Chemogenomics

Hugo Kubinyi

Germany

E-Mail kubinyi@t-online.de
HomePage www.kubinyi.de

Hugo Kubinyi, www.kubinyi.de

„Chemical Biology“

screening of chemical libraries in biological systems (e.g. whole cells), to detect new phenotypes.

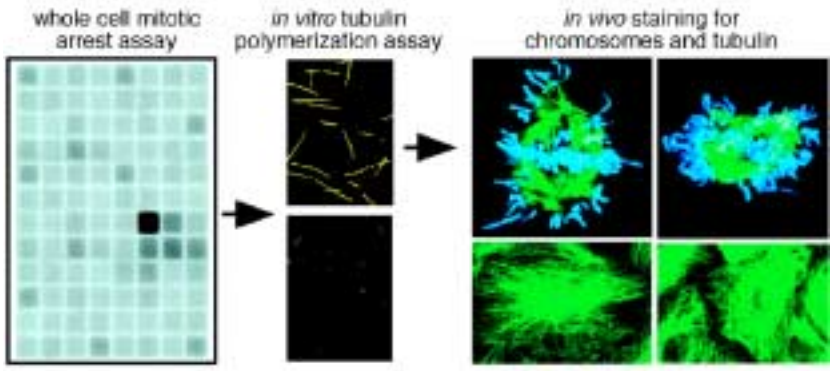
„Chemical Genetics“

investigation of specific signalling pathways, e.g. by the design of orthogonal ligand-protein pairs

„Chemogenomics“

aims to discover active and/or selective ligands for biologically related targets in a systematic manner, i.e. library screening vs. target families (GPCRs, integrins, nuclear receptors, protein kinases, proteases, phosphatases, etc.).

Discovery of Monastrol, a Small Molecule Inhibitor of Mitotic Spindle Bipolarity



microtubules (green), chromatin (blue)

T. U. Mayer et al., Science 286, 971-974 (1999)

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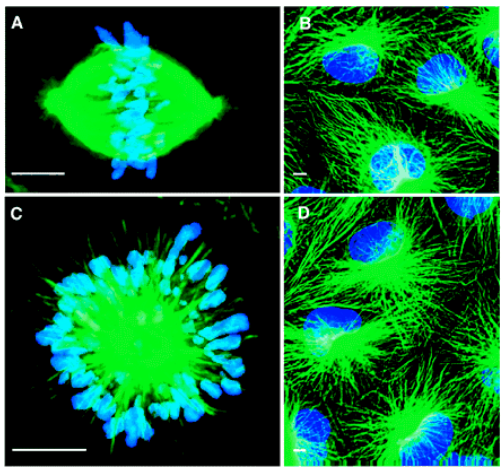
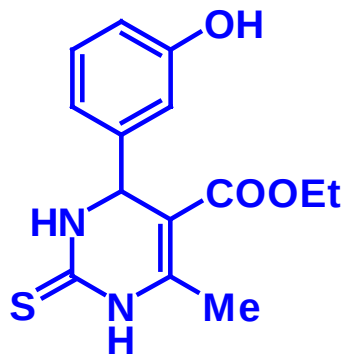
Discovery of Monastrol, a Small Molecule Inhibitor of Mitotic Spindle Bipolarity

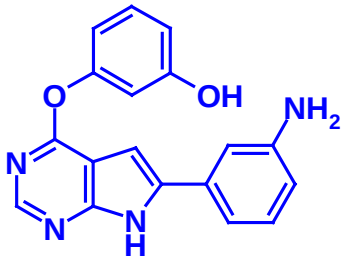


Control cells (A, B) and Monastrol-treated cells (C, D).



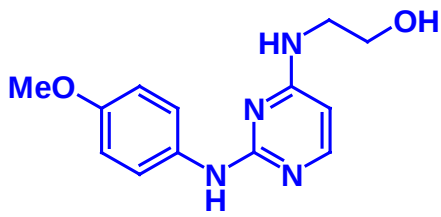
T. U. Mayer et al., Science 286, 971-974 (1999)

In vitro Differentiation of Embryonic Stem Cells



TWS 119 induces neuron formation from embryonic stem cells by modulation of glycogen synthase kinase 3ß (GSK 3ß)

S. Ding et al, Proc. Natl. Acad. Sci. USA 100, 7632-7637 (2003)



Cardiogenol C, from a 100,000-member hetero-cycles library, induces cardiac muscle cell formation from embryonic stem cells

X. Wu et al., J. Am. Chem. Soc. 126, 1590-1591 (2004)

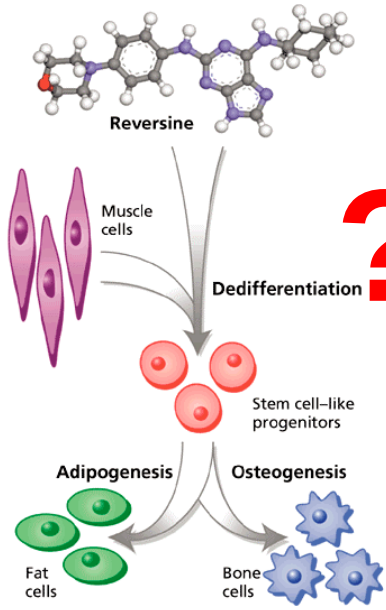
Dedifferentiation and Redifferentiation in Amphibia

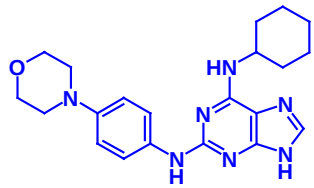
Newt

regenerates limbs, tail and eye lense

P. A. Tsonis, Molecular Interventions 4, 81-83 (2004)

Reversine Dedifferentiates Adult Murine Cells

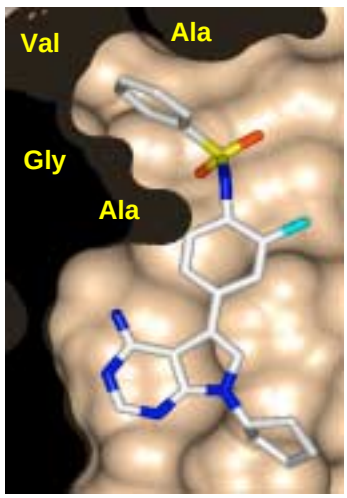




discovered in kinase inhibitor libraries, dedifferentiates adult murine myotube cells to mesenchymal progenitor cells

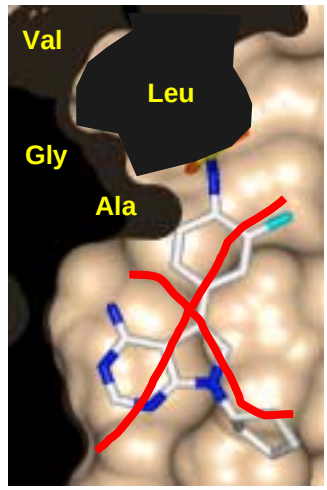
S. Ding and P.G. Schultz, Nat. Biotechnol. 22, 833-840 (2004); S. Chen et al., J. Am. Chem. Soc. 126, 410-411 (2004)

Chemical Genetics: Inhibitor-insensitive Kinases



active, wildtype kinase

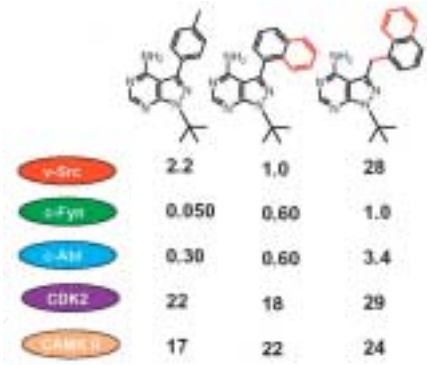
mutagenesis



active, inhibitor-insensitive kinase

B. Klebl et al., in H. Kubinyi and G. Müller, Eds., Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 167-190

Chemical Genetics - Orthogonal Ligand-Protein Pairs for the Study of Signalling Pathways



modified ligands

A. C. Bishop et al., Nature 407, 395-401 (2000)

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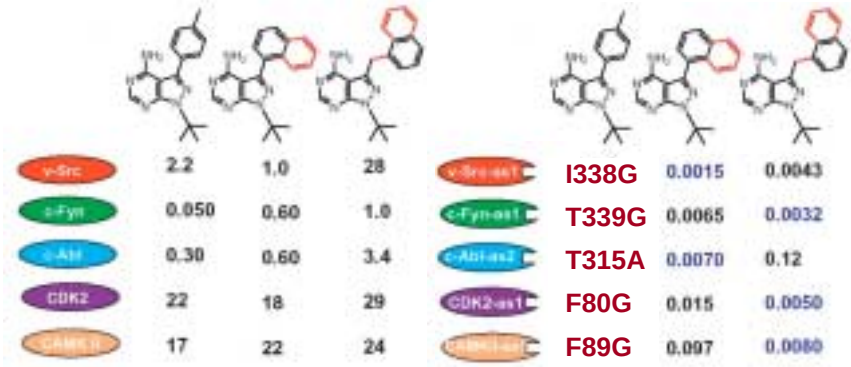
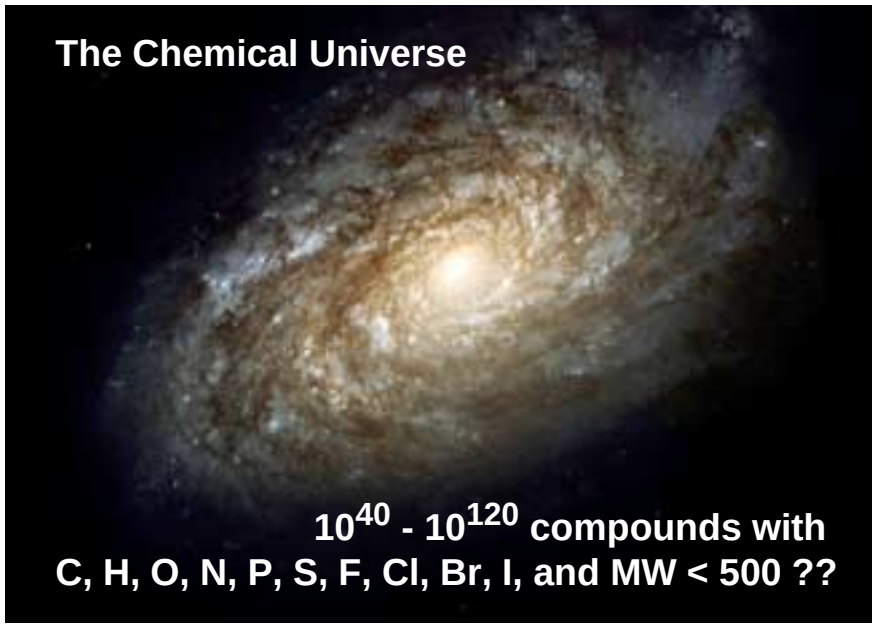
Chemical Genetics - Orthogonal Ligand-Protein Pairs for the Study of Signalling Pathways



modified ligands **modified kinases**

A. C. Bishop et al., Nature 407, 395-401 (2000)

The Chemical Universe



10^{40} - 10^{120} compounds with
C, H, O, N, P, S, F, Cl, Br, I, and MW < 500 ??

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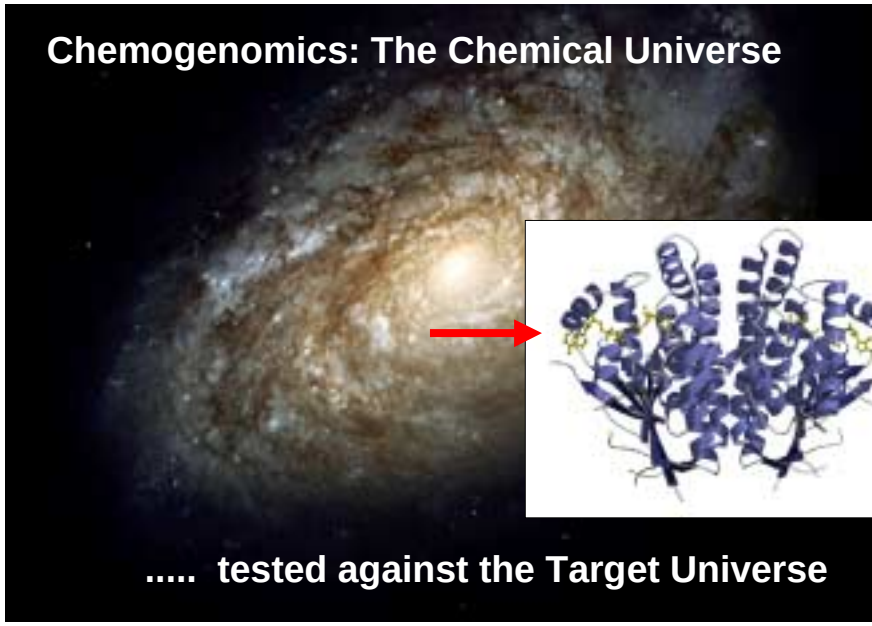
Chemogenomics: The Chemical Universe



..... tested against the Target Universe

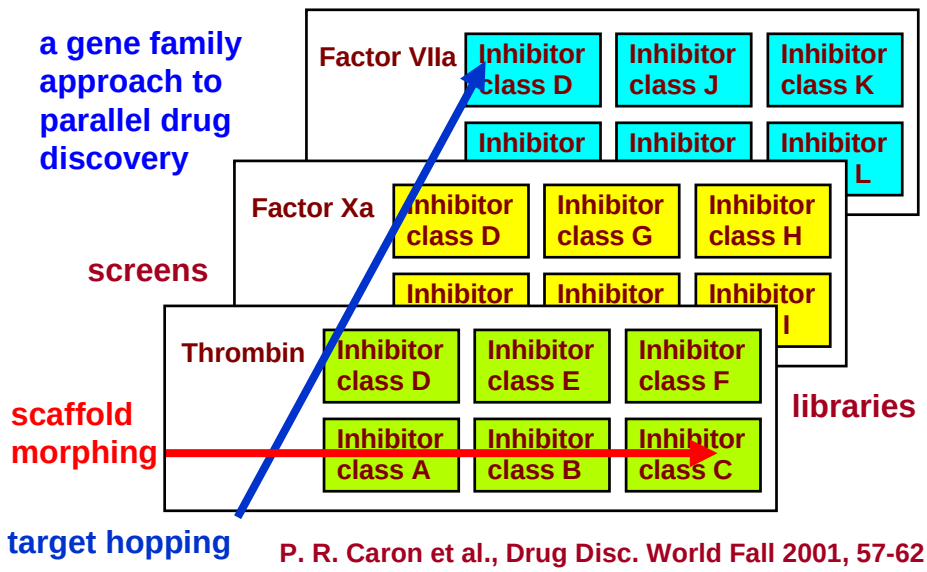
Chemogenomics

Principle: screening of all possible compounds against all possible targets (chemical world vs. the target world)

Real world: screening of compound classes, enriched compound collections, targeted or focused libraries against classes of related proteins (target families)

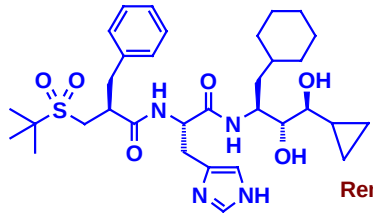
Target families: GPCRs, integrins, nuclear receptors, tyrosine and serine/threonine protein kinases, metalloproteases, serine proteases, aspartyl proteases, etc.

Strategies in Chemogenomics

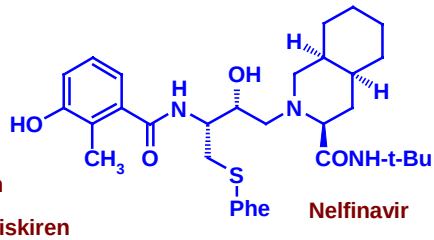


P. R. Caron et al., Drug Disc. World Fall 2001, 57-62

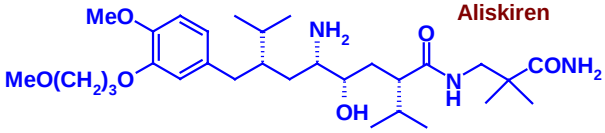
Chemogenomics: Aspartyl Protease Inhibitors



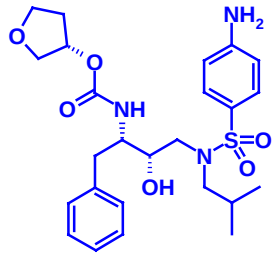
Remikiren



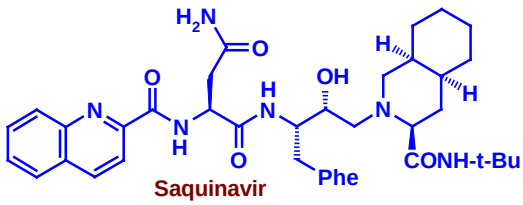
Nelfinavir



Aliskiren



Amprenavir



Saquinavir

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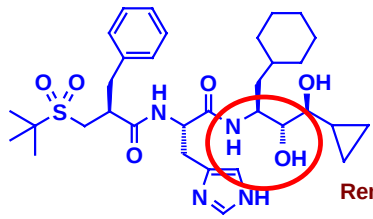
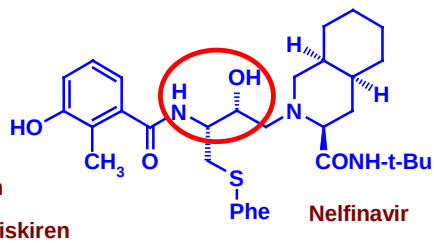
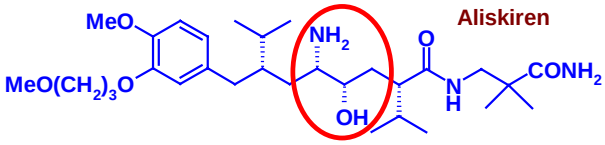
Chemogenomics: Aspartyl Protease Inhibitors



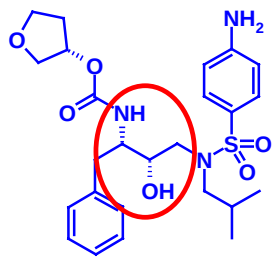
Remikiren



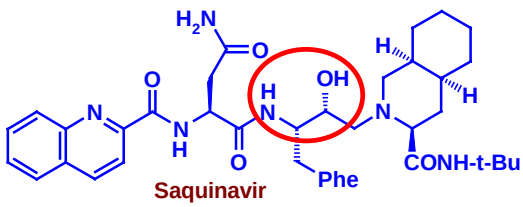
Nelfinavir



Aliskiren

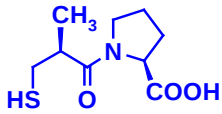


Amprenavir



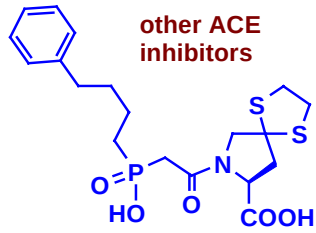
Saquinavir

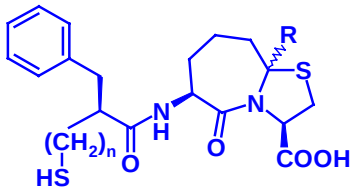
Chemogenomics: Metalloprotease Inhibitors

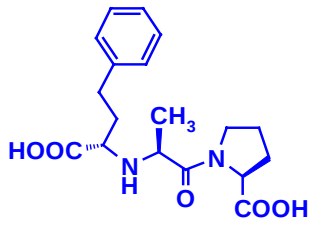


captopril
IC_{50} = 23 nM

other ACE inhibitors

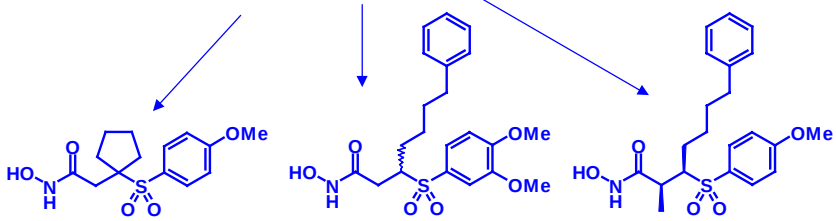






IC_{50} values	R = α-H n = 1	R = α-H n = 0	R = β-H n = 0
NEP 24.11	1.1 nM	11.5 nM	2 820 nM
ACE	5.5 nM	16 nM	11.5 nM

SAR of Metalloprotease Inhibitors



K_i [μM] MMP-1: 0.2
MMP-2: 0.01
MMP-3: 0.05

IC_{50} [μM] PDE4: > 1

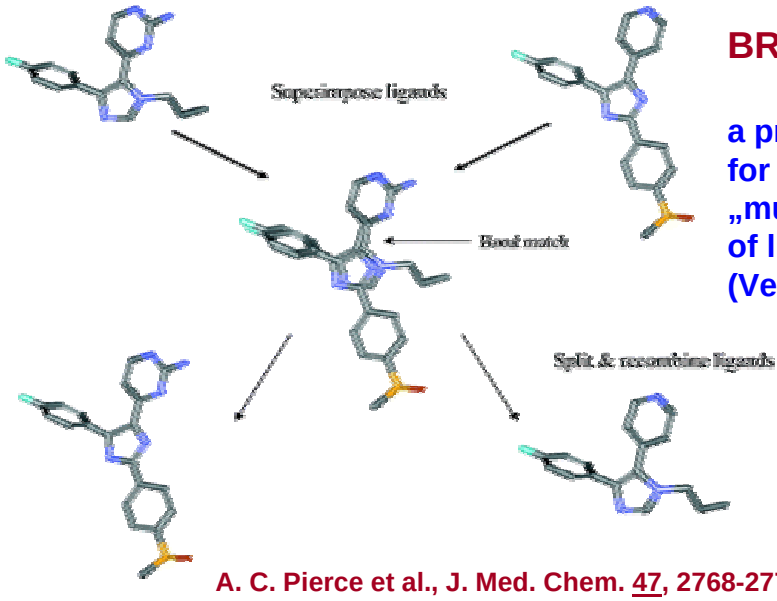
K_i [μM] MMP-1: > 10
MMP-2: > 10
MMP-3: > 10

IC_{50} [μM] PDE4: 0.001

K_i [μM] MMP-1: 1.0
MMP-2: 0.01
MMP-3: 0.5

IC_{50} [μM] PDE4: 0.03

G. Müller, Target family-directed masterkeys and chemogenomics, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, 2004, pp. 7-41



BREED

a program for the „mutation“ of ligands (Vertex)

A. C. Pierce et al., J. Med. Chem. 47, 2768-2775 (2004)

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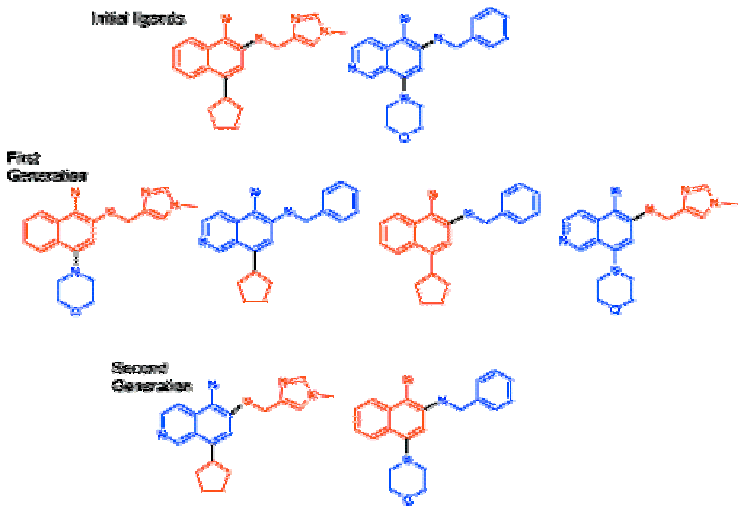
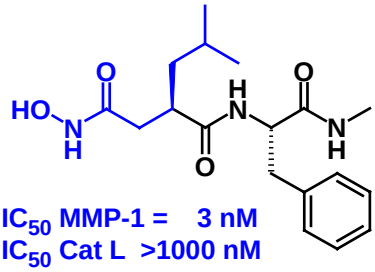


BREED

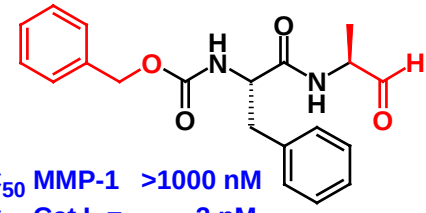
a program for the „mutation“ of ligands (Vertex)

A. C. Pierce et al., J. Med. Chem. 47, 2768-2775 (2004)

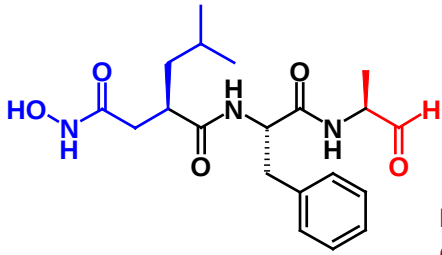
Design of Dual Zn^{++}/Cysteine Protease Inhibitors



IC_{50} MMP-1 = 3 nM
IC_{50} Cat L >1000 nM



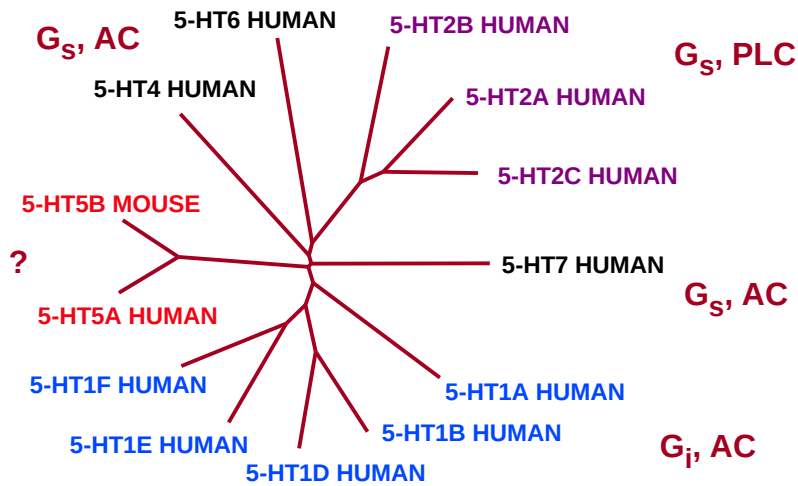
IC_{50} MMP-1 >1000 nM
IC_{50} Cat L = 3 nM



IC_{50} MMP-1 = 25 nM
IC_{50} Cat L = 15 nM

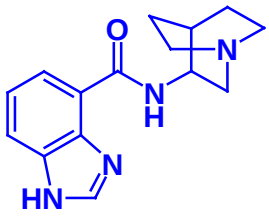
M. Yamamote et al., Bioorg. Med. Chem. Lett. 12, 375-378 (2002)

5-HT Receptor Subtypes (only GPCR's)



J. Kelder, Organon, personal communication, 2001

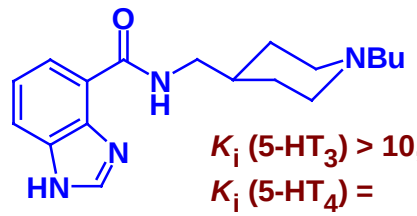
Selectivity of 5-HT Receptor Ligands



K_i (5-HT$_3$) = 3.7 nM

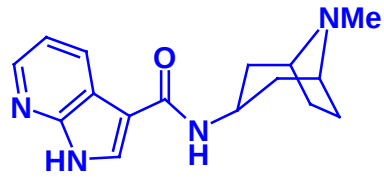
K_i (5-HT$_4$) > 1,000 nM

M. L. Lopez-Rodriguez et al., J. Comput.-Aided Mol. Design 11, 589-599 (1997)



K_i (5-HT$_3$) > 10,000 nM

K_i (5-HT$_4$) = 13.7 nM

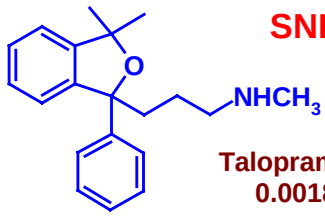


cf. DF-1012 - orally active antitussive (guinea pig)

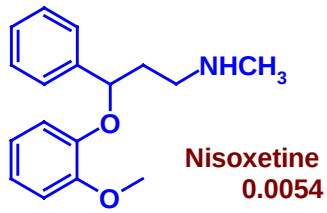
Ann. Rep. Med. Chem. 36, 38 (2001)

Selectivity of Uptake Inhibitors

SNRI's

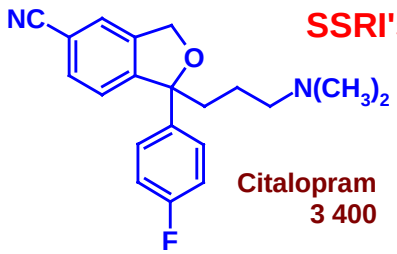


Talopram
0.0018

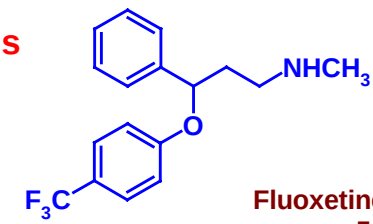


Nisoxetine
0.0054

SSRI's



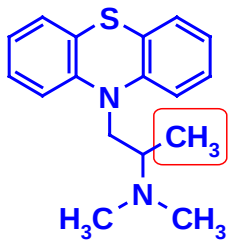
Citalopram
3 400



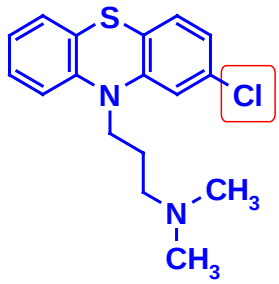
Fluoxetine
54

NA vs. 5-HT transporter IC_{50} ratio (K. Gundertofte et al., in: Computer-Assisted Lead Finding and Optimization, HCA and VCH, 1997; pp. 445-459)

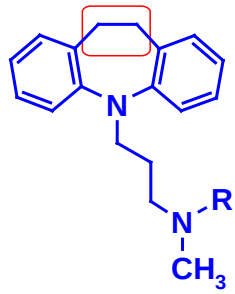
Different Modes of Action of Chemically Similar Molecules



promethazine
(H_1 antagonist)



chlorpromazine
(dopamine antagonist)



a, R = CH_3, imipramine
b, R = H, desipramine
(uptake blocker)

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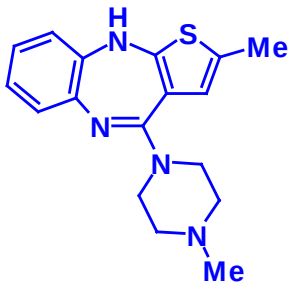
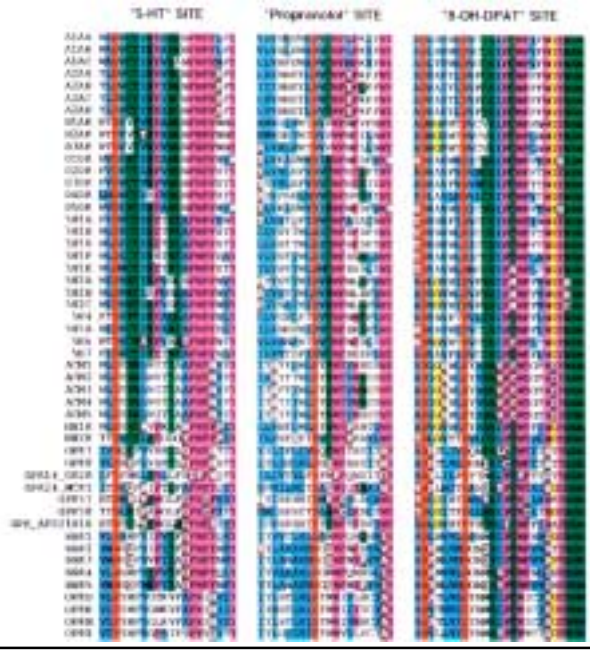
Many Ligands Bind to Several GPCRs



Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

a) F. P. Bymaster et al., Neuropsychopharmacology 14, 87-96 (1996)
b) F. P. Bymaster et al., Schizophrenia Research 37, 107-122 (1999)

	a)	b)
K_i 5-HT_{2A} =	4 nM	2.5 nM
K_i 5-HT_{2B} =		12 nM
K_i 5-HT_{2C} =	11 nM	2.5 nM
K_i 5-HT_3 =	57 nM	
K_i dop D_1 =	31 nM	119 nM
K_i dop D_2 =	11 nM	
K_i dop D_4 =	27 nM	
K_i musc M_1 =	1.9 nM	2.5 nM
K_i musc M_2 =	18 nM	18 nM
K_i musc M_3 =	25 nM	13 nM
K_i musc M_4 =	13 nM	10 nM
K_i musc M_5 =		6 nM
K_i adr α_1 =	19 nM	19 nM
K_i adr α_2 =	230 nM	
K_i hist H_1 =	7 nM	7 nM

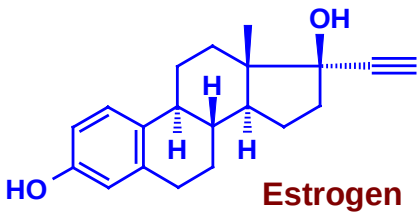


Similarity of Various GPCR's (BLAST analysis)

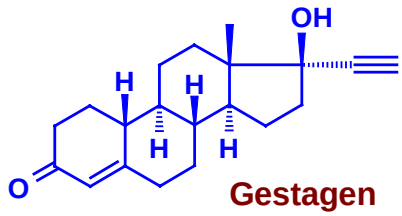
light blue: aliphatic
green: polar
red: negative charge
cyan: aromatic
yellow: pro, gly

E. Jacoby, Quant. Struct.-Act. Relat. 20, 115-123 (2001)

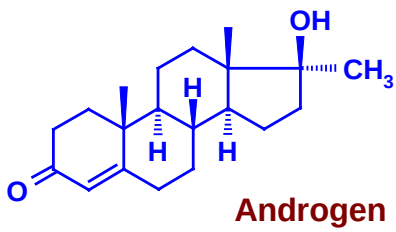
Different Modes of Action of Similar Molecules



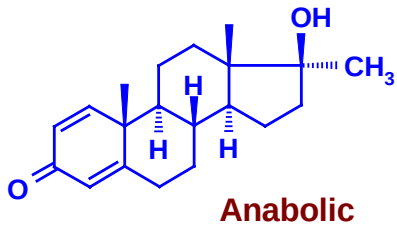
Estrogen



Gestagen

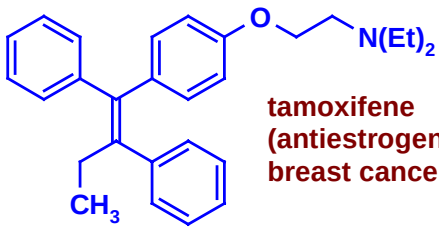


Androgen

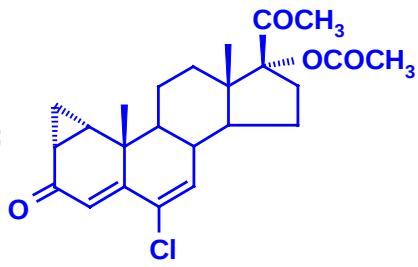


Anabolic

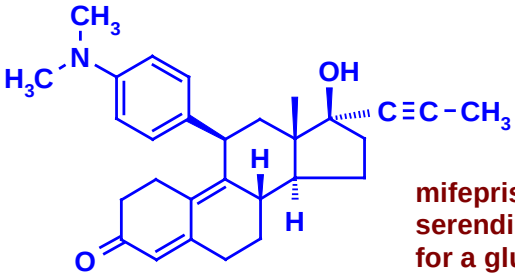
Steroid Analogs With Different Activities



tamoxifene
(antiestrogenic;
breast cancer)



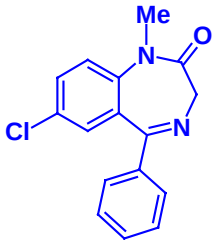
cyproterone acetate
(antiandrogenic;
prostate cancer)



mifepristone (antigestagenic;
serendipitous discovery in search
for a glucocorticoid antagonist)

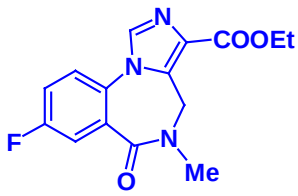
Hugo Kubinyi, www.kubinyi.de

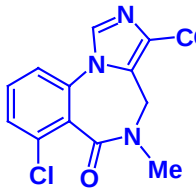
Activities of Benzodiazepines



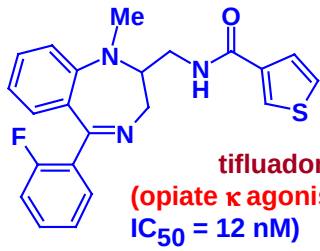
diazepam (agonist)
positive intrinsic
activity at the
$GABA_A$ receptor
(tranquilizer)

flumazenil (antagonist)
no intrinsic activity
at the $GABA_A$ receptor
(antidot in intoxication)





Ro 15-3505
(inverse agonist)
negative intrinsic
activity at the
$GABA_A$ receptor
(proconvulsant)



tifluadom
(opiate κ agonist,
IC_{50} = 12 nM)

C. Wermuth, The Practice of Medicinal Chemistry, 1996, p. 548;
D. Römer et al., Nature 298, 759-760 (1982)

The Concept of „Privileged Structures“

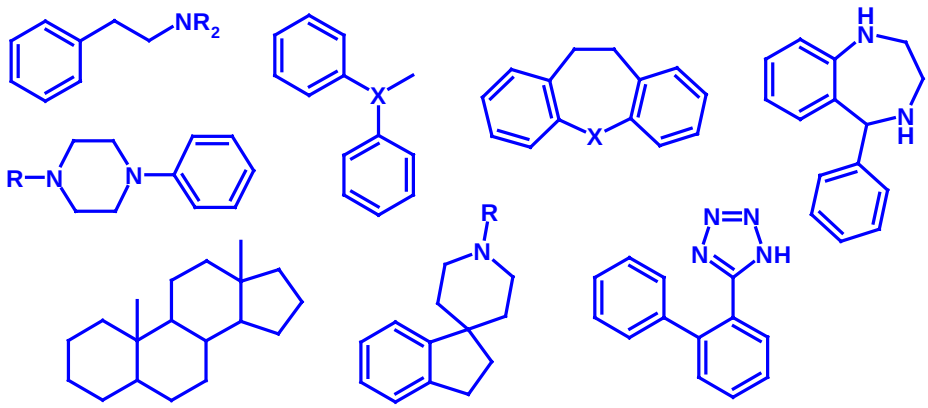
„these structures appear to contain common features which facilitate binding to various ... receptor surfaces, perhaps through binding elements different from those employed for binding of the natural ligands ....

... what is clear is that certain „privileged structures“ are capable of providing useful ligands for more than one receptor and that judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists.“

B. E. Evans et al., J. Med. Chem. 31, 2235-2246 (1988)

Hugo Kubinyi, www.kubinyi.de

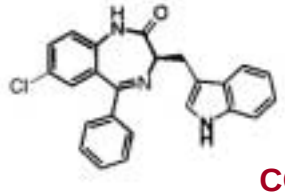
The Concept of „Privileged Structures“



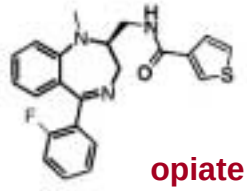
B. E. Evans et al., J. Med. Chem. 31, 2235-2246 (1988); A.A. Patchett, R.P. Nargund, Annu. Rep. Med. Chem. 35, 289-298 (2000); H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004

Privileged Structures

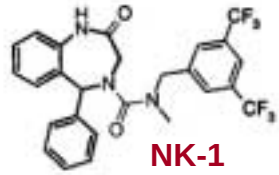
a) benzodiazepines (originally tranquilizers)



CCK

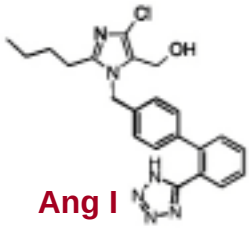


opiate

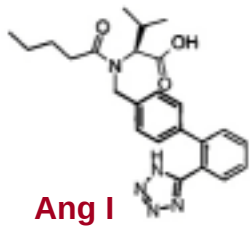


NK-1

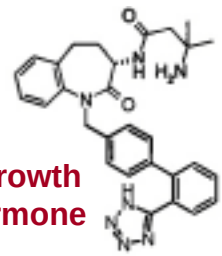
b) biphenyltetrazoles



Ang I



Ang I

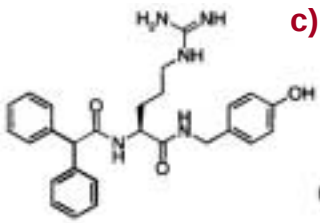


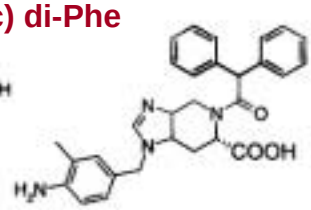
growth hormone

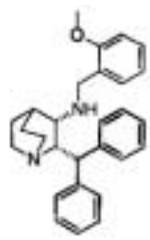
Hugo Kubinyi, www.kubinyi.de

Privileged Structures

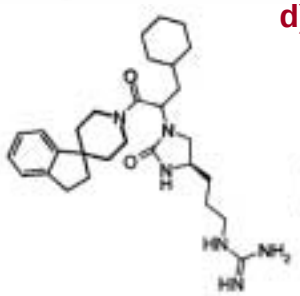
c) di-Phe

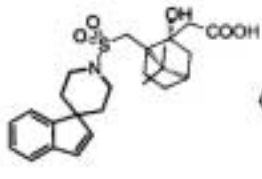


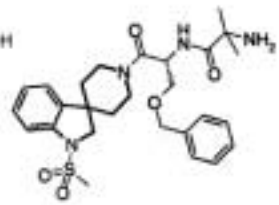




d) spiropiperidines

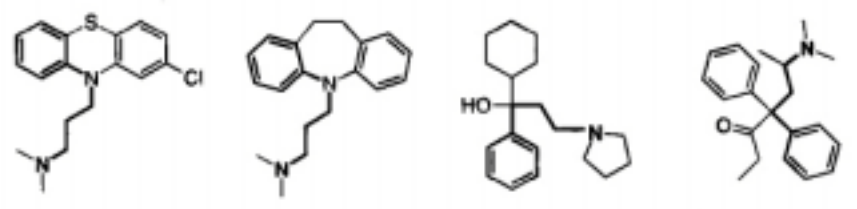




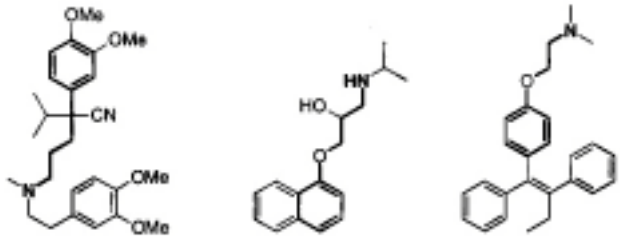


Privileged Structures

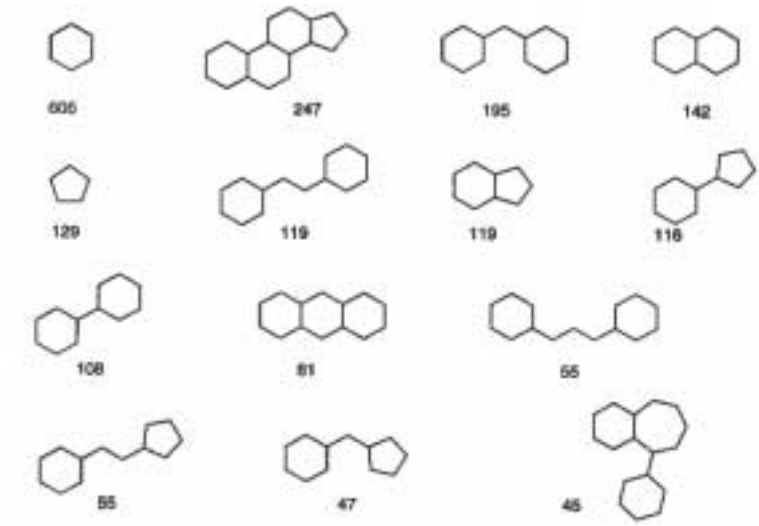
d) CNS-active phenylalkylamines



e) Aralkyl- and -aralkoxyamines with no CNS activity

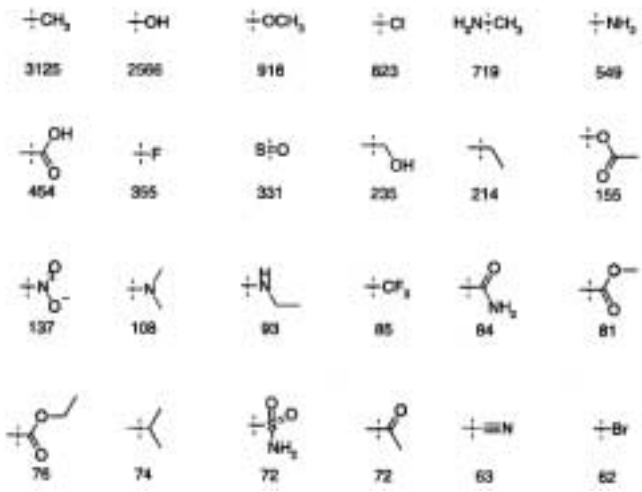


Privileged Ring Systems (in 5120 drugs)



G. W. Bemis and M. A. Murcko, J. Med. Chem 39, 2887-2893 (1996)

Most common side chains (of 5120 drugs)



G. W. Bemis and M. A. Murcko, J. Med. Chem 42, 5095-5099 (1999)

Hugo Kubinyi, www.kubinyi.de

Change of Therapeutic Focus

Mercurials
- antisyphilitic drugs - diuretics

Aspirin
- antiinflammatory - thrombozyte aggregation inhibition / cardioprotective - antitumour activity?

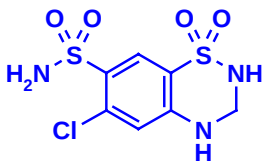
Sulfonamides
- antibacterials - diuretics, antihypertensives - antiglaucoma drugs - antidiabetics

Tricyclic drugs
- antihistaminics - neuroleptics - antidepressives

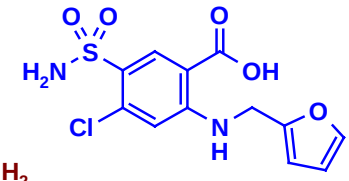
Verapamil
- coronary drug - antiarrhythmic - antihypertonic

Cyclosporin
- antimycotic - immunosuppressant

Diuretic, Antidiabetic and Anti-Glaucoma Agents from Antibacterial Sulfonamides

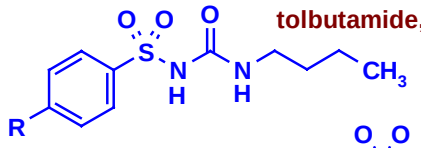


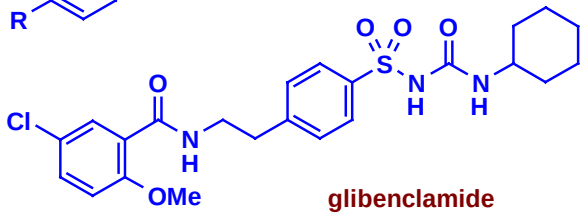
hydrochloro-thiazide



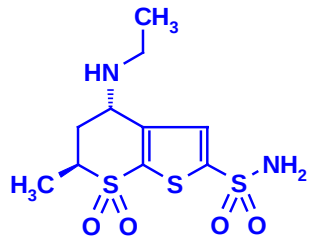
furosemide

carbutamide, R = NH_2
tolbutamide, R = CH_3



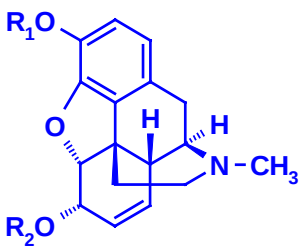


glibenclamide

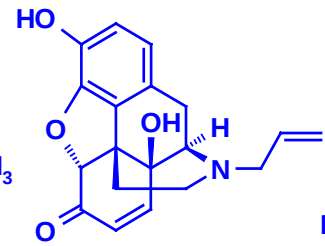


dorzolamide

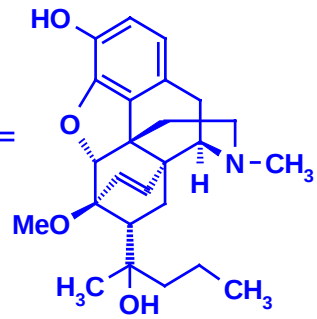
Morphine and its Derivatives



morphine, $R_1 = R_2 = H$
heroin, $R_1 = R_2$ = acetyl
(opiates)
codeine, R1 = Me, R2 = H
(antitussive)

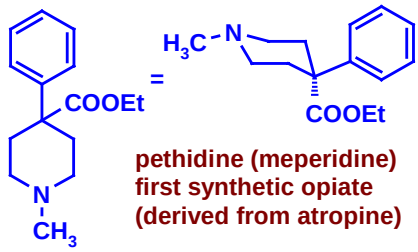


naloxone
(morphine
antagonist)

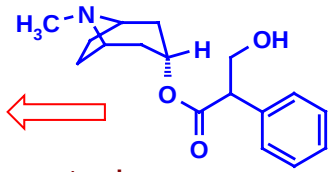


etorphine
(2,000-10,000
times more active
than morphine)

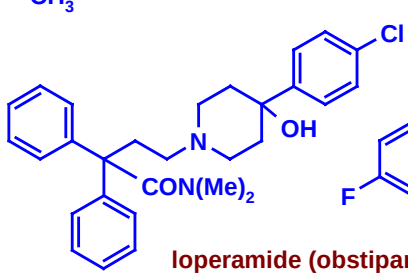
Distant Morphine Analogs



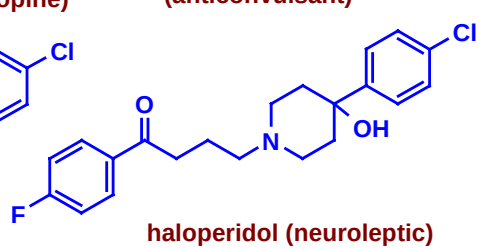
pethidine (meperidine)
first synthetic opiate
(derived from atropine)



atropine
(anticonvulsant)



loperamide (obstipant)

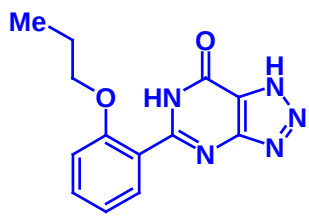


haloperidol (neuroleptic)

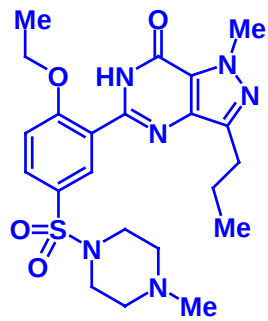
Which Important Drug

started from an anti-allergic lead, which was optimized to an antihypertensive drug but was finally clinically tested as an antianginal drug?

However, in a 10-day toleration study in Wales, an unusual side effect turned up ....

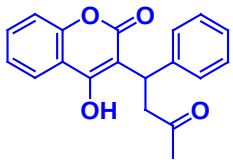


Zaprinast
unspecific PDE inhibitor; antiallergic, vasodilator.

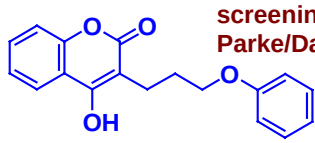


Sildenafil (Viagra®), specific cGMP PDE5 inhibitor; male sexual dysfunction.

HIV-Protease Inhibitors from Anticoagulants

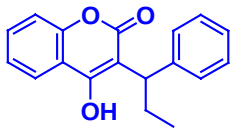


warfarin
(screening
at Upjohn)
IC_{50} = 30 µM

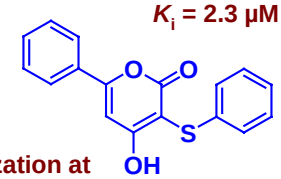


screening at
Parke/Davis

K_i = 2.3 µM

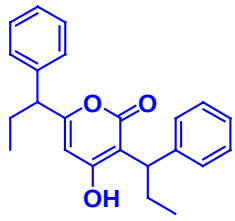


phenprocoumon
(similarity search
at Upjohn)
IC_{50} = 1 µM

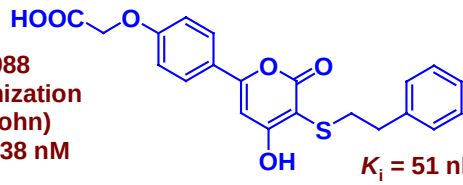


optimization at
Parke-Davis/NCI

K_i = 1.1 µM



U-96 988
(optimization
at Upjohn)
IC_{50} = 38 nM

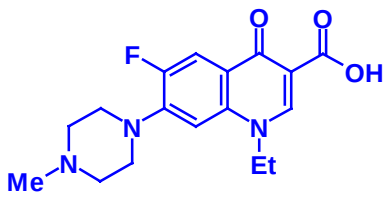


K_i = 51 nM

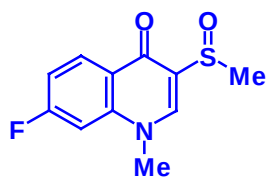
The SOSA Approach - Selective Optimization of Side Activities

„The most fruitful basis for the discovery of a new drug is to start with an old drug“

Sir James Black, Nobel Prize 1988



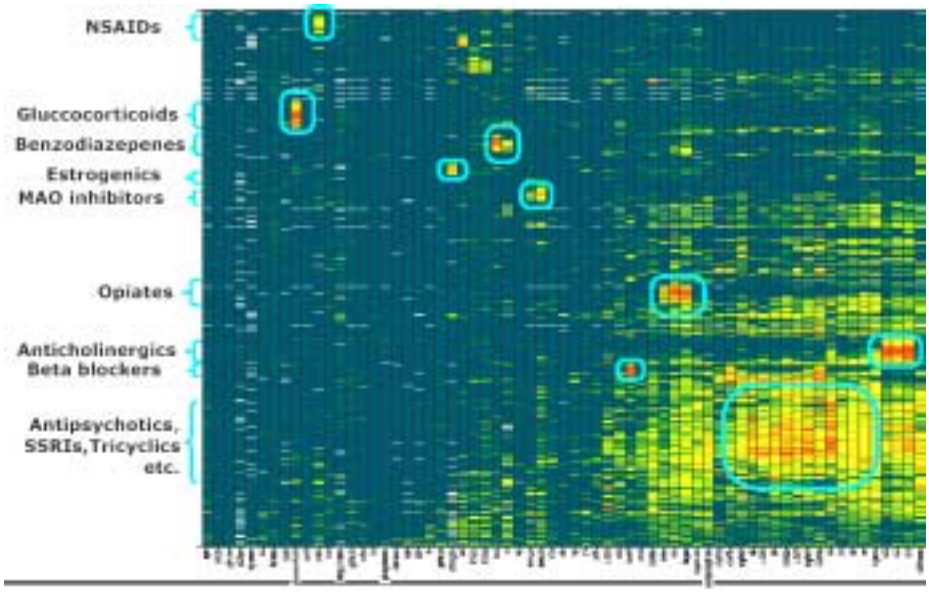
norfloxazin, an antibiotic



flosequinan, a mixed arterial and venous vasodilator

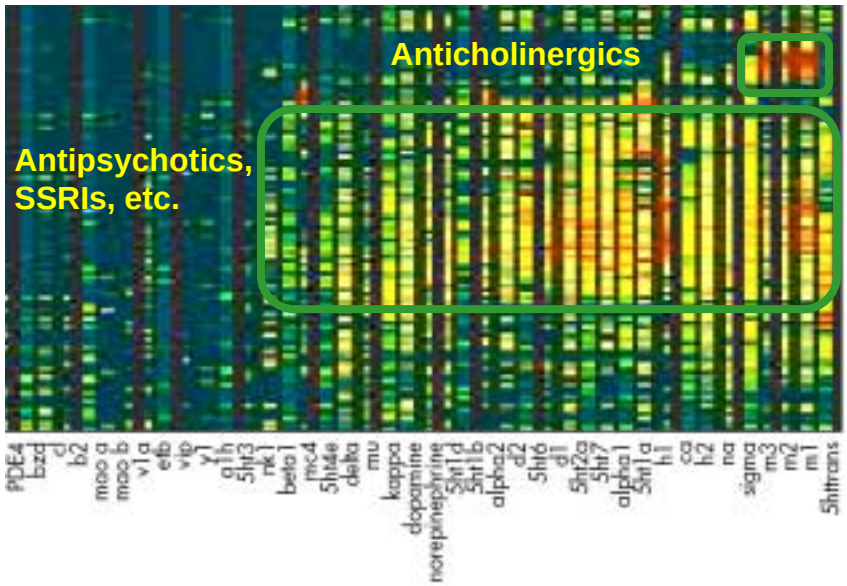
C. G. Wermuth, Med. Chem. Res. 10, 431-439 (2001); C. G. Wermuth, J. Med. Chem. 47, 1303-1314 (2004); H. Kubinyi, in H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 43-67

Bioprint Database (Cerep; www.cerep.fr)

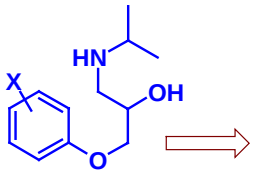


Hugo Kubinyi, www.kubinyi.de

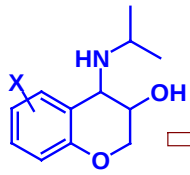
Bioprint Database (Cerep; www.cerep.fr)



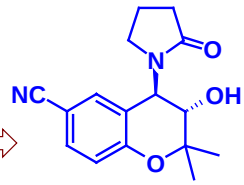
„Selective Optimization of Side Activities“



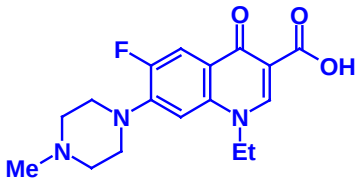
ß-blocker prototype



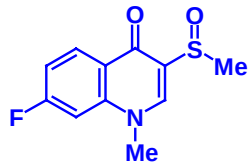
cyclized analog



levocromakalim, a hypotensive potassium channel opener



norfloxazin, an antibiotic



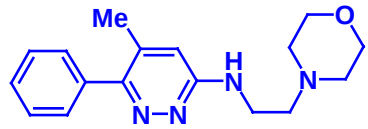
flosequinan, a mixed arterial and venous vasodilator

C. Wermuth, The „SOSA“ Approach, Med. Chem. Res. 10, 431-439 (2001)

Hugo Kubinyi, www.kubinyi.de

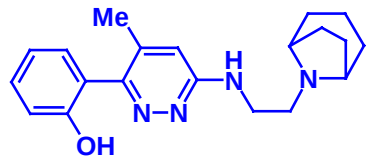
„Selective Optimization of Side Activities“

minaprine, an antidepressant
K_i musc M_1 = 17,000 nM



5-methyl isomer of minaprine
K_i musc M_1 = 550 nM

tropane analog
K_i musc M_1 = 60 nM

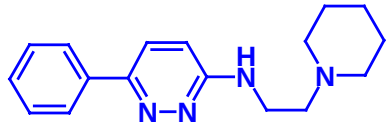


ortho-hydroxy substitution
K_i musc M_1 = 3 nM

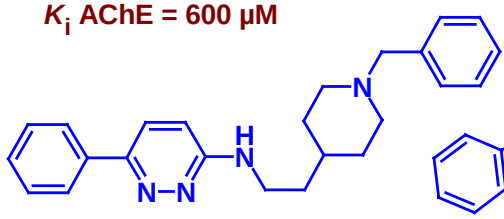
C. Wermuth, The „SOSA“ Approach, Med. Chem. Res. 10, 431-439 (2001)

„Selective Optimization of Side Activities“

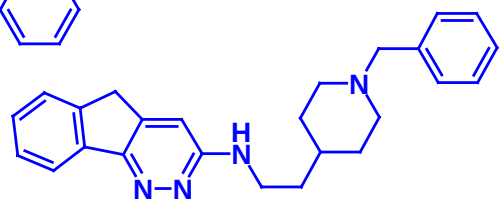
minaprine, an antidepressant
K_i AChE = 600 µM



desoxo,desmethyl-minaprine
K_i AChE = 13 µM



N-benzyl analog
K_i AChE = 120 nM

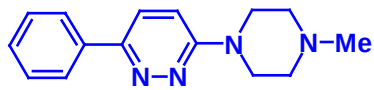


rigid analog
K_i AChE = 10 nM

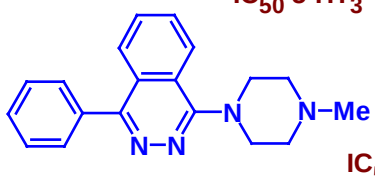
C. Wermuth, The „SOSA“ Approach, Med. Chem. Res. 10, 431-439 (2001)

3-Aminopyridazines as 5-HT_3 Antagonists

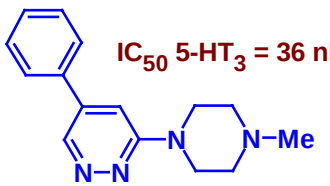
minaprine, an antidepressant



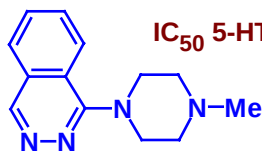
IC_{50} 5-HT_3 = 425 nM



IC_{50} 5-HT_3 = 370 nM



IC_{50} 5-HT_3 = 36 nM



IC_{50} 5-HT_3 = 10 nM

Y. Rival et al., J. Med. Chem. 41, 311-317 (1998)

Protein 3D Structure Similarity

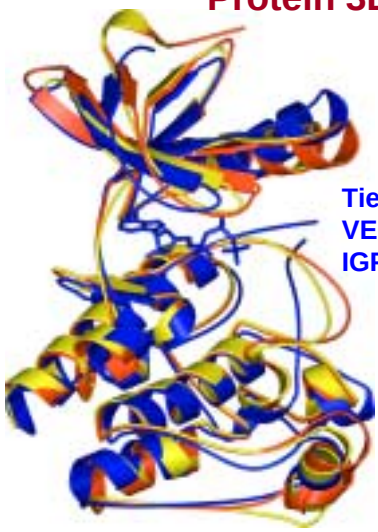
estrogen sulfotransferase (green) with cofactor PAP and substrate E2 (yellow)

uridylate kinase (blue) with cofactor ADP and substrate analog (red)

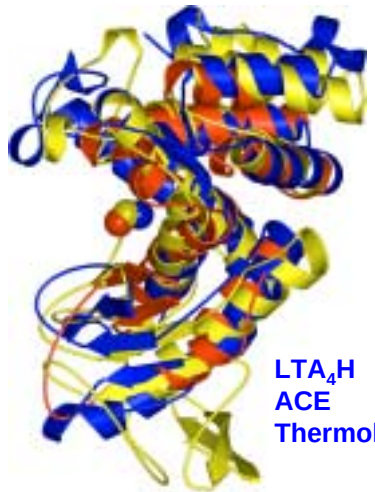
M. A. Koch and H. Waldmann, in H. Kubinyi and G. Müller, Eds., Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 377-403

Hugo Kubinyi, www.kubinyi.de

Protein 3D Structure Similarity



Tie-2 TK
VEGFR-3
IGF1R

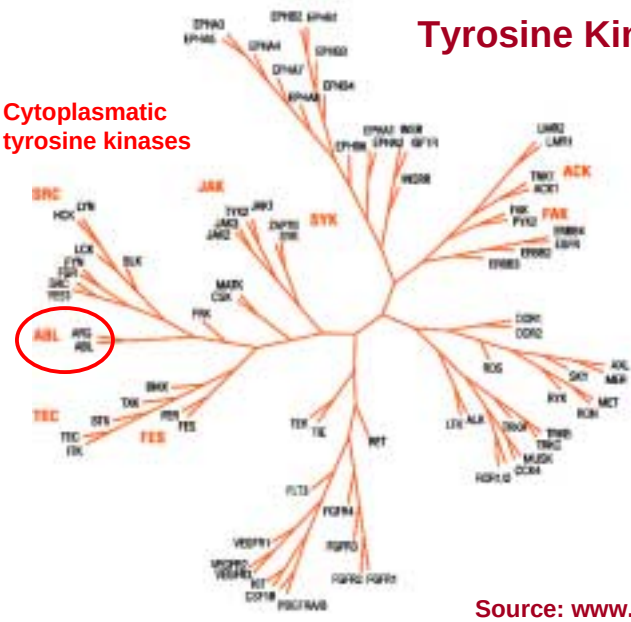


LTA_4H
ACE
Thermolysin

M. A. Koch and H. Waldmann, in H. Kubinyi and G. Müller, Eds., Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 377-403

Tyrosine Kinases

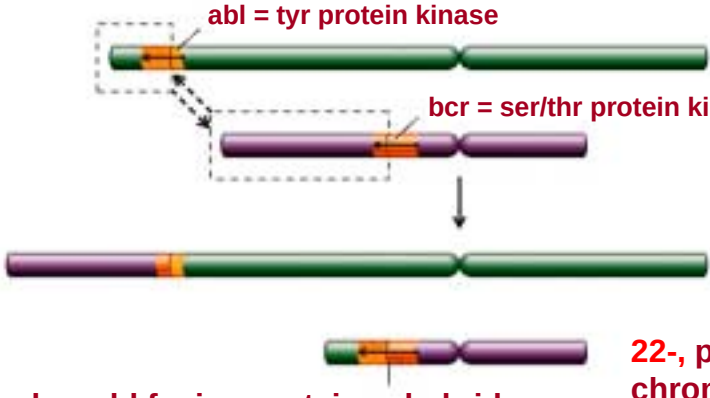
Cytoplasmatic tyrosine kinases



Receptor tyrosine kinases

Source: www.cellsignal.com

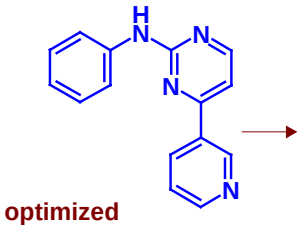
Chromosome Translocation in CML



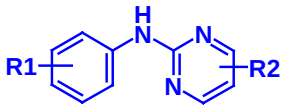
bcr-abl fusion protein, a hybrid with constitutionally enhanced tyrosine protein kinase activity

22-, philadelphia chromosome, present in 90+% of all cases of chronic mye-logenous leukemia

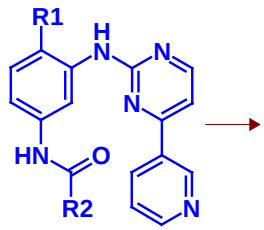
Development of STI 571 (Imatinib, Glivec®)



optimized lead, strong PKC inhibition

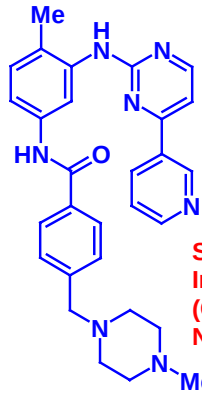


lead structure, active against PKC



amides inhibit also tyrosine kinases, such as bcr-abl

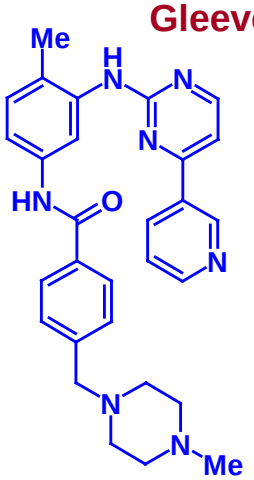
R1 = Me (instead H) abolishes undesired PKC affinity

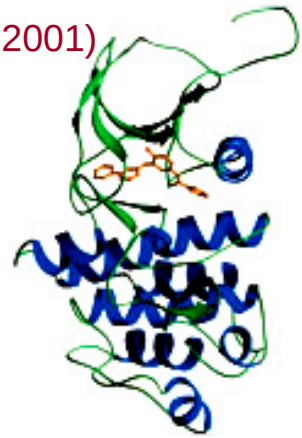


STI 571, Imatinib (Glivec, Novartis)

N-Me-piperazine increases solubility

Gleevec® (May 2001)



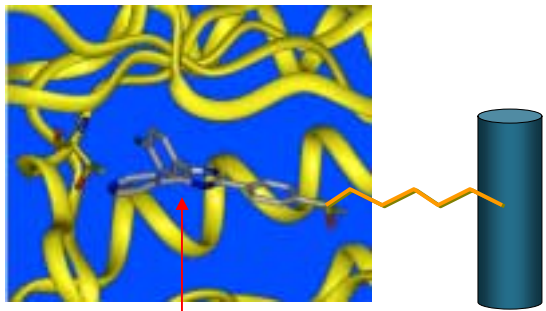


1fpu, 1iep

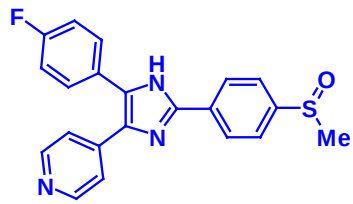
Glivec®, Imatinib (Novartis), for the treatment of chronic myelogenous leukemia

K_i ABL = 38 nM; K_i PGDFR = 50 nM (PDGFR = platelet-derived growth factor receptor); > 1000-fold selective vs. EGFR, c-src, PKA, PKCα (R. Capdeville et al., Nature Rev. Drug Discov. 1, 493-502 (2002))

Affinity Chromatography Using Immobilised Kinase Inhibitors



coupled compounds:
e.g. SB203580

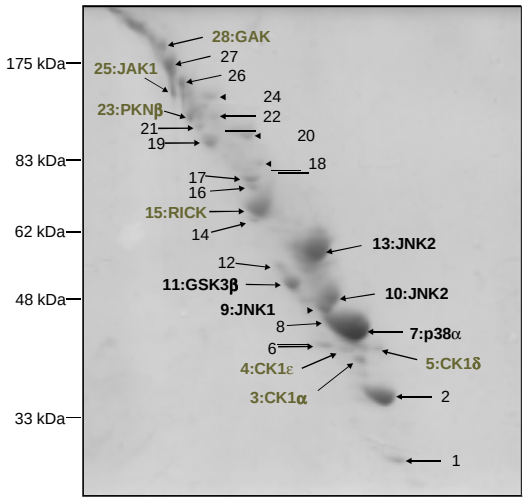


SB203580,
p38 MAP
kinase inhibitor

B. Klebl et al., in H. Kubinyi and G. Müller, Eds., Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 167-190

Hugo Kubinyi, www.kubinyi.de

Preparative Analysis of SB203580-bound Proteins



Protein spots excised

↓

Trypsin digestion

↓

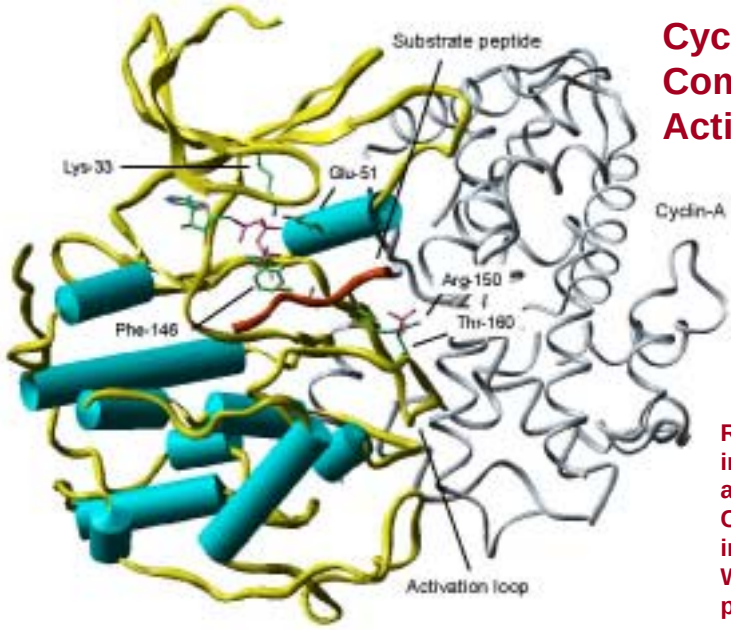
Mass spectrometry analysis

↓

Identification of several new protein kinase targets of the p38 inhibitor SB203580

B. Klebl et al., in H. Kubinyi and G. Müller, Eds., Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 167-190

Cyclin-CDK2 Complex in its Activated Form

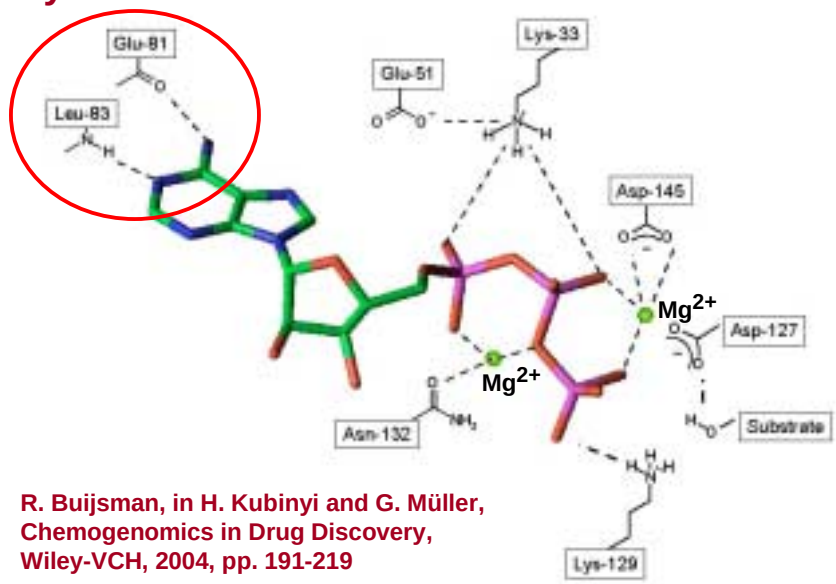


R. Buijsman, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

ATP Binding Site Pockets of Protein Kinases

R. Buijsman, in: H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

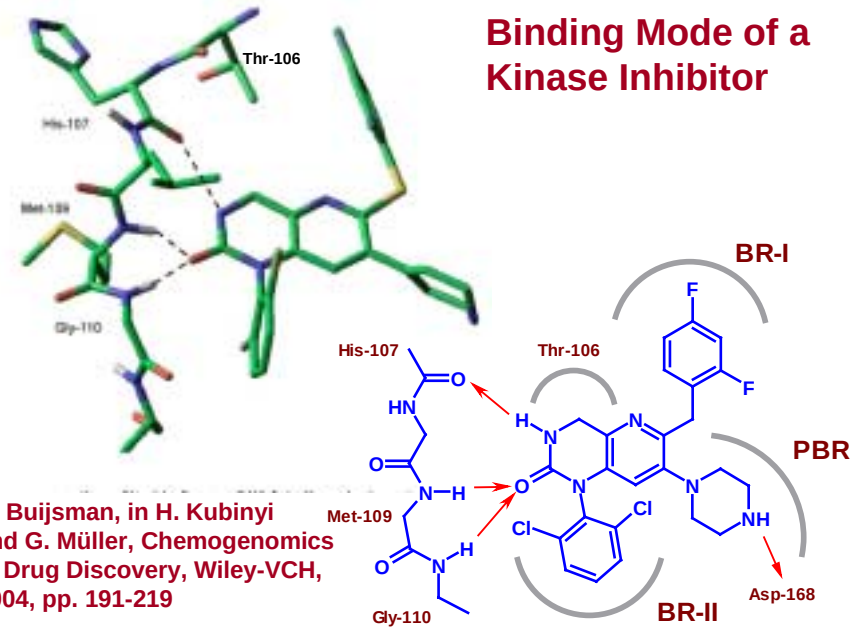
Key Interactions of ATP in the CDK2 Active Site



R. Buijsman, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

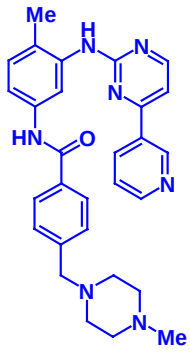
Hugo Kubinyi, www.kubinyi.de

Binding Mode of a Kinase Inhibitor

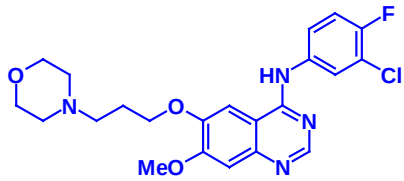


R. Buijsman, in H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 191-219

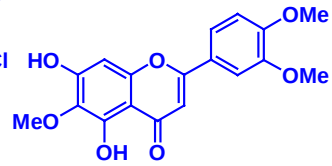
Kinase Inhibitors in Human Therapy



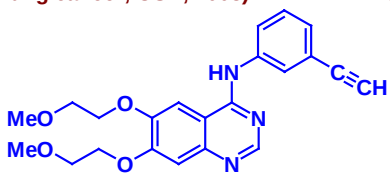
Imatinib (bcr-abl, KIT and PDFRB; CML and GIST; USA, 2001)



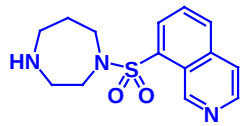
Gefitinib (EGFR; non-small-cell lung cancer; USA, 2003)



Eupatilin (ERK1, ERK2 and CDKs;gastritis; Korea, 2003)



Erlotinib (EGFR; non-small-cell lung cancer; USA, 2004)

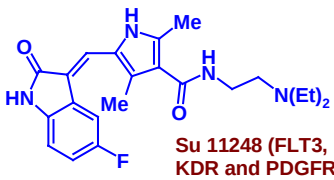


Fasudil (ROCK1; i.v., brain hemorrhage; Japan, 1995)

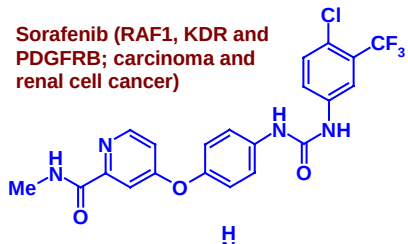
M. Vieth et al., Drug Discov. today 10, 839-846 (2005)

Hugo Kubinyi, www.kubinyi.de

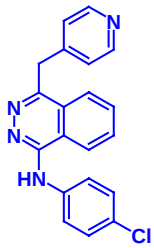
Kinase Inhibitors in Phase III Studies



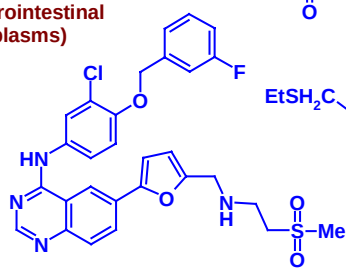
Su 11248 (FLT3, KIT, KDR and PDGFRB; renal cell cancer and gastrointestinal neoplasms)



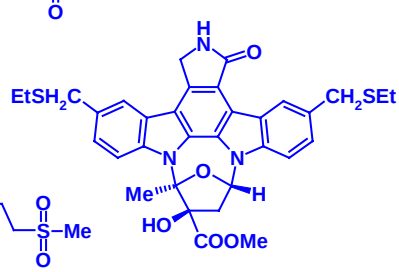
Sorafenib (RAF1, KDR and PDGFRB; carcinoma and renal cell cancer)



Vatalanib (KDR; colorectal, colonic and rectal neoplasms)

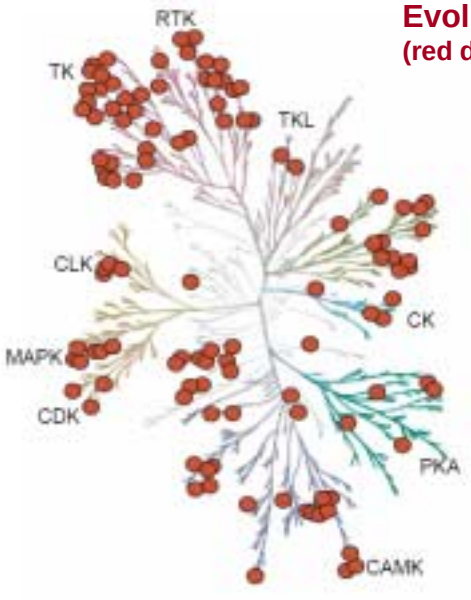


Lapatinib (EGFR and ERBB2; metastatic breast cancer)



CEP 1347 (MAPK8 and MAPK9; Parkinson's disease)

M. Vieth et al., Drug Discov. today 10, 839-846 (2005)



Evolutionary Tree of Kinases
(red dots indicate 113 tested kinases)

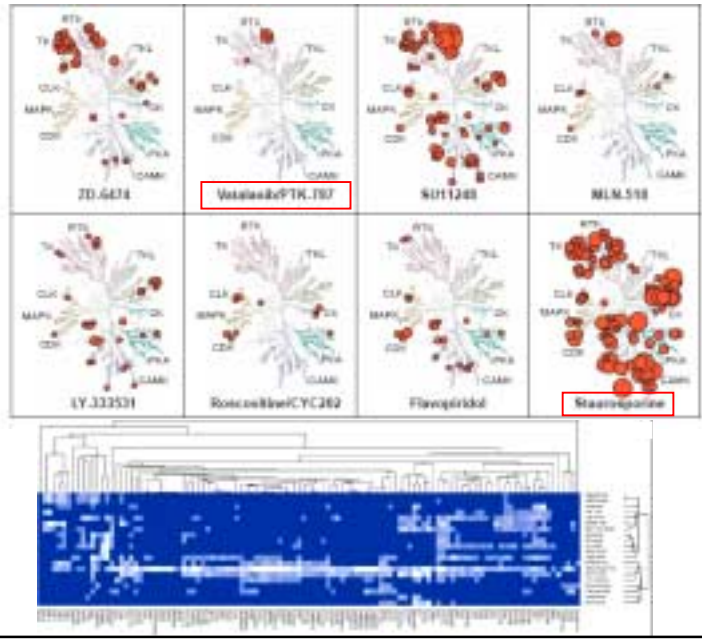
TK	**= non-receptor tyrosine kinases**
RTK	**= receptor tyrosine kinases**
TKL	**= tyrosine kinase-like kinases**
CK	**= casein kinase family**
PKA	**= protein kinase A family**
CAMK	**= calcium/calmodulin-dependent kinases**
CDK	**= cyclin-dependent kinases**
MAPK	**= mitogen-activated kinases**
CLK	**= Cdk-like kinases**

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

Hugo Kubinyi, www.kubinyi.de

Selectivity of Kinase Inhibitors
(20 inhibitors tested vs. 113 kinases)

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

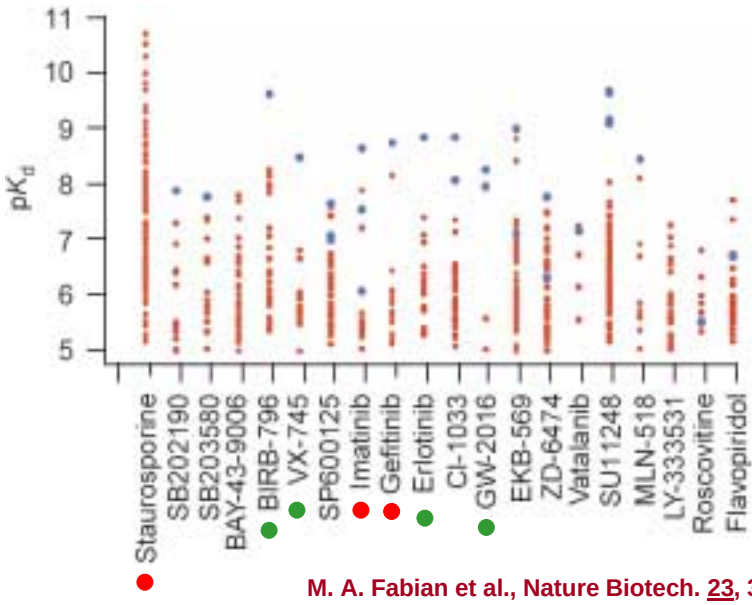


Selectivity of Kinase Inhibitors

(20 inhibitors tested vs. 113 kinases)

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

Hugo Kubinyi, www.kubinyi.de

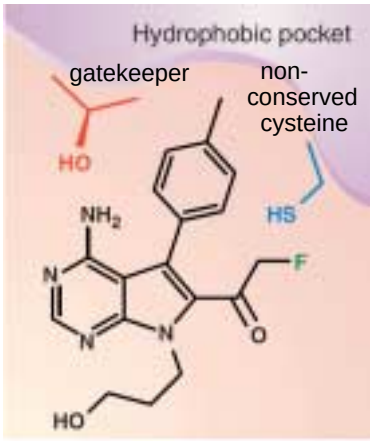


Selectivity of Kinase Inhibitors

blue dots = targets
red dots = off-targets

M. A. Fabian et al., Nature Biotech. 23, 329-336 (2005)

Design of a Highly Selective RSK1 and RSK2 Inhibitor

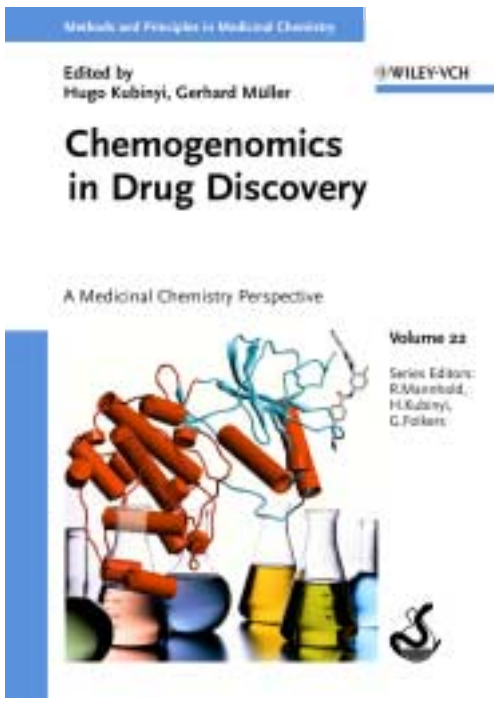


M. S. Cohen et al., Science 308, 1318-1321 (2005); figure from N. G. Ahn and K. A. Resing, Science 308, 1266-1267 (2005)

a) only 11 out of 491 related kinases have a non-conserved cysteine in position 436
b) only 3 of these 11 kinases have a (small) threonine in the „gatekeeper“ position 493
c) irreversible reaction with Cys436 produces a highly specific RSK1 and RSK2 inhibitor

RSK2 inhibition, IC_{50} in µM	
wild type	0.015
Cys436Val	>10
Thr493Met	3.4

d) other kinases, with only one „filter“, are not inhibited; single point mutation of either one amino acid produces inhibitor-sensitive kinases (e.g. a Fyn Val285Cys mutant, a v-Src Val281Cys mutant, and a MSK1 Met498Thr mutant)



Privileged structures
GPCRs
Ion channels
Kinases
Phosphodiesterases
Binding site similarity
Natural product libraries
etc.,

Wiley-VCH, 2004