Pharmaceutical industry best practices in lessons learned: eln implementation of merck's reaction review policy

Roger Sayle and john mayFIELD

Nextmove software, cambridge, uk

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motivation

- The pharmaceutical industry has an interest in reducing laboratory accidents by learning lessons from previous incidents.
- Projects such as the Pistoia Alliance's Chemical Safety Library (CSL) and iRAMP are examples from this.
- Here we present our experience implementing Merck's published rules in another pharmaceutical company's ELN.

Industry vs. academia

- Relative risk depends upon context...
  - Keep out of reach of children.
  - Read label before use.
  - Do not pierce or burn, even after use.
  - Do not eat, drink or smoke when using this product.
  - Do not get in eyes, on skin or on clothing.
  - Avoid contact during pregnancy/while nursing.
  - If medical advice is needed, have product container at hand.

Organic Process Research & Development

Safety/Environmental Report

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Merck's Reaction Review Policy: An Exercise in Process Safety

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ABSTRACT: Process safety is an important consideration not only when conducting reactions on manufacturing scale, but also on lab and kilo lab scale. This contribution presents a discussion of Merck's Reaction Review policy, originally specific to Process Chemistry and now applied broadly across the whole chemistry organization. Details of the policy and case studies are included.

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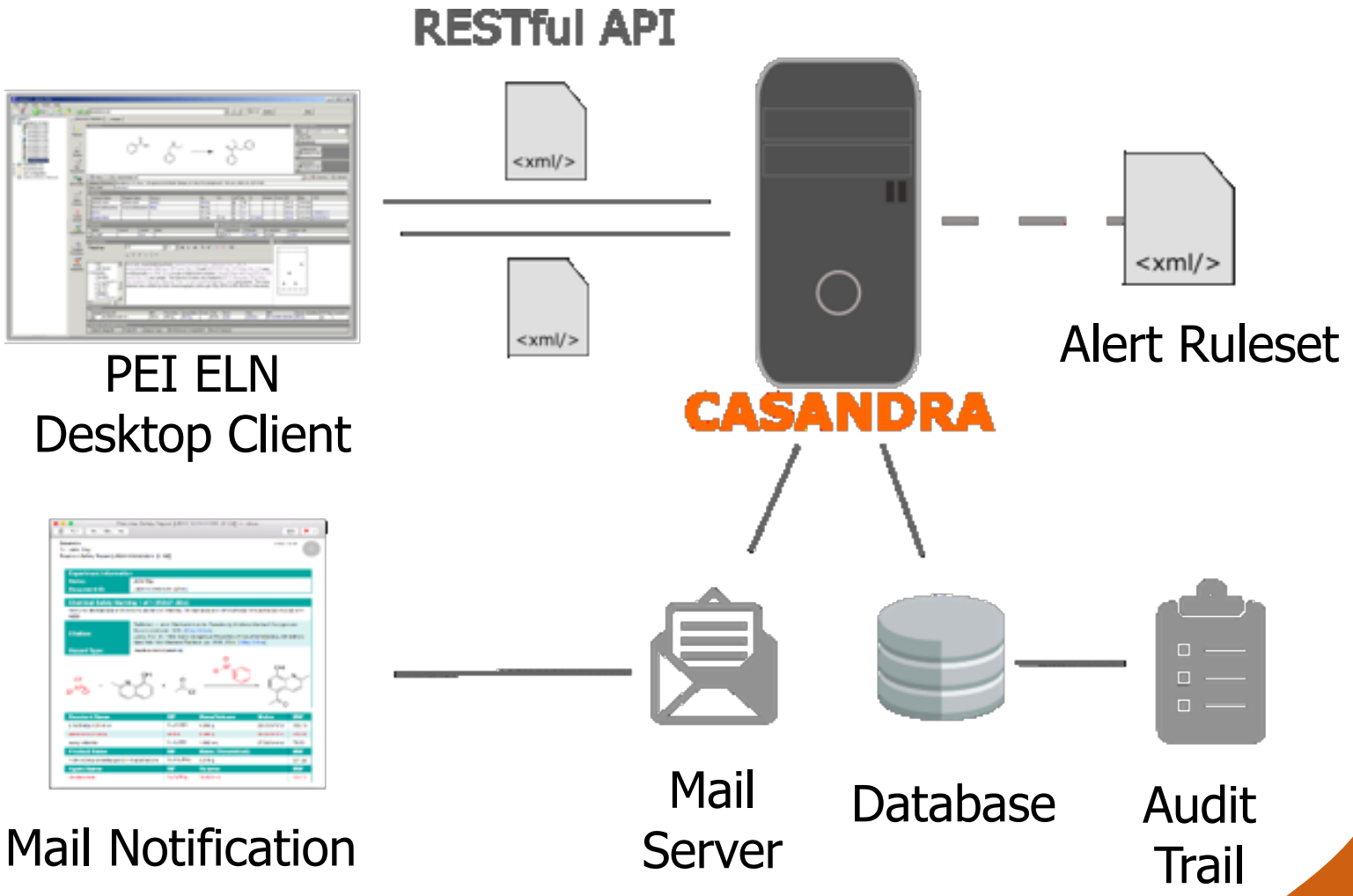
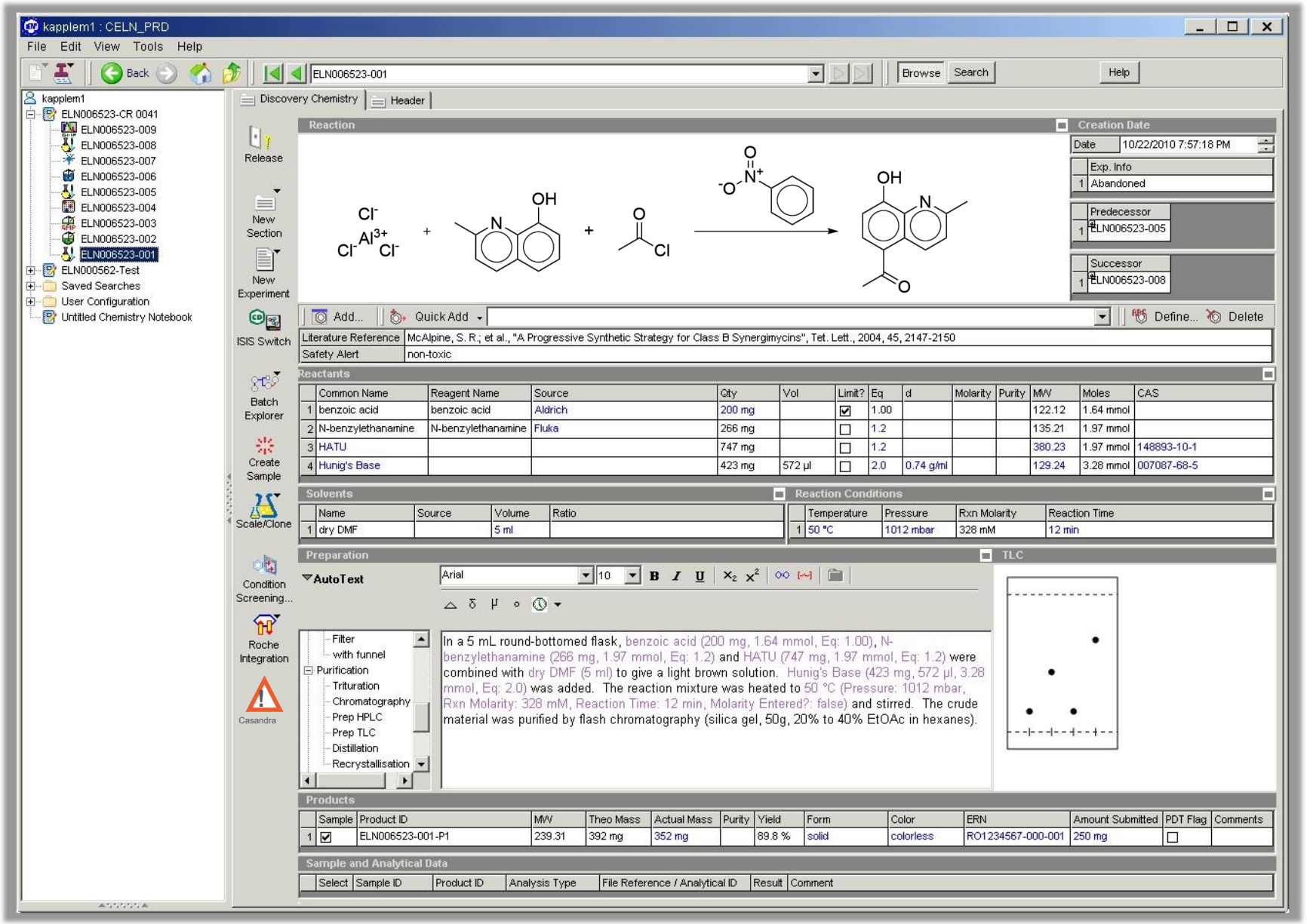
Background of Merck's RRP

- Prior to 2009, Rahway prep laboratories (typically 0.5-5 kg scale for intermediates/APIs) had only an "ad hoc" safety review.
- In 2009, it was decided to formalize this process to complement the Pilot Plant review.
- The necessity for a "Hazardous Reaction Review" for even much smaller scale was realized when a senior level scientist incurrent a serious hand injury upon isolating a diazonium salt on <5 g scale.
- In 2012, RRP was extended to Discovery Chemistry.

Implementation architecture

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ELN006523-002
ELN006523-001
ELN000562-Test
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User Configuration
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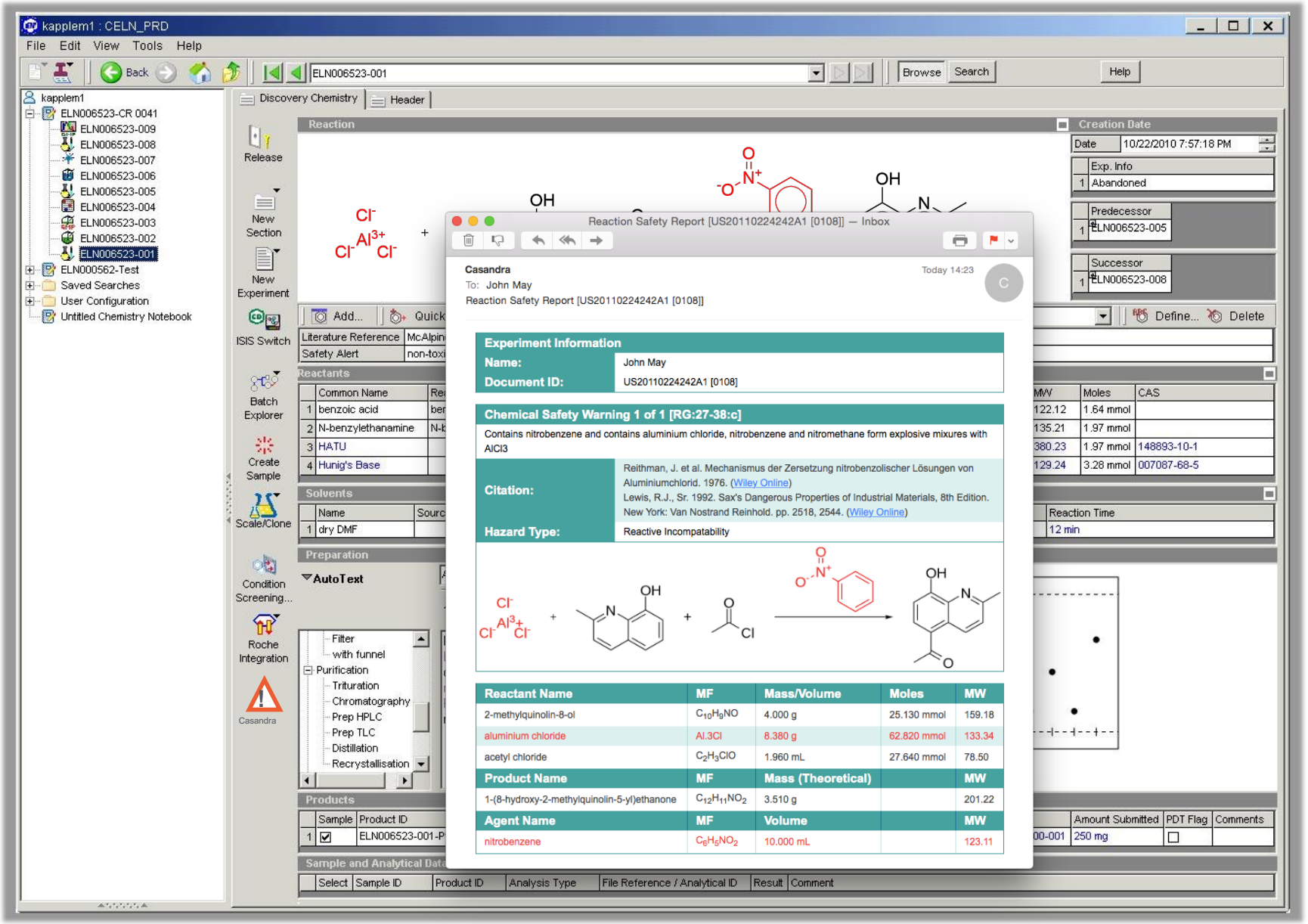
Discovery Chemistry
Header
Release
New Section
New Experiment
ISIS Switch
Batch Explorer
Create Sample
Scale/Clone
Condition Screening...
Roche Integration
Casandra
Reaction
Creation Date
Date 10/22/2010 7:57:18 PM
Exp. Info
1 Abandoned
Predecessor
1 ELN006523-005
Successor
1 ELN006523-008
Add...
Quick Add
Define...
Delete
Literature Reference McAlpine, S. R.; et al., "A Progressive Synthetic Strategy for Class B Synergimycins", Tet. Lett., 2004, 45, 2147-2150
Safety Alert non-toxic
Reactants
Common Name | Reagent Name | Source | Qty | Vol | Limit? | Eq | d | Molarity | Purity | MW | Moles | CAS
1 benzoic acid | benzoic acid | Aldrich | 200 mg | | | 1.00 | | | | 122.12 | 1.64 mmol |
2 N-benzylethanamine | N-benzylethanamine | Fluka | 266 mg | | | 1.2 | | | | 135.21 | 1.97 mmol |
3 HATU | | | 747 mg | | | 1.2 | | | | 380.23 | 1.97 mmol | 148893-10-1
4 Hunig's Base | | | 423 mg | 572 µl | | 2.0 | 0.74 g/ml | | | 129.24 | 3.28 mmol | 007087-68-5
Solvents
Name | Source | Volume | Ratio
1 dry DMF | | 5 ml |
Reaction Conditions
Temperature | Pressure | Rxn Molarity | Reaction Time
1 50 °C | 1012 mbar | 328 mM | 12 min
Preparation
AutoText
Arial
10
Filter
with funnel
Purification
Trituration
Chromatography
Prep HPLC
Prep TLC
Distillation
Recrystallisation
In a 5 mL round-bottomed flask, benzoic acid (200 mg, 1.64 mmol, Eq: 1.00), N-benzylethanamine (266 mg, 1.97 mmol, Eq: 1.2) and HATU (747 mg, 1.97 mmol, Eq: 1.2) were combined with dry DMF (5 ml) to give a light brown solution. Hunig's Base (423 mg, 572 µl, 3.28 mmol, Eq: 2.0) was added. The reaction mixture was heated to 50 °C (Pressure: 1012 mbar, Rxn Molarity: 328 mM, Reaction Time: 12 min, Molarity Entered?: false) and stirred. The crude material was purified by flash chromatography (silica gel, 50g, 20% to 40% EtOAc in hexanes).
TLC
Products
Sample | Product ID | MW | Theo Mass | Actual Mass | Purity | Yield | Form | Color | ERN | Amount Submitted | PDT Flag | Comments
1 ELN006523-001-P1 | 239.31 | 392 mg | 352 mg | | 89.8 % | solid | colorless | RO1234567-000-001 | 250 mg
Sample and Analytical Data
Select | Sample ID | Product ID | Analysis Type | File Reference / Analytical ID | Result | Comment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Discovery Chemistry
Header
Reaction
Creation Date
Date 10/22/2010 7:57:18 PM
Exp. Info
Abandoned
Predecessor
ELN006523-005
Successor
ELN006523-008
Reaction Safety Report [US20110224242A1 [0108]] — Inbox
Casandra
Today 14:23
To: John May
Reaction Safety Report [US20110224242A1 [0108]]
Experiment Information
Name: John May
Document ID: US20110224242A1 [0108]
Chemical Safety Warning 1 of 1 [RG:27-38:c]
Contains nitrobenzene and contains aluminium chloride, nitrobenzene and nitromethane form explosive mixures with AlCl3
Citation:
Reithman, J. et al. Mechanismus der Zersetzung nitrobenzolischer Lösungen von Aluminiumchlorid. 1976. (Wiley Online)
Lewis, R.J., Sr. 1992. Sax's Dangerous Properties of Industrial Materials, 8th Edition. New York: Van Nostrand Reinhold. pp. 2518, 2544. (Wiley Online)
Hazard Type: Reactive Incompatability
Reactant Name | MF | Mass/Volume | Moles | MW
2-methylquinolin-8-ol | C10H9NO | 4.000 g | 25.130 mmol | 159.18
aluminium chloride | Al.3Cl | 8.380 g | 62.820 mmol | 133.34
acetyl chloride | C2H3ClO | 1.960 mL | 27.640 mmol | 78.50
Product Name | MF | Mass (Theoretical) | | MW
1-(8-hydroxy-2-methylquinolin-5-yl)ethanone | C12H11NO2 | 3.510 g | | 201.22
Agent Name | MF | Volume | | MW
nitrobenzene | C6H5NO2 | 10.000 mL | | 123.11
Reactants
Common Name
1 benzoic acid
2 N-benzylethanamine
3 HATU
4 Hunig's Base
MW Moles CAS
122.12 1.64 mmol
135.21 1.97 mmol
380.23 1.97 mmol 148893-10-1
129.24 3.28 mmol 007087-68-5
Solvents
1 dry DMF
Reaction Time
12 min
Preparation
AutoText
Products
Sample Product ID
ELN006523-001-P
Amount Submitted 250 mg
PDT Flag
Comments
Sample and Analytical Data
Select Sample ID Product ID Analysis Type File Reference / Analytical ID Result Comment
Release
New Section
New Experiment
ISIS Switch
Batch Explorer
Create Sample
Scale/Clone
Condition Screening...
Roche Integration
Casandra
Filter with funnel
Purification
Trituration
Chromatography
Prep HPLC
Prep TLC
Distillation
Recrystallisation
kapplem1
ELN006523-CR 0041
ELN006523-009
ELN006523-008
ELN006523-007
ELN006523-006
ELN006523-005
ELN006523-004
ELN006523-003
ELN006523-002
ELN006523-001
ELN000562-Test
Saved Searches
User Configuration
Untitled Chemistry Notebook

The influence of scale

- Different thresholds are applied for “bench” (typically lab hood) vs. prep lab (0.5 – 5 kg).
  - The amount of material is larger
  - Heat removal is less efficient
  - Time cycles are long; Because the time vs. temperature profile is increased, decomposition exotherms can triggered that don’t at small scale.

ELN support for “vessel size”

- Merck’s RRP defines “Prep. Lab scale” to be defined as reactions run in a vessel >5 L, even if the actual reaction volume is less.
- An extra field was added to the Cambridgesoft/PEI ELN to capture “Reaction Vessel Size”
  - ≤100 mL
  - >100 ml – 5 L
  - >5L
- For existing ELN installations, “Vessel Size” can be approximated/estimated from material quantities.

Beware of Bretherick's: 1,3-dinitrobenzene

- Accidents involving maintenance of railway tankers are probably not relevant at the laboratory scale.

A vessel containing dinitrobenzene for drying, after washing out styphnic and picric acid by products in alkali, retained a heel of some hundreds of litres, with a residue of rust, after emptying. This was cleaned out with low pressure steam at 130°C every two years. During cleaning, the tank burst and burnt out. It was supposed that residual nitrophenol salts had accumulated on the rust, which was shown to thermally sensitise them, and deflagrated, initiating the dinitrobenzene.

Avoiding alert fatigue

- One usability aspect of Casandra was (for some types of alerts) to avoid repeating warning within a specified period of time.
- Alerts about use of non-green solvents may only fire at most once a month. Alerts on policy and laboratory certification might only fire once a year.
- The server maintains a log of which alerts have been seen by which chemists.

“Need to know” policy

- Depending upon configuration some alerts are reported and/or e-mailed to the chemist, optionally e-mailed to his/her supervisor, and rarely to the site manager or reaction review board.

highly toxic/dangerous reagenT

1. Unusually toxic solids (typically IDLH < 30 ppm)
   - Cyanide, OsO4, phosgene/diphosgene/triphosgene, iodine, PCl_5.
2. Unusually toxic liquids (typically IDLH < 30 ppm)
   - MeI, HF, $SOCl_2$, oxalyl chloride, bromine, Hg (all forms), CS_2, fuming H_2SO_4.
3. Known or strongly suspected carcinogens
   - Benzene, CCl4, Cr(VI) reagents, dimethyl sulfate
4. Pyrophoric materials
   - AlR_3, BR_3, PR_3, ZnR_2, RLi, RMgX, 95% NaH, $LiAlH_4$, Na, K, Li, Raney Ni
5. Unusually strong oxidizers
   - >30% H2O2, ozone, conc. HNO_3, O_2.
6. Known or suspected sensitizers
   - DCC, formic acid, bromobenzyl bromide, limonene, omeprazole, beta-lactams.
7. OEB 5 or comparable materials

Oeb 5 = GHS category 1

- Explosives: H200, H201, H202, H203, H204, H205
- Desensitized explosives: H206
- Flammability: H220, H222, H224, H228, H229
- Physical Hazard: H250, H251, H260, H270, H290.
- Toxicity: H300, H304, H310, H314, H317, H318, H330, H334, H340, H350, H360, H370, H372
- Environmental hazards: H400, H410, H420

ghs pictograms are not enough

- Unfortunately, GHS labels are insufficient.
- Both methanol and dimethylmercury are labelled with warnings indicating toxic and health hazard if swallowed or exposed to skin respectively.

Merck Solution: ghs categories

- The solution is to only alert on GHS category 1 or NFPA category 4 hazards (by default).
- These reflect unusual or unanticipated hazards.
  - Unstable explosive, and explosive vs. fire hazard/may explode in fire.
  - Extremely flammable gas (H220) vs Flammable gas (H221)
  - Extremely flammable liquid (H224) vs Flammable liquid (H225)
  - Fatal if inhaled (H330)

Challenge: data coverage

- Unfortunately, SDS/MSDS data sheets exist for a very small fraction chemicals.
- Of the 91M compounds in PubChem, Safety information is available for 11487 (~0.01%), and GHS information for 5060 (~0.006%).
- Additionally, unlike high-school and undergraduate practicals, pharmaceutical medicinal chemistry R&D produces previously unsynthesized compounds.
- It's important to check reactants **and** products.

Solution: deriving categories

- GHS and NFPA categories are (mostly) derived from physical properties measured by experimental testing and legally mandated thresholds.
- These may also be looked up in a database or calculated algorithmically to categorize/triage compounds.
- Flor A. Quintero, Suhani J. Patel, Felipe Muñoz and M. Sam. Mannan, "**Review of Existing QSAR/QSPR Models Developed for Properties used in Hazardous Chemicals Classification System**", *Industrial and Engineering Chemistry Research*, Vol. 51, pp. 16101-16115, 2012.

Effectively Adding ghs diamonds

Evolution of Hazard alerting

1. Chemical Compound/Substance (MSDS) Lookup
   1a. Exact name/MFCD/Synonym comparison
   1b. Name-to-structure canonical match (spelling correction)
   1c. Normalized representation (InChI) match
2. Chemical Incompatibility Lookup
3. Substructure Patterns
4. Chemical Class Incompatibility
5. Reaction Mechanism Recognition
6. Physical Property Thresholds

Case study #1: h224

- GHS hazard H224 is “Extremely flammable”.
- The logic for this categorization is:
  - Flash point < 23°C and boiling point ≤ 35°C = H224 (1)
  - Flash point < 23°C and boiling point > 35°C = H225 (2)
  - Flash point ≥ 23°C and ≤ 60°C = H226 (3)
  - Flash point > 60°C = (4)
- Hence trans-2-pentene (SIAL 111260) which has a NIST reported boiling point of 36.25 ± 0.5 °C (NIST Webbook) can’t possibly be H224.

Case study #2: h330

- GHS hazard H330 is “Fatal if inhaled”.
- Applicable to poison gasses such as phosgene.
- The set of gasses is finite, but this categorization is also to vapours, dusts and mists.
- This categorization is based on LC_{50} in ppm/V.
- A surprise discovery was that the natural product Aconitine (MW ~646) is categorized as H330, even though used therapeutically, and no reported LC_{50}.
- It turns out this categorization is required by law!?

Energetic substructures

- UN recommendations on “Transport of Dangerous Goods” lists the following function groups as being associated with explosive properties:
  - **C-C unsaturation**: Acetylenes, acetylides, 1,2-dienes.
  - **C-Metal, N-Metal**: Grignard reagents, organo-lithium compounds.
  - **N-N**: Azides, aliphatic azo compounds, diazonium salts, hydrazines, sulfonylhydrazides.
  - **O-O**: Peroxides, ozonides.
  - **N-O**: Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles.
  - **N-Halogen**: Chloramines, fluoramines.
  - **O-Halogen**: Chlorates, perchlorates, iodosyl compounds.

Oxygen balance

- Oxygen Balance (OB%) is used to indicate the degree to which an explosive can be oxidized.
- $$OB\% = \frac{-1600}{Mol.wt.of\ compound} \times \left(2X + \left(\frac{Y}{2}\right) + M - Z\right)$$
  - X = number of carbon atoms
  - Y = number of hydrogen atoms
  - Z = number of oxygen atoms
  - M = number of metallic atoms
- TNT ($C_7H_5N_3O_6$) has MW of 227.1 and OB of -74%.

Theoretical DSC OF TNT

- Heat of Decomposition
  - $C_7H_5N_3O_6 \rightarrow 2.5H_2O + 1.75CO_2 + 5.25C + 1.5N_2$

    H_f=-63.2 →H_f=2.5*-240.6 + 1.75*-393.5 = -1290.12kJ/mol

    ΔH_d = -1226.92 kJ/mol
- Heat of Combustion
  - $C_7H_5N_3O_6 + 5.25O_2 \rightarrow 2.5H_2O + 7CO_2 + 1.5N_2$

    H_f=-63.2 →H_f=2.5*-240.6 + 7*-393.5 = -3356kJ/mol

    ΔH_c = -3292.8 kJ/mol

Structures aren’t enough

Material Properties					Chemistry		Planned Amount		Actual Amount		Density		Strength		Calculated Amounts (Planned)					Calculated Amounts (Actual)					Actual Yield
Name	Class	Phase	MW	Lot Number	LR	SC	Value	Units	Value	Units	Value	Units	Value	Units	g	mL	mmoles	equiv	moles/mol-pure-LR	g	mL	mmoles	equiv	moles/mol-pure-LR	%
Acetic Acid	Chemical	Liquid	60.05	61780705001730			5	equiv (molar)	5	equiv (molar)	1.048	g/mL	100.00	wt/wt%	1.26	1.20	20.99	5.00	5.00	1.26	1.20	20.99	5.00	5.00	n/a
30% Hydrogen Peroxide in water	Chemical	Liquid	34.01				10	equiv (molar)	10	equiv (molar)	1.105	g/mL	30.00	wt/wt%	4.76	4.31	41.97	10.00	10.00	4.76	4.31	41.97	10.00	10.00	n/a
Sodium Iodide	Chemical	Solid	149.89				0.05	equiv (molar)	0.05	equiv (molar)	1	g/mL	100.00	wt/wt%	0.03	0.03	0.21	0.05	0.05	0.03	0.03	0.21	0.05	0.05	n/a
Piperidine	Chemical	Liquid	85.15				3	equiv (molar)	0	mL	0.8608	g/mL	100.00	wt/wt%	1.07	1.25	12.59	3.00	3.00	0.00	0.00	0.00	0.00	0.00	n/a
Benxoxazole	Reactant	Solid	119.12		☑	1	500	mg	500	mg	1	g/mL	100.00	wt/wt%	0.50	0.50	4.20	1.00	1.00	0.50	0.50	4.20	1.00	1.00	n/a
Morpholino benzoxazole	Product	Solid	204.23			1	0.86	g	0.7	g	1	g/mL	100.00	wt/wt%	0.86	0.86	4.20	1.00	1.00	0.70	0.70	3.43	0.82	0.82	81.66

Material Properties				
Name	Class	Phase	MW	Lot Number
Acetic Acid	Chemical	Liquid	60.05	61780705001730
30% Hydrogen Peroxide in water	Chemical	Liquid	34.01	
Sodium Iodide	Chemical	Solid	149.89	
Piperidine	Chemical	Liquid	85.15	
Benxoxazole	Reactant	Solid	119.12	
Morpholino benzoxazole	Product	Solid	204.23	

Future work: mixture handling

- Because the OEB/GHS category can depend upon concentration, phase and physical state efforts are being made to capture this more accurately in the ELN/Casandra system.
- It is hoped that recent work by IUPAC on the MInChI (Mixture InChI) may solve many of the remaining representational challenges.

Future work: property prediction

Tetko *et al. J Cheminform (2016) 8:2*
DOI 10.1186/s13321-016-0113-y

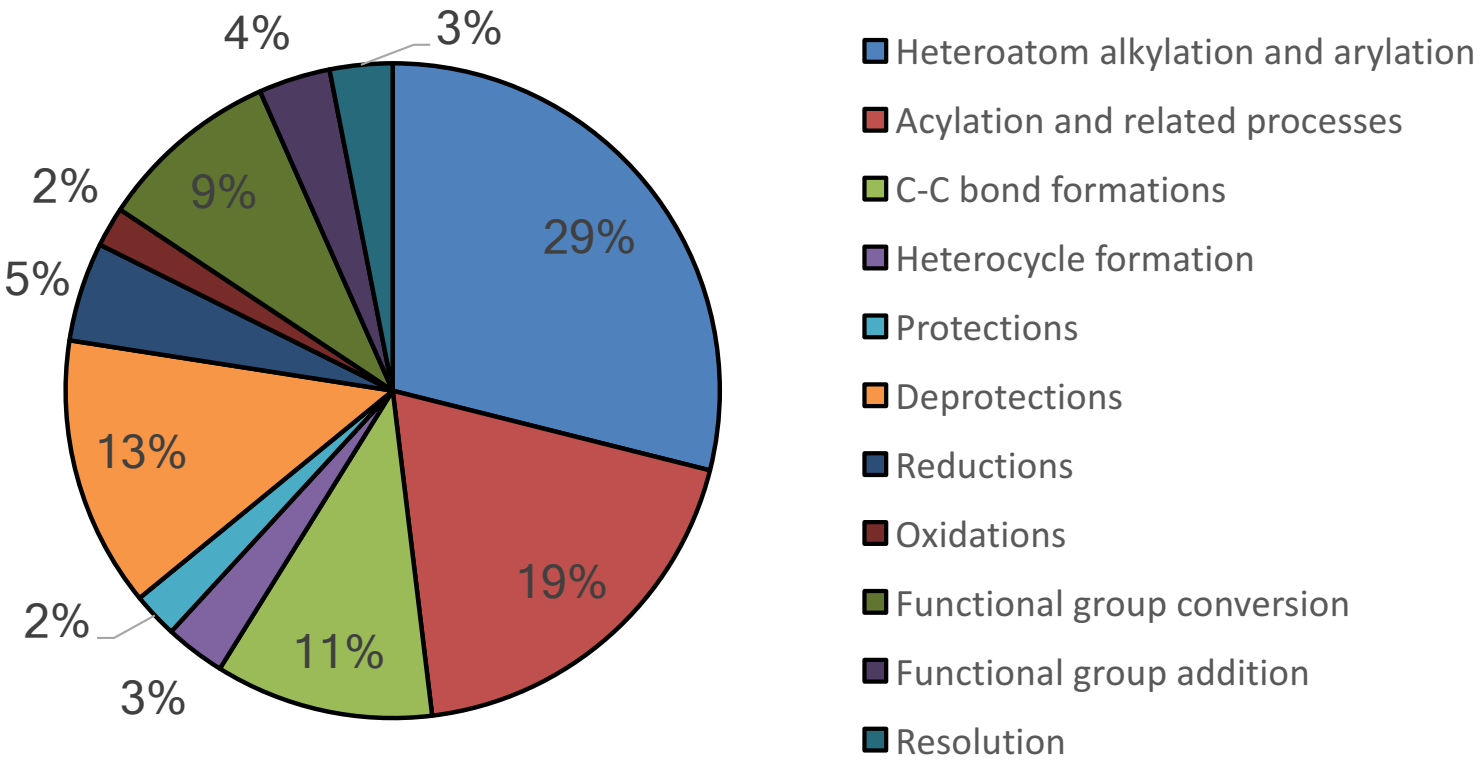
Journal of Cheminformatics
a SpringerOpen Journal

RESEARCH ARTICLE Open Access

The development of models to predict melting and pyrolysis point data associated with several hundred thousand compounds mined from PATENTS

Igor V. Tetko[1,2*], Daniel M. Lowe[3] and Antony J. Williams[4]

Future work: namerxn integration



1. J. Carey, D. Laffan, C. Thomson, M. Williams, *Org. Biomol. Chem.* 2337, 2006.
2. S. Roughley and A. Jordan, *J. Med. Chem.* 54:3451-3479, 2011.

Future work: ontogrep integration

- nitrogen containing heterocycles
- cationic ring systems
- cyclic alkanes
- branched acyclic alkanes
- transuranic elements
- zinc compounds
- binary compounds
- Lewis acids
- atropisomers
- polyspiro ring systems
- polyatomic elements
- inorganic salts
- radioactive compounds
- radioactive elements
- monocyclic ring systems
- neutral compounds
- uncharged compounds
- zwitterionic compounds
- carbon containing inorganics
- zinc oxides
- metal chlorides
- iron halides
- inorganic salts

Conclusions/insights

- The technology exists to alert/flag experiments in ELNs against published “best practice” guidance.
- Merck’s reaction review policy requires modifying an ELN to more fields, such as reaction vessel size.
- Applicability of these alerts can be extended by QSAR models (algorithms for compound property prediction).

acknowledgements

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- Dana Vanderwall, Ramesh Durvasula, Dong Li and Carol Mcnab from Bristol-Myers Squibb.
- Leah McEwen, Evan Bolton and Ralph Stuart at iRAMP.
- Chemical Safety Library (CSL) project, Pistoia Alliance.
- The rest of the team at NextMove Software.

Derek lowe vs. common sense

- "**Ignorance is No Defence:** In A Chemistry Lab, What you don't know really can hurt you", by Derek Lowe, *Chemistry World*, 14th January 2015.

  https://www.chemistryworld.com/opinion/ignorance-is-no-defence/8150.article
- Lists as hazardous both:
  1. Dimethylmercury
  2. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
- The exposure risks of each are not really comparable:
  1. Hazardous when handling even with gloves.
  2. Hazardous if injected intravenously.

H280: irrelevant to pubchem?

- Hazard code H280 is “Contains gas under pressure; may explode if heated”.
- This warning concerns the container that a product may shipped in, and isn’t a fundamental hazard of the chemical itself.
- Any gas at 200 kPa (i.e. in a gas cylinder) has this hazard.
- Currently, 88 PubChem CIDs have this “feature”, including CID 1119 (Sulfur dioxide).