Second Annual McKim Conference

Superfragment Generation

How it aids in assigning Toxic Alerts

Part of the OECD Toolbox

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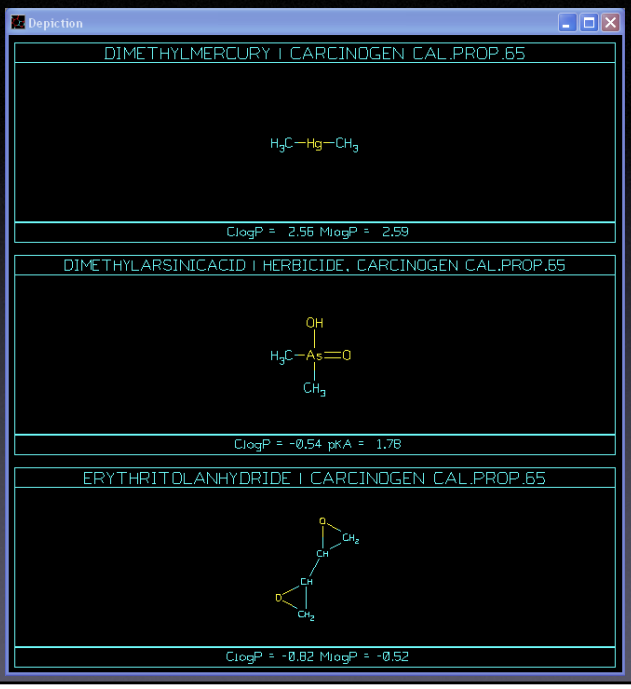
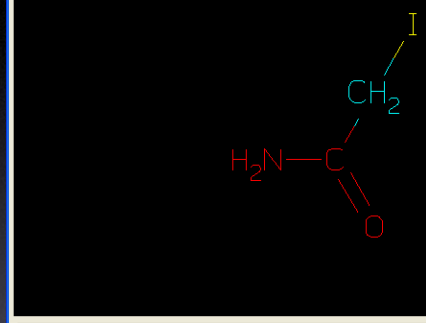
BioByte Corporation
Claremont, CA

Obvious Alert Hazards



IODOACETAMIDE :



Class	Type	Log(P) Contribution Description	Comment	Value
Fragment	# 1	NH2-Amide [A]	Measured	-1.990
Fragment	# 2	Iodide [A]	Measured	.590
Carbon		1 aliphatic isolating carbon		.195
ExFragment	Hydrog	2 hydrogens on isolating carbons		.454
ExFragment	Bonds	1 chain and 0 alicyclic (net)		-.120
Proximity	Y2-X1	Effect for Y-fragment #1		.900
RESULT	DB=23	All fragments measured	CLOGP=5	.029

Interactive 'extended fragment' analysis

Interactive 'extended fragment' analysis

Enter SMILES, name or CAS: iodoacetamide

Cut-off value (default is .89):

Submit

SMILES:
NC(=O)CI

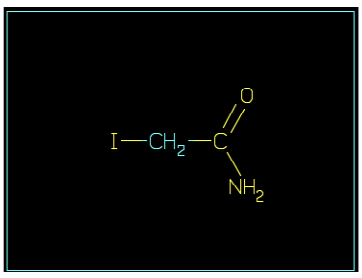
Fragments:

1	NH2-Amide [A]	Measured	-1.99	
2	Iodide [A]	Measured	.59	

Proximity:

Y2-X1	Effect for Y-fragment #1		.90

Whole molecule is an extended fragment.



Interactive 'extended fragment' analysis

Interactive 'extended fragment' analysis

Enter SMILES, name or CAS: ICCC(=O)N

Cut-off value (default is .80):

Submit

SMILES:
NC(=O)CCI

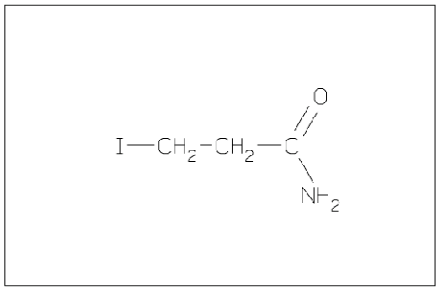
Fragments:

1	NH2-Amide [A]	Measured	-1.99
2	Iodide [A]	Measured	.59

Proximity:

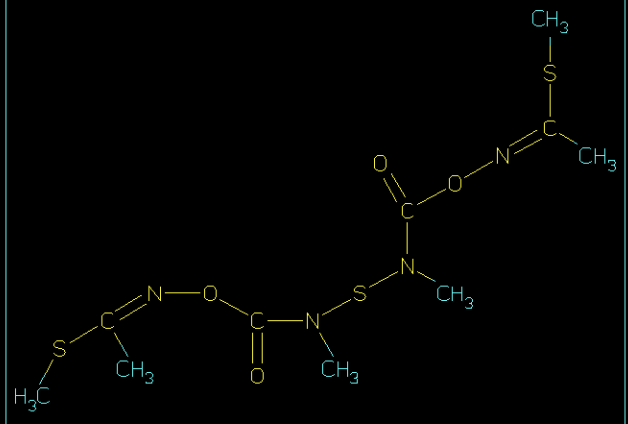
XCCY	0 F and 1 non-F interactions		.35

No superfragments found!

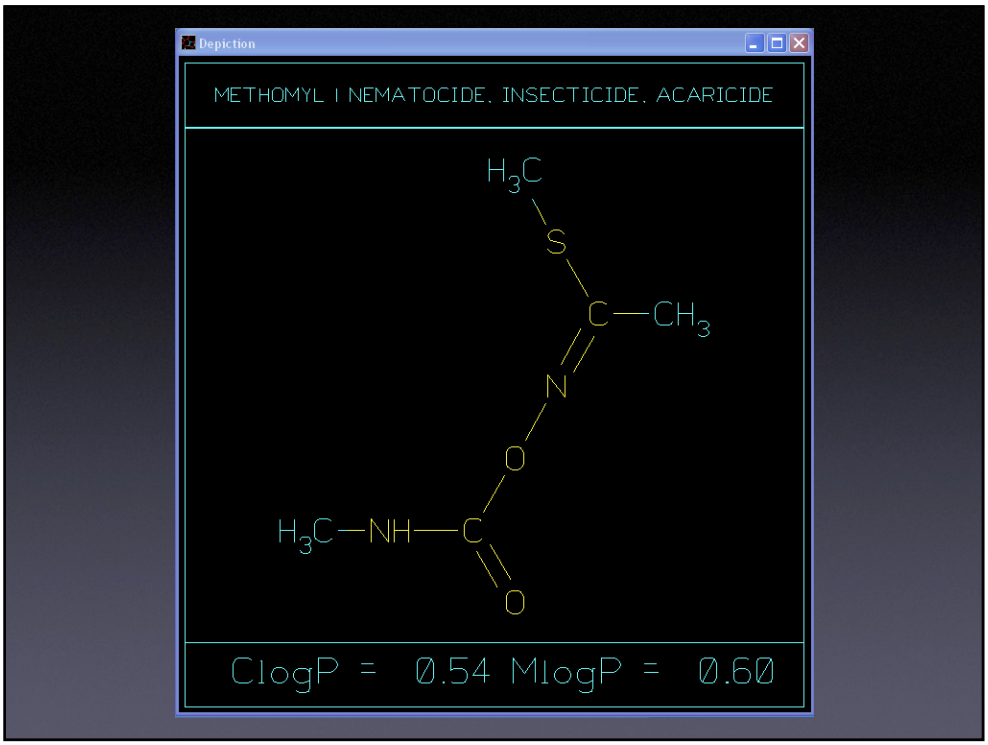


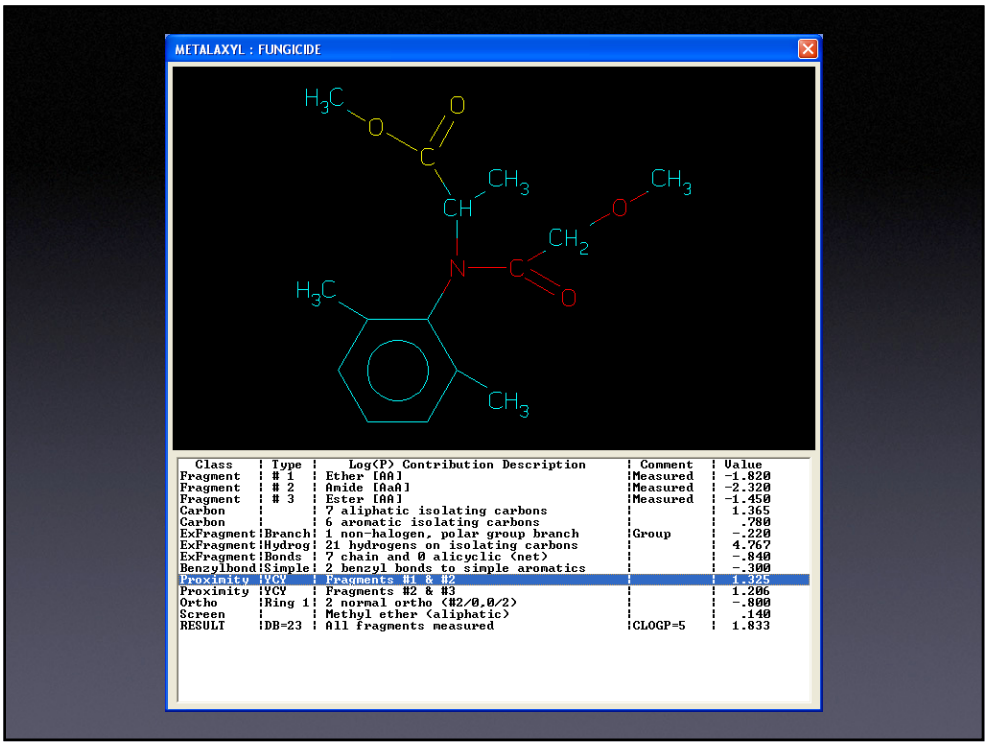
Depiction

THIODICARB I INSECTICIDE, CARCINOGEN CAL.PROP.65



ClogP = 1.70 MlogP = 1.70





Class	Type	Log(P) Contribution Description	Comment	Value
Fragment	# 1	Ether [AA]	Measured	-1.820
Fragment	# 2	Amide [AaA]	Measured	-2.320
Fragment	# 3	Ester [AA]	Measured	-1.450
Carbon		7 aliphatic isolating carbons		1.365
Carbon		6 aromatic isolating carbons		.780
ExFragment	Branch	1 non-halogen, polar group branch	Group	-.220
ExFragment	Hydrog	21 hydrogens on isolating carbons		4.767
ExFragment	Bonds	7 chain and 0 alicyclic (net)		-.840
Benzylbond	Simple	2 benzyl bonds to simple aromatics		-.300
Proximity	VCV	Fragments #1 & #2		1.325
Proximity	VCV	Fragments #2 & #3		1.206
Ortho	Ring 1	2 normal ortho (#2/0,0/2)		-.800
Screen		Methyl ether (aliphatic)		.140
RESULT	DB=23	All fragments measured	CLOGP=5	1.833

Interactive 'extended fragment' analysis

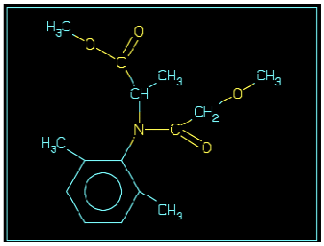
Interactive 'extended fragment' analysis

Enter SMILES, name or CAS: metalaxyl

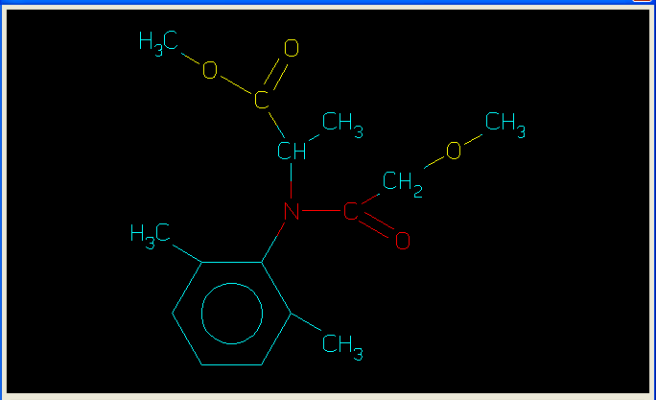
Cut-off value (default is .89):

Submit

```
SMILES:
COCC(=O)N(C(C)C(=O)OC)c1c(C)cccc1C

Fragments:
   1   | Ether [AA]                          |Measured  | -1.82
   2   | Amide [AaA]                         |Measured  | -2.32
   3   | Ester [AA]                          |Measured  | -1.45

Proximity:
YCY    | Fragments #1 & #2                   |          |  1.32
YCY    | Fragments #2 & #3                   |          |  1.20

Extended fragments (proximity cut-off: 0.89):
 126.1 C4N1O4    *CCC(=O)N(*)C(*)C(=O)O*
```



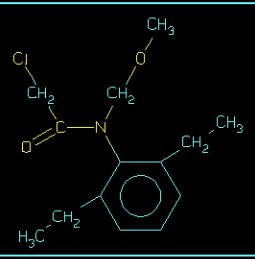
METALAXYL : FUNGICIDE



Class	Type	Log(P) Contribution Description	Comment	Value
Fragment	# 1	Ether [AA]	Measured	-1.820
Fragment	# 2	Amide [AaA]	Measured	-2.320
Fragment	# 3	Ester [AA]	Measured	-1.450
Carbon		7 aliphatic isolating carbons		1.365
Carbon		6 aromatic isolating carbons		.780
ExFragment	Branch	1 non-halogen, polar group branch	Group	-.220
ExFragment	Hydrog	21 hydrogens on isolating carbons		4.767
ExFragment	Bonds	7 chain and 0 alicyclic (net)		-.840
Benzylbond	Simple	2 benzyl bonds to simple aromatics		-.300
Proximity	YCY	Fragments #1 & #2		1.325
Proximity	YCY	Fragments #2 & #3		1.206
Ortho	Ring 1	2 normal ortho (H2/0.0/2)		-.896
Screen		Methyl ether (aliphatic)		.140
RESULT	DB=23	All fragments measured	CLOGP=5	1.833

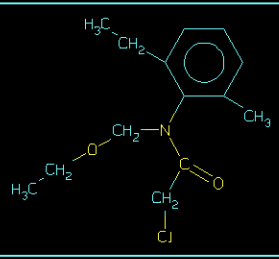
Depiction

ALACHLOR I HERBICIDE, CARCINOGEN CAL.PROP.65



ClogP = 3.03 MlogP = 3.06

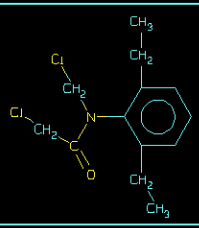
ACETOCHLOR I HERBICIDE, CARCINOGEN CAL.PROP.65



ClogP = 2.89 MlogP = 3.03

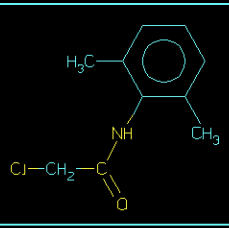
Depiction

ACETAMIDE2CHLORONCHLOROMETHYLN26DIETHYLPHENYL
HIGH VOLUME INDUSTRIAL CHEM. EPA



ClogP = 3.59

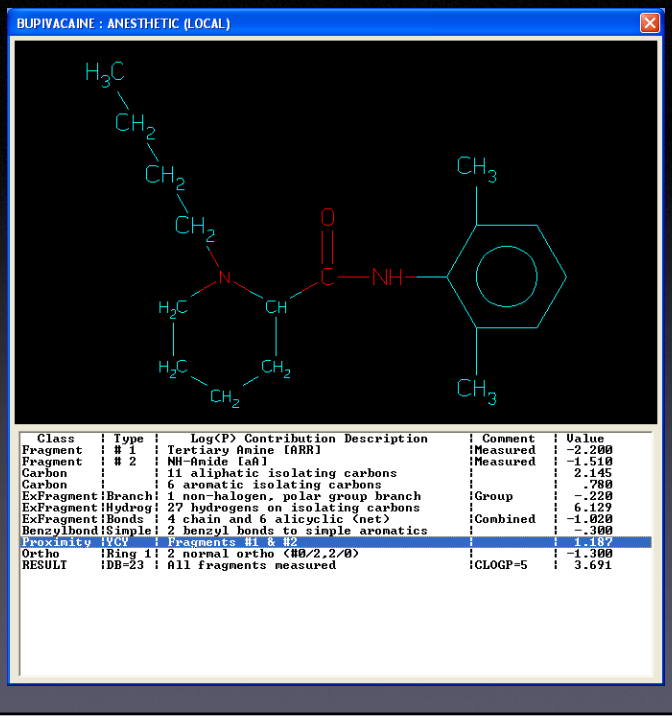
ACETAMIDE2CHLORON26DIMETHYLPHENYL
HIGH VOLUME INDUSTRIAL CHEM. EPA



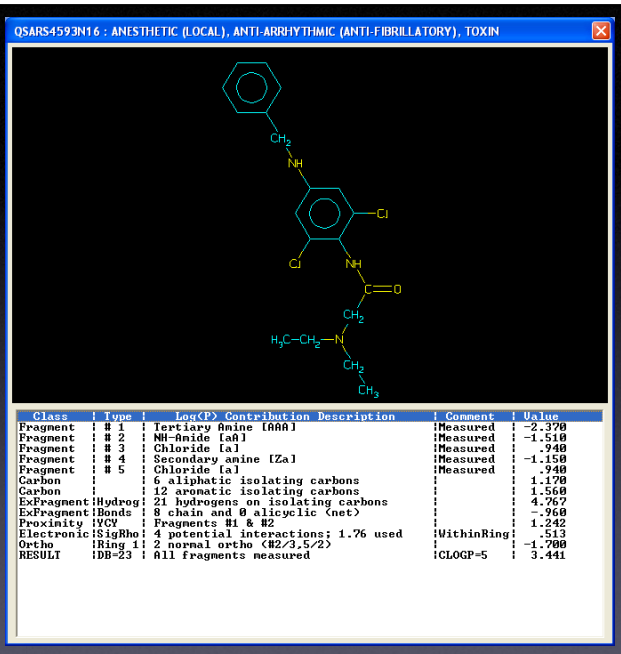
ClogP = 1.47

Current Masterfile Contents

67,169	Structures
89,875	Names
40,139	Activity Types
>3100	HVIC (High Volume)
344	Mutagens
260	Cal Prop 65
84	Tested NOT Carcinogenic
560	Herbicides
492	Insecticides
85	Fungicides
80	Endocrine Disruptors (EDC List)
14,330	pKas
13,500	'Starlist' - reliably measured log $P_{(oct)}$
~20,000	Structures linked to QSARs

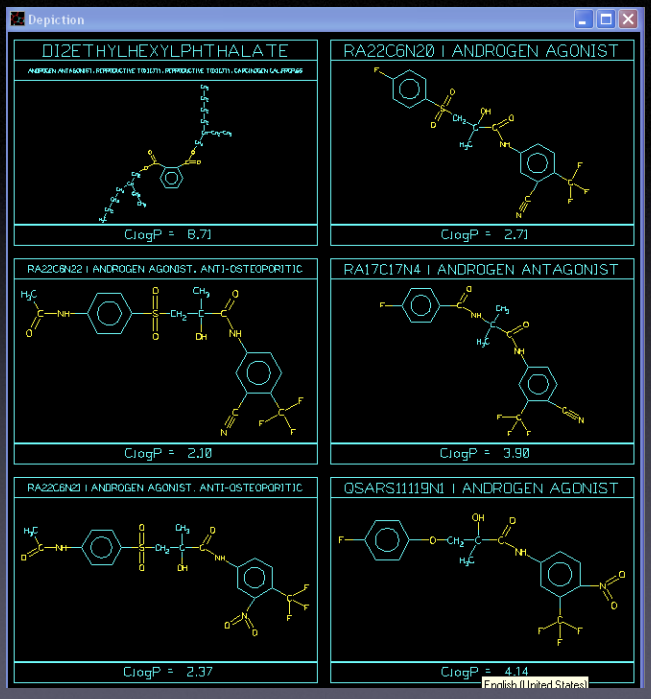


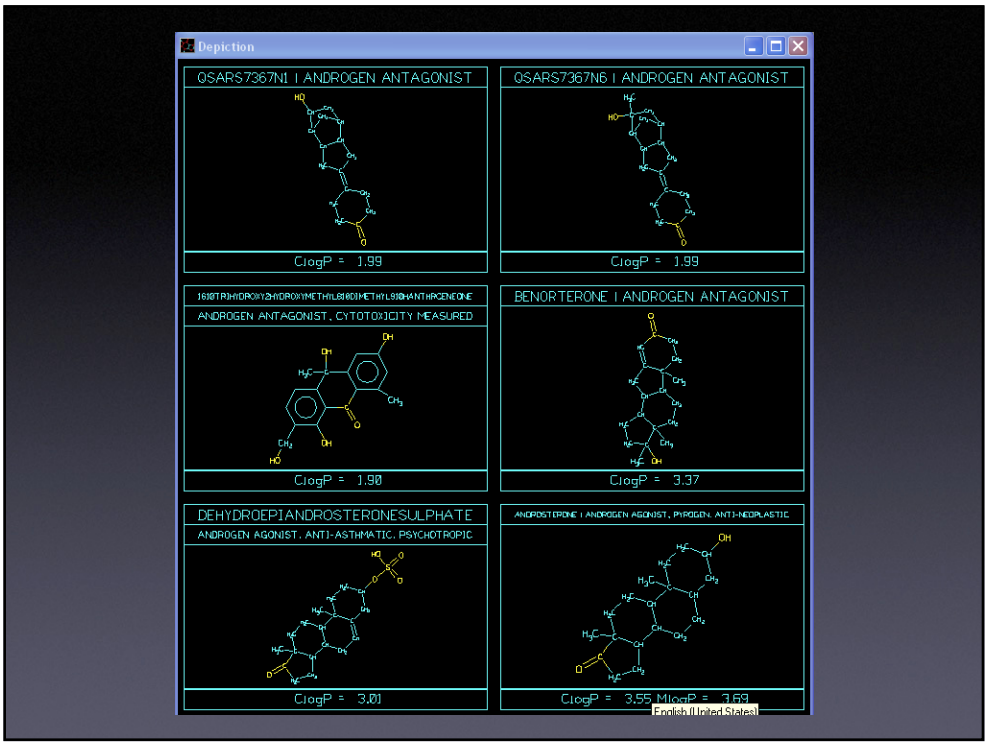
Class	Type	Log(P) Contribution Description	Comment	Value
Fragment	# 1	Tertiary Amine [ARR]	Measured	-2.200
Fragment	# 2	NH-Amide [aA]	Measured	-1.510
Carbon		11 aliphatic isolating carbons		2.145
Carbon		6 aromatic isolating carbons		.780
ExFragment	Branch	1 non-halogen, polar group branch	Group	-.220
ExFragment	Hydrog	27 hydrogens on isolating carbons		6.129
ExFragment	Bonds	4 chain and 6 alicyclic (net)	Combined	-1.020
Benzylbond	Simple	2 benzyl bonds to simple aromatics		-.300
Proximity	VCy	Fragments #1 & #2		1.187
Ortho	Ring 1	2 normal ortho (#0/2,2/0)		-1.300
RESULT	DB=23	All fragments measured	CLOGP=5	3.691

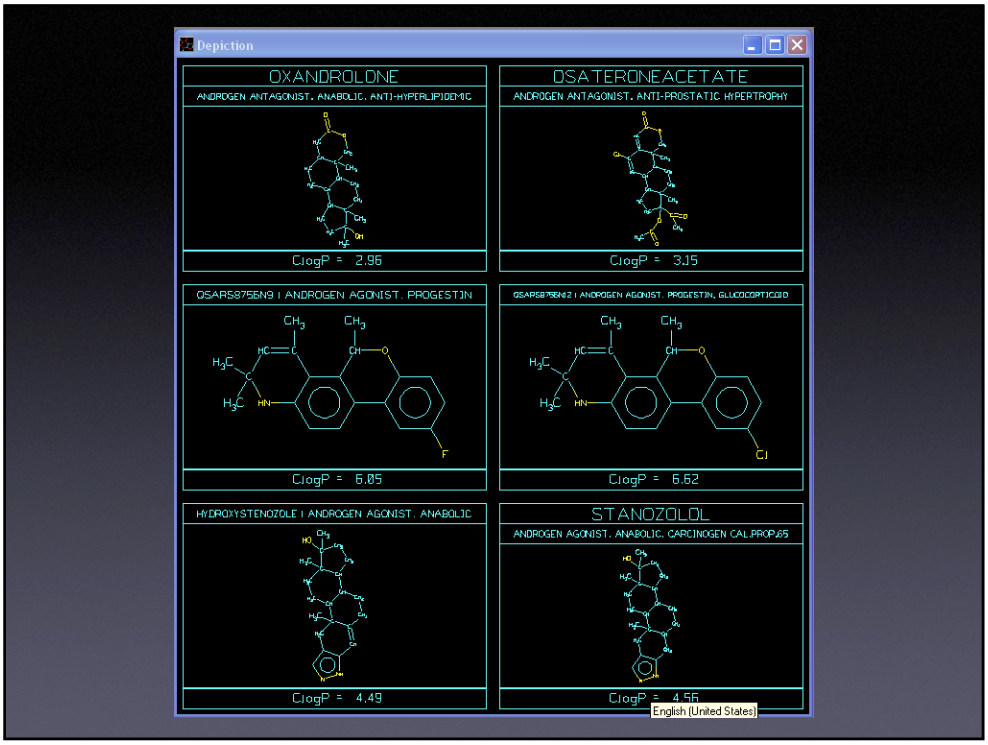


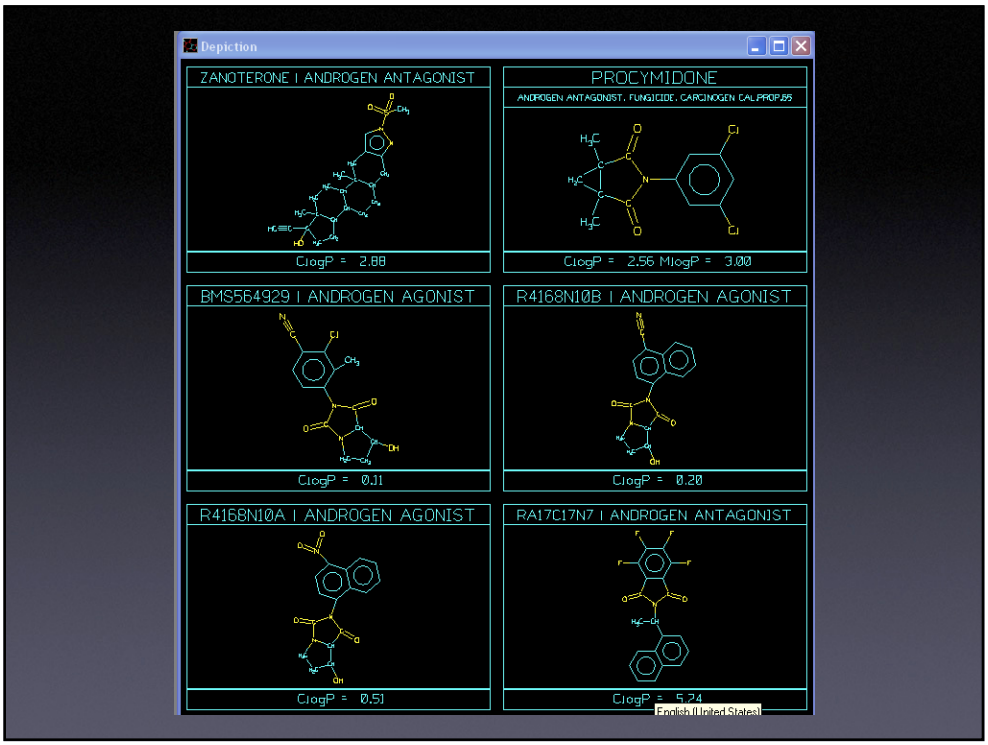
$\log {}^{1}/_{C} = 0.8\ \text{ClogP} - 0.2\ \text{ClogP}^2 + 0.2\ pK_a + 1.4$

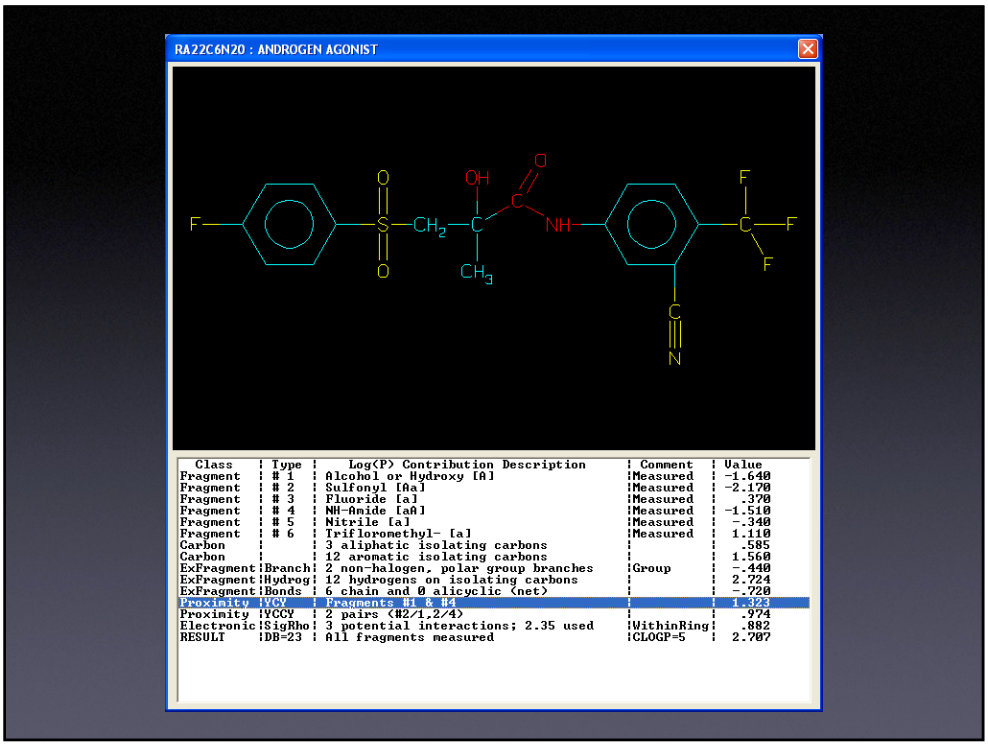
$SD = 0.162;\ R^2 = 0.867;\ Q^2 = 0.790;\ opt = 2.552$

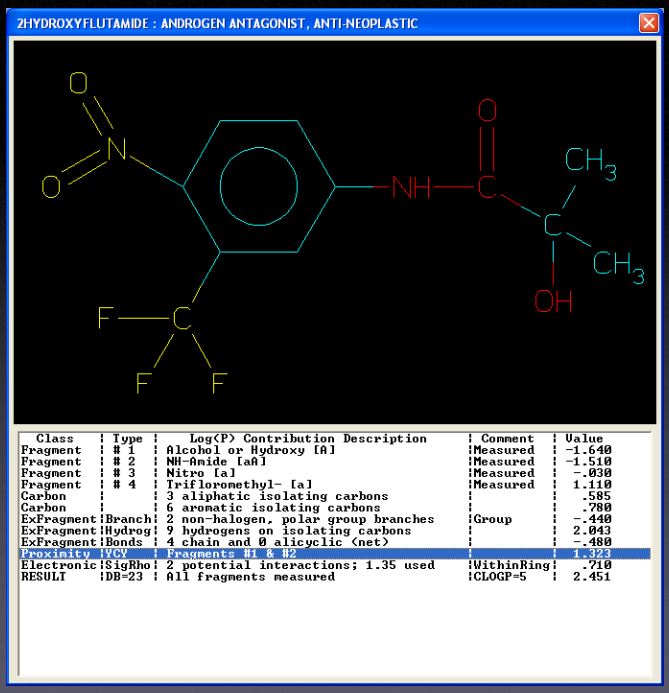



Depiction
QSARS7367N1 | ANDROGEN ANTAGONIST
ClogP = 1.99
QSARS7367N6 | ANDROGEN ANTAGONIST
ClogP = 1.99
16BETA-HYDROXY-2-HYDROXYMETHYL-5ALPHA-METHYL-5ALPHA-ANTHRACENEONE
ANDROGEN ANTAGONIST, CYTOTOXICITY MEASURED
ClogP = 1.90
BENORTERONE | ANDROGEN ANTAGONIST
ClogP = 3.37
DEHYDROEPIANDROSTERONESULPHATE
ANDROGEN AGONIST, ANTI-ASTHMATIC, PSYCHOTROPIC
ClogP = 3.01
ANDROSTERONE | ANDROGEN AGONIST, PYROGEN, ANTI-NEOPLASTIC
ClogP = 3.55 MlogP = 3.69
English (United States)


Depiction
OXANDROLONE
ANDROGEN ANTAGONIST, ANABOLIC, ANTI-HYPERLIPIDEMIC
ClogP = 2.96
OSATERONEACETATE
ANDROGEN ANTAGONIST, ANTI-PROSTATIC HYPERTROPHY
ClogP = 3.15
QSARS875EN9 | ANDROGEN AGONIST, PROGESTIN
ClogP = 6.05
QSARS875EN12 | ANDROGEN AGONIST, PROGESTIN, GLUCOCORTICOID
ClogP = 6.62
HYDROXYSTENOZOLE | ANDROGEN AGONIST, ANABOLIC
ClogP = 4.49
STANOZOLOL
ANDROGEN AGONIST, ANABOLIC, CARCINOGEN CAL,PROP,65
ClogP = 4.56
English (United States)


Depiction
ZANOTERONE | ANDROGEN ANTAGONIST
ClogP = 2.88
PROCYMIDONE
ANDROGEN ANTAGONIST, FUNGICIDE, CARCINOGEN CALPROP.95
ClogP = 2.56 MlogP = 3.00
BMS564929 | ANDROGEN AGONIST
ClogP = 0.11
R4168N10B | ANDROGEN AGONIST
ClogP = 0.20
R4168N10A | ANDROGEN AGONIST
ClogP = 0.51
RA17C17N7 | ANDROGEN ANTAGONIST
ClogP = 5.24
English (United States)


RA22C6N20 : ANDROGEN AGONIST
Class | Type | Log(P) Contribution Description | Comment | Value
Fragment | # 1 | Alcohol or Hydroxy [A] | Measured | -1.640
Fragment | # 2 | Sulfonyl [Aa] | Measured | -2.170
Fragment | # 3 | Fluoride [a] | Measured | .370
Fragment | # 4 | NH-Amide [aA] | Measured | -1.510
Fragment | # 5 | Nitrile [a] | Measured | -.340
Fragment | # 6 | Trifloromethyl- [a] | Measured | 1.110
Carbon | | 3 aliphatic isolating carbons | | .585
Carbon | | 12 aromatic isolating carbons | | 1.560
ExFragment | Branch | 2 non-halogen, polar group branches | Group | -.440
ExFragment | Hydrog | 12 hydrogens on isolating carbons | | 2.724
ExFragment | Bonds | 6 chain and 0 alicyclic (net) | | -.720
Proximity | VCCY | Fragments #1 & #4 | | 1.423
Proximity | VCCY | 2 pairs (#2/1,2/4) | | .974
Electronic | SigRho | 3 potential interactions; 2.35 used | WithinRing | .882
RESULT | DB=23 | All fragments measured | CLOGP=5 | 2.707



Class	Type	Log(P) Contribution Description	Comment	Value
Fragment	# 1	Alcohol or Hydroxy [A]	Measured	-1.640
Fragment	# 2	NH-Amide [aA]	Measured	-1.510
Fragment	# 3	Nitro [a]	Measured	-.030
Fragment	# 4	Trifluoromethyl- [a]	Measured	1.110
Carbon		3 aliphatic isolating carbons		.585
Carbon		6 aromatic isolating carbons		.780
ExFragment	Branch	2 non-halogen, polar group branches	Group	-.440
ExFragment	Hydrog	9 hydrogens on isolating carbons		2.043
ExFragment	Bonds	4 chain and 0 alicyclic (net)		-.480
Proximity	VOL	Fragments #1 & #2		1.321
Electronic	SigRho	2 potential interactions; 1.35 used	WithinRing	.710
RESULT	DB=23	All fragments measured	CLOGP=5	2.451

Simple "Survey Tools"

SuperFragment Identification
Searching Similar Scaffolds

Elucidating Mechanisms

Links to Searching 2-D QSAR [>13,000]
Building 3-D QSAR
[Bioorg.& Med. Chem., 14, 7160-7174, 2006]

Hazard Alert Assignment

Needs Survey Tools
More Dependable if Mechanisms Known

Credits

- Gil Veith, for believing in the basic concept of Superfragments
- Dave Hoekman for pulling out the needed information from the 'old standby' CLOGP program and making it Tool Box compatible (with help and urging from Gil).
- Alka Kurup for keeping my lack of any academic training in Medicinal Chemistry and Toxicology from becoming too apparent.
- Michael Medlin for putting together this presentation.

McKim Encore

The task of establishing reliable Hazard Alerts for Endocrine Disruptors can be aided by the efforts of medicinal chemists who have searched for "Non-Steroidal" androgens and estrogens. These may contain "pharmacophores" that lead us to look more closely at fragments and superfragments that were not previously considered to relate to endocrine action. In a different context, the NSAIDs were found to reduce inflammation by eicosanoid depression, the same way in which the steroids like cortisone did, but without some of the side effects. Previously I showed some interesting Superfragments found in non-steroidal structures with androgen activity. They may alert us to fragments not previously considered in an Endocrine Disruptor class. Other activities that may also be interesting in this context are: estrogen and anti-estrogen (SERMs).

The main motivation for medicinal chemists to investigate structures with anti-estrogen activity was its role in controlling breast cancer. Masterfile contains 85 such structures, and sorting them by scaffold similarity, one finds some interesting features of those that are not obvious steroids. The fragment: Ar-O-CH_2CH_2-N< appears to be at least a "subsidiary pharmacophore." It is present in > 75% of the non-steroidal anti-estrogens. If the ether oxygen were aliphatic-attached, these would qualify as Superfragments. Lowering the minimum limit to 0.64 from 0.89 (now possible in the Superfragment Identification program) these aromatic analogs are included. The breakdown is as follows:

Total anti-estrogens	85	
Steroidal anti-estrogens	14	
		with amino ether
Non-steroidal anti-estrogens	71	55 (>75%)
but DES analog (e.g. Tamoxifen)	23	23
not steroid or stilbene	32	32