



In silico predictions of N-nitrosamines: likelihood, mechanism, and real-world examples

Dr Jonathan Lockett

Scientist

jonathan.lockett@lhasalimited.org



Introduction



- Knowledge-based *in silico* predictions of degradants
- Uses **transformations** to convert an API (or reactant) into a degradant
- N-Nitrosamine transformations have recently been added into Zeneth's knowledge base

What is a transformation?

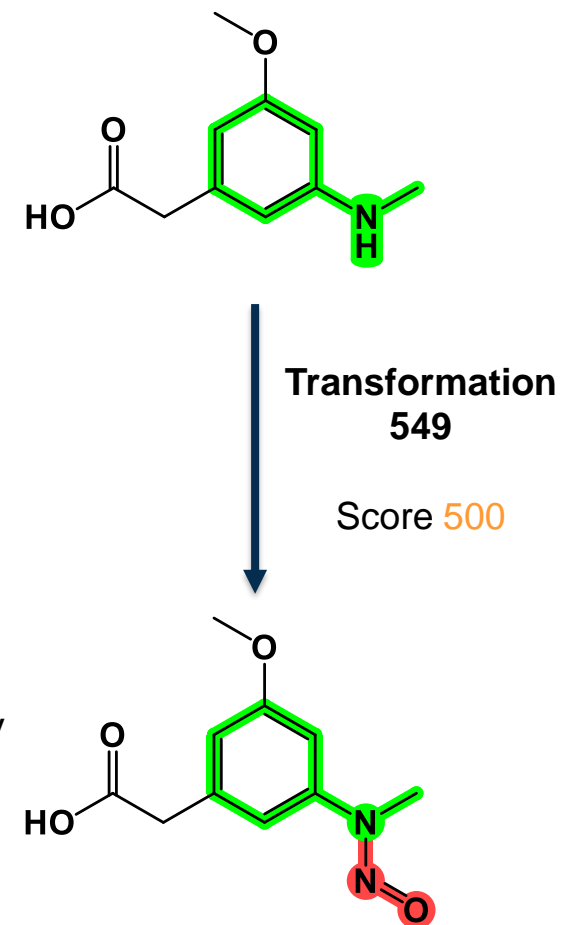
- Zeneth matches an API to relevant transformations through structure-matching

1. Knowledge base containing all transformations



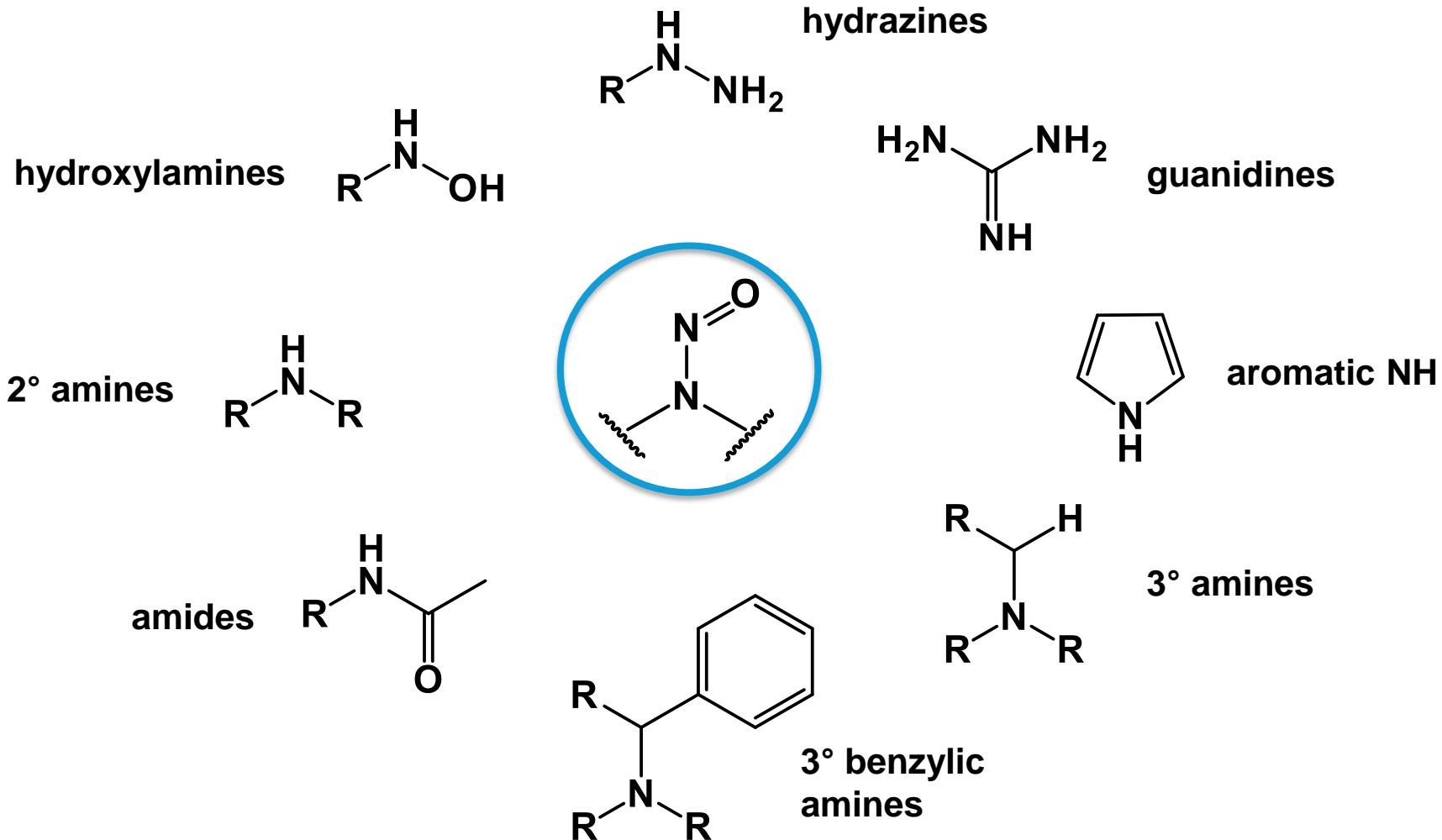
2. Query API matches relevant transformations

3. Transformation performs chemistry and generates a degradant



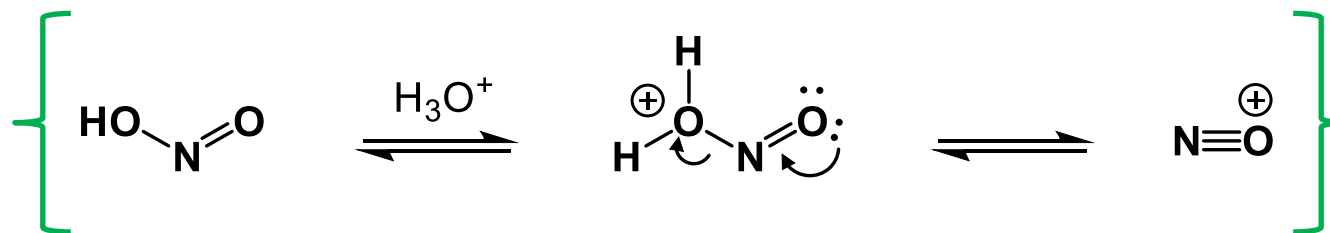
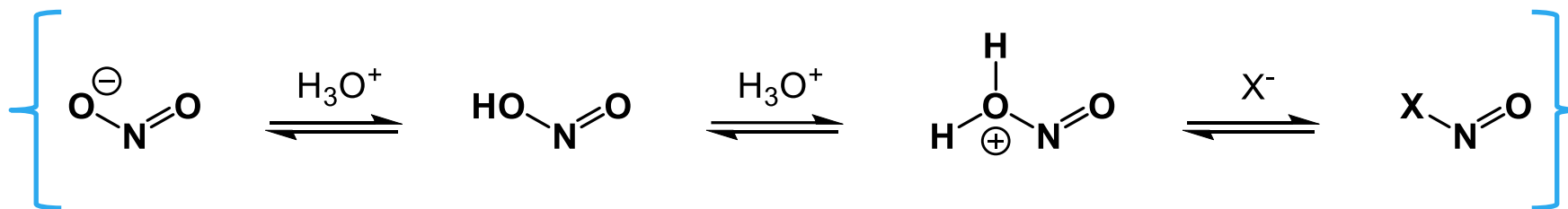
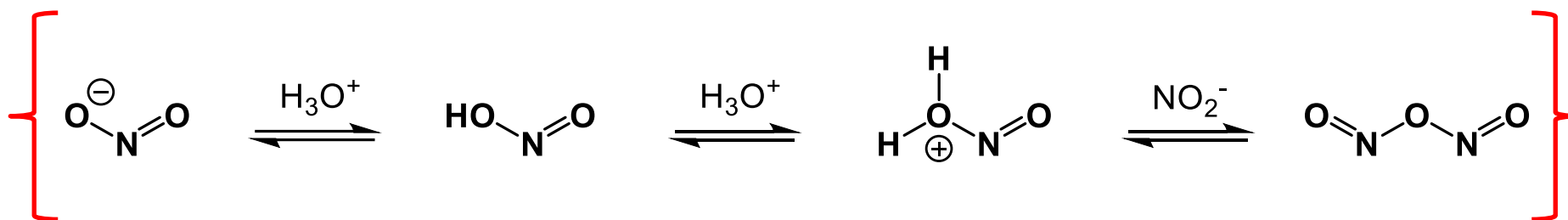
N-Nitrosation transformations

- Zeneth contains 8 transformations that predict the formation of N-nitrosamines

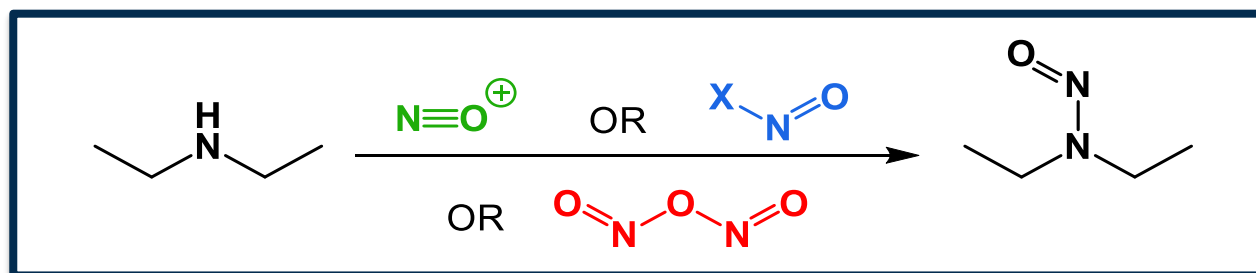


Mechanism of N-nitrosamine formation

Nitrites and acidic media are the best known reagents for N-nitrosation reactions



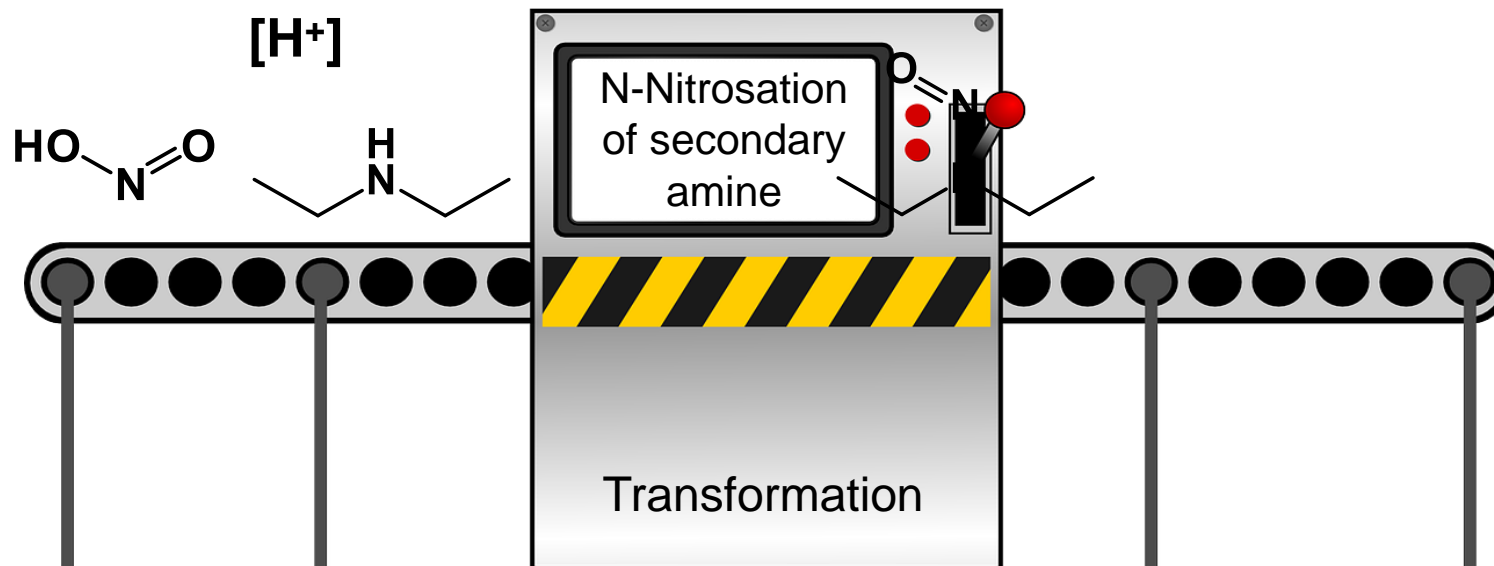
[HNO ₂]	pH	Other Nu?
High	< -0.6	No
High	> -0.6	No
All	Acidic	Yes



How to fire a N-nitrosamine transformation and score

How can you see these N-nitrosation transformations in Zeneth?

- You'll need a vulnerable amine (see earlier slide for scope)
- Nitrous acid
- Acidic pH



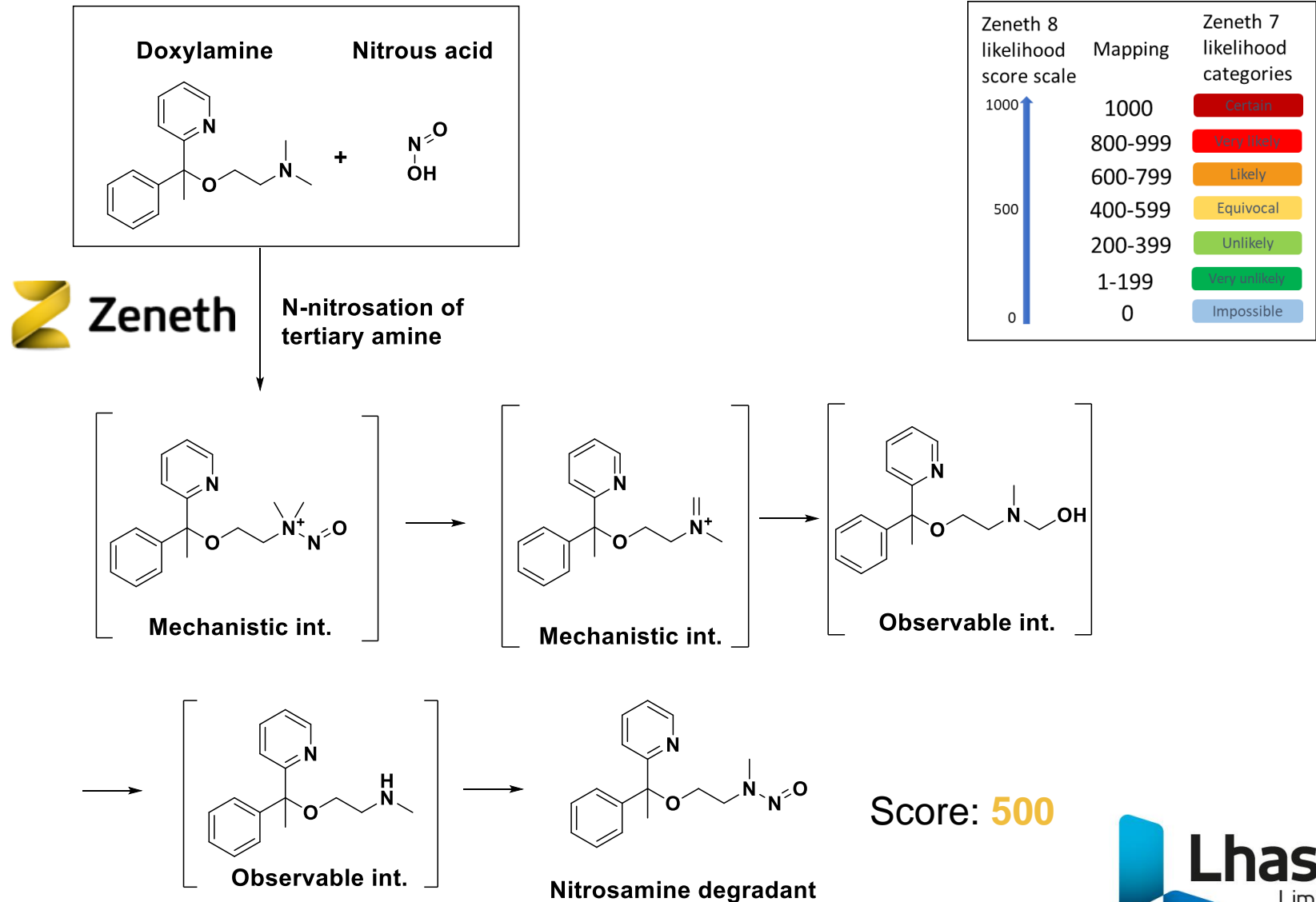
Score: 700

Zeneth 8 likelihood score scale	Mapping	Zeneth 7 likelihood categories
1000	1000	Certain
	800-999	Very likely
	600-799	Likely
500	400-599	Equivocal
	200-399	Unlikely
	1-199	Very unlikely
0	0	Impossible

Case study: Doxylamine

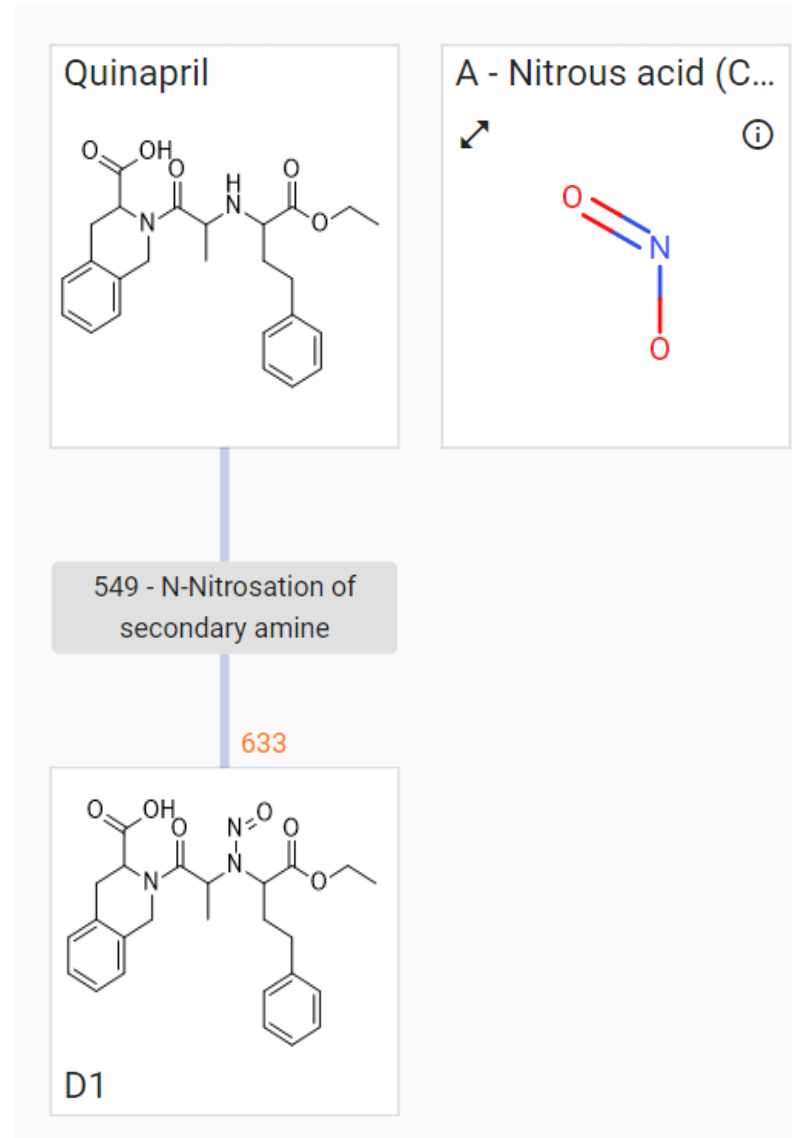
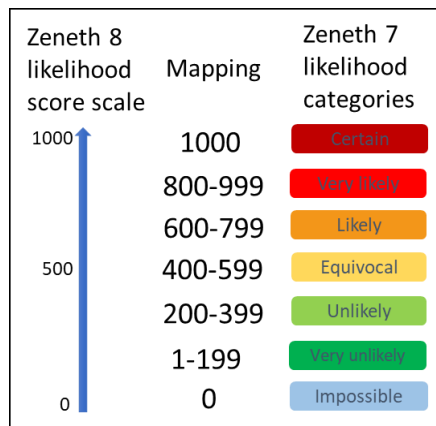
Doxylamine – acts as an antihistamine and treats short-term insomnia

It contains a tertiary amine, which proceeds through a different mechanism to secondary amines – this information is found within Zeneth



Case study: Quinapril

- Quinapril has been highlighted by the FDA as having potential nitrosamine issues
- Contains a secondary amine
- Nitrosamine formation will be predicted by Zeneth in the presence of nitrous acid
- Score 633 (2° amine) is higher than that of Doxylamine (3° amine, score 500)



Conclusion

- Zeneth will predict the N-nitrosation of various nitrogen-containing groups
- The mechanism by which they form is visible within Zeneth
- The likelihood of N-nitrosation depends on the nature of the amine group and is reflected by their predicted likelihood score

Thanks for listening!