An Approach toward the Prediction of Chemical Degradation Pathways

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Abstract

In forced degradation studies, drugs (formulated or pure) are exposed to harsh conditions to study their degradation behaviour. Many degradation products may be formed, some of them unexpectedly. A major challenge is posed by the elucidation of degradation pathways and structural identification of the products, making a predictive expert system a very useful tool.

The new system, called Zeneth, is based on existing functionality in the Meteor system for metabolism prediction.[1,2] Thus Zeneth contains a chemical engine allowing the description and application of degradation transformations, a reasoning engine allowing the assessment of transformation likelihoods,[3] and a graphical interface allowing the entry of query structures and the display of prediction results. To arrive at a degradation prediction system, a number of major changes and extensions were carried out: support of bimolecular reactions (reactions between two query molecules), handling of reaction conditions including their manipulation by the reasoning engine, and the capability to perform a number of related predictions (*e.g.* with different reaction conditions) automatically. Last but not least, a knowledge base of chemical degradation transformations has been developed.

Zeneth predicts degradation under the influence of reaction conditions and optionally in the presence of other compounds such as excipients. Two of the main advantages of a system such as Zeneth are total recall and the absence of bias. A further major benefit is the steady accumulation of knowledge about degradation chemistry in an accessible form, which can also be a major asset in training. Zeneth is under continuous development, both in program functionality and in knowledge base content. Further information can be found at http://www.lhasalimited.org/zeneth/.

References

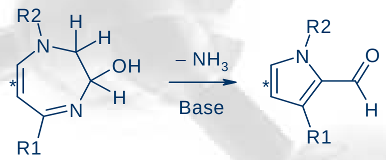
1. Marchant, C.A.; Briggs, K.A.; Long, A. *Toxicol. Mech. Methods* **2008**, 18, 177-187.
2. Balmat, A.-L.; Judson, P.; Long, A.; Testa, B. *Chem. Biodivers.* **2005**, 2, 872-885.
3. Button, W.G.; Judson, P.N.; Long, A.; Vessey, J.D. *J. Chem. Inf. Comput. Sci.* **2003**, 43, 1371-1377.

Membership

Zeneth development is currently sponsored by a collaborative group of five companies (Eli Lilly & Co, GlaxoSmithKline, Johnson & Johnson, Amgen and Pfizer). These members collaborate on the expansion of the knowledge base, sharing data and transforming confidential data into non-confidential knowledge. In addition, they co-direct development of the software. Further sponsors are welcome.

Methods

Patterns



R1 = aromatic carbon
R2 = hydrogen or carbon
The bond marked * is in an aromatic ring

Patterns define both the nature of the transformation and its scope.

Reasoning

Absolute reasoning is used to asses the likelihood of a transformation.

The likelihood levels are:

- Very likely
- Likely
- Equivocal
- Unlikely
- Very unlikely

Relative reasoning is used to assess competition between transformations.

Reaction conditions

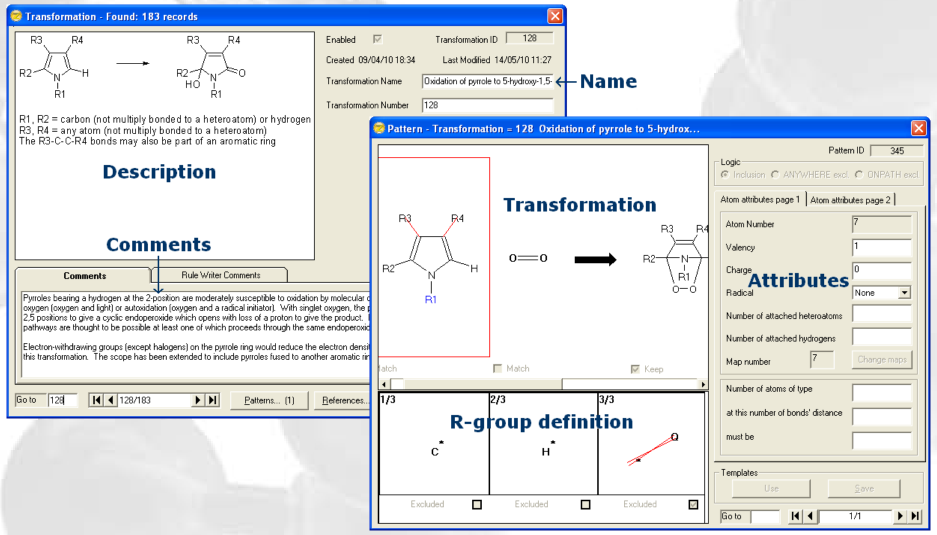
- Heat (temperature)
- Acid and base catalysis (pH)
- Hydrolysis (H_2O)
- Molecular oxygen (O_2)
- Peroxides (*e.g.* H_2O_2)
- Radical initiator (*e.g.* AIBN)
- Metal (Fe[III] or Cu[II])
- Photochemical (hν)

Temperature and pH are numerical.

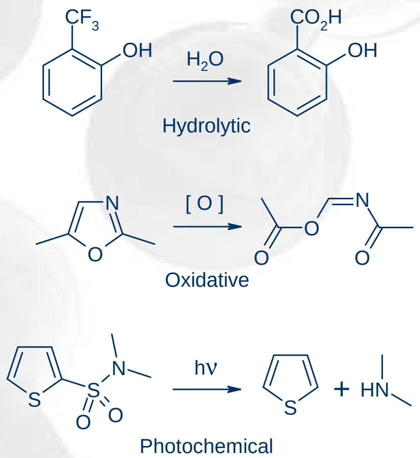
To predict degradation reactions, the system employs a knowledge base containing chemical patterns and reasoning rules. The user specifies the reaction conditions and then submits a query compound. For each pattern matching the query compound, the associated transformation will be applied. Its likelihood is assessed through reasoning rules, taking into account reaction conditions and alternative transformations.

Results

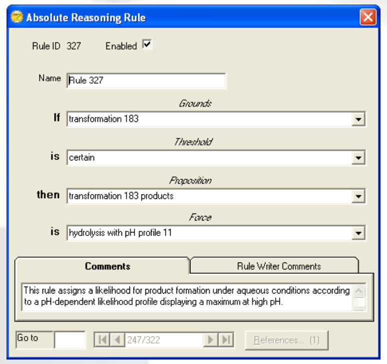
Knowledge base editor



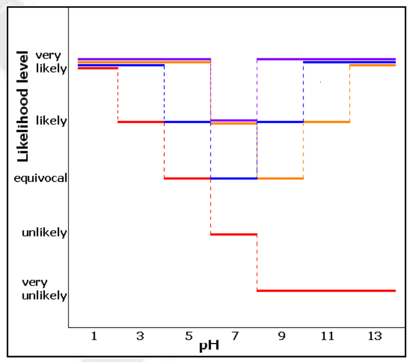
Sample degradation chemistry



Reasoning rule editor



Sample pH profiles



Knowledge base contents

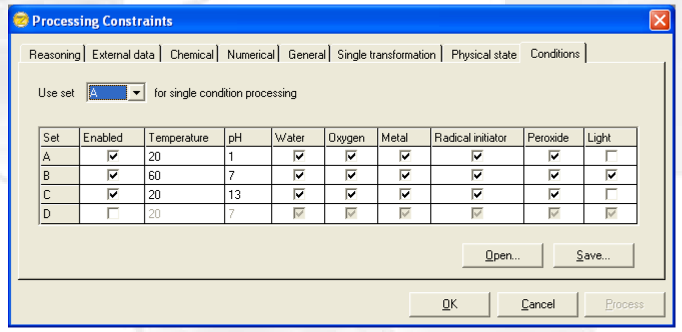
Numbers of transformations:

Hydrolyses	51
Oxidations	47
Additions	30
Eliminations	20
Isomerisations	21
Photolyses	14
Total	**183**

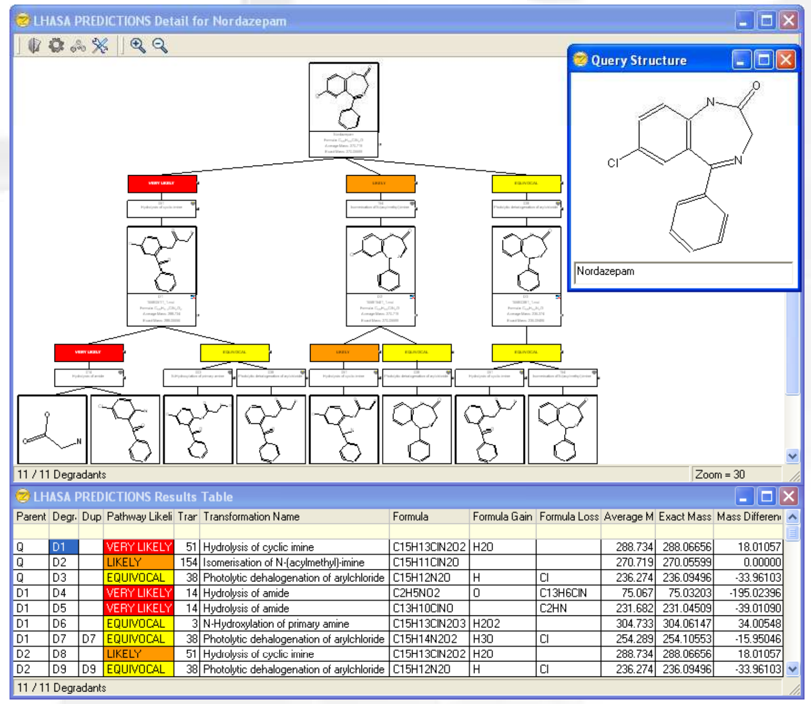
A chemical transformation is added through a dedicated knowledge base editor, allowing the entry of patterns, literature references and reasoning rules. For transformations depending on pH (commonly hydrolyses), their likelihood is expressed by reasoning rules in the form of a pH profile. Other transformations require specific conditions, *e.g.* oxygen; this is also expressed through rules. Principal knowledge sources are the primary chemical and pharmaceutical literature, chemistry textbooks and member expertise.

Results (continued)

Automatic processing

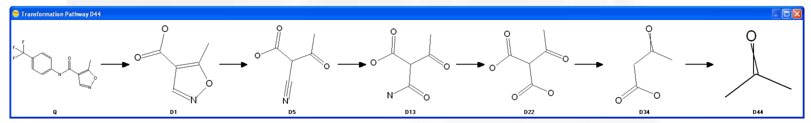


Prediction of results: tree diagram and table



Parent	Degr.	Dup	Pathway Likeli	Trar	Transformation Name	Formula	Formula Gain	Formula Loss	Average M	Exact Mass	Mass Differen
Q	D1		VERY LIKELY	51	Hydrolysis of cyclic imine	C15H13ClN2O2	H2O		288.734	288.06656	18.01057
Q	D2		LIKELY	154	Isomerisation of N-(acylmethyl)-imine	C15H11ClN2O			270.719	270.05599	0.00000
Q	D3		EQUIVOCAL	38	Photolytic dehalogenation of arylchloride	C15H12N2O	H	Cl	236.274	236.09496	-33.96103
D1	D4		VERY LIKELY	14	Hydrolysis of amide	C2H5NO2	O	C13H6ClN	75.067	75.03203	-195.02396
D1	D5		VERY LIKELY	14	Hydrolysis of amide	C13H10ClNO		C2HN	231.682	231.04509	-39.01090
D1	D6		EQUIVOCAL	3	N-Hydroxylation of primary amine	C15H13ClN2O3	H2O2		304.733	304.06147	34.00548
D1	D7	D7	EQUIVOCAL	38	Photolytic dehalogenation of arylchloride	C15H14N2O2	H3O	Cl	254.289	254.10553	-15.95046
D2	D8		LIKELY	51	Hydrolysis of cyclic imine	C15H13ClN2O2	H2O		288.734	288.06656	18.01057
D2	D9	D9	EQUIVOCAL	38	Photolytic dehalogenation of arylchloride	C15H12N2O	H	Cl	236.274	236.09496	-33.96103

Prediction of results: pathway



Multiple predictions can be made automatically in batch mode, *e.g.* using different conditions. Prediction results are presented as trees, with additional data (molecular masses and formulas) listed in a table. Structures and pathways can be expanded. Various types of reports can be generated (*e.g.* Excel, SDFile).

Conclusion

Zeneth is an expert system for the prediction of chemical degradation. It employs a knowledge base of patterns and reasoning rules to suggest the most likely reactions under various conditions. Current work is focused on the development of the knowledge base to increase the sensitivity and selectivity of the predictions.