Chemoinformatics in Europe: Research and Teaching

Chemical informatics: where are we headed?

Robert Glen, Cambridge, UK

Can Chemoinformatics move to a new paradigm ?

- Previously
  - Data……modelling……..prediction
- Future
  - Information……knowledge…..decision

What is changing ?

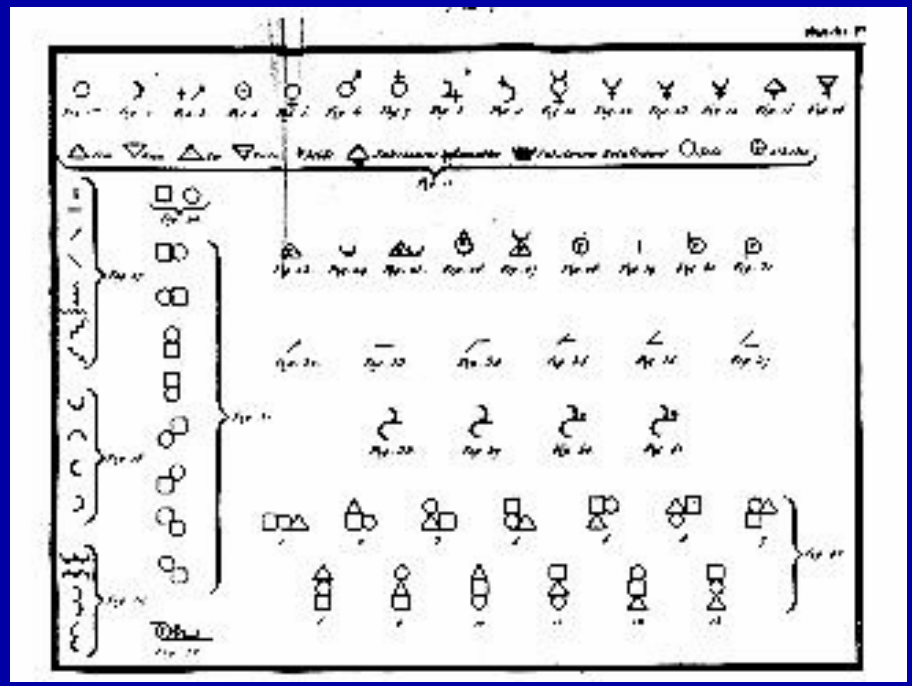
- Previously
  - Data……modelling……..prediction
    - Data : numbers, pictures, descriptions without context, disconnected and incomplete – single use databases, no metadata
    - Modelling : localised in analysis, unconnected, often artifactual, not phenomenological (most of QSAR)
    - Prediction : limited to one application, data dependant, not transferable – or often not reproducible
- Future
  - Information……knowledge…..decision
    - Information is contextual, marked up, transferrable, can be integrated with other data, adheres to standards
  - Knowledge
    - Abstractions from relationships between data, deeper understanding of underlying rules, more robust prediction, amenable to natural language queries
  - Decision
    - Moving from single predictions e.g. a compound is predicted active in an assay to
    - What factors influence activity, is a compound fit for development, what experiments need to be done, is there a market, has it been made before?

A bit of history on how molecules are described and how this affects what we can do…..

- How molecules have been represented
- Early ‘Informatics’

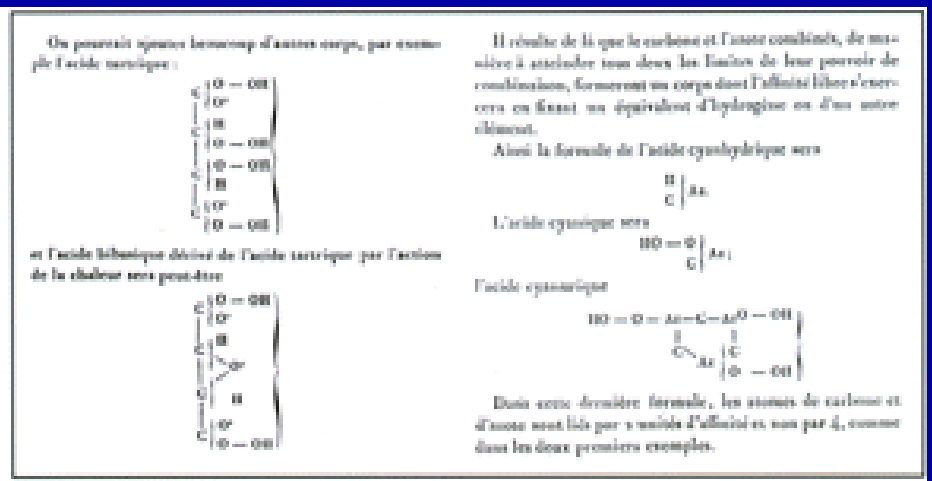
Representing compounds as pictures

- Early chemical symbols and those created by Jean Henri Hassenfratz and Pierre Auguste Adet to complement the *Methode de Nomenclature Chimique* (1787).



Courtesy Edgar Fahs Smith Memorial Collection, Dept. of Special Collections, University of Pennyslvania Library

Berzelius : introduced our familiar alphabetic symbols, isolated cerium, selenium, and thorium, and invented words such as allotropy, isomerism, and protein catalyst.



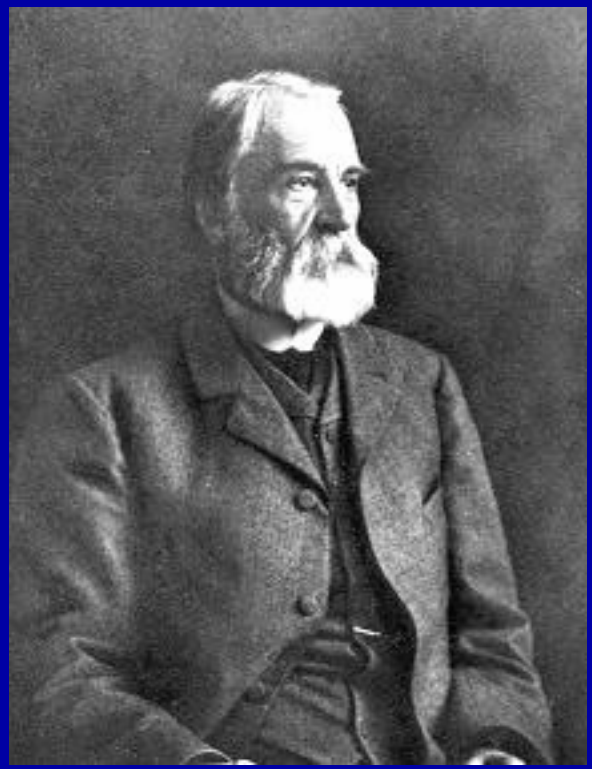
Archibald Scott Couper's bond lines.

He proposed that names for chemicals should be ‘definitions of the composition of the substances’ – gave rise to our atomic symbols

The ‘connections’ between symbols of Scott-Couper gave rise to structural diagrams

An early application of infomatics

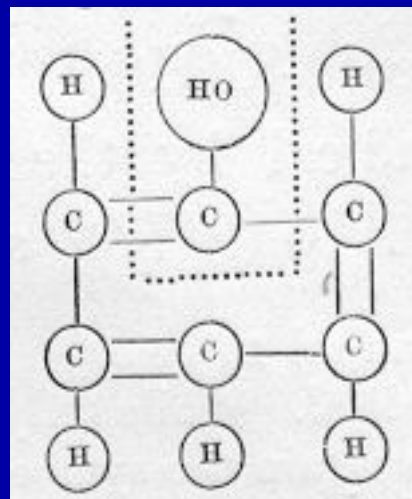
Frederick Beilstein



In the Handbuch the naming of compounds was an integral part of their storage and retrieval from indexes.

This drive for efficient indexing dominated chemical information for the next half century

(still does today)

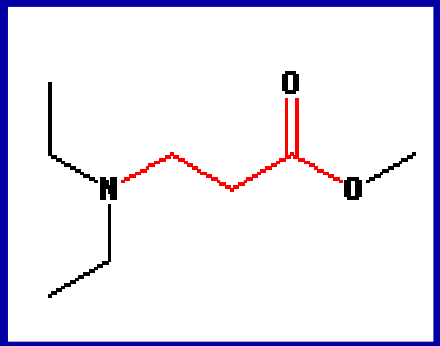


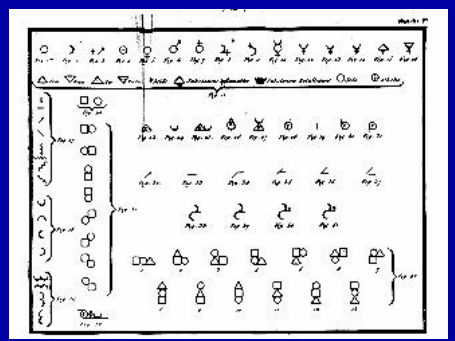
Frederick Beilstein.
Courtesy Edgar Fahs Smith Memorial Collection,
Dept. of Special Collections,University of Pennsylvania Library.

Machine readable structure representation.

- Line Notations
  - WLN
    - L66J BMR& DSWQ IN1&1
  - ROSDAL
    - 1=-5-=10=5,10-1,1-11N-12-=17=12,3-18S-19O,18=20O,18=21O,8-22N-23,22-24
  - SMILES
    - c1ccccc1Nc2cc(S(=O)(=O)O)cc3c2cc(N(C)C)cc3

Example of an SD file





```
GABA analog
28 27
2.8660    0.0000    0.0000 N   0  0  0  0  0  0  0  0  0  0  0
.                    Atom block :    X  Y  Z  SYMBOL  MASS  CHARGE  STEREO
.                    Bond block:   ATOM1  ATOM2  TYPE  BOND ST  NX  TOPOL
 1  2  1  0  0  0  0
 1  3  1  0  0  0  0
.
.
> <E_CAS>
5351-01-9
$$$$
```

I could ask the question –
How much have we moved on ?
Until recently, encoding chemistry has got stuck (the ‘format’ I used in 1970 (.mol) is still used…..– but that’s changing

Encoding chemistry

- Cheminformatics has concentrated on:
  - Re-writing chemical structures and data (from the literature) for computer storage and retrieval – usually based solely on structure
  - Construction of ‘single use’ databases – structure and searching capability are fixed
  - Centralised database resources updated infrequently
  - Annotation is fixed and not transferable
  - We deal with abstract connection tables – not properties of substances
- This approach has served us well, but with the capabilities of the internet, markup of data, metadata, pipelining of procedures (the ‘GRID’), multiple databases, high throughput data production, a huge increase in the literature…new opportunities emerge
- Appropriate data can be aggregated from multiple sources, checked, annotated further and analysed with more complex queries

XML and molecules

- XML is a computer language that allows ‘metadata’ to be stored along with the primary data
- Chemical Markup Language (CML) is being developed specifically for chemistry
  - Structure
  - Reactions
  - Calculations
  - Measurement
- In the future, much more information will be stored with molecules allowing greater re-use of data
  - E.g. not just melting point, but its range, units, method etc…
- see : Chemical Markup, XML and the World-Wide Web. Part I. Basic principles. P. Murray-Rust and H. S. Rzepa, J. Chem. Inf. Comp. Sci., 1999, 39, 928.

Some questions…

- Where do we find chemical data (data discovery)
  - literature, trusted sites, computation, in-house
    - Can we automate the process
- Is the data appropriate
  - are the units compatible, consistent among multiple sources, relevant to the questions asked
    - Can the data be audited
- Is it validated
  - Misprints, mistyped, missing, wrong, inconsistent
    - Can the data be checked
- Can we share it
  - No access, copyright, incomplete, hidden
    - Is data deposition open to a new paradigm ?
    - Will publishers share data ?

So, the first step, putting data into the computer How useful is the data ?

- Can be wrong – so we can use -
  - computational methods to check it (best before it appears in a database – authoring tools)
- However, a more serious problem is that the data can simply be inappropriate to the problem
  - E.g. modelling and the real world don't match
- Start with some examples of data checking (authoring) and move on to data correction and data abstraction

Using information from Legacy data

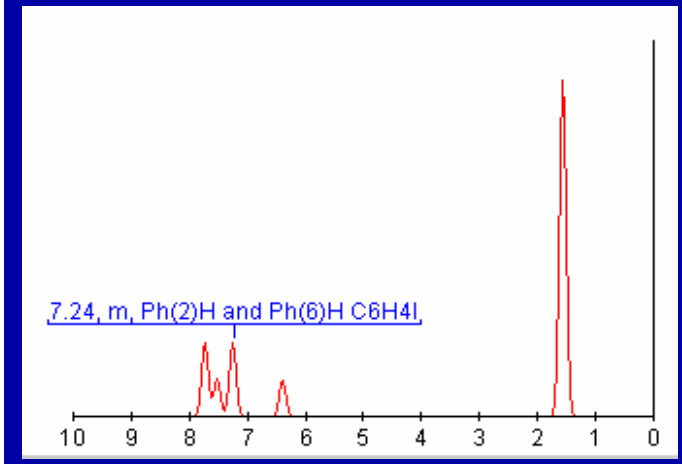
- 100 years of chemistry – in books
- 20 years of data destruction – PDF
- How can it be read and checked? Increasingly can validate using ‘robots’

- However
  - Need data to be abstracted to a computer readable form
  - Need data to be standardised
  - Need data to be available to ‘robots’ for processing, checking, analysis – and to ‘talk’ to other robots

RSC/UCC markup project

- Uses CML, natural language processing, knowledge of chemistry
- An authoring tool
- A data checker
- Data abstraction from chemistry papers -> computer readable database

Experimental data checker: better information for organic chemists S. E. Adams, J. M. Goodman, R. J. Kidd, A. D. McNaught, P. Murray-Rust, F. R. Norton, J. A. Townsend and C. A. Waudby *Org. Biomol. Chem.* 2004, **2**, 3067-3070. Highlighted in *Chemical Science* 2004, **1**, C33.
Chemical documents: machine understanding and automated information extraction J. A. Townsend, S. E. Adams, C. A. Waudby, V. K. de Souza, J. M. Goodman and P. Murray-Rust *Org. Biomol. Chem.* 2004, **2**, 3294-3200



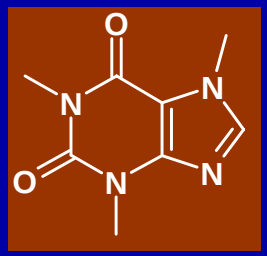
6a: 6,7b-Dihydro-3(2H)-oxepinone. Eluent for flash chromatography: pentane-Et2O 9 : 1; colourless oil; yield 70%; HRMS calcd. for C6H8O2: 112.0524. Found: 112.0524; max/cm-1 (neat) 2932, 1655; H (250 MHz, CDCl3) 6.59 (1 H, td, J 12.4, 4.4), 6.07 (1 H, td, J 12.4, 1.8), 4.33 (2 H, s), 3.96 (2 H, t, J 5.4), 2.71 (2 H, dq, J 5.4, 1.8); C (63 MHz, CDCl3) 204.4, 145.2, 130.3, 78.9, 69.6, 35.2; m/z (EI) 112 (43, M+), 84 (83), 83 (43), 81 (54), 55 (20), 54 (100), 53 (41).

6b: 2,3,7,8-Tetrahydro-4H-oxocin-4-one. Eluent for flash chromatography: pentane-EtOAc 1 : 1; colourless oil; yield 73%; HRMS calcd. for C7H10O2: 126.0680. Found: 126.0681; max/cm-1 (neat) 2950, 1659; H (250 MHz, CDCl3) 6.49 (1 H, td, J 12.1, 8.0), 6.23 (1 H, d, J 12.1), 3.91 (2 H, t, J 6.8), 3.69 (2 H, t, J 6.6), 2.90 (2 H, t, J 6.8), 2.76 (2H, q, J 6.6); C (63 MHz, CDCl3) 201.0, 139.0, 136.0, 65.03, 64.98, 44.2, 29.4; m/z (EI) 126 (21, M+), 99 (29), 96 (14), 81 (11), 68 (100), 54 (50).

Once the data is in, automated calculation can aid database quality

Reliability of data ?

Caffein solubility



Temperature	Solubility g/l	Reference
25	2.132	[1]
25	896.2	[2]

[1] Oliveri-Mandala, E. (1926), *Gazzetta Chimica Italiana 56*, 896-901

[2] Ochsner, A. B., Belloto, R. J., and Sokoloski, T. D. (1985), *Journal of Pharmaceutical Sciences 74*, 132-135

Reliability of data ?

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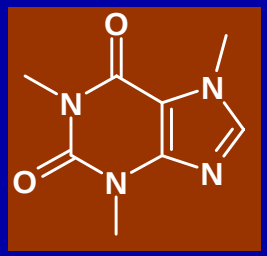

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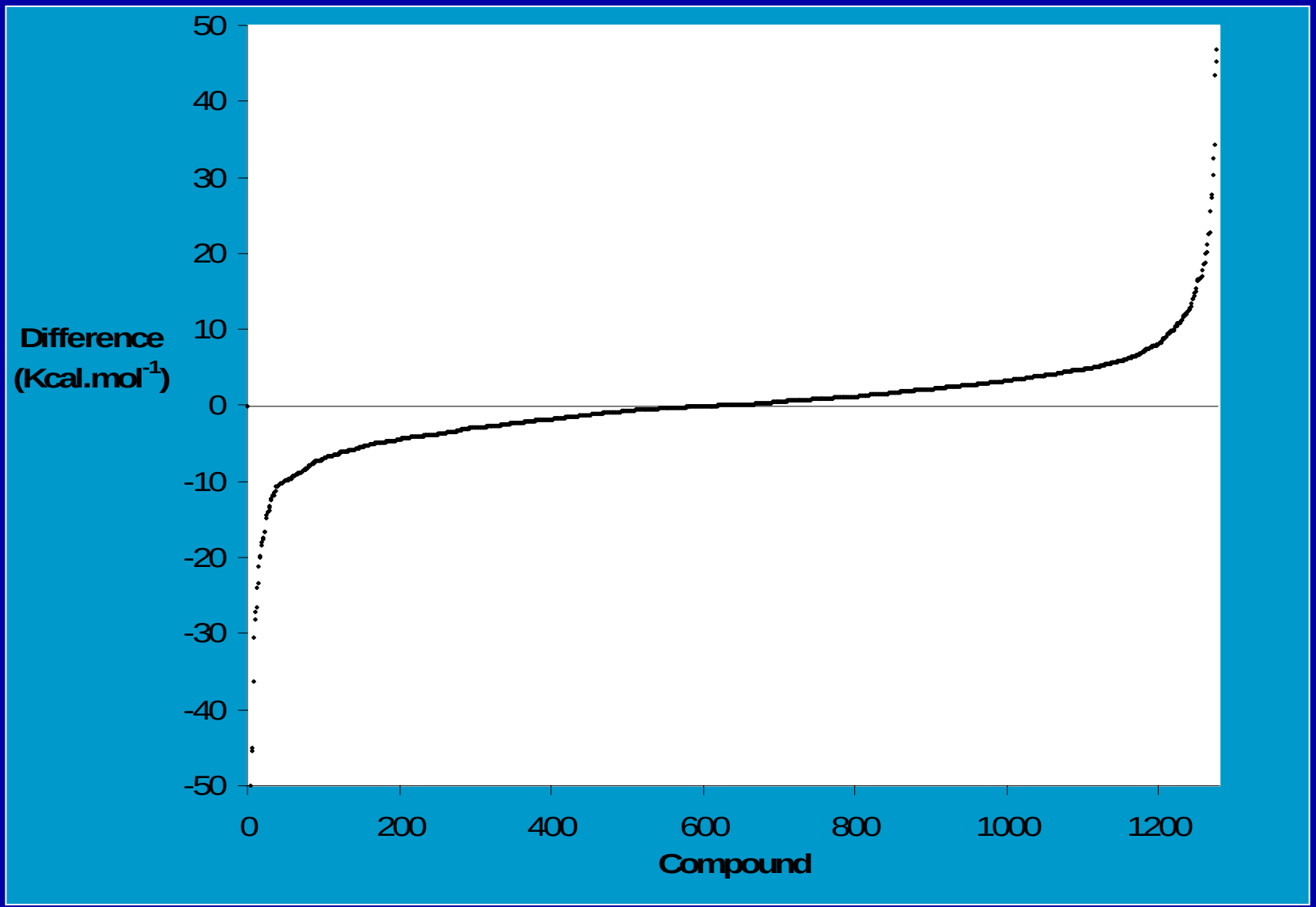
Conclusion : from 1926 to 1985, the solubility of caffeine increased at a rate of ca. 15 g/l/year

More seriously, there are ten different definitions of solubility, the value is the solubility of what form, under what conditions, with what solid form ? This could all be marked up.

Heats of formation Errors Detected by Calculation on the NIST Databook (from James JP Stewart)

Compound	Formula	Expt. ΔH_f	This Work		B88-LYP	
			Calc. ΔH_f	Diff	Calc. ΔH_f	Diff
Pentafluoroiodobenzene	C_6F_5I	-131.1± 3.0	-176.6	-45.5	-178.1	-47.0
Perfluorobutadiene	C_4F_6	-225.2	-253.4	-28.2	-241.6	-16.4
Bis-(n-perfluoropropyl ether)	C_6OF_{14}	-742.1±0.8	-769.3	-27.2	-757.3	-15.2
Dodecafluorocyclohexane	C_6F_{12}	-566.5± 2.0	-590.5	-24.0	-587.4	-20.9
Bromopentafluorobenzene	C_6F_5Br	-170.2±1.3	-191.3	-21.1	-191.8	-21.6
Perfluoroacetone	C_3OF_6	-325.2	-342.6	-17.4	-337.7	-12.5
Hexafluorobenzene	C_6F_6	-228.5±0.29	-242.5	-14.0	-241.6	-13.1
Thietane	C_3H_6S	14.6± 0.3	4.4	-10.2	8.0	-6.6
DL-3,4-di-1-cyclohexen-1-yl-2,2,5,5-tetramethyl hexane	$C_{22}H_{38}$	-62.1±1.5	-50.4	11.7	-17.5	44.6
Dioxybismethanol	$C_2H_6O_4$	-136.6±1.6	-124.5	12.1	-119.2	17.4
2,5,8-Trioxanonane	$C_6H_{14}O_3$	-138.9±0.25	-124.6	14.3	-124.2	14.7
2,4,6-Trimethylphenyl isocyanide	$C_{10}H_{11}N$	40.0	56.6	16.6	48.8	8.8
6-(1,1-dimethylethyl)-2,3-dihydro-1,1-dimethyl-1H-Indene	$C_{15}H_{22}$	-41.7	-24.9	16.7	-19.2	22.4
n-Perfluorobutane	C_4F_{10}	-533.9	-515.3	18.6	-515.2	18.7
5,6-Dibutyl-5,6-bis(4-tert-butylphenyl)decane	$C_{38}H_{62}$	-83.8?0.8	-58.6	25.2	-40.1	43.7

Distribution of Differences



Conclusions from this work:

- Most errors in original work is caused by arithmetic errors, typographic errors, transcription errors, and not by the experimental work.

- Semiempirical methods can be used for predicting heats of formation of well-behaved systems.

- About 4-5% of all reference thermochemical data are inaccurate by at least 2 kcal/mol.

- Computational methods can, *and should*, be used for checking entries in thermochemical reference data compendia.

1 Stewart J. J. P., "Comparison of the Accuracy of Semiempirical and some DFT Methods for predicting Heats of Formation", J. Mol. Modelling 10, 6-12 (2004).

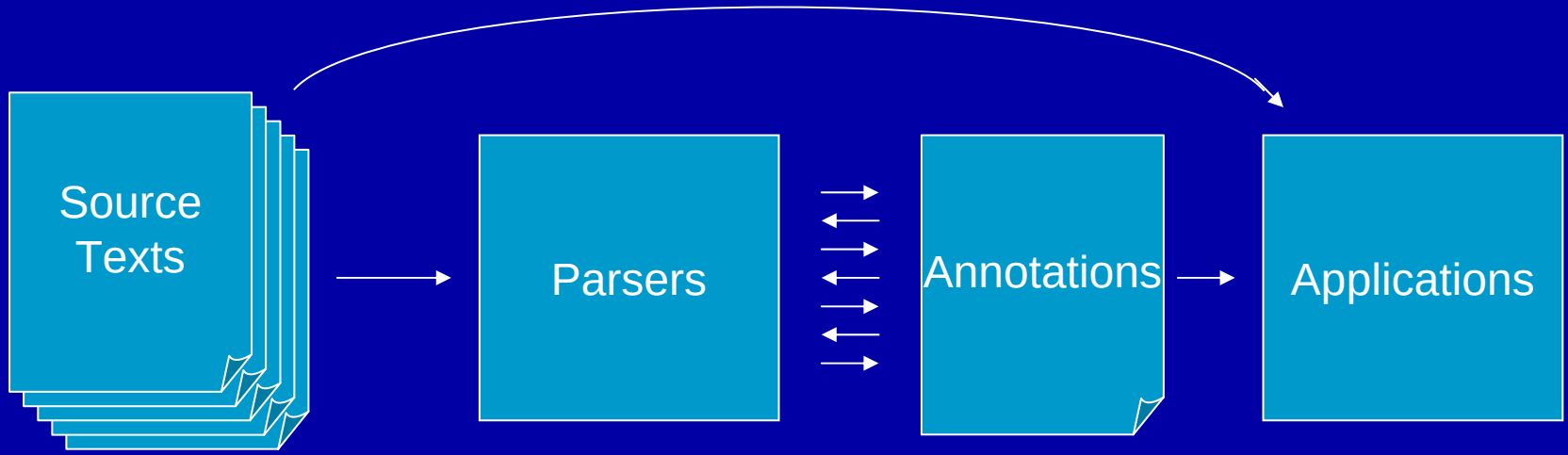
Given that Chemistry is ‘all over the place’ – how can we explore chemistry

- Cheminformatics discovery
  - Our current paradigm is to construct a database, extract relevant information when required, create relationships (e.g. SAR, trends in properties) and rebuild the database periodically
  - Another option is to dynamically update or acquire data interactively – data discovery – since much of the data is in the literature, this requires ‘journal eating robots’ to aggregate the data we require.
  - In paper-based publication the medium and message are inextricably linked and can normally only be processed by humans – this needs separated and marked up
  - For documents to be reliably machine-processable the paper image is not sufficient. It is necessary to identify the various components of a document, both in their intrinsic nature and their role in the document structure. This process is termed *markup* and has been adopted by many publishers through the standard generalised markup language (SGML)
  - -a lot of what we require is available internally to publishers

Encoding chemistry

- The representation of information in electronic form usually involves several layers: encoding, syntax, semantics, and ontology.
  - Creating *a generally agreed tag set*.
  - Adding *programmatic functionality through (modular) code*.
  - Linking *to glossaries/ontologies/metadata*.
  - **Ontologies.** These represent formal descriptions of terms, concepts, behavior, etc.
    - Information loss between software, and ontological loss (or corruption e.g. bond order, consistently. In some systems bond orders are related to measured lengths, in others to calculated properties, and in others to electron counts.)
- Chemists are trained to recognize features in molecules and frequently to make mental translations between them. Common examples might be tautomers, delocalized systems, conformations, and representations of bond types (double, dative, bipolar). This is not possible completely in a computer program, but some limited progress is being made

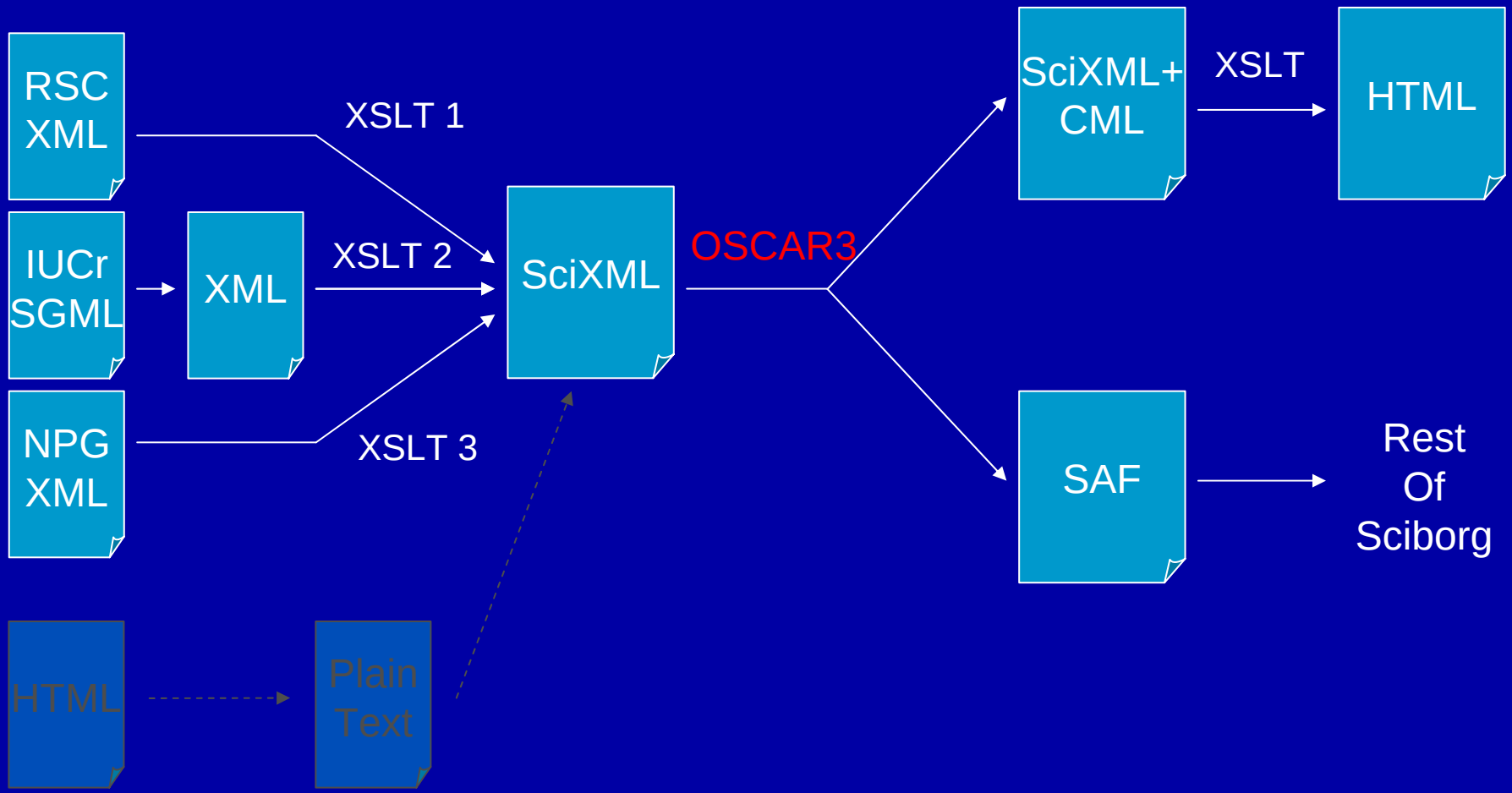
Reading chemistry – development of enhanced annotation, recognition and natural language processing



Sentence splitters
POS Taggers
Tokenisers
RASP
PET/ERG
OSCAR3
etc.

Information Extraction
Information Recall
Citation Mapping
Data Checking
Rich Browsing
etc.

OSCAR3 In Context



Name Recognition

- From lists
- Bayesian analysis:
  - Divide word into 4-letter fragments
    - “^ace” “acet” “ceto” “eton” “tone” “one$”
  - Compare against smoothed fragment frequencies in English and Chemical training data
  - Factor in features from context, suffix etc.
  - Calculate a score

Name Recognition

- From lists
- Bayesian analysis
- Regular Expressions
  - E.g. Formulae
  - like: ((H|He|Li|B|Be|etc)\d*)+ but more complicated

Name Recognition

- From lists
- Bayesian analysis
- Regular Expressions

- Tokenisation + Chunking Rules
  - Hexane-ethyl acetate vs. tert-butyl peroxide

Name Resolution

- Attachment of structural information to names
- Output in SMILES, InChI, CML
- Vision: data to CML

The problem of language and name recognition…

- It was a cold January day in St. Louis (MO), USA
- I went into a shop (Famous Barr)
- I asked where the ‘jumpers’ were
- The assistant asked who it was for
- Me, I said

- My picture of a ‘jumper’

(and Marks and Spencers
A large store in Great Britain)

Cotton-Rich Jumper from £7.00 to £14.00

- The assistants picture of a ‘jumper

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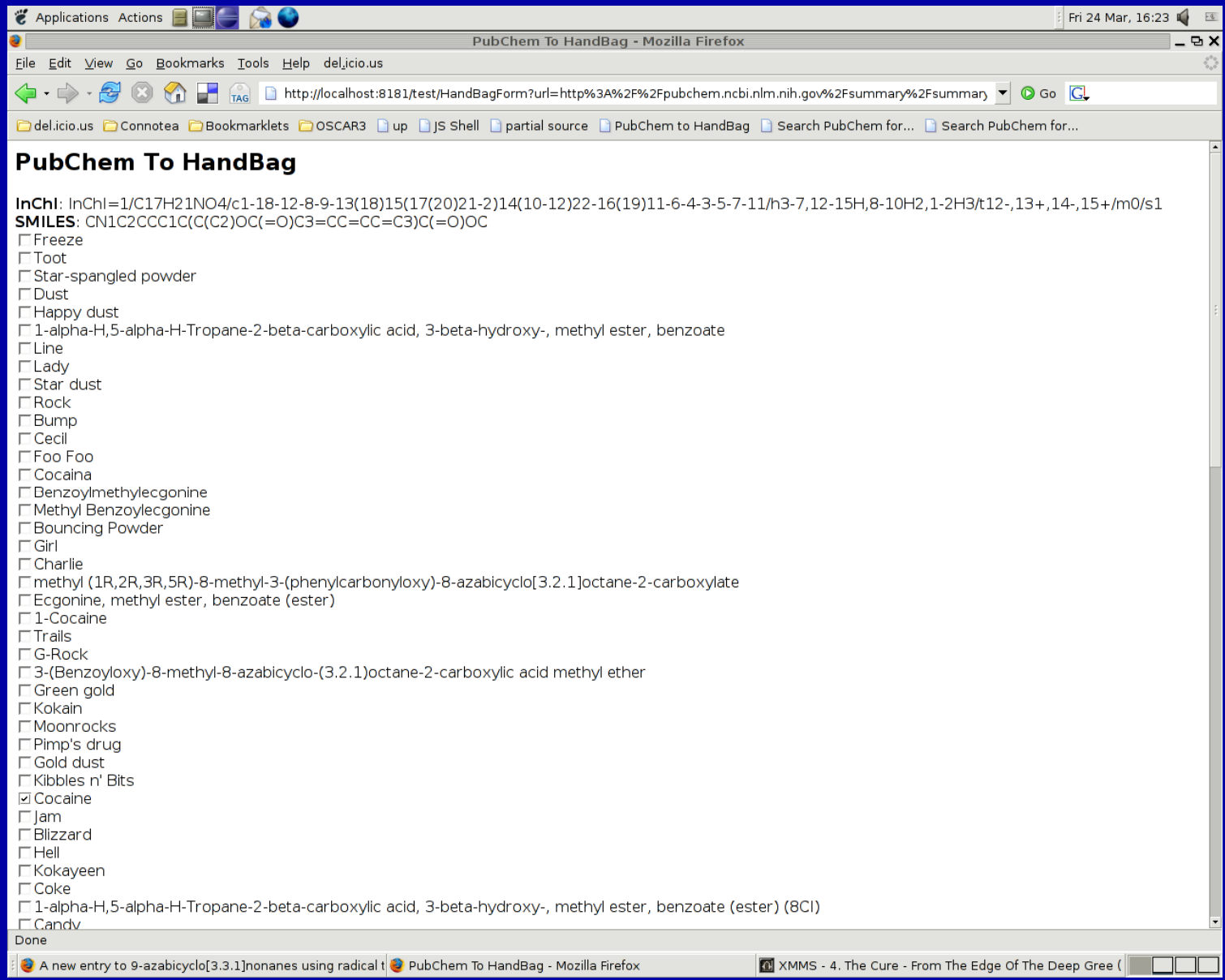
- The assistants picture of a ‘jumper’

Girls’ @ Class Khaki Twill Jumper with Side Pleats

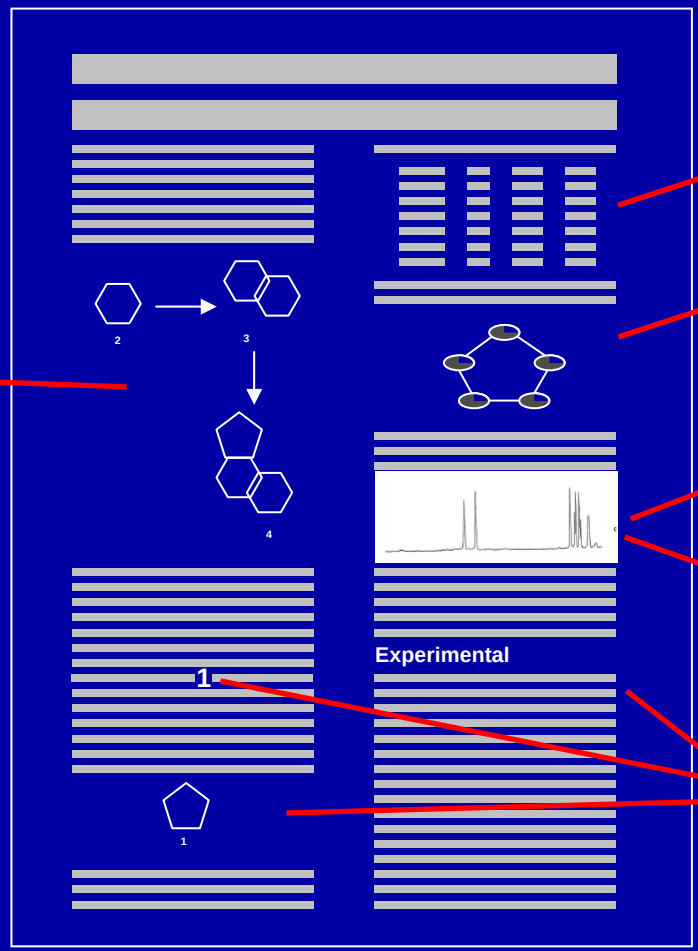
Serious problem with a ‘similar’ language

Names for cocaine…….



The result

CML



<cml:table>

<cml:crystal>

AnIML
(In supporting
Information)

Full Data

<cml:reaction>

ALSO **NB**

<cml:module>
(computation)

Peaks

<cml:spect>

Assignment

<cml:molecule>

XSD Schema + further validation by JUMBO

was subjected to desilylation, ozonolysis, and subsequent 1,2-transposition of the resulting carbonyl group to give 9-benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one, a potential precursor for the synthesis of (±)-euphococcinine.

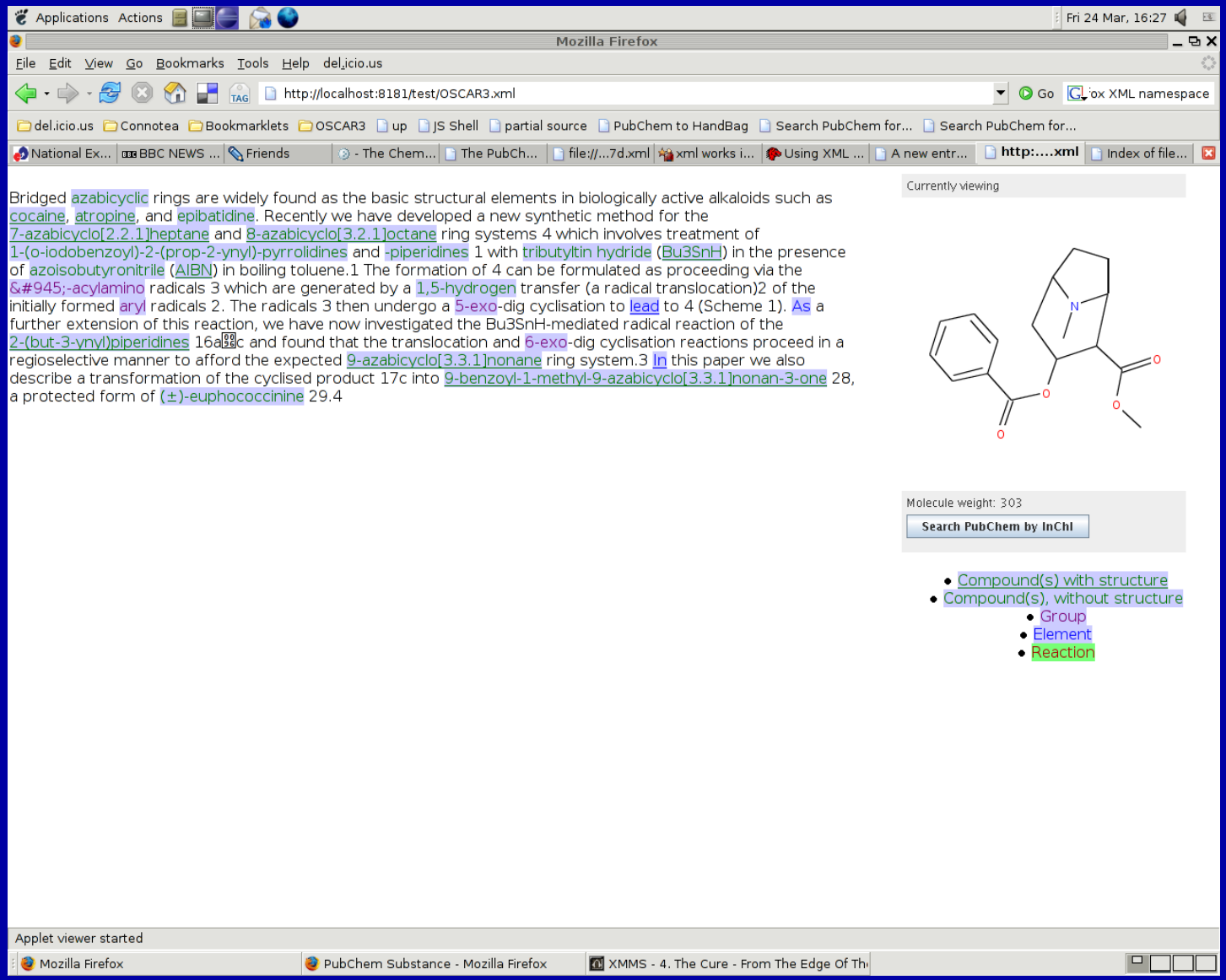
Introduction

Bridged azabicyclic rings are widely found as the basic structural elements in biologically active alkaloids such as cocaine, atropine, and epibatidine. Recently we have developed a new synthetic method for the 7-azabicyclo[2.2.1]heptane and 8-azabicyclo[3.2.1]octane ring systems **4** which involves treatment of 1-(*o*-iodobenzoyl)-2-(prop-2-ynyl)-pyrrolidines and -piperidines **1** with tributyltin hydride (Bu_3SnH) in the presence of azoisobutyronitrile (AIBN) in boiling toluene.[1] The formation of **4** can be formulated as proceeding *via* the α-acylamino radicals **3** which are generated by a 1,5-hydrogen transfer (a radical translocation)[2] of the initially formed aryl radicals **2**. The radicals **3** then undergo a 5-*exo*-*dig* cyclisation to lead to **4** (Scheme 1). As a further extension of this reaction, we have now investigated the Bu_3SnH-mediated radical reaction of the 2-(but-3-ynyl)piperidines **16a–c** and found that the translocation and 6-*exo*-*dig* cyclisation reactions proceed in a regioselective manner to afford the expected 9-azabicyclo[3.3.1]nonane ring system.[3] In this paper we also describe a transformation of the cyclised product **17c** into 9-benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one **28**, a protected form of (±)-euphococcinine **29**.[4]

Results and discussion

The radical precursor **16a** was prepared starting from methyl *N*-Boc-pipecolinate **5**[5] according to the procedures previously described for the synthesis of the pyrrolidine congener[1d] (Scheme 2). Thus, **5** was subjected to allylation, and

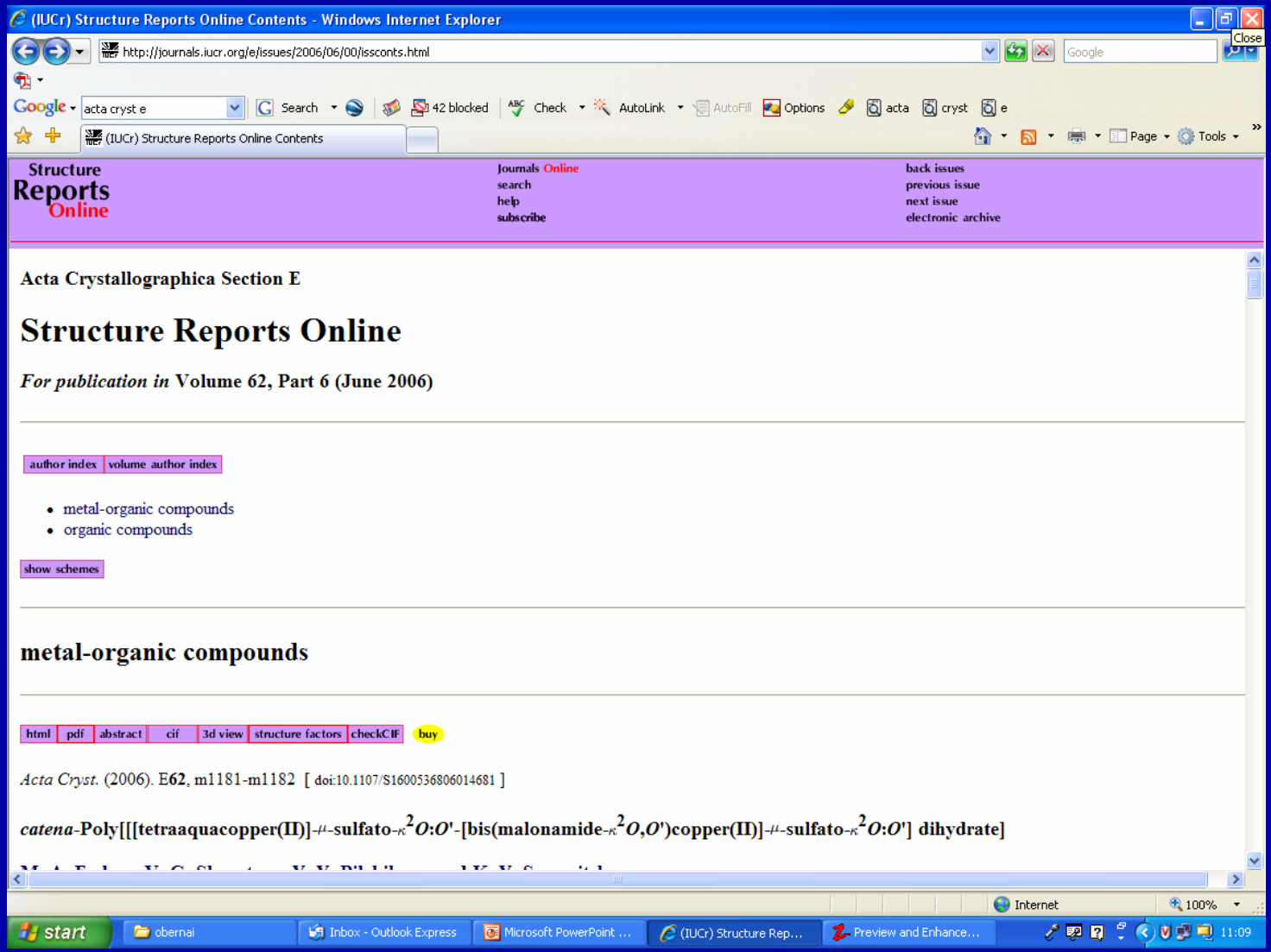
Document marked up, structure recognised and displayed
(like a spell checker, if the structure is not recognised, it can be added and in future, recognised and displayed)

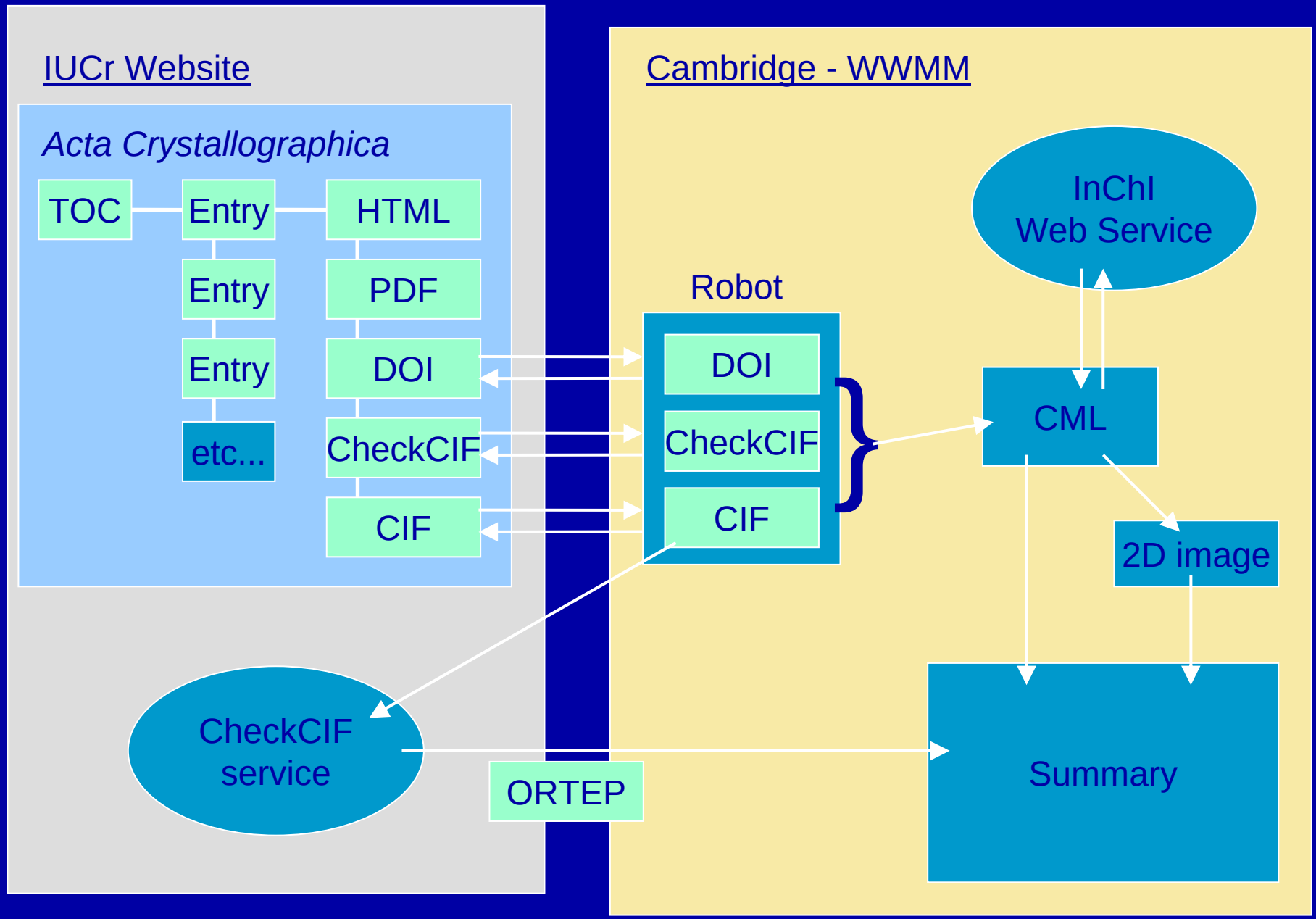


Example – extracting the latest information from Acta. Cryst

- Regularly updated journal with small molecule X-ray structures
- Articles contain associated structure files in supplemental data. These can be extracted.
- Data is annotated/marked up and associated with the article.
- Gives - Instant data access, RSS feeds, document summary, data checking, enhanced data searching (e.g. Google via InChI), additional computed properties.

Example structure from Acta Cryst. E.




IUCr Website
Acta Crystallographica
TOC
Entry
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Entry
etc...
HTML
PDF
DOI
CheckCIF
CIF
Cambridge - WWMM
Robot
DOI
CheckCIF
CIF
InChI
Web Service
CML
2D image
CheckCIF
service
ORTEP
Summary

Example data capture from the latest literature

Fetch Documents

Access new edition
Of Acta Cryst-E

Download HTML from
Table of Contents

Parse into XML

Xpath query to get each
Separate entry

Each entry- extract each
Link to CIF and Check-CIF

Send out Robot to
Get text (CIF (in ASCII)
And HTML (CheckCif)

Process documents

Convert CIF to CML

Recalculate CheckCIF

Makes XML document from checkCIF

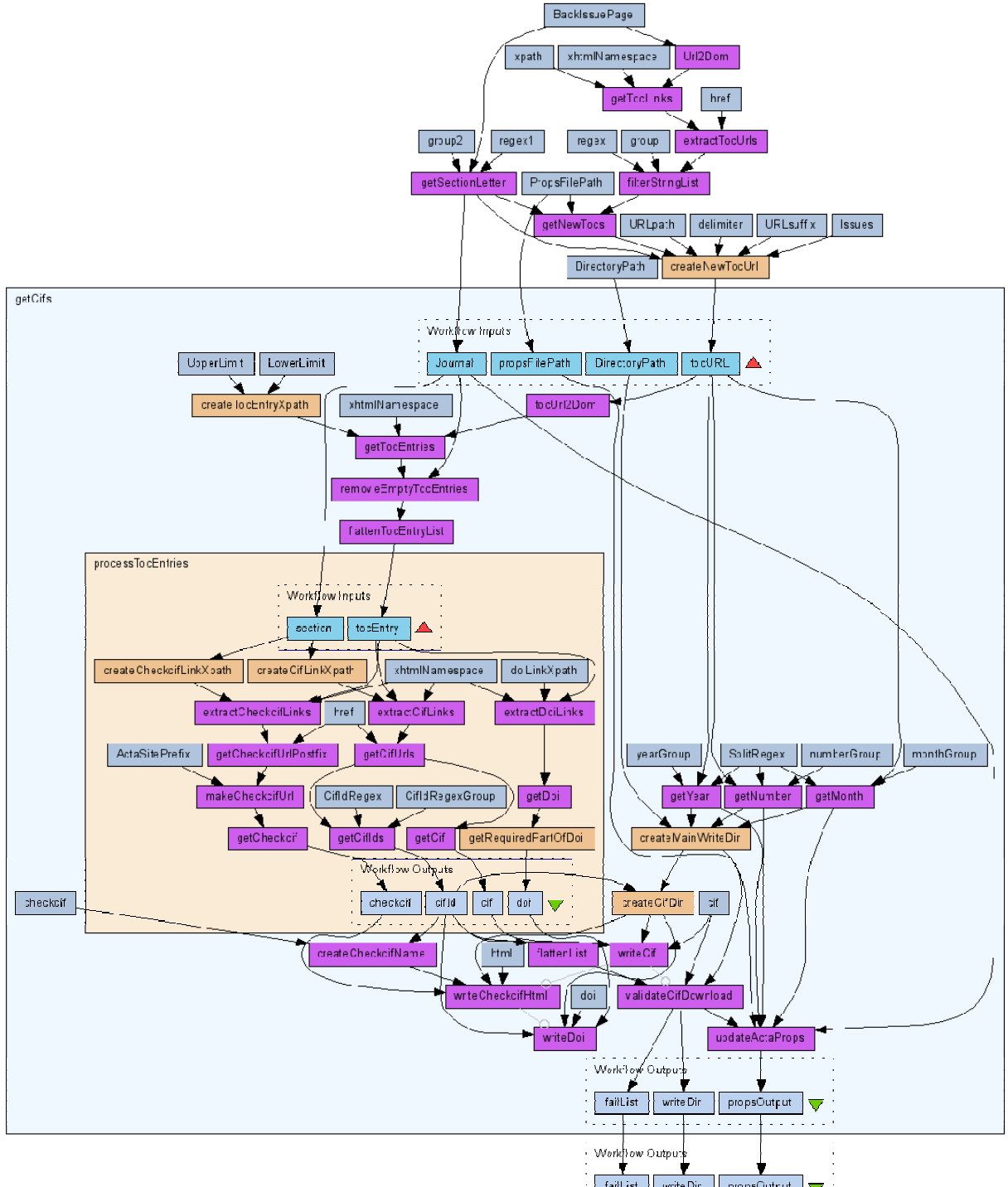
Calculate InChI

Add InCHi/DOI/CheckCIF to CML

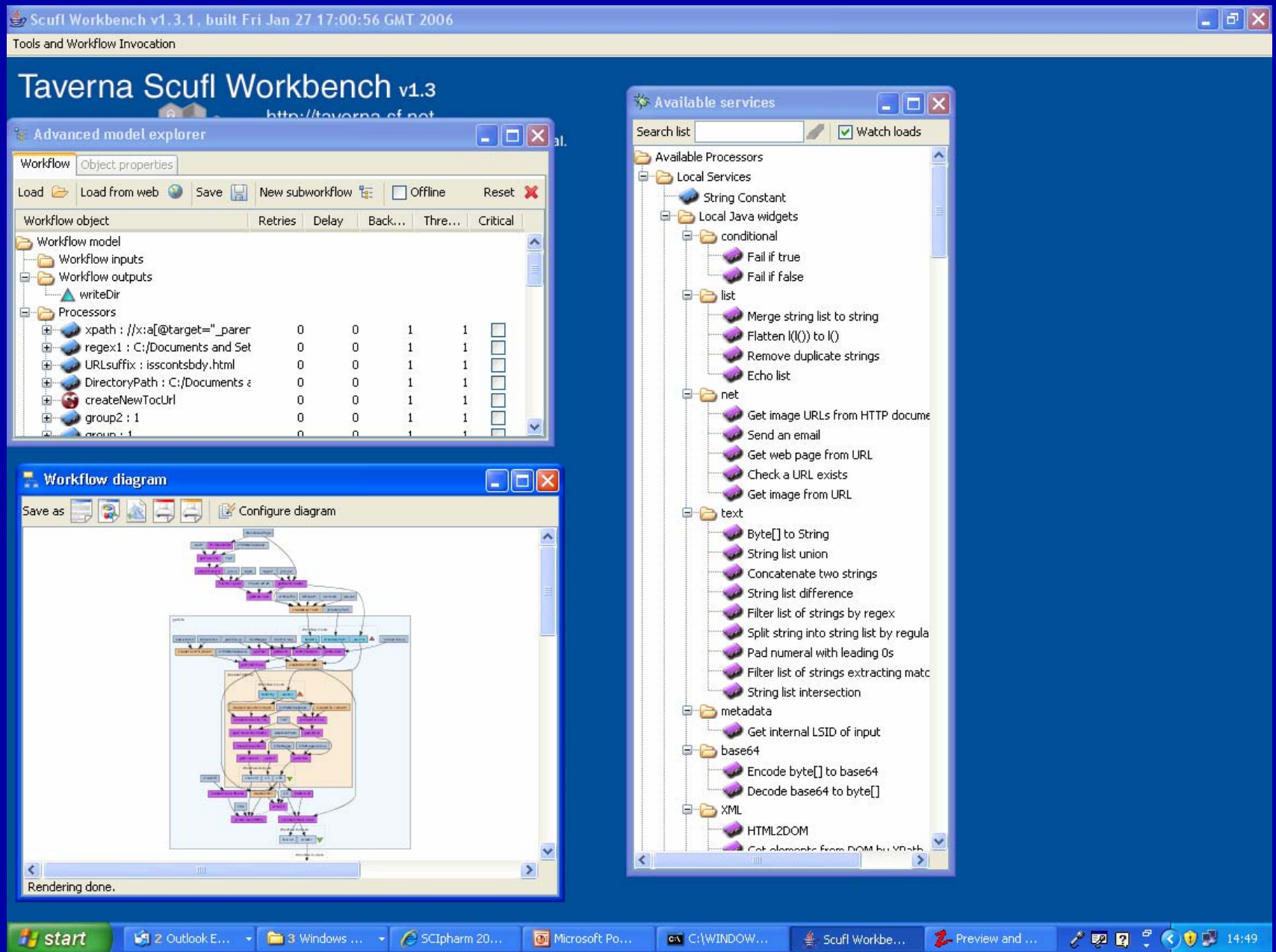
Get a CIF summary from CML

Create summary page

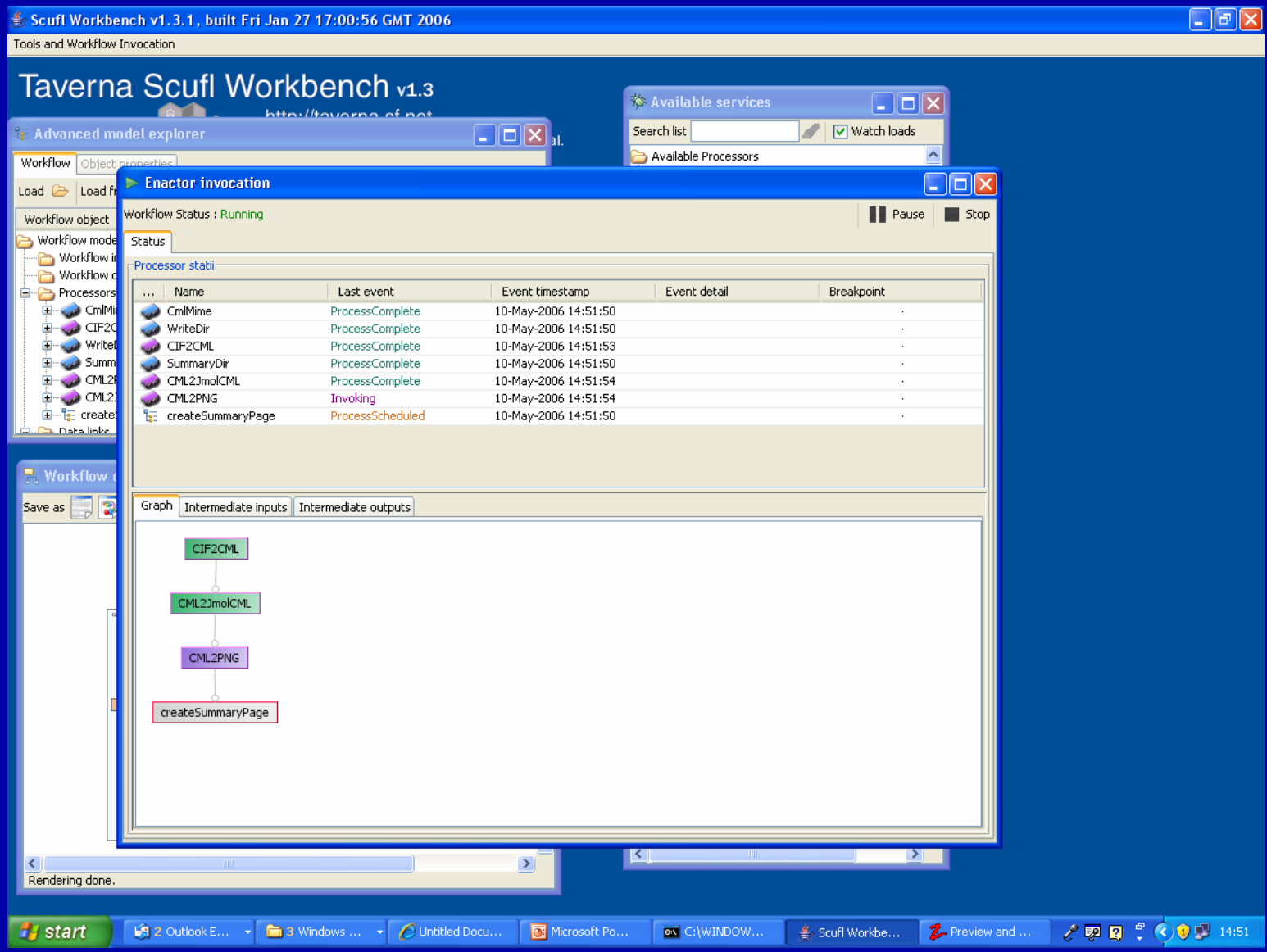
Using a workflow approach
- Using open source components
e.g. Taverna, JMOL, checkCIF etc. and online access to Acta Cryst E.



Workflow for discovering and extracting the latest structures



Workflow for annotation and storing latest structures (running)



Results from the latest journal issue

Untitled Document - Mozilla Firefox

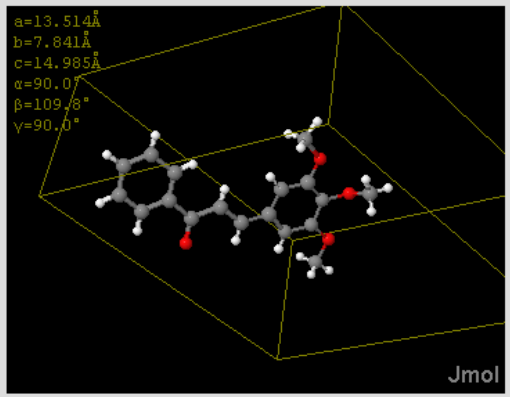
File Edit View Go Bookmarks Tools Help

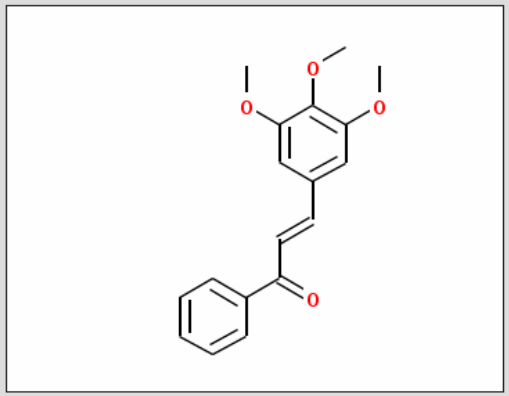
file:///C:/Documents%20and%20Settings/rcg28/Desktop/actademo/summary/index.html

Customize Links Free Hotmail Windows Marketplace Windows Media Windows

Acta Crystallographica - Summary

Published Formula	Article Link	Summary
$C_{19}H_9N_5O_8$	yes	yes
$C_{16}H_{10}N_2OS$	yes	yes
$C_{18}H_{18}O_4$	yes	yes
$(C_{14}H_{14}NO^{+1})(C_7H_7O_3S^{-1})$	yes	yes
$C_{15}H_{11}BrO$	yes	yes
$C_{11}H_{12}O_3$	yes	yes
$C_{13}H_{19}NO_3$	yes	yes
$C_{28}H_{24}N_6O_4$	yes	yes

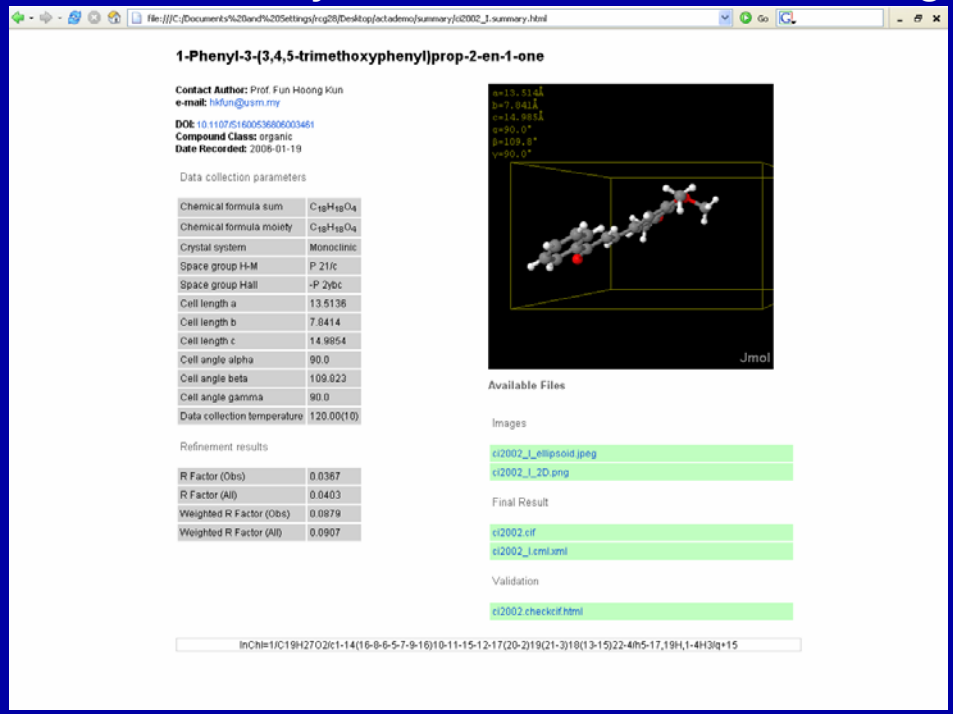




Jmol script completed

start 2 Outlook E... 3 Windows ... Microsoft Po... C:\WINDOW... Scufl Workbe... Preview and ... Untitled Doc... 14:54

Summary for each molecule, including automatic CIF checking, adding InCHI



1-Phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

Contact Author: Prof. Fun Hoong Kun
e-mail: hkfun@usm.my

DOI: 10.1107/S1600536806003461
Compound Class: organic
Date Recorded: 2006-01-19

Data collection parameters

Chemical formula sum	$C_{19}H_{18}O_4$
Chemical formula moiety	$C_{19}H_{18}O_4$
Crystal system	Monoclinic
Space group H-M	P 21/c
Space group Hall	-P 2ybc
Cell length a	13.5136
Cell length b	7.8414
Cell length c	14.9854
Cell angle alpha	90.0
Cell angle beta	109.823
Cell angle gamma	90.0
Data collection temperature	120.00(10)

Refinement results

R Factor (Obs)	0.0367
R Factor (All)	0.0403
Weighted R Factor (Obs)	0.0879
Weighted R Factor (All)	0.0907

a=13.514Å
b=7.841Å
c=14.985Å
α=90.0°
β=109.8°
γ=90.0°

Jmol

Available Files

Images

ci2002_l_ellipsoid.jpeg
ci2002_l_2D.png

Final Result

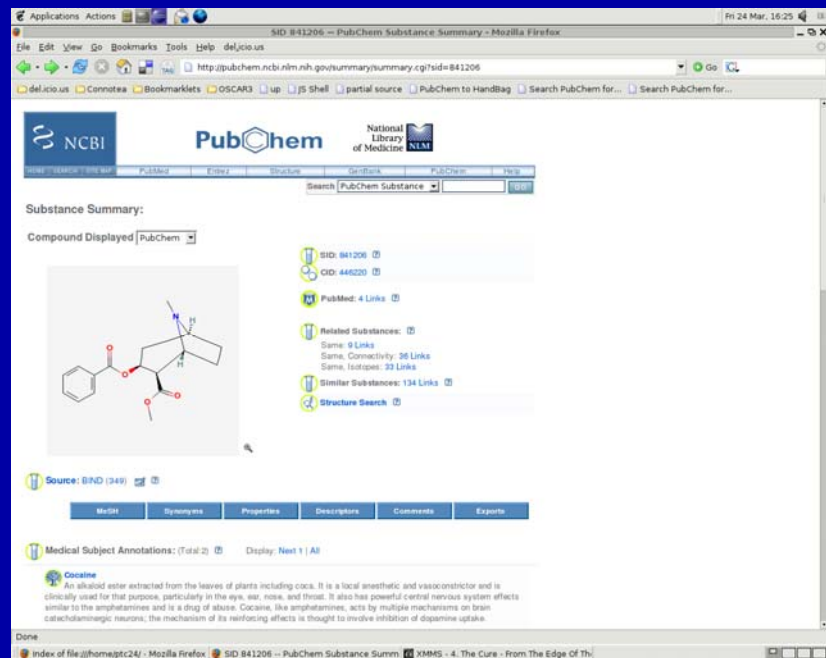
ci2002.cif
ci2002_l.cml.xml

Validation

ci2002.checkcif.html

InChI=1/C19H27O2/c1-14(16-8-6-5-7-9-16)10-11-15-12-17(20-2)19(21-3)18(13-15)22-4/h5-17,19H,1-4H3/q+15

Can also exchange Information with PubChem



The kind of problem that could be addressed with this approach…

- A good example is newsfeeds – news is highly time dependant
  - What are the latest molecules active in my area of science ?
  - What patents have been filed recently ?
  - Is there information not yet in the abstracts ?
  - Have different groups obtained the same answer (e.g. solubility of a compound)
  - Provide a summary that is up to the minute
  - Also, Robots can do data checking/annotation/add value to information before we receive it
  - Natural language processing can refine or expand our search

Conclusion

Chemistry has a language that is in some ways quite formal and systematic. However, like most languages, there is a degree of ‘artistic licence’ and converting this into a computer representation is challenging, but allows a new way of doing science, knowledge discovery. In earlier years, we have been to some extent limited in that we have applied the standard scientific method of hypothesis and experiment followed by acceptance or revision of the hypothesis (QSAR is an excellent example). There are of course many examples of successes in drug discover or property prediction using this approach. However, with large amounts of data, the internet and cheminformatics tools, science can be performed in a new way in which hypotheses are generated from relationships between the data, sometimes revealing unexpected results. Indeed, serendipity could potentially be systematised. Although we are not there yet, I believe that this is where we are headed. Recent applications are designed to both improve the quality of data, and also to discover new relationships between cheminformatics data.

Acknowledgements

- Previous OSCAR Authors
  - Chris Waudby, Sam Adams, Joe Townsend, Jonathan Goodman, Peter Murray-Rust, Peter Corbett
  - Support from DTI, RSC & NPG
- James Stewart