Paths to drug discovery and the role of computational chemistry

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Dec, 2013
TUM
My research lines

From enzymatic function to drug discovery

www.devivolab.org
My research lines

- From basic to applied science -

✓ Computational Enzymology – Reaction mechanism

✓ From enzymatic function to mechanism of inhibition

✓ Structure-Based Drug Discovery
Topics of the day

1. The process of Drug Discovery & Development

2. Computational Drug Design
   Structure-based Drug Design
Enzymes and catalytic activity

Protein substrate

Catalytic function

Pocket

Protein target
Protein binding and inhibition

Small molecules

Pocket

Great binder!

Protein target
Drug design

From a good inhibitor to a potential drug
Drug design

Similar binding but DIFFERENT properties!
Small molecules drugs

- **Prozac** (antidepressant)
- **Abilify** (antipsychotic)
- **Plavix** (antiplatelet agent)
- **Cymbalta** (pain and anxiety)
- **Etoposide** (cancer)
- **Nexium** (gastric acid)
- **Gleevec** (cancer)
- **Lipitor** (Cholesterol)
- **Ibuprofen** (inflammation)
- **Viagra** (erectile dysfunction)
"Is there really a case where a drug that’s on the market was designed by a computer?"

When asked this, I invoke the professorial mantra ("All questions are good questions.")], while sensing that the desired answer is "no". Then, the inquisitor could go back to the lab with the reassurance that his or her choice to avoid learning about computational chemistry remains wise. The reality is that the use of computers and computational methods permeates all aspects of drug discovery today. Those who are most proficient with the computational tools have the advantage for delivering new drug candidates more quickly and at lower cost than their competitors.
The Many Roles of Computation in Drug Discovery

William L. Jorgensen

SCIENCE  VOL 303  19 MARCH 2004

"Is there really a case where a drug that's on the market was designed by a computer?"

However, the phrasing of the question suggests misunderstanding and oversimplification of the drug discovery process (..) It is inconceivable that a human with or without computational tools could propose a single chemical structure that ends up as a drug; there are far too many hurdles and subtleties along the way.
What is a Target: any bio-macromolecule (e.g., enzymes or channels)

Target Identification aims to determine a biological macromolecule that is related to the development or to the life cycle of a certain pathology

Target validation aims to establish the link between inhibition/modulation of the target activity and the potential cure of the disease.
- Tricky issue: different “levels” of validation.
NEWS & ANALYSIS
Reliability of ‘new drug target’ claims called into question

Bayer halts nearly two-thirds of its target-validation projects because in-house experimental findings fail to match up with published literature claims, finds a first-of-a-kind analysis on data irreproducibility.

Asher Mullard

NATURE REVIEWS | DRUG DISCOVERY
VOLUME 10 | SEPTEMBER 2011 | 643
Ligand-target affinity

How do we measure it ???
What is a Hit: small-molecule inhibitor with low affinity for the target

Inhibitory Concentration (IC)\textsubscript{50}: The half maximal inhibitory concentration
Drug Discovery & Development

Drug Discovery process

What is a Hit: small-molecule with low (but promising!) affinity for the target

Relationship between \( K_i \) and \( IC_{50} \) (Cheng-Prusoff equation):

\[
K_i = \frac{IC_{50}}{[1 + \frac{[S]}{K_M}]} \quad \text{For competitive inhibitors}
\]

\([S] = \text{Substrate concentration}\)

When \([S] \approx 0 \Rightarrow K_i \approx IC_{50}\)

Hit compounds have low affinity (or IC50) - \(~10-1 \mu M\)
Drug Discovery & Development

Drug Discovery process

Target Discovery  Hit Identification  Hit-to-Lead  Lead Optimization  Preclinical Development  Drug Candidate

Methods for hit identification:
- High Throughput Screening (HTS)
- NMR screening
- Crystallography
- Computational methods

Required:
- Assay development

Goal: identify possible active “scaffolds”
Drug Discovery & Development

Drug Discovery process

Target Discovery → Hit Identification → Hit-to-Lead → Lead Optimization → Preclinical Development → Drug Candidate

What is a scaffold: the simplest substructural element of a molecule

The scaffold often represents the “core” of the molecule, and it greatly affects the physicochemical properties of the molecule (for instance, solubility).

For this reason, DIVERSITY in screening is the KEY.

Source: Scaffold composition and biological relevance of screening libraries
Drug Discovery process

Example, a good hit:

Melanocortin 4 receptor (MC4R)
Millennium Pharmaceuticals & Abbot

\[
Ki = 2.7 \ \mu M
\]

Vos, TJ et al. 2004 J Med Chem 47 1602 - 04
Drug Discovery & Development

Drug Discovery process

Target Discovery > Hit Identification > Hit-to-Lead > Lead Optimization > Preclinical Development > Drug Candidate

**What is a Lead:** a compound with improved affinity for the target

**Methods for hit-to-lead:**
- Medicinal chemistry
- Computational methods
- Crystallography
- In vitro testing

Lead compounds have high affinity (or IC50) - < 1 μM or better

**Goals:**
1. improve compound activity (better affinity)
2. create series of active compounds

**Series of compounds:** compounds sharing the same scaffold.
What is a Lead: a compound with improved affinity for the target

\[ Y = \text{CH}_2, \text{S are equivalent; two atoms linker is optimal} \]

In \( A \), substitutions are tolerated only in \( 3' \)

In \( B \), cyclic amidine is necessary; \( R = \text{H}, \text{alkyl are equivalent; } n = 1,0 \text{ are equivalent} \)

\[ R \]

\[ \text{Vos, TJ et al. 2004 J Med Chem 47 1602 - 04} \]
Drug Discovery & Development

Drug Discovery process

Target Discovery → Hit Identification → Hit-to-Lead → Lead Optimization → Preclinical Development

What is a Lead: a compound with improved affinity for the target

**MC4R Antagonist Lead**

Ki = 2.7 μM → Potency improved almost two orders of magnitude → Ki = 0.04 μM

Vos, TJ et al. 2004 J Med Chem 47 1602 - 04
Drug Discovery & Development

Drug Discovery process

**Example:** non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs).

![Chemical structures and image](image)

Optimization of Azoles as Anti-Human Immunodeficiency Virus Agents Guided by Free-Energy Calculations
Jorgensen W et al
J. AM. CHEM. SOC. **2008**, 130, 9492–9499
Best leads are optimized in terms of their drug-likeness: Improved affinity is coupled with a promising pharmacokinetic (PK) profile.

PK includes ADMET characterization:

- **Absorption** (e.g., bioavailability, F)
- **Distribution** (e.g., binding to serum proteins)
- **Metabolism** (metabolites, e.g., cytochrome P450)
- **Excretion** (kidneys system)
- **Toxicity** (e.g., Affinity towards h-ERG)

The route of administration (e.g., intravenous, oral) and the site of action of the drug (e.g., brain, skin, organs) critically influence the desired ADMET profile.
**Drug Discovery & Development**

**Drug Discovery process**

- Target Discovery
- Hit Identification
- Hit-to-Lead
- Lead Optimization
- Preclinical Development

**Methods for lead optimization:**
- Computational methods
- Medicinal chemistry
- Crystallography
- In vitro testing
- In vivo testing *(key for lead optimization)*

**Additional issue:**
*Target specificity* – Assays development involved.

**Ultimately:**
Lead optimization aims to develop and identify promising compounds within a given series of compounds suitable for preclinical development.
Drug Discovery & Development

Drug Discovery process

Target Discovery → Hit Identification → Hit-to-Lead → Lead Optimization → Preclinical Development → Drug Candidate

**MC4R Antagonist Lead**

![Chemical structure of MC4R Antagonist Lead](image)

\[ \text{Ki} = 0.04 \, \mu \text{M} \]

**ML00253674**

![Chemical structure of ML00253674](image)

\[ \text{Ki} = 0.16 \, \mu \text{M} \text{ but BETTER PK profile!} \]

Vos, TJ et al. 2004 J Med Chem 47 1602 - 04

Marsilje, T et al. 2004 Bioorg Med Chem Letters 14 3721 - 3725
Drug Discovery & Development

Drug Discovery process

Goals:
1. determination of the lead’s ultimate safety profile.
2. determination of a safe starting dose of the drug for clinical trials

Methods:
- Synthetic chemistry (scale up)
- Further in vivo pharmacology
- Further Tox/safety Pharmacology
Drug Discovery & Development

Drug Discovery process

Target Discovery  >  Hit Identification  >  Hit-to-Lead  >  Lead Optimization  >  Preclinical Development  >  Drug Candidate

Drug Candidate:
Winner molecule.
Molecule that will be moved into clinical trials.
(tough decision… big gamble…)

Note:
For those scientists involved in drug discovery research, to contribute to the creation of a drug candidate is a great achievement.
Although getting a drug out if it… would make it better … 😊
Computational Drug Design

Two approaches:

✧ **Structure-Based Drug Design - SBDD**

Drug design based on the interaction of the ligand with the 3D dimensional structure of the receptor.

✧ **Ligand-Based Drug Design - LBDD**

Unknown structure of the receptor.

Drug design based on the key features of active compounds.

Hypothesis:

Ligands similar to an active ligand are more likely to be active than random ligands. *(pharmacophore models)*
Computational Drug Design

Approaches and methods:

✧ Structure-Based Drug Design - SBDD

Docking (Glide, Dock, Autodock, ICM… etc)
Kitchen D., Nat. Review Drug Discovery Vol. 3 Nov. 2004

De novo design (BOMB, SMoG, BREED.. etc)

✧ Ligand-Based Drug Design - LBDD

Quantitative Structure-Activity Relationship (QSAR)

Ligand similarity approaches (2D or 3D)
Computational methods

Quantum Mechanics (QM) (Wave Function based)

Advantages:
- Electronic Structure
- Optimize structures
- Compute energy profiles
- HOMO/LUMO
- Excited state
- etc...

Disadvantages:
- Computationally expensive
- Small system size

Molecular Mechanics (MM) (Force field based)

Advantages:
- Large systems
- Stability (RMSD)
- Flexibility (in Binding)
- Diffusion
- Structure refinement
- etc...

Disadvantages:
- Limited reactivity
- Limited accuracy

The Nobel Prize in Chemistry 2013

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems".

[Images of Martin Karplus, Michael Levitt, and Arieh Warshel]
THE FORCE FIELD
Molecular Mechanics

Each atom, a sphere with a given mass and charge. Each bond, a spring.

Force Field equation *(Potential of the inter- and intra- atomic interaction):*

\[
E_{MM} = \sum_{\text{bonds}} K_r (r - r_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)]
\]

\[
+ \sum_{i<j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\varepsilon R_{ij}} \right].
\]

- Based on physics, but uses simplified “ball-and-spring” models (classical physics, Newton equation)
- FF are empirical, i.e. calibrated to describe the quantum nature of chemical bonds and short-range interactions
THE FORCE FIELD
Molecular Mechanics

A parameter file

- atom types

```
PARM99 for DNA,RNA,AA, organic molecules, TIP3P water, Polariz. & LP incl. 02/04/99
C 12.01 0.516 sp2 C carboxyl group
CA 12.01 0.360 sp2 C pure aromatic (benzene)
CE 12.01 0.360 sp2 aromatic C, 5 & 6 membered ring junction
CC 12.01 0.360 sp2 aromatic C, 5 memb. ring HIS
CD 12.01 0.360 sp2 C atom in the middle of: C-CD-CD-C
CK 12.01 0.360 sp2 C 5 memb. ring in purines
CM 12.01 0.360 sp2 C pyrimidines in pos. 5 & 6
CN 12.01 0.360 sp2 C aromatic 5/6 memb. ring junct. (TRP)
CO 12.01 0.360 sp2 C in 5 memb. ring of purines between 2 N
CR 12.01 0.360 sp2 C atos as CO but in HIS
CT 12.01 0.376 sp3 aliphatic C
CV 12.01 0.360 sp2 arom. 5 memb. ring w/ 1 N and 1 H (HIS)
CV 12.01 0.360 sp2 arom. 5 memb. ring w/ 1 N-H and 1 H (HIS)
C* 12.01 0.360 sp2 arom. 5 memb. ring w/ 1 subst. (TRP)
CY 12.01 0.360 nitrile C (Howard et al. JCC, 16, 243, 1995)
CZ 12.01 0.360 sp C (Howard et al. JCC, 16, 243, 1995)
CG 40.08 calcium
H 1.008 0.161 H bonded to nitrogen atoms
HC 1.008 0.135 H aliph. bond. to C without electrd. group
HI 1.008 0.135 H aliph. bond. to C with 1 electrd. group
```

AMBER FF (parm99)

THE FORCE FIELD
Molecular Mechanics

A parameter file

• bond types

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<td>0.9572</td>
<td>! TIP3P water</td>
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<td>HW-HW</td>
<td>553.0</td>
<td>1.5136</td>
<td>TIP3P water</td>
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<td>C-C</td>
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<td>1.525</td>
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<td>C-CA</td>
<td>469.0</td>
<td>1.409</td>
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<td>C-CB</td>
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<td>1.444</td>
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<td>C-CT</td>
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<td>JCC,7,(1986),230; AA</td>
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<td>JCC,7,(1986),230; CYT</td>
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• angle types

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<td>104.52</td>
<td>TIP3P water</td>
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<tr>
<td>HW-HW-OW</td>
<td>0.0</td>
<td>127.74</td>
<td>(found in crystallographic water with 3 bonds)</td>
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<td>126.00</td>
<td>Jummei et al, 1999 acrolein</td>
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<td>C-C-OH</td>
<td>80.0</td>
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<td>Jummei et al, 1999</td>
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<td>changed from 85.0 bsd on C=H6 rmode; AA</td>
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<td>CA-C-OH</td>
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<td>126.00</td>
<td>AA (not used in tyr)</td>
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<td>NA</td>
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<td>126.80</td>
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<td>CH-C-NA</td>
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<td>114.10</td>
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<td>117.00</td>
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**Structure-Based Drug Design**

**MUST:** 3-dimensional structure of the target.

Sources of structures:
1. Crystallography
2. NMR structures
3. Homology structures
Structure-Based Drug Design

**MUST:** 3-dimensional structure of the target.

Sources of structures:
1. Crystallography
2. NMR structures
3. Homology structures

Average of multiple structures
Structure-Based Drug Design

**MUST:** 3-dimensional structure of the target.

Sources of structures:
1. Crystallography
2. NMR structures
3. Homology structures

AAB24882

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TYHMCQFHCRYVNNHSGEKLYECNERSKAFCSPSHLQCHKRRQIGEKTHEHNQCGKAFFT
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60

AAB24881

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---------------------YECNQCGKAFAQHSSLKCHYKTHIGEKPYEHNQCGKAFSK
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40

AAB24882

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```

116

AAB24881

```
HSHLQCHKRTHTGEKPYEHNQCGKAFSQHGLQRHKTHTGEKPYMNVINMVKPLHNS
```

98
Docking

Molecule

Target
Ligand Docking

Two problem to solve:
1. Posing (the easy part)
2. Scoring (the tough part)
Ligand Docking - Posing

The posing problem (the easy part):

The posing is a “solved” problem!

Docking methods can place a ligand with great accuracy in a binding pocket, reproducing crystallographic data.

The challenging issue is to rank different poses, according to their score and identify the “best one”.

Docking and scoring in virtual screening for drug discovery: methods and applications
Douglas B. Kitchen et al
Drug Discovery, Vol. 3, Nov 2004
Conformational Sampling – DOCK4.0

**Posing**

**DOCK4.0** is based on an incremental construction algorithm named **anchor and grow**

- Anchor Selection
- Anchor Docking
- Conformation Expansion
- Conformation Pruning

The thoroughness of sampling is enhanced by on-the-fly optimization. The optimization is based on the Simplex minimizer

Ewing T. *et al*, J CAMD 2001 15 411-428
CONTRIBUTIONS TO BINDING AFFINITY

**Electrostatic Contribution**
- H-bonds
- Salt-Bridges
- $\pi - \pi$ interactions, $\pi - \text{cation}$ interactions
- coordination

**Solvation/Desolvation Effect**
- Water Molecules bridging Ligand and Receptor
- Solvent Entropy

**Loss of Conformational Entropy**
- Roto/Translational Entropy
- Conformational Mobility
Ligand Docking - Scoring

Scoring Functions FOR DOCKING CALCULATIONS:

• Force-Field Based
• Empirical
• Knowledge-based

Consensus Scoring

Consensus scoring are more often applied in Virtual Screening
**www.iit.it**

**Force Field - Scoring**

\[
\Delta G_{\text{bind}} = E_{\text{MM}} - T\Delta S_{\text{solute}} + \Delta G_{\text{solvent}}
\]

\[E_{\text{MM}} \text{ from } \text{FF:}\]

\[E_{\text{MM}} = \sum_{\text{bonds}} K_r (r - r_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\varepsilon R_{ij}} \right].\]

\[\Delta S_{\text{solute}}: \text{The solute entropy consists of four terms, namely translational, rotational, vibrational, and conformational entropy.}\]

\[\Delta g_{\text{solvent}}: \text{The solvent free energy consists of the two terms: 1) a nonpolar and a polar term.}\]
Total energy is given by the sum of energy terms.

For two atoms $i$ and $j$, $A_{ij}$ and $B_{ij}$ are van der Waals parameters for given atom types, $d_{ij}$ is the interatomic distance, $q_i$ and $q_j$ are atomic partial charges, and $\varepsilon (d_{ij})$ is a distance-dependent dielectric function.
Ligand Docking - Scoring

Ligand Binding

The quantitative modeling of receptor – ligand interactions can be achieved by determining the equilibrium binding constant $K_{eq}$. The binding constant $K_{eq}$ is directly related to the Gibbs free energy:

$$\Delta G_{bind} = -RT \ln K_{eq}$$

$$\Delta G_{bind} = \Delta H - T \Delta S = G_{complex} - (G_{receptor} + G_{ligand}).$$

Why it is so difficult to score compounds:

Experimental range of binding affinities: from $10^{-2}$ M (mM) to $10^{-12}$ M (pM)

At $T=298K$ the enthalpic contribution to the $\Delta G_{binding}$ is between -2.4 kcal/mol and -16.7 kcal/mol

In other words, a change in binding (free) energy of ~1.5 kcal/mol alters the binding affinity of one order of magnitude ($T=298$) !!!!
Virtual screening

An exercise carried out by computational means aimed at predicting which molecules from an ensemble will likely display some activity against a target.

VLS is usually implemented as an iterative docking simulation at the target binding site.

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<td>kcal/mol</td>
<td>-37.9</td>
<td>-29.7</td>
<td>-27.3</td>
<td>-9.8</td>
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 MDV
How can we evaluate the virtual screening performance?

**Enrichment factor:**

Example:
Suppose to have 10 active cmpds in a database of 1000 cmpds (1% of active compounds)

Random pick: 1 out of 100 should be active. (1% chance)
Ligand Docking - Scoring

Speed

- Docking
- Virtual Screening
- Etc..

Accuracy

- Molecular Dynamics
- Quantum Mechanics
- Etc..

Marco De Vivo
The difference in free energies of binding for the ligands X and Y then comes from:

\[ \Delta \Delta G_b = \Delta G_x - \Delta G_y = \Delta G_f - \Delta G_c \]
The difference in free energies of binding for the ligands X and Y then comes from:

\[ \Delta \Delta G_b = \Delta G_x - \Delta G_y = \Delta G_f - \Delta G_c \]
**Structure-based drug design**

**From hit to lead**

**Example:** non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs).

**HIT**

![Chemical structure](image)

**EC**$_{50}$ = 5 µM

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<th>X</th>
<th>Y</th>
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Computationally-Guided Optimization of a Docking Hit to Yield Catechol Diethers as Potent Anti-HIV Agents

Jørgensen W et al

**J. MED. CHEM. 2011, 54, 8582–8591**
Structure-based drug design
From hit to lead

Example: non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs).

**HIT**

\[
\text{EC}_{50} = 5 \ \mu\text{M}
\]

**Lead**

\[
\text{EC}_{50} = 55 \ \text{pM}
\]

Computationally-Guided Optimization of a Docking Hit to Yield Catechol Diethers as Potent Anti-HIV Agents
Jorgensen W et al
J. MED. CHEM. 2011, 54, 8582–8591
Crystal Structures of HIV-1 Reverse Transcriptase with Picomolar Inhibitors Reveal Key Interactions for Drug Design

Kathleen M. Frey,† Mariela Bollini,† Andrea C. Mislak,† José A. Cisneros,† Ricardo Gallardo-Macias,† William L. Jorgensen,*† and Karen S. Anderson*†

†Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, United States
‡Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06520-8066, United States

Crystal Structures of HIV-1 Reverse Transcriptase with Picomolar Inhibitors Reveal Key Interactions for Drug Design

Jorgensen W et al
J. Am. Chem. Soc. 2012, 134, 19501

EC$_{50} = 55$ pM

X-Ray structure (HIV-1 RT)
Structure-Based Drug Design

**Step 1**
- Binding design - new inhibitors
  - X-ray Structure
  - X-ray Structure refinement
  - Compound (De novo) Design
  - Synthesis
  - In vitro test

**Step 2**
- From inhibitors to drugs
  - Computed ADME profile
  - SAR with experiments
  - Hypothesis generation & Determination of key descriptors
  - Predictive statistical model
  - Compound design (optimization)
  - Synthesis and test
Drug-likeness (‘druggability’)

When is a compound drug-like?

Lipinski’s Rule of Five
1. Not more than 5 hydrogen bond donors (NH, OH groups)
2. Not more than 10 hydrogen bond acceptors (N and O)
3. A molecular weight under 500
4. An octanol-water partition coefficient less than 5 (logP < 5)

\[
\text{Log } P_{\text{oct/wat}} = \log \left( \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{water}}} \right)
\]

\[
\text{Log } P_{\text{oct/wat}} = 0 \text{ ration 1:1 oct/wat}
1 \text{ ration 10:1 oct/wat}
-1 \text{ ration 1:10 oct/wat}
\]


“The rule of five was not intended to be a metric to distinguish drugs from non-drugs; rather, the aim was to help improve the probability of success.”

“An Audience with… Chris Lipinski”
NATURE REVIEWS | DRUG DISCOVERY
DEC 2012 | VOLUME 11
Drug-likeness (‘druggability’)  

When is a compound drug-like?

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$$\text{Log } P_{\text{oct/wat}} = \log \left( \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{water}}} \right)$$

- Log $P_{\text{oct/wat}} = 0$  ration 1:1 oct/wat
- 1  ration 10:1 oct/wat
- -1  ration 1:10 oct/wat

Several exceptions!
For instance: Macrolides (antibiotics) are good drugs, but do not comply with the Lipinski’s Rule of five!

Drug-likeness (‘druggability’)

ARTICLES
PUBLISHED ONLINE: 24 JANUARY 2012 | DOI: 10.1038/NCHEM.1243

Quantifying the chemical beauty of drugs

G. Richard Bickerton¹, Gaia V. Paolini², Jérémy Besnard¹, Sorel Muresan³ and Andrew L. Hopkins¹*

\[
\text{QED}_w = \exp \left[ \frac{W_{MW} \ln d_{MW} + W_{ALOGP} \ln d_{ALOGP}}{W_{MW} + W_{ALOGP}} + \frac{W_{HBA} \ln d_{HBA} + W_{HBD} \ln d_{HBD}}{W_{HBA} + W_{HBD}} + \frac{W_{PSA} \ln d_{PSA} + W_{ROT} \ln d_{ROT}}{W_{PSA} + W_{ROT}} + \frac{W_{AROM} \ln d_{AROM} + W_{ALERTS} \ln d_{ALERTS}}{W_{AROM} + W_{ALERTS}} \right]
\]

A bit more elaborated…
Inflammation and pain

- Tens of millions of people afflicted worldwide
- Current therapies have major limitations (gastric lesions, kidney damage, vascular events, CNS penetration related issues)
- A number of inflammatory/pain pathways exist
- Yet an unmet medical need

I. Melnikova, Nature Reviews Drug Discovery 2010, 9, 589
The arachidonic acid pathway

- Among the oldest medicines ever
- Still widely used
- Not always effective
- Several side-effects

The cannabinoid pathway

- Relatively new
- Beneficial effects of CBs stimulation without severe side effects

Multitarget FAAH-Cyclooxygenases (COXs)

- Dual-target Single Compound
- Dual-binding & Inhibition
- Synergistic effect
- Biological response
- Neuropathic and Inflammatory pain treatment
Multitarget FAAH-Cyclooxygenases (COXs)

Similarity in binding pockets

Hydrophilic (light blue) and hydrophobic (orange) isocontour surfaces
From single to dual target inhibitors

Docking COX inhibitors in FAAH

~380 COXs inhibitors from DrugBank and DUD were docked into the structure of FAAH

25 compounds purchased and tested

![Tree based on the pairwise Tanimoto-fingerprint distances between the 25 COX inhibitors tested in the present study. The heat map highlights the distances calculated in the first 5 principal components space (% variance explained > 90%) originating from 10 physico-chemical descriptors (i.e. net charge, MW, LogP, LogS, HBD, HBA, PSA, no. of atoms, no. of rings and no. of rotatable bonds).](image)

![physico-chemical similarity](image)
From single to dual target inhibitor

Carprofen, **ARN0120**

- Known COX inhibitor
- Marketed as Rimadyl® for the treatment of arthritic symptoms in geriatric dogs (available as a racemate)
- Used in humans from 1988 to 1998 (withdrawn after Advil® launch)

<table>
<thead>
<tr>
<th>FAAH IC$_{50}$ (μM)</th>
<th>COX-1 IC$_{50}$ (μM)</th>
<th>COX-2 IC$_{50}$ (μM)</th>
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</thead>
<tbody>
<tr>
<td>79</td>
<td>22</td>
<td>4</td>
</tr>
</tbody>
</table>
FAAH in complex with Carprofen

X-ray crystallography

Unique non-covalent FAAH binding site
Resolution: 2.3 Å

“A binding site for non-steroidal anti-inflammatory drugs in Fatty Acid Amide Hydrolase”
Bertolacci L, …, De Vivo M, Piomelli D, Garau G
De novo drug design

**Modus operandi:**
1. Individuation of key interactions in the binding pocket (binding hypothesis).
2. Evaluations of starting seeds and their interaction with key residues in the pocket.
3. Incremental construction of compounds by screening of fragments as building blocks.
4. CONSTANT interaction with synthetic chemists, in order to build feasible compounds. (for instance, avoid stereo-centers!)
DE NOVO DESIGN produces novel molecular structures FROM SCRATCH, by incremental construction of a ligand model within a model of the receptor or enzyme active site.

**Major advantages:**

1. Investigation of chemical space outside the chemical space contained in a chemical collection/dataset (docking).

2. Optimization of the receptor/ligand interaction with ad-hoc modification of the ligand.
DE NOVO DESIGN produces novel molecular structures FROM SCRATCH, by incremental construction of a ligand model within a model of the receptor or enzyme active site.

**Major limitations:**

1. The number of chemically feasible, drug-like molecules has been estimated to be in the order of $10^{60}$–$10^{100}$. **Huge chemical space!**

2. Is there an available route for synthesis to make the promising compounds?
Improving the affinity

- **De novo design using BOMB**
  - Starting point for step-wise growth and decorations

- Solution 1 -> Score
- Solution 2 -> Score
- Solution 3 -> Score
- ...
- ..
- Solution n -> score

BOMB 2.7 and MCPRO 2.1, Prof. W. Jorgensen, Yale
Improving the affinity

- De novo design using BOMB
  - Starting point for step-wise growth and decorations

BOMB 2.7 and MCPRO 2.1, Prof. W. Jorgensen, Yale
## De novo design using BOMB

- Starting point for step-wise growth and decorations

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# 811 cyclopropyl

cyclopropyl benzene

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bond 0016-0017

conformer 1

| 15 | H   | 140 | 140 | 1.088498 | 3   | 113.999882 | 4   | 60.000000 |

conformer 2

| 15 | H   | 140 | 140 | 1.088498 | 3   | 113.999882 | 4   | 60.000000 |

# 812 C(C(H)3)

1-butyl benzene

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```

BOMB 2.7 and MCPRO 2.1, Prof. W. Jorgensen, Yale
SAR exploration around ARN0120

Cl essential for COX activity

\[ \text{ARNO120} \]

COOH essential for COX activity

alkyls, acyls, ureas, carbamates, sulfonamides

Most chemical functions are tolerated on FAAH

COX activity is highly dependant on the substitution

\[ \text{ARNO426} \]

FAAH : IC\(_{50}\) 22 µM

COX-1 : IC\(_{50}\) 74 µM

COX-2 : IC\(_{50}\) 72 µM
SAR exploration around ARN0426

- Change the position of Cl on the pendant phenyl ring
- Replace Cl by another atom/group
- Identify alternative pendant rings

**ARN0426**

- FAAH: IC<sub>50</sub> 22 μM
- COX-1: IC<sub>50</sub> 74 μM
- COX-2: IC<sub>50</sub> 72 μM

**ARN1406**

- FAAH: IC<sub>50</sub> 20 μM
- COX-1: inactive
- COX-2: inactive

**ARN1313**

- FAAH: IC<sub>50</sub> 60 μM
- COX-1: inactive
- COX-2: inactive

**ARN2579**

- FAAH: inactive
- COX-1: inactive
- COX-2: inactive
We identified multitarget inhibitors that block simultaneously FAAH, COX-1 and COX-2 activities, which are among the most active dual FAAH/COX inhibitors so far reported.

![Chemical structures of ARN0120, ARN0426, and ARN1421](image)

**ARN0120**
- FAAH: IC$_{50}$ 79 µM
- COX-1: IC$_{50}$ 22 µM
- COX-2: IC$_{50}$ 4 µM

**ARN0426**
- FAAH: IC$_{50}$ 22 µM
- COX-1: IC$_{50}$ 74 µM
- COX-2: IC$_{50}$ 72 µM

**ARN1421**
- FAAH: IC$_{50}$ 85 µM
- COX-1: IC$_{50}$ 30 µM
- COX-2: IC$_{50}$ >200 µM

*Identification and characterization of carprofen as a multitarget FAAH/COX inhibitor*
Favia AD, .., and De Vivo M
IND:
Investigational New Drug application to the FDA (Food & Drug Administration) containing results of preclinical studies, results of chemical manufacturing controls (including details of active ingredients, stability and purity) and other laboratory results requesting permission to conduct studies in humans.
Drug development process

Drug Discovery & Development

Phase I
- Phase I Clinical Trials:
  20-100 healthy subjects; First-in-man safety studies.

SAFETY!
Drug development process

Phase 1
IND

Phase II

Phase III
NDA

FDA review and approval

Market

Drug Candidate

CLINICAL TRIALS

Phase 2 Clinical Trials:
100-500 subjects; Primary focus is efficacy and includes additional safety and side effect analysis. Dosage guidelines formulated.

Efficacy ! (& Safety)
Drug Discovery & Development

Drug development process

Phase I

Phase II

Phase III

FDA review and approval

Market

IND

NDA

Drug development process

Drug Candidate

Phase I

Phase II

Phase III

CLINICAL TRIALS

IND

NDA

Market

Phase 3 Clinical Trials:
1,000-5,000 subjects; Pivotal trials. Drugs that complete Phase III have ~60% chance of FDA approval. Safety profiles and side effects further studied to establish the benefit-risk relationship.

Efficacy & Safety on Larger Number of Patients
Drug Discovery & Development

Drug development process

Drug Candidate → Phase I → Phase II → Phase III → FDA review and approval → Market

IND

NDA:
Submission of New Drug Application to the FDA Center for Drug Evaluation and Research requesting clearance to market the drug. This application contains information on every patient from the clinical trials, and information on the company’s drug production.
FDA approval for a NME (New Molecular entity)
A new small-molecule drug can be referred to as a NME.
Drug Discovery & Development

Drug development process

Drug Candidate → Phase I → Phase II → Phase III → FDA review and approval → Market

IND → CLINICAL TRIALS → NDA

Example
Drug on the market (ZYVOX)

1 linezolid
Drug on the market (Zyvox)

1993: first synthesis
1995: clinical trials – Phase I
mid-1996: phase II
1998: Phase III
April, 18 2000: FDA approval

Impact on patients:
About 2 million patients in hospitals in U.S. every year find that they have contracted a hospital-acquired or so-called nosocomial infection (including: methicillin-resistant Staphylococcus aureus (MRSA)).

It is estimated that nosocomial infections lead to 90 000 deaths per year in the U.S. and that 70% of these infections are caused by bacterial pathogens.

About 3.7 million patients have been cured with Zyvox since 2000.

Economic return:
Zyvox: ~1 Bn $ only in 2008, (Pfizer).
Drug on the market (Zyvox)

1993: first synthesis
1995: clinical trials – Phase I
mid-1996: phase II
1998: Phase III
April, 18 2000: FDA approval

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It is estimated that nosocomial infections lead to 90 000 deaths per year in the U.S. and that 70% of these infections are caused by bacterial pathogens.

Linezolid (ZYVOX), the First Member of a Completely New Class of Antibacterial Agents for Treatment of Serious Gram-Positive Infections
After the drug is approved and reaches the market:

**Phase 4 Clinical Trials**
Ongoing surveillance for side effects in routine use for as long as the drug remains on the market.

Example:
Vioxx (Merck product for pain relief) was approved by FDA in 1999 and then withdrawn from the market in 2004, for safety concerns.
Drug Discovery & Development

Average time requested for it

Target Discovery | Hit Identification | Hit-to-Lead | Lead Optimization | Preclinical Development | Drug Candidate

Time zero → 1.5 → 1.5 → 2 → 1
(~6 years for discovery)

IND → CLINICAL TRIALS → NDA

Phase I → Phase II → Phase III

1.5 → 2.5 → 2.5 → 1
(~7.5 years for development)

Total time (on average) = ~13.5 years
Drug Discovery & Development

Average cost requested for it

Target Discovery  Hit Identification  Hit-to-Lead  Lead Optimization  Preclinical Development

Drug Candidate

(~820 $ Million for discovery)

IND  CLINICAL TRIALS  NDA

Phase I  Phase II  Phase III

Drug Candidate

(~960 $ Million for development)

Market

Total cost on average = ~1.78 $ Billion for one NME

Source: How to improve R&D productivity: the pharmaceutical industry’s grand challenge
Steven M. Paul, Nat. Review Drug Discovery March Vol. 9 2010
Drug Discovery & Development

- Some facts -

Reasons for attrition of drugs in clinical trials:

In the period 1991 –2000, the highest % of attrition of drug in clinical development was due to sub-optimal PK/bioavailability properties

Source: Can the pharmaceutical industry reduce attrition rates?
Success rates from first-in-man to registration.

The overall clinical success rate is 11% (2004 estimate)

Patent:
FDA approved drug patent lasts 20 (+extension) years.
Time start from patent approval, which means that life of protection for an on-the-market drug varies a lot.

Best 3 blockbusters on the market (2011):

- **Lipitor** (Pfizer) treats high cholesterol - ~ 7.4 bl $ per year
- **Plavix** (BMS/Sanofi-Aventis) used for heart disease - ~ 6.5 bl $ per year
- **Nexium** (AstraZeneca) for gastroesophageal reflux disease - ~ 6.0 bl $ per year

Lipitor peak was ~13 bl $ (2006-2007)

Data from: www.drugs.com
The patent cliff:

Table 1 | Selected drugs facing patent expiry in the United States

<table>
<thead>
<tr>
<th>Branded drug (INN drug name; company)</th>
<th>Indication</th>
<th>Worldwide 2009 sales (billion)*</th>
<th>Expected patent expiry</th>
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<tbody>
<tr>
<td>Aricept (donepezil; Eisai/Pfizer)</td>
<td>Alzheimer's-type dementia</td>
<td>¥303.8 (US$3.61)</td>
<td>Nov 2010</td>
</tr>
<tr>
<td>Lipitor (atorvastatin; Pfizer)</td>
<td>High cholesterol</td>
<td>US$11.43</td>
<td>2011</td>
</tr>
<tr>
<td>Zyprexa (olanzapine; Eli Lilly &amp; Company)</td>
<td>Schizophrenia, bipolar I disorder</td>
<td>US$4.92</td>
<td>2011</td>
</tr>
<tr>
<td>Lexapro (escitalopram; Forest Laboratories/Lundbeck)</td>
<td>Depression and anxiety</td>
<td>DKK 7.77 (US$1.37)</td>
<td>2012</td>
</tr>
<tr>
<td>Actos (pioglitazone; Takeda)</td>
<td>Type 2 diabetes</td>
<td>¥334.5 (US$3.98)*</td>
<td>2012</td>
</tr>
<tr>
<td>Plavix (clopidogrel; Sanofi–Aventis/Bristol-Myers Squibb)</td>
<td>Clot-related cardiovascular events</td>
<td>US$6.15</td>
<td>2012</td>
</tr>
<tr>
<td>Lovenox (enoxaparin; Sanofi–Aventis)</td>
<td>Acute deep vein thrombosis</td>
<td>€3.04 ($4.03)</td>
<td>2012</td>
</tr>
<tr>
<td>Seroquel (quetiapine; AstraZeneca)</td>
<td>Schizophrenia, bipolar disorder, major depressive disorder</td>
<td>US$4.87</td>
<td>2012</td>
</tr>
</tbody>
</table>

*Data from company annual reports. †Europe and the Americas. INN, international nonproprietary name.

Source: The patent cliff steepens
Harrison C., Nat. Review Drug Discovery Jan Vol. 10 2011

Dangling from the patent cliff
Harrison C., Nat. Review Drug Discovery Jan Vol. 12 2013

The impending patent cliff is anticipated to erode US$78 billion in worldwide sales from branded drugs that are facing patent expiry between 2010 and 2014.
Best 3 blockbusters on the market (2011):

**Lipitor** (Pfizer) treats high cholesterol - ~ 7.4 bl $ per year
**Plavix** (BMS/Sanofi-Aventis) used for heart disease - ~ 6.5 bl $ per year
**Nexium** (AstraZeneca) for gastroesophageal reflux disease - ~ 6.0 bl $ per year

Best 3 blockbusters on the market (**Q3 2013**):

**Abilify** (Otsuka Pharmaceuticals) antipsychotic medication - ~ 4.7 bl $ per year
**Nexium** (AstraZeneca) for gastroesophageal reflux disease - ~ 4.4 bl $ per year
**Cymbalta** (Eli Lilly) used for general anxiety disorder - ~ 4.0 bl $ per year

Data from: www.drugs.com
FDA drug approvals
19 NMEs approved in 2009.

Source: 2009 FDA drug approval
Bethan Hughes,
Nat. Review Drug Discovery Feb Vol. 9 2010
- Some facts -

2012 FDA drug approval

39 New Drugs Approved – 20 first-in-class agents!
15-year high !!!

Source:
Asher Mullard,
Nature Reviews Drug Discovery 12, 87-90 (February 2013)
Drug Discovery & Development

- Some facts -

2012 FDA drug approval

39 New Drugs Approved – 20 first-in-class agents!
15-year high !!!

Source:
Asher Mullard,
Nature Reviews Drug Discovery 12, 87-90 (February 2013)
**FDA approvals for the first half of 2013**

**13 New Drugs Approved in the first 6 months**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lead company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>Takeda</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Mipomersen sodium</td>
<td>Genzyme</td>
<td>Homozygous familial hypercholesterolaemia</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Celgene</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine*</td>
<td>Genentech</td>
<td>HER2-positive metastatic breast cancer</td>
</tr>
<tr>
<td>Osmepifene</td>
<td>Shionogi</td>
<td>Moderate to severe dyspareunia</td>
</tr>
<tr>
<td>Technetium Tc-99m tilmanocept</td>
<td>Navidea</td>
<td>Lymphatic mapping in patients with breast cancer or melanoma</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>Guerbet</td>
<td>Contrast agent to visualize disruption of the blood–brain barrier</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Biogen Idec</td>
<td>Relapsing multiple sclerosis</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Janssen</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Fluticasone furoate plus vilanterol trifenate</td>
<td>GlaxoSmithKline</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Radium Ra-223 dichloride</td>
<td>Bayer</td>
<td>Castration-resistant prostate cancer</td>
</tr>
<tr>
<td>Dabrafenib mesylate</td>
<td>GlaxoSmithKline</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Trametinib dimethyl sulphoxide</td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Approved as a biologics license application.

**Source:**
*Nature Reviews Drug Discovery* (August 2013)
Drug discovery is interdisciplinary!
At the end of the Preclinical Development phase, the clinical candidate is selected, and all the data that have been generated are gathered to prepare the documents to be submitted to the regulatory agencies for approval of the clinical program – the Investigational New Drug (IND) package for the Food and Drug Administration (FDA) in the US; the Investigational Medicinal Product Dossier (IMPD) and the Investigator’s Brochure (IB) for the Ethics Committees of the EU sites where clinical trials will be conducted.
Rational design of a new hybrid scaffold

**HYBRID SCAFFOLD**
Potentially active on FAAH and COX-1/2

URB524, ARN1303
Well-known FAAH inhibitor

R = H Flurbiprofen, ARN0116
Well-known COX inhibitor

R = OEt or OMe
COX-activity maintained
Rational design of a new hybrid scaffold

Docking + Classical MD simulations
Amber FF; 200 ns per system
RESP charges; Time Step = 2 fs;

MDV
Linear alkyl carbamates

\[ \text{Lead Compound} \]

ARN2508
- FAAH: IC\(_{50}\) 31 nM
- COX-1: IC\(_{50}\) 12 nM
- COX-2: IC\(_{50}\) 430 nM

SAR