Polypharmacology: Drug promiscuity and its trends

Presented by Arunabh Sharma

Introduction

- **Polypharmacology**

  - property of bioactive compounds to act on multiple physiological targets

- **Promiscuity**

  - ability of small molecules to specifically bind to multiple targets

Promiscuity progression

- Statistically significant trends can be deduced from large activity datasets
- Trends can be detected by observing promiscuity over time

Data sets

- **High confidence**

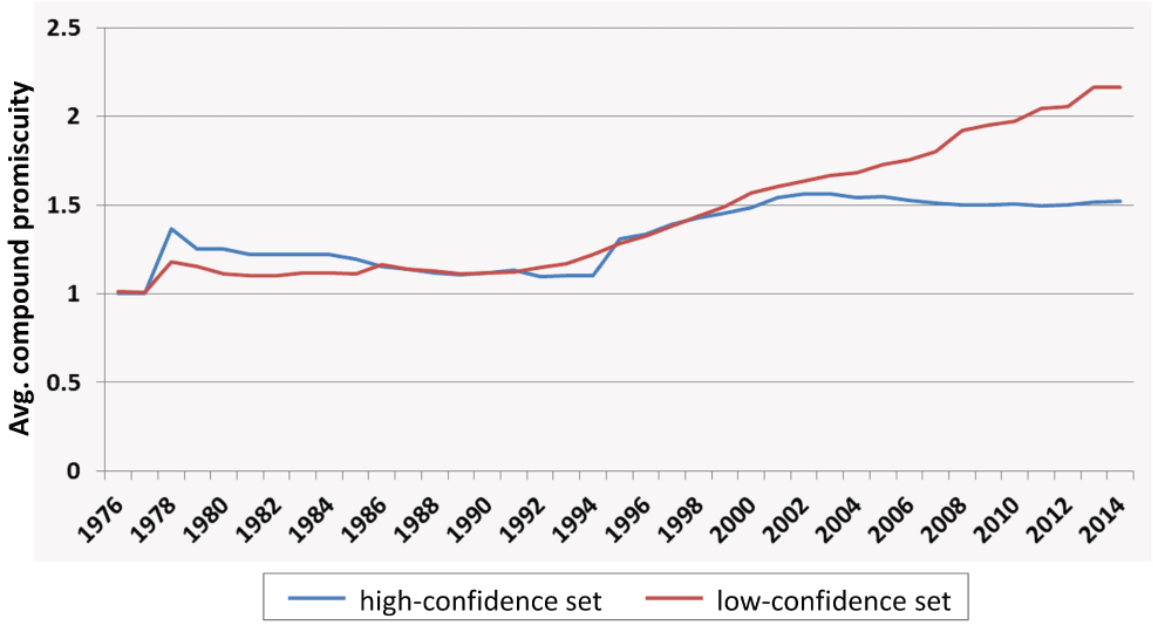
  - Assay confidence score 9

  - Assay relationship type “D”

  - Compounds with explicitly defined K_i and/or IC_{50} values

- **Low confidence**

Promiscuity over time



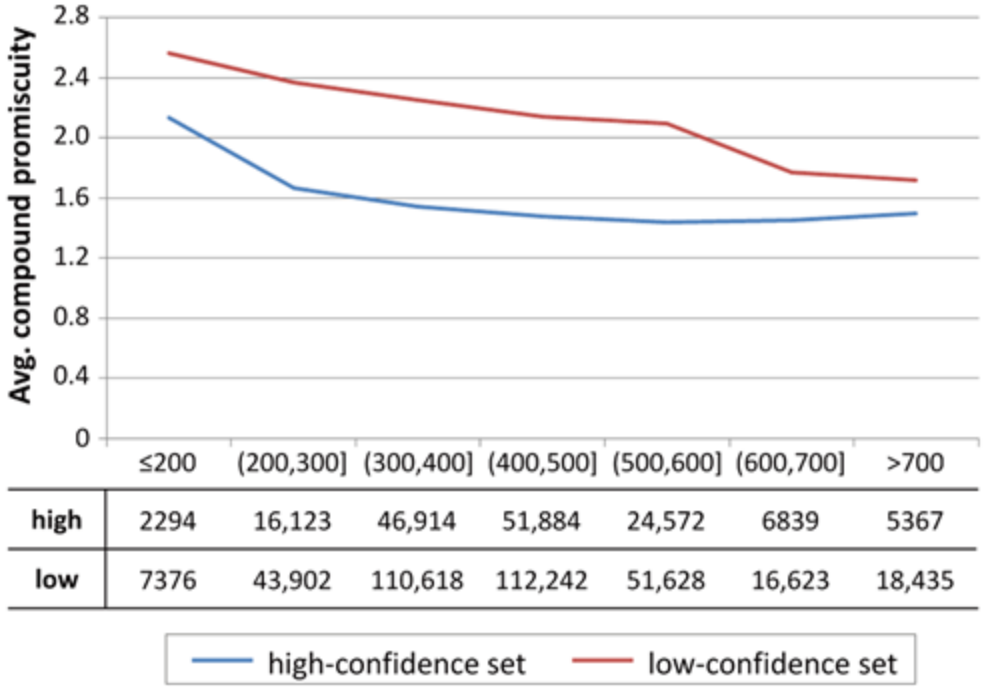
Promiscuity degrees

ΔPromiscuity	#Compounds	
	High-confidence	Low-confidence
0	151,786	352,466
1	1239	4099
2	469	1721
3	220	816
4	102	398
5	65	305
6-10	130	698
11-20	40	283
21-50	9	137
> 50	2	236

Constant degree of promiscuity

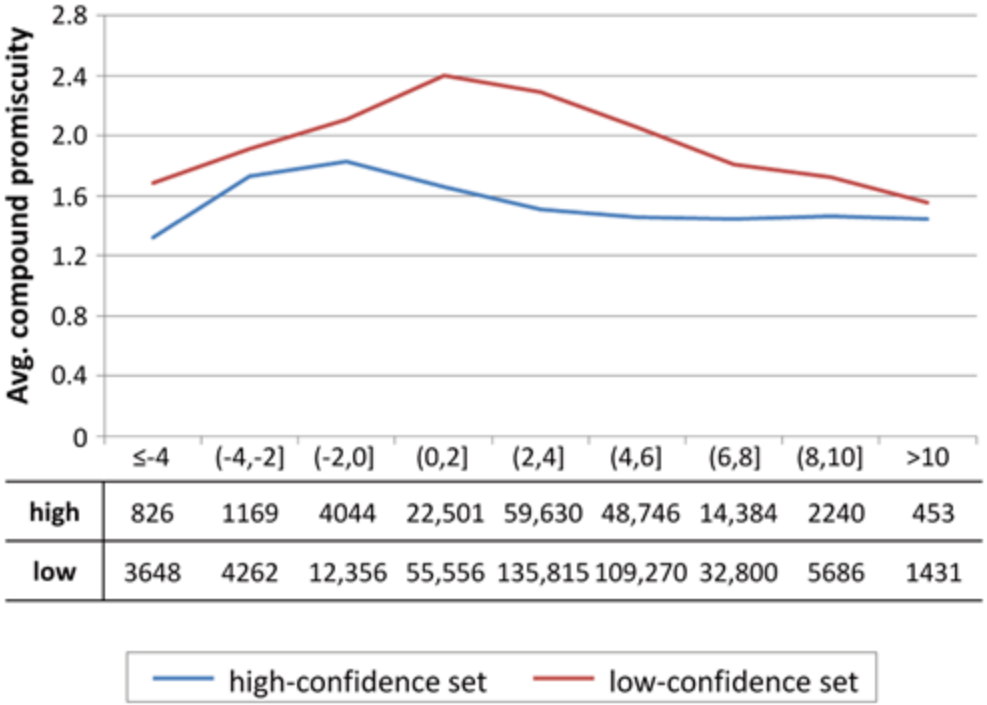
- 98.5% of high-confidence set
- 97.6% of low-confidence set

Molecular weight and promiscuity



	≤200	(200,300]	(300,400]	(400,500]	(500,600]	(600,700]	>700
high	2294	16,123	46,914	51,884	24,572	6839	5367
low	7376	43,902	110,618	112,242	51,628	16,623	18,435

Lipophilicity and promiscuity



	≤-4	(-4,-2]	(-2,0]	(0,2]	(2,4]	(4,6]	(6,8]	(8,10]	>10
high	826	1169	4044	22,501	59,630	48,746	14,384	2240	453
low	3648	4262	12,356	55,556	135,815	109,270	32,800	5686	1431

Conclusions

- Generally low degree of promiscuity for bioactive compounds over time
- Promiscuity was constant for most compounds in ChEMBL
- Small influence of data confidence levels on promiscuity progression

Such a PAIN(S)!


INTRODUCING... THE PAINS
Come hither.
Mashy-mashy!
I'm always around.
Let's go the wrong way.
1 TON
I ♥ METAL
"The Redox Rogue"
"Covalent Con"
"Membrane Masher"
"The False Profit"
"All-Over Ogre"
"Triple Threat"
"Reviewer's Remorse"
"No-no Quinones"

Further reading

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Rules for Identifying Potentially Reactive or Promiscuous Compounds

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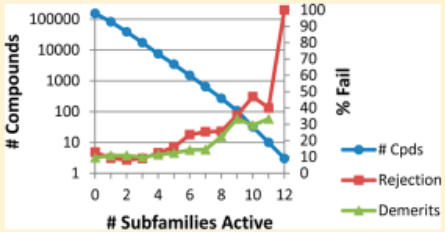
Supporting Information

ABSTRACT: This article describes a set of 275 rules, developed over an 18-year period, used to identify compounds that may interfere with biological assays, allowing their removal from screening sets. Reasons for rejection include reactivity (e.g., acyl halides), interference with assay measurements (fluorescence, absorbance, quenching), activities that damage proteins (oxidizers, detergents), instability (e.g., latent aldehydes), and lack of druggability (e.g., compounds lacking both oxygen and nitrogen). The structural queries were profiled for frequency of occurrence in druglike and nondruglike compound sets and were extensively reviewed by a panel of experienced medicinal chemists. As a means of profiling the rules and as a filter in its own right, an index of biological promiscuity was developed. The 584 gene targets with screening data at Lilly were assigned to 17 subfamilies, and the number of subfamilies at which a compound was active was used as a promiscuity index. For certain compounds, promiscuous activity disappeared after sample repurification, indicating interference from occult contaminants. Because this type of interference is not amenable to substructure search, a "nuisance list" was developed to flag interfering compounds that passed the substructure rules.



References

- Hu Y, Jasial S & Bajorath J. Promiscuity progression of bioactive compounds over time [v2; ref status: indexed, f1000r.es/5h4] F1000Research 4(Chem Inf Sci):118 (doi: 10.12688/f1000research.6473.1), 2015.

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- Baell, Jonathan, and Michael A. Walters. "Chemical con artists foil drug discovery." Nature 513.7519 (2014): 481-483.