Identification of PCP-Related Compound Using NIST Hybrid Search and Chemistry/SciFinder

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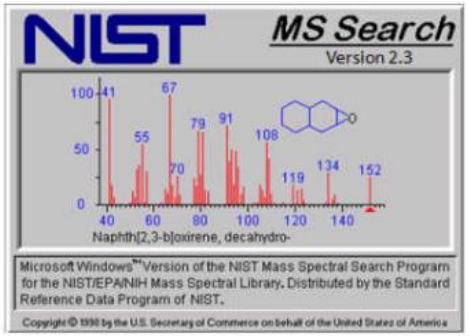
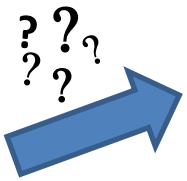
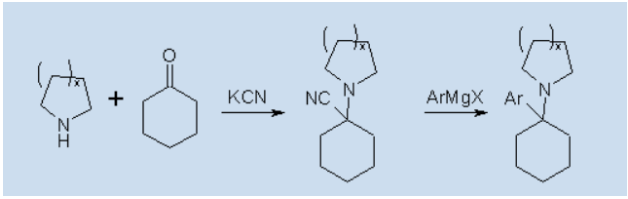


White Powder



CAS SciFinder^{n}



Novel NIST Hybrid Search*

Program Description:

- Hybrid search generates a similarity score matching both fragments *and* neutral losses
- Greatly extends the scope of libraries by including "nearest neighbor" compounds that differ from library compounds by one or more chemical moieties
- Success requires the presence of similar compounds in the searched libraries
- Mass differences must be confined to a single region of molecule and no significant alteration of fragmentation behavior
- DeltaMass is the mass difference between the molecular weights of the query and library compound and reflects the modification of the molecule
- DeltaMass value is used to shift neutral loss peaks in the library spectrum to match corresponding neutral loss peaks in the query spectrum

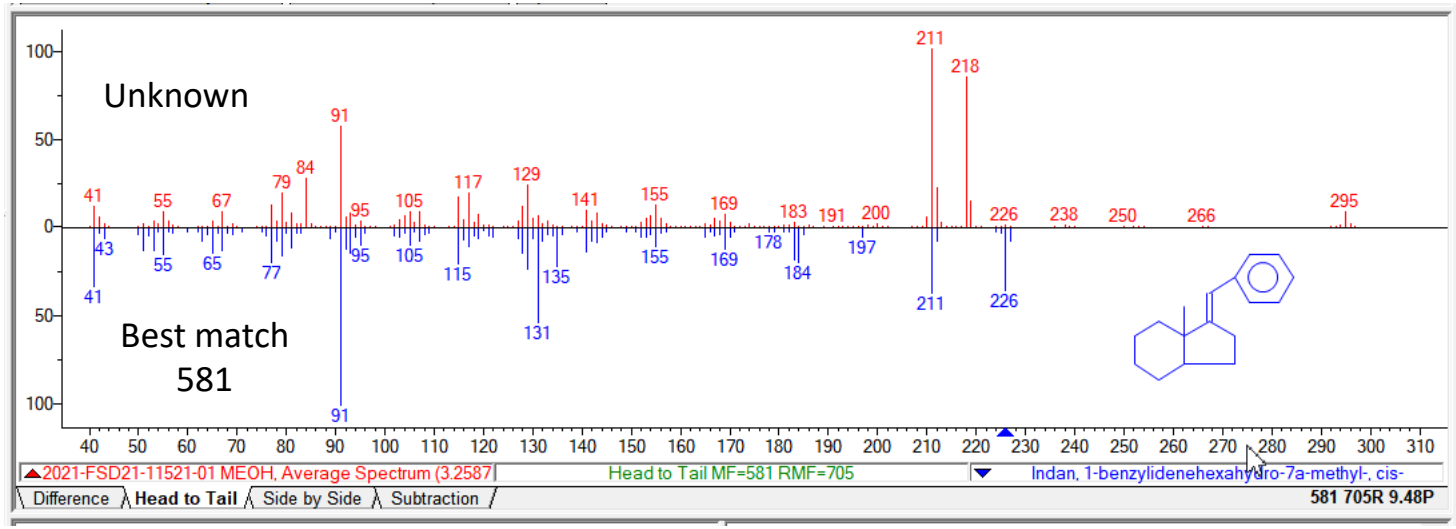
My Personal Experience:

- Used for over >40,000 hybrid searches in 3 years
- *Routinely amazed* by the types of similar compounds with high match factors
- Often successful when *no useful results* in standard "identity" search
- Utility in finding similar model compounds, support for fragmentation mechanisms, and identification of unknowns

*"Combining Fragment-Ion and Neutral-Loss Matching during Mass Spectral Library Searching: A New General Purpose Algorithm Applicable to Illicit Drug Identification," A. Moorthy, W. Wallace, A. J. Kearsley, D. Tchekhovskoi, and S. Stein, *Analytical Chemistry* **2017** *89* (24), 13261-13268.

Standard Identity Search Results for EI GC/MS

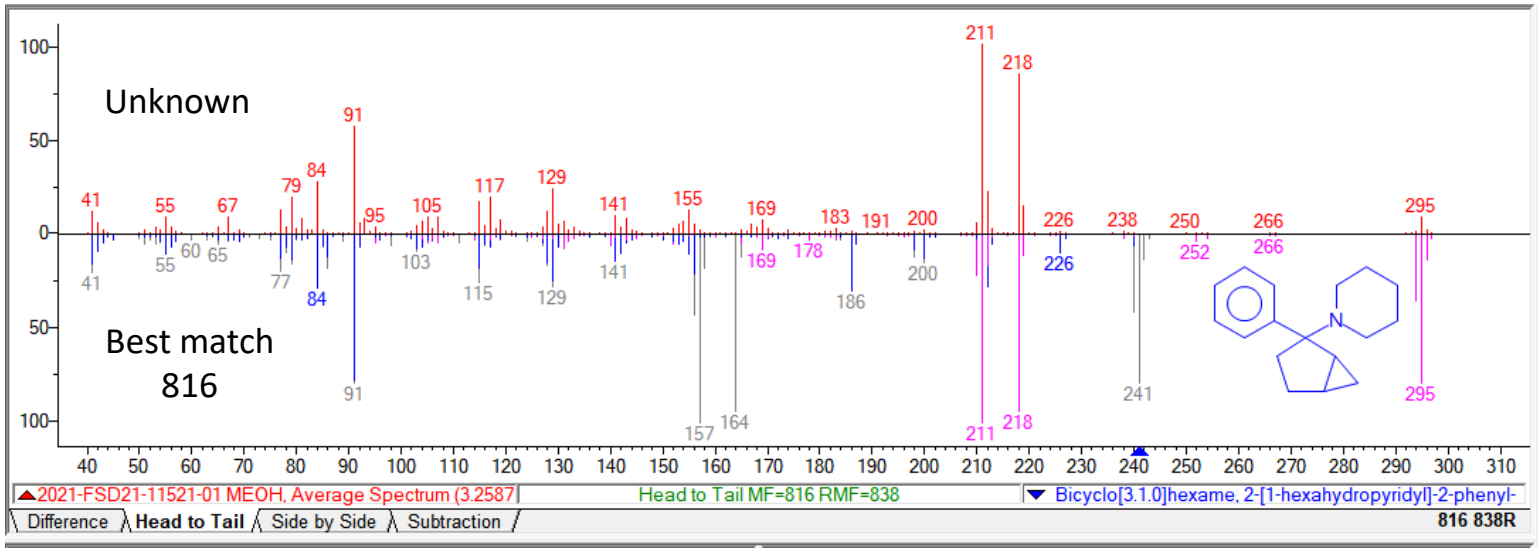
- Standard identify MS search *failed*
- Match is <600
- *No* useful results



#	Lib.	Match	Prob. (%)	R.Match	Syn	DBs	Name
⊞ 1	M	581	9.48	705	2	0	Indan, 1-benzylidenehexahydro-7a-methyl-, cis-
⊞ 2	M	580	9.11	706	1	0	1H-Indene, octahydro-7a-methyl-1-(phenylmethylene)-
3	M	570	6.43	661	1	0	9-Borabicyclo[3.3.1]nonane, 9-(1,2-diphenylethyl)-
4	M	563	4.92	665	1	0	1-Ethoxy-7-phenylvinylidene-bicyclo[4.1.0]heptane
5	M	563	4.92	662	0	0	(5R,6S)-6-Phenyl-5-(phenylsulfonyl)-1-(prop-2-yn-1-yl)...

Hybrid Search Results for EI GC/MS

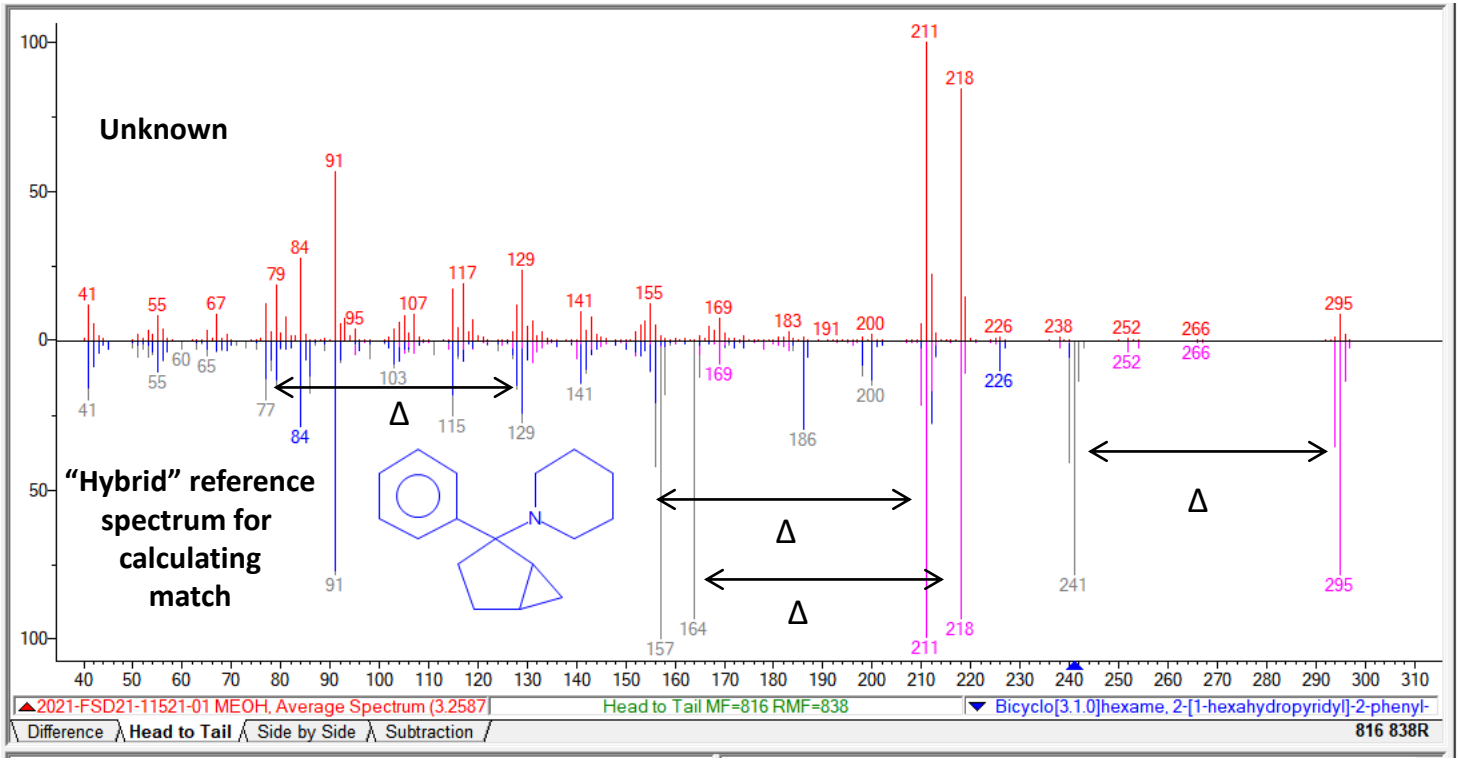
- Hybrid search yields one promising hit
- Match is >800
- DeltaMass = 54



#	Lib.	DeltaM...	Match	R.Match	o.Match	NumMP	o.NumMP	Syn	DBs	Name
1	M	54	816	838	348	142	93	1	0	Bicyclo[3.1.0]hexame, 2-[1
2	M	77	756	761	337	161	100	3	0	1,3-Cyclohexanedione, 5-(
3	M	53	731	733	345	166	125	4	1	Methyl 4-hydroxy-3,5-dinitr
4	M	54	727	729	364	169	134	0	0	N-Allyl-N-methyl-1-phenylh
5	M	55	703	706	563	172	137	1	0	1-Ethoxy-7-phenylvinylider
⊞ 6	M	69	699	750	587	149	97	2	0	Indan, 1-benzylidenehexah

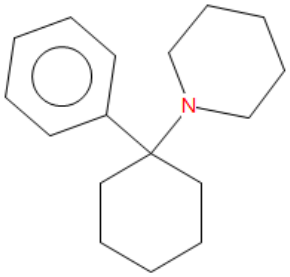
Closer Look at Middle Display

- Bottom spectrum, ions in grey shifted by DeltaMass = 54 to magenta (Δ)
- DeltaMass = $(MW_{unknown})$ - $(MW_{reference})$ = 295 - 241 = 54
- Ions not shifted in bottom spectrum, remain in blue
- Resulting "Hybrid" reference spectrum, blue ions + magenta, used to calculate match factor of >800

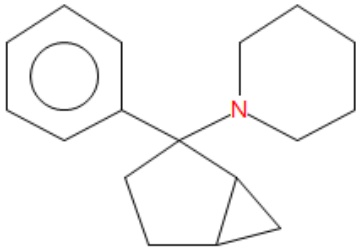


Summary of MS Results

- Hybrid search indicates PCP-related compound
- ∆mass = 54 from the hybrid search *not* easily associated with group attached
- Accurate mass data for the unknown indicated a molecular formula of $C_{21}H_{29}N$ via DART MS analyses
- Best match has a molecular formula of $C_{17}H_{23}N$
- Indicates addition of C_4H_6
- Plus, additional double bond equivalent (DBE)
- See addendum for fragmentation of PCP-related species



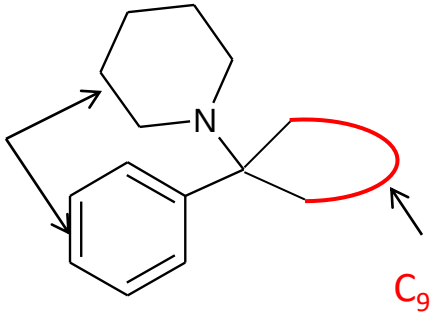
"Angel Dust"
Phenylcyclohexyl piperidine
PCP
Phencyclidine



Best Match
$C_{17}H_{23}N$
MW 241
7 DBE's

$+C_4H_6$

$C_{12}H_{15}N$
5 DBE's



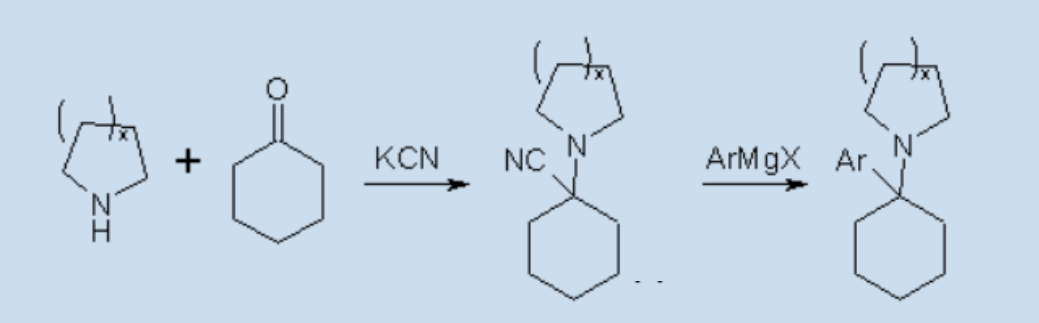
C_9H_{14}
3 DBE's

Total Structure
$C_{21}H_{29}N$
MW 295
8 DBE's

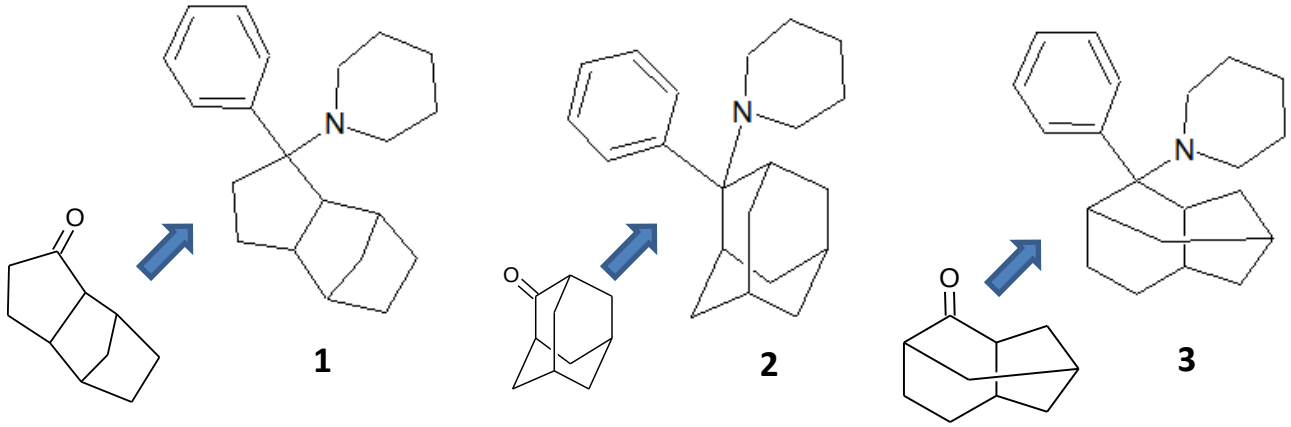
Structures Proposed from Chemistry

- Considered chemistry * to propose 3 structures
- PCP related species *could* be made with the reaction below from 3 commonly available ketones

Proposed Chemistry



3 Proposed Structures from Chemistry and Easily Obtained Ketones

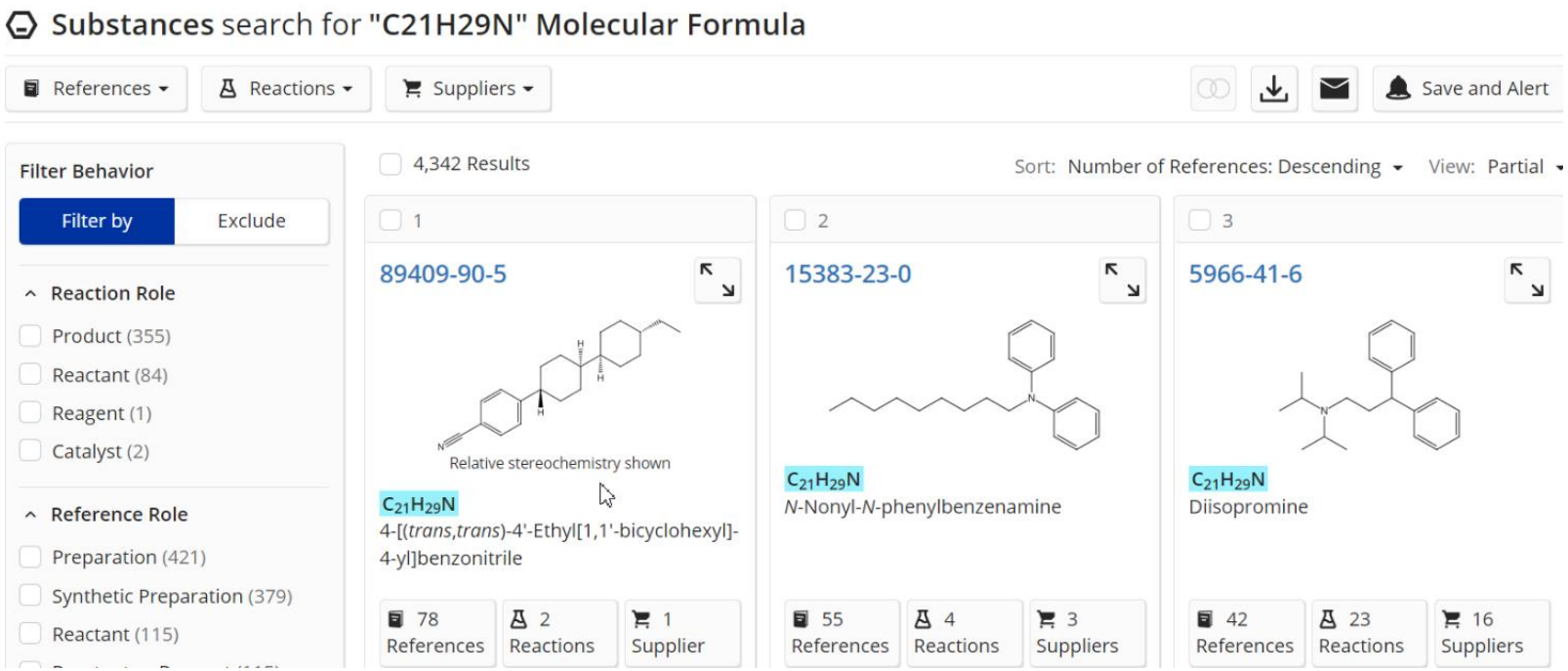


***Illicit Synthesis of Phencyclidine (PCP) and Several of Its Analogs**
by A.T. Shulgin and D.E. Mac Lean, *Clin. Toxicol. 9(4), 553-560 (1976)*

https://www.designer-drug.com/pte/12.162.180.114/dcd/chemistry/pcp.shulgin.html

Additional Information Obtained from SciFinder

- SciFinder using molecular formula search routinely used for unknown identifications*
- Results of SciFinder search for $C_{21}H_{29}N$ sorted by #'s of associated references
- *4,342 Too many* to be useful
- Needed to *refine* search

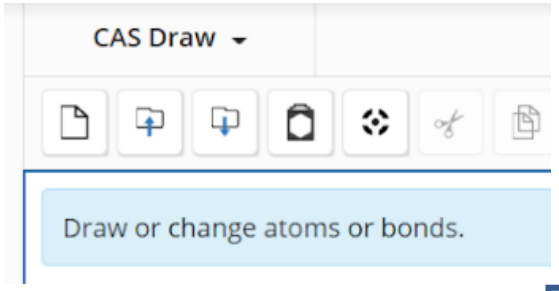


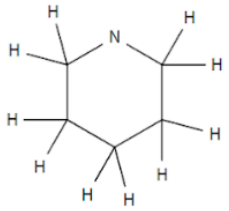
* "MS the Practical Art: Identifying "Known Unknowns" in Commercial Products by Mass Spectrometry," James L. Little, Curtis D. Cleven, Adam S. Howard, Editor Kate Yu, LCGC Europe, Volume 26, Issue 3, pp. 163-168, March 2013.

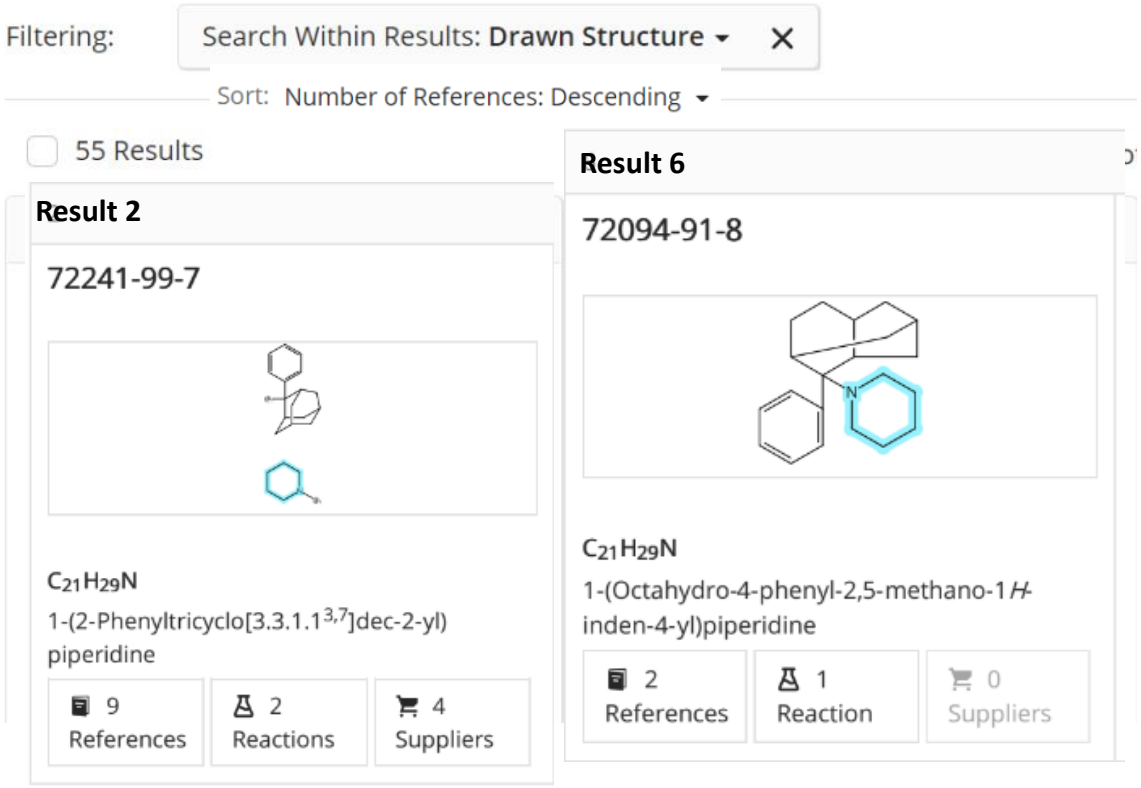
https://littlemsandsailing.files.wordpress.com/2013/12/lcgc_article.pdf

Refined Search by Groups Attached to Piperidine Ring in SciFinder

- Approach *not* included in initial "known unknown" reference
- Allow only substitution on nitrogen by including hydrogens and a molecular formula of $C_{21}H_{29}N$
- Only 2 our of the 55 results had structures consistent with EI mass spectrum
- Result #2 had 9 references and 4 suppliers, Result #6 had 2 references and 0 suppliers

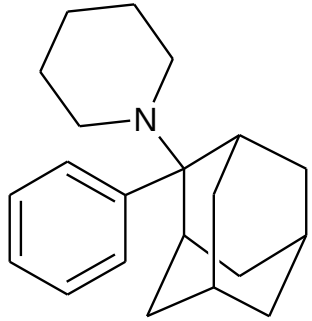






Conclusions

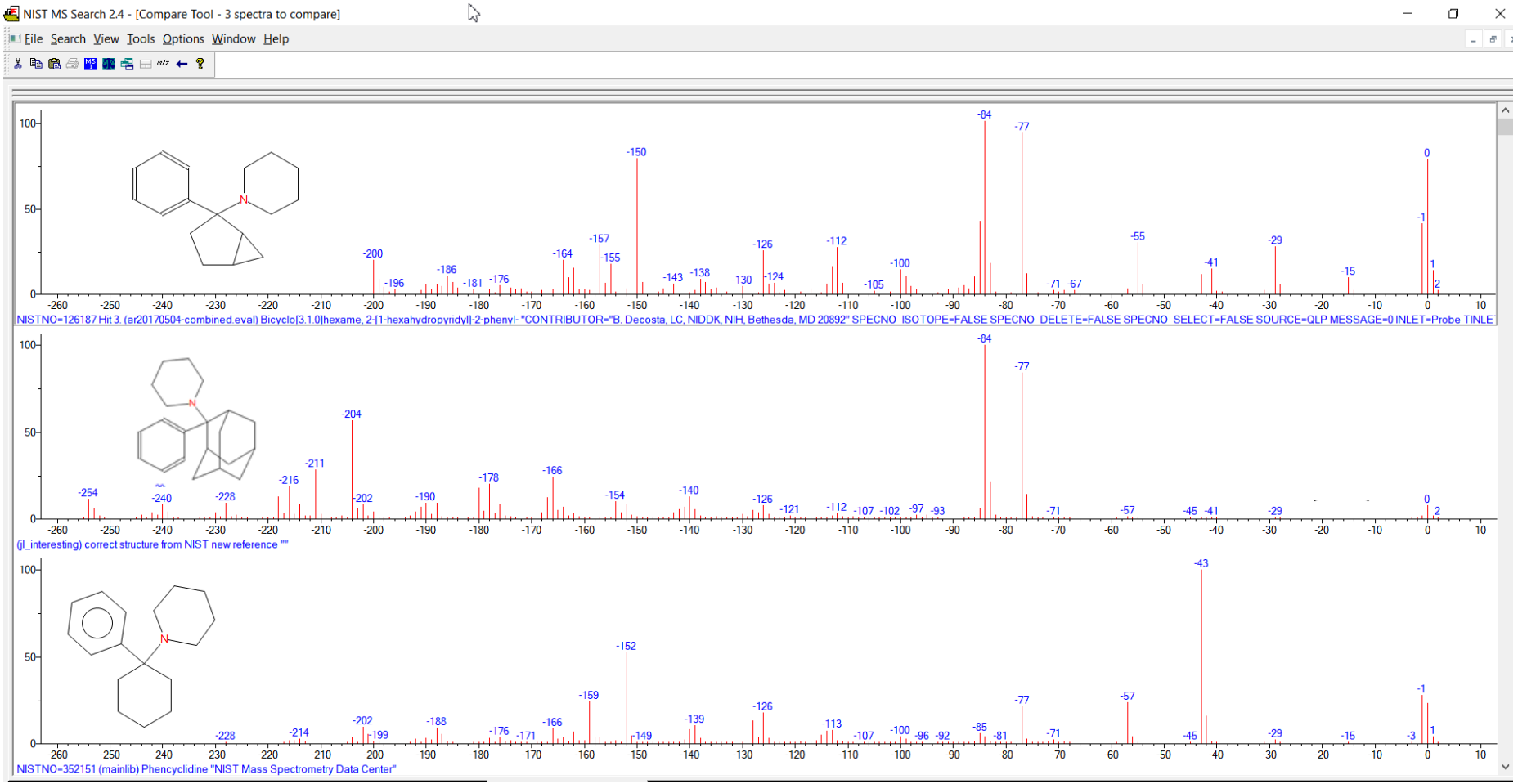
- Hybrid search was critical in suggesting PCP-related substructure
- DeltaMass was not easily associated to a definitive fragment
- Molecular formula from accurate mass and DBE's plus chemistry to proposed 3 structures
- Narrowed by SciFinder by refining with substructure and examining the resulting list to find 2 that correlated with our EI fragmentation data
- Structure *confirmed* with reference EI spectrum of purchased material
- Structure confirmed by proton NMR from an outside source
- Another compound, CAS No. 72094-91-8 from SciFinder search, *not* commercially available



Identity of PCP-Related Unknown
CAS No. 72241-00-7

Addendum: Differences in EI Fragmentation of PCP-Related Compounds

- Surprised by differences between neutral loss spectra of the three compounds below
- Thought the parent compound, PCP ("Angel Dust") would be more similar to other 2
- Used NIST structure search for PCP-related materials, the presence of fused cyclohexyl ring drives loss of 43, C_3H_7
- Same mechanism for loss of 43 ***not*** accessible by other two compounds
- If best hit with MW of 241 not present, hybrid search ***would have failed*** to yield useful information



Contributor

- Adam Howard, MS/SciFinder Expert, Eastman Chemical Company, Kingsport, TN

Active Links to Useful Resources

Identification of "known unknowns" utilizing accurate mass data and chemical abstracts service databases, Little James L; Cleven Curtis D; Brown Stacy D, Journal of the American Society for Mass Spectrometry (2011), 22(2), 348-59.
Identification of "Known Unknowns" Utilizing Accurate Mass Data and ChemSpider, James L. Little, Antony J. Williams, Alexey Pshenichnov, Valery Tkachenko, Journal of The American Society for Mass Spectrometry, Volume 23, Number 1, 179-185, DOI: 10.1007/s13361-011-0265-y, 2012.
"MS the Practical Art: Identifying "Known Unknowns" in Commercial Products by Mass Spectrometry," James L. Little, Curtis D. Cleven, Adam S. Howard, Editor Kate Yu, LCGC Europe, Volume 26, Issue 3, pp. 163-168, March 2013.
Course on Using NIST EI Software for Identifying Unknowns Including Hybrid Search
Adam Howard, Refining SciFinder Search by Substructure