Structure based drug design and LIE models for GPCRs

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The $\beta_2$-adrenergic receptor
- Docking against $\beta_2$AR
- Ligands
- Ligand Efficacy

LIECE
- The approach
- Earlier examples
- LIECE for $\beta$-adrenergic receptors

Conclusions
T4-lysozyme → (for stability)

Cerezov et al.,
Science 318:1258-1265

Rosenbaum et al.,
Science 318:1266-1273
Cerezov et al.,
Science 318:1258-1265
Rosenbaum et al.,
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Cerezov et al.,
Science 318:1258-1265
Rosenbaum et al.,
Science 318:1266-1273
A beautiful binding site
- Calculations were done with DOCK 3.5.54.
- Docking spheres were distributed based on the positions of the heavy atoms of carazolol and slightly altered to achieve more uniform coverage.
- The T4-lysozyme insertion was removed, as it carried a net charge of +9.
- We docked the lead-like subset of the ZINC database, which contains about 1M molecules.
Four classes of substrates have been predicted:

- “classic” compounds with all canonical pharmacophoric features of antagonists.
- “bridge” compounds connecting the two walls of the binding pocket (Thr195 to Tyr308).
- sulfonamide compounds.
- others.

We managed to acquire 12, 9, 2 and 2 compounds of each class, respectively.
Results

- Classic compounds: 4 hits.
- Bridge compounds: 0 hits.
- Sulfonamides: 0 hits.
- Others: 2 hits.

6 hits out of 25 tested → 24% hit rate
The six hits

1. 0.009 μM, rank 6
2. 2.0 μM, rank 37
3. 0.47 μM, rank 42
4. 0.75 μM, rank 104
5. 1.1 μM, rank 97
6. 3.2 μM, rank 156

Kolb et al. PNAS, accepted.
The six hits

1. **1** 0.009 µM  
   rank 6

2. **2** 2.0 µM  
   rank 37

3. **3** 0.47 µM  
   rank 42

4. **4** 0.75 µM  
   rank 104

5. **5** 1.1 µM  
   rank 97

6. **6** 3.2 µM  
   rank 156

Kolb et al. PNAS, accepted.
For comparison: five $\beta_2$ antagonists

ICI 118551
Carvedilol
Carazolol
CGP 20712A
Alprenolol
The hits are all inverse agonists
The search for hay in a haystack

- GPCRs
- kinases
- proteases
- LGICs
- β2AR
- β-lactamase

% of library with significant assignment

Number of molecules with significant assignment

National Meeting, March 24, 2009 – p.13/26
LIECE

\[
\Delta G_{\text{bind}} \approx \alpha \cdot \Delta E^{vdW} + \beta \cdot \Delta E^{elec} + \gamma \\
\Delta E = E_{\text{complex}} - (E_{\text{protein}} + E_{\text{ligand}}) \text{ by CHARMM.}
\]

\[
\Delta E^{elec} = \Delta E^{coul} + \Delta G^{solv}
\]

\(\Delta G^{solv}\) is calculated with the PBEQ solver in CHARMM. Known inhibitors are needed to calibrate \(\alpha, \beta\) and \(\gamma\).
<table>
<thead>
<tr>
<th>protein</th>
<th>α</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-secretase</td>
<td>0.2737</td>
<td>0.1795</td>
</tr>
<tr>
<td>standard deviation</td>
<td>±0.0395</td>
<td>±0.0461</td>
</tr>
<tr>
<td>HIV1-PR</td>
<td>0.1690</td>
<td>0.0168</td>
</tr>
<tr>
<td>standard deviation</td>
<td>±0.0196</td>
<td>±0.0199</td>
</tr>
</tbody>
</table>

Two proteases, yet clearly different coefficients → parameters are not transferable, right?
[The human kinome]
For kinases, parameters seem to be transferable. Consequently, we tried to derive a “universal model”.

<table>
<thead>
<tr>
<th>protein</th>
<th>α</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK2</td>
<td>0.2866</td>
<td>0.0520</td>
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<tr>
<td>standard deviation</td>
<td>±0.0171</td>
<td>±0.0183</td>
</tr>
<tr>
<td>Lck</td>
<td>0.2735</td>
<td>0.0046</td>
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<tr>
<td>standard deviation</td>
<td>±0.0182</td>
<td>±0.0237</td>
</tr>
<tr>
<td>P38</td>
<td>0.2699</td>
<td>0.0264</td>
</tr>
<tr>
<td>standard deviation</td>
<td>±0.0210</td>
<td>±0.0170</td>
</tr>
</tbody>
</table>
\[ \Delta G_{calc} = 0.2898 \cdot \Delta E_{vdW} + 0.0442 \cdot (\Delta E_{coul} + \Delta G_{solv}) \]

Kolb et al. J Med Chem 51:1179-1188
## Kinase hits

<table>
<thead>
<tr>
<th>compound</th>
<th>structure</th>
<th>enzymatic assays</th>
<th>cell-based assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MW [Da]</td>
<td>IC$_{50}$ [µM]</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>349</td>
<td>76</td>
</tr>
<tr>
<td>2-8</td>
<td><img src="image2.png" alt="Structure 2-8" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| R=       |          |          |          |          |          |          |          |
| 2        | −(CH$_2$)$_4$OH | 353 | 1.4, 1.8 | 6.8 | 5.6, 7.9 | neg. | -11.0 |
| 3        | −(CH$_2$)$_3$CH$_3$ | 337 | 1.5, 1.5 | 8.3 | n.d. | neg. | -10.7 |
| 4        | −(CH$_2$)$_2$CH$_3$ | 323 | 1.9 | n.d. | n.d. | neg. |          |
| 5        | ortho-methoxy-phenyl | 387 | 27 | n.d. | n.d. | 14% @ 20 µM |          |
| 6        | −(CH$_2$)$_3$OCH$_3$ | 353 | 50 | n.d. | n.d. | 28% @ 20 µM |          |
| 7        | −(CH$_2$)$_2$Ph | 385 | 30% @ 14 µM$^{c}$ | n.d. | n.d. | 34% @ 20 µM |          |
| 8        | −(CH$_2$)$_2$-meta-methylphenyl | 399 | 29% @ 5 µM$^{c}$ | n.d. | n.d. | 14% @ 20 µM |          |
LIECE for GPCRs
What we used for $\beta_2$AR

- 7 ligands, all enantiopure, from Dallanoce et al., BMC 14, 4393.
- 20 ligands that belong to the “well-known” set of antagonists (all $S$) and are described in Baker et al.

Issues on the ligand side:
- chirality
- conformational flexibility
- different efficacies
\[ \Delta G_{\text{pred}} = 0.4584 \cdot \Delta E_{\text{vdW}} + 0.1780 \cdot \Delta E_{\text{coul}} + 0.2047 \cdot \Delta G_{\text{solv}} \]

\[ q^2 = 0.6639 \]

\[ \text{RMSE} = 1.23 \ \text{kcal/mol} \]
$\Delta G_{pred} = 0.4584 \cdot \Delta E_{vdW} + 0.1780 \cdot \Delta E_{coul} + 0.2047 \cdot \Delta G_{solv}$

$q^2 = 0.6639$

$RMSE = 2.24 \text{ kcal/mol}$
A combined model for $\beta_1$AR and $\beta_2$AR

\[
\Delta G_{\text{pred}} = 0.3806 \cdot \Delta E_{\text{vdW}} + 0.1424 \cdot \Delta E_{\text{coul}} + 0.1576 \cdot \Delta G_{\text{solv}}
\]

$q^2 = 0.5542$

$RMSE = 1.40 \text{ kcal/mol}$

$RMSE = 1.75 \text{ kcal/mol}$
Docking to the $\beta_2$-adrenergic receptor worked nicely . . .
- . . . we get a high hit rate (24%) with one potent binder.
- . . . we see two previously unexplored scaffolds.
- . . . some of it is due to the bias in present-day libraries.

LIECE models for GPCRs are difficult because . . .
- . . . the receptors are rather flexible and there are at least two distinct states (activated/inactivated) $\neq$ rigid receptor.
- . . . most molecules are chiral and flexible.
- We get reasonably predictive models, however.
- VdW is still the most important contribution, but electrostatics is similar.