Prospecting for chemistry in publishing

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ICIC 2008
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DANKE!

What are we marking up?

- Chemical compounds (InChI, ChEBI)
- Chemical classes and parts (ChEBI)
- Chemical terms from the IUPAC Gold Book
- Reactions and techniques (RXNO)

- Gene products: function, process, location (GO)
- Nucleotide and polypeptide sequence terms (SO)
- Cell types (CL)

Manuscript DOI 10.1039/b804987d Compound information for BINOL - Microsoft I...

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Compound information 'BINOL'

Synonyms:

- (S)-BINOL
- 1,1'-Binaphthyl-2,2'-diol
- 2,2'-binaphthol
- BINOL
- 1,1'-binaphthol
- 1,1'-binaphthyl-2,2'-diol

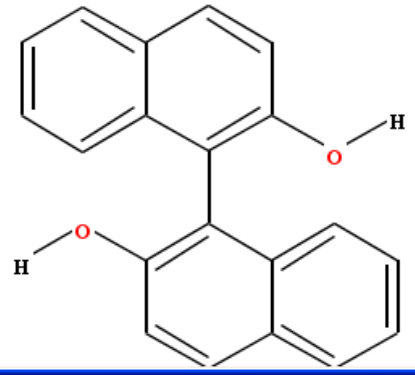
SMILES: [H]Oc2ccc1ccccc1c2c4c(ccc3ccccc34)O[H]

InChI: InChI=1/C20H14O2/c21-17-11-9-13-5-1-3-7-15(13)19(17)20-16-8-4-2-6-14(16)10-12,21-22H

InChIKey: InChIKey=PPTXVXKCQZKFBN-UHFFFAOYAX

CML (Chemical Markup Language) Representation: Download File

2-D Representation:



catalytic system, which led to the identification of a new

Done

Lewis ..... (DOI: 10.10 - Microsoft Internet Expl...

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Manuscript DOI 10.1039/b804987d Compound information for BINOL - Microsoft I...

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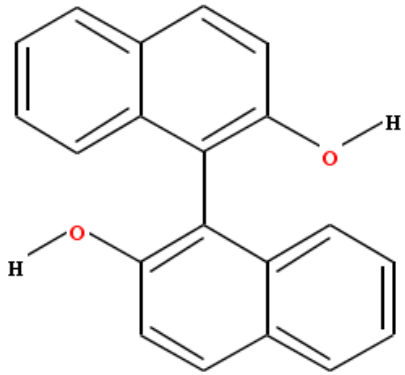
12,21-22H

InChIKey: InChIKey=PPTXVXKCQZKFBN-UHFFFAOYAX

CML (Chemical Markup Language) Representation: Download File

2-D Representation:



Other resources:

- Search for this compound in PubChem
- Search for this compound in SureChem patents

Other articles referencing this compound:

- **Ligand accelerated indium(III)-catalyzed asymmetric alkynylation of aldehydes with 2-methyl-3-butyn-2-ol as an ethyne equivalent donor**
  DOI: 10.1039/b614958h

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Trusted sites

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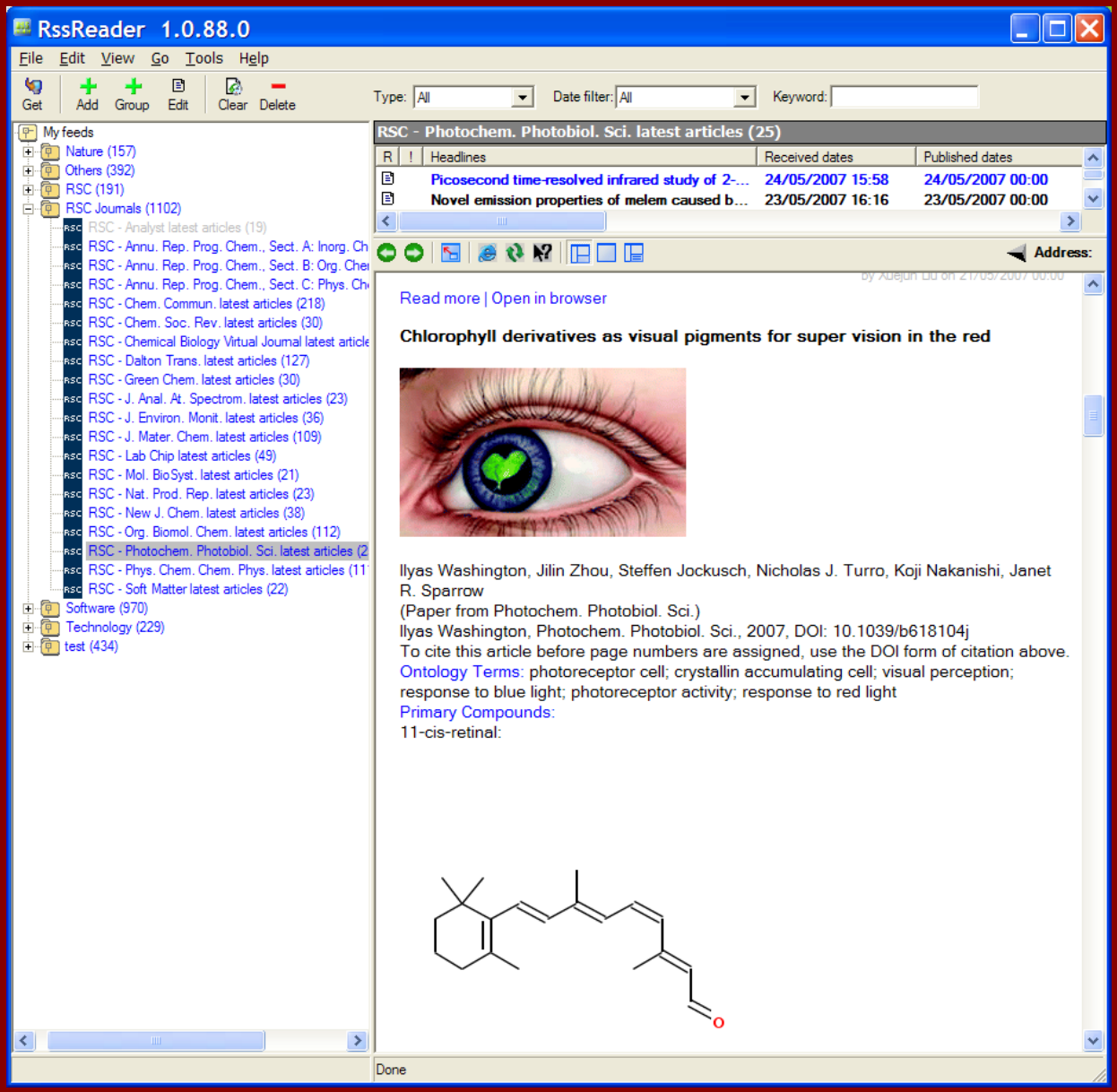
RSS for human readers



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RSS for computers

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<item rdf:about=http://xlink.rsc.org/?DOI=b716356h&amp;RSS=1>
<title> [… title] </title>
<link>http://xlink.rsc.org/?DOI=b716356h&RSS=1</link>
<description> [… blah] </description>
<content:encoded> [… human-readable stuff</content:encoded>
[… dublin core stuff …]
<content:items>
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  <rdf:li>
   <content:item rdf:about="info:inchi/InChI=1/C22H22NO4/c1-13-16-11-21(26-
   4)20(25-3)10-15(16)8-18-17-12-22(27-5)19(24-2)9-14(17)6-7-23(13)18/h6-
   12H,1-5H3/q+1"/>
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Text search

- “not in the Top 5” ;-(
  - Maik Annies, Syngenta, ICIC 2008

- Improved simple/advanced search under test
- Also need web service to return subject & compound results

Chemical structure search

Prospect Structure Search Results

The results show any enhanced HTML articles containing an exact match for the structure you are searching for. Similar structures are also shown.

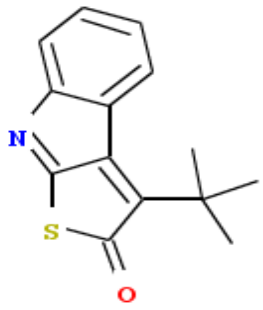
The structure searching is at present restricted to the RSC journal articles which have been enhanced as part of RSC Project Prospect. Please email the Project Prospect team with any queries, feedback or suggestions for improvements.

Results

Searching for SMILES:
CC(C)(C)C=3C(=O)SC2=NC1=CC=CC=C1C2=3

InChI:
InChI=1/C14H13NOS/c1-14(2,3)11-10-8-6-4-5-7-9(8)15-12(10)17-13(11)16/h4-7H,1-3H3

2-D Representation:



Exact Matches

Thiocarbonyl induced heterocumulenic Pauson–Khand type reaction: expedient synthetic method for thieno[2,3-*b*]indol-2-ones
Takao Saito, Hiroshi Nihei, Takashi Otani, Toshiyuki Suyama, Naoki Furukawa, Masatoshi Saito, *Chem. Commun.*, 2008, (2), 172-174
DOI: 10.1039/b712739a

Show close matches
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Bernard Donovan President
ALPSP/Charlesworth Award for Publishing Innovation
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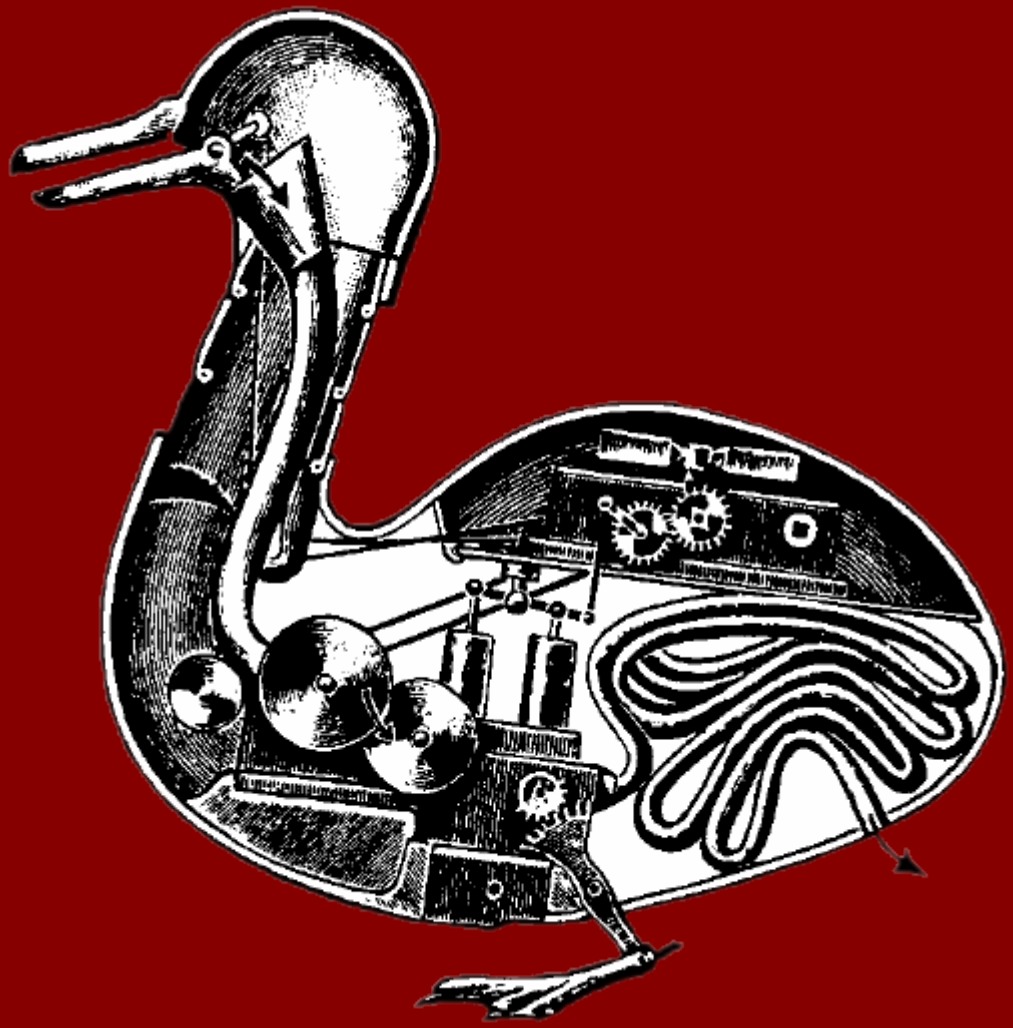
Royal Society of Chemistry

How does this really work?



LaTeX

Data capture

XML

XML

Editing and proof-reading

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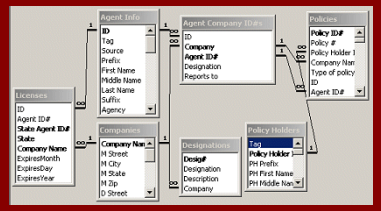
XML

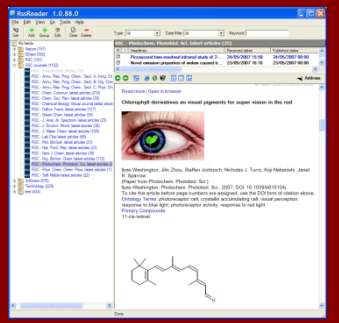
Text mining (Oscar)

Manual QA

Enhanced HTML



Database



Enhanced RSS

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Oscar

Unilever Cambridge
Centre For Molecular Science Informatics

Tokenizer
Morphological analyser
Name to structure converter
Workflow component
Annotation environment

http://oscar3-chem.sourceforge.net/

Why is this hard?

How many numbered compounds actually are named in a given paper?

iloprost (**1**)
tributyl-1-hexynylstannane (**2**)
the desired 2-heptyne (**3**)
methyl–Pd(II) iodide **4** or **4′**
alkynylstannane **5**
the hypervalent stannate **6**
(alkynyl)(methyl)Pd(II) complex **7**
the desired methylalkyne **8**
compounds **9**–**14**

the stannyl precursors **15** and **16**
methylated compounds **17** and **18**
stannyl precursor **19**
iloprost methyl ester **20**

“iloprost methyl ester” is the real name, but you need to know that iloprost is a monocarboxylic acid!

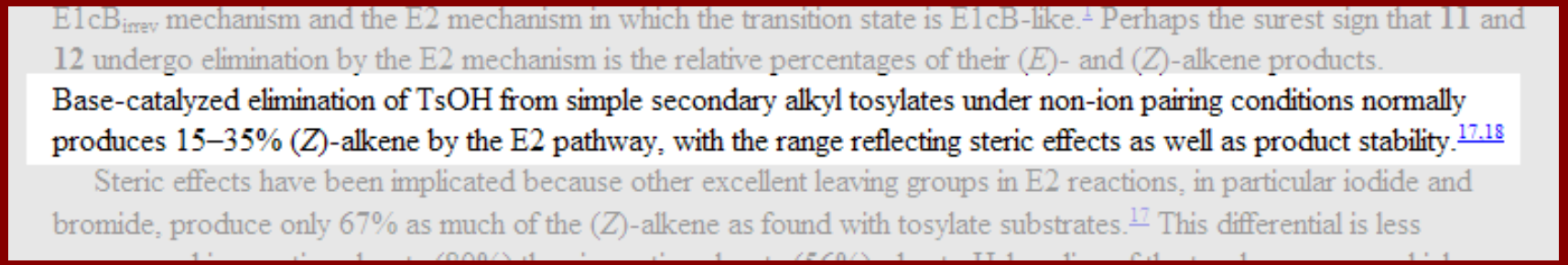
Annotate this...

A series of mono and di-N-2,3-epoxypropyl N-phenylhydrazones have been prepared on a large scale by reaction of the corresponding N-phenylhydrazones of 9-ethyl-3-carbazolecarbaldehyde, 9-ethyl-3,6-carbazoledicarbaldehyde, 4-dimethyl-amino-, 4-diethylamino-, 4-benzylethylamino-, 4-(diphenylamino)-, 4-(4,4-4'-dimethyl-diphenylamino)-, 4-(4-formyldiphenylamino)- and 4-(4-formyl-4'-methyldiphenyl-amino)benzaldehyde with epichlorohydrin in the presence of KOH and anhydrous Na(2)SO(4).

From *Molecules*, via the BioNLP list

…and it gets worse

Part of speech ambiguity: tosylates; noun or verb?



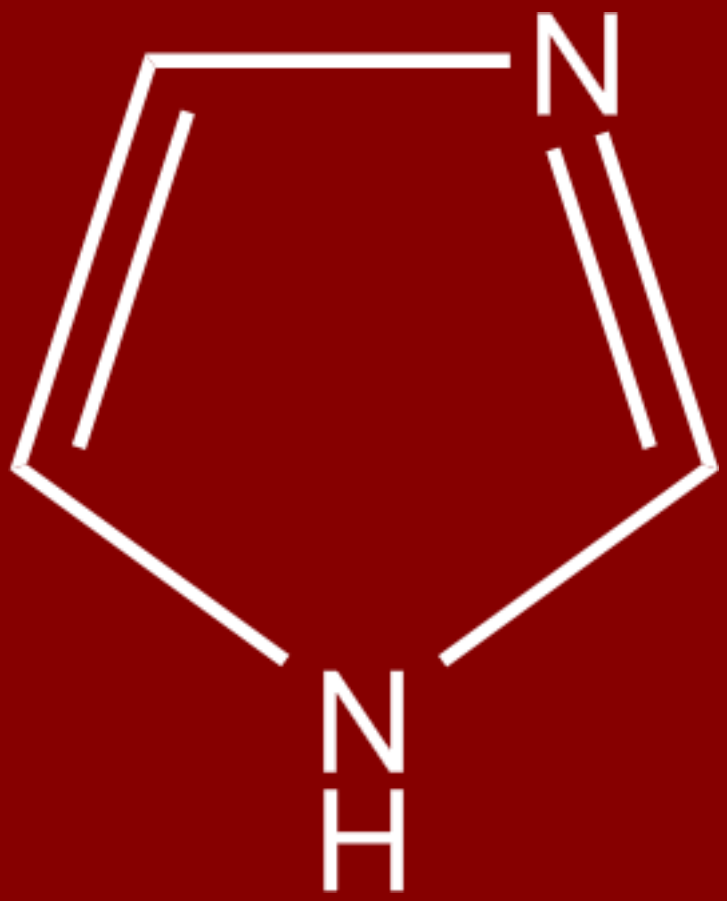
E1cB$_{irrev}$ mechanism and the E2 mechanism in which the transition state is E1cB-like.[4] Perhaps the surest sign that **11** and **12** undergo elimination by the E2 mechanism is the relative percentages of their (*E*)- and (*Z*)-alkene products.

Base-catalyzed elimination of TsOH from simple secondary alkyl tosylates under non-ion pairing conditions normally produces 15–35% (*Z*)-alkene by the E2 pathway, with the range reflecting steric effects as well as product stability.[17,18]

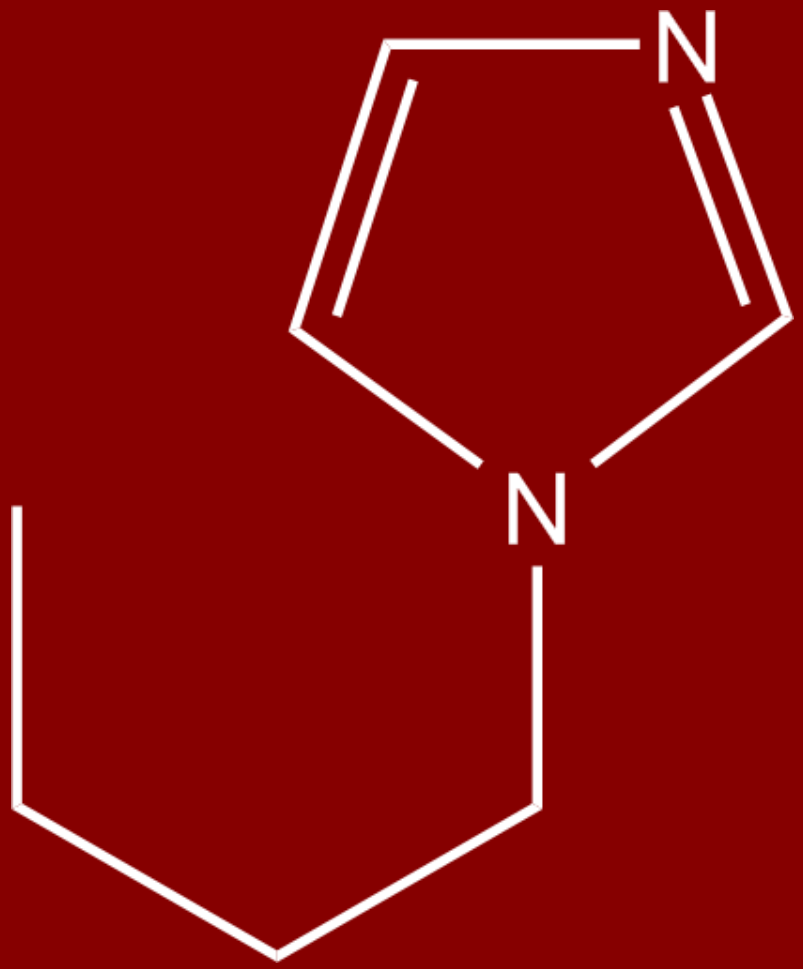
Steric effects have been implicated because other excellent leaving groups in E2 reactions, in particular iodide and bromide, produce only 67% as much of the (*Z*)-alkene as found with tosylate substrates.[17] This differential is less

Even a simple chemical name can mean more than one thing…

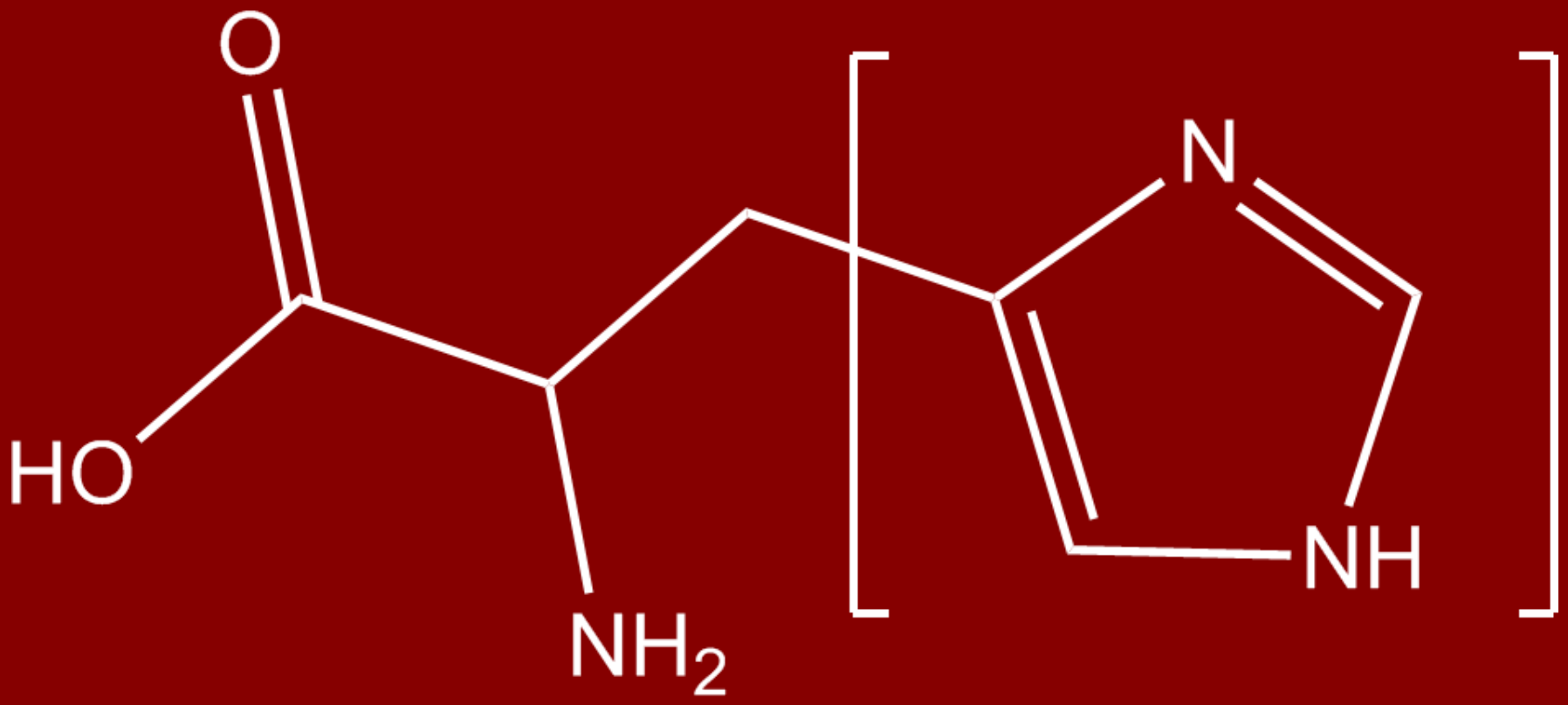
Imidazole



An imidazole



The imidazole side-chain/ group/ring/*etc.*



Can ChEBI handle this?

- Imidazoles (CHEBI:24780)
- Imidazole (CHEBI:16069)

- Imidazole ring not yet
- Imidazolyl group not yet (but methyl, benzyl, *etc.*)

… and there are no disambiguation cues

Where do we get the structures?

For compound names:

~60% text mining from OSCAR (Corbett and Murray-Rust 2006, Batchelor and Corbett 2007)

~20% PubChem

~20% ChemDraw

For compound numbers (**7**, *cis*-**8**, **23b**)

~70% author ChemDraw

~30% technical editors

InChI: cans and can’ts

Can tell us:

- What atoms are in a system.
- What the ligands are.
- How the non-metals are connected.
- What the geometry is around C, P, As, *etc.*

Can’t tell us:

- What the geometry is around a metal.
- How the metals are connected (at least, not easily).
- Anything about polymers.

But that’s enough to be going on with…

fertilisation (hpf), and come to lie in the midline. By 24 hpf their vacuoles are expanding and straightening of the trunk and tail is underway. The multiple functions of the notochord are reflected in the abundance and diversity of relevant mutants identified in l

mutagenesis screens.[13,14] Thus, mutations affecting specification of early notochord cells have profound defects on body patterning.[15–17] Another larger class of mutants affect notochord differentiation and structural roles, thus *bashful*, *grumpy*, *sneezy* and *happy* are all very shortened and have unvacuolated notochord cells. Molecular characterisation of these and related loci reveal that they are defective in either secretion or notochord sheath components.[18–20] While these mutants have been characterised molecularly, another class affecting notochord morphogenesis remains uncloned. Amongst these are *leviathan*, *crash test dummy*, *gulliver* and *quasimodo*[13,14] which, in contrast to *sleepy* and related mutants, display well-differentiated notochord cells, but with a violently distorted arrangement in both dorsomedial and mediolateral planes. Importantly, whilst *gulliver* and *quasimodo* mutants show additional characteristics, *leviathan* and *crash test dummy* show only a notochord defect. These latter mutants were isolated in separate screens and may well be allelic.

Animal classification

- those that belong to the Emperor,
- embalmed ones,
- those that are trained,
- suckling pigs,
- mermaids,
- fabulous ones,
- stray dogs,
- those included in the present classification,
- those that tremble as if they were mad,
- innumerable ones,
- those drawn with a very fine camelhair brush,
- others,
- those that have just broken a flower vase,
- those that from a long way off look like flies.

Allegedly from "Celestial Emporium of Benevolent Knowledge"
The Analytical Language of John Wilkins, Jorge Luis Borges

Classification problems

2,4,6-trinitrotoluene biosynthesis

“This term is obsolete as 2,4,6-trinitrotoluene is not synthesized by living organisms“

From the Gene Ontology

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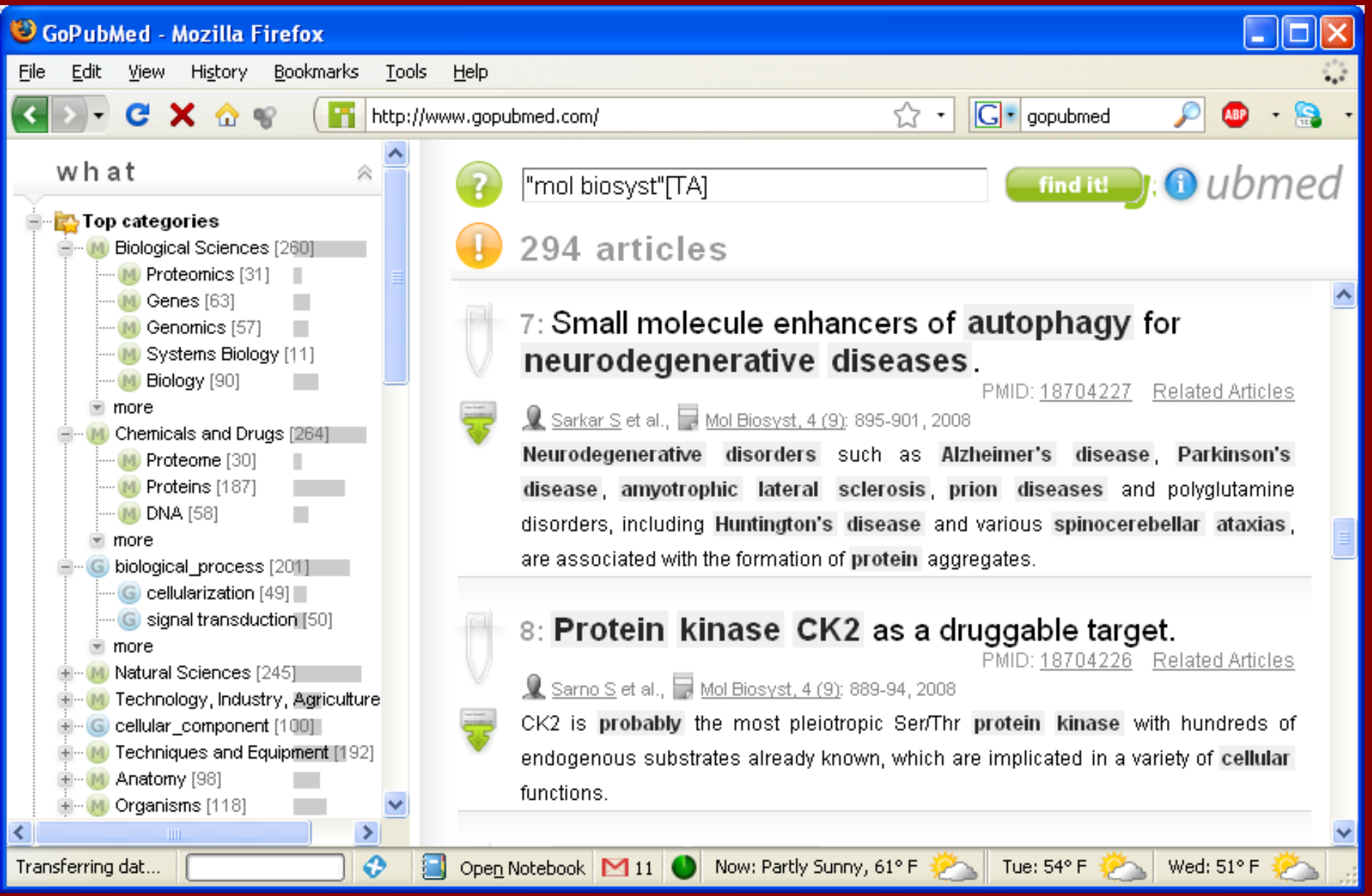
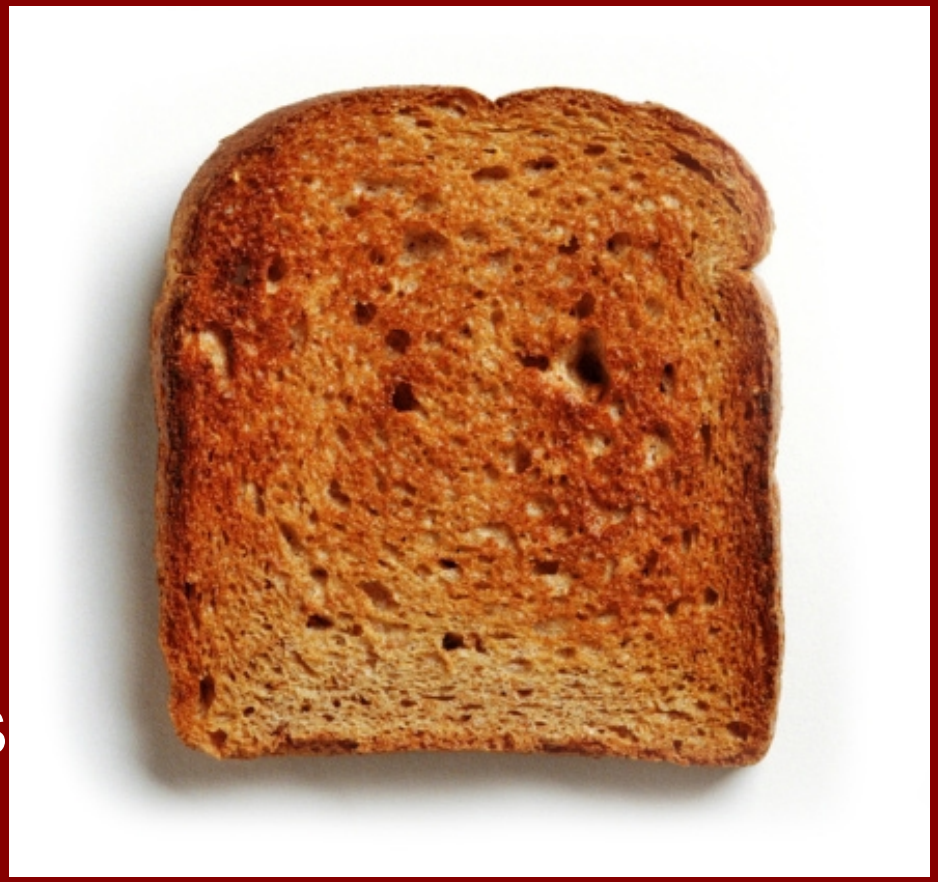


Making ontologies

"T.O.A.S.T."

- Tiny ontologies all strung together

- RXNO
- Molecular processes



RXNO
the name reaction ontology

- Every chemist knows about famous chemists like Wittig, Cannizzaro, Diels, Alder, benzoin
- They're pretty unambiguous and well-suited to logical definitions

- But what organizing principle do we use?

RXNO
the name reaction ontology

- Sort reactions by what they do to the ‘skeleton’ of the molecule.

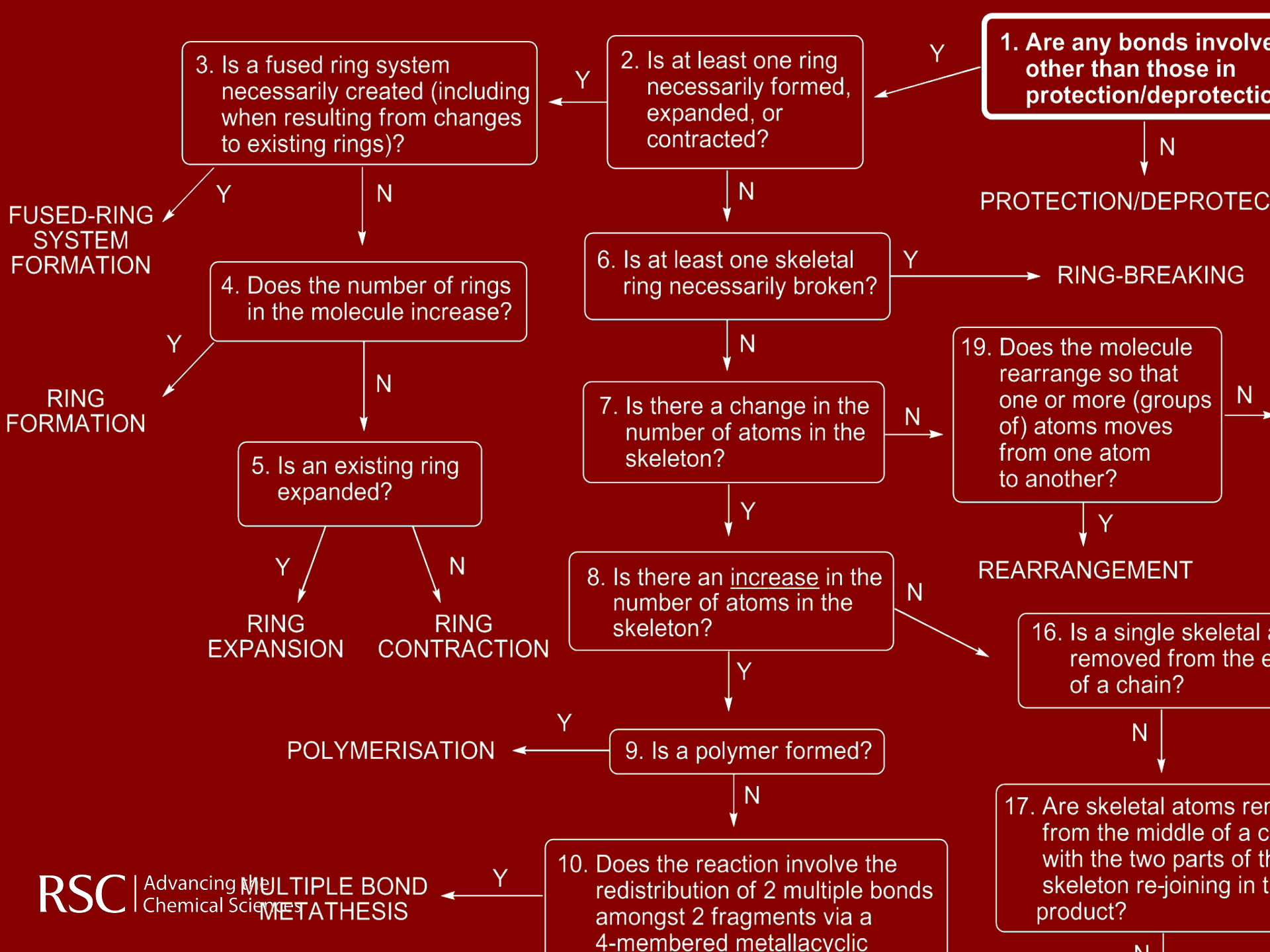
- Skeleton-changing reactions:
  - Joinings, cleavings, rearrangements, ring formation, ring expansion
- Skeleton-preserving reactions:
  - Additions, eliminations, substitutions, protections, deprotections

RXNO
the name reaction ontology

- Quality? Subjectivity?

- Get our curators to assign reactions to categories check percentage agreement, discuss disagreements, improve guidelines, iterate to convergence.

Will be open ontology, curated by RSC. Soon.


1. Are any bonds involve other than those in protection/deprotectio
Y
N
PROTECTION/DEPROTEC
2. Is at least one ring necessarily formed, expanded, or contracted?
Y
N
3. Is a fused ring system necessarily created (including when resulting from changes to existing rings)?
Y
N
FUSED-RING SYSTEM FORMATION
4. Does the number of rings in the molecule increase?
Y
N
RING FORMATION
5. Is an existing ring expanded?
Y
N
RING EXPANSION
RING CONTRACTION
6. Is at least one skeletal ring necessarily broken?
Y
RING-BREAKING
N
7. Is there a change in the number of atoms in the skeleton?
N
Y
19. Does the molecule rearrange so that one or more (groups of) atoms moves from one atom to another?
N
Y
REARRANGEMENT
8. Is there an increase in the number of atoms in the skeleton?
N
Y
16. Is a single skeletal
removed from the e
of a chain?
N
9. Is a polymer formed?
Y
POLYMERISATION
N
17. Are skeletal atoms re
from the middle of a c
with the two parts of t
skeleton re-joining in t
product?
10. Does the reaction involve the redistribution of 2 multiple bonds amongst 2 fragments via a 4-membered metallacyclic
Y
MULTIPLE BOND METATHESIS
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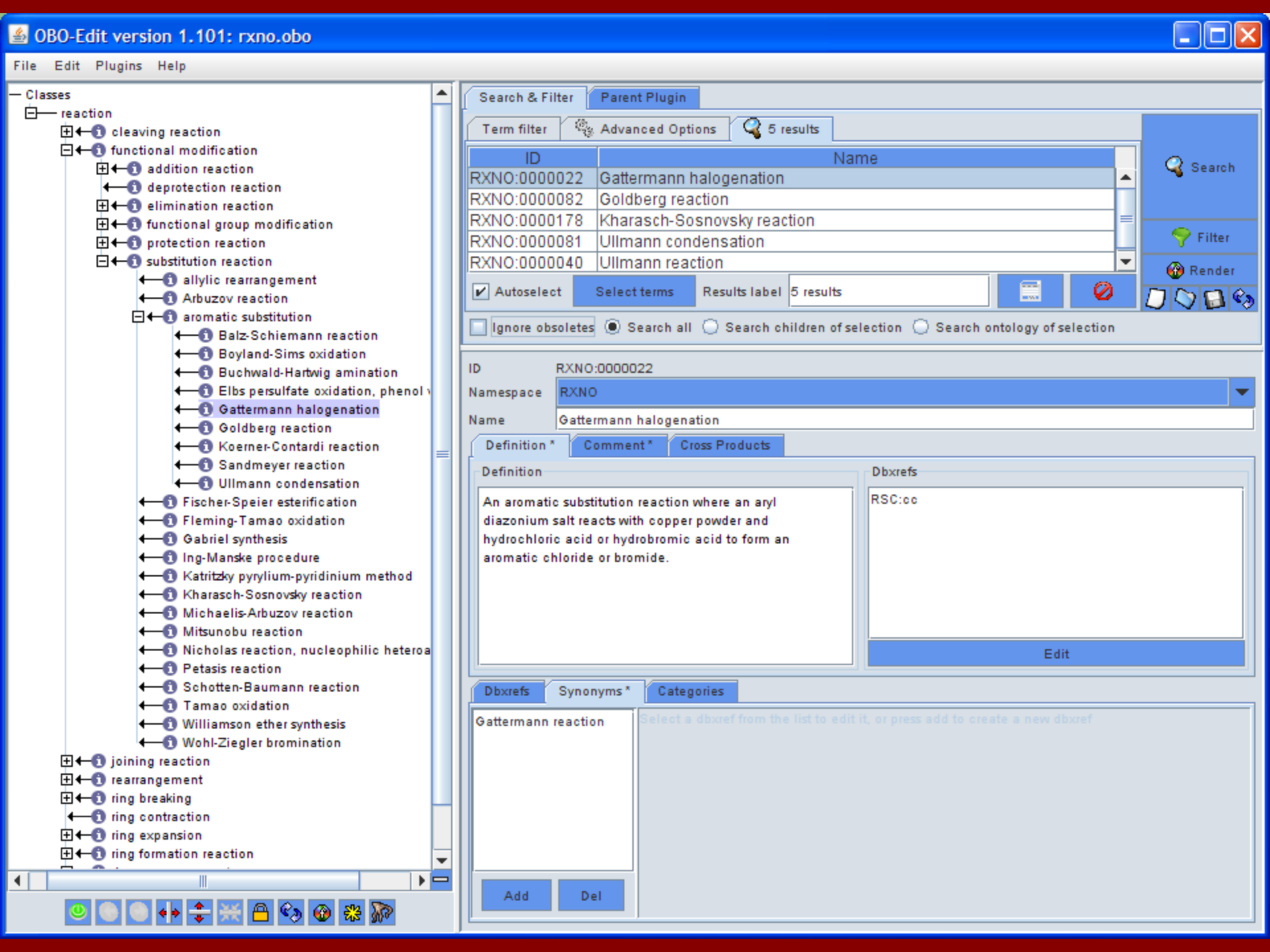
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cleaving reaction
functional modification
addition reaction
deprotection reaction
elimination reaction
functional group modification
protection reaction
substitution reaction
allylic rearrangement
Arbuzov reaction
aromatic substitution
Balz-Schiemann reaction
Boyland-Sims oxidation
Buchwald-Hartwig amination
Elbs persulfate oxidation, phenol
Gattermann halogenation
Goldberg reaction
Koerner-Contardi reaction
Sandmeyer reaction
Ullmann condensation
Fischer-Speier esterification
Fleming-Tamao oxidation
Gabriel synthesis
Ing-Manske procedure
Katritzky pyrylium-pyridinium method
Kharasch-Sosnovsky reaction
Michaelis-Arbuzov reaction
Mitsunobu reaction
Nicholas reaction, nucleophilic heteroa
Petasis reaction
Schotten-Baumann reaction
Tamao oxidation
Williamson ether synthesis
Wohl-Ziegler bromination
joining reaction
rearrangement
ring breaking
ring contraction
ring expansion
ring formation reaction
Search & Filter
Parent Plugin
Term filter
Advanced Options
5 results
ID
Name
RXNO:0000022
Gattermann halogenation
RXNO:0000082
Goldberg reaction
RXNO:0000178
Kharasch-Sosnovsky reaction
RXNO:0000081
Ullmann condensation
RXNO:0000040
Ullmann reaction
Search
Filter
Render
Autoselect
Select terms
Results label
5 results
Ignore obsoletes
Search all
Search children of selection
Search ontology of selection
ID
RXNO:0000022
Namespace
RXNO
Name
Gattermann halogenation
Definition *
Comment *
Cross Products
Definition
An aromatic substitution reaction where an aryl diazonium salt reacts with copper powder and hydrochloric acid or hydrobromic acid to form an aromatic chloride or bromide.
Dbxrefs
RSC:cc
Edit
Dbxrefs
Synonyms *
Categories
Gattermann reaction
Select a dbxref from the list to edit it, or press add to create a new dbxref
Add
Del

Molecular process ontology

- But what about methylations, dihydroxylations and so forth that don't have special reagents and aren't named after a 19th century notable?
- Create a "cross-product" ontology by fitting content from an already existing ontology into a template.

Molecular process ontology

Template for <group>ation:
"The replacement of a hydrogen atom in a molecule with a <group>."

Template for de<group>ation:
"The replacement of a <group> substituent in a molecule with a hydrogen atom."

Template for *N*-<group>ation:
"The replacement of a hydrogen atom bound to a nitrogen atom with a <group> substituent."

…and so forth.

Molecular process ontology

Group terms in ChEBI:

531 -yl groups
143 -o groups
45 -ene groups
32 -oxy groups
11 -yne groups

Total: 762

Patterns:

((N|O|P|S)-)?
(de?)<group>ation

Ten kinds of molecular process per group.

Equals…

Molecular process ontology

A more-or-less free ontology, inheriting the internal links from ChEBI, with

7620 terms.

Will be open ontology, curated by RSC. Soon.

More creative criticism...

Against Idiosyncrasy in Ontology

Abstract. The world of ontology development is full of mysteries. Recently, ISO Standard 15926 ("Lifecycle Integration of Process Plant Data Including Oil and Gas Production Facilities"), a data model initially designed to support the integration and handover of large engineering artefacts, has been proposed by its principal custodian for general use as an upper level ontology. As we shall discover, ISO 15926 is, when examined in light of this proposal, marked by a series of quite astonishing defects, which may however provide general lessons for the developers of ontologies in the future.

L
Univers

B. Bennett and C. Fellbaum (Eds.), *Formal Ontology and Information Systems*, (FOIS 2006), Baltimore November 9-11 2006

Data

- Experimental data checker
  - Validation
  - Visualisation

2-Methyl-2-hydroxymethyl-2,5-dihydrofuran **9** (50 mg, 0.51 mmol) was oxidised using OsO_4, TMEDA to yield the crude products [6 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (petrol-EtOAc, 4 : 1) to afford the pure title compound as a colourless oil (116 mg, 83%); ν_{max} (film)/cm^{-1} 2977, 2929, 1746, 1374, 1230, 1046; δ_H (300 MHz; $CDCl_3$) 5.43 (1H, q, *J* 5), 5.17 (1H, d, *J* 5), 4.26-4.09 (3H, m), 3.89 (1H, dd, *J* 10 and 5), 2.10 (6H, s), 2.08 (3H, s), 1.36 (3H, s); δ_C (75 MHz; $CDCl_3$) 170.6, 169.8, 169.5, 80.8, 76.2, 71.2, 68.9, 65.3, 22.3, 20.6, 20.4, 18.3; Found (CI) 292.1392, $C_{12}H_{22}NO_7 + NH_4$ requires 292.1396.

***anti*-2-Methyl-2-(acetoxymethyl)tetrahydrofuran *anti*-15**

2-Methyl-2-hydroxymethyl-2,5-dihydrofuran **9** (50 mg, 0.51 mmol) was oxidised using UpJohn conditions to yield the crude products [2 : 1 (*anti* : *syn*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (petrol-EtOAc, 4 : 1) to afford the product mixture as a colourless oil (110 mg, 79%) as an inseparable mixture of isomers (*anti* major compound); ν_{max} (film)/cm^{-1} 2989, 2944, 1746, 1379, 1232, 1046; δ_H (300 MHz; $CDCl_3$) 5.46-5.39 (1H, m), 5.26 (1H, d, *J* 6), 4.26-3.85 (4H, m), 2.11 (3H, s), 2.10 (6H, s), 1.26 (3H, s); δ_C (75 MHz; $CDCl_3$) 170.4, 169.8, 169.6, 81.2, 72.7, 71.9, 69.3, 67.9, 20.7, 20.5, 20.4, 18.3; Found (CI) 292.1400, $C_{12}H_{22}NO_7$ requires 292.1396,

***syn*-1,2,4-Triacetoxycyclohexane *syn*-16**

Cyclohex-3-en-1-ol **11** (50 mg, 0.51 mmol) was oxidised using OsO_4, TMEDA to yield the crude mixture of products [3 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (EtOAc) to afford a colourless oil (121 mg, 92%) as an inseparable mixture of isomers; mixture: ν_{max} (film)/cm^{-1} 2953, 1745, 1370, 1235, 1028; ***syn*-16** δ_H (300 MHz; $CDCl_3$) 5.17-5.11 (1H, m), 4.84-4.72 (2H, m), 2.04 (3H, s), 1.98 (3H, s), 1.86 (3H, s), 2.05-1.45 (6H, m); δ_C (75 MHz; $CDCl_3$) 170.1, 170.0, 169.9, 69.5, 69.3, 67.9, 31.4, 25.3, 24.7, 21.1, 20.9, 20.8; ***anti*-16**; δ_H (300 MHz; $CDCl_3$) 5.08-5.01 (1H, m), 4.81-4.67 (2H, m), 1.99 (9H, s), 2.05-1.45 (6H, m); δ_C (75 MHz; $CDCl_3$) 170.3, 170.2, 170.1, 69.7, 68.8, 68.6, 31.8, 25.9, 25.3, 23.6, 21.1, 20.9; mixture Found (CI) 276.1437, $C_{12}H_{22}NO_6$ requires 276.1447.

***anti*-1,2,4-Triacetoxycyclohexane *anti*-16**

Cyclohex-3-en-1-ol **11** (50 mg, 0.51 mmol) was oxidised using UpJohn conditions to yield the crude mixture of products [1 : 1 (*syn* : *anti*) by ^{1}H NMR]. The resulting oil was purified by flash chromatography (EtOAc) to afford the product mixture as a colourless oil (115 mg, 88%) as an inseparable mixture of isomers; All data are consistent with *syn*- and ***anti*-16** prepared previously.

***syn*-1,2,4,5-Tetraacetoxycyclohexane *syn*-17**

Future development

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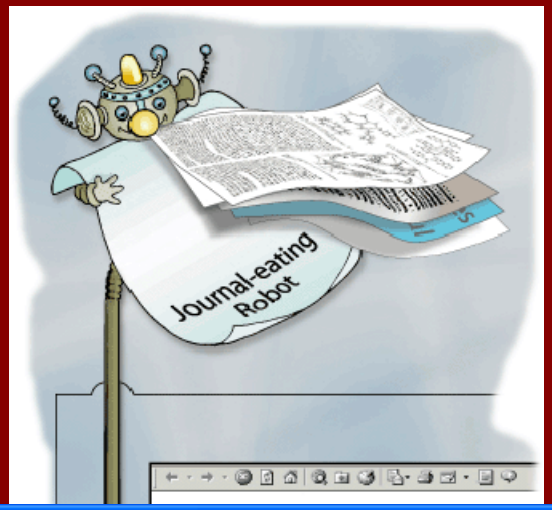
- Researchers
- Publishers



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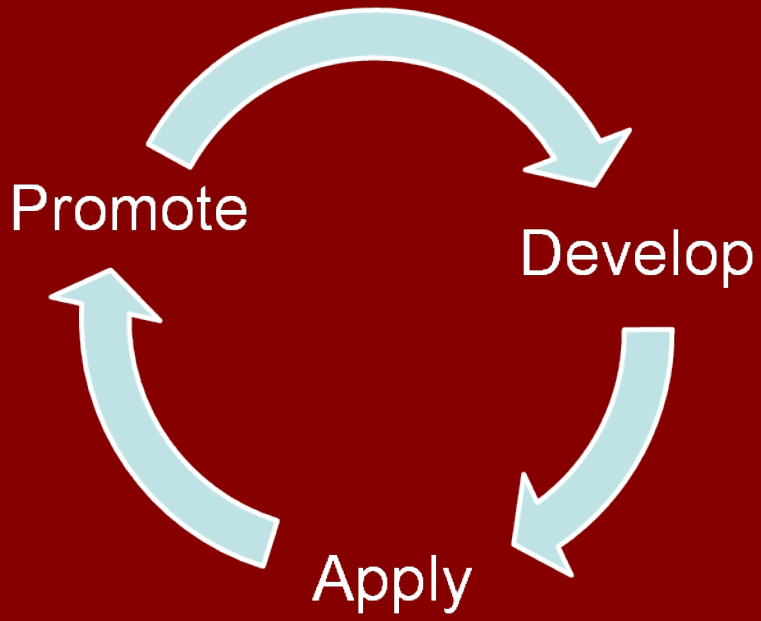
What we will do



- InChI implementation
- Ontology development
- Follow the science

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Chemical Semantic Web

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Centre For Molecular Science Informatics

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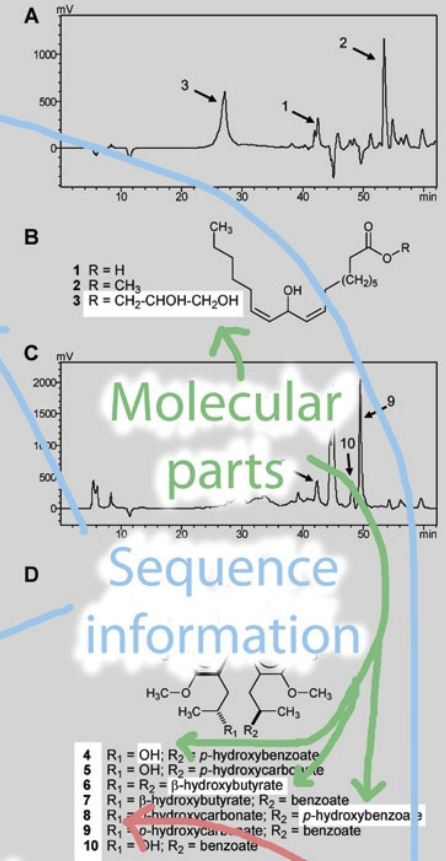
metabolite profiles indicating that epigenetic modifiers impacted fungi in a manner that was functionally distinct from that of a general cytotoxic response. Interestingly, a combination treatment, composed of a DNA methyltransferase inhibitor and histone deacetylase inhibitor, was tested and determined to be only modestly effective due to significant growth restriction and/or generation of metabolite profiles dominated by the effects of a single component in the mixture (*e.g.* effects of individual compound treatments were not additive as a mixture).

In order to probe the nature of metabolic remodeling induced by epigenetic modifier treatment, two fungi were selected for scale-up studies. The first isolate was obtained from a tidal pool along the coastline of Casco Bay, Portland, Maine, USA, and identified as *Cladosporium cladosporioides* by analysis of a 300 base pair sequence of the D2 region of the 26S large ribosomal subunit rRNA gene and morphological considerations.† This culture exhibited divergent responses to the small-molecule epigenetic modifiers 5-azacytidine and suberoylanilide hydroxamic acid which led to dramatic restructuring of its secondary metabolome with both treatments (Fig. 1A,C). Treatment of *C. cladosporioides* with 5-azacytidine elicited the *de novo* production of several oxylipins, three of which were characterized by NMR and MS analysis† as (9*Z*,12*Z*)-10-hydroxyoctadeca-9,12-dienoic acid (**1**), its methyl ester (**2**), and glycerol conjugate (**3**) in substantial yields (Fig. 1B). The production of these compounds is of considerable interest since these types of metabolites are widely recognized for their important roles as intra- and inter-species cell signaling molecules. In contrast, suberoylanilide hydroxamic acid induced the production of a complex array of perylenequinones, two of which were characterized as new metabolites, cladochromes F (**4**) and G (**5**), along with four known cladochromes A (**6**), B (**7**), D (**8**), and E (**9**) and calphostin B (**10**) (Fig. 1D. and see ESI†). This is remarkable since this is the first reported co-occurrence of such an extensive range of cladochrome/calphostin metabolites from a single source. Moreover, the identification of **6** and **7** under epigenetic stimulation is significant since these compounds were first unique products of *Cladosporium* infection of seedlings, yet could not be obtained from an extensive mono-culture fermentations.[10] While it was [illegible] that **6** and **7** might be the products of mixed biosynthesis, their selective production in suberoylanilide hydroxamic acid treated *Cladosporium* that their biogenesis is normally tightly regulated some yet undefined host-specific signaling event.

The second fungal isolate was obtained from the foregut of a fifth instar luna moth (*Actias luna*; Saturniidae) larva that was cultured on an exclusive diet of sweet gum (*Liquidambar styraciflua* L.; Hamamelidaceae) leaves. Initial characterization of the fungus by analysis of the 26S rRNA gene gave homology to *Diatrype disciformis*. While control cultures of this *Diatrype* sp. were relatively void of any secondary metabolites, addition of 5-azacytidine triggered a significant change in the organism's metabolic profile (Fig. 2A), resulting in the production of two new polyketides, lunalides A (**11**) and B (**12**) (Fig. 2B). It is interesting to note that one other non-epigenetic culture treatment, elicitation with *E. coli*,† resulted in the biosynthesis of **11** and **12** which were otherwise repressed under axenic culture conditions. The results suggest that their production is under specific control of a unique environmental cue.



. 1 Differen[illegible]atograms an[illegible]tures of *C. cladosporioides* [illegible]odifiers. [illegible]en cul-[illegible]l organi extract [illegible]e at 210 nm) Differ-[illegible]tograms were generated by subtracting the chromatogram of the untreated control from the treatment groups. Peaks phasing upward represent metabolites expressed only upon epigenetic treatment or produ[illegible]at[illegible]ntrations. (A) Difference chromatogram [illegible]ation yielding oxylipins **1**–**3** (B). (C) [illegible]strating the effect of suberoylanilide hydroxamic acid on secondary metabolite expression leading to the production [illegible]-**10**. C[illegible]ounds were characterized by HRESIM[illegible]son to values published in the litera[illegible]

The succ[illegible] new natural products from fung[illegible]min[illegible]le epigenetic modifiers indicates that this technique is a very promising and rational approach for the native expression of silent biosynthetic pathways.

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