Chemical Biology and Chemogenomics in Drug Discovery

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Classical and Chemical Genetics

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<thead>
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<th>forward genetics</th>
<th>reverse genetics</th>
<th>forward chemical genetics</th>
<th>reverse chemical genetics</th>
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<td>classical genetics</td>
<td>knock-outs, siRNA models</td>
<td>animal models, chemical biology</td>
<td>in vitro test models, HTS, chemogenomics</td>
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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).

**In vitro Differentiation of Embryonic Stem Cells**

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


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


**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);

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

Revitalization of Aging Cells


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

Compound PTC124 Targets Genetic Disorders Caused by Nonsense Mutations

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


Chemogenomics: Aspartyl Protease Inhibitors
Chemogenomics in Selectivity Optimization

$\text{IC}_{50}$ values

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<tr>
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<th>R = $\alpha$-H</th>
<th>R = $\beta$-H</th>
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<tbody>
<tr>
<td>NEP</td>
<td>n = 1</td>
<td>n = 0</td>
</tr>
<tr>
<td>11.5 nM</td>
<td>2 820 nM</td>
<td>11.5 nM</td>
</tr>
<tr>
<td>ACE</td>
<td>5.5 nM</td>
<td>16 nM</td>
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$K_i$ (5-HT$_3$) = 3.7 nM
$K_i$ (5-HT$_4$) > 10,000 nM
$K_i$ (5-HT$_4$) = 13.7 nM


Selectivity of Uptake Inhibitors

SNRI's

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<tr>
<td></td>
<td>0.0018</td>
<td>0.0054</td>
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<tr>
<td>Talopram</td>
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<td></td>
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<tr>
<td>Nisoxetine</td>
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SSRI's

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<tr>
<td></td>
<td>3 400</td>
<td>54</td>
</tr>
<tr>
<td>Citalopram</td>
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<tr>
<td>Fluoxetine</td>
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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

Lotrafiban (SB 214 857)
- $K_i$ GPIIb/IIIa = 2.5 nM
- $K_i$ $\alpha\nu\beta3$ = 10,340 nM

SB 223 245
- $K_i$ GPIIb/IIIa = 30,000 nM
- $K_i$ $\alpha\nu\beta3$ = 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 (antidote in intoxication)

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

tifluadom
- (opiate $\kappa$ agonist, $IC_{50} = 12$ nM)

The Concept of „Privileged Structures“


Different Modes of Action of Chemically Similar Molecules

promethazine (H₁ antagonist)
chlorpromazine (dopamine antagonist)
a, R = CH₃, 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)
Anticholinergics

Antipsychotics, SSRIs, etc.
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

\[
\begin{align*}
\text{minaprine (antidepressant)} & \quad K_i \text{ AChE} = 10 \text{ nM} \\
\text{K]i musc M}_1 & = 3 \text{ nM}
\end{align*}
\]


"Selective Optimization of Side Activities"

β-blocker prototype  viloxacine antidepressant  propafenone 1c antiarrhythmic  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