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QSAR Models to Anticipate the Degradation of Common Chemical Functional Groups

K. Reiss and S. Chakravarti
MultiCASE Inc., Mayfield Heights, OH

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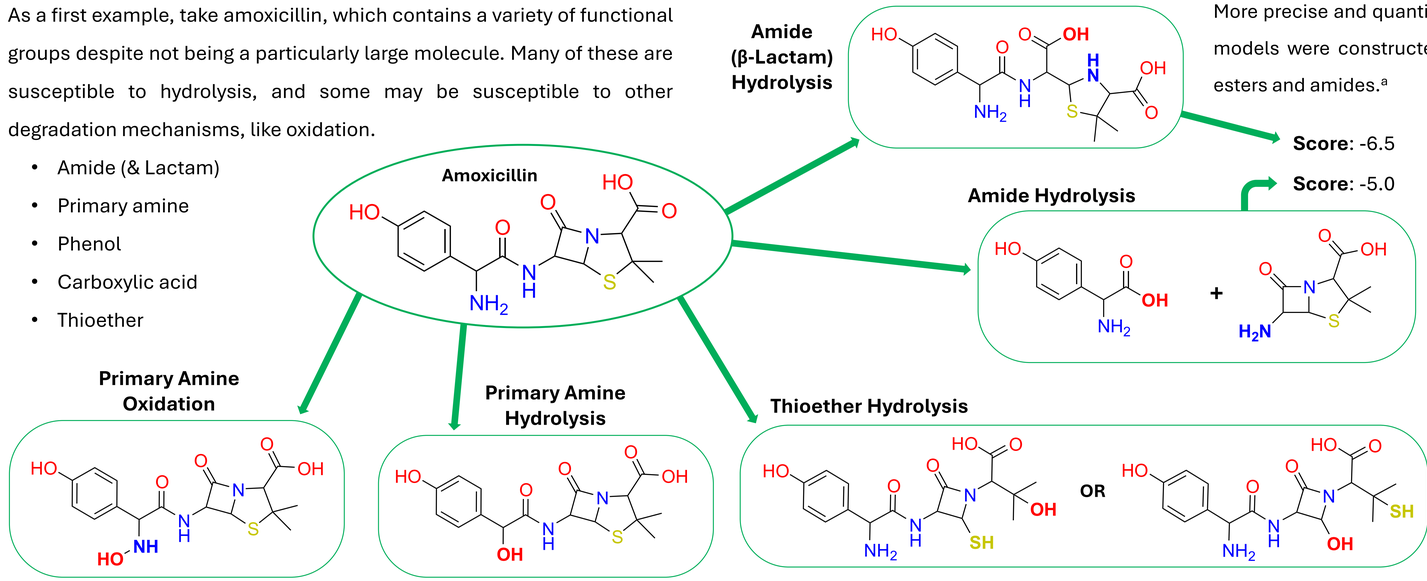
Background & Purpose

When determining the toxicity of pharmaceuticals and other chemical products, significant consideration must go towards the presence of impurities, some of which can form spontaneously through degradation as chemicals sit in storage. Degradation can be catalyzed by external factors, such as pH, and structural factors, such as the presence of a β-hydrogen. Which factors have an effect depends on both the degradation mechanism (hydrolysis vs. oxidation) and the parent functional group (ether vs. amide). Our goal is to create a tool to automatically predict possible degradation products for any small molecule and to ideally also predict the likelihood or rate of that reaction.

Example 1: Amoxicillin

As a first example, take amoxicillin, which contains a variety of functional groups despite not being a particularly large molecule. Many of these are susceptible to hydrolysis, and some may be susceptible to other degradation mechanisms, like oxidation.

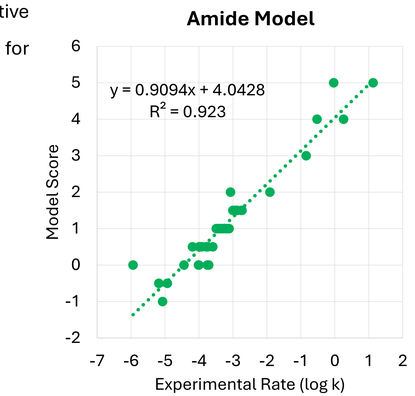
- Amide (& Lactam)
- Primary amine
- Phenol
- Carboxylic acid
- Thioether



More precise and quantitative models were constructed for esters and amides.[a]

Score: -6.5

Score: -5.0



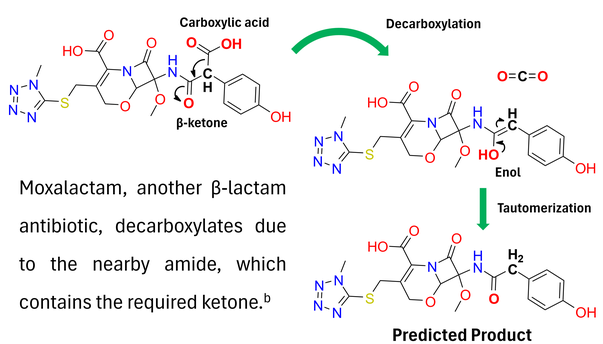
Some groups, like thioethers, may have two or more possible outcomes. A more detailed model is required to determine which is more likely.

Methods

For all functional groups, degradation products are automatically generated based on the appropriate mechanism for each parent group. If a functional group's degradation is dependent on a secondary feature, such as a β-hydrogen, that is taken into account when determining how the molecule will degrade. If a more precise QSAR model was created for that functional group and mechanism (dependent on sufficient experimental data), the rate-based score is reported. Only first-level products are currently predicted, but these could also break down.

Example 2: Moxalactam

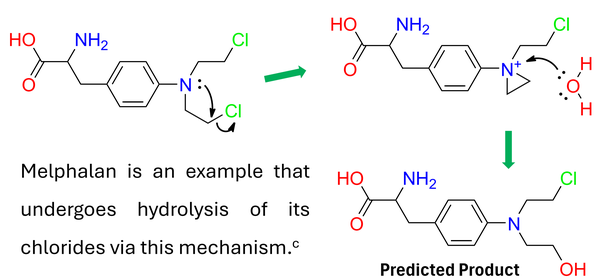
The degradation pathways of some functional groups require a secondary feature. For carboxylic acid, it can be cleaved if a β-ketone is present, which forms an enol intermediate.



Moxalactam, another β-lactam antibiotic, decarboxylates due to the nearby amide, which contains the required ketone.[b]

Example 3: Melphalan

Halides can be hydrolyzed and are made more labile by a nitrogen or sulfur attached to the β-carbon, making that an activating feature. The heteroatom's lone pair can attack the electrophilic α-carbon to form a cyclized intermediate.



Melphalan is an example that undergoes hydrolysis of its chlorides via this mechanism.[c]

Conclusions

- If sufficient data is available, precise quantitative models can be made based on simple rules.
- With more limited data, basic features or yes/no rules can make qualitative structure predictions.
- 2nd-level degradants will be predicted using the same rules, but degradants may also react with one another, creating new pathways to consider.

References

a) Mabey W and Mill T. Critical review of hydrolysis of organic compounds in water under environmental conditions. *J. Phys. Chem. Ref. Data*. Vol 7. **1978**:400.
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e) Li M. *Organic Chemistry of Drug Degradation*. Cambridge: The Royal Society of Chemistry, **2012**:16.