Combinatorial Chemistry in Drug Research

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New Strategies in Drug Research

Targets from genomics and proteomics

Transgenic animals for "proof of concept"

Combinatorial chemistry

High-throughput screening (HTS, uHTS)

Virtual screening: Bioavailability rules, drug-like character

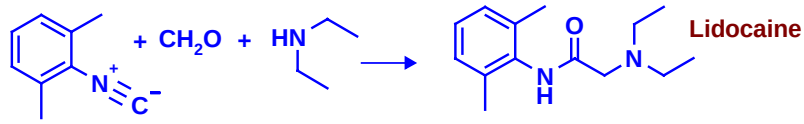
From protein 3D-structures to ligands

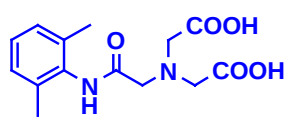
Disadvantages of Traditional Medicinal Chemistry

- Complex and time-consuming syntheses
- Low diversity (insufficient for new lead discovery)
- Synthetic output too small
- Slow development of structure-activity profiles within a class of compounds
- Slow optimization in evolutionary cycles
- Insufficient patent coverage
- High costs (about 5,000 – 10,000 US-$ per compound)

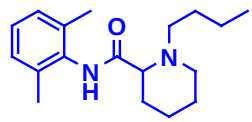
Application of the Ugi Multicomponent Reaction

A library of therapeutically used local anesthetics

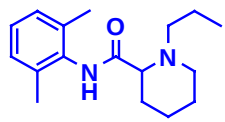




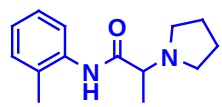
Lidofenin



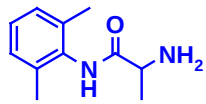
Bupivacaine



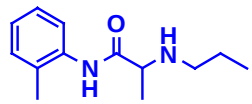
Ropivacaine



Aptocaine

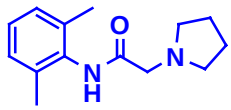


Tocainide

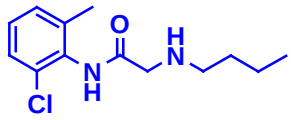


Prilocaine

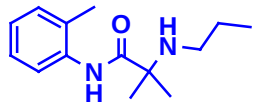
© L. Weber, Morphochem, Munich, Germany



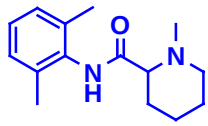
Pyrrocaine



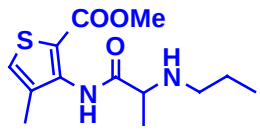
Butanilicaine



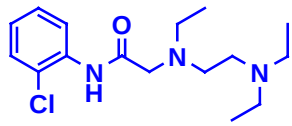
Quatacaine



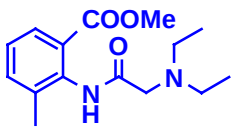
Mepivacaine



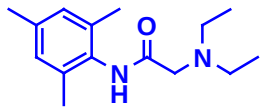
Articaine



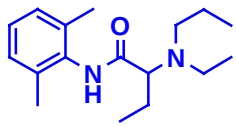
Clodacaine



Tolycaine

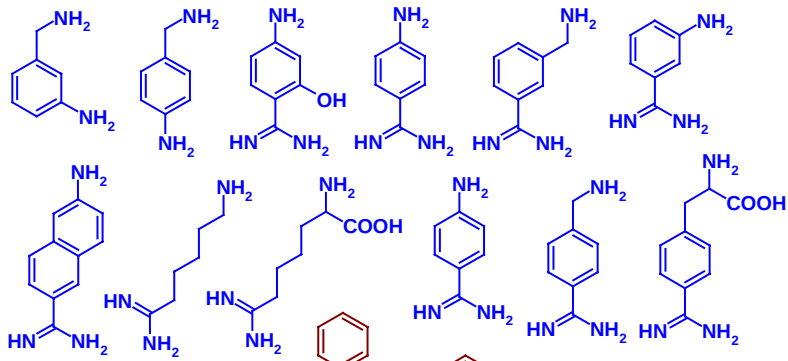


Trimecaine



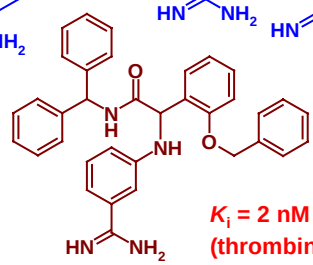
Etidocaine

Thrombin Inhibitors From an Ugi-Type Reaction



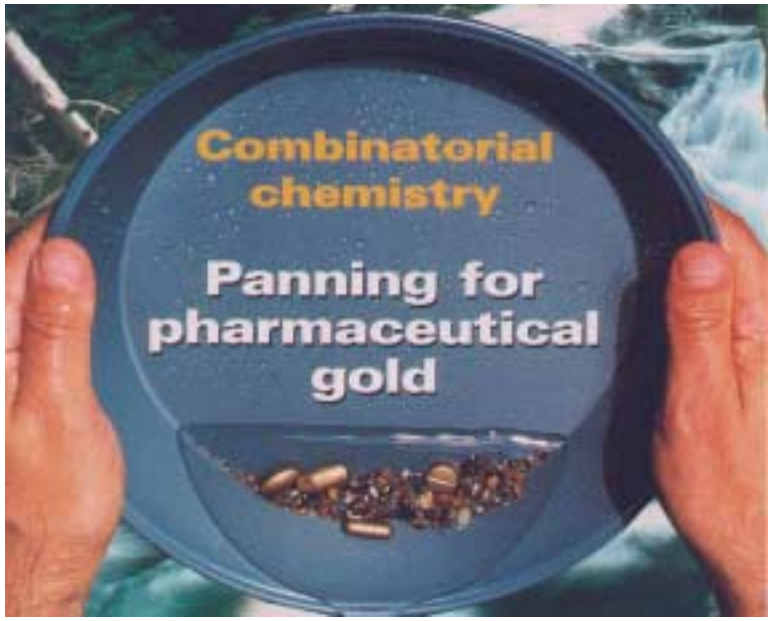
a 15,360-member library from

12 amines, 80 aldehydes, 16 isonitriles



K_i = 2 nM (thrombin)

K. Illgen et al., Chem. Biol. 7, 433-441 (2000)



Drug Space: Small Islands in a Huge Ocean

Lead Discovery:
search an island

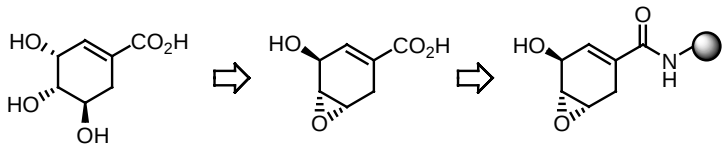
Lead Validation:
explore the island

Lead Hopping:
find adjacent islands

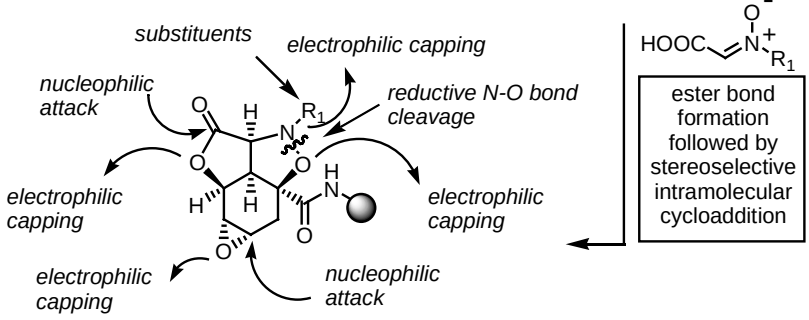
Lead Optimization:
search for highest peaks

Chemogenomics is the systematic exploration of all islands

A Natural Product-Like Library (n = 2.18 mio)



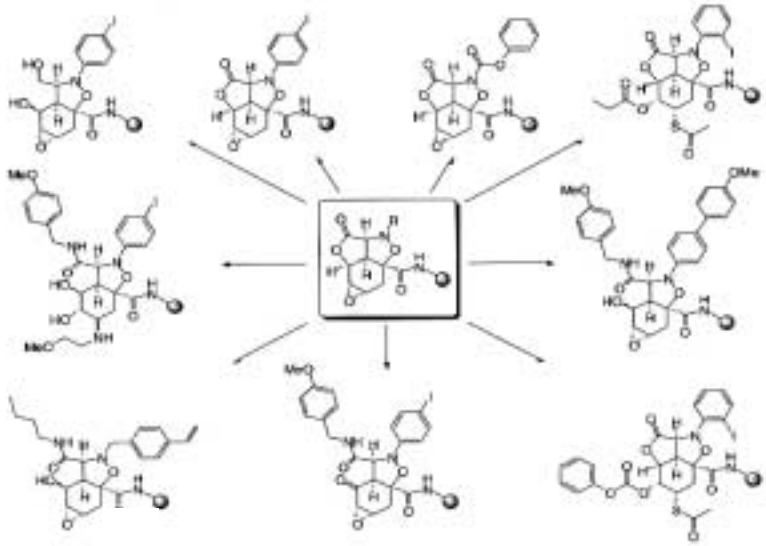
Shikimic acid



D. S. Tan et al., J. Am. Chem. Soc. 121, 9073-9087 (1999)

Hugo Kubinyi, www.kubinyi.de

A Natural Product-Like Library (n = 2.18 mio)



D. S. Tan et al., J. Am. Chem. Soc. 121, 9073-9087 (1999)

Chris Rescues CombiChem and Screening Collections

Advanced Drug Delivery Reviews 23 (1997) 3–25

advanced drug delivery reviews

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

Christopher A. Lipinski*, Franco Lombardo, Beryl W. Dominy, Paul J. Feeney

Central Research Division, Pfizer Inc., Groton, CT 06340, USA

Received 9 August 1996; accepted 14 August 1996

Abstract

Experimental and computational approaches to estimate solubility and permeability in discovery and development settings are described. In the discovery setting 'the rule of 5' predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (MWT) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP > 4.15). Computational methodology for the rule-based Moriguchi Log P (MLogP) calculation is described. Turbidimetric solubility measurement is described and applied to known drugs. High throughput screening (HTS) leads tend to have higher MWT and Log P and lower turbidimetric solubility than leads in the pre-HTS era. In the development setting, solubility calculations focus on exact value prediction and are difficult because of polymorphism. Recent work on linear free energy relationships and Log P approaches are critically reviewed. Useful predictions are possible in closely related analog series when coupled with experimental thermodynamic solubility measurements.

The Ultimate Goal in Pharmaceutical Industry

How to Achieve?

„Drug-like“ Compounds

Development of Combinatorial Chemistry

- From peptides to organic molecules
- From large to small libraries
- From mixtures to single compounds
- From combinatorial synthesis to automated parallel syntheses of molecules with drug-like character

→ From chemistry to biological activity: focused design of combinatorial libraries

Goals: Search for new lead structures and optimization of their target affinity (= activity), selectivity, ADME properties (absorption, distribution, metabolism, elimination), reduction of toxicity and elimination of undesirable side effects.

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Combinatorial Chemistry in Drug Research

Drug research is an evolutionary process

Nature developed higher organisms from more primitive forms.
Over the decades, lead structure search and optimization followed the same principles.

Combinatorial chemistry speeds up drug discovery

Automated parallel syntheses reduce the time needed for each evolutionary cycle.

Drug-like character of libraries

Biological properties are more important than synthetic accessibility.

Similarity and diversity

Similarity can be better defined than diversity, the ”lack of similarity”.

Size and diversity of libraries

Huge libraries are most often a waste of time and resources, because of the time spent for chemistry optimization and limited diversity.

Combinatorial Chemistry in Drug Research

Combinatorial chemistry and rational drug design

Structure-based and computer-assisted design and virtual screening (LUDI, FlexX et al.) of protein ligands supplement combinatorial chemistry.

Combinatorial design of drugs

The necessary tools are already available but scoring functions have to be improved.

Success criteria in drug research

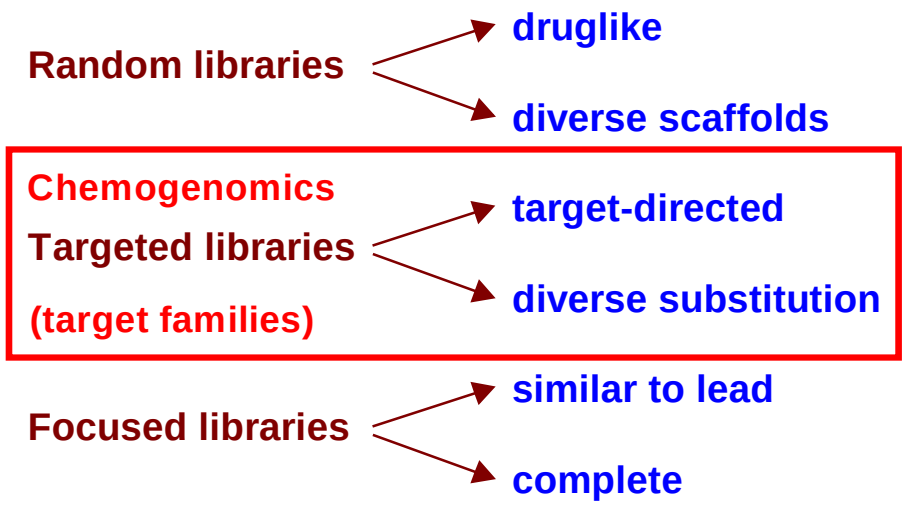
Decisive for industrial success is not "*me too*" but "*me better*", "*me faster*", "*me first*" or "*me only*".

Scope and limitations

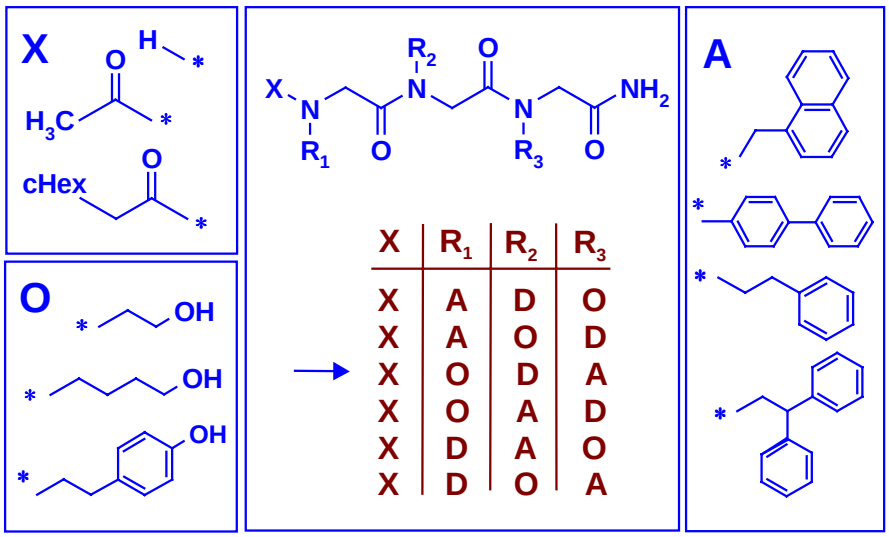
Combinatorial chemistry and automated parallel synthesis will not replace classical chemistry.

They are powerful tools in lead discovery and optimization.

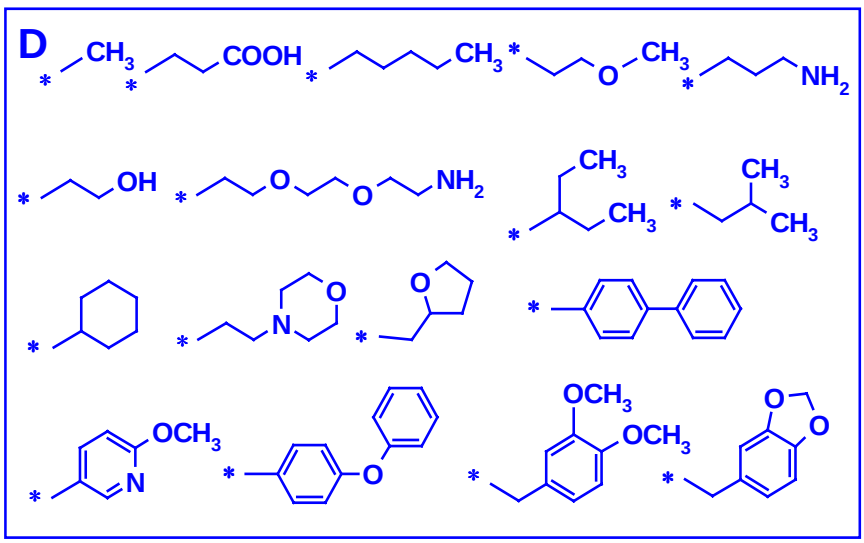
Types and Features of Combinatorial Libraries



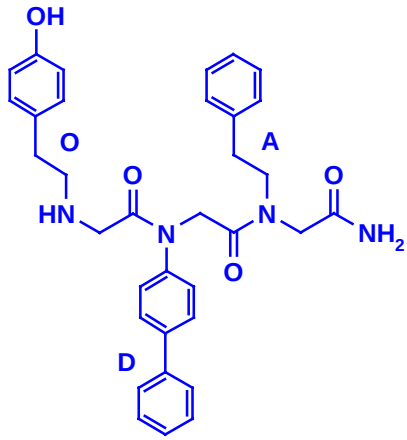
Synthesis of a Peptoid Library



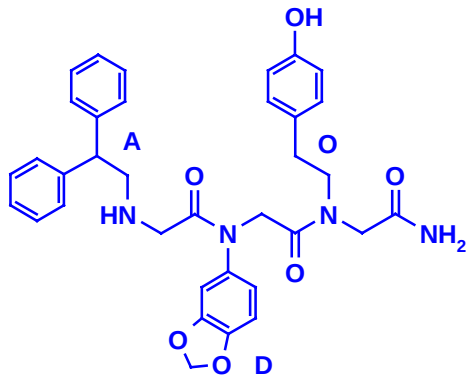
X	R_1	R_2	R_3
X	A	D	O
X	A	O	D
X	O	D	A
X	O	A	D
X	D	A	O
X	D	O	A



R. N. Zuckermann, E. J. Martin, D. C. Spellmeyer, et al., J. Med. Chem. 37, 2678-2685 (1994).

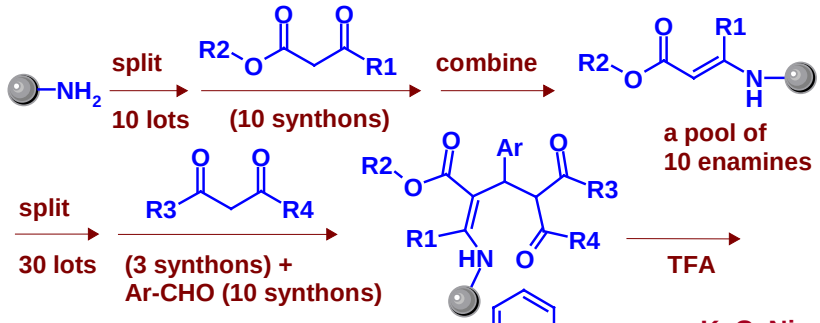


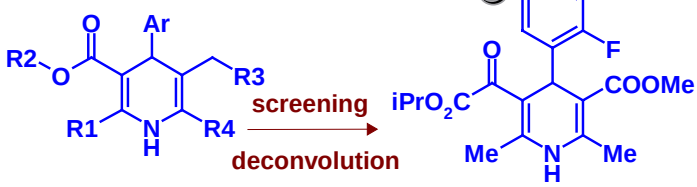
K_i (α_1-adrenergic receptor) = 5 nM



K_i (μ-specific opiate receptor) = 6 nM

A Dihydropyridine Library (n = 300)

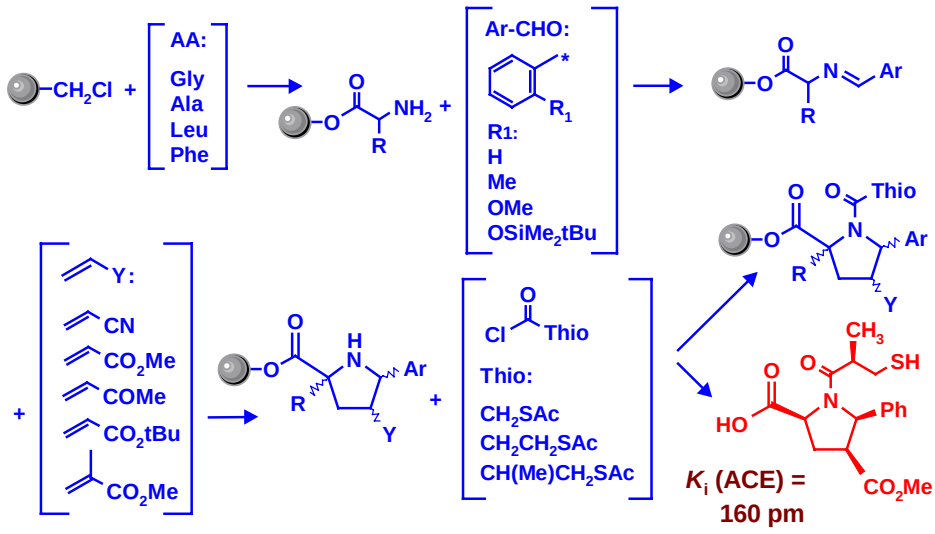




IC_{50} (calcium channel) = 14 nM

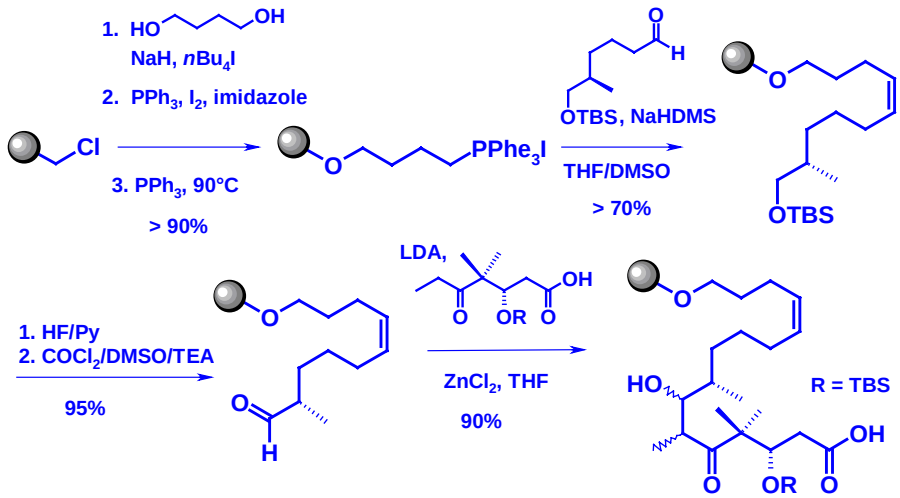
K. C. Nicolaou et al. (2002), Handbook of Combinatorial Chemistry, Wiley-VCH, pp. 659-660

Synthesis of an ACE Inhibitor Library



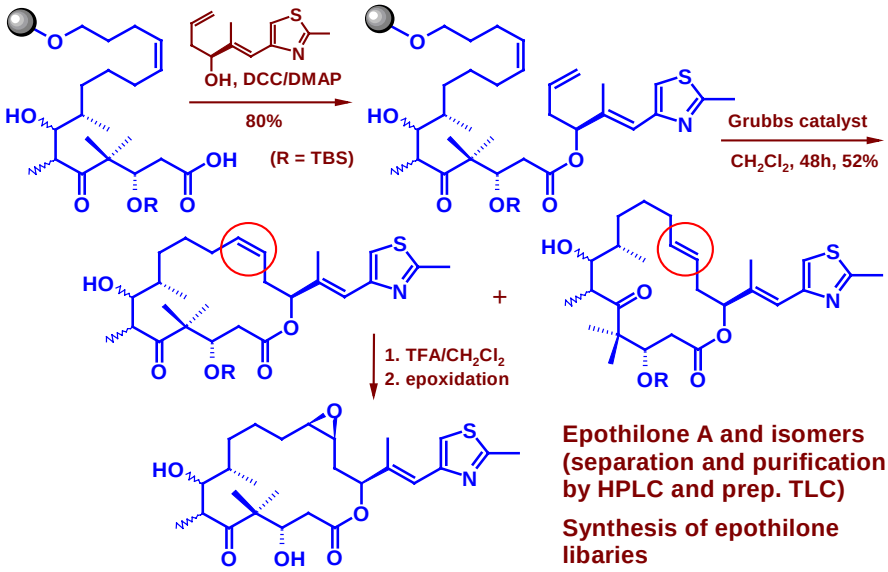
M. M. Murphy et al., J. Am. Chem. Soc. 117, 7029-7030 (1995).

Solid Phase Synthesis of Epothilone, I



K. C. Nicolaou et al., a) Nature 387, 268-272 (1997);
b) Angew. Chem. Int. Ed. Engl. 36, 2097-2103 (1997)

Solid Phase Synthesis of Epothilone, II



Epothilone A and isomers (separation and purification by HPLC and prep. TLC)

Synthesis of epothilone libaries

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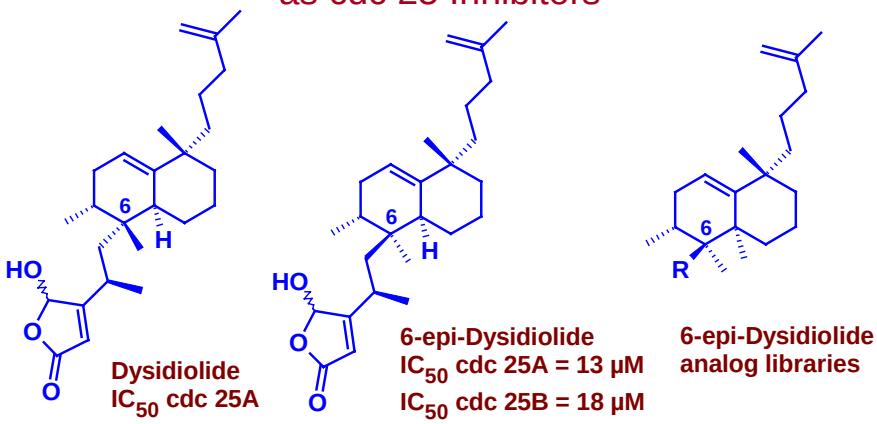
Dysidiolide Analog Libraries

as cdc 25 Inhibitors



Dysidiolide
IC_{50} cdc 25A = 9.4 µM

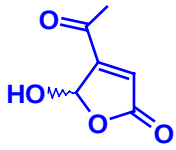
6-epi-Dysidiolide
IC_{50} cdc 25A = 13 µM
IC_{50} cdc 25B = 18 µM
IC_{50} cdc 25C = 5.1 µM

6-epi-Dysidiolide analog libraries

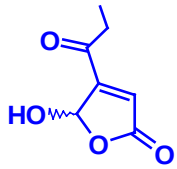
D. Brohm et al., J. Am. Chem. Soc. 124, 13171-13178 (2002);
D. Brohm et al., Angew. Chem. Int. Ed. 41, 307-311 (2002)

Dysidiolide Analog Libraries
as cdc 25C Inhibitors

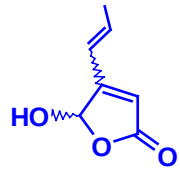
R =



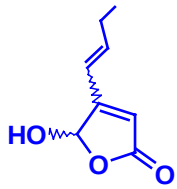
IC_{50} = 0.8 µM



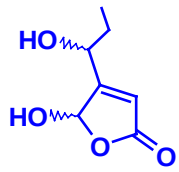
IC_{50} = 1.5 µM



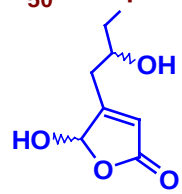
IC_{50} = 6.8 µM



IC_{50} = 2.4 µM



IC_{50} = 6.1 µM



IC_{50} = 9 µM

D. Brohm et al., J. Am. Chem. Soc. 124, 13171-13178 (2002);
D. Brohm et al., Angew. Chem. Int. Ed. 41, 307-311 (2002)

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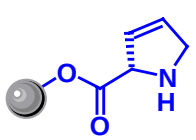
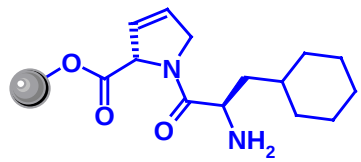
Serine Protease Inhibitors
Convergent Solid Phase Synthesis, Part I



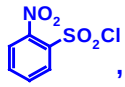
P2 fragment

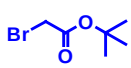
1) FMOC-D-Cha-OH, DIEA, TBTU, DMF

2) piperidine/DMF



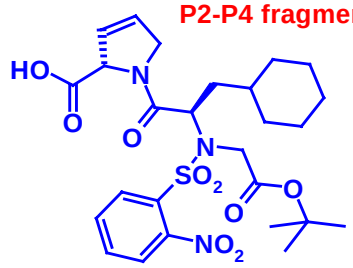
P2-P3 fragment

1)  , DIEA, CH_2Cl_2

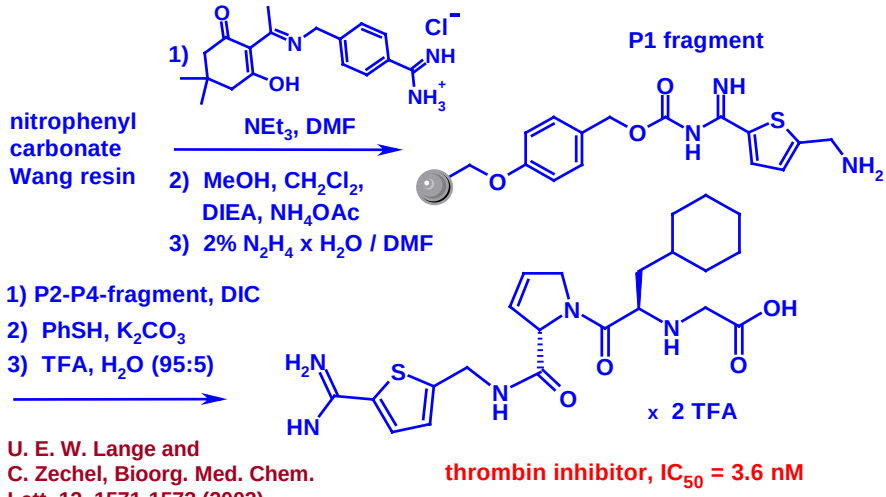
2)  , Cs_2CO_3, NMP

3) HOAc, CH_2Cl_2, TFE (1:3:1)

P2-P4 fragment



Serine Protease Inhibitors
Convergent Solid Phase Synthesis, Part II



U. E. W. Lange and C. Zechel, Bioorg. Med. Chem. Lett. 12, 1571-1573 (2002)

thrombin inhibitor, IC_{50} = 3.6 nM

Hugo Kubinyi, www.kubinyi.de

Serine Protease Inhibitors
Convergent Solid Phase Synthesis, Results

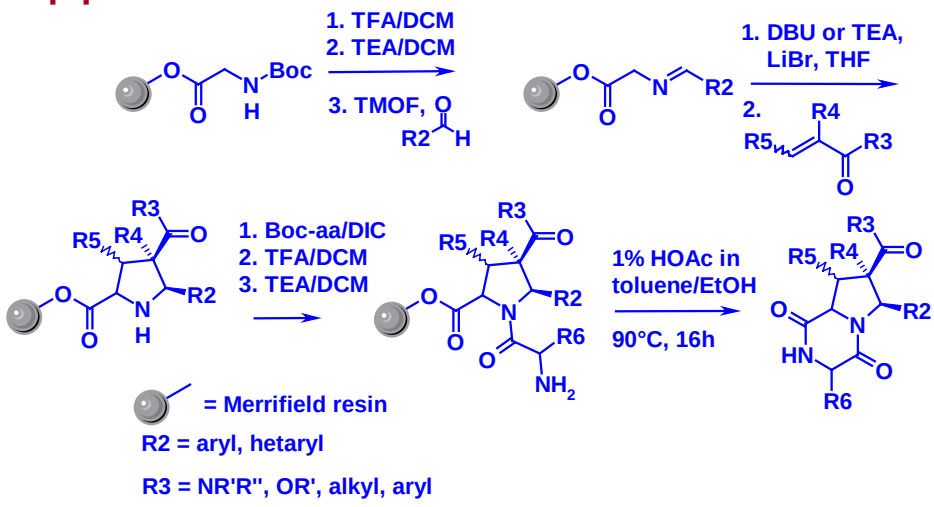
2 FTE's, 4 months reaction optimisation
Several nanomolar thrombin inhibitors

New Serine Protease Program (Organ Protection)

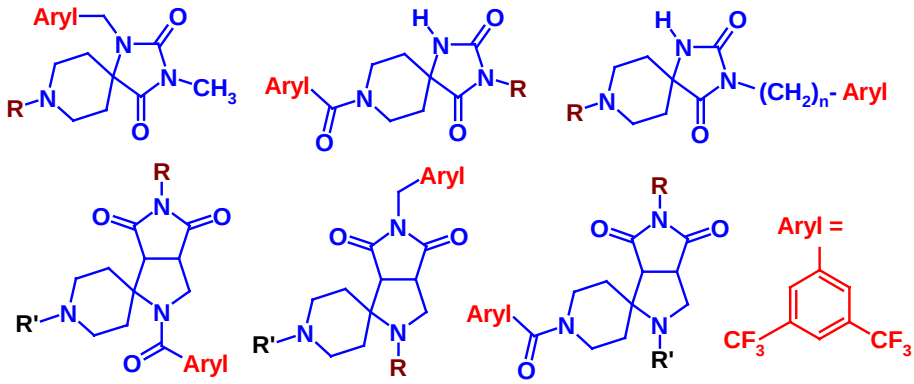
HTS of BASF library	**no hits**
BASF thrombin inhibitors	**no hits**

Homology modelling
Binding site hypothesis
SPS of 40 analogs (2 weeks) **submicromolar hits**

Solid Phase Synthesis of Pyrrolidinodiketo-piperazines



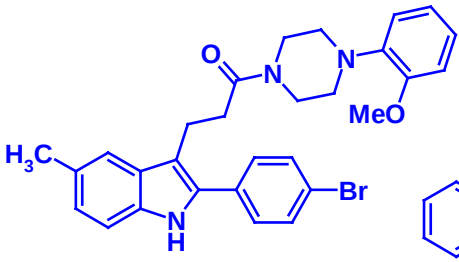
Hoffmann La Roche Neurokinin Receptor Ligands



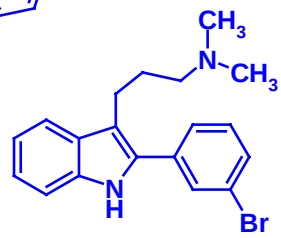
Spirohydantoins (upper row) are low-affinity ligands but selected spiropyrrolidino-pyrrolidines (lower row) show 5 to 8 nM affinities.

K. H. Bleicher et al., Bioorg. Med. Chem. Lett. 12, 2519-2522 and 3073-3076 (2002); A. Lee and J. G. Breitenbucher, Curr. Opin. Drug Discov. Dev. 6, 494-508 (2003).

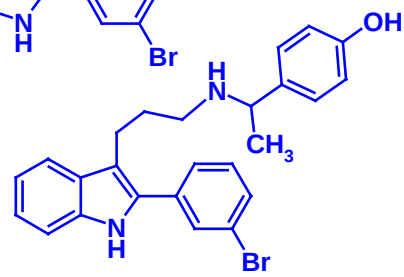
Merck Lead Discovery Libraries, I



NK_1 0.8 nM
NK_2 >10 μM
NK_3 >10 μM



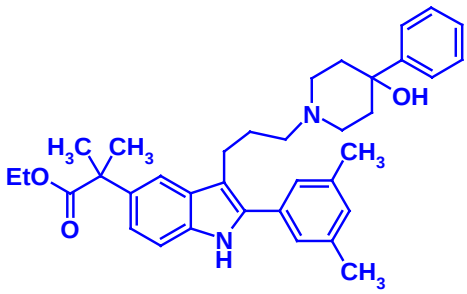
$5\text{-}HT_6$ 0.7 nM
$5\text{-}HT_7$ 300 nM
$5\text{-}HT_{1a}$ > 1 μM
$5\text{-}HT_{5a}$ > 1 μM



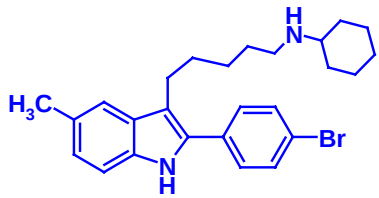
NPY_5 0.8 nM
NPY_1 >10 μM

C. A. Willoughby et al., Bioorg. Med. Chem. Lett. 12, 93-96 (2002); A. Lee and J. G. Breitenbucher, Curr. Opin. Drug Discov. Dev. 6, 494-508 (2003).

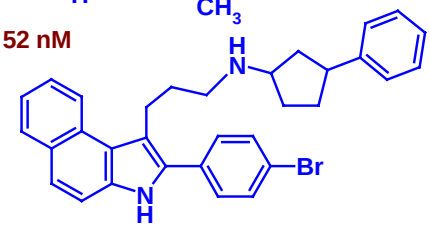
Merck Lead Discovery Libraries, II



GnRH 52 nM



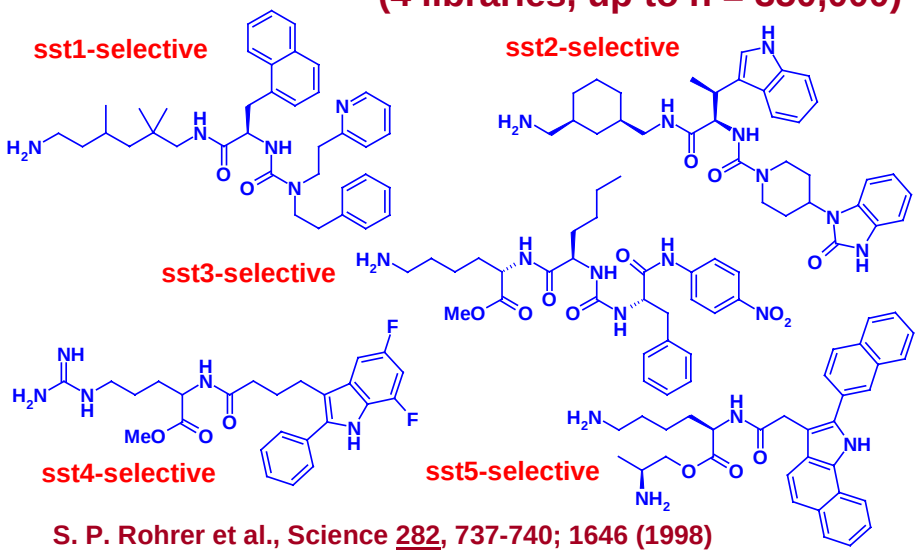
MC4R 612 nM



CCR5	1,190 nM
CCR1	>10 μM
CCR2	>10 μM
CCR3	920 nM
CXCR3	>10 μM
CXCR4	1,520 nM

C. A. Willoughby et al., Bioorg. Med. Chem. Lett. 12, 93-96 (2002); A. Lee and J. G. Breitenbucher, Curr. Opin. Drug Discov. Dev. 6, 494-508 (2003).

Merck Somatostatin Mimics Library (4 libraries, up to n = 350,000)



S. P. Rohrer et al., Science 282, 737-740; 1646 (1998)

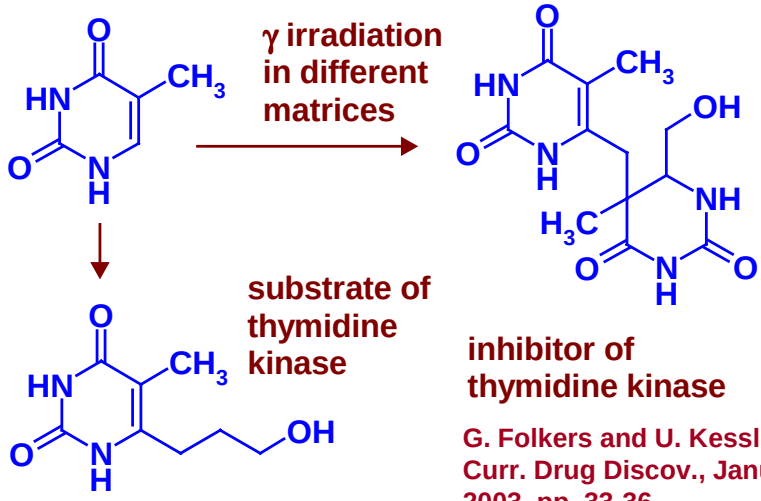
Subtype Spezificities of Somatostatin Mimetics

(K_d values in nM)

Compound	sst1	sst2	sst3	sst4	sst5
somatostatin	0.4	0.04	0.7	1.7	2.3
1	1.4	1,875	2,240	170	3,600
2	2,760	0.05	729	310	4,260
3	1,255	> 10,000	24	8,650	1,200
4	199	4,720	1,280	0.7	3,880
5	3.3	52	64	82	0.4

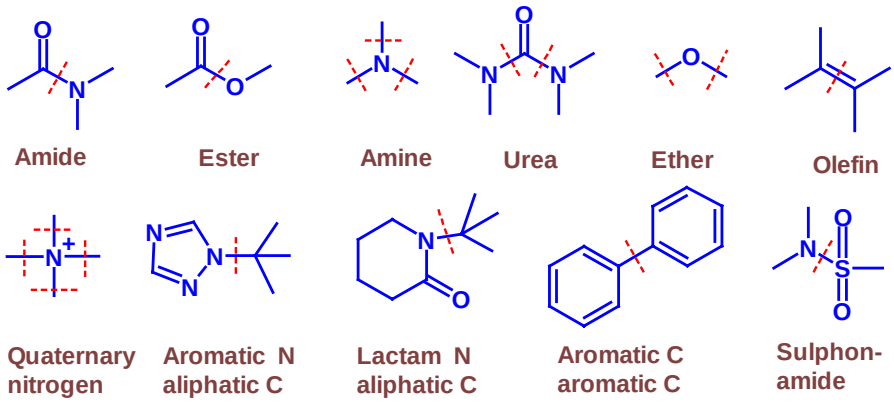
S. P. Rohrer et al., Science 282, 737-740; 1646 (1998)

Random Chemistry: An Unbiased Approach to New Chemical Entities



G. Folkers and U. Kessler, Curr. Drug Discov., January 2003, pp. 33-36

RECAP - a Retrosynthetic Combinatorial Analysis Procedure (applied to WDI)



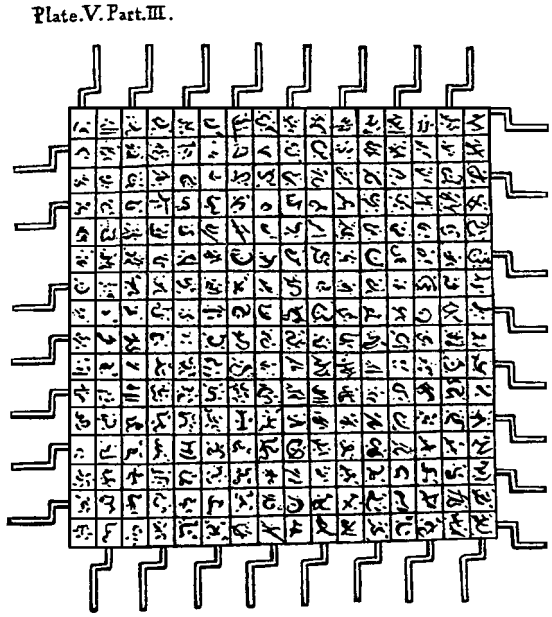
X. Q. Lewell et al., J. Chem. Inf. Comput. Sci. 38, 511-522 (1998)

„Good Combinatorial Chemistry Practice“

- Drug Design is an evolutionary procedure
- Combinatorial chemistry speeds up drug discovery
- Lead discovery libraries shall have a high degree of chemical diversity
- Lead optimisation libraries shall have a high degree of similarity, to cover the chemical space around a lead structure
- Several small libraries generate a higher diversity than one large library
- Drug-like character is more important than synthetic accessibility

The Projectors of Speculative Learning of the Academy of Sciences of Lagado

Jonathan Swift Gulliver‘s Travels, 1726
Part III. A voyage to Laputa, Balnibarbi, Glubbdubdrib, Luggnagg and Japan.



Citations from Literature

ArQule, http://www.arqule.com/html/combi2.htm about large libraries:

”Combinatorial chemistry is the synthesis of all possible combinations of chemical building blocks. When it first originated only a few years ago, the ability of this technology to generate millions of novel compounds seemed highly desirable. As scientists in the industry have grown more knowledgeable, however, it has become clear that the generation of such vast numbers of random compounds results in an overwhelming amount of unproductive work.
Moreover, the range of synthetic organic reactions remained relatively small and identification of individual bioactive compounds was complicated. In addition, cell assays of mixtures were plagued with ambiguity, and mixtures frequently gave rise to meaningless positive responses”.

Hugo Kubinyi, www.kubinyi.de

Citations from Literature

Anthony W. Czarnik, Vice President Chemistry, IRORI, in Chemical & Engineering News, April 6, 1998, about large libraries:

"The motivating theme for combinatorial chemistry might be to be able to make a million variants of any structural template and screen them. Cheaper and faster are better. When we can accomplish this within a week, then perhaps the intellectual challenges will be gone. However, I can assure you that we are far, far from that vision today".

Mario Geysen, ”Inventor” of Combinatorial Chemistry and Head of the Combinatorial Chemistry Group at Glaxo Wellcome (cited from G. Karet, Drug Discovery & Development, January 1999, pp. 32-38) about compound quantities in large libraries (1-2 ng):

”If you want to increase the numbers, the quantities have to be small; otherwise you are going to break the bank trying to make that library”.