Chemical properties that affect binding of enzyme-inhibiting drugs to enzymes

Research proposal by Dan Nacu
Global Pharmaceutical Industry

$400,000,000,000
Drug Development

Computer Simulations
How can it be done?

Simulation Models

Shape Complementarity  Chemical Properties
How can it be done?

Chemical Properties

- Solvent Accessible Surface Area
- Hydrophobicity
- Electrostatics
- Van Der Waal’s Forces
- Residue Pair potential
- Desolvation Energies
- Atomic Contact Energies
- Complementary Determining Regions
- etc...

A lot of options...
It's been done before... in a different way.

Li et al, 2007

Their Equation

\[
\text{Score} = w_1 E_{RP} + w_2 E_{ACE} + w_3 E_{\text{attr}} + w_4 E_{\text{rep}} + w_5 E_{\text{sa}} + \ldots
\]
It's been done before... in a different way.

Li et al, 2007

<table>
<thead>
<tr>
<th>Name</th>
<th>Successful structures out of all Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease/Inhibitor</td>
<td>16/17</td>
</tr>
<tr>
<td>Enzyme/Inhibitor</td>
<td>6/6</td>
</tr>
<tr>
<td>Antibody/Antigen</td>
<td>18/19</td>
</tr>
<tr>
<td>Other</td>
<td>11/15</td>
</tr>
</tbody>
</table>
How will this be different?

Introducing HINT

Hydropathic INTeractions

\[ b_{ij} = a_i \ a_j \ S_i \ S_j \ T_{ij} \ R_{ij} + r_{ij} \]

The HINT Equation
Why HINT?

Its more true to life
$b_{ij} = a_i \ a_j \ S_i \ S_j \ T_{ij} \ R_{ij} + r_{ij}$

two atoms

HINT
HINT

\[ b_{ij} = a_i a_j S_i S_j T_{ij} R_{ij} + r_{ij} \]

affinity score for single interaction

All interactions are summed at end
\[ b_{ij} = a_i a_j S_i S_j T_{ij} R_{ij} + r_{ij} \]

- Hydrophobic atom constant \( a_i \) and \( a_j \)
- Hydrophobic character of interaction \( S_i S_j T_{ij} R_{ij} \)
- Sum

\( \text{Log P}_{\text{1-octanol/water}} \)
\[ b_{ij} = a_i a_j S_i S_j T_{ij} R_{ij} + r_{ij} \]
HINT

\[ b_{ij} = a_i a_j S_i S_j T_{ij} R_{ij} + r_{ij} \]

Electrostatics

hydrophobic-hydrophobic
hydrophobic-polar
acid-base
hydrogen bond
polar-polar
acid-acid
base-base

returns +1 or -1
HINT

\[ b_{ij} = a_i a_j S_i S_j T_{ij} R_{ij} + r_{ij} \]

Atomic Distance

decreased interaction
HINT

\[ b_{ij} = a_i \ a_j \ S_i \ S_j \ T_{ij} \ R_{ij} + r_{ij} \]

Lennard-Jones Potential

too close  |  too far  |  just right
What can be done?

By weighing each variable in HINT, the most important chemical property for enzyme/inhibitor complexes can be found.

\[ b_{ij} = (a_i a_j)^w (S_i S_j)^w (T_{ij})^w (R_{ij})^w + (r_{ij})^w \]

Why exponents?
Why exponents?

Li et al.

\[
\text{Score} = w_1 E_{RP} + w_2 E_{ACE} + w_3 E_{\text{attr}} + w_4 E_{\text{rep}} + w_5 E_{\text{ele}} \\
+ w_6 E_{\text{ele}} + w_7 E_{\text{la}} + w_8 E_{\text{lr}},
\]

HINT

\[
b_{ij} = (a_i a_j)^w (S_i S_j)^w (T_{ij})^w (R_{ij})^w + (r_{ij})^w
\]
Overview of Experiment

Benchmark 5 PDB File

Modified Equation

Similarity to True-Structure

Decision
What's the experiment?

Start with 46 enzyme inhibitor complexes from the Benchmark 5.
What's the experiment?

Bound

FTDock

Unbound

What's FTDock?
FTDock

Rotation & translation in 3D space to find all possible configurations.

product 1  product 2  product 3  product 4  etc...
What’s the experiment?

FTDock

Huge list of possible complexes
What's the experiment?

Huge list of possible complexes

L_RMSD Testing

Ligand_Root-Mean-Square-Deviation

What's L_RMSD Testing?
L_RMSD Testing

$$\sqrt{\sum_{\text{total # of atoms}} (\text{atom } x_1 - \text{atom } x_2)^2}$$
What’s the experiment?

L_RMSD Testing

Top 20 Structures
What’s the experiment?

Top 20 Structures

For 46 complexes = 920 simulated structures.
For both bound and unbound, 1,840 total

Let’s look at just one
What's the experiment?

20 Possible complexes

5 Testable Variables

- $a$
- $S$
- $T$
- $R$
- $r$

5 Possible Exponents

- 0
- 0.5
- 1
- 1.5
- 2

Why these exponents?
What’s the experiment?

In the end...

23,000 HINT Scores for Bound
23,000 HINT Scores for Unbound

6,325,000 scores

46\times20\times5\times5 = 23,000
What’s the experiment?

Highest 50 HINT Scores for each complex

L_RMSD Testing

Find best match for each complex
Interpreting result

Enzyme-Inhibitor Simulated Complex

Best L_RMSD Score: 4 Å

HINT weight used: \( b_{ij} = a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij} \)

Electrostatics
## Possible Results

<table>
<thead>
<tr>
<th>Complex</th>
<th>Final L_RMSD Score</th>
<th>Weighing Used</th>
<th>Significant Chemical Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Bound</td>
<td>4 Å</td>
<td>$a_i a_j (S_i S_j)^{1.5} T_{ij} R_{ij} + r_{ij}$</td>
<td>Solvent Accessible Surface Area</td>
</tr>
<tr>
<td>#1 Unbound</td>
<td>6 Å</td>
<td>$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$</td>
<td>Electrostatics</td>
</tr>
<tr>
<td>#2 Bound</td>
<td>2 Å</td>
<td>$a_i a_j S_i S_j T_{ij} (R_{ij})^{0.5} + r_{ij}$</td>
<td>Atomic Distance</td>
</tr>
<tr>
<td>#2 Unbound</td>
<td>4 Å</td>
<td>$a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij}$</td>
<td>Electrostatics</td>
</tr>
<tr>
<td>#3 Bound</td>
<td>3 Å</td>
<td>$a_i a_j (S_i S_j)^{1.5} T_{ij} R_{ij} + r_{ij}$</td>
<td>Solvent Accessible Surface Area</td>
</tr>
<tr>
<td>#3 Unbound</td>
<td>5 Å</td>
<td>$a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij}$</td>
<td>Electrostatics</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>#46 Bound</td>
<td>2 Å</td>
<td>$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$</td>
<td>Electrostatics</td>
</tr>
<tr>
<td>#46 Unbound</td>
<td>6 Å</td>
<td>$(a_i a_j)^{0.5} S_i S_j T_{ij} R_{ij} + r_{ij}$</td>
<td>Hydrophobic Atom Constant</td>
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### Possible Results

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<td>$a_i a_j (S_i S_j)^1 T_{ij} R_{ij} + r_{ij}$</td>
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<td>$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$</td>
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In the future...

Different models (besides HINT)
Different complexes (besides enzyme/inhibitor)
Questions?
Extras
Electrostatics Table

Table 1. Tij interaction matrix

<table>
<thead>
<tr>
<th>Atom Type</th>
<th>H (apolar) [a &gt; 0]</th>
<th>H (polar) [a &gt; 0]</th>
<th>C (apolar) [a &gt; 0]</th>
<th>Polar (N, O, etc.) [a &lt; 0]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (apolar) [a &gt; 0]</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>H (polar) [a &gt; 0]</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>C (apolar) [a &gt; 0]</td>
<td>+1</td>
<td>-1</td>
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<td>+1</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
</tr>
</tbody>
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Notes: green: hydrophobic-hydrophobic; red: hydrophobic-polar; blue: acid-base or hydrogen bond; yellow: polar-polar (horizontal stripes: acid-acid, vertical stripes: base-base).

1 By convention, all hydrogen atoms have a > 0 [13].