www.kubinyi.de

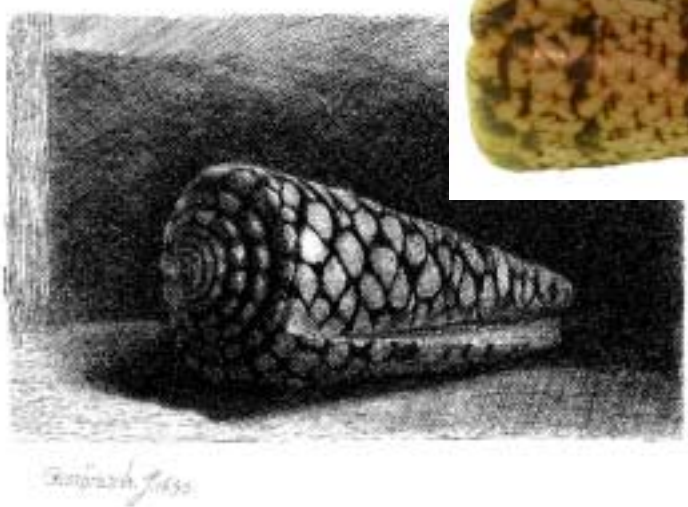


A Giant Stag-Beetle (organic matter)



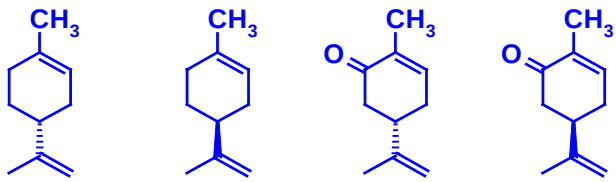
and a Marine Snail (anorganic matter?)

Right or Left ?



Conus nicobaricus (Natural History Museum, London)

Biological Effects of Enantiomers

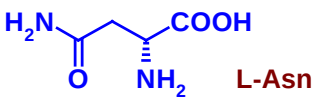


(R)-(+)- Limonene — odor: orange

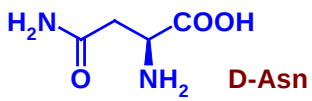
(S)-(-)- — lemon

(S)-(+)- Carvone — caraway

(R)-(-)- — peppermint



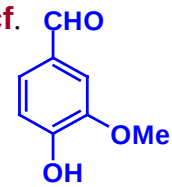
L-Asn



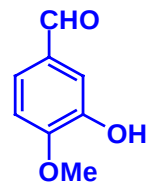
D-Asn

taste: bitter — sweet

cf.

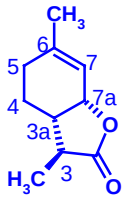


vanillin
strong odor

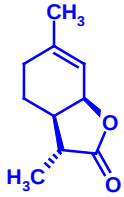


isovanillin
no odor

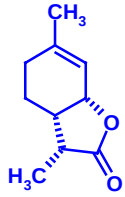
Odor Threshold Values of Isomeric Wine Lactones



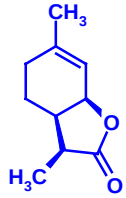
3S,3aS,7aR
0.00002 ng/l



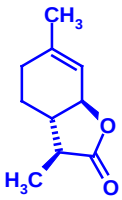
3R,3aR,7aS
> 1,000 ng/l



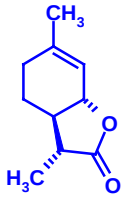
3R,3aS,7aR
0.25 ng/l



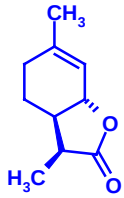
3S,3aR,7aS
120 ng/l



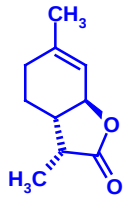
3S,3aS,7aS
0.01 ng/l



3R,3aR,7aR
20 ng/l

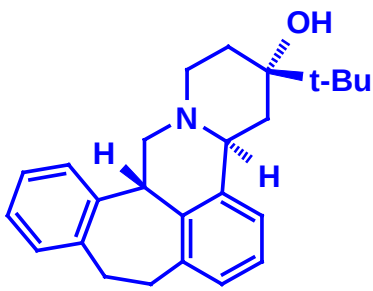


3S,3aR,7aR
0.1 ng/l



3R,3aS,7aS
12 ng/l

Biological Activities of Enantiomers

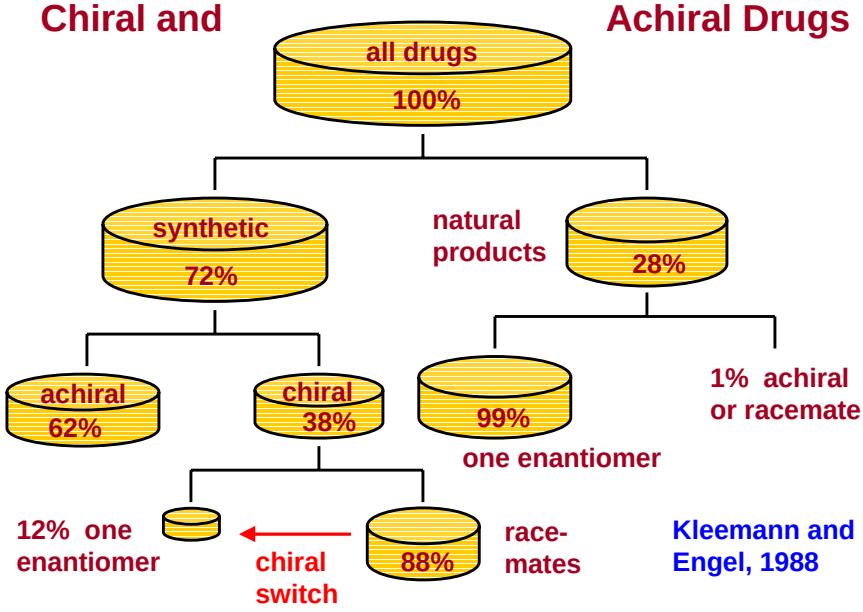


(+)-Butaclamol

Eudismic ratio =
affinity ratio of (+)- and (-)-enantiomers

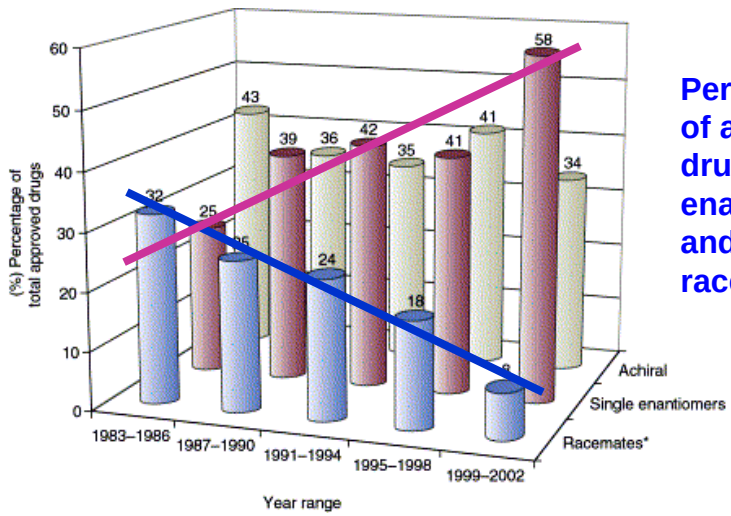
α_1 receptor	73
D_2 receptor	1 250
r-HT_1 receptor	8
5-HT_2 receptor	73
muscarinic ACh receptor	0.5

Chiral and Achiral Drugs



Kleemann and Engel, 1988

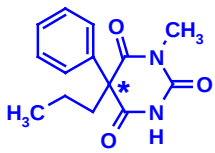
Chiral and Achiral Drugs, 1983-2002



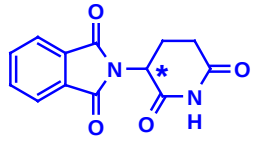
Percentage of achiral drugs, single enantiomers and racemates

H. Caner et al., Drug Discov. today 9, 105-110 (2004)

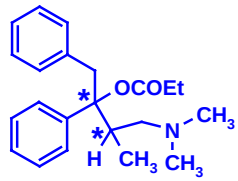
Biological Activities of Enantiomers



N-methyl-phenyl-propylbarbiturate

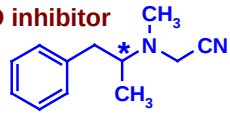


thalidomide

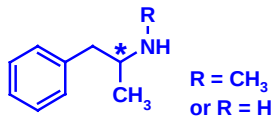


propoxyphen

MAO inhibitor

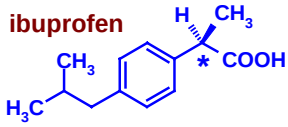


metabolic degradation



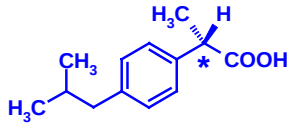
R = CH_3 or R = H

ibuprofen



metabolic inversion

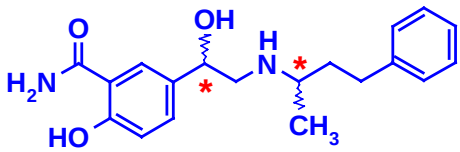
no inversion



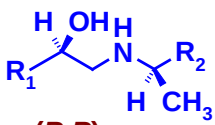
(R)-(-) form

(S)-(+) form

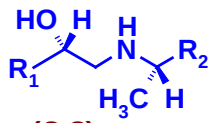
Biological Activities of Diastereomers



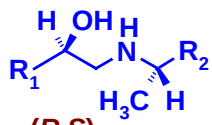
Labetalol
(E. J. Ariens: "A racemate is a compound containing 50% impurity")



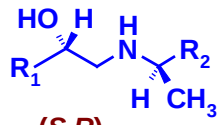
(*R*,*R*)



(*S*,*S*)



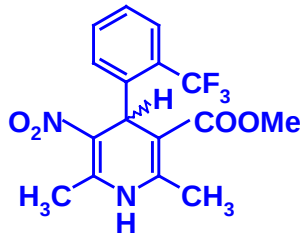
(*R*,*S*)



(*S*,*R*)

pA_2 values	*R,R*	*S,S*	*R,S*	*S,R*
a_1 rezeptor	5.87	5.98	5.50	7.18
$ß_1$ receptor	8.26	6.43	6.97	6.37
$ß_2$ receptor	8.52	<6.0	6.33	<6.0

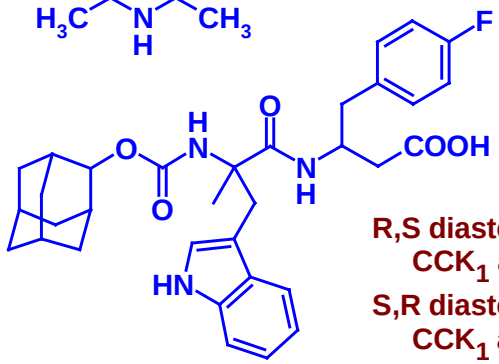
Enantiomers as Agonists and Antagonists



Bay k 8644

(*S*)-(-) form: agonist

(*R*)-(+) form: weak antagonist

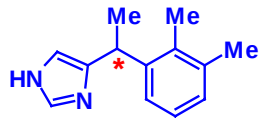


R,S diastereomer: CCK_1 agonist

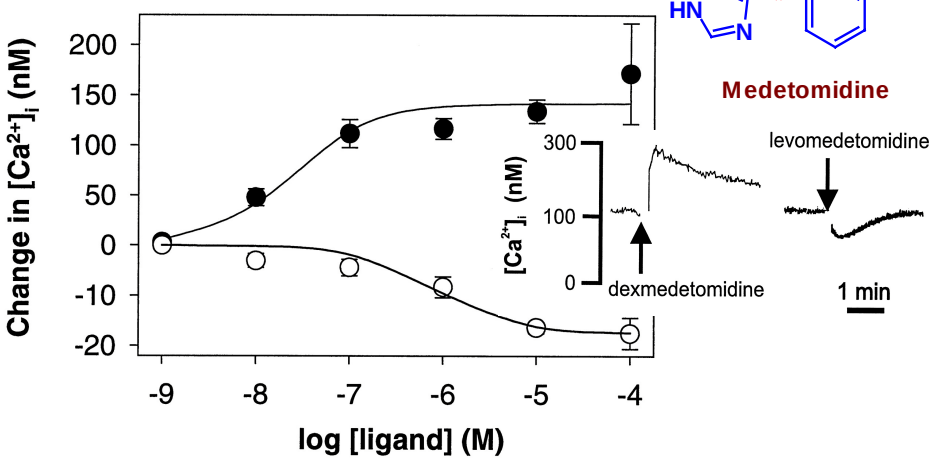
S,R diastereomer: CCK_1 antagonist

Enantiomers as α_{2A} Agonists and Inverse Agonists

(influence on intracellular Ca^{2+} concentration)

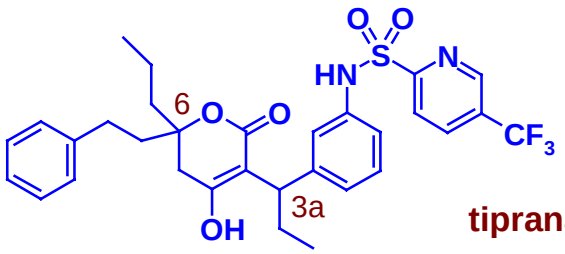


Medetomidine



C.C. Jansson et al., Mol. Pharmacol. 53, 963-968 (1998)

Comparable Activities of Diastereomers



tipranavir

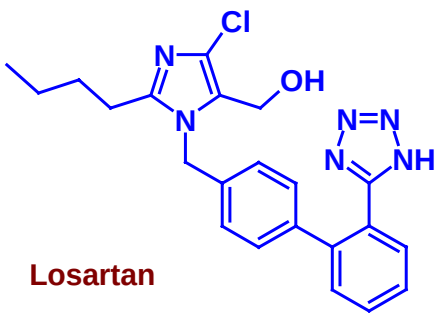
(PNU 140 690)

Diastereomer	K_i pM	IC_{50} µM	IC_{90} µM
R,R	8	0.03	0.10
R,S	18	0.14	0.84
S,R	32	0.41	1.8
S,S	220	1.7	3.0

S. R. Turner et al., J. Med. Chem. 41, 3467-3476 (1998)

Hugo Kubinyi, www.kubinyi.de

Losartan Binding to the Angiotensin II Receptor



Losartan

Saralasin =

[Sar1,Ala8]Angiotensin II

The rat AT1a receptor binds Angiotensin II, Saralasin and Losartan with nanomolar affinities.
The frog ATa receptor (from Xenopus laevis) binds only Angiotensin II and Saralasin.

The amino acids involved in Losartan binding are in the TM helices II - VII. There is a 95% amino acid homology among mammalian receptors, but only about 60% homology to avian and amphibian receptors.

Losartan Binding: From Frogs to Rats

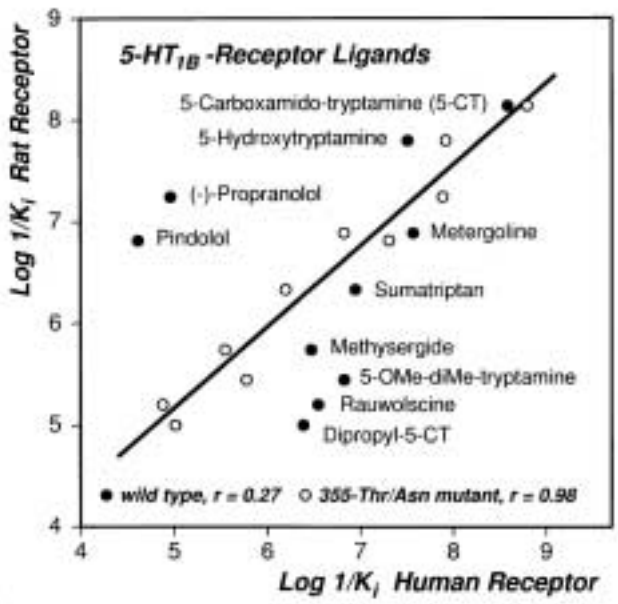
(H. Ji et al., Proc. Natl. Acad. Sci. USA 92, 9240-44 (1995))

	Saralasin binding	Losartan binding
Rat rAT_{1b} receptor	1.7 nM	2.2 nM
Frog xAT_a receptor	19 nM	>50,000 nM
Rat rAT_{1b} receptor mutant A73S, V108I, S109I, A163S, P192M, T198A, F248L, S252C, L300F, F301L	14 nM	>50,000 nM
Frog xAT_a receptor mutant S74A, I109V, T110S, T115A, T116S, S164A, M193P, A199T, L247F, C251S, S294N, F299L, L300F	16 nM	2.0 nM

5-HT_{1B} Receptor Ligands: From Humans to Rats

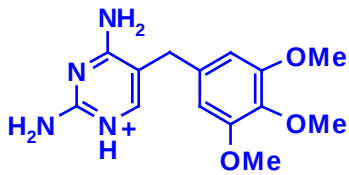
E. M. Parker et al., J. Neurochem. 60, 380-383 (1993)

Compound	Rat	Human	
		wild type	Thr355Asn
5-Hydroxytryptamine (5-HT)	0.016	0.03	0.012
5-Carboxamidotryptamine (5-CT)	0.007	0.003	0.002
Sumatriptan	0.47	0.11	0.64
N,N-Dipropyl-5-CT	>10	0.41	9.7
5-Methoxy-N,N-dimethyltryptamine	3.6	0.15	1.7
Methysergide	1.8	0.34	2.8
Metergoline	0.13	0.03	0.15
Rauwolscine	6.3	0.28	13.2
(-)-Propranolol	0.06	10.9	0.013
(±)-Pindolol	0.15	24.3	0.05
Log K_i (Rat) *vs.* log K_i (Human)		r ≈ 0.27	r ≈ 0.98



5-HT$_{1B}$ Receptor Ligands: From Humans to Rats

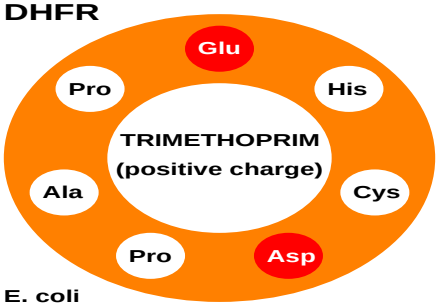
Trimethoprim vs. Different Species and Mutants



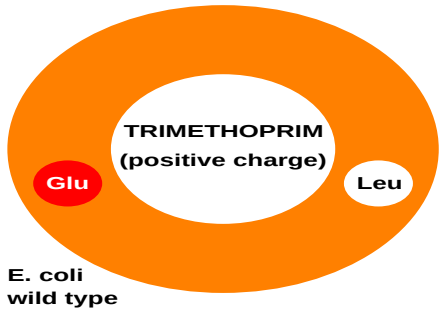
(positively charged form at pH = 7.4)

DHFR from	K_D in nM
E. coli	0.02
E. coli, Gln 118 mutant	0.09
E. coli, Arg 28, Gln 118 mutant	3.8
L. casei	0.4
N. gonorrhoeae	15
Chicken, Mouse	3 500
Cattle	330
Man	1 000

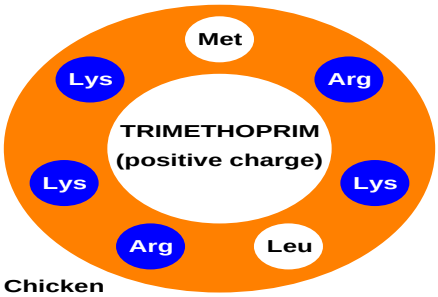
DHFR



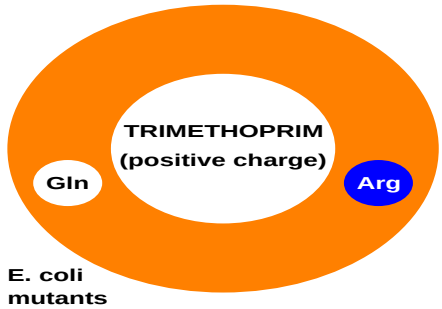
E. coli



E. coli
wild type



Chicken



E. coli
mutants

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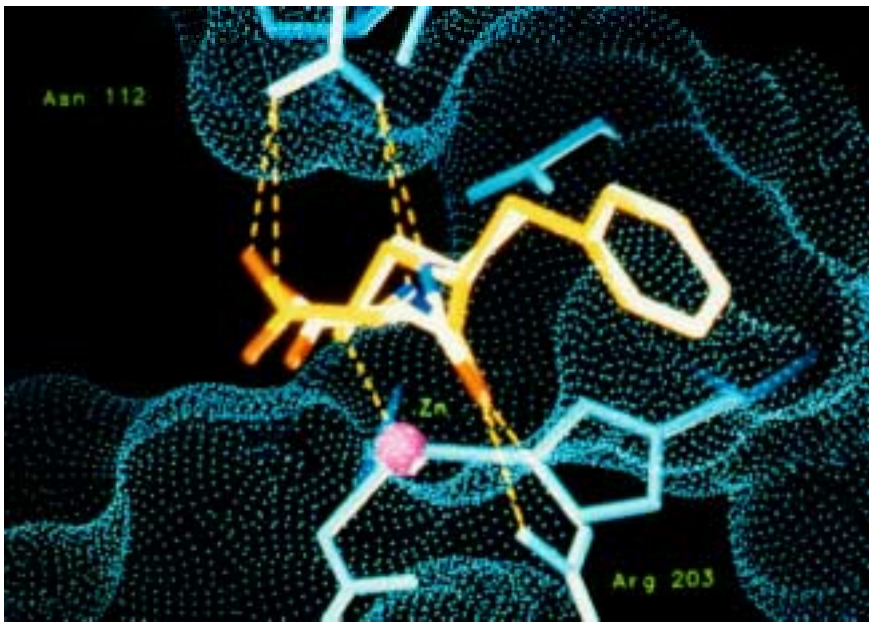

References

H. Kubinyi, Chemical Similarity - A Medicinal Chemist's View, Erlanger Historical Lectures, 07.03.2002 (see www.chemie.uni-erlangen.de/clark/multimedialabor/_lectures/online_drug_design/lecture_02/index.html).

H.-J. Böhm, G. Klebe and H. Kubinyi, Wirkstoffdesign, Spektrum Akademischer Verlag, Heidelberg, 1996.

P. M. Dean, Ed., Molecular Similarity in Drug Design, Blackie Academic & Professional, London, 1995.

H. Kubinyi, Similarity and dissimilarity: a medicinal chemist's view, in 3D QSAR in Drug Design. Ligand-Protein Interactions and Molecular Similarity, H. Kubinyi, G. Folkers and Y. C. Martin, Eds. Kluwer Academic Publishers, Dordrecht, 1998, S. 225-252; also published in Persp. Drug Discov. Design 9-11, 225-252 (1998).

G. A. Patani and E. J. LaVoie, Bioisosterism: A rational approach in drug design, Chem. Rev. 96, 3147-3176 (1996).

A. Burger, Isosterism and bioisosterism in drug design, Prog. Drug. Res. 37, 287-371 (1991).