Mining promiscuous substructures in PubChem using molecular matching pairs

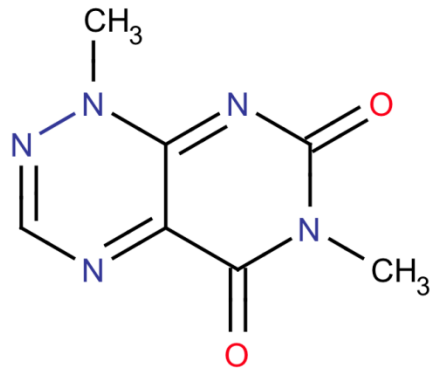
Oleg Ursu

University of New Mexico

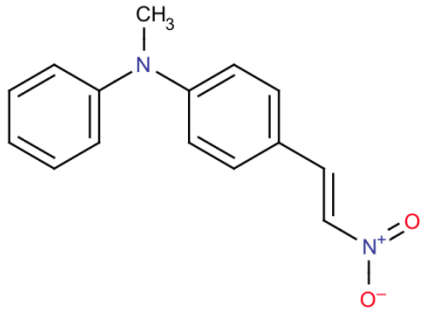
The University of New Mexico • Health Sciences Center
SCHOOL OF MEDICINE

Frequent hitters

- Hits in many unrelated HTS assays
  - Promiscuous compounds (aggregation, reactive, etc.)
  - Assay interference (fluorescence, quenchers, etc.)
- Experts knowledge/SMARTS rules
- Not available in public domain



558/194

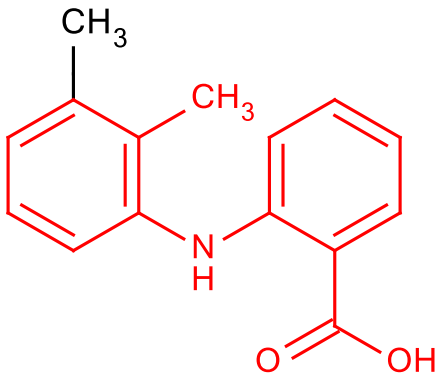


452/62

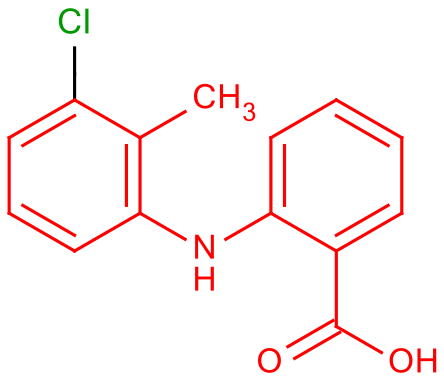
Molecular matching pairs

Molecular pair

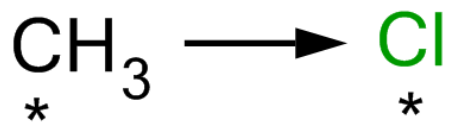
Molecular transformation



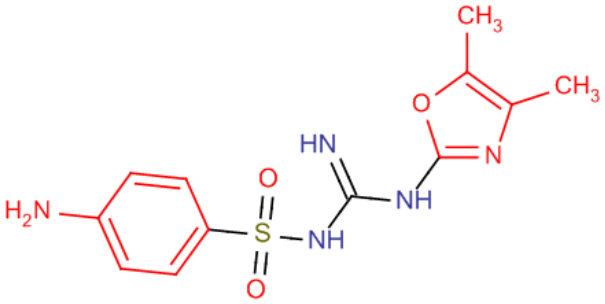
Mefenamic acid



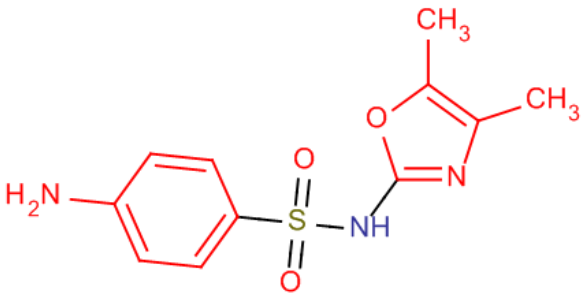
Tolfenamic acid



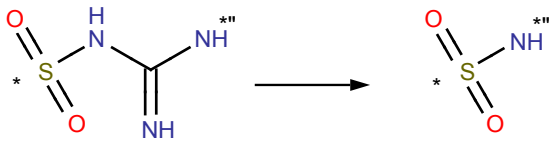
Single cut



Sulfaguanole



Sulfamoxole



Double cut

MMPs applications and implementations

- Identify molecular transformations in a series of chemical structures
- Map molecular transformations to changes in biological/chemical/physical properties
- Study bioisosterism, activity cliffs, SAR
- Guide optimization of: aqueous solubility, plasma protein and hERG biding, P450 metabolism
- Leatherface[1], WizePairZ[2], Hussain[3]

1. Cheminformatics in Drug Discovery, 2004, 271-285
2. J. Chem. Inf. Model. 2010, 50, 1350-1357
3. J. Chem. Inf. Model. 2010, 50, 339-348

PubChem database

- Chemical and biological activity database, NIH funded
- Data deposited by 9 Molecular Libraries centers
- Additional data from NCI, ChEMBL, Pharma, etc.

	Total	Molecular Libraries
Substances	~ 85 mil	~ 400k
Assays	504,228	3,860 (0.77%)
Screening data points	~142 mil	**~134 mil (94%)**

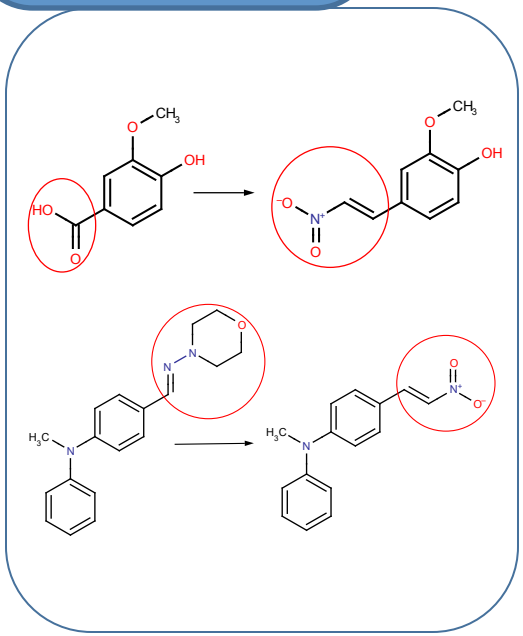
August 2011

Frequent hitters to promiscuous substructures

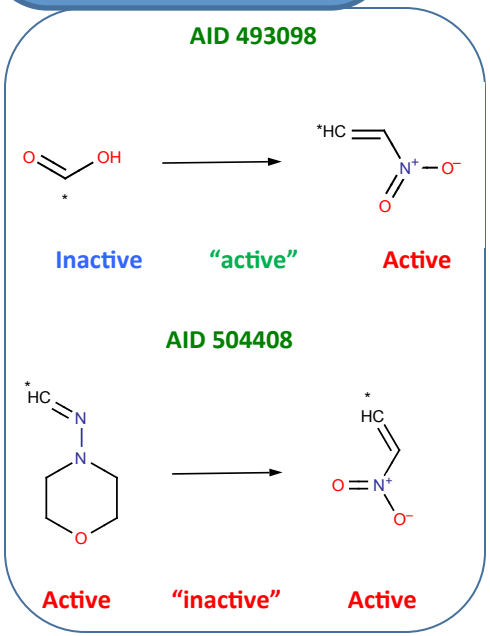
Download and clean MLSMR library from PubChem

- Salt and solvent removal
- Tautomers

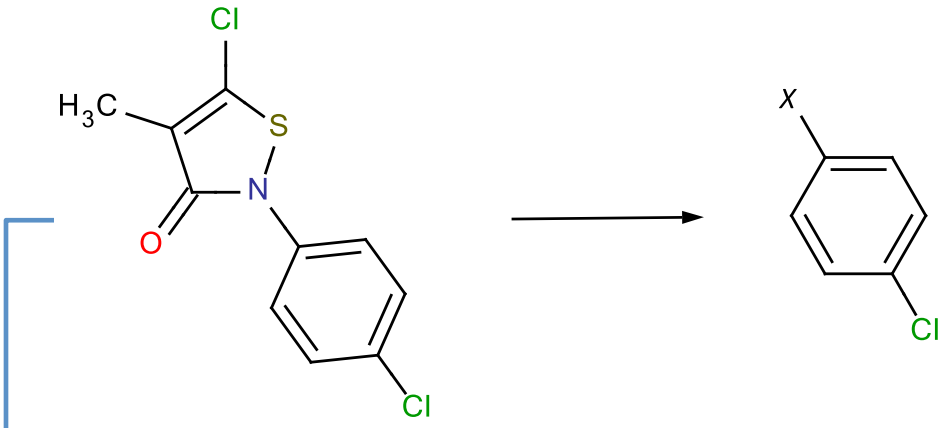
Identify all non-redundant single, double, and triple cut MMPs



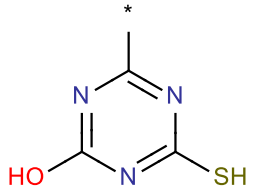
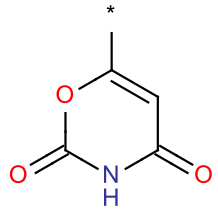
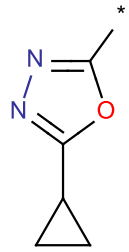
Map "active" MMPs to HTS assays



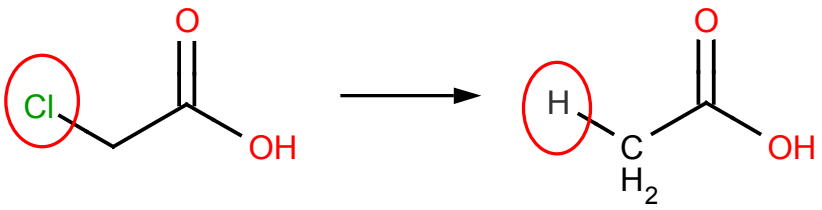
“Promiscuous” fragments

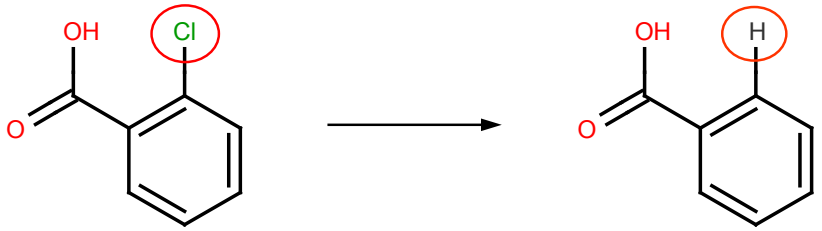


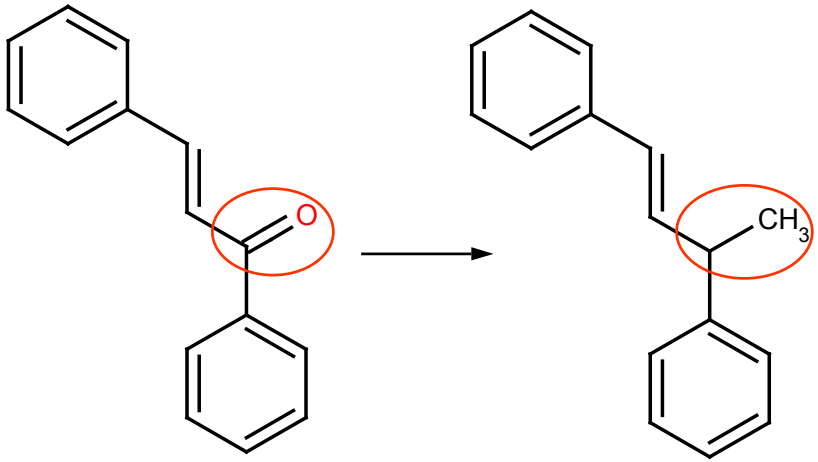
24792062
Tested assays 359
Active assays 75

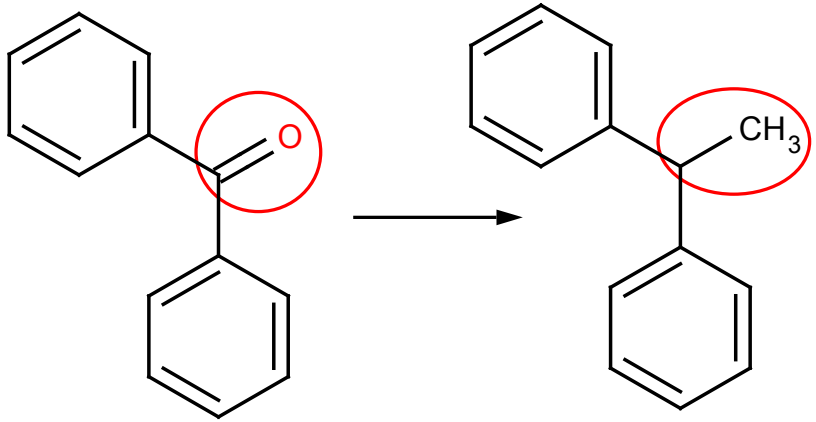
X	Tested assays	Active assays
 26731534	354	1
 26728462	354	1
 26728988	348	1

MMP environments









Promiscuity score

$$score = \frac{active\ subst.}{tested subst. + median(tested subst.)} \times$$

$$\frac{active\ mmps}{tested\ mmps + median(tested\ mmps)} \times$$

$$\frac{active\ assays}{tested assays + median(tested assays)} \times$$

$$\frac{active\ samples}{tested samples + median(tested samples)} \times 1600$$

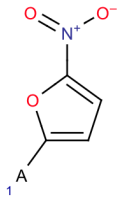
# of substances with 1 or more "active" MMPs

of "active" MMPs for each component

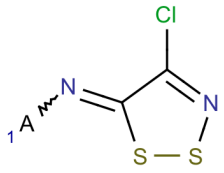
distinct assays with 1 or more "active" MMPs

of samples mapped to each "active" MMP

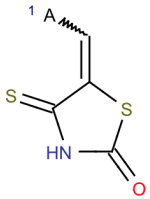
Top promiscuous fragments



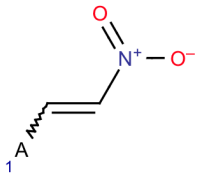
25/24
61/59
421/97
7436/395
7.16



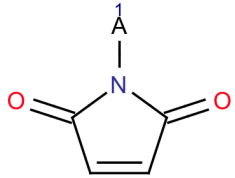
23/23
1113/1101
576/79
7736/410
5.83



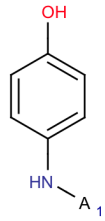
6/6
268/264
416/76
2195/140
5.53



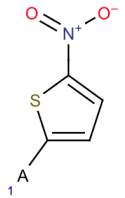
32/24
208/198
453/110
10729/460
5.48



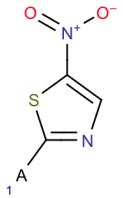
29/24
378/336
470/79
6275/340
4.92



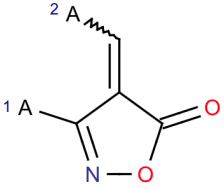
12/12
96/96
564/72
4242/221
4.40



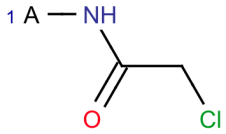
21/19
50/46
397/70
5649/268
4.01



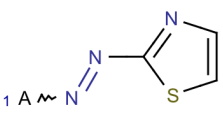
42/35
256/185
470/100
11104/394
3.49



6/6
520/498
465/60
2070/109
3.32



70/56
344/323
472/92
24694/587
2.81



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444/79
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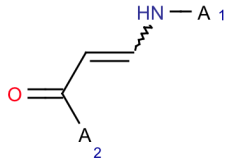
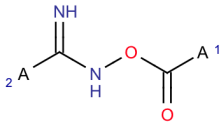


40/35
890/769
568/80
13417/388
2.64



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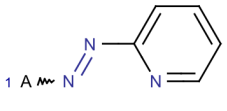
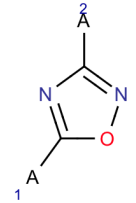
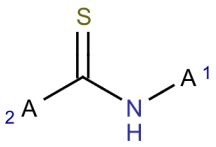
568/537
474/65
17155/475
2.56



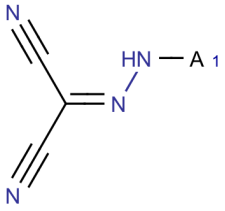
4/3
189/114
446/69
976/100
2.53



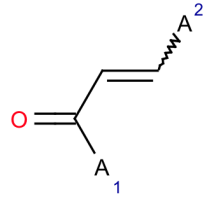
59/46
499/456
578/101
22394/509
2.50



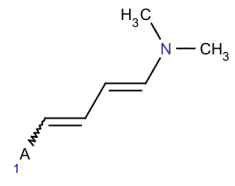
10/10
329/296
552/65
3625/128
2.48



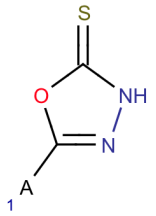
9/9
254/249
452/52
3283/116
2.32



39/35
204/154
454/80
11226/250
1.99



2/2
16/15
396/59
692/63
1.93



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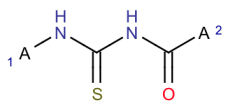
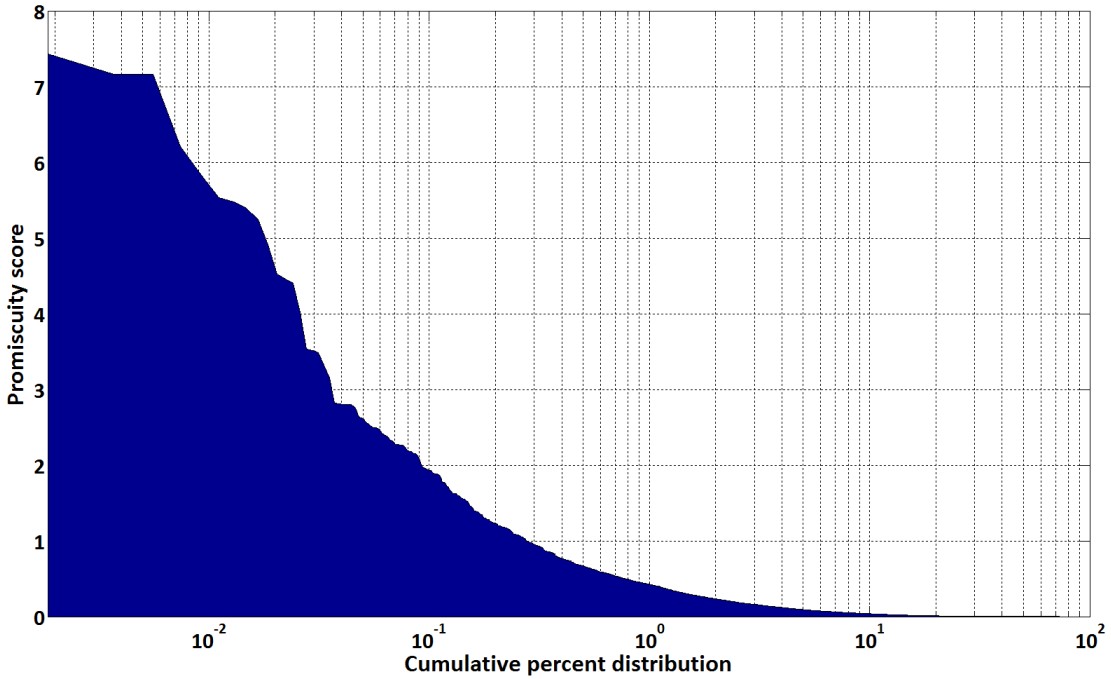


91/51
424/347
454/70
28318/454
0.91

tested substances/active substances
tested MMPS/active MMPS
tested assays/active assays
tested samples/active samples
promiscuity score

Promiscuity score distribution

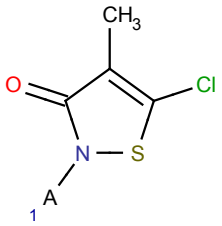
- 651,299 unique single cut MMPs
- 777,931 unique double cut MMPs
- 73,191 unique triple cut MMPs
- 53,993 number of unique fragments



Preclinical Development

Molecular Cancer Therapeutics

Tyrosine Phosphatase Inhibitor-3 Sensitizes Melanoma and Colon Cancer to Biotherapeutics and Chemotherapeutics



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

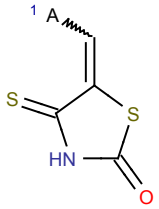
journal homepage: www.elsevier.com/locate/bmc

Synthesis of isothiazol-3-one derivatives as inhibitors of histone acetyltransferases (HATs)

Stephen G 6716
Michael Ja

J. Med. Chem. **2009**, *52*, 6716–6723
DOI: 10.1021/jm901016k

Journal of Medicinal Chemistry Article

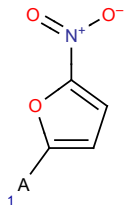


Multidentate Small-Molecule Inhibitors of *Vaccinia* H1-Related (VHR) Phosphatase Decrease Proliferation of Cervix Cancer Cells†

Shuangding Wu,‡,§ Sofie Vossius,⊥,‡ Souad Rahmouni,‡,⊥ Ana V. Miletic,§ Torkel Vang,§ Jesus Vazquez-Rodriguez,§ Fabio Cerignoli,§ Yu Tomas Mustelin,§ an

OPEN ACCESS Freely available online

PLoS one



The ERAD Inhibitor Eeyarestatin I Is a Bifunctional Compound with a Membrane-Binding Domain and a p97/VCP Inhibitory Group

Qiuyan Wang[1],
Wiestner[2], Willi

1 Laboratory of Molecular
America, 2 Hematology Br
Biochemistry and Biology,
4 The Genomics Core Lab
America

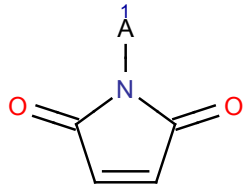
J. Med. Chem. 1996, *39*, 1692−1703

Design, Synthesis, and Biochemical Evaluation of *N*-Substituted Maleimides as Inhibitors of Prostaglandin Endoperoxide Synthases†

Amit S. Kalgutkar, Brenda C. Crews, and Lawrence J. Marnett*

A. B. Hancock, Jr., Memorial Laboratory for Cancer Research, Department of Biochemistry, Center in Molecular Toxicology and Vanderbilt Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Received November 29, 1995[⊗]



N-(Carboxyalkyl)maleimides are rapid as well as time-dependent inhibitors of prostaglandin endoperoxide synthase (PGHS). The corresponding *N*-alkylmaleimides were only time-dependent inactivators of PGHS, suggesting that the carboxylate is critical for rapid inhibition. Several *N*-substituted maleimide analogs containing structural features similar to those of the nonsteroidal anti-inflammatory drug aspirin were synthesized and evaluated as inhibitors of PGHS. Most of the aspirin-like maleimides inactivated the cyclooxygenase activity of purified ovine PGHS-1 in a time- and concentration-dependent manner similar to that of aspirin. The peroxidase activity of PGHS was also inactivated by the maleimide analogs. The cyclooxygenase

Conclusions

- Automated tool to identify promiscuous patterns in a database of biological activities
- Uses ChemAxon JChem/Marvin API for:
  - I/O; fragmentation; SMARTS match/generation; SMIRKS generation; chemical structure/patterns depiction
- Filter unwanted HTS hits
- Questions?