Pair-wise analysis of structure solubility relationships

Application to Drug Design to Enhance the Solubility of NCEs

PhysChem FORUM 10

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Pfizer WorldWide R&D

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Agenda

- Introduction
- Solubility and Discovery
- Data Quality and Quantity for Development of Solubility Prediction
- Pairwise Analysis
- Conclusion
- Acknowledgement

Introduction

Solubility is an import factor through every stage of drug discovery

(1) Low soluble compounds may show

- inappropriate PK (absorption) profile
- inaccurate results in *in vitro* biological/toxicological tests, which provides inaccurate SAR to medicinal chemists (ex. 10 uM = 5 ug/mL: MW 500)

(2) Low solubility compounds may cause significant challenges in

- *in vivo* pharmacological evaluation
- achieving target exposure in preclinical/clinical studies
- formulation development (enabling formulation is great but not a magic)
- *in vitro* pharmacological/safety profiling

For drug discovery and development effectiveness ➔ medicinal chemist need tools to help design compounds potent as well as soluble.

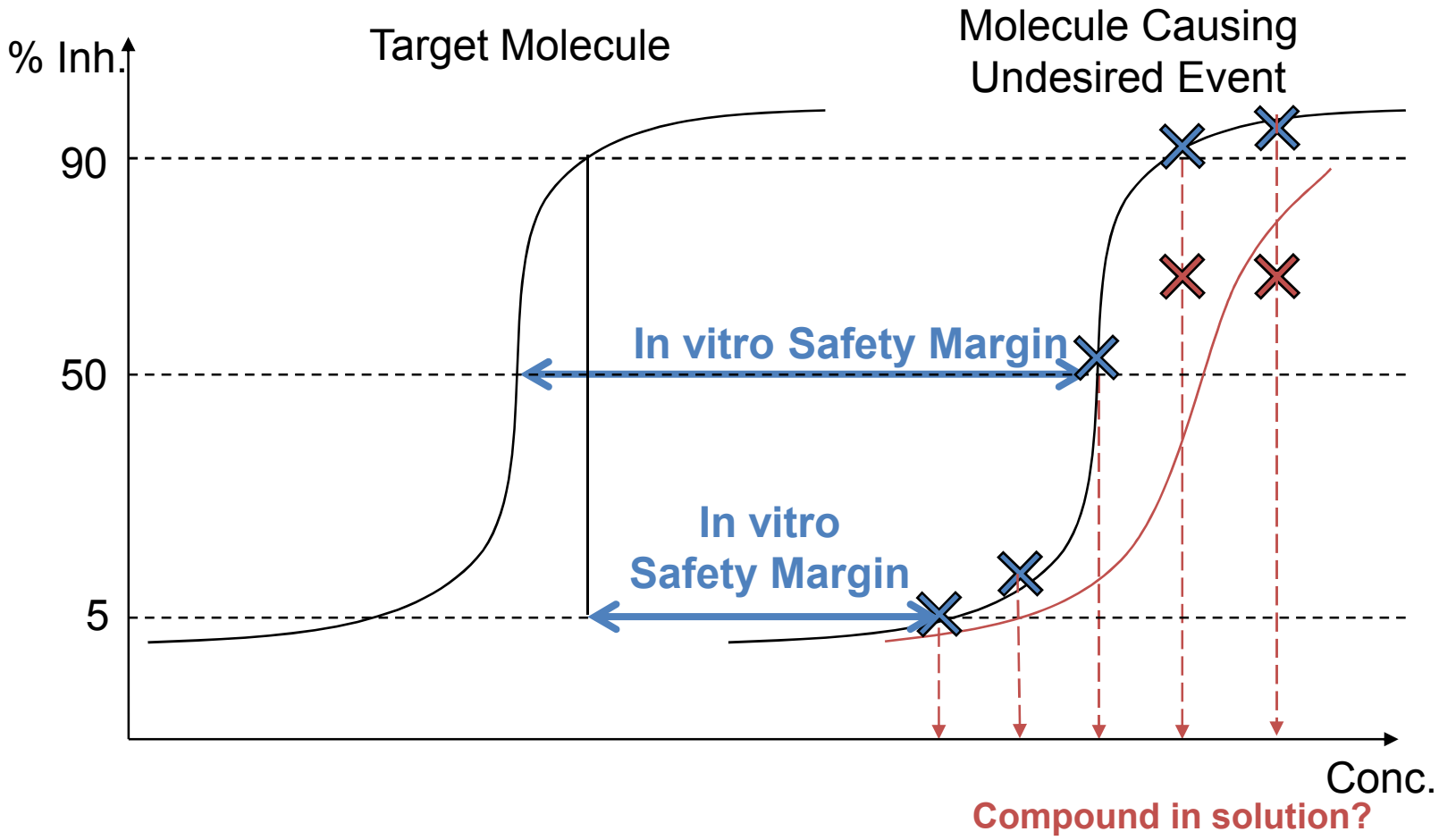
Robust tools for solubility prediction is strongly required.

Solubility Screening

	In vitro broad assay panel	SAR	Biorelevant	Extended
Purpose	Underwrite in vitro assay	SAR for oral exposure	SAR/in-vivo interpretation for oral administration	Basic data for formulation development
Timing	Broad Ligand Profiling	ADME Screening	In-vivo pharmacology/PK	Compound Selection
Crystallinity	N/A	PLM (residue only)	PLM (residue)	PLM (initial and residue) (will move to PXRD)
Equilibration Time (hour)	24	>20	24	24, 48
Buffer	PBS (pH 7.4)	50 mM PBS (pH 6.5)	SGF (pH1.2), 50 mM PBS, Fassif (pH 6.5)	SGF, PBS (pH 6.5), FaSSIF, FeSSIF, 0.1 N NaOH (opt'l)
Replicates (sample)	N = 1 (from DMSO)	N = 2 (from DMSO)	N = 1 (from powder)	N = 1 – 3 (from powder)
Requirement	10 mM	20 µL of 30 mM	15 mg	50 mg
Dynamic Range	0.5 – 200 µM (0.25-100 µg/mL, if MW: 500)	0.1 – 300 µM	0.3 – 300 µg/mL	0.3 – 300 µg/mL (– 3 mg/mL for SGN)
Throughput	–	~96 cpd/week	~32 cpd/week	~2 – 4 cpd/month
Timelines	–	1 week from compound receipt	1 week from compound receipt	2 weeks from compound receipt

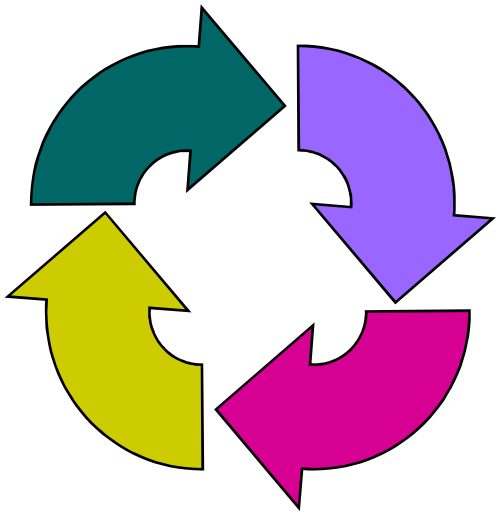
PLM: Polarised Light Microscopy; PXRD; Powder X-Ray Difraction; PBS: Phosphate Buffered Saline; SGF: Simulated Gastric Fluid (w/o enzyme); FaSSIF: Fasted State Simulated Intestinal Fluid; FeSSIF: Fed State Simulated Intestinal Fluid

Solubility needed in *in vitro* assay



Discovery loop

Design – Synthesis – Characterisation – Analysis



Design
"Brain"
computation

Synthesis
purity
in-plate stability

Analysis
"Eye ball"
computation

Characterisation
primary screening
pharmacol. characterisation
ADME/T

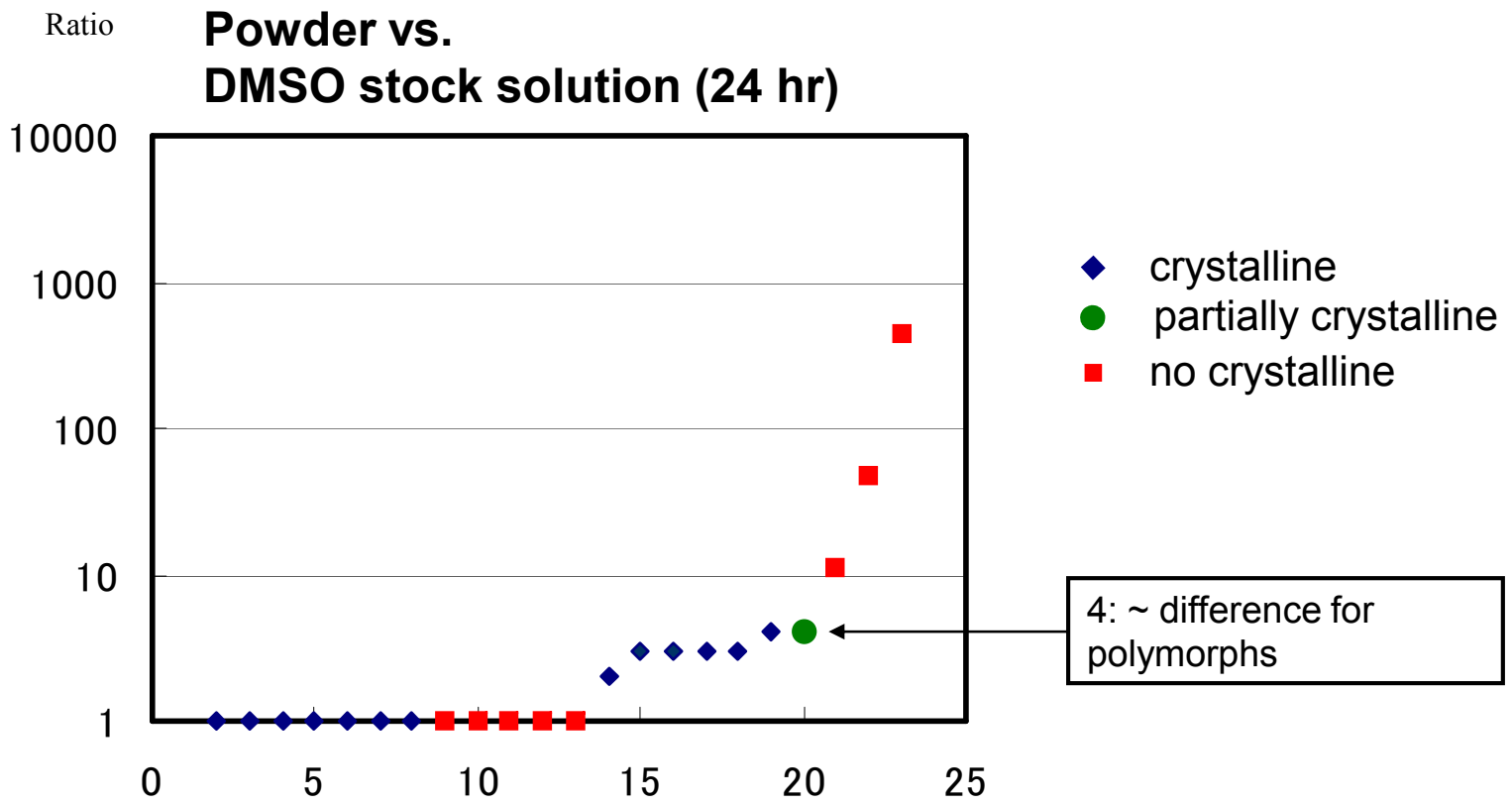
Solubility Prediction Models:
tool to help medicinal chemists
design molecules having higher solubility

Training Data Issue?

- **ADME In Silico Modeling: Towards Prediction Paradise?**
  - H. Van De Waterbeemd, E. Gifford. *Drug Discovery* **2003**, *2*, 192–204.
    - ••• However, at present, no approaches are robust enough to accurately predict low solubility.
    - Many current predictive solubility programs use training data from different experimental conditions. Hopefully, by measuring many compounds under standardized conditions, current predictive models can be improved.

What needs to be measured under which condition?

Solubility Difference Between Crystalline & Amorphous States



High Throughput Solubility Measurement With Automated Polarized Light Microscopy Analysis. K. Sugano, T. Kato, K. Suzuki, K. Kako, T. Sujaku, T. Mano. *J. Pharm. Sci.* **2006**, *95*, 2115–2122. Also see: Discovery Pharmaceutics—Challenges and Opportunities. X.-Q. Chen, M. D. Antman, C. Gesenberg, O. S. Gudmundsson. *The AAPS Journal* **2006**, *8*, E402–E408; What is the True Solubility Advantage for Amorphous Pharmaceuticals? B. C. Hancock, M. Parks. *Pharm. Res.* **2000**, *17*, 397−404. Predicted: 10−1600 times; Experimental: 1−25 times; Impact of Solid State Properties on Developability Assessment of Drug Candidates L.-F. Huang, W.-Q. Tong. *Adv. Drug Delivery Reviews* **2004**, *56*, 321−334. Experimental: 1.1−500-1000 times

Balancing Quality and Quantity

- **The quality and quantity of data to develop solubility prediction tools in this presentation**
  - Quality
    - Solubility data with crystalline residue
      - By PLM
    - Dynamic range: 0.3–300 μg/mL
    - Vehicle/pH: Phosphate buffered saline/pH 6.5
  - Quantity
    - Approx. 1,000 in-house powder compounds
    - Selected based on similarity

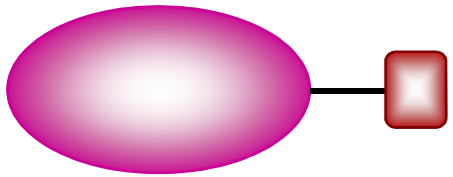
Prediction Approaches

What guides design of soluble molecule?

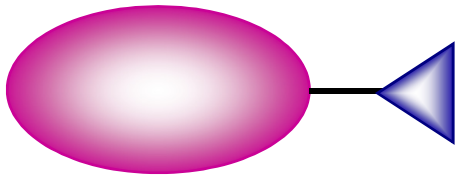
- **Empirical rules/principles, personal experiences through project work➔** Would be a first option to rely on but not so versatile enough to cover large chemical space of pharmaceutical entities.
- **Classification model ➔** Useful for rough prediction of solubility of a large number of compounds (e.g., from combinatorial virtual library or compound subset). ***However, not useful for singleton molecule design*** (helpful in HTS triage or lead seeking stage)
- **Regression model ➔** Only valid within local chemical space covered by training set molecules
- **Pairwise analysis ➔** What minor modification improve solubility? This analysis provides a table of some examples for pairs of two molecules whose solubility difference is high despite high similarity to each other. (applicable in lead development stage)

Pairwise Analysis (Matched-Pair Analysis)

- To find useful relationships between (minor) changes in structure and changes in properties.



Compound A
Parameter R = X

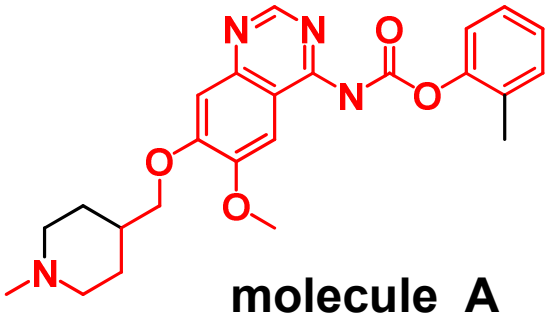


Compound B
Parameter R = Y

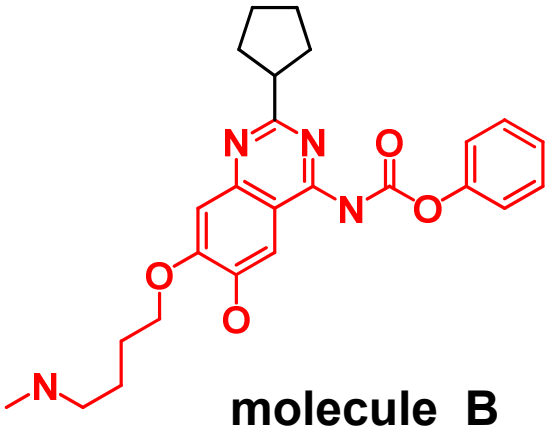
- The analysis on solubility would help medicinal chemists to design compounds with higher solubility.
- Pfizer has a huge database of solubility values for discovery compounds.

Matched Molecular Pairs as a Guide in the Optimization of Pharmaceutical Properties; a Study of Aqueous Solubility, Plasma Protein Binding and Oral Exposure A. G. Leach, H. D. Jones, D. A. Cosgrove, P. W. Kenny, L. Ruston, P. MacFaul, J. M. Wood, N. Colclough, B. Law. *J. Med. Chem.* **2006,** *49,* 6672-6682

Pairwise Analysis, MCS similarity



molecule_A



molecule_B

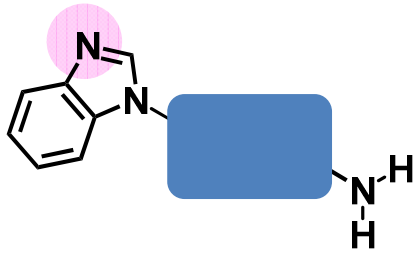
Similarity Calculation ➔ MCS (maximum common substructure) similarity

```
Vmcs    atom number of mcs
Emcs    bond number of mcs
Va      atom number of molecule_A
Vb      atom number of molecule_B
Ea      bond number of molecule_A
Eb      bond number of molecule_B
```

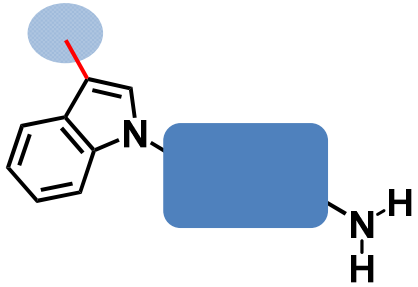
`Similarity = (Vmcs+Emcs)*(Vmcs+Emcs)/(Va+Ea)*(Vb+Eb)`

From dataset, pick up pair of two molecules whose similarity is > 0.8 while the ratio of solubility is larger than a threshold value.

Results

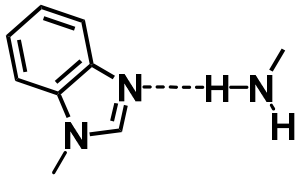


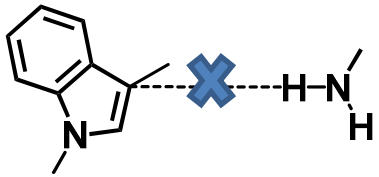
17 μg/ml

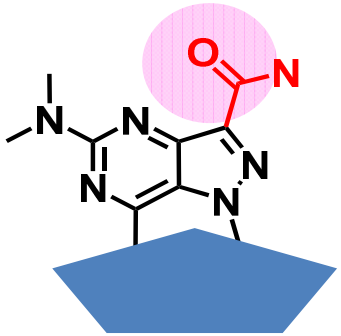


640 μg/ml

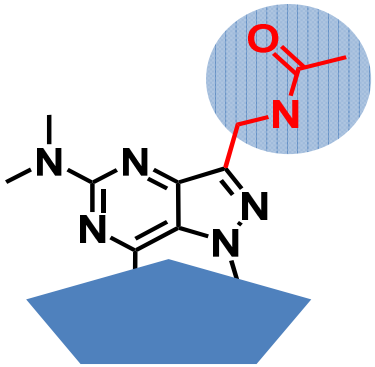
Indole – imidazole transformation decreases solubility ➔ Remarkable contrast with general trend (clogp)





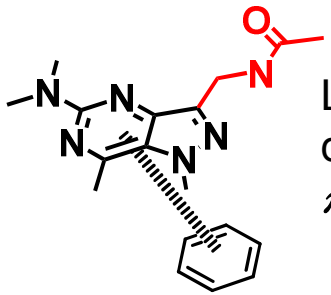


7.5 μg/ml

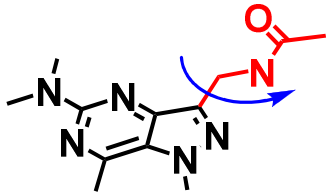


2551.5 μg/ml

Insertion of one methylene group increases solubility by order of 10^3 ➔ (1) destroy planarity (2) larger decrease in Gibbs free energy in dissolution process

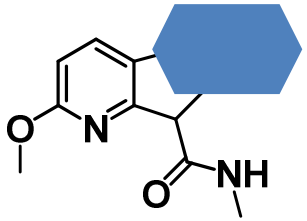


Low planarity can be detrimental for effective π–π stacking

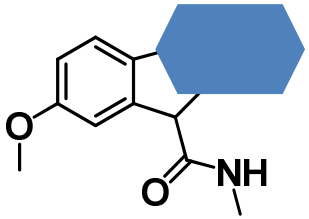


The number of accessible conformations would increase (significant entropy increase in dissolution process)

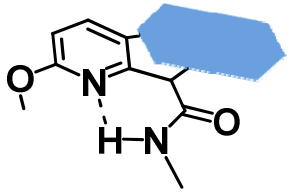
Results



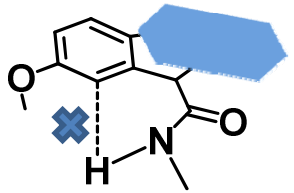
7.0 μg/ml



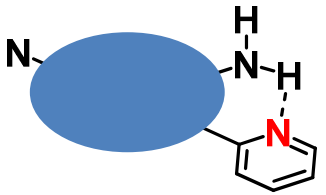
77.0 μg/ml

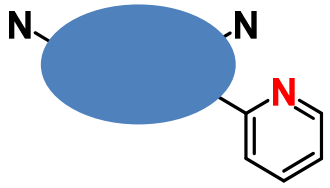


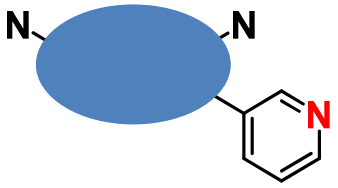
adopt pseudo tricyclic structure

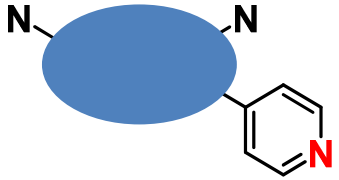


Aromatic nitrogen can form intramolecular hydrogen bond ➔ makes the molecule more planar



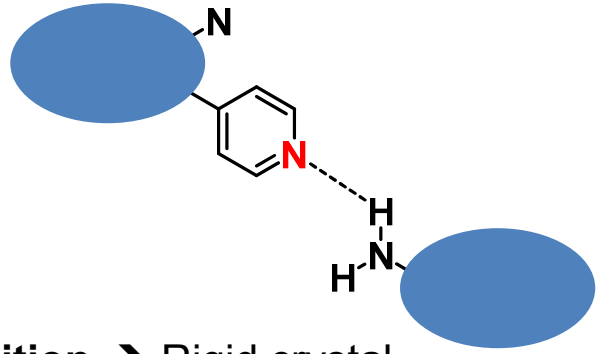






110 μg/ml 1400 μg/ml 580 μg/ml

Ortho-position ➔ Increase in planarity due to intramolecular hydrogen bond

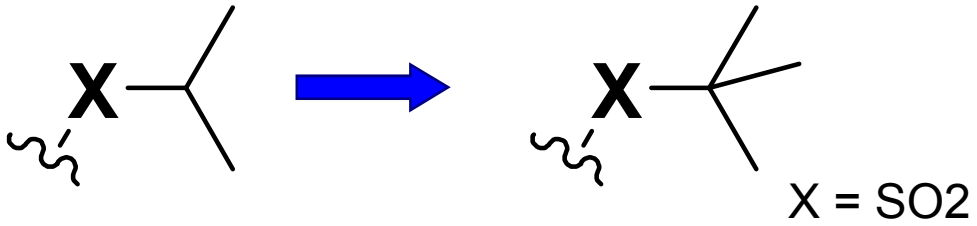


Solubility changes depending on position of an aromatic nitrogen ➔ suggests importance of planarity and intermolecular hydrogen bond in solubility

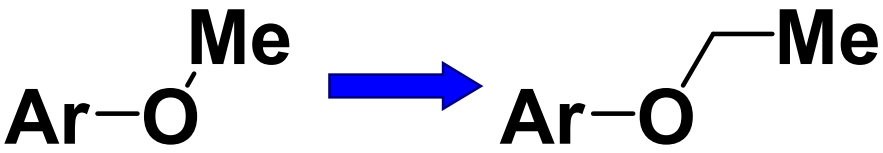
Para-position ➔ Rigid crystal packing network through intermolecular hydrogen bond

More than one pair examples

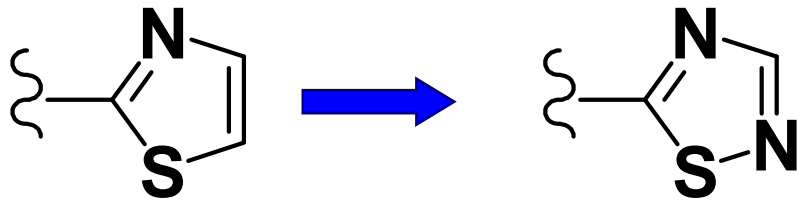
Solubility improvement



×10.4 – 10.9 (n = 2)

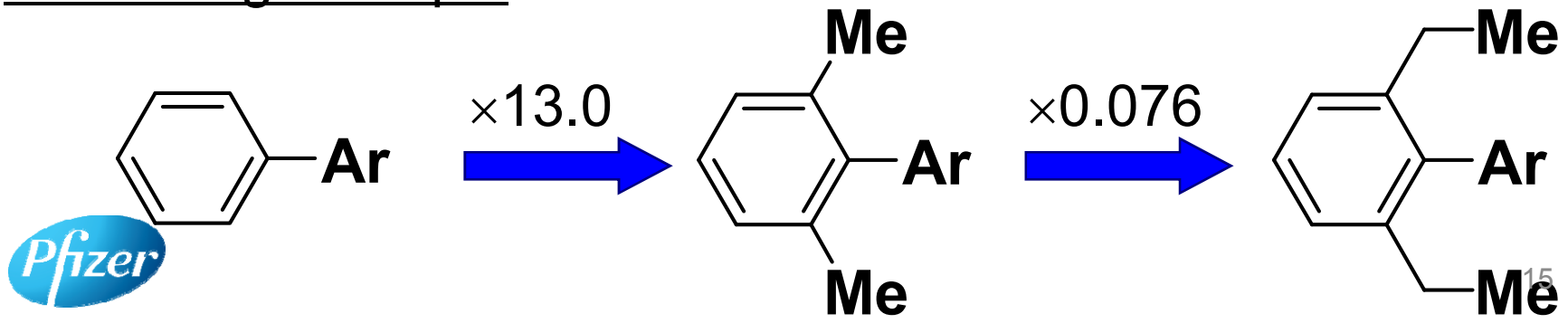


×13.0 – 19.0 (n = 2)

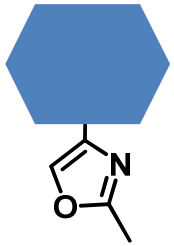


×71.4 – 208 (n = 2)

Interesting example

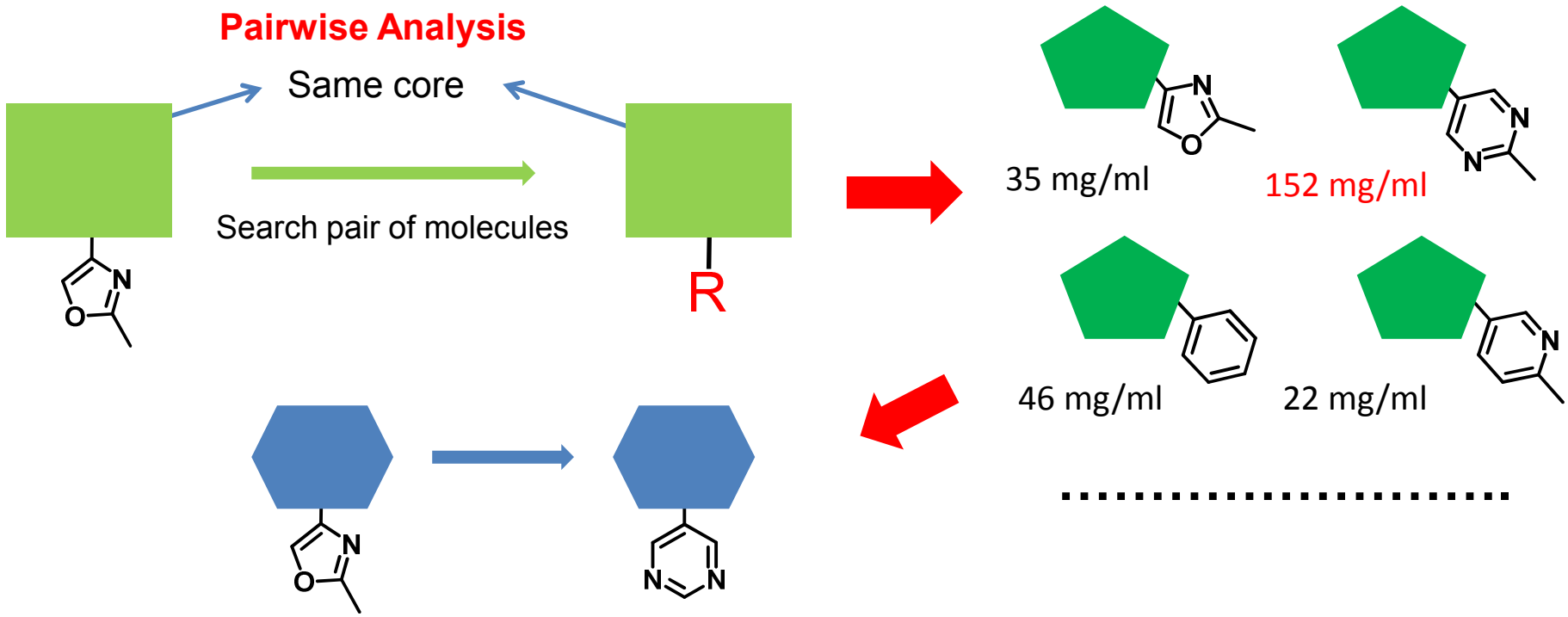


Usage from medicinal chemistry viewpoint (1)



Compound_A
Lead molecule in a project but very insoluble and easy to crystallise ➔ How we can make this molecule soluble?

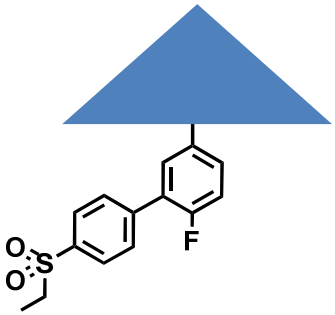
SAR (Structure-Activity Relationship) for activity against the project target ➔ The oxazole ring can replaced by diverse groups without large disruption in activity



Compound_A

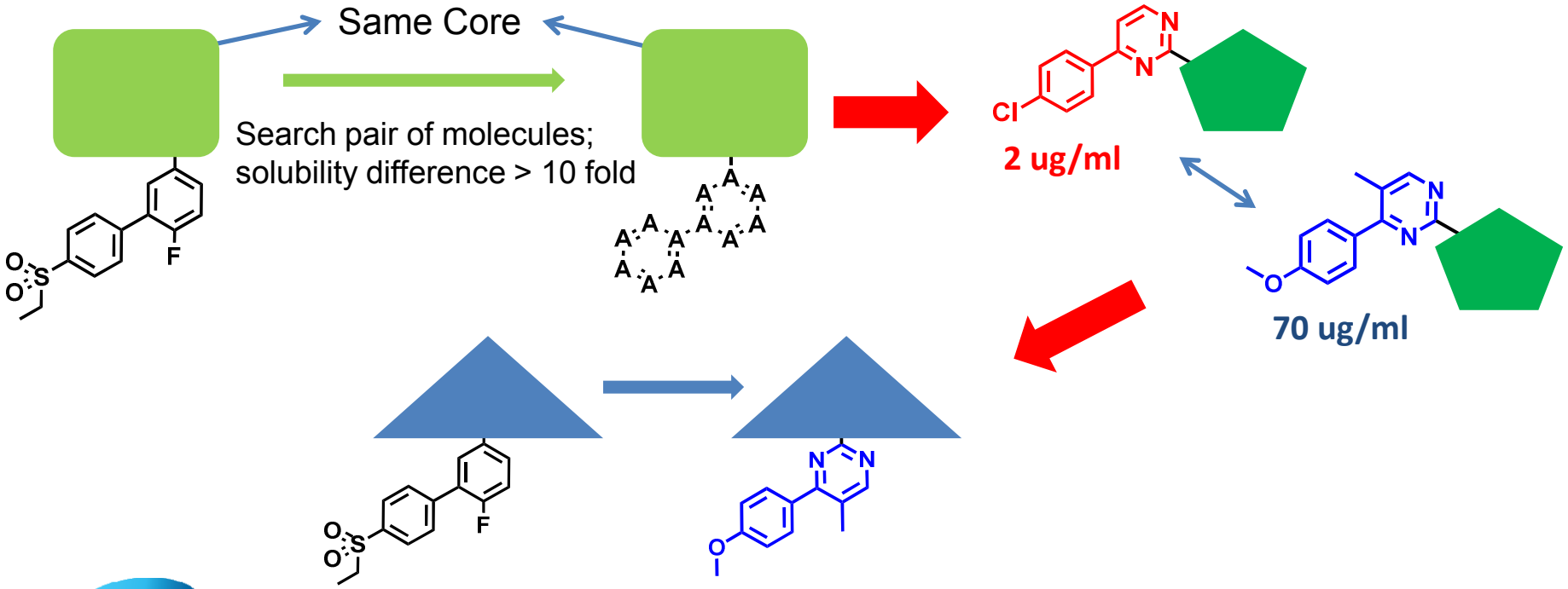
An idea of effective modification to make the framework soluble

Usage from medicinal chemistry viewpoint (2)



Compound_B
Lead molecule in a project but very insoluble and easy to crystallise ➔ How we can make this molecule soluble?

SAR for activity against the project target ➔ The biphenyl group can be replaced by different aromatic-aromatic framework without loss in activity against the project target.



Conclusion

Quality models ← Quality data

1. **A novel tool for pairwise analysis was successfully developed by selecting proper dataset on solubility and crystallinity.**

2. **Pairwise analysis on solubility is useful to help medicinal chemists to design high-solubility compounds.**

Acknowledgement

Brian Henry

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Richard J. Manley

Samuel Thomas