Leveling up chemical information for the era of big data

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CDD VAULT®
Complexity Simplified

Background

- **Big Data**: more like **Large Data** (+ inconvenience)
- We can have aspirations
- For any established subset of chemistry: vast amounts of data exists...
- ... but not in a way computers can use it

History

- Early 20th century: science was a small town, everyone knew each other

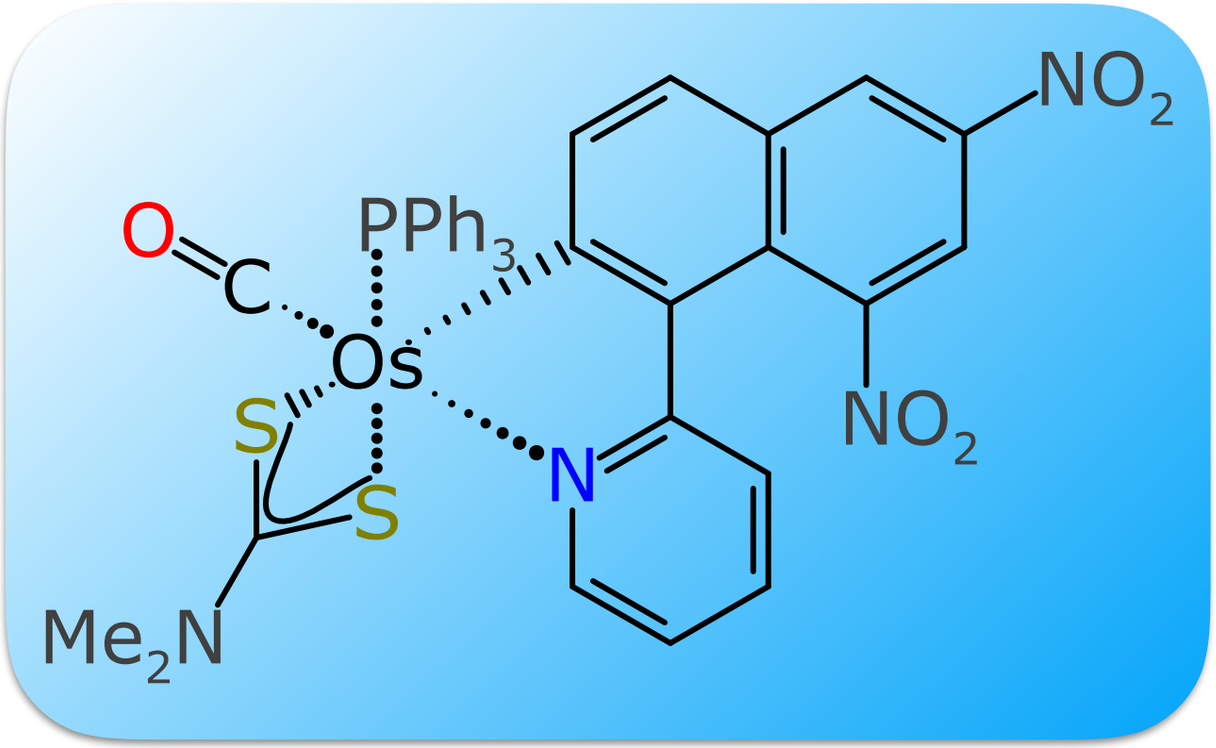
- The dead tree model of publishing scaled nicely

- 1990s: my grad advisor (W.R. Roper) knew all the players in organometallics, read everything

- 2000s: my postdoc advisor (C.A. Reed) opined we were *drowning in peer reviewed literature*

Grains of sand on a beach

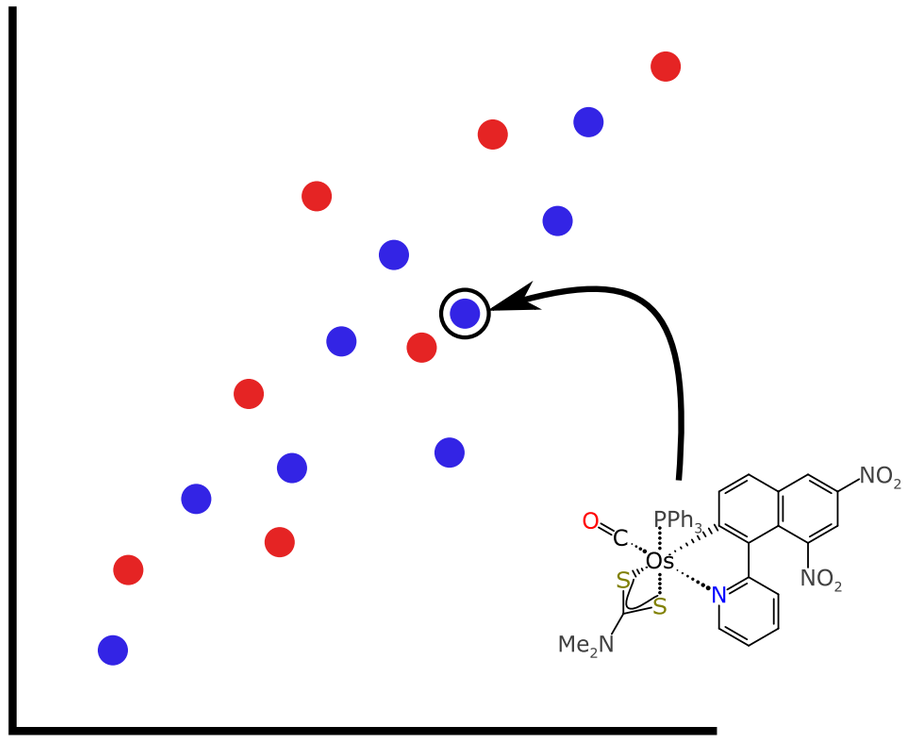
- From my graduate research...



- ... and a hundred more much like it.

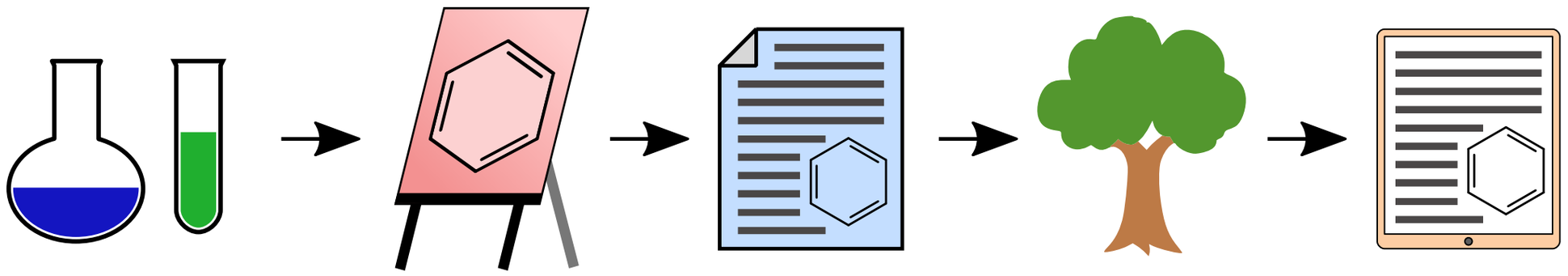
- Pure academic research: to see if we can
- Published in respectable journals: a few citations, mostly forgotten in dusty tomes & PDF files
- All that time & effort & funding... for what?

To be a datapoint



- Every unit of science has *potential* value, but no way to be sure when or to whom
- Nobody can read it all, but the solution is not to publish less
- We need to rethink the target audience: it's not humans... it's **machines**
- They can handle the scale...
- ... but they cannot interpret the input data.

Digital trees



- Computers for writing & reading since 1990s
- Yet we use tech to pretend we're with Newton & friends in early days of the Royal Society
- Each step is digital, but the process is modelled on typewriters and wood carvings
- What little data existed in the intermediate documents is destroyed during the final production

Progress?

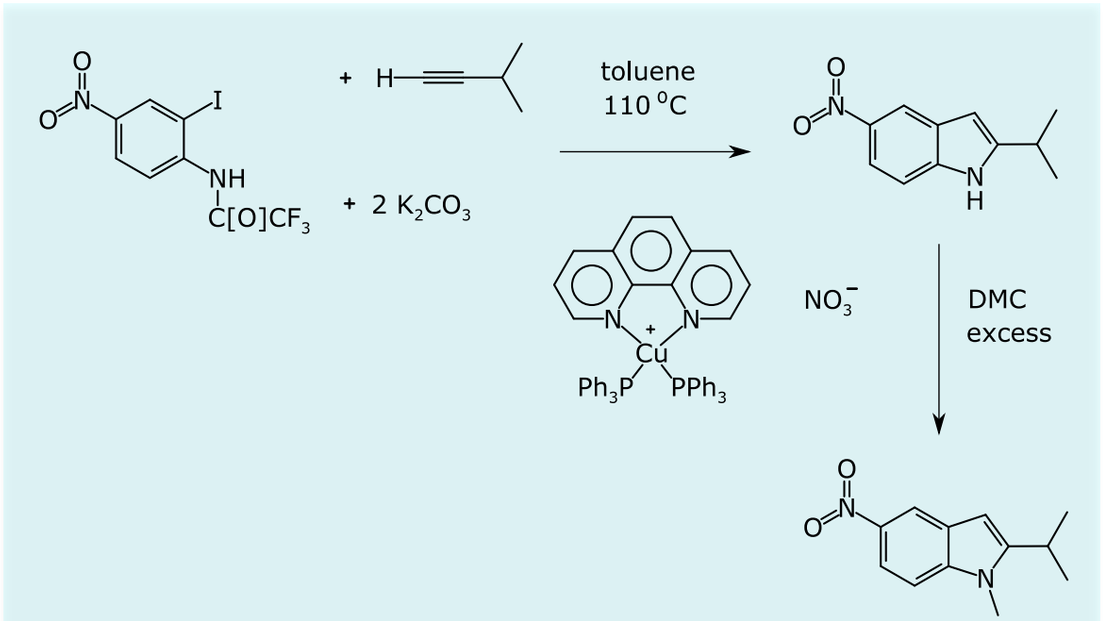
- Most chemical data is silo'd and opaque
- Drug discovery is very motivated: there are structure-activity datasets that are **free**, **large**, **useful** *and* **accurate** (previously: pick zero)
- Now: **ChEMBL**, **PubChem** & others (SAR data)
- Improved accessibility:
  - open access is growing (still not data though)
  - APIs to the patent literature
  - FAIR data movement: building steam

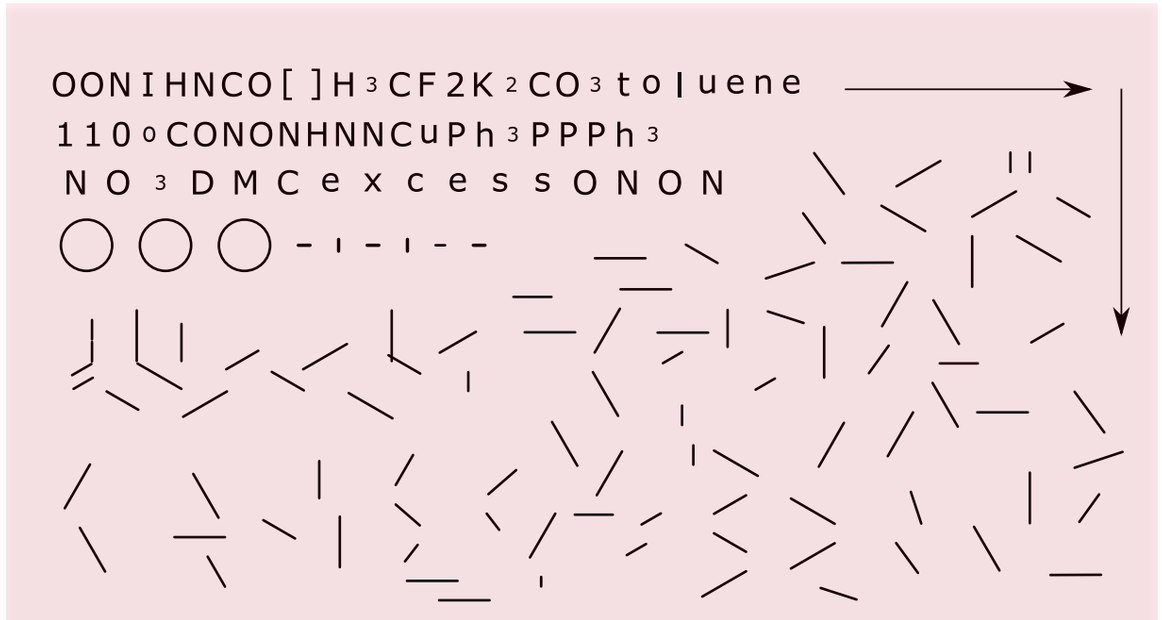
Dark data

- Almost all published chemical research is visible only to humans, and effectively dark to machines
- This is almost as true now as it was in 1700
- Solutions have distinct categories:
  - **fix the past**: curate old publications using descriptive data formats - machine learning and text mining can help, but still need expensive expert humans
  - **fix the present** (+ future): publish new data using file formats that target machines *and* humans - need better tools and different attitudes

Case 1: Figures

- Chemists painstakingly draw molecules & reactions

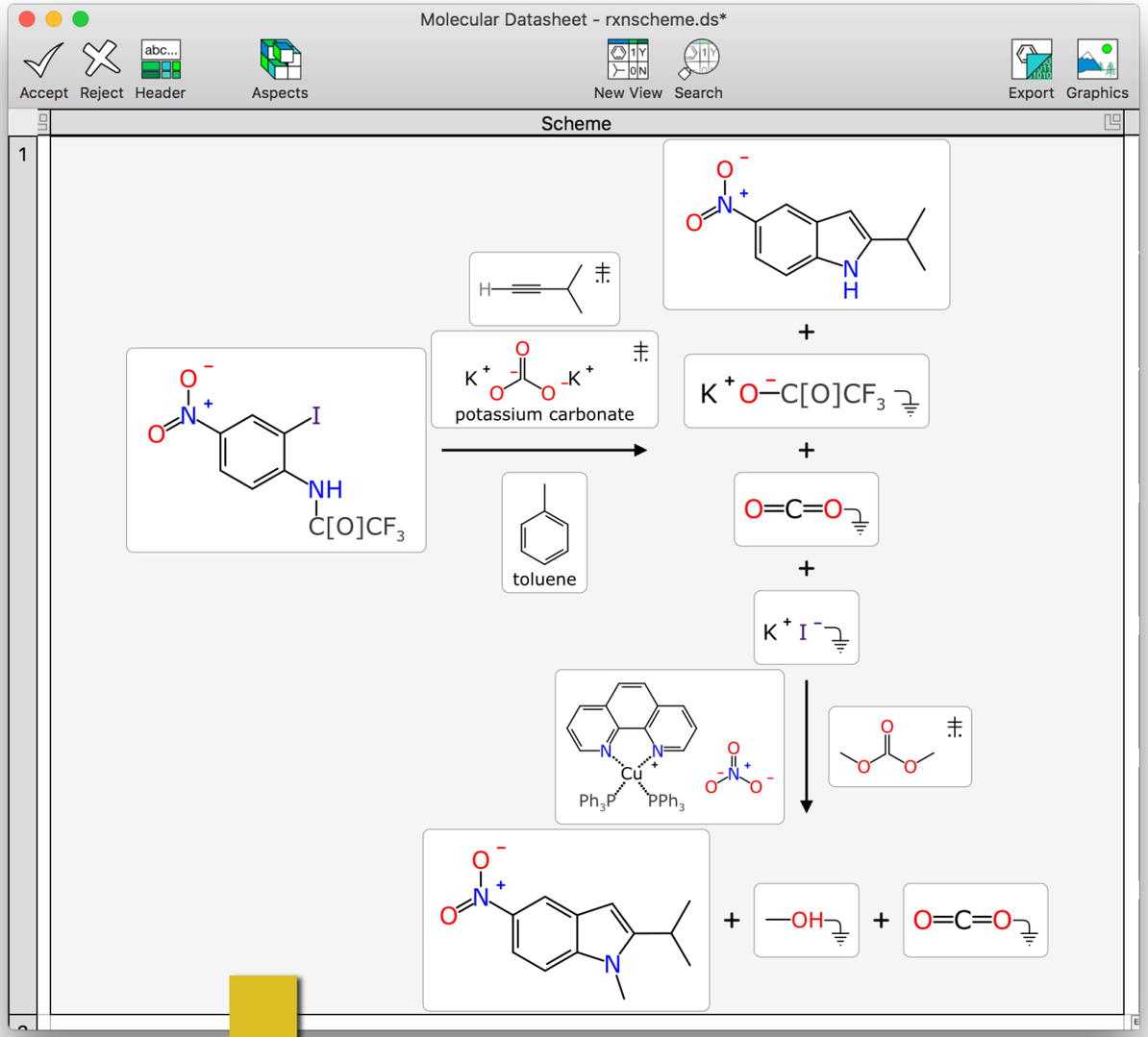


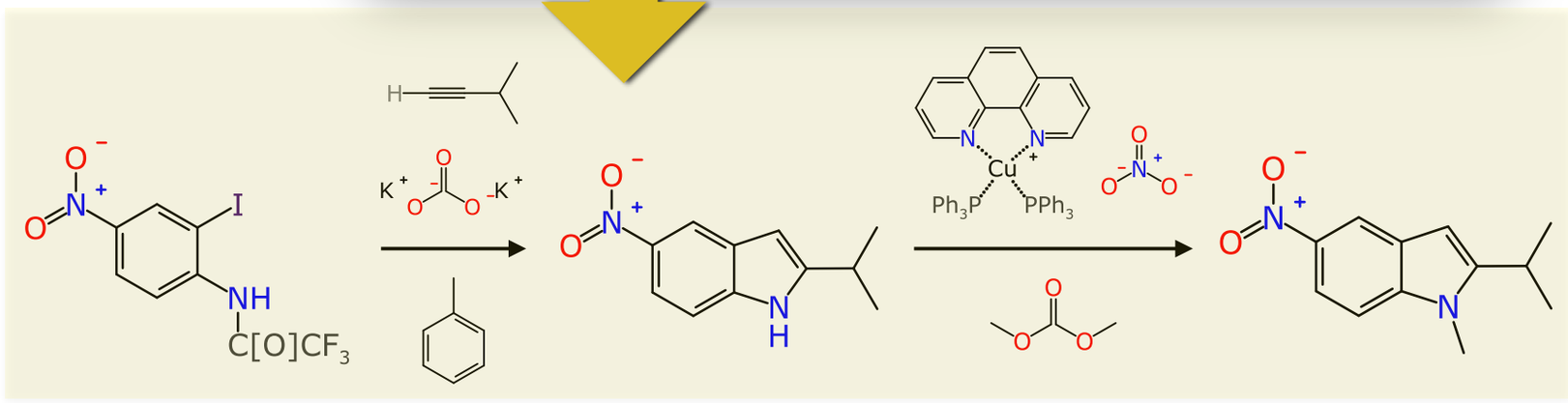


- Interpretability is high for other chemists...
- ... and surprisingly low for machines.

Cheminformatics first

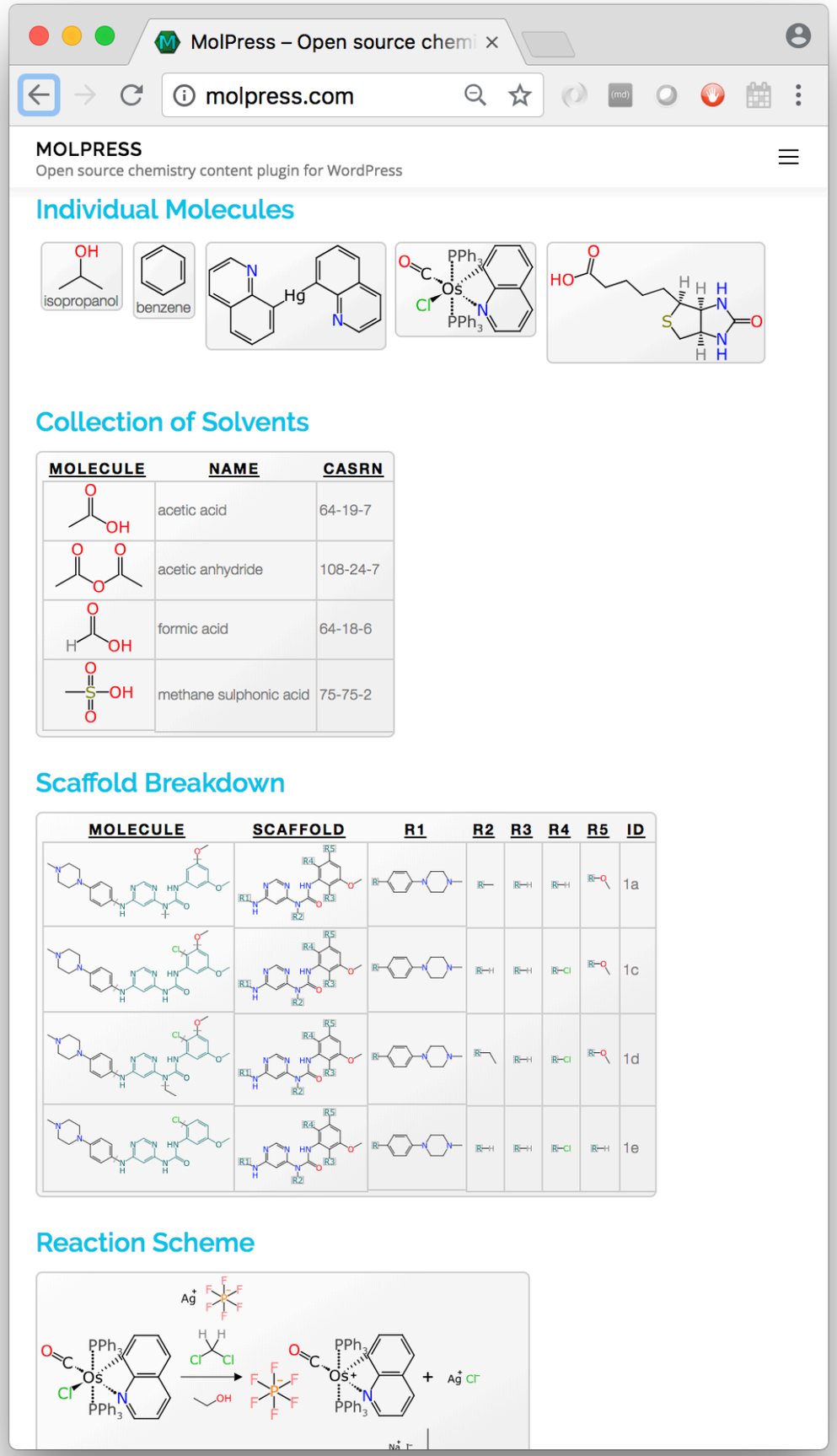
- Similar amount of effort to draw fully defined content
- e.g. **Molecular Notebook**
- Draw structures & reaction components for computers
- Let algorithms do the rendering...





Internet-era manuscripts

- Using standard wordprocessor is not good for data
- WordPress plugin **MolPress**:
  - insert & retain raw data
  - plugin handles rendering
  - open source
- Use blogging software as an electronic lab notebook



Case 2: Assay Central

- Rare & neglected diseases: long tail, few resources
- Premise: the data is out there
- Pragmatism: grab & fix, by any means necessary
- Sources:
  - **ChEMBL**, **PubChem** (parts thereof)
  - curation, collaboration, importing, scraping
- Goal: seed *all* targets with only good data

Provenance

- Some data is good: just have to label (e.g. target), others must sample, validate by flagging
- Merging: standardise, group by, build models
- Project ➔ **GitHub** repository: a molecular build system

Assay Central

Assay Central Predictions

draw, paste or drag molecule

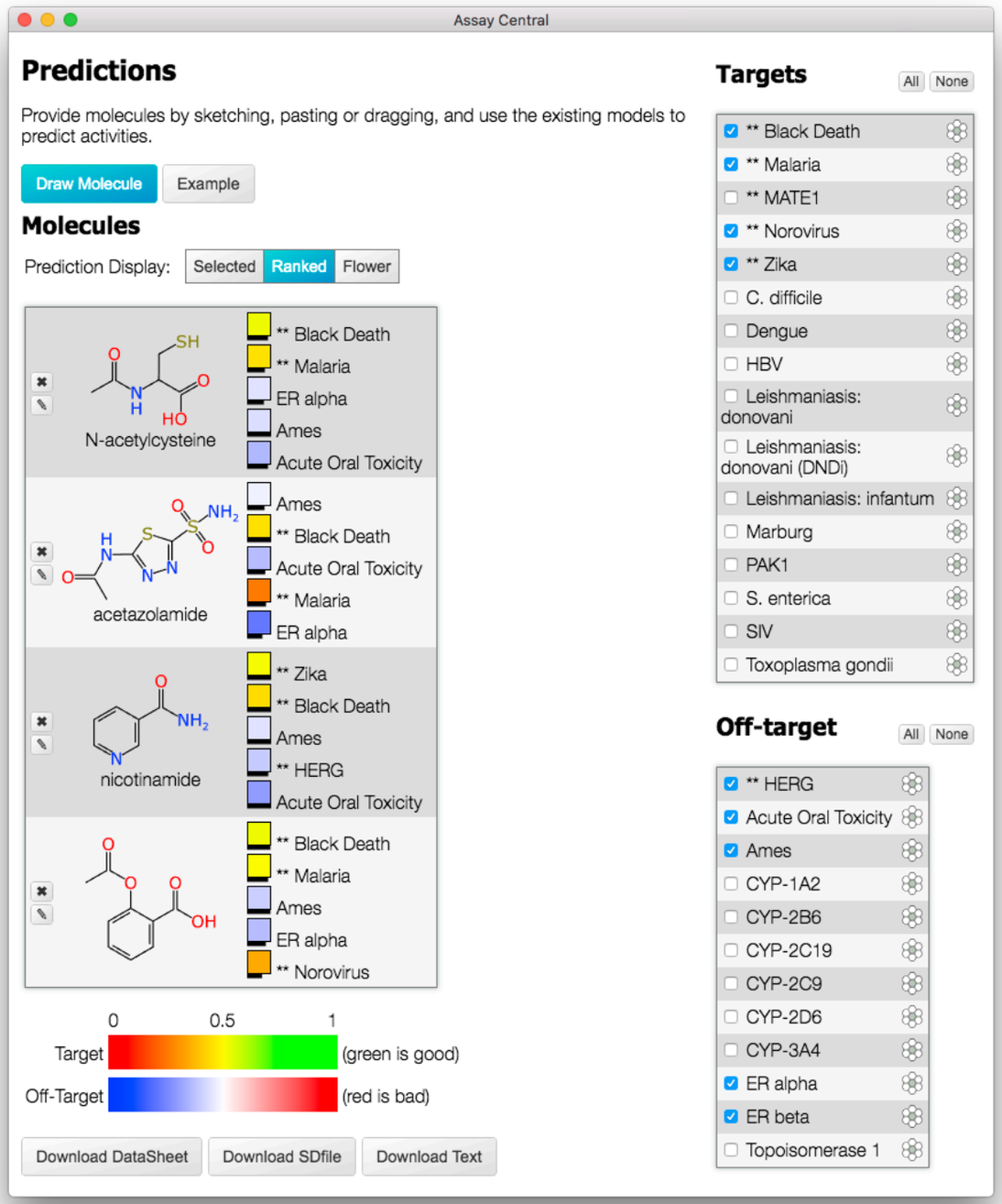
Predict

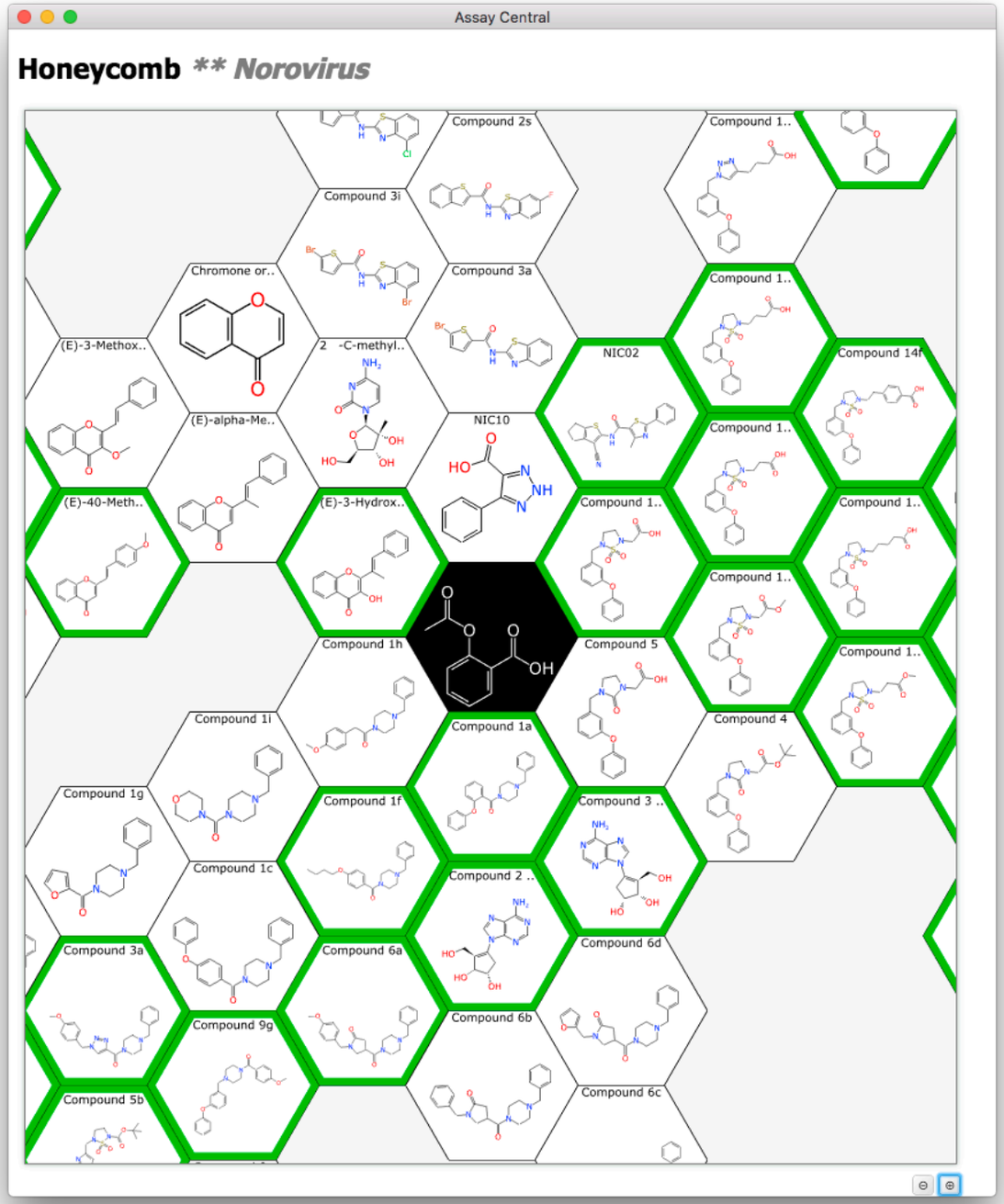
Available Assay Datasets

						Bayesian						Random Forest	
List / Tree	Title ↑	Target	Organism	Actives	Size	ROC	F1	Kappa	MCC	Domain	Invalid	RMS	R2
Data Model	Influenza A	Influenza A virus	Influenza A virus	400	820	0.8834	0.8278	0.6679	0.6681	0.2679	549	0.8665	0.4328
Data Model	Influenza A (H1N1)	Influenza A virus (H1N1)	Influenza A virus	103	466	0.9298	0.8122	0.7519	0.7586	0.2084	38	0.7510	0.6426
Data Model	Influenza A (H3N2)	Influenza A virus (H3N2)	Influenza A virus	12	33	0.8849	0.8000	0.6784	0.6798	0.1547	3	1.020	0.2581
Data Model	Influenza A (H5N1)	Influenza A virus (H5N1)	Influenza A virus	3	21	1.0000	1.0000	1.0000	1.0000	0.1103		1.007	0.4656
Data Model	Influenza B	Influenza B virus	Influenza B virus	111	228	0.8639	0.8318	0.6834	0.6851	0.2101	30	0.8669	0.4926

Visualisation

- Deployable web app, data & models:



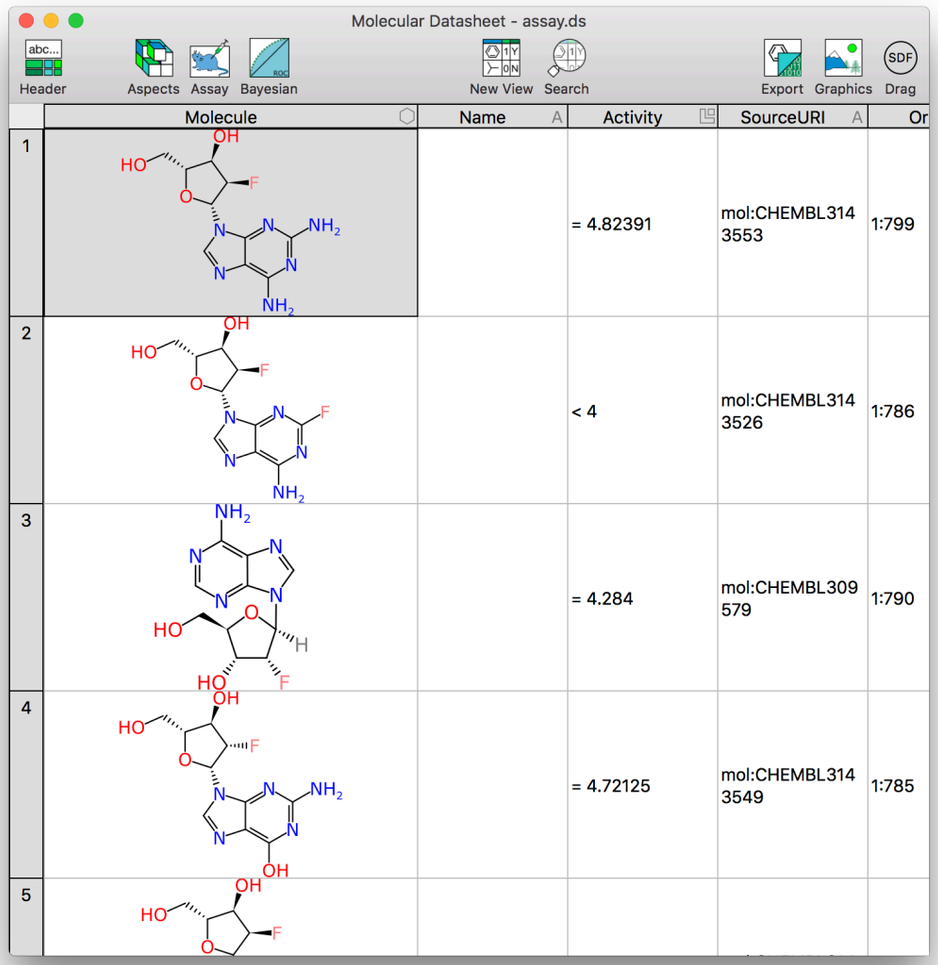


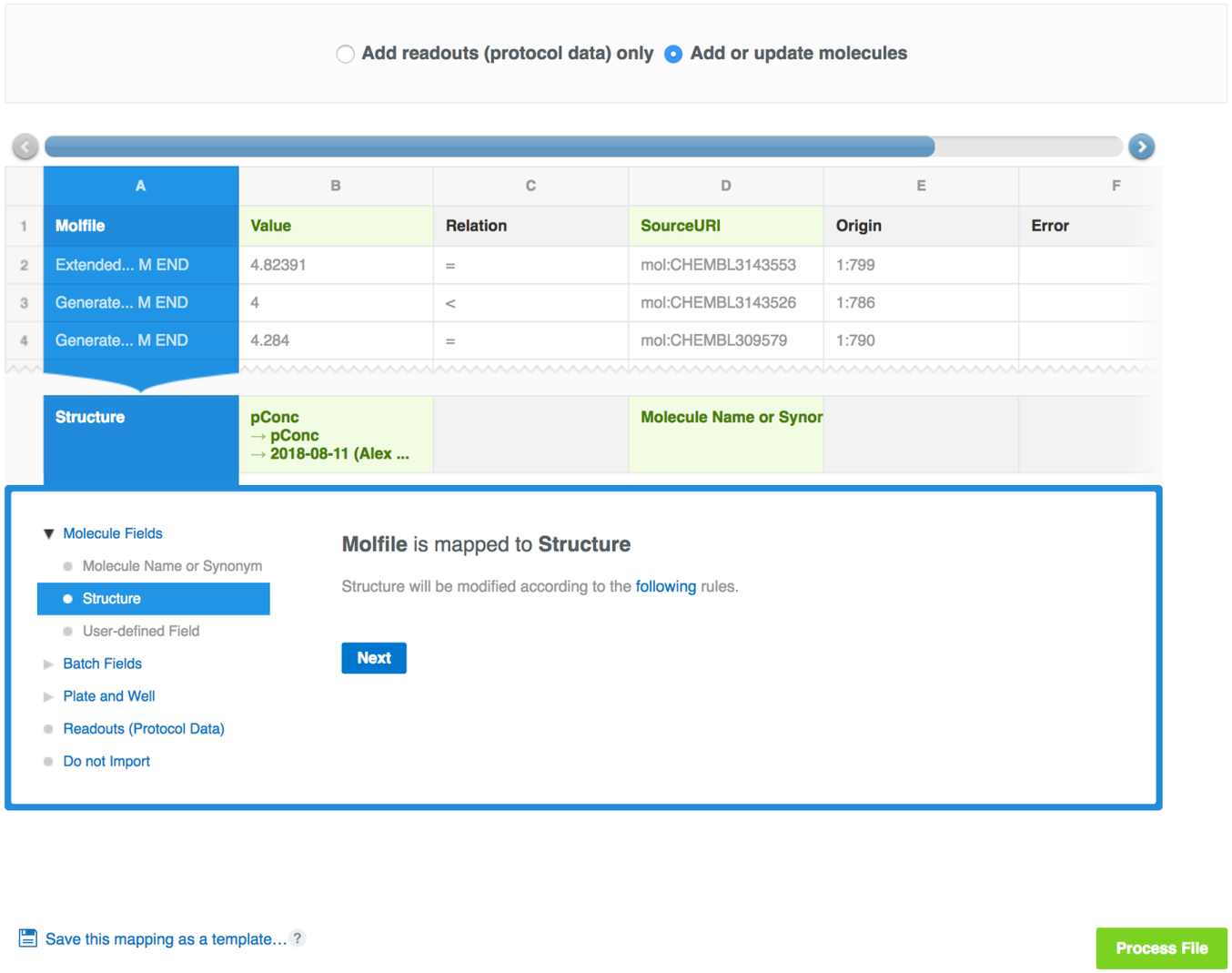
Virtuous cycle

- Initial data integration is labour intensive
- Build models & other decision support
- Can generate *prescribed* molecules
  - high predictions for desired target(s)
  - low predictions for undesirable off-targets
- Collaborators can order & test these candidates, and return the data in **model-ready format**

Case 3: CDD Vault

- Entry point is an *import* process: effort is up front...





- ... after that, everything else just works.

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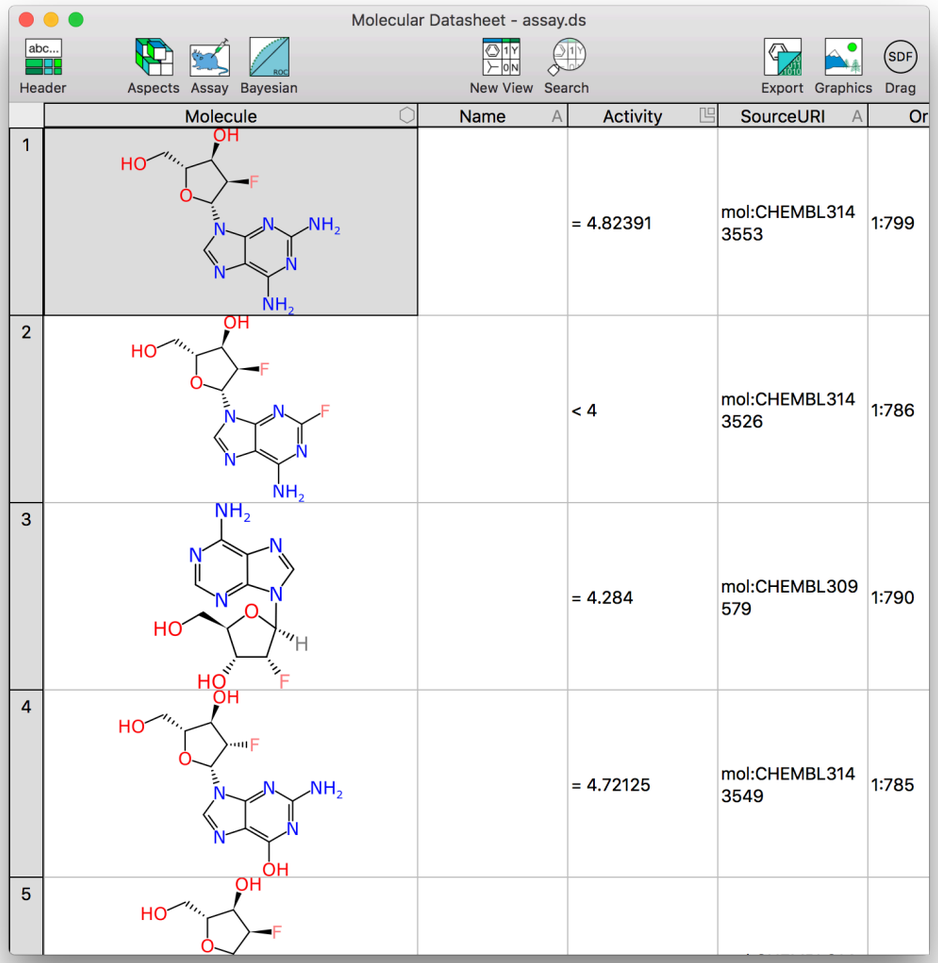
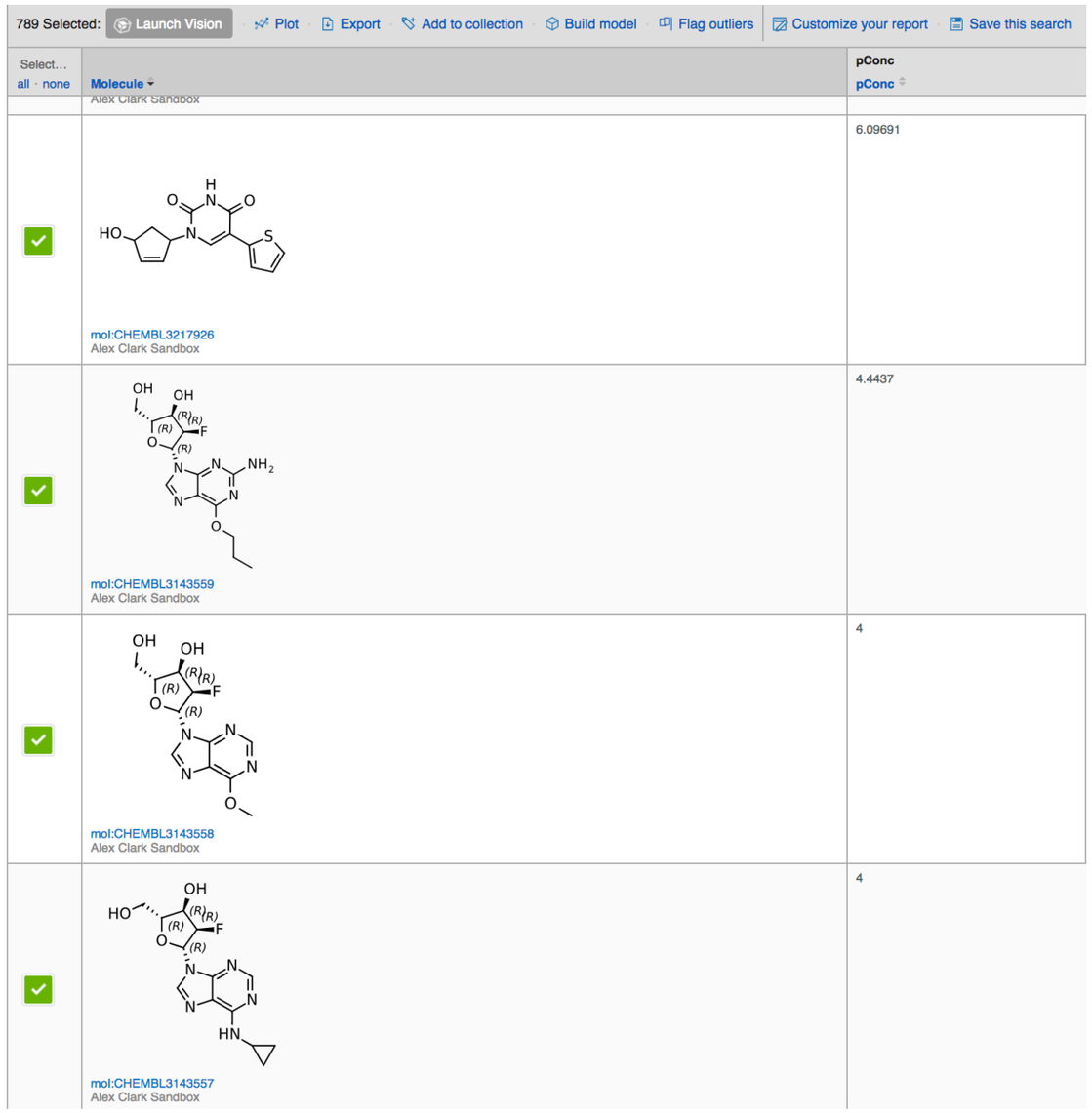




- ... after that, everything else just works.

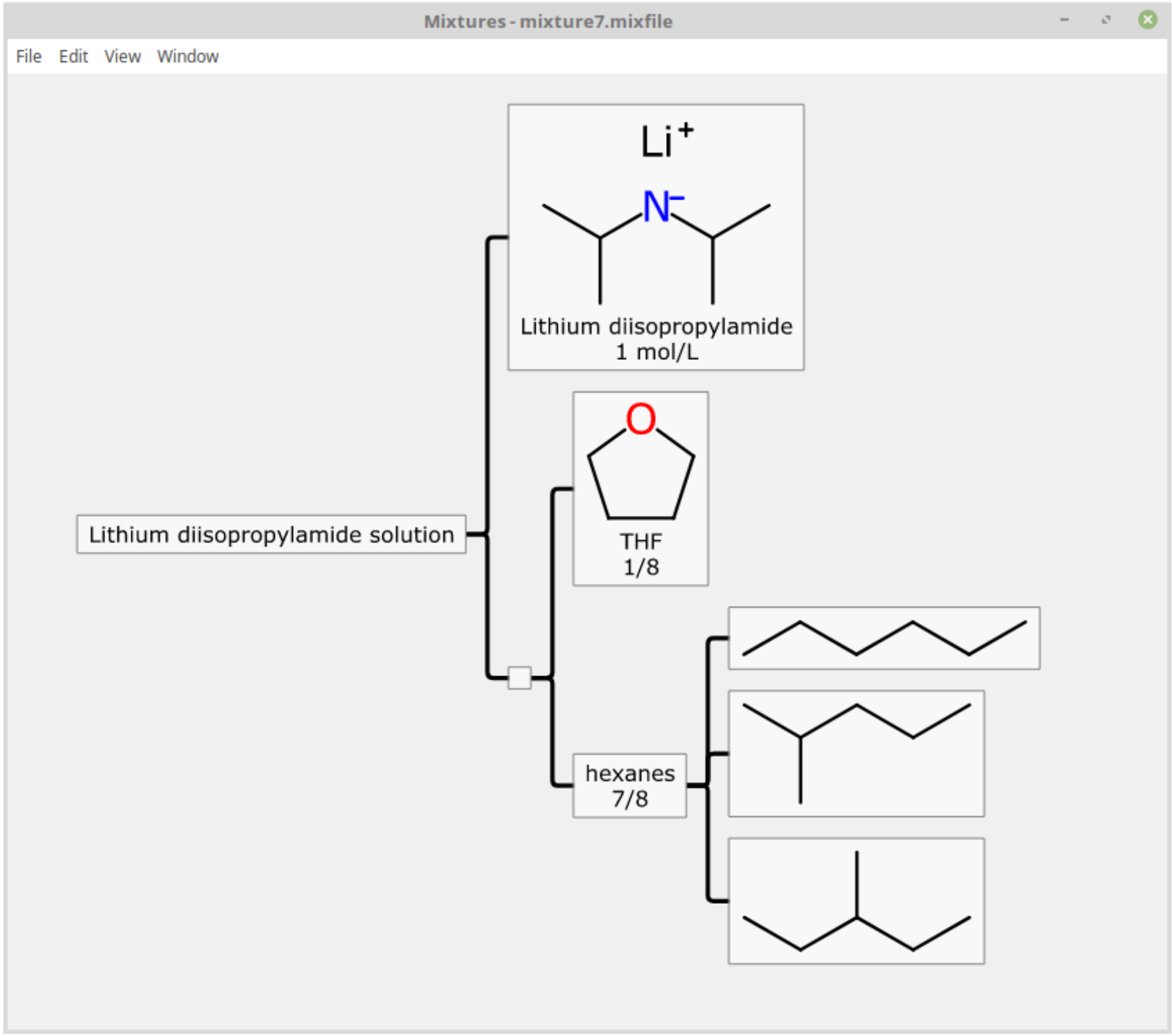
Case 4: Mixtures

- Mixtures of compounds: ad hoc is the way, e.g.
  - **osmium tetroxide 2.5 wt. % in *tert*-butanol**
  - ***n*-butyllithium 2.5M in hexanes**
- Long overdue for a well defined open format
  - **Mixfile**
- High priority: text-extraction importer
- Working with IUPAC: data feedstock

Molfile → InChI
Mixfile → MInChI

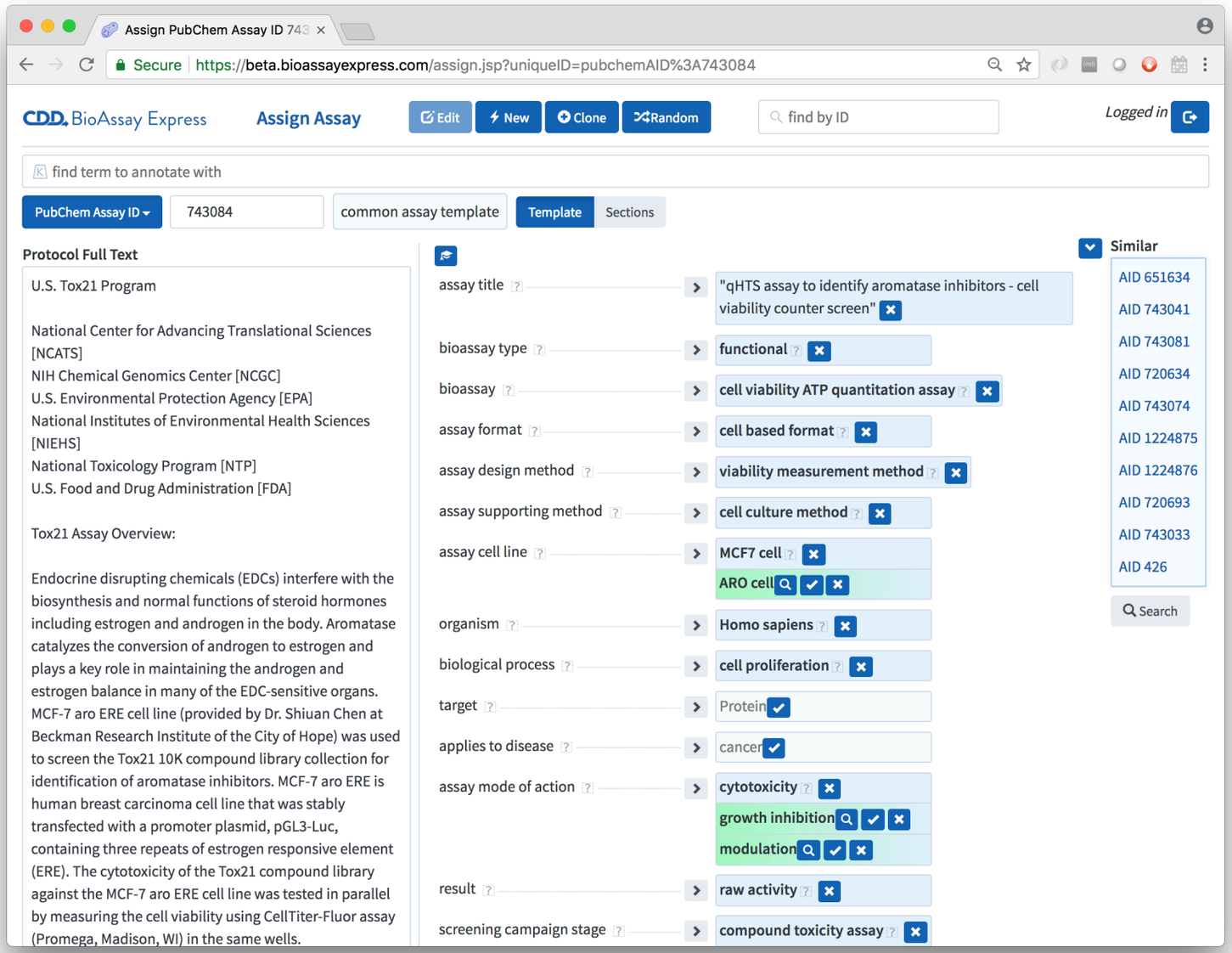
Mixfile editor

- Verbose
- Hierarchical
- Cross-platform
- Open source
- JSON-based



Case 5: Bioassay protocols

- Assay protocols usually just text: enrich by describing them with *semantic web terms* (e.g. BAO, DTO, CLO...)
- Curated assays are machine readable
- Legacy: ML-support
- Current: ELN-style
- Began 2014
- See Wednesday

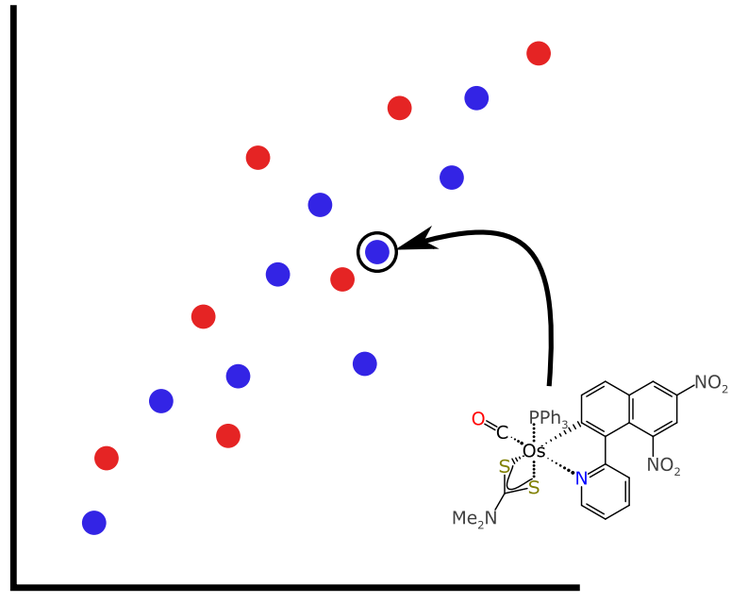


Case 6: Data are valuable

- The only way forward: machine readability at source
- Scientists must be "**persuaded**" to get on board
- Better tools can help, but mostly social engineering
- Who controls much of the culture of science?

Journal publishers

- Only the human-readable parts of a manuscript are peer reviewed (text & figures)
- What if the **data** were part of the formal process...
- ... if an algorithm can't understand it, send it back.
- Supplementary information becomes the most important part of the article
- Open it to everyone's model



Example

- Can start small, e.g. with organic/drug discovery

protein kinase inhibitor, but was found in a zebrafish embryo dorsalization assay to selectively inhibit BMP signaling through SMAD1/5/8.[6] Further development led to **LDN-193189**,[7] **LDN-212854**,[8] and **ML347**,[9] which had improved microsomal stability, potency, and selectivity. In addition, these molecules demonstrated efficacy in mouse models of FOP.[8] However, these compounds have a number of kinase off-targets and display dose-limiting toxicity with a 10% loss in body weight in animal models.[10] A second series of inhibitor based on a pyridine core (e.g., **K02288**[11] and **LDN-214117**[12]), with equivalent biochemical potency and improved kinome selectivity, has also been reported (Figure 1).

RESULTS

We identified 6-pyrazole quinazolinone, **1**, as a ligand efficient inhibitor of ALK2 (IC_{50} = 8.2 μM; LE = 0.45) through cross-screening of a focused kinase fragment library, using Invitrogen's LanthaScreen binding assay. **1** shares features with reported ALK5 inhibitors such as **PF-03671148**[13] and compound **19**.[14] These are known to bind to the hinge of ALK5 through a single polar contact at the *N*-1 position of the quinazolinone moiety, with the 2-methylpyridine directing toward the ALK5 Ser280 gatekeeper residue, forming a key water mediated hydrogen bond to Lys232 (Figure 2).[14]

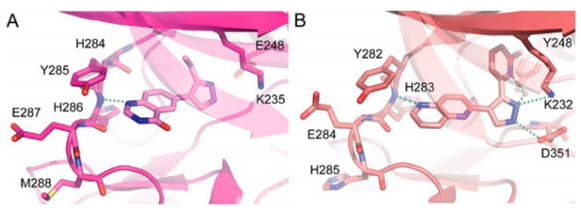
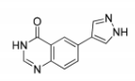
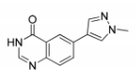
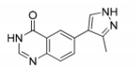
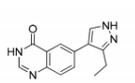
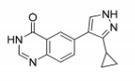
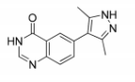
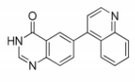
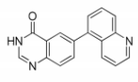
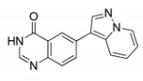


Figure 2. (A) Docking pose of **4** in ALK2 (structure used: 3Q4U). (B) X-ray structure of analogous naphthyridine-based inhibitor (compound **19**) of ALK5[14] (PDB 1VJY).

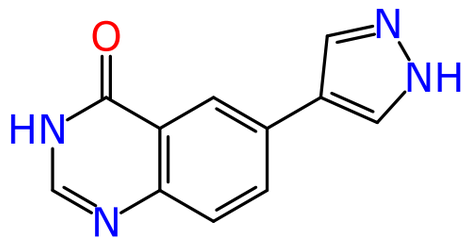
Interestingly, **PF-03671148** has been shown to be selective against ALK1 likely due a larger gate keeper (Thr) causing a clash with the pyridine substituent.[13] Given that ALK2 also

Table 1. SAR at Quinazolinone 6-Position[a]

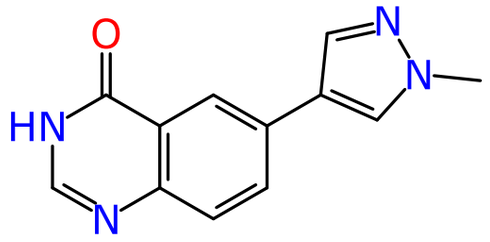
No°		ALK2 IC_{50} (μM)	LE	LiPE	TPSA
1		8.20	0.45	4.79	70.14
2		18.2	0.39	4.43	59.28
3		2.30	0.46	5.38	70.14
4		1.00	0.47	5.21	70.14
5		0.386	0.47	5.71	70.14
6		0.293	0.51	6.30	70.14
7		0.167	0.47	4.90	54.35
8		0.344	0.45	4.60	54.35
9		0.653	0.43	4.65	58.76

[a] IC_{50} data is an average of 2–4 measurements by LanthaScreen Eu kinase binding assay.

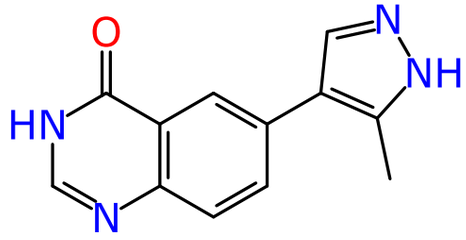
1.mol



2.mol



3.mol



data.csv

```
ID,ALK2IC50,LE,LiPE,TPSA
-,uM,uM,uM,uM
1,8.20,0.45,4.79,7014
2,18.2,0.39,4.43,59.28
3,2.30,0.46,5.38,70.14
```

- Author provides the files, middleware does basic validation, reviewer opens and verified

What are you waiting for?

- A whole industry & community exists for support
- Best of breed tools have open source options
- One publisher has to go first...

- … **who**?

Acknowledgments

- Royal Society of Chemistry & ACS CINF
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- Peter Gedeck, Hande Küçük-McGinty **(BAE)**
- Sean Ekins, Kim Zorn **(CPI)**
- Leah McEwen **(IUPAC)**

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