

Design and Linkage of Compound Filters to HTS Assay Promiscuity

Bradley C. Pearce, Michael J. Sofia, Dieter M. Drexler,
David A. Stock
Bristol-Myers Squibb, Wallingford, CT

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BMS Screening Deck Flags / Filters

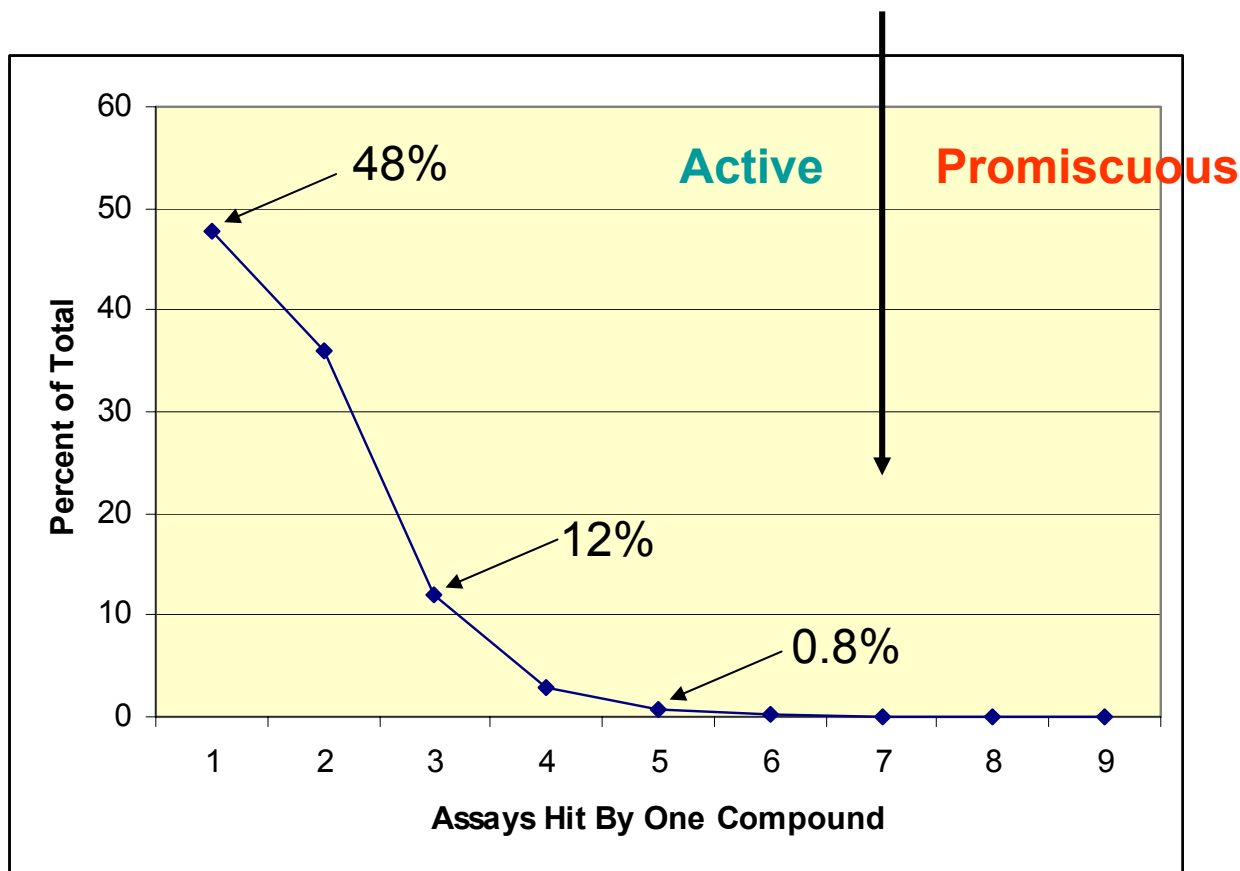
- *Property flags: Compounds flagged ≥ 2
 - MW > 639 & absolute cutoff if MW ≤ 130 or ≥ 900
 - cLogP < -3 or > 5.5
 - HBD > 5
 - HBA > 9
 - RTB > 14
- Functional group queries
 - Annotation flags
 - Exclusion filters
 - Daylight SMARTS-based
- How effective are these flags / filters?

* Wenlock et al. J. Med. Chem. 2003, 46, 1250-1256.

Linkage of Property and Functional Group Filters to Promiscuous HTS Data

- Used verified primary HTS data
 - Unfiltered – No HTS triage biases
 - 12 Years of data
 - Greater than 61 million data points
 - Annotated by screeners – Inactive 0, Active 1
- Definitions:
 - *Inactive* = Inactive and have seen > 15 assays
 - *Active* = Active in ≥ 1 and < 7 assays
 - *Promiscuous* = Active in ≥ 7 assays

Active Primary HTS Data

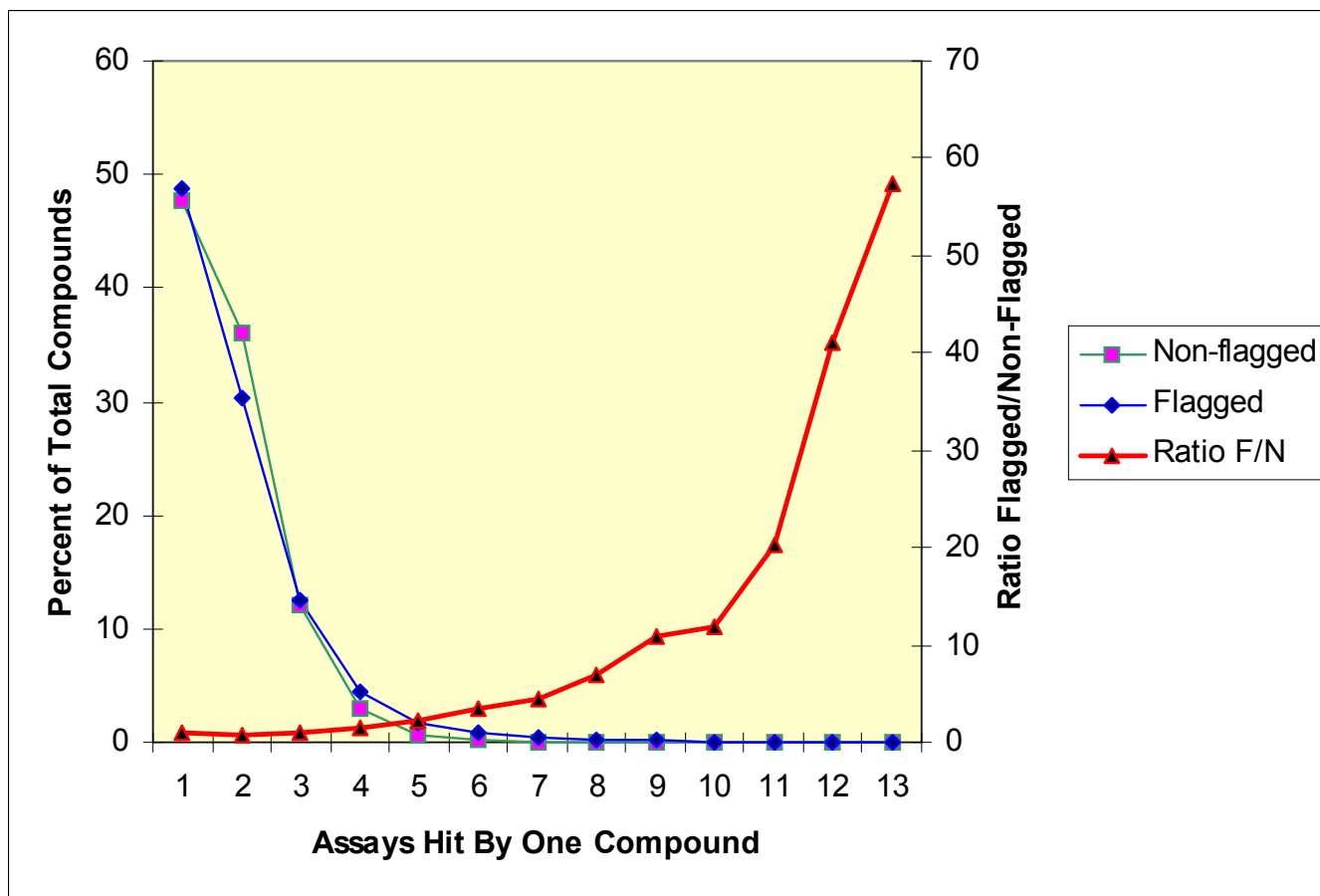


Evaluation of Property and Functional Group Filters Using HTS Data

HTS Classification	% Property Fails	% Functional Group Fails
Inactive	3.3	4.3
Active	4.8	5.5
Promiscuous	4.4	10.9

- Compound Promiscuity
 - Weak correlation to property filters
 - Strong correlation to functional group filters

Active Primary HTS Data Functional Group Filter Impact

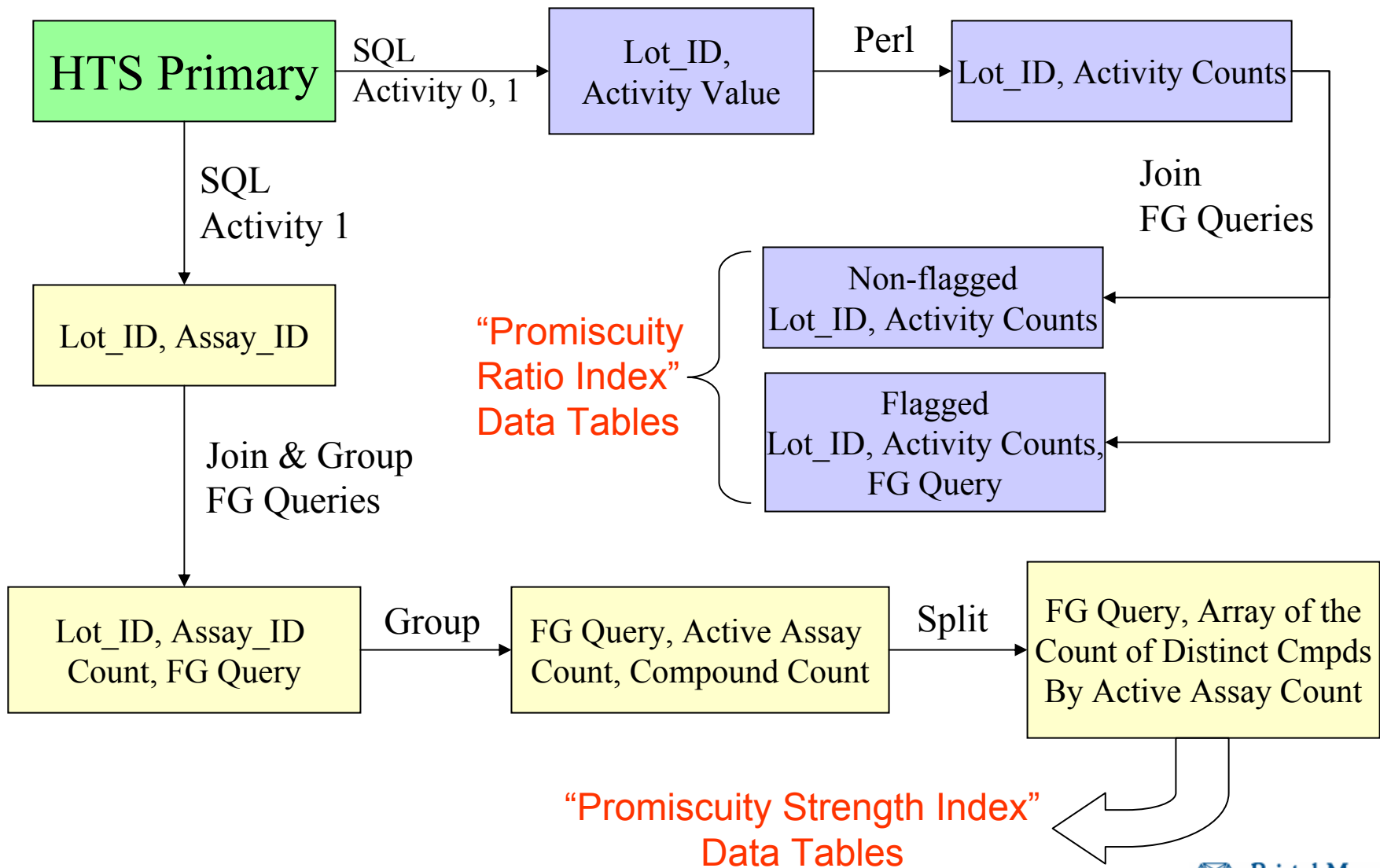


➤ Promiscuity strongly associated with functional group flagged compounds

Functional Group Filter Analysis

- Lajiness et al. J. Med. Chem. 2004, 47, 4891-4896.
 - Any two med chemists agree only 28% of the time !
 - The same med chemist is only 50% consistent !
- Filter design is highly dependent on personal biases
- Reduce subjectivity by relying on empirical data
 - In-depth analysis of primary HTS data and FG filters
 - Linkage of compound screening promiscuity to FG filter
 - Expected percentage of actives relative to HTS
 - How the actives translate across multiple assays
- For this analysis we used the entire set of annotation and exclusion-based SMARTS

Process Map for Determining “Promiscuity Ratio Index” (PRI) and “Promiscuity Strength Index” (PSI)



Promiscuity Ratio Index (PRI) Calculation & Statistical Method

The PRI is a measure of how strongly compounds grouped or flagged by a particular functional group filter are active in assays versus background HTS (HTS)

- $PRI = \text{mean FG filter \% actives} / 1.925$
- Statistical analysis
 - 95% Confidence intervals constructed for a ratio
- Rule classifications:
 - *Less* is where confidence bounds < 1
 - *Same* is where confidence bounds contain 1
 - *Greater* is where confidence bounds > 1

Promiscuity Strength Index (PSI) Calculation & Statistical Method

The PSI is a measure of how strongly active compounds grouped or flagged by a particular functional group filter express that activity across an increasing number of assays

- Weighted mean of the number of actives for each compound flagged by a particular functional group filter
- $PSI = 3.29 \pm 0.004 \text{ SE}$ for HTS benchmark
- Standard t-statistics applied
- Rule classifications:
 - *Less* is where $PSI < 3.29$ and $p\text{-value} < 0.05$
 - *Same* is where $p\text{-value} > 0.05$
 - *Greater* is where $PSI > 3.29$ and $p\text{-value} < 0.05$

HTS Filter Promiscuity Linkage

Linkage Rating Based on Statistical Rule Classes:

- LOW (9%)
 - PRI & PSI both *less* or one *same* one *less*

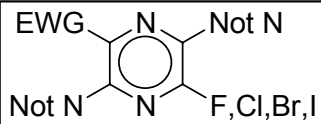
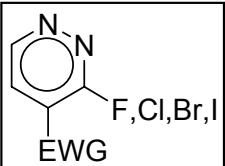
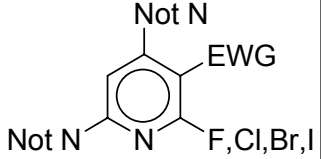
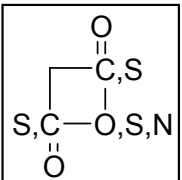
- MEDIUM (18%)
 - PRI & PSI both *same* or one *greater* one *less*

- HIGH (64%)
 - PRI & PSI both *greater* or one *same* one *greater*

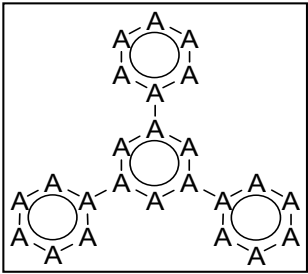
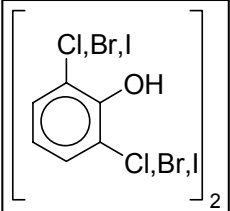
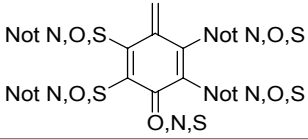
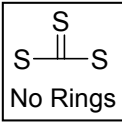
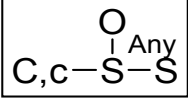
Structural Integrity (SI) Data

- Connectivity between functional group filter flag and screening data depend on compound SI
- Coupled LC/MS: compound identity and integrity
- SI passes where purity > 75% with expected MW
- Limited set of historic SI data on deck compounds
- Non or under-represented flagged compounds supplemented by additional SI analyses
- Current data does not necessarily link to past conditions
- General guide to suspected reactivity patterns

Functional Group Filter Linkage to HTS Data – Some LOW Examples

Functional Group Filter	Distinct Cmpds	Query Structure	PRI	PRI Class	PSI	PSI Class	% Pass SI	Linkage
2halo pyrazine 5EWG	78		0.11	Less	1	Same	0	LOW
2halo pyridazine 3EWG	40		2.08	Same	1.09	Less	30	LOW
2halo pyridine 3EWG	890		0.82	Less	2.72	Less	56	LOW
Activated 4mem ring	28		0.15	Less	5	Same	0	LOW

Functional Group Filter Linkage to HTS Data – Some HIGH Examples

Functional Group Filter	Distinct Cmpds	Query Structure	PRI	PRI Class	PSI	PSI Class	% Pass SI	Linkage
Branched polycyclic aromatic	729		3.73	Greater	9.49	Greater	50	HIGH
Polyhalo phenol d	40		9.84	Greater	23.3	Greater	25	HIGH
Quinone methide	160		6.91	Greater	9.1	Greater	29	HIGH
Thio xanthate	52		4.68	Greater	14.78	Greater	33	HIGH
thiosulfoxide	6		4.92	Greater	11	Greater	0	HIGH

Functional Group Filter Linkage to HTS Data – Controls

Functional Group Filter	PRI	PRI Class	PSI	PSI Class	% Pass SI	Linkage
All HTS Data	1	NA	3.29	NA	73	NA
diphenylmethane	1.23	Greater	3.75	Greater	74	HIGH
ethylcarbamate	0.83	Less	3.81	Greater	79	MED
hydantoin	0.91	Less	4.18	Greater	83	MED
indole	0.83	Less	3.88	Greater	80	MED
isoquinoline	0.74	Less	3.52	Same	92	LOW
phenethylamine	1.43	Greater	3.20	Less	86	MED
SI > 75% purity	1.47	Greater	4.50	Greater	100	HIGH
SI < 50% purity	2.05	Greater	5.10	Greater	0	HIGH

- Indole & phenethylamine ⇒ Considered GPCR privileged structures
 - Levels of promiscuity similar to HTS background
- Diphenylmethane ⇒ Prevalent substructure in many drug databases
 - Higher level of promiscuity but still on low end of high class
- Ethylcarbamate, hydantoin, isoquinoline ⇒ no particular bias
 - None of these differ strongly from HTS
- Structural Integrity Flags
 - Modest trend of highly impure compounds being more promiscuous

Functional Group Filter Implementation

- Example of LOW: 2-Halo Pyridine 3-EWG
 - Low PRI and PSI values
 - In general, these halo-substituted π -deficient systems are not showing high linkages to promiscuity

Action \Rightarrow filter removal
- Example of MED: Trichloromethyl Ketone
 - Similar to HTS means with respect PRI and PSI
 - Typical of other reversible electrophiles

Action \Rightarrow compound annotation flag
- Example of HIGH: Polyhalo Phenol D
 - Excessively high PRI and PSI values

Action \Rightarrow compound exclusion from screening

Future Directions

- Only 15% of the promiscuous HTS hits are flagged by current FG filters
 - Other mechanisms of compound promiscuity
 - Compound aggregation
Shoichet et al. J. Med. Chem. 2002, 45, 1712-1722.
- Cheminformatic approaches:
 - New SMARTS functional group queries
 - Bayesian modeling (SciTegic)
 - Other software such as LeadScope
 - Understanding new descriptor linkages using statistical mapping to HTS data

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