Chemical Biology and Chemogenomics in Drug Discovery

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Classical and Chemical Genetics

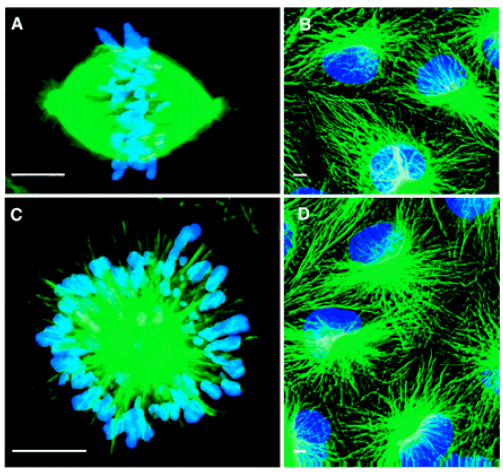
forward genetics	reverse genetics	forward chemical genetics	reverse chemical genetics
set a random mutation	destroy / silence a certain gene	test library in biological system	test library against a target
observe new phenotype	observe the phenotype	observe new phenotype	observe the phenotype
identify the mutated gene		identify the target	

Classical and Chemical Genetics

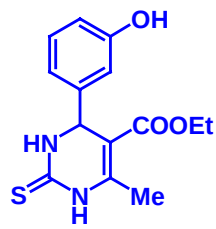
forward genetics	reverse genetics	forward chemical genetics	reverse chemical genetics
set a random mutation	destroy / silence a certain gene	test library in biological system	test library against a target
observe new phenotype	observe the phenotype	observe new phenotype	observe the phenotype
identify the mutated gene		identify the target	
classical genetics	knock-outs, siRNA models	animal models, chemical biology	*in vitro* test models, HTS, chemogenomics

B. R. Stockwell, Nature Rev. Genetics 1, 116-125 (2000)

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



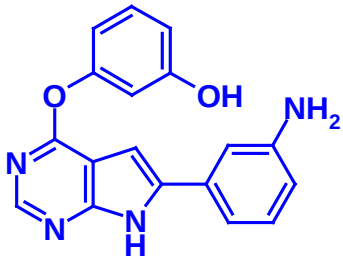
Control cells (A, B) and Monastrol-treated cells (C, D).



Monastrol

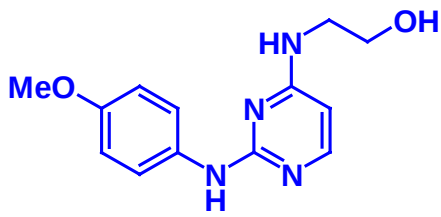
T. U. Mayer et al., Science 286, 971- 974 (1999)

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)

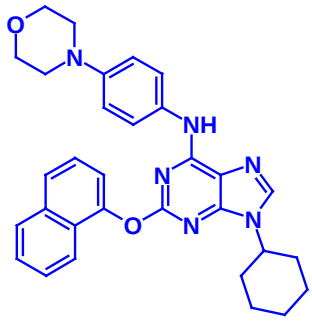
S. Ding et al, Proc. Natl. Acad. Sci. USA 100, 7632-7637 (2003)



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

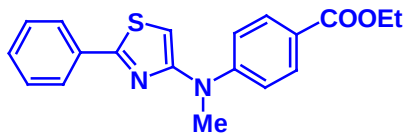
X. Wu et al., J.Am. Chem. Soc. 126, 1590-1591 (2004)

Differentiation of Pluripotent Progenitor Cells



Purmorphamine, from a 50,000-member heterocycles library, induces osteoblast formation from multipotent mesenchymal progenitor cells; activates the Hedgehog pathway by targeting Smoothened.

X. Wu et al., J.Am. Chem. Soc. 124, 14520-14521 (2002);
S. Sinha and J.K. Chen, Nat. Chem. Biol. 2, 29-30 (2006).

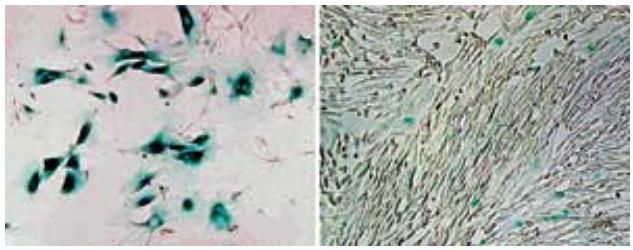


Neuropathiazol, from a 50,000 member heterocycles library, induces neuronal differentiation of adult hippocampal neural progenitor cells.

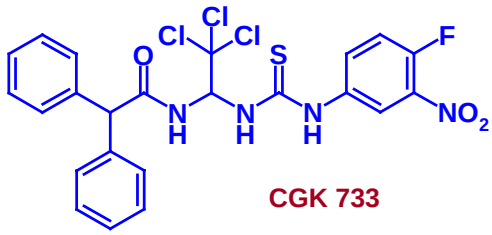
M. Warashina et al., Angew. Chem. Int. Ed. Engl. 45, 591-593 (2006)

Revitalization of Aging Cells

aging cells



cells treated with CGK 733

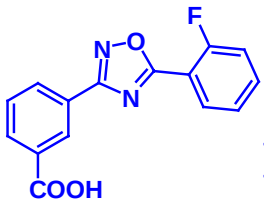


CGK 733

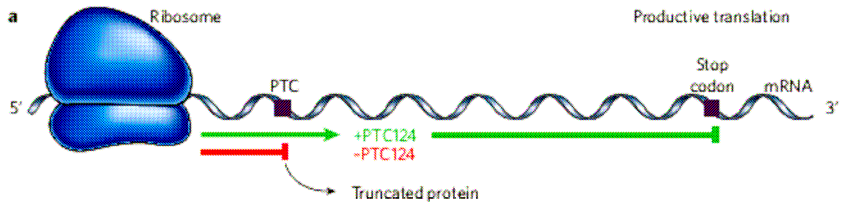
from a 20,000 member synthetic library, reversibly reverts aging cells to prolong their lifetime by 25% (about 20 cell divisions)

J. Won et al., Nat. Chem. Biol. 2, 369-374 (2006)

Compound PTC124 Targets Genetic Disorders Caused by Nonsense Mutations

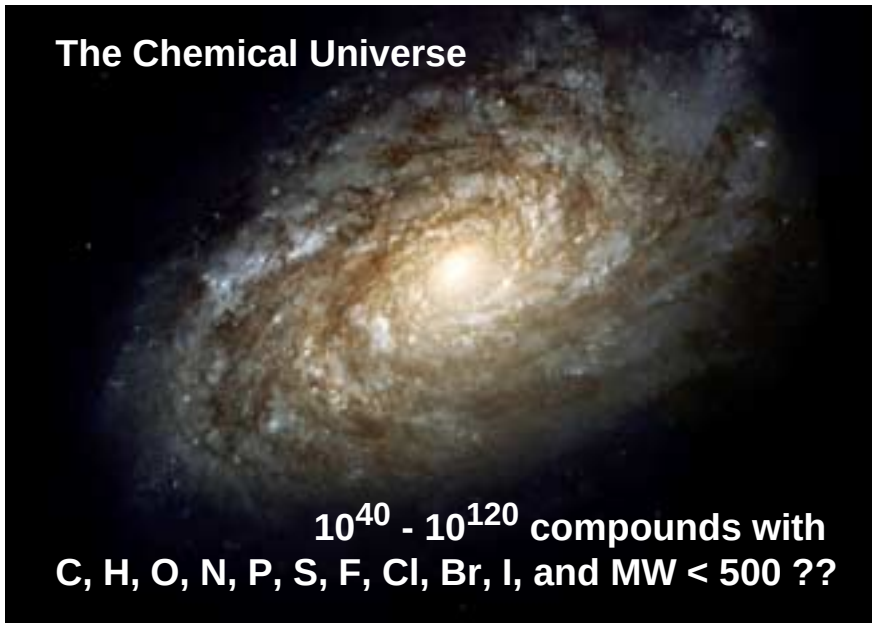


PTC124, from a 800,000 small-molecule library, prevents the formation of truncated proteins, in this manner being a possible therapeutic in Duchenne muscular dystrophy (now in phase II trials), cystic fibrosis, but also cancer. It "repairs" the effect of a nonsense mutation to a "premature termination codon" (PTC) UGA. UAG or UAA.



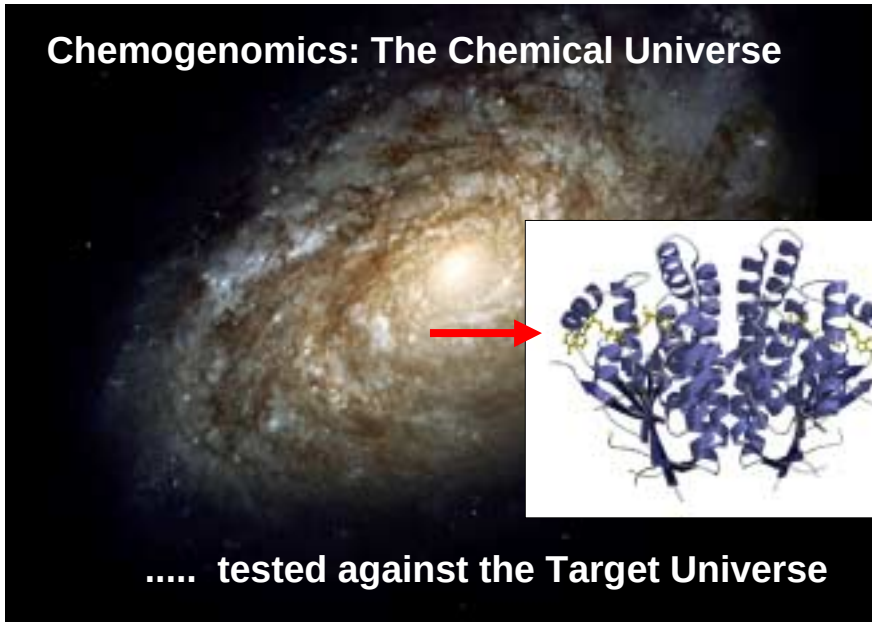
E. M. Welch et al., Nature 447 (May 03, 2007), pp. 87-91; comment by A. Schmitz and M. Famulok, Nature 447 (May 03, 2007), pp. 42-43

The Chemical Universe



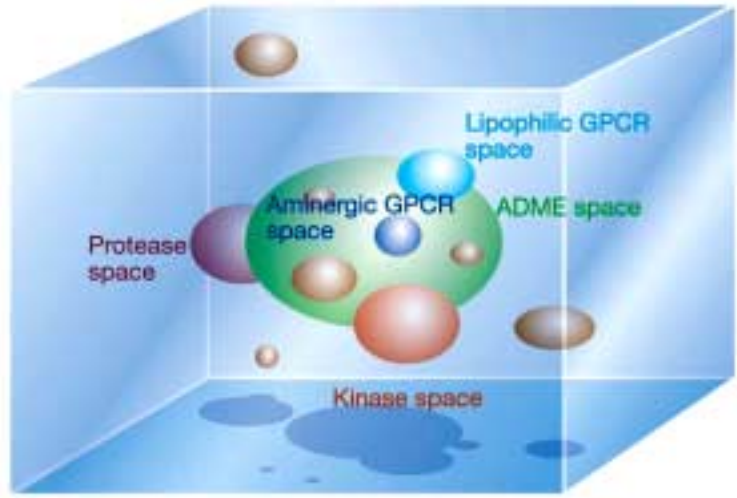
10^{40} - 10^{120} compounds with
C, H, O, N, P, S, F, Cl, Br, I, and MW < 500 ??

Chemogenomics: The Chemical Universe



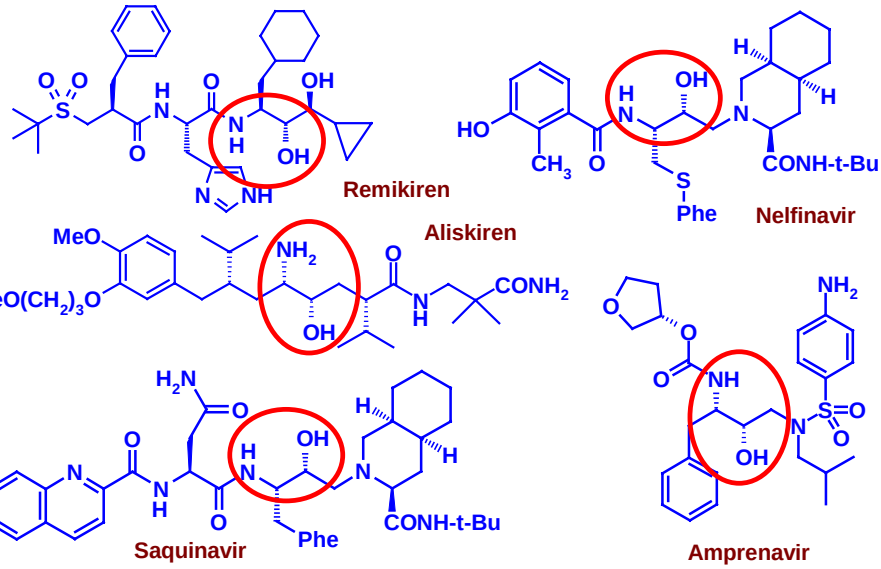
..... tested against the Target Universe

The Medicinal Chemistry Space

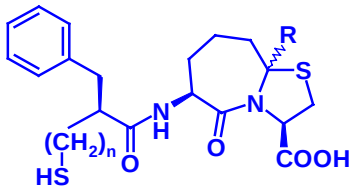


C. Lipinski and A. Hopkins, Nature 432, 855-861 (2004)

Chemogenomics: Aspartyl Protease Inhibitors

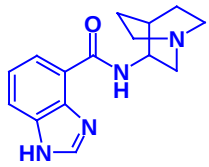


Chemogenomics in Selectivity Optimization

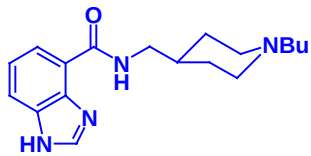


IC_{50} values	R = α-H n = 1	R = α-H n = 0	R = β-H n = 0
NEP 24.11	1.1 nM	11.5 nM	2 820 nM
ACE	5.5 nM	16 nM	11.5 nM

W. A. Slucharchyk et al., Bioorg Med. Chem. Lett. 7, 753-758 (1995)



K_i (5-HT_3) = 3.7 nM
K_i (5-HT_4) > 1,000 nM

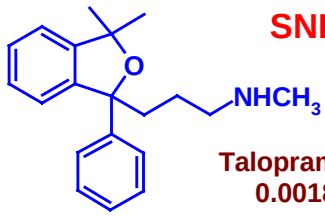


K_i (5-HT_3) > 10,000 nM
K_i (5-HT_4) = 13.7 nM

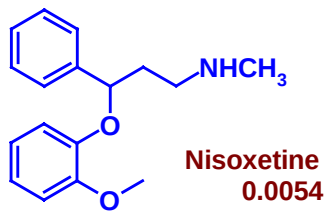
M. L. Lopez-Rodriguez et al., J. Comput.-Aided Mol. Design 11, 589-599 (1997)

Selectivity of Uptake Inhibitors

SNRI's

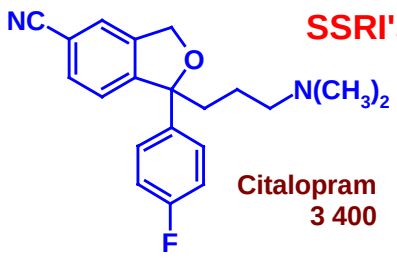


Talopram
0.0018

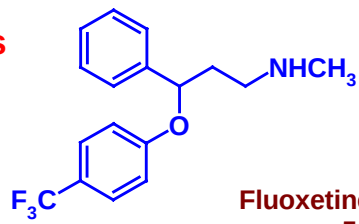


Nisoxetine
0.0054

SSRI's



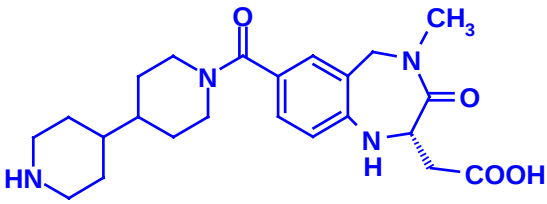
Citalopram
3 400



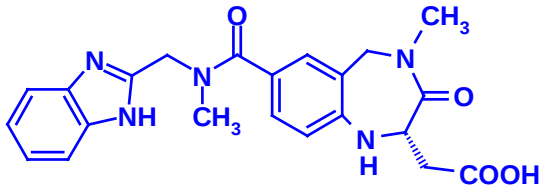
Fluoxetine
54

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)

Highly Selective Integrin Receptor Ligands



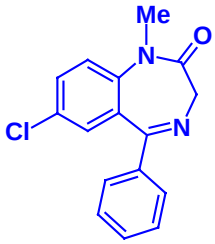
Iotrafiban (SB 214 857)
K_i GPIIb/IIIa = 2.5 nM
K_i αvβ3 = 10,340 nM



SB 223 245
K_i GPIIb/IIIa = 30,000 nM
K_i αvβ3 = 2 nM

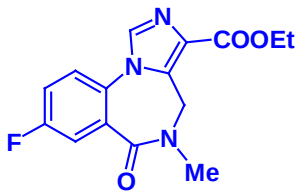
Lotrafiban failed in phase III, due to lack of activity and increased mortality (J.-M. Dogné et al., Curr. Med. Chem. 9, 577-589 (2002))

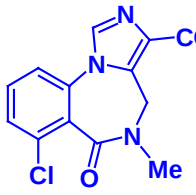
Activities of Benzodiazepines



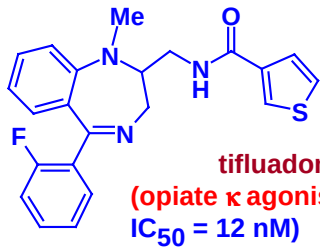
diazepam (agonist)
positive intrinsic activity at the $GABA_A$ receptor (tranquilizer)

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





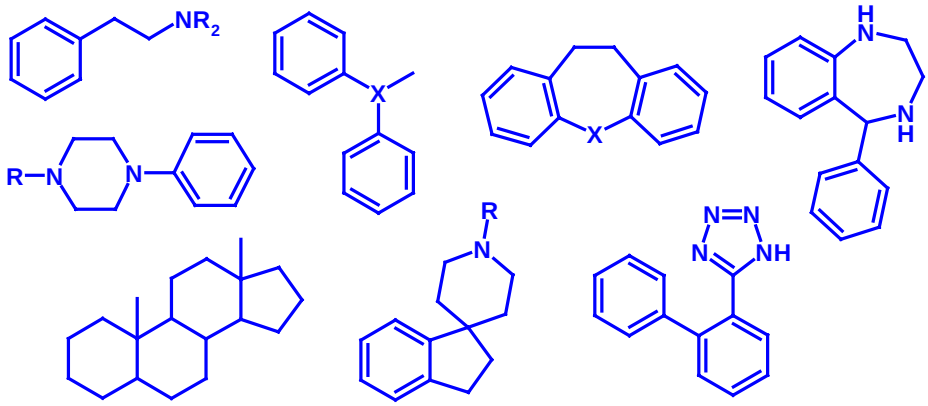
Ro 15-3505
(inverse agonist)
negative intrinsic activity at the $GABA_A$ receptor (proconvulsant)



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

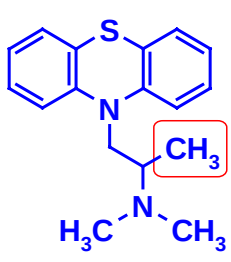
C. Wermuth, The Practice of Medicinal Chemistry, 1996, p. 548;
D. Römer et al., Nature 298, 759-760 (1982)

The Concept of „Privileged Structures“

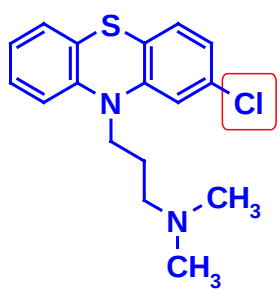


B. E. Evans et al., J. Med. Chem. 31, 2235-2246 (1988); A.A. Patchett, R.P. Nargund, Annu. Rep. Med. Chem. 35, 289-298 (2000); H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004

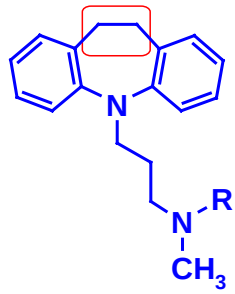
Different Modes of Action of Chemically Similar Molecules



promethazine (H_1 antagonist)

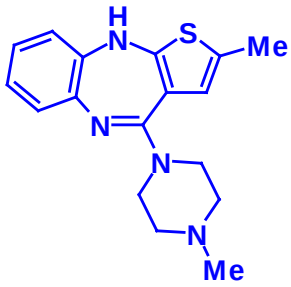


chlorpromazine (dopamine antagonist)



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

Many Ligands Bind to Several GPCRs



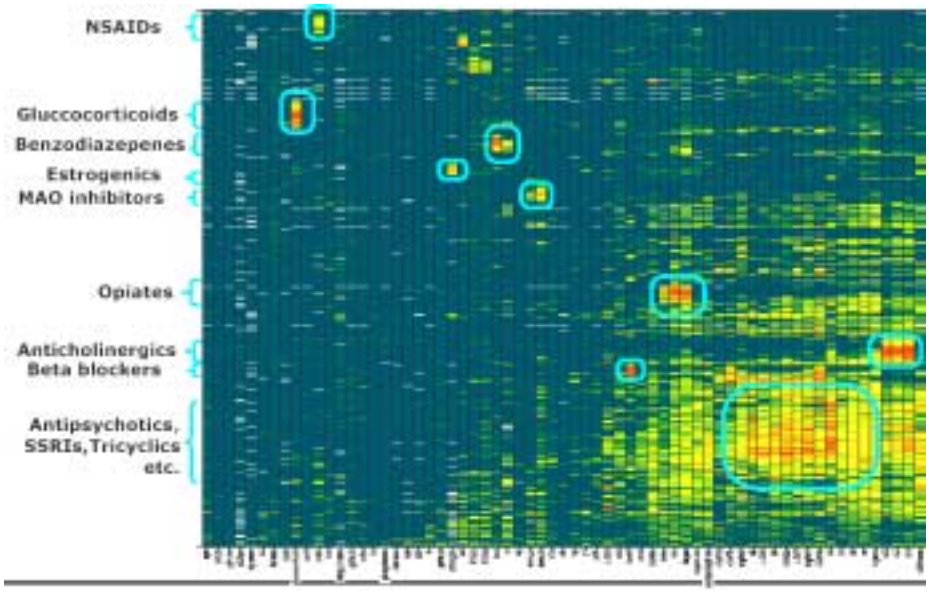
Olanzapine, a clozapine-like „atypical“ neuroleptic with a promiscuous binding pattern

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

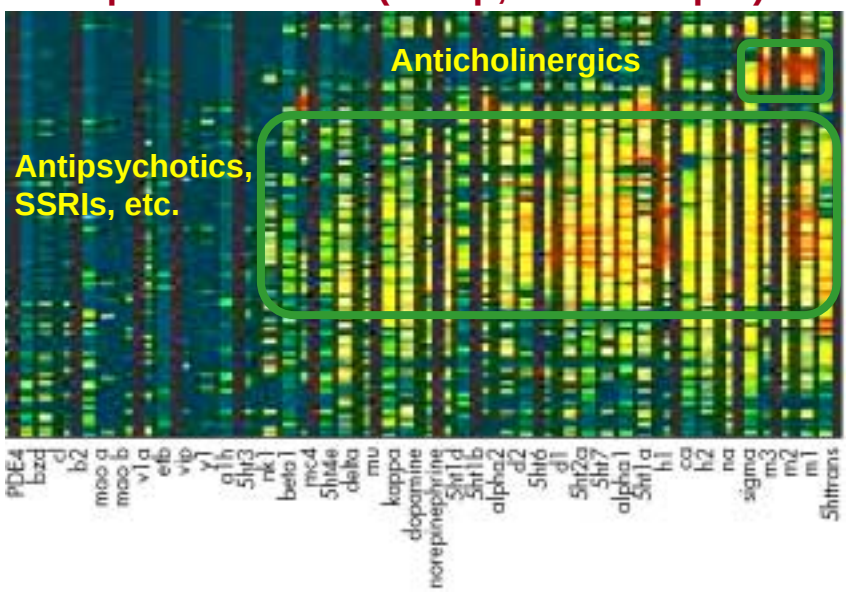
"Discouraging data on the antidepressant."

Bioprint Database (Cerep; www.cerep.fr)



Hugo Kubinyi www.kubinyi.de

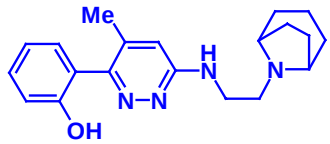
Bioprint Database (Cerep; www.cerep.fr)



The SOSA Approach

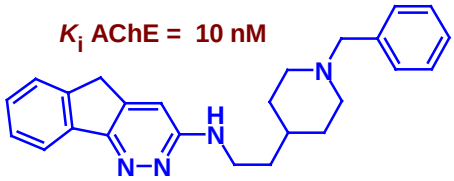
„The most fruitful basis for the discovery of a new drug is to start with an old drug“ Sir James Black, Nobel Prize 1988

minaprine (antidepressant)

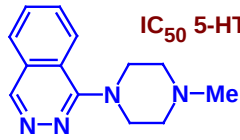


K_i musc M_1 = 3 nM

K_i AChE = 10 nM

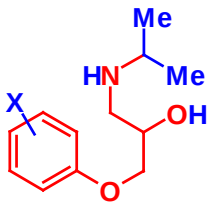


IC_{50} 5-HT_3 = 10 nM

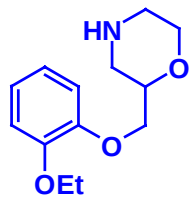


C. G. Wermuth, Med. Chem. Res. 10, 431-439 (2001); C. G. Wermuth, J. Med. Chem. 47, 1303-1314 (2004); H. Kubinyi, in H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 43-67

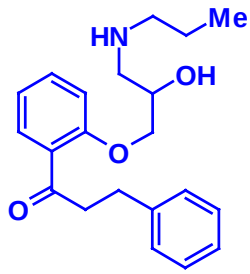
„Selective Optimization of Side Activities“



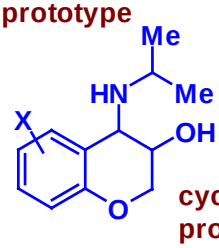
ß-blocker prototype



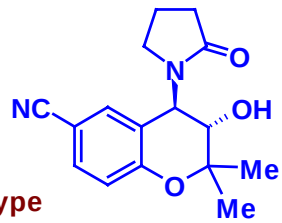
viloxacine antidepressant



propafenone 1c antiarrhythmic

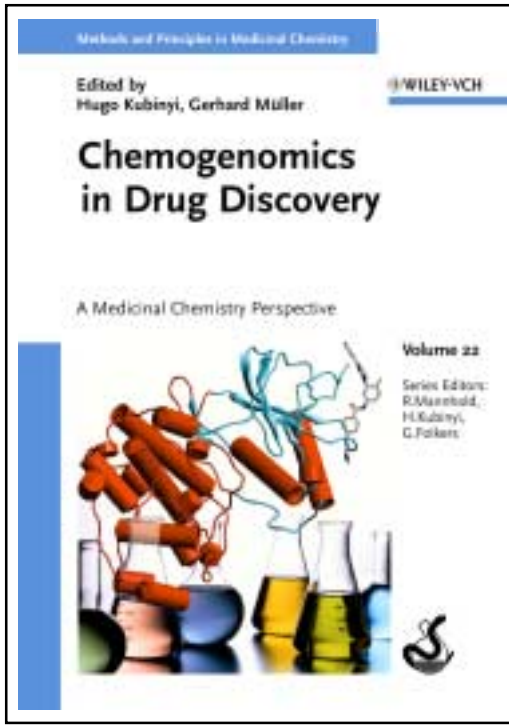


cyclic prototype



levocromakalim K channel opener

H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004



Privileged structures

GPCRs

Ion channels

Kinases

Phosphodiesterases

Binding site similarity

Natural product libraries

etc.,

Wiley-VCH, 2004