Qualitatively Predicting Compound-Protein Interactions by Multi-Task Learning

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outline

- Quantitatively predicting compound-protein interactions by multi-task learning
- Paper Review on Compound-Protein Interactions.

Part I

Quantitatively predicting compound-protein interactions by multi-task learning

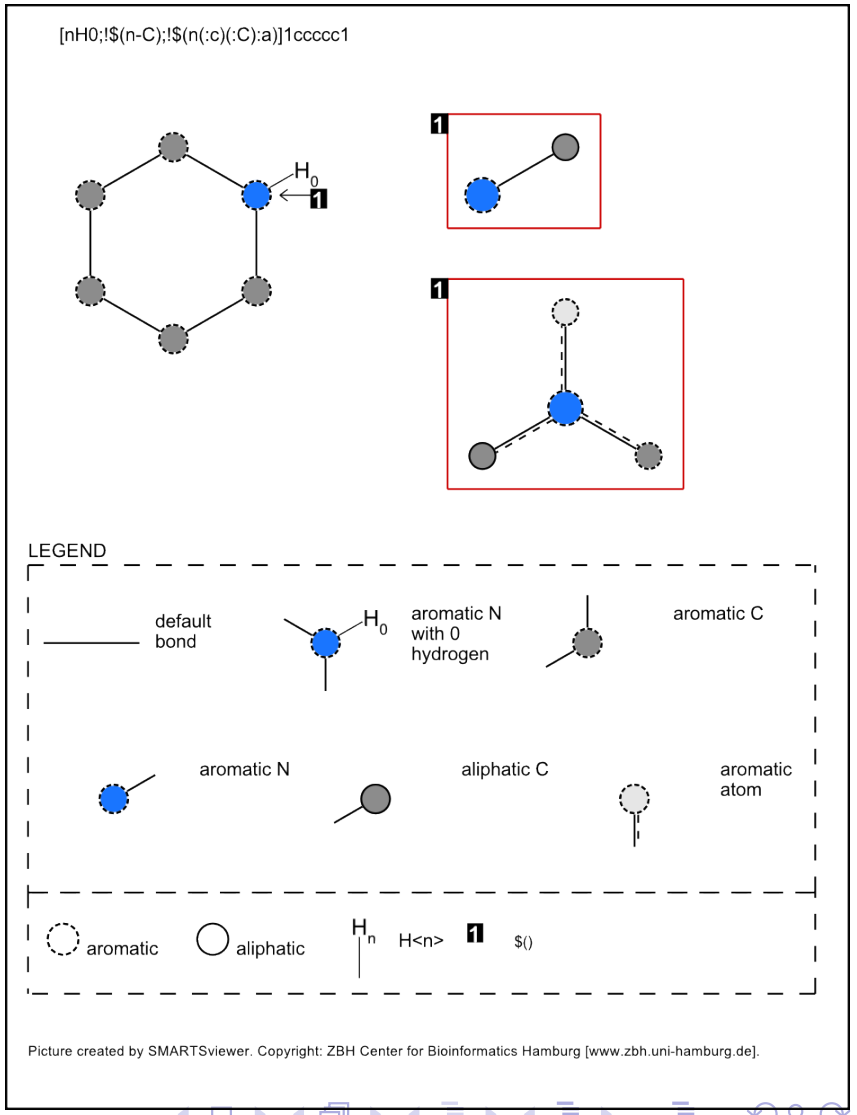
background

Methods for predicting compound-protein interactions (CPIs):

- structure-based molecular dynamics
  - depend on proteins' 3D structures.
- ligand-based method
  - can be independent of proteins' 3d structures.
  - large-scale known CPIs data
  - mainly dependent on machine learning approaches.

Machine learning on CPIs

- Compounds represented by topological fingerprints. The similar as proteins.
- CPIs recorded as binary variable or continuous variables.
- Classification or regression models then are used.



Modeling on a single protein

Keiser M.J. *et al.*, *Nature* 2009, developed the SEA method to predict drugs' new molecular targets.

- Each target represented by its set of known ligands.
- Drugs computationally screen against a panel of proteins by comparing the similarity of ligands against these proteins.
- The similarities expressed as E-values, adapting the BLAST algorithm.

Modeling on a single protein

Besnard J. *et al*., *Nature* 2012, used naive Bayesian model to predict compounds' polypharmacology profiling.

- 215,000 activity data including 133,061 compounds and 784 proteins were used.
- Every compounds represented by the binary vectors of ECFP6 representations.
- For every protein, a Laplacian-modified naive models was built for classification.

Modeling on a protein family

Yabuuchi H. *et al.*, *Molecular Systems Biology* 2011 developed the CGBVS framework.

- 5207 CPIs data (including 317 GPCRs and 866 ligands)
- Compounds' structure and proteins' sequences converted into 929- and 400-dimensional vectors
- SVM then used.

Machine Learning on CPIs

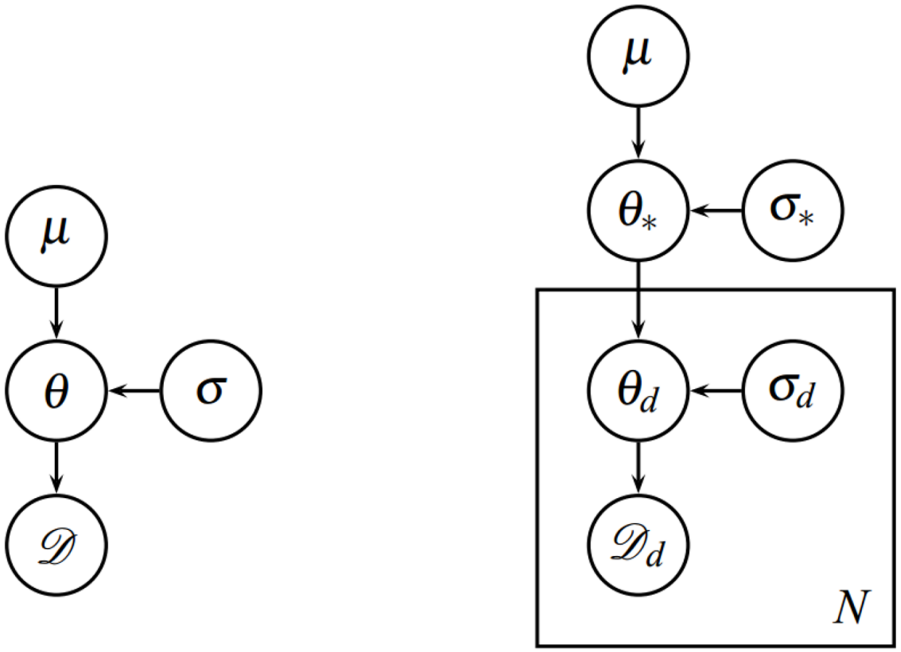
Current machine learning on predicting CPIs

- Modeling on a single protein
  More specificity Lots of data needed
- Modeling on a protein family
  Data sharing Less specificity

Multi-Task Learning

Can we combine the two approaches ?

- Learning different but similar tasks at the same time. (Finkel J.R. and Mannning C.D., 2009)
- Quantitative prediction.



Hierarchical Bayesian Model

Suppose $\mathcal{D}_j = \{\mathbf{X}_j, \mathbf{y}_j\}, j = 1, ..., m$, and $\mathbf{X}_j \in \mathbb{R}^{d \times n_j}$. Then we have

$$\mathbf{y}_j \sim \mathcal{N}\left(\mathbf{X}_j^T \omega_j, \sigma_y^2 \mathbf{I}\right) \tag{1}$$

Since different groups data may share similar features, we assume ω_j have the same mean on the prior distribution.

$$\omega_j \sim \mathcal{N}\left(\omega_*, \sigma_j^2 \mathbf{I}\right) \tag{2}$$

In which,

$$\omega_* \sim \mathcal{N}\left(\mu, \sigma_*^2 \mathbf{I}\right) \tag{3}$$

Suppose, for simplicity, that $\mu = \mathbf{0}$, $p(\sigma_y^2) \propto 1$, and that σ_j^2 and σ_* are fixed. Let $\Theta = \{\omega_j, j = 1, ..., m, \omega_*, \sigma_y^2\}$. We have

$$\begin{aligned}
&\mathcal{L}_{hier}(\mathcal{D};\Theta) = \mathcal{L}_{orig}(\mathcal{D}|\Theta) + logp(\Theta) \\
&= \sum_j \left(logp(\mathcal{D}_j|\omega_j) - \frac{\| \omega_j - \omega_* \|^2}{2\sigma_j^2} \right) - \frac{\| \omega_* \|^2}{2\sigma_*^2} \\
&\overbrace{- \sum_j \frac{d}{2} log(2\pi\sigma_j^2) - \frac{d}{2} log(2\pi\sigma_*^2)}^{Const} \\
&= \sum_j \left(- \frac{\| \mathbf{y}_j - \mathbf{X}_j^T \omega_j \|^2}{2\sigma_y^2} - \frac{\| \omega_j - \omega_* \|^2}{2\sigma_j^2} \right) - \frac{\| \omega_* \|^2}{2\sigma_*^2} - \sum_j \frac{n_j}{2} log(2\pi\sigma_y^2) \\
&\overbrace{- \sum_j \frac{d}{2} log(2\pi\sigma_j^2) - \frac{d}{2} log(2\pi\sigma_*^2)}^{Const}
\end{aligned} \tag{4}$$

L-BFGS-B optimization method is then used following the gradient below.

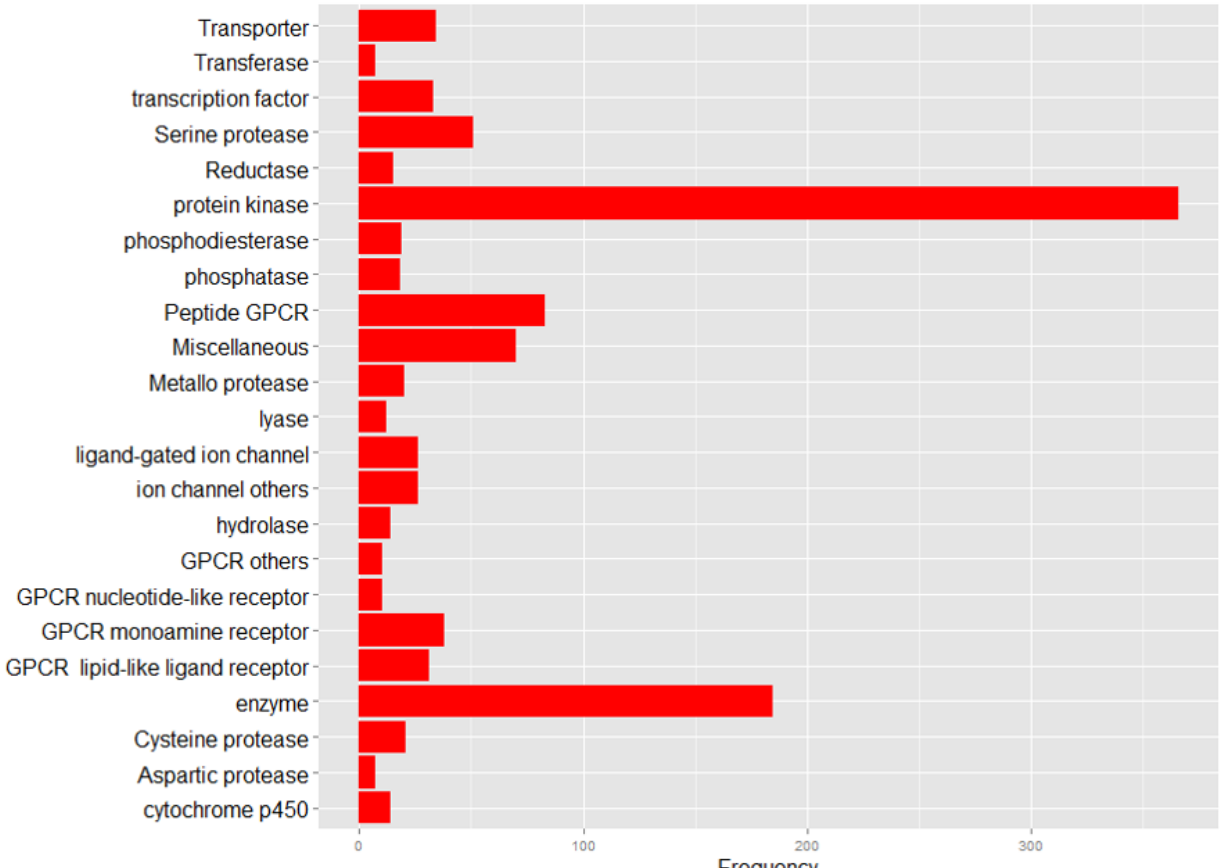
$$\begin{aligned}\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \omega_j} &= -\frac{1}{2\sigma_y^2}\frac{\| \mathbf{y}_j - \mathbf{X}_j^T\omega_j \|^2}{\partial \omega_j} - \frac{1}{2\sigma_j^2}\frac{\| \omega_j - \omega_* \|^2}{\partial \omega_j} \\ &= \frac{\mathbf{X}_j\mathbf{y}_j}{\sigma_y^2} + \frac{\omega_*}{\sigma_j^2} - \left(\frac{\mathbf{X}_j\mathbf{X}_j^T}{\sigma_y^2} + \frac{1}{\sigma_j^2}\mathbf{I}\right)\omega_j\end{aligned} \tag{5}$$

$$\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \omega_*} = -\sum_j \frac{\omega_* - \omega_j}{\sigma_j^2} - \frac{\omega_*}{\sigma_*^2} \tag{6}$$

$$\frac{\partial \mathcal{L}_{hier}(\mathcal{D};\Theta)}{\partial \sigma_y^2} = \frac{\sum_j \| \mathbf{y}_j - \mathbf{X}_j^T\omega_j \|^2}{2(\sigma_y^2)^2} - \frac{n}{2\sigma_y^2} \tag{7}$$

where n is the total number of samples in all the groups.

- 210,000 CPIs including more than 1,000 proteins from 20 protein families, and 150,000 compounds.
- 22 physicochemical properties and 881 chemical substructures as the compounds' features.

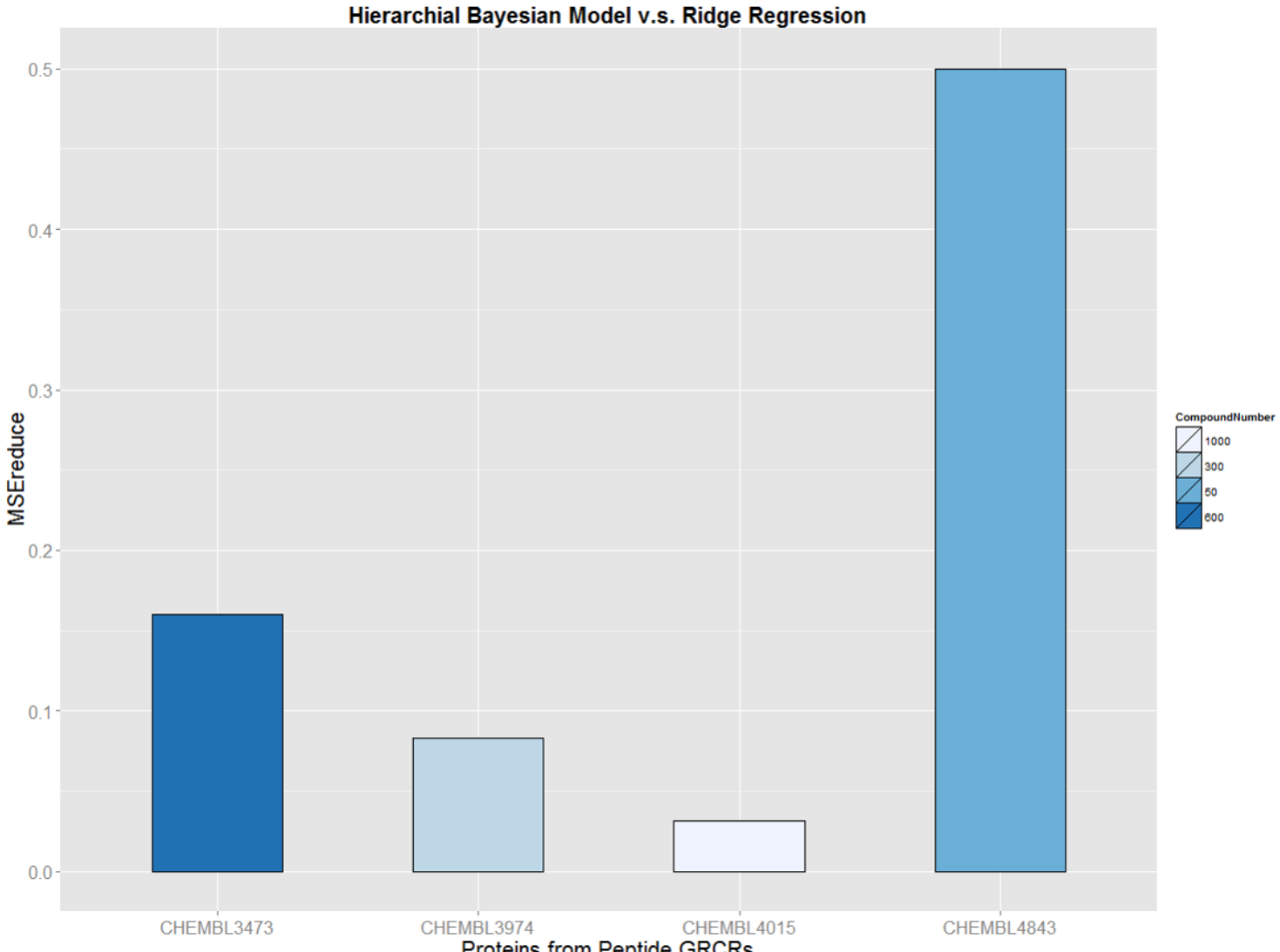


Feature Selection

The protein family of Peptide GPCR including 85 proteins as examples.

- Based on the definitions of chemical fingerprints, SUB1-SUB115, SUB264-SUB327 are removed.
- Chemical fingerprints with too low or high frequencies are removed.
- Non-parametric dynamic slicing method for marginal feature selection.
- 284 features are finally kept.

Comparison with Ridge Regression



Discussion

- More compounds' fingerprints are being collected by the open-source chemoinformatics and machine learning package termed RDKit.
- Computational issue:
  - High dimension v.s. Sparsity
    Colinearity
  - Linear v.s. Nonlinear

Part II

Paper Review

A systems approach to TOM

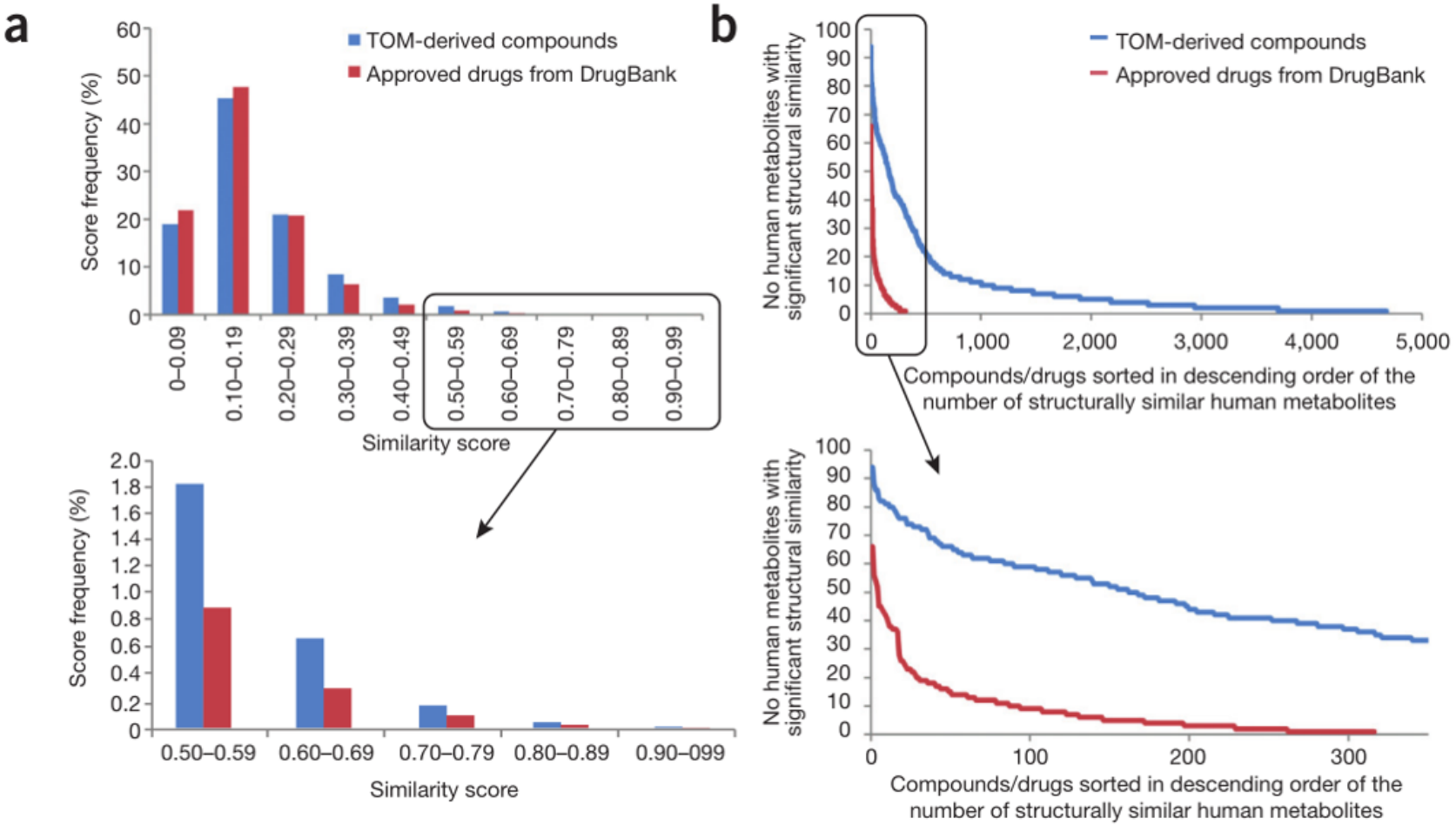
Hyun Uk Kim *et al.*, Nature Biotechnology, March 2015.

- Analyzed the structural similarities between the compounds derived from TOM and human metabolites.
- Explained 38 TOM-derived synergistic combination, i.e., connected the Major, Complementary, Neutralizing, and Delivery/retaining with the molecular biological views.
  - Complementary action: Major and Complementary
  - Neutralizing action: Major and Neutralizing
  - Facilitating action/Pharmacokinetic potentiation: Major and Delevery/retaining.

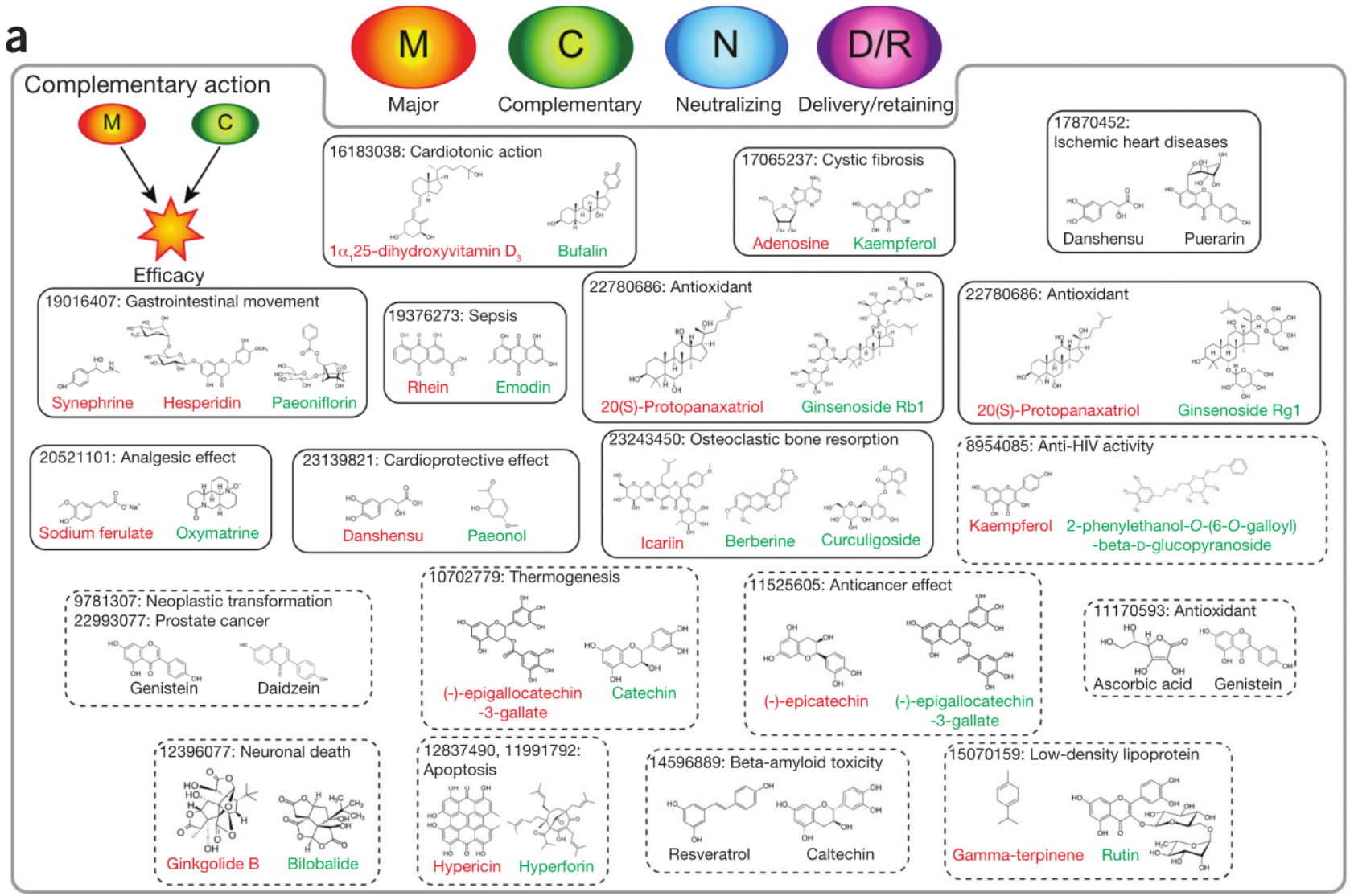
Data Summary

- 4,679 active compounds in TOMs were from TCM Database at Taiwan. 38 synergistic combinations of TOM compounds were identified by the literature since 2000.
- The human metabolites were downloaded from KEGG.
- As a control, 316 approved drugs were downloaded from the DrugBank 3.0.

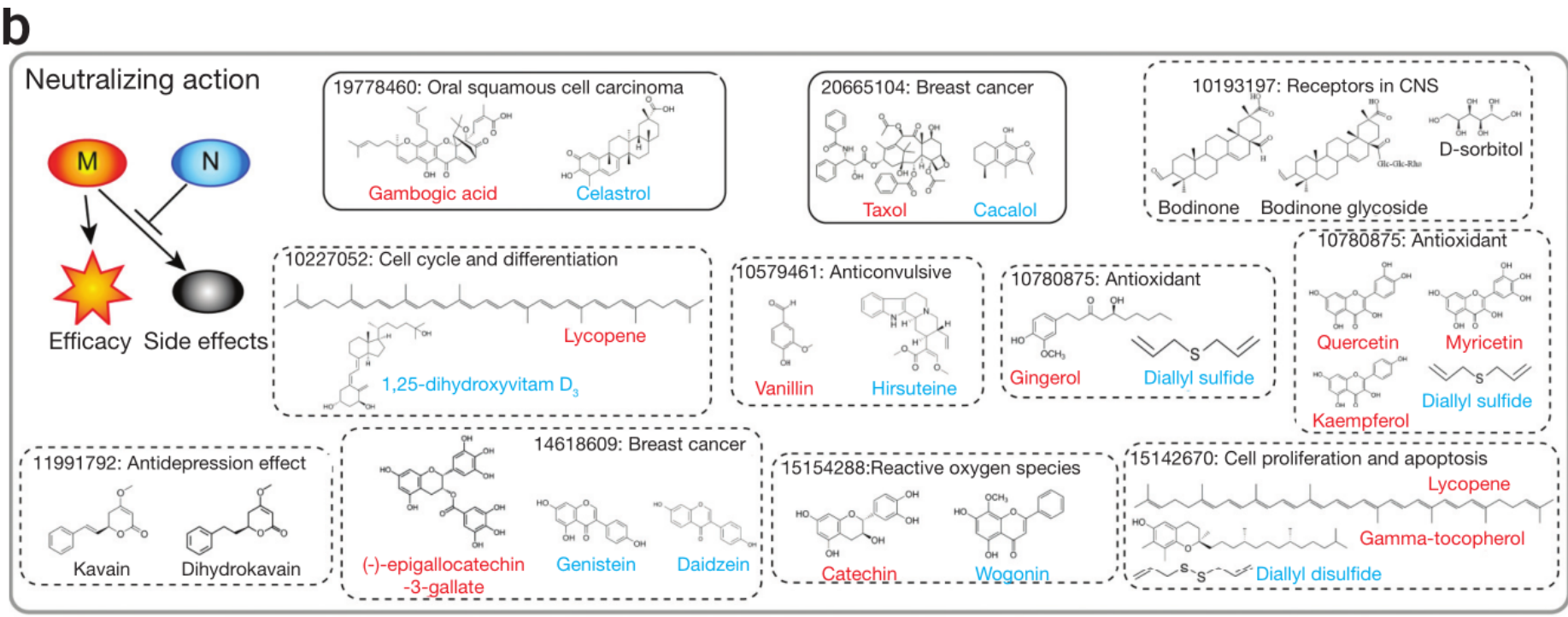
Compared with Metabolites



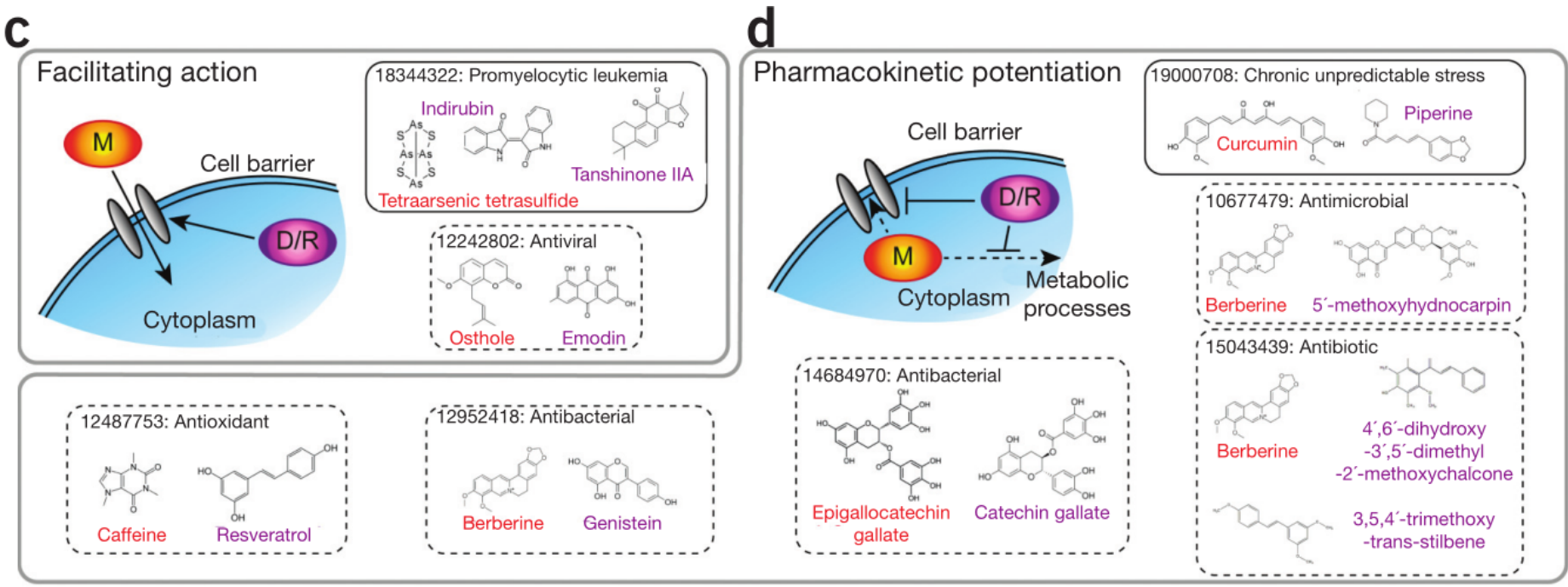
Complementary action



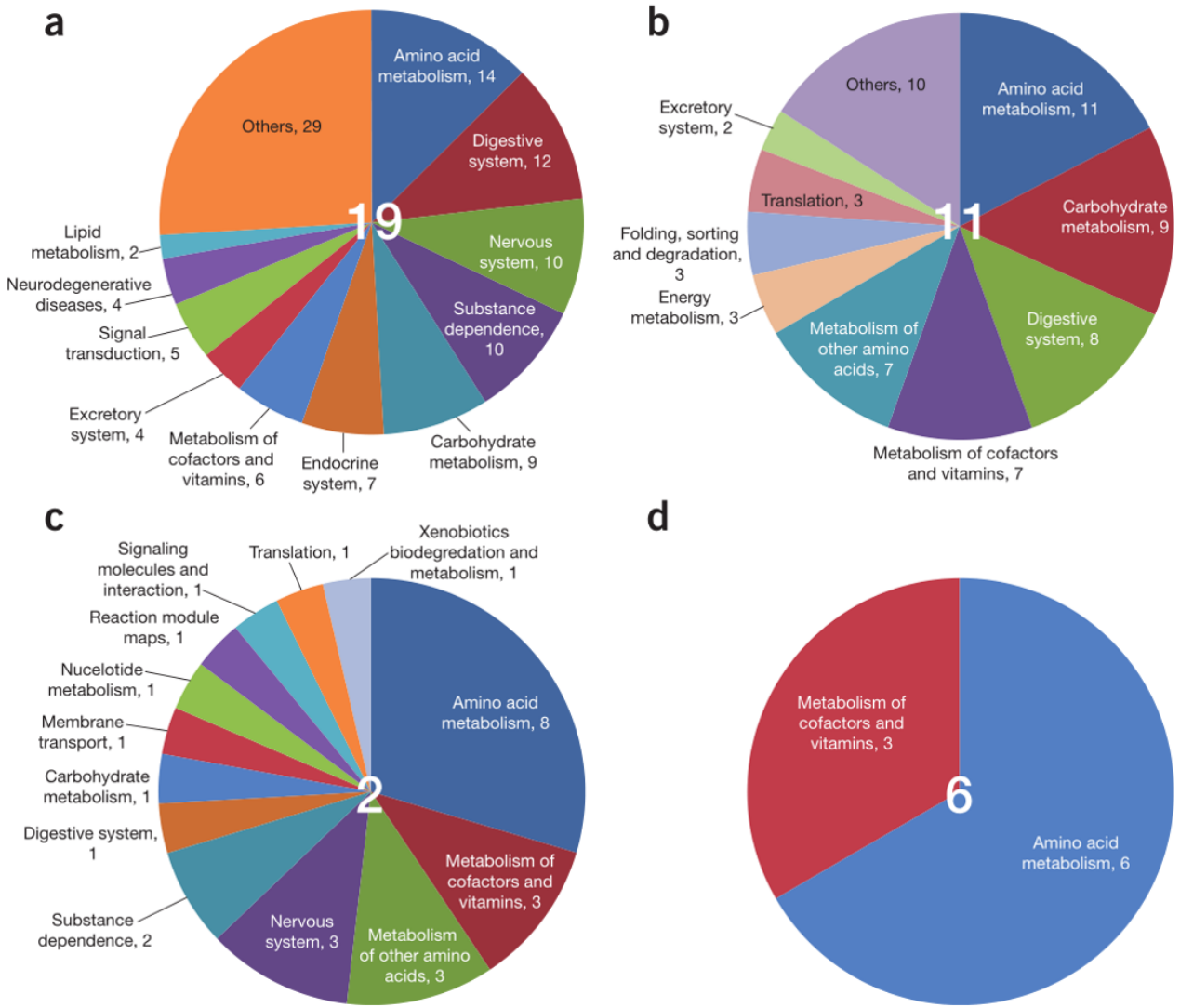
Neutralizing action



Facilitating action and Pharamacokinetic potentiation



Elucidating the mechanism of action



Part III

Integrating multi-level similarities to improve the network-based prediction on CPIs

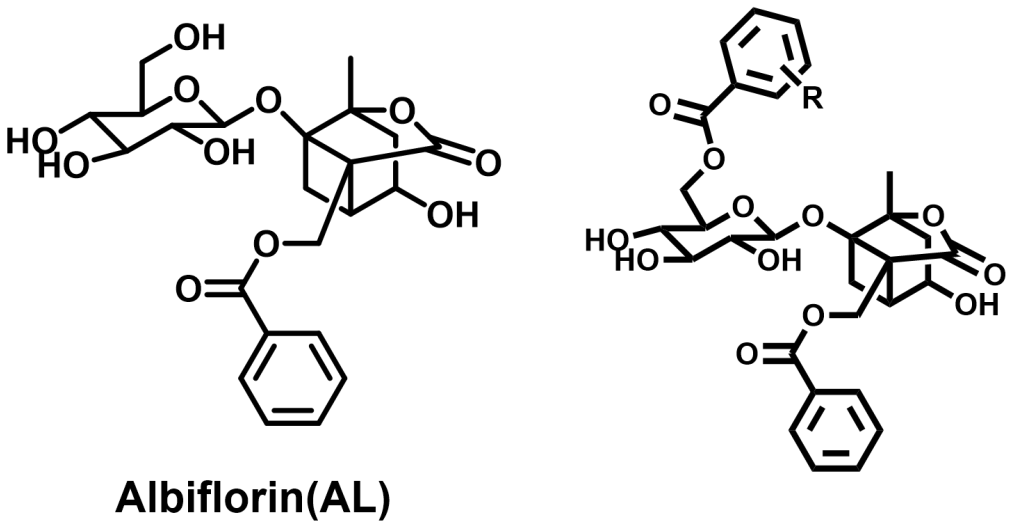
Part IV

Application on the Modification of Natural Products

Lead Discovery From TCM Herbs

- Natural products important sources for drug discovery.
- By DrugCIPHER, several compounds from traditional Chinese Medicine (TCM) Herbs are predicted to have the antitumor activities.
- Many of them have been reported, but one compound called *Albiflorin* few researches.

- Our experiments: *Albiflorin* has the antitumor activities with low potency.
- Its biological mechanism is unknown.



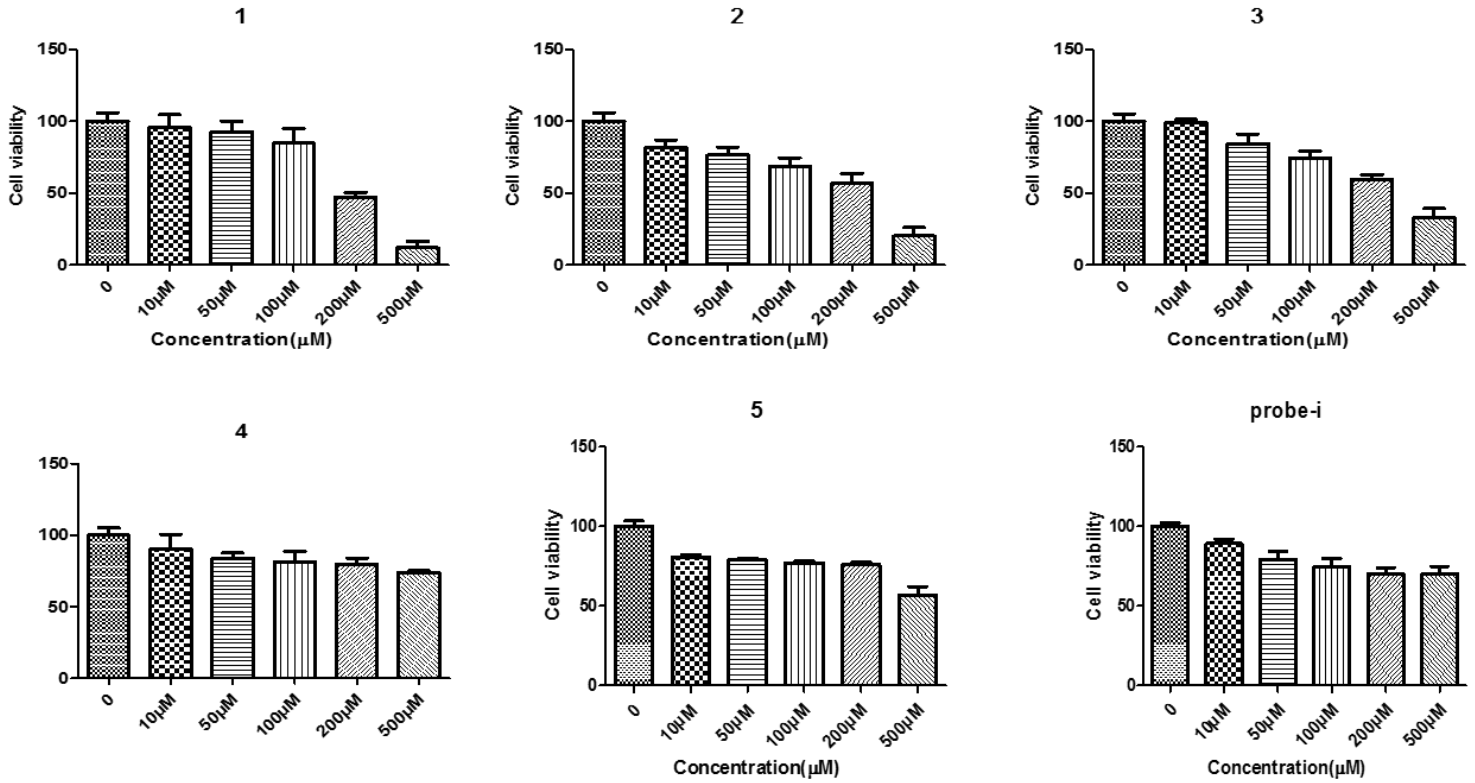
Albiflorin(AL)

- *Albiflorin*, a typical example from natural products.
  - Low potencies or activities
  - Unknown targets
- Direct experiments difficult to discover the mechanisms.
  - Low potencies $\longrightarrow$ false negative
  - Unknown targets $\longrightarrow$ hard to design analogs
  - Complex structures

Method

- Firstly, several analogs are designed based on the chemical experience as a starting point.
- Then MTT assays are used to test their biological activities on tumor growth.
- Next structure-activity relationship (SAR) analysis is performed to predicted its possible functional mechanism.
- Simulation and Filtering
  - Computational simulation of all the possible analogies.
  - Quantitatively predicting their targets.
- Experimental design and validation.

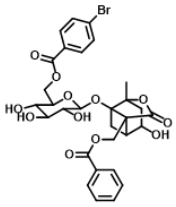
MTT Assay

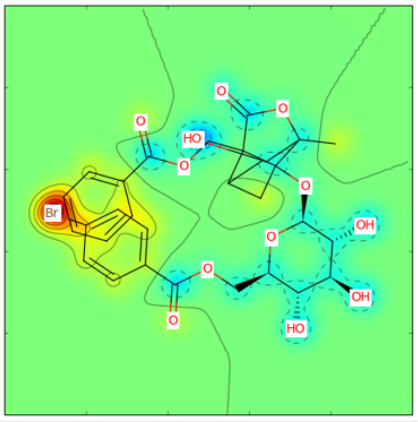


Drug	1	2	3	4	5	probe-i
HCT116(ic50μM)	205.6	184.9	269.5	16887	2811	3256

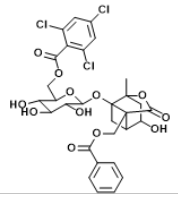
LogP Analysis

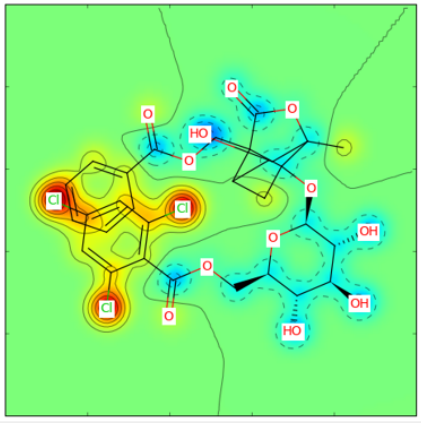
AL-1
logP: 1.11



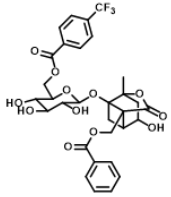


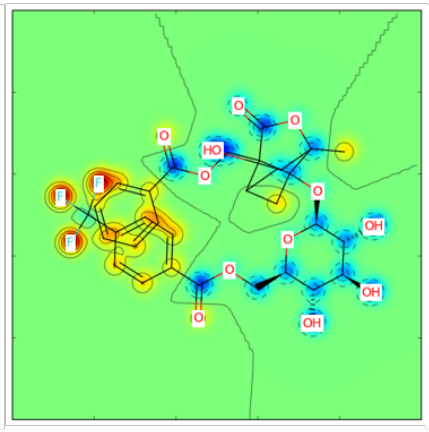
AL-2
logP: 2.31



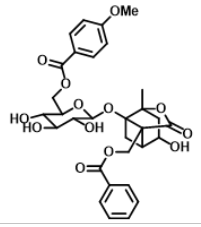


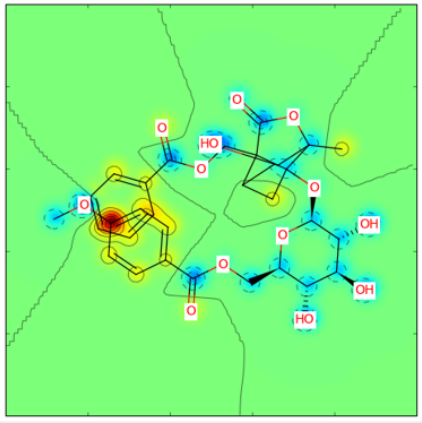
AL-3
logP: 1.37



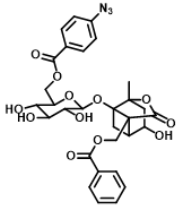


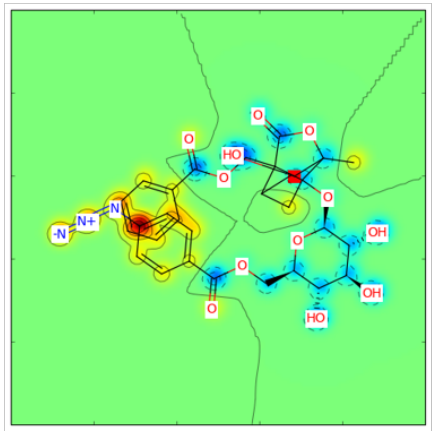
AL-4
logP: 0.36



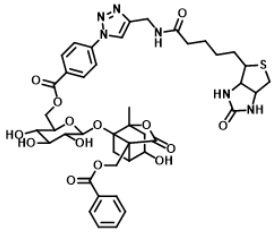


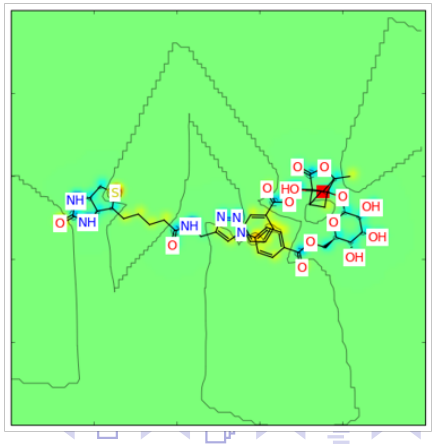
AL-5
logP: 1.29





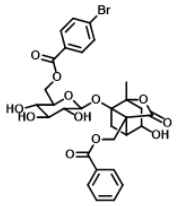
AL-Probe
logP: 0.27

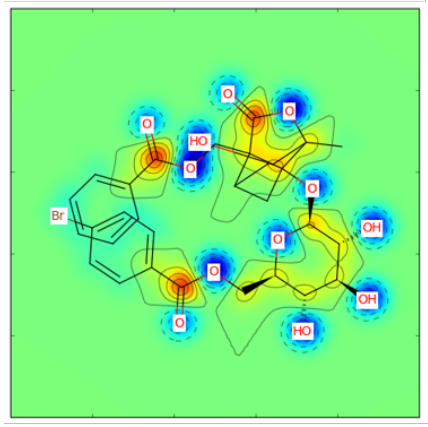




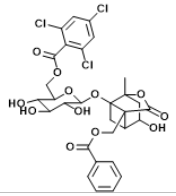
Partial Charge

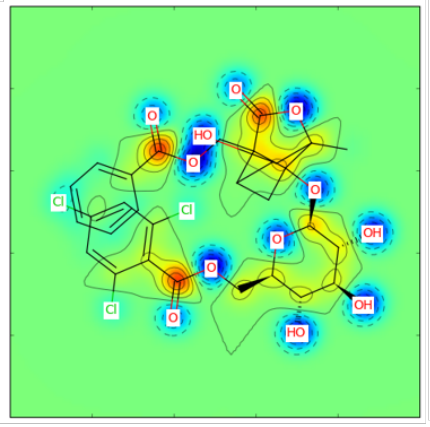
AL-1



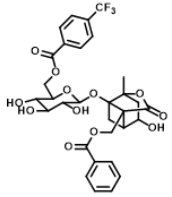


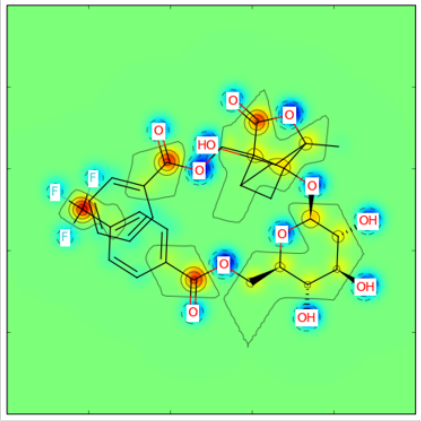
AL-2



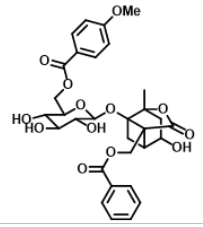


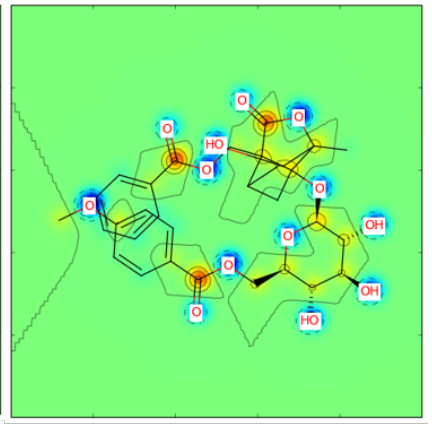
AL-3



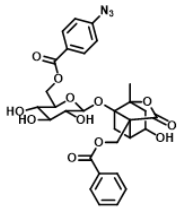


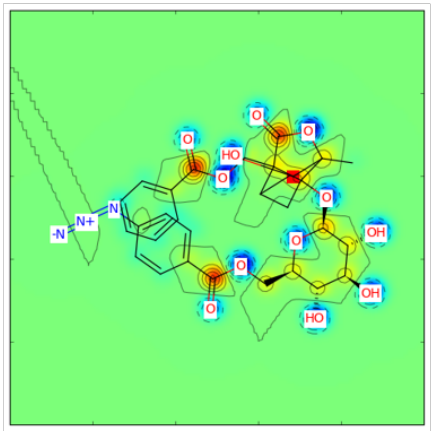
AL-4



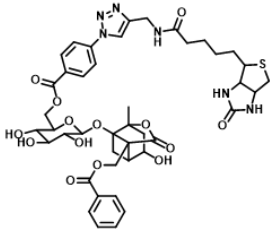


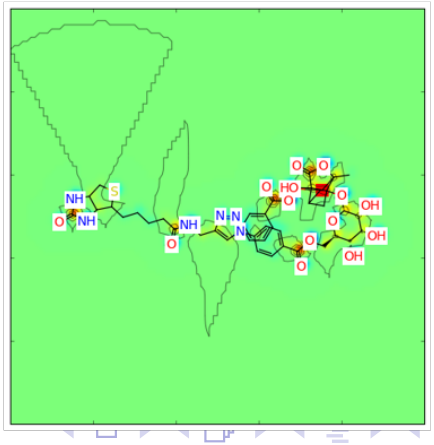
AL-5





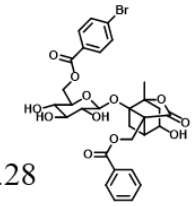
AL-Probe

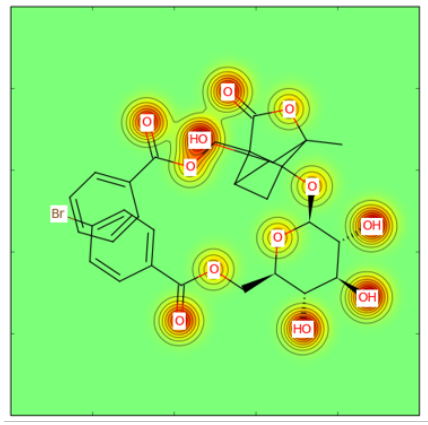




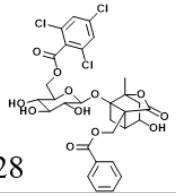
TPSA

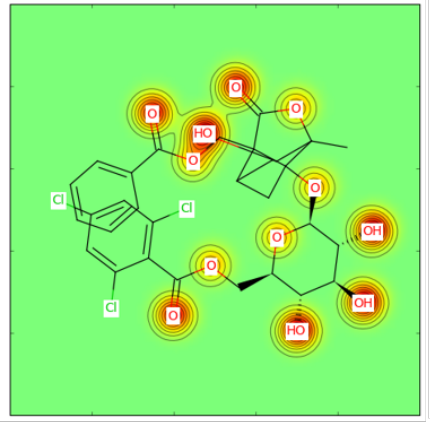
AL-1
TPSA = 178.28



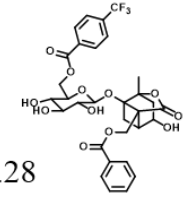


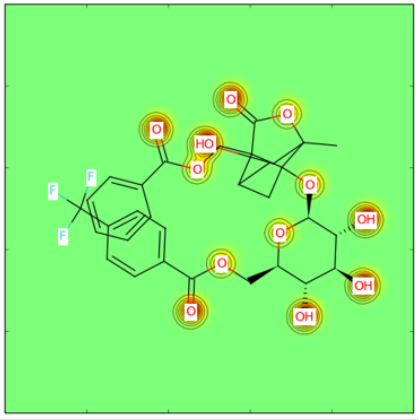
AL-2
TPSA=178.28





AL-3
TPSA=178.28





AL-4
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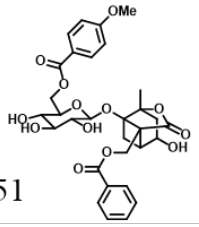

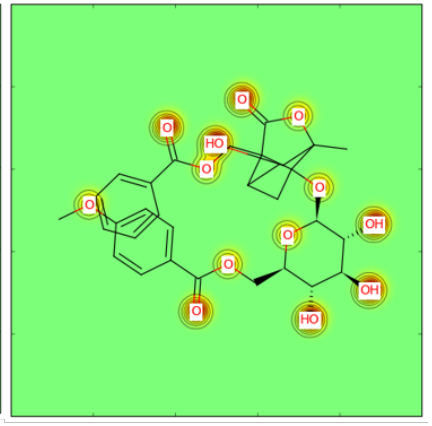

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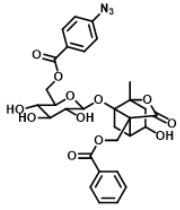

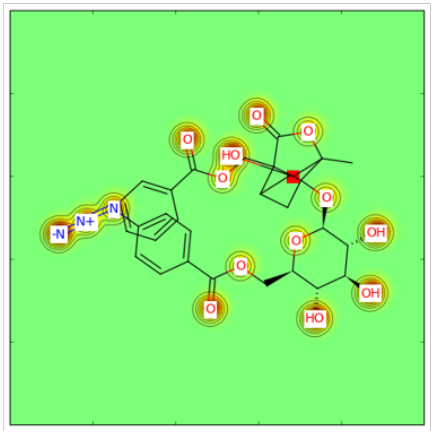

AL-Probe
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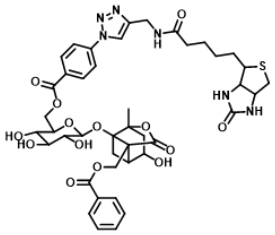

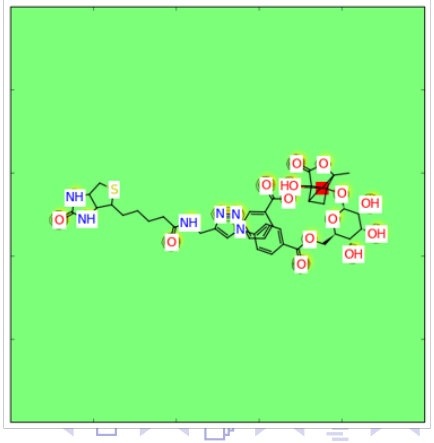

Discussion

Explore a new strategy to study natural products.

- Discovery by computational methods.
- Biological experiments validation.
- Computational Simulation and analysis all the possible analogs.
- Medicinal chemistry-based experiments validation.