Lhasa Limited

Zeneth

A knowledge-based system for the prediction of forced degradation of organic compounds

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Contents

- Introduction to Lhasa Limited
- Regulatory requirements for forced degradation
- Degradation knowledge space
- Overview of Zeneth – what it is / how it works
- Future developments
- Summary

Lhasa Limited

Introduction

- Established in 1983
- Located in central Leeds, UK
- Scientific software company driven by our members
- Produces predictive and database systems for the life sciences industry
- Not-for-profit organisation & educational charity

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Membership worldwide

Pharmaceutical, Education, Regulatory bodies

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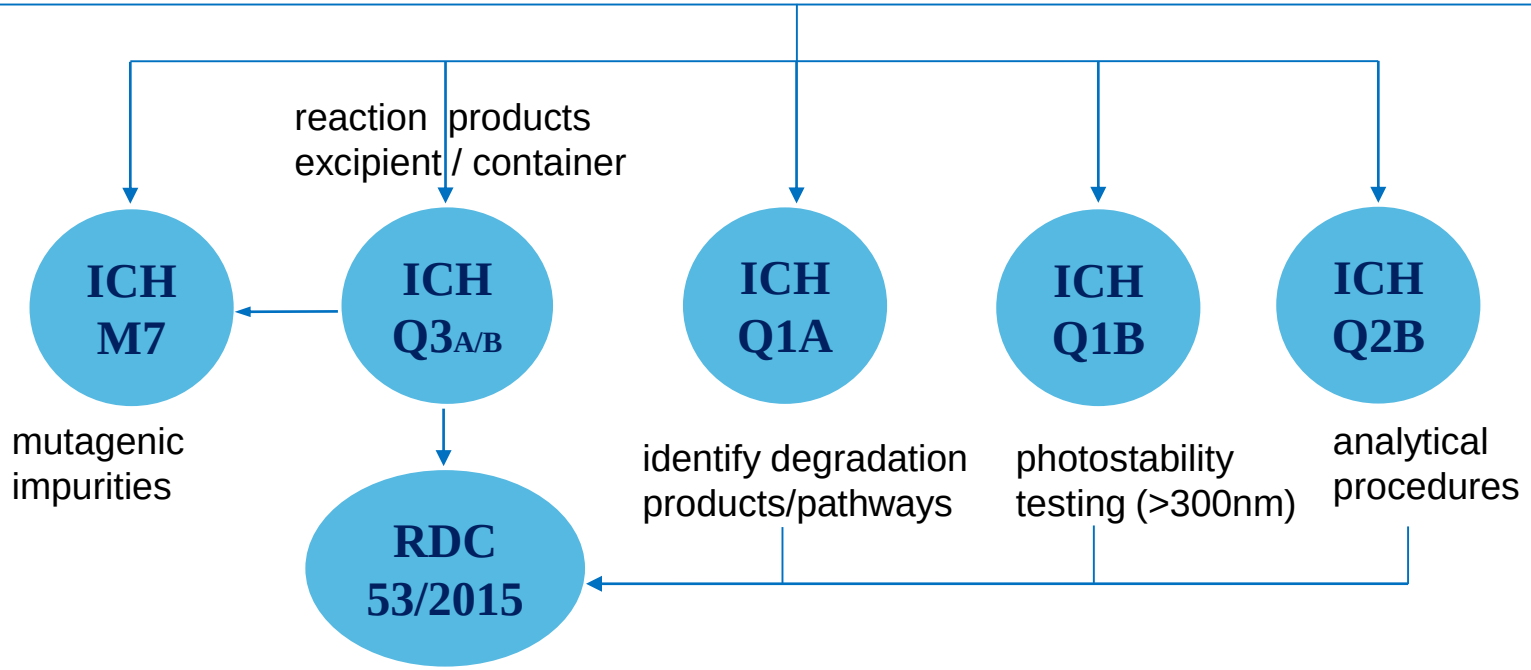
Regulatory requirements

Degradation Product: A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system.



Forced degradation studies are performed to:

- Identify all potential degradation products & pathways
- Assess the intrinsic stability of the drug substance (API) & product
- Validate the stability-indicating methods/procedures

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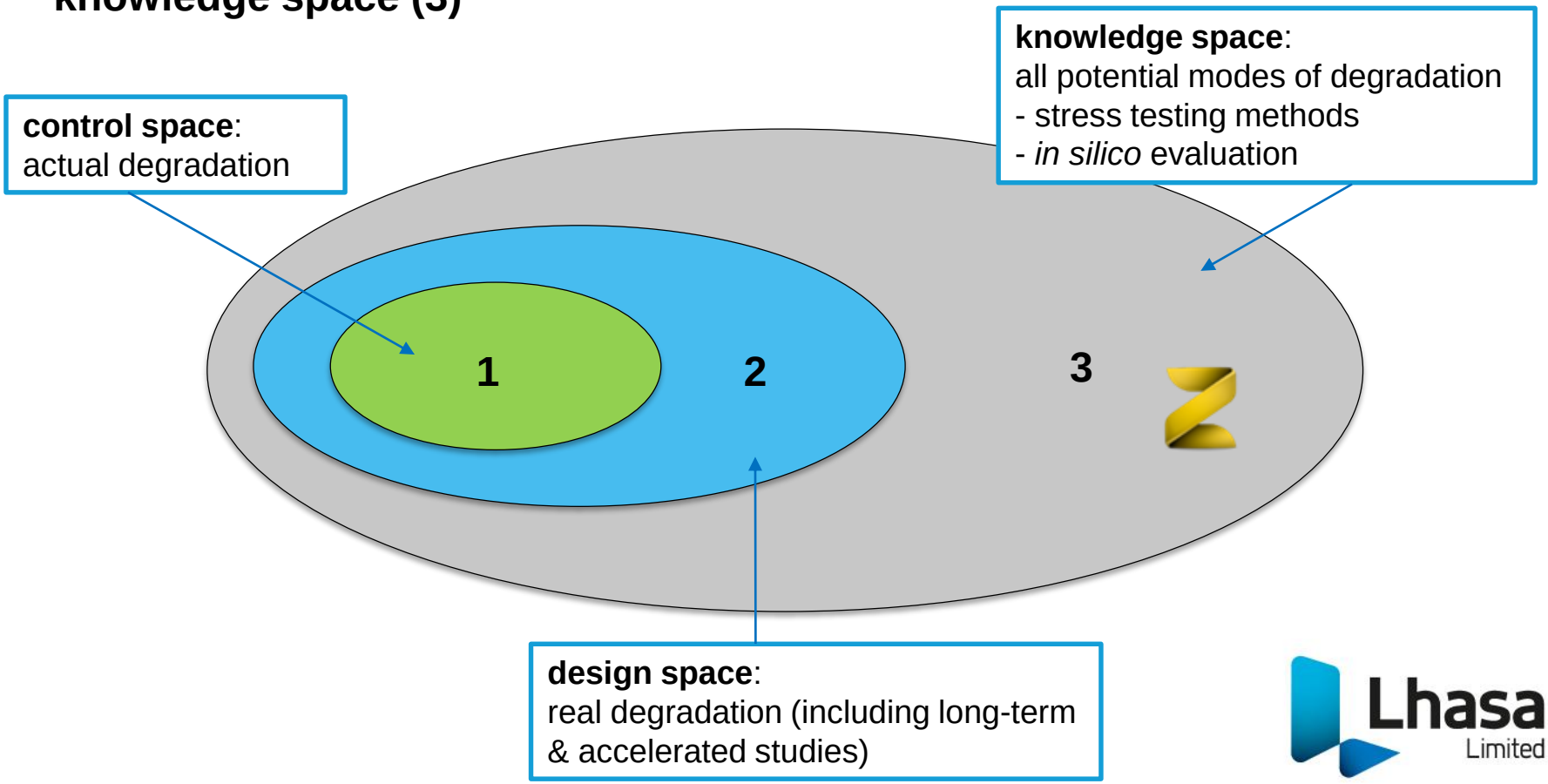
Degradation knowledge space

Aim of forced degradation studies on the drug product/API:

- Ensure all relevant degradation products are “known” by applying stress conditions
- Increase the confidence of the **control space (1)** by having a well designed **knowledge space (3)**



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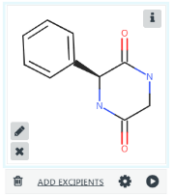
What is Zeneth?

…..Expert knowledge-based system for the prediction of forced degradation



Q

Environmental Conditions

Knowledge Base

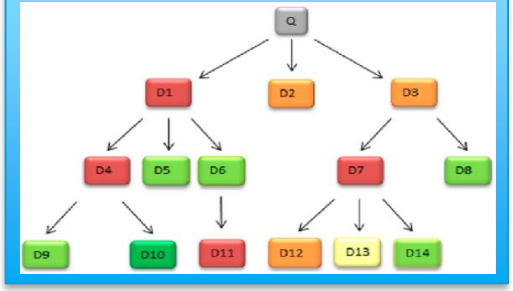
- Transformation dictionary [507]
- Reaction patterns
- Conditions
- Comments
- References
- Excipients [189]

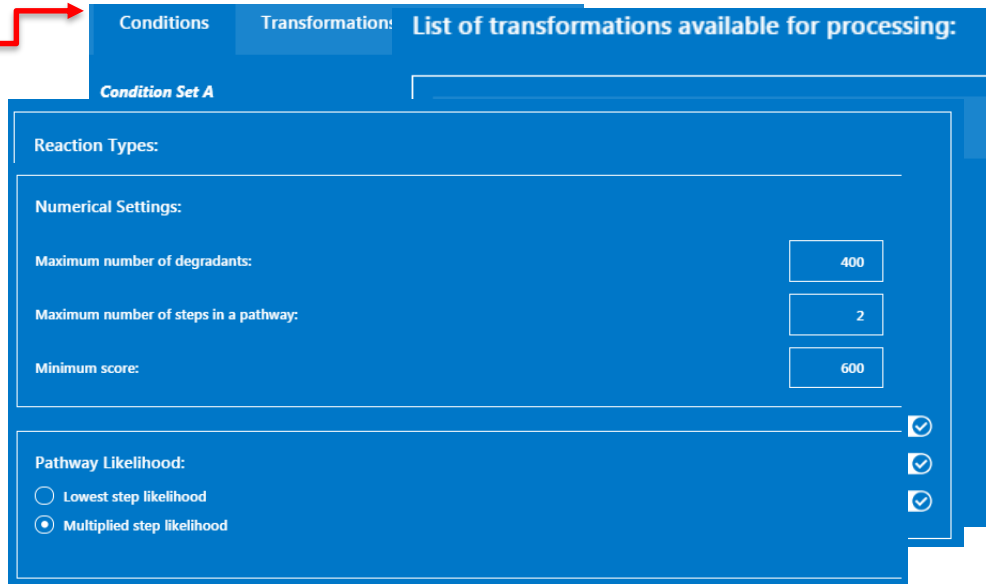
"Knowledge Manager"

- Hydrolysis → H_2O, pH
- Oxidation → O_2, H_2O_2, AIBN
- Thermal → Temperature
- Photolytic → Light

"Predictor"

Potential degradants

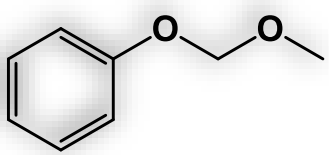




What is Zeneth?

Query Compound

Q

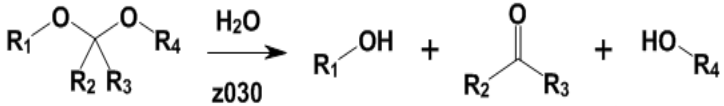


Structural physico-chemical evaluation

Environmental Conditions

- Water
- pH 3

Knowledge Base



"Hydrolysis of acetal"

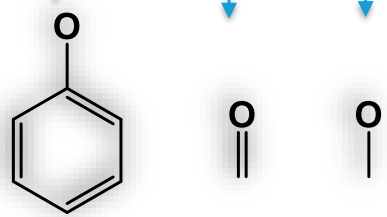
pH profile

reaction catalysed by acid

Pattern matching

No Prediction

Potential Degradants



Prediction Score = 700

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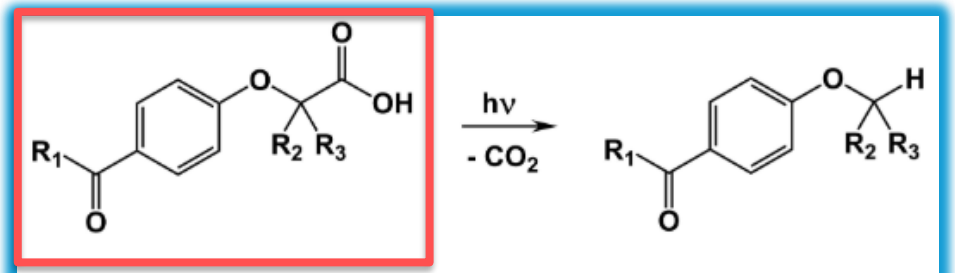
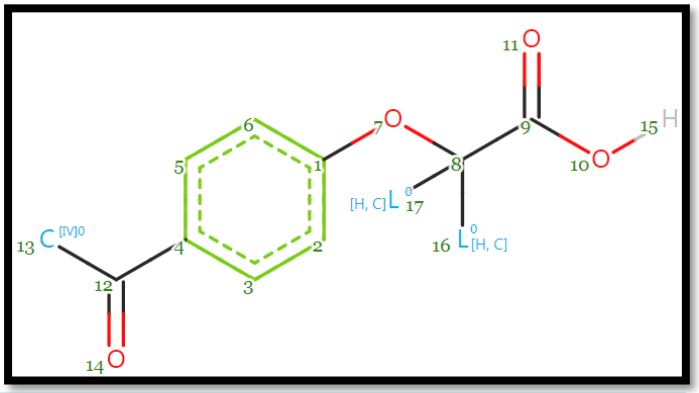
Chemical patterns

z457:
Photodecarboxylation of aryloxyacetic acid



R1 = aromatic carbon
R2, R3 = aliphatic carbon (not multiply bonded and not attached to a heteroatom) or aromatic carbon or hydrogen

Explora language **1**



Atom 13: requiredBondType(AROMATIC)

Atoms 16, 17: (heteroCount == 0 and allowedBondType(SINGLE)) or requiredBondType(AROMATIC)

Script [LTL] **2**

```
breakBond(10, 15);
hideStructure(15);
breakBond(8, 9);
setBondType(9, 10, DOUBLE);
hideStructure(9);
setCharge(8, -1);
captureIntermediate("");
setIntermediateTypeMechanistic();
setIntermediateAsPresumed();
unsetCharge(8);

setScore(0.7);
```

Prediction

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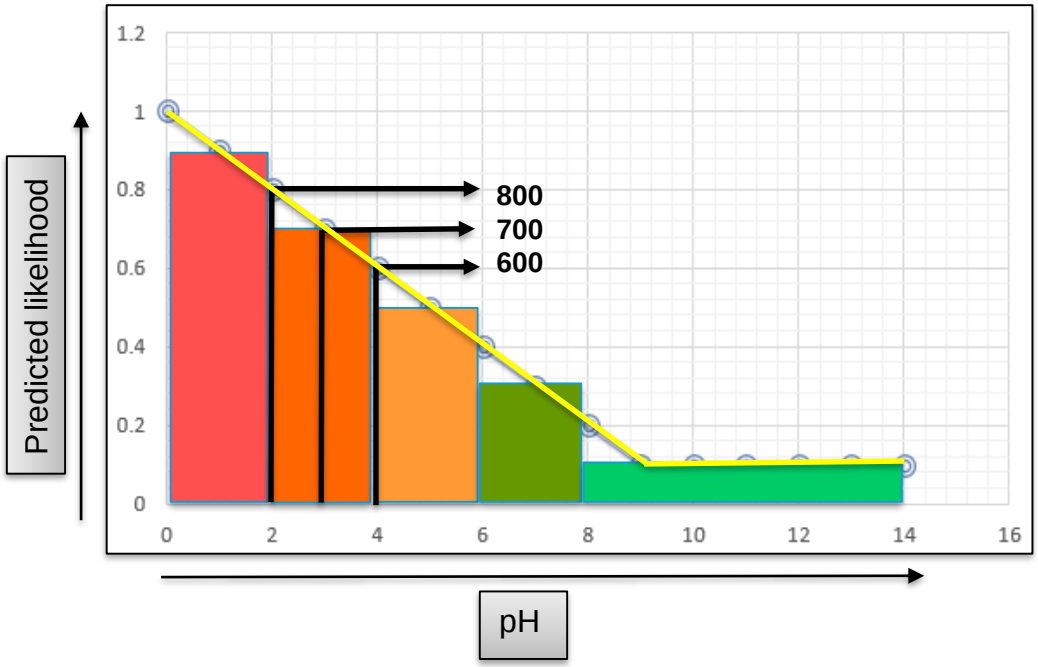
Degradant likelihood/scoring

Most transformations have a pH profile:

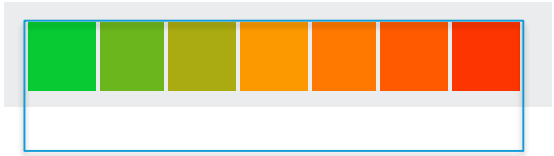
- Rule 34: If [transformation 030] is [certain] then [transformation 030 products] is [hydrolysis with pH profile 5]
  - Rule 121: If [conditions: water] is [certain] then [hydrolysis with pH profile 5] is [likelihood with pH profile 5]
    - Rule 80: If [pH >= 8] is [certain] then [likelihood with pH profile 5] is [very unlikely]
    - Rule 81: If [6 <= pH < 8] is [certain] then [likelihood with pH profile 5] is [unlikely]
    - Rule 82: If [4 <= pH < 6] is [certain] then [likelihood with pH profile 5] is [equivocal]
    - **Rule 83: If [2 <= pH < 4] is [certain] then [likelihood with pH profile 5] is [likely]**
    - Rule 84: If [pH < 2] is [certain] then [likelihood with pH profile 5] is [very likely]

pH 2 = likely
pH 3 = likely
pH 3.9 = likely

Line Formula =MIN(MAX(-pH/10+1, 0.1)) x 1000 → score



Score:



0 — 500 — 1000

Impossible — equivocal — certain

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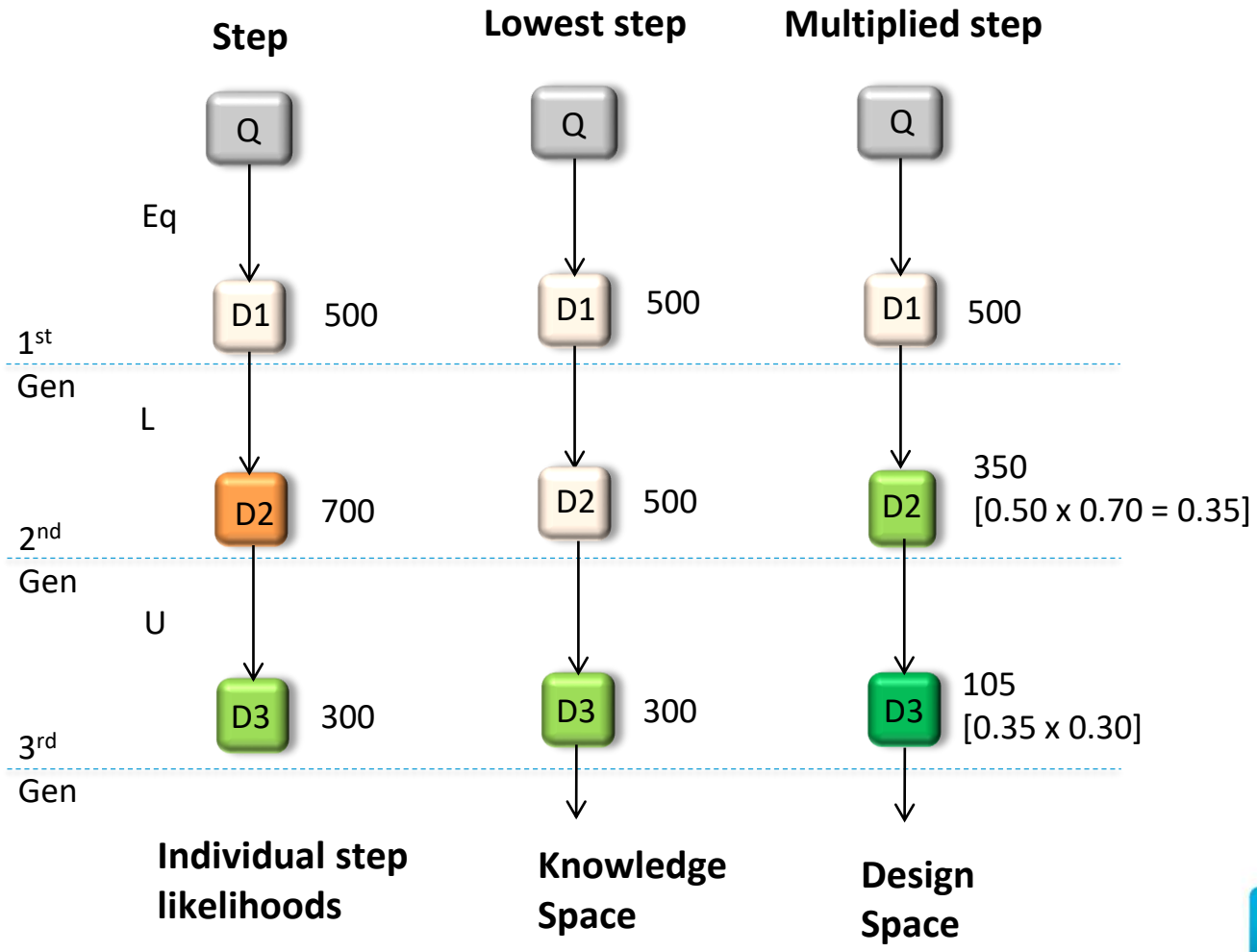
Scoring: multiplied step likelihood

Child degradant cannot have a higher score than the parent



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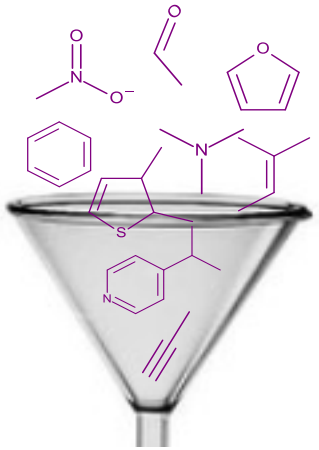
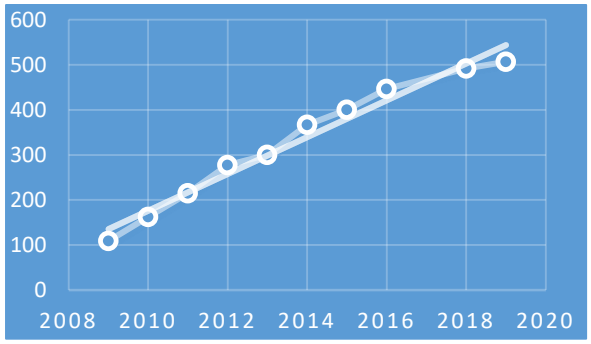
Building the knowledge base



Knowledge base

- Oxidation [148]
- Hydrolysis [118]
- Condensation [109]
- Elimination [60]
- Isomerisation [28]
- Photolysis [44]

- External requests (members)
  - provide data for a reaction
  - proprietary data via data sharing initiatives
- Group discussion with members
  - discuss proposals for new reactions
  - provide feedback on new & existing chemistry
- Internal requests, updates to existing knowledge
  - general maintenance
  - investigation of primary literature
  - specialised degradation chemistry books
- Strategic decision (e.g. cover a new reaction type)



New knowledge added & existing knowledge continuously maintained

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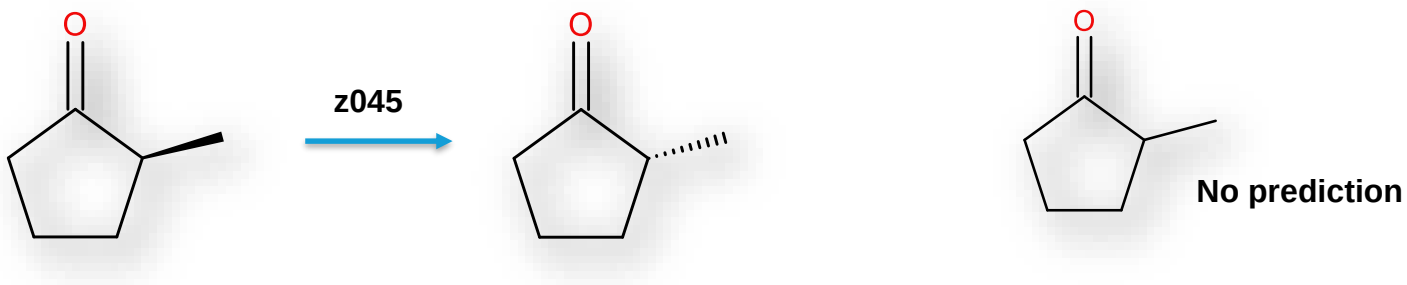
Stereochemistry

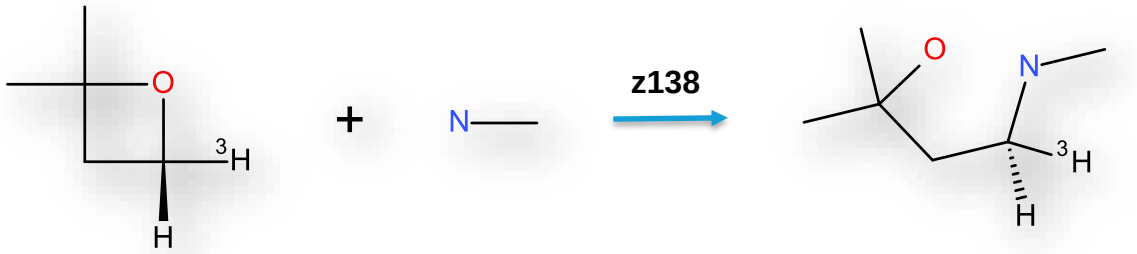
- Epimerisations

This transformation operates only on carbon centres that have a defined stereocentre:



- Nucleophilic substitutions

S_N2-type reactions exhibit inversion of configuration at a stereocentre:



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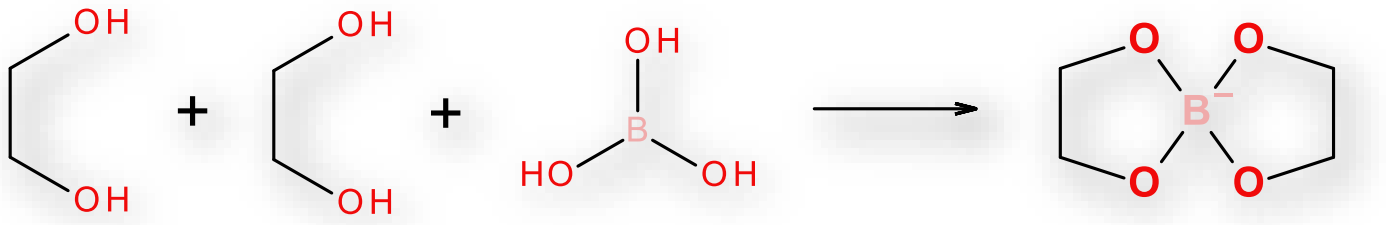
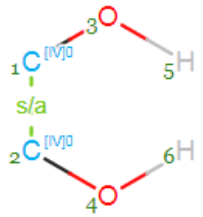
Three-component reactions

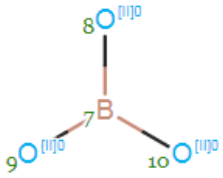
The program has the capacity to express three-component reactions:

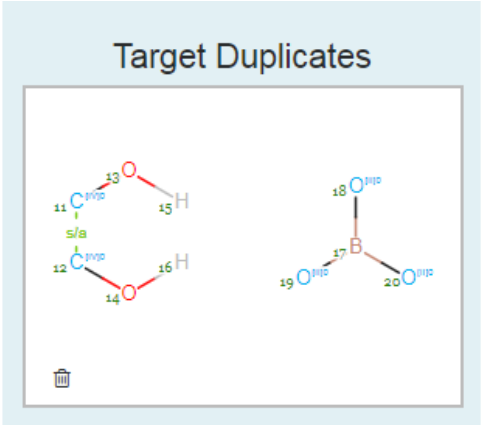
New transformation z505



2 oxygen nucleophiles boric acid spiroborate anion

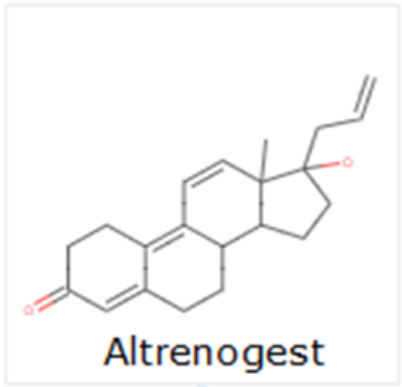







```
1  breakBond(3, 5);
2  hideStructure(5);
3  breakBond(7, 8);
4  hideStructure(8);
5  makeBond(3, 7, SINGLE);
6  captureIntermediate("");
7  setIntermediateTypeObservable();
8  breakBond(4, 6);
9  hideStructure(6);
10 breakBond(7, 9);
11 hideStructure(9);
12 makeBond(4, 7, SINGLE);
13 captureIntermediate("");
14 setIntermediateTypeObservable();
15 breakBond(13, 15);
16 hideStructure(15);
```

Intramolecular cycloadditions

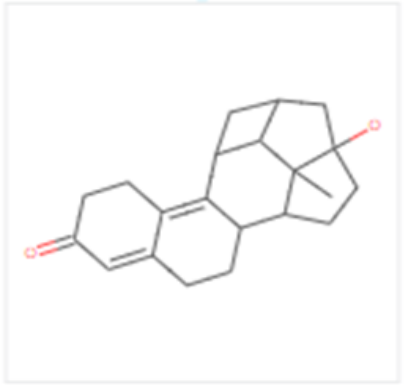


Altrenogest

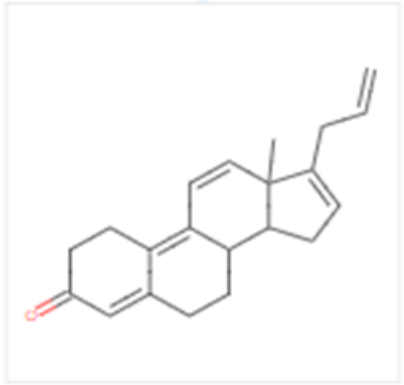
267 - Intramolecular photochemical cycloaddition of two alkenes

064 - Dehydration of alcohol

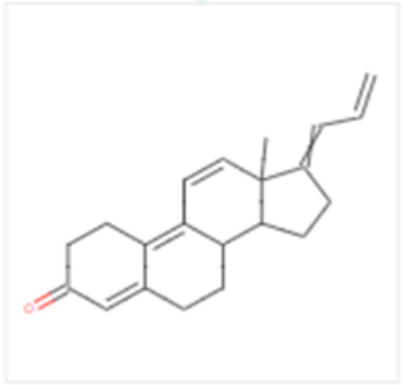
700



300



300



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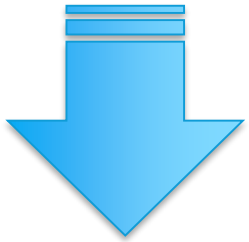
Chemical descriptors

- pK_a
- Bond Dissociation Energy (BDE)
- Electrophilicity/Nucleophilicity
- Photochemical Reactivity
- Aromaticity
- Steric Hindrance



Reasoning Engine

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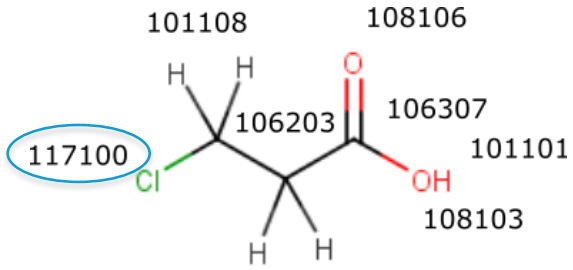
pK_a Calculator

- pK_a of a molecule determines its protonation state at a given pH
- pK_a tends to be governed by electronic effects that decrease with the distance from the centre of protonation
- Generate a distance spectrum for each atom type from the pK_a centre



Dist	101101	101108	106307	106203	108103	108106	117100
1	1		1				
2				0.25		0.25	
3		0.22		0.11			
4		0.12					0.06
Sum	1	0.34	1	0.36	0	0.25	0.06

= distance spectrum

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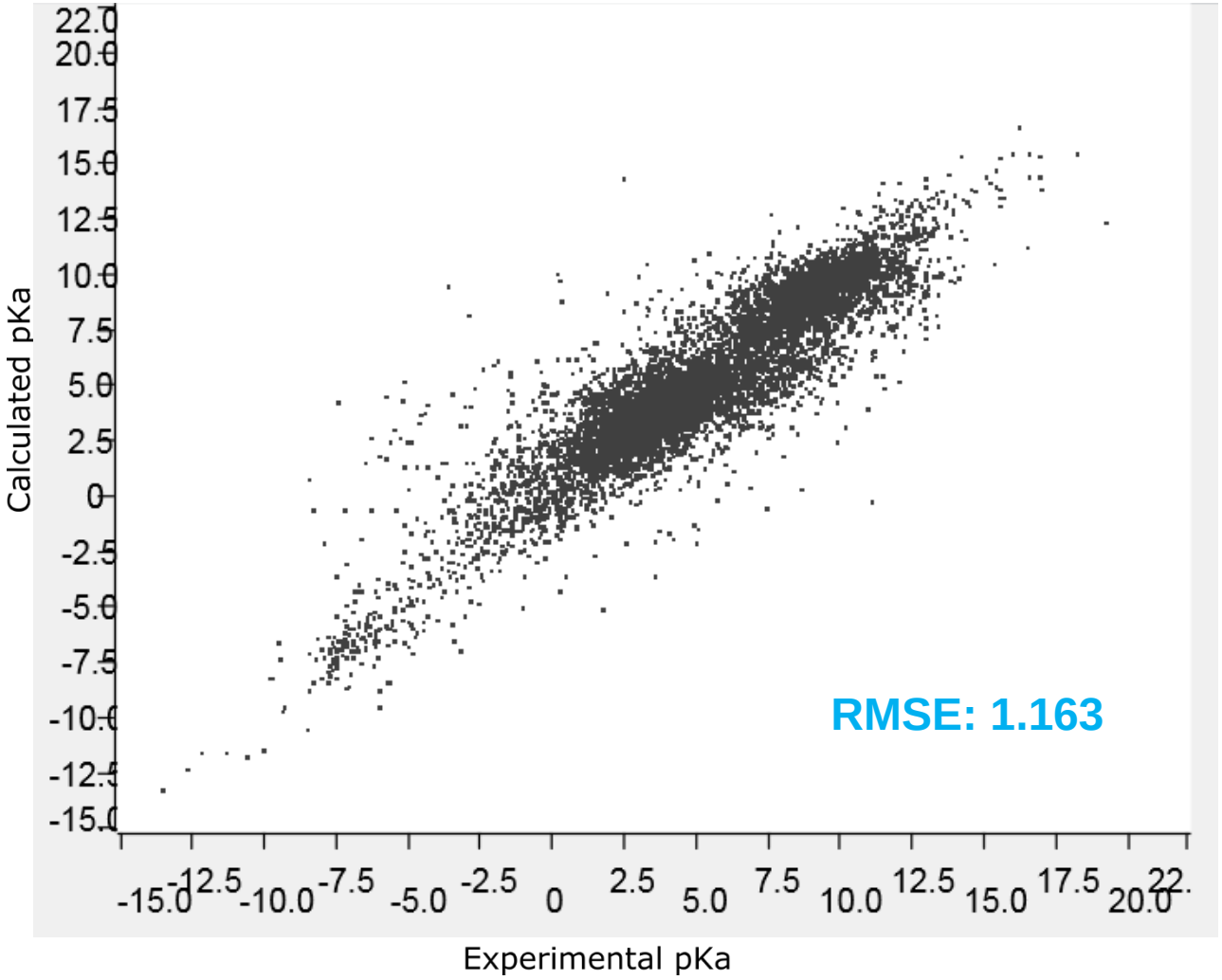
pK_a Performance

Preliminary results using 5-fold cross-validation



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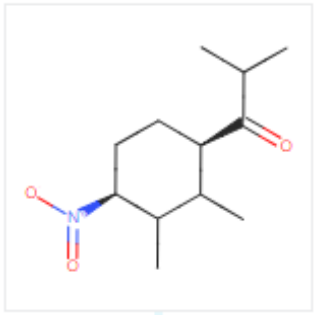
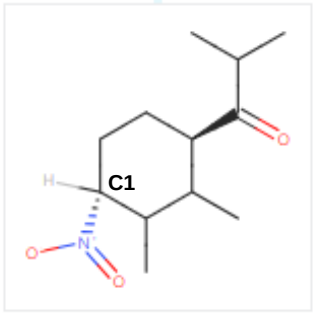
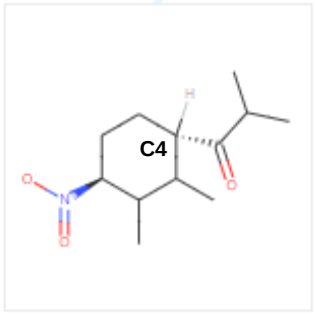
pK_a Calculator implemented



045 - Epimerisation alpha to electron-withdrawing group

900 777





pH = 12

z045:
Epimerisation alpha to electron-withdrawing group

```
if (!isDefinedStereocentre(1)) { abort(); }
if (isBridgehead(1)) { abort(); }

substitutionWithInversion(4, 1, 3);
hideStructure(3);

real pH = getpH();
real pKa = getpKa(1);
real raw_score = (max(pH, 14 - pH) + 6 - pKa) / 10;
if (raw_score < 0.1) { abort(); }

setScore(min(raw_score, 0.9));
```

Epimerisation is more likely at C1 than C4

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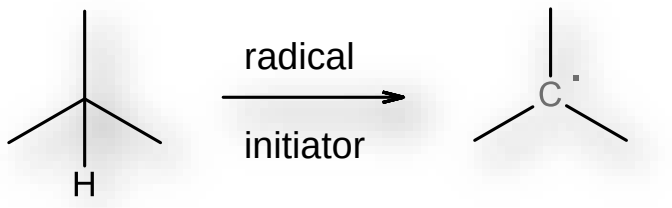
Other descriptors: BDE

General pathway of a transformation initiated by hydrogen abstraction:



- The radical initiator considered in forced degradation is peroxyl (R-O-O•)
- Peroxyl is quite selective and attacks mainly “labile” C-H bonds e.g. allylic, benzylic, α to a heteroatom etc.
- The incorporation of a BDE descriptor would aid the assessment of likelihood of these reactions

BUT …

To implement it within the Zeneth reasoning framework, both speed and performance is critical

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Summary

- Zeneth is an expert knowledge-based system for the prediction of forced degradation
- Helps understand mechanistic pathways as well as aid degradant identification and structure elucidation
- Zeneth generates predictions from its knowledge base which currently contains 507 transformations
- Our members drive the development of the Zeneth program and directly influence the scientific content
- Zeneth has recently undergone a complete re-design with the result of massively improved usability as well as improvements to the quality and speed of predictions.

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Acknowledgements

Zeneth Team, Lhasa Limited

Scientists: Martin Ott, Rachel Hemingway and Tony Long

Development Team:

Andrzej Paetz, Alan Hayward, Christos Wild, Daragh Connolly, Diane Bureau, Lucy Wilcock, Mohit Garg, Nandini-Arjun Mandya, Paul Cunningham, Pawel Maslej, Piotr Gorny, Roderic Green, Tony Clay and Jeff Plante

Account Manager: Maggie Coombs

Business Analysts: Lisa Leivers, Faye Stringer

Meet the team at Booth 4!

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Thank you for you attention!

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Multiplied step likelihood

Likelihood values:								
VL/L/Eq/U/VU:				0.900	0.700	0.500	0.300	0.100
Bin boundaries:				0.999	0.800	0.600	0.400	0.200

Two-step pathways:

*		bin		VL	L	Eq	U	VU
VL	0.900	0.800	1.000	0.810	0.630	0.450	0.270	0.090
L	0.700	0.600	0.800	0.630	0.490	0.350	0.210	0.070
Eq	0.500	0.400	0.600	0.450	0.350	0.250	0.150	0.050
U	0.300	0.200	0.400	0.270	0.210	0.150	0.090	0.030
VU	0.100	0.000	0.200	0.090	0.070	0.050	0.030	0.010

Three-step pathways:

VL	0.900	bin		VL	L	Eq	U	VU
VL	0.900	0.800	1.000	0.729	0.567	0.405	0.243	0.081
L	0.700	0.600	0.800	0.567	0.441	0.315	0.189	0.063
Eq	0.500	0.400	0.600	0.405	0.315	0.225	0.135	0.045
U	0.300	0.200	0.400	0.243	0.189	0.135	0.081	0.027
VU	0.100	0.000	0.200	0.081	0.063	0.045	0.027	0.009

L	0.700	bin		VL	L	Eq	U	VU
VL	0.900	0.800	1.000	0.567	0.441	0.315	0.189	0.063
L	0.700	0.600	0.800	0.441	0.343	0.245	0.147	0.049
Eq	0.500	0.400	0.600	0.315	0.245	0.175	0.105	0.035
U	0.300	0.200	0.400	0.189	0.147	0.105	0.063	0.021
VU	0.100	0.000	0.200	0.063	0.049	0.035	0.021	0.007

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