Degradation Plot

Prediction of degradation products and pathways

Report

Client:
Altox

Username:
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Study Number:
Altox_Metamizole_DegradationPlot_20230918170923

Date:
2023/09/18 - 17:09:26

Program Version:
1.3.3

Molecular Query

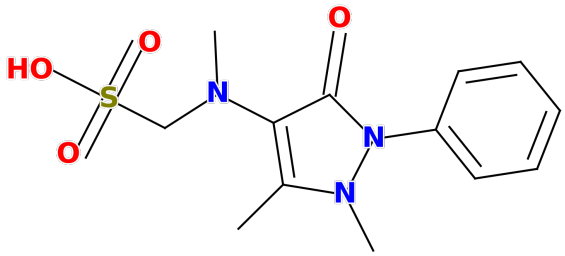
Name:
Metamizole

CAS:
50567-35-6

Exact Mass:
311.09397721

Common Name:
Metamizole

Iupac Name:
[(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)-methylamino]methanesulfonic acid



CID:
3111

SMILES:
CC1N(C)N(C2C=CC=CC=2)C(=O)C=1N(CS(O)(=O)=O)C

Model Summary

The critical analysis for drug degradation is the step before the practical experimentation and comprehends bibliographic search, evaluation of the possible drug degradation pathways, and in silico predictions. The drugs, usually, have one or more functional groups that are susceptible to different degradation processes, thereby the Degradation Plot is a knowledge-based tool for drug degradation prediction. In other words, it uses templates to search for the possible degradation products. This tool uses an iterative process in that the degradation products of one iteration are the input to the next - called here as "Degradation Steps".

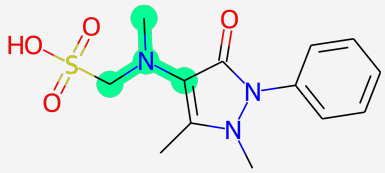
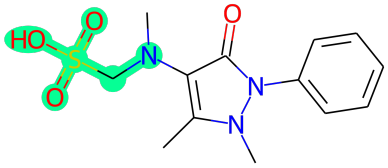
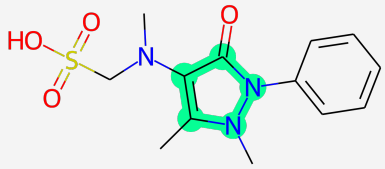
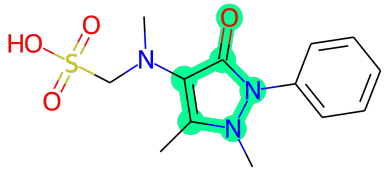
The Degradation Plot currently contains 132 distinct reactions for 60 labile groups, some of which are quite complex, such as dimerization, ring opening/formation, and 2+2 addition. Therefore, this application tends to be an all inclusive list of every degradation product that can actually be observed in stability studies. Due to the fact that the amount of products generated increases exponentially for some molecules, only two degradation steps will be performed; additionally, for certain alkenes reactions, only one degradation step will be evaluated.

In this report, five sections were created from results of the degradation reactions generated by Degradation Plot. Section model 1 highlights the reactive group and gives basic information, whereas the next section provides more thorough information about each functional group. Section model 2 shows statistics of the reactions and products generated, such as the amount of products formed in each degradation step and also the amount of reactions that each functional group performed. Section model 3 brings in a table all the degradation products formed, along with their respective labels and reaction conditions, while the overview section shows a general diagram of all starting molecules and their degradation

products.

Model 1 - Map of fragments susceptible to degradation

The result below refers to the groups susceptible to degradation reaction found in our knowledge-based, including the name and brief information about each labile group.

Molecule	Susceptible Fragments	Conditions and degradation pathways
	tertiary amine	Aliphatic amines are subject to simple acid and base-catalyzed hydrolysis to the resulting hydroxyl compound or elimination to form a double bond. When amines are unprotonated, they are nucleophilic, more easily oxidized.
	sulfenic acid next to amine or oxygen	This group can undergo a hydrolysis reaction resulting in the elimination of the sulfenic group or substitution by OH.
	pyrazole and derivatives	The pyrazole and derivatives can be hydrolyzed to corresponding hydroxides.
	pyrazole and derivatives next to carbonyl	The carbonyl of this group can be hydrolyzed to the respective diol as an intermediate, followed by a ring opening reaction.

Details about fragments susceptible to degradation

Tertiary amine

Amines are a very common functional group in pharmaceuticals and are prone to a variety of degradation reactions. Amines can be primary, secondary, or tertiary, aryl or alkyl. Aliphatic amines are subject to simple acid and base-catalyzed hydrolysis to the resulting hydroxyl compound or elimination to form a double bond. In either case, ammonia is eliminated from the API. When amines are unprotonated (i.e., in the neutral “free base” form), they are nucleophilic, more easily oxidized, and more volatile. Primary and secondary amines are nucleophilic and will react readily with electrophiles such as aldehydes (as present in excipients such as glucose, lactose, etc.) to undergo the first steps of the Maillard reaction. Amines may also react with trace levels of formaldehyde (or other aldehydes adventitiously present) to form hemiaminals with the potential for dehydration to imines and/or cross-linking with other amines or nucleophiles.[1-15]

Sulfenic acid next to amine or oxygen

There are multiple oxidative mechanisms for the oxidation of thiols. First, thiols react with peroxide to form sulfenic, sulfinic, and sulfonic acids, as well as disulfides and thiosulfinate. These reactions are accelerated under basic conditions.[16,17]

Pyrazole and derivatives and Pyrazole and derivatives next to carbonyl

Pyrazole and derivatives can undergo hydrolysis reactions in acidic media to form the respective hydroxides and also a possible ring opening reaction. In some intermediates, oxidation to pyrazole-linked amines may occur to form formamides.

Model 2 - Statistical Information about Degradation Reactions

The result below provides statistical information based on the forced degradation reactions and this analyses cover the following degradation conditions: hydrolysis, oxidation, heating and photolysis. On the cards, the total number of degradation products generated, the number of different functional groups that reacted in both degradation steps, and the number of degradation steps performed are all visualised respectively. Figure 1 shows the amount of compounds generated in each degradation step, which can be proportional to the amount of groups susceptible to react. Figure 2 illustrates the number of reactions that each labile group performed in the degradation step 1 and 2, it can be an alert about which functional group should be more attentive when evaluating possible experiments. Figure 3 indicates the number of reactions that occurred throughout each degradation step; this number can be an indication to determine the type of reaction that will occur preferably in a reaction medium.

Deg. Products:	Func. Groups:	Steps:
52	13	2

Figure 1 - Quantity of products generated by degradation steps

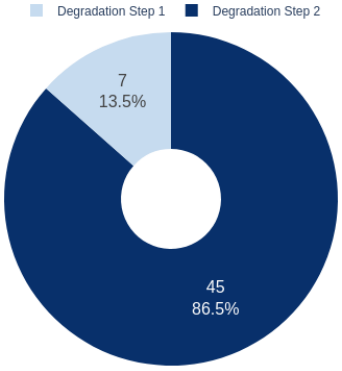


Figure 2 - Number of reactions by functional groups in each degradation step.

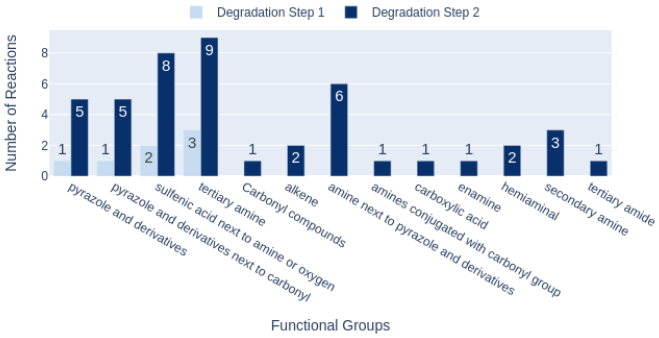
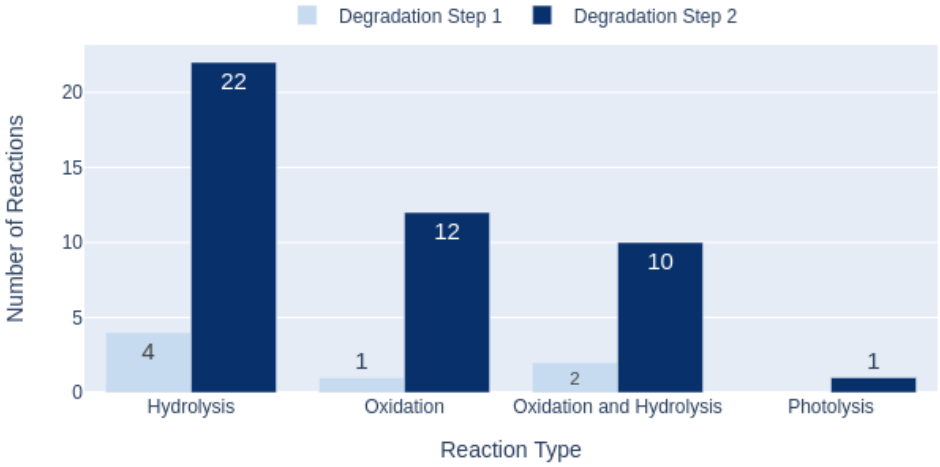


Figure 3 - Number of reaction conditions in each degradation step.



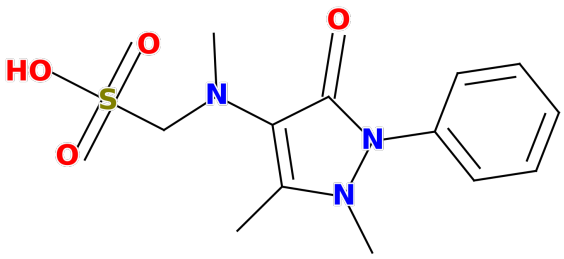
Model 3 - Degradation Steps

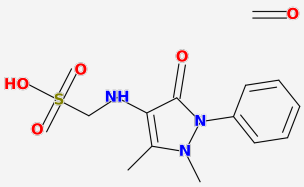
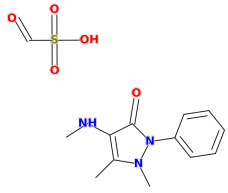
The results presented in the tables refer to the degradation products of the molecule centered before each table. All degradation product generated will be labelled with the type DP-X-Y, where X indicates the degradation step in which the product was formed and Y represents the product's number. The products generated during the reaction of specific alkenes will be labelled Alkenes-X, where X is the compound's number. Although the code for each produced product is unique, it is possible for a specific degradation product to be formed multiple times via distinct pathways. Certain reactions may produce two or more components, in this case, the products will be reported in the same SMILES code separated by dots.

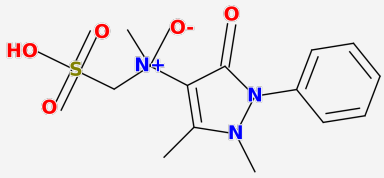
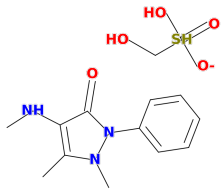
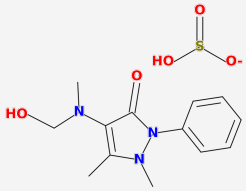
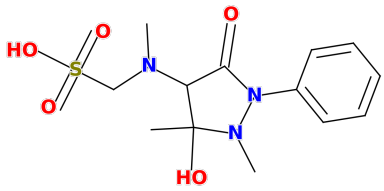
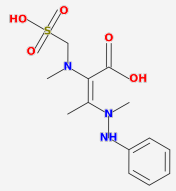
These reactions are classified based on specialists knowledge considering the chemoselectivity and lability of functional groups and stress conditions to be accessed, taking into account activation energy required for the reactants to proceed and producing the degradation product[18-24]. In this way, the reactions are classified as probable, Expect, Rare and improbable.

Showing all reactions with all likelihoods.

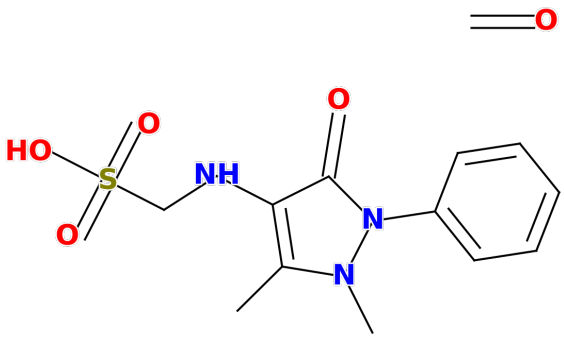
Degradation Step 1 - Input

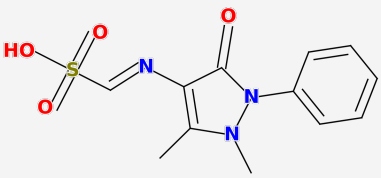
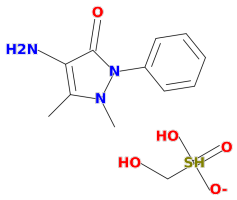
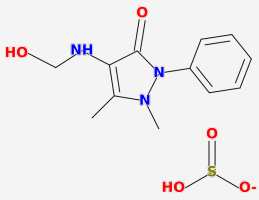


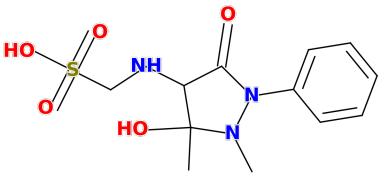
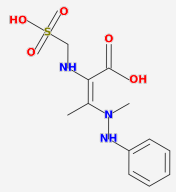
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 C=O.Cc1c(NCS(=O)(=O)O)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (712) Already Reported - PubChem (19145)	DP-1-1	30.01056 297.07833	CH_2O $C_{12}H_{15}N_3O_4S$	Oxidation and Hydrolysis	Probable
 CNc1c(C)n(C)n(-c2ccccc2)c1=O.O=CS(=O)(=O)O Already Reported - PubChem (10618) Already Reported - PubChem (13180177)	DP-1-2	217.12151 109.96738	$C_{12}H_{15}N_3O$ CH_2O_4S	Oxidation and Hydrolysis	Probable

Product	Name	Mass	Formula	Condition	Reaction Likelihood
 Cc1c([N+](C)([O-])CS(=O)(=O)O)c(=O)n(-c2ccccc2)n1C	DP-1-3	327.08889	$C_{13}H_{17}N_3O_5S$	Oxidation	Probable
 CNc1c(C)n(C)n(-c2ccccc2)c1=O.O=[SH]([O-])(O)CO	DP-1-4	217.12151 112.9914	$C_{12}H_{15}N_3O$ CH_5O_4S-	Hydrolysis	Probable
 Cc1c(N(C)CO)c(=O)n(-c2ccccc2)n1C.O=S([O-])O Already Reported - PubChem (6428562) Already Reported - PubChem (104748)	DP-1-5	247.13208 80.96519	$C_{13}H_{17}N_3O_2$ HO_3S-	Hydrolysis	Probable
 CN(CS(=O)(=O)O)C1C(=O)N(c2ccccc2)N(C)C1(C)O	DP-1-6	329.10454	$C_{13}H_{19}N_3O_5S$	Hydrolysis	Expected
 CC(=C(C(=O)O)N(C)CS(=O)(=O)O)N(C)Nc1ccccc1	DP-1-7	329.10454	$C_{13}H_{19}N_3O_5S$	Hydrolysis	Expected

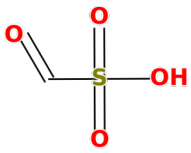
Degradation Step 2 - DP-1-1

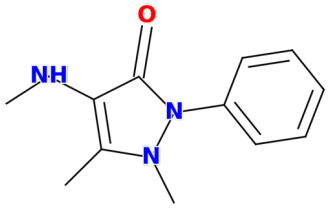


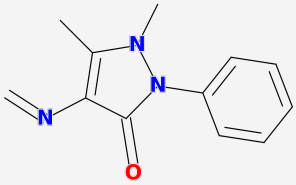
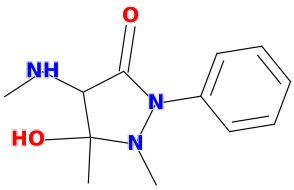
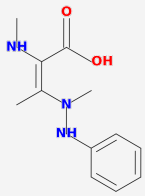
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 Cc1c(N=CS(=O)(=O)O)c(=O)n(-c2ccccc2)n1C	DP-2-1	295.06268	$C_{12}H_{13}N_3O_4S$	Oxidation	Probable
 Cc1c(N)c(=O)n(-c2ccccc2)n1C.O=[SH]([O-])(O)CO	DP-2-2	203.10586 112.9914	$C_{11}H_{13}N_3O$ CH_5O_4S-	Hydrolysis	Probable
 Cc1c(NCO)c(=O)n(-c2ccccc2)n1C.O=S([O-])O Already Reported - PubChem (296277) Already Reported - PubChem (104748)	DP-2-3	233.11643 80.96519	$C_{12}H_{15}N_3O_2$ HO_3S-	Hydrolysis	Probable

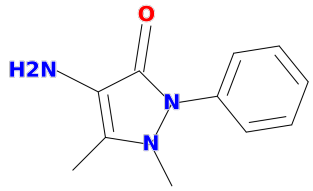
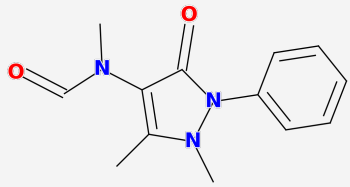
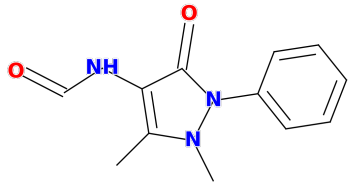
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CN1N(c2ccccc2)C(=O)C(NCS(=O)(=O)O)C1(C)O	DP-2-4	315.08889	$C_{12}H_{17}N_3O_5S$	Hydrolysis	Expected
 CC(=C(NCS(=O)(=O)O)C(=O)O)N(C)Nc1ccccc1	DP-2-5	315.08889	$C_{12}H_{17}N_3O_5S$	Hydrolysis	Expected

Degradation Step 2 - DP-1-2

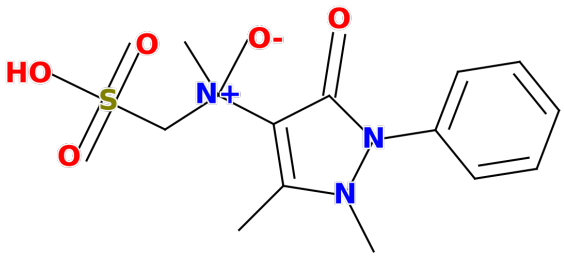


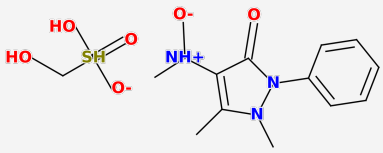
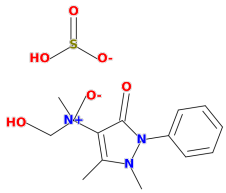
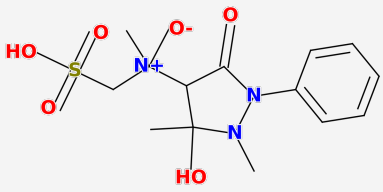
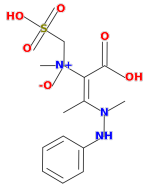


Product	Name	Mass	Formula	Condition	Reaction Likelihood
 C=Nc1c(C)n(C)n(-c2ccccc2)c1=O Already Reported - PubChem (10036222)	DP-2-6	215.10586	$C_{12}H_{13}N_3O$	Oxidation	Probable
 CNC1C(=O)N(c2ccccc2)N(C)C1(C)O	DP-2-7	235.13208	$C_{12}H_{17}N_3O_2$	Hydrolysis	Expected
 CNC(C(=O)O)=C(C)N(C)Nc1ccccc1	DP-2-8	235.13208	$C_{12}H_{17}N_3O_2$	Hydrolysis	Expected

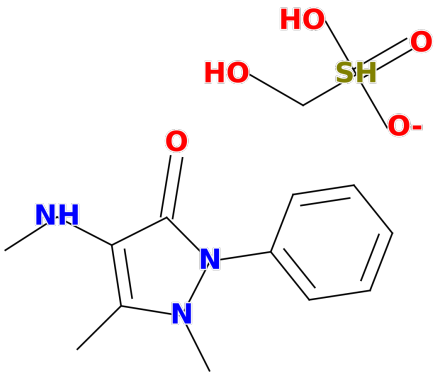
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 Cc1c(N)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (2151)	DP-2-9	203.10586	$C_{11}H_{13}N_3O$	Oxidation	Expected
 Cc1c(N(C)C=O)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (13020513)	DP-2-10	245.11643	$C_{13}H_{15}N_3O_2$	Oxidation and Hydrolysis	Probable
 Cc1c(NC=O)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (72666)	DP-2-11	231.10078	$C_{12}H_{13}N_3O_2$	Oxidation and Hydrolysis	Probable

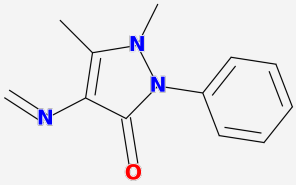
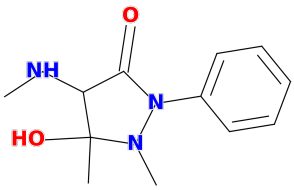
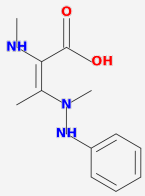
Degradation Step 2 - DP-1-3

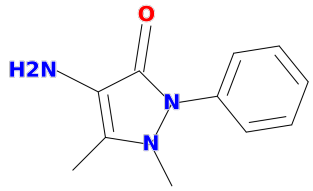
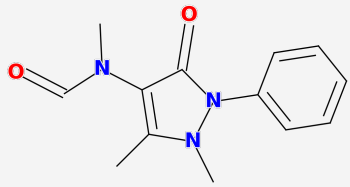
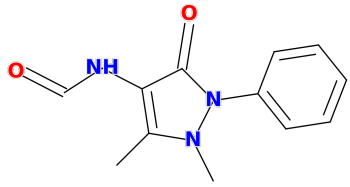


Product	Name	Mass	Formula	Condition	Reaction Likelihood
 Cc1c([NH+](C)[O-])c(=O)n(-c2ccccc2)n1C.O=[SH]([O-])(O)CO	DP-2-12	233.11643 112.9914	$C_{12}H_{15}N_3O_2$ CH_5O_4S-	Hydrolysis	Probable
 Cc1c([N+](C)([O-])CO)c(=O)n(-c2ccccc2)n1C.O=S([O-])O	DP-2-13	263.12699 80.96519	$C_{13}H_{17}N_3O_3$ HO_3S-	Hydrolysis	Probable
 CN1N(c2ccccc2)C(=O)C([N+](C)([O-])CS(=O)(=O)O)C1(C)O	DP-2-14	345.09946	$C_{13}H_{19}N_3O_6S$	Hydrolysis	Expected
 CC(=C(C(=O)O)[N+](C)([O-])CS(=O)(=O)O)N(C)Nc1ccccc1	DP-2-15	345.09946	$C_{13}H_{19}N_3O_6S$	Hydrolysis	Expected

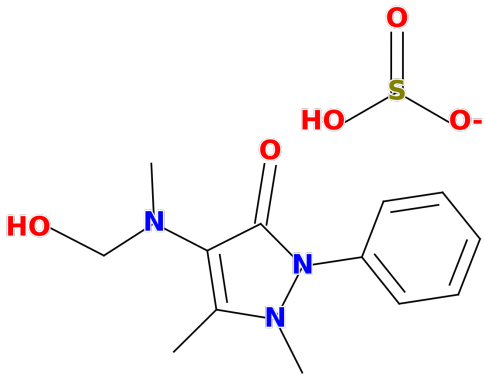
Degradation Step 2 - DP-1-4

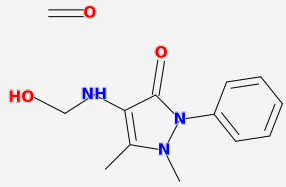
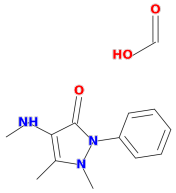
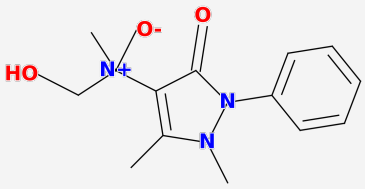


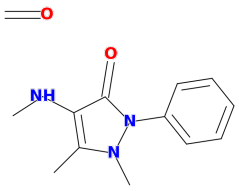
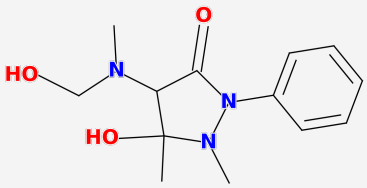
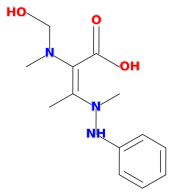
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 C=Nc1c(C)n(C)n(-c2ccccc2)c1=O Already Reported - PubChem (10036222)	DP-2-16	215.10586	$C_{12}H_{13}N_3O$	Oxidation	Probable
 CNC1C(=O)N(c2ccccc2)N(C)C1(C)O	DP-2-17	235.13208	$C_{12}H_{17}N_3O_2$	Hydrolysis	Expected
 CNC(C(=O)O)=C(C)N(C)Nc1ccccc1	DP-2-18	235.13208	$C_{12}H_{17}N_3O_2$	Hydrolysis	Expected

Product	Name	Mass	Formula	Condition	Reaction Likelihood
 Cc1c(N)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (2151)	DP-2-19	203.10586	$C_{11}H_{13}N_3O$	Oxidation	Expected
 Cc1c(N(C)C=O)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (13020513)	DP-2-20	245.11643	$C_{13}H_{15}N_3O_2$	Oxidation and Hydrolysis	Probable
 Cc1c(NC=O)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (72666)	DP-2-21	231.10078	$C_{12}H_{13}N_3O_2$	Oxidation and Hydrolysis	Probable

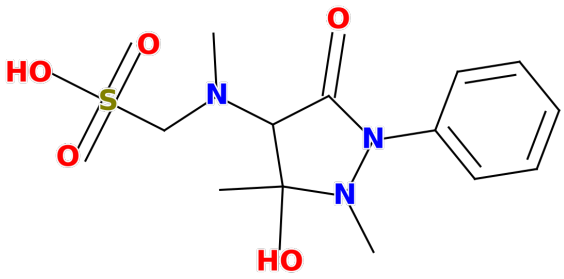
Degradation Step 2 - DP-1-5

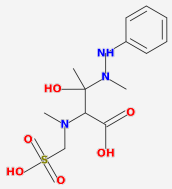
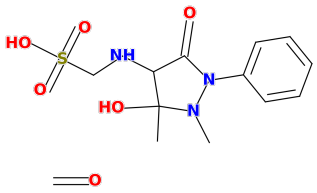
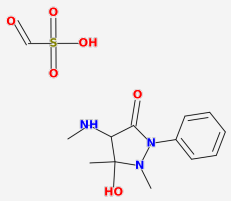
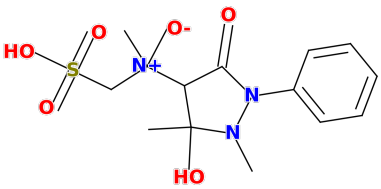


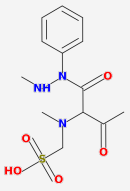
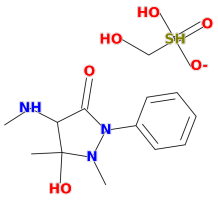
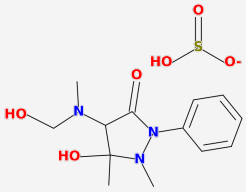
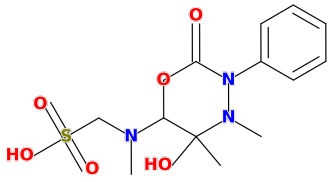
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 C=O.Cc1c(NCO)c(=O)n(-c2ccccc2)n1C Already Reported - PubChem (712) Already Reported - PubChem (296277)	DP-2-22	30.01056 233.11643	CH_2O $C_{12}H_{15}N_3O_2$	Oxidation and Hydrolysis	Probable
 CNc1c(C)n(C)n(-c2ccccc2)c1=O.O=CO Already Reported - PubChem (10618) Already Reported - PubChem (284)	DP-2-23	217.12151 46.00548	$C_{12}H_{15}N_3O$ CH_2O_2	Oxidation and Hydrolysis	Probable
 Cc1c([N+](C)([O-])CO)c(=O)n(-c2ccccc2)n1C	DP-2-24	263.12699	$C_{13}H_{17}N_3O_3$	Oxidation	Probable

Product	Name	Mass	Formula	Condition	Reaction Likelihood
 C=O.CNc1c(C)n(C)n(-c2ccccc2)c1=O Already Reported - PubChem (712) Already Reported - PubChem (10618)	DP-2-25	30.01056 217.12151	CH_2O $C_{12}H_{15}N_3O$	Hydrolysis	Probable
 CN(CO)C1C(=O)N(c2ccccc2)N(C)C1(C)O	DP-2-26	265.14264	$C_{13}H_{19}N_3O_3$	Hydrolysis	Expected
 CC(=C(C(=O)O)N(C)CO)N(C)Nc1ccccc1	DP-2-27	265.14264	$C_{13}H_{19}N_3O_3$	Hydrolysis	Expected

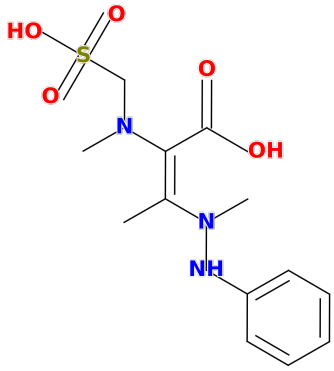
Degradation Step 2 - DP-1-6

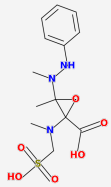
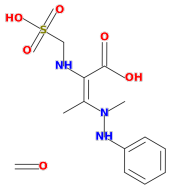
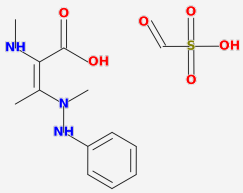


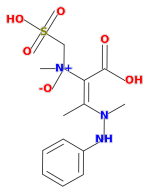
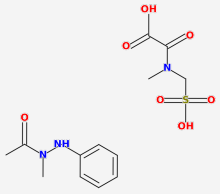
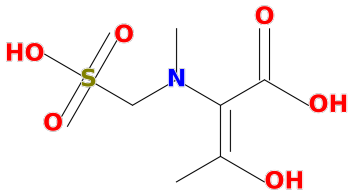
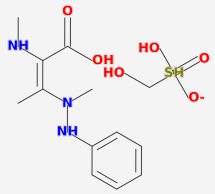
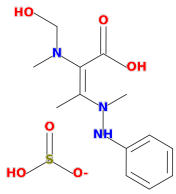
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CN(CS(=O)(=O)O)C(C(=O)O)C(C)(O)N(C)Nc1ccccc1	DP-2-28	347.11511	$C_{13}H_{21}N_3O_6S$	Hydrolysis	Probable
 C=O.CN1N(c2ccccc2)C(=O)C(NCS(=O)(=O)O)C1(C)O	DP-2-29	30.01056 315.08889	CH_2O $C_{12}H_{17}N_3O_5S$	Oxidation and Hydrolysis	Probable
 CNC1C(=O)N(c2ccccc2)N(C)C1(C)O.O=CS(=O)(=O)O	DP-2-30	235.13208 109.96738	$C_{12}H_{17}N_3O_2$ CH_2O_4S	Oxidation and Hydrolysis	Probable
 CN1N(c2ccccc2)C(=O)C([N+](C)([O-])CS(=O)(=O)O)C1(C)O	DP-2-31	345.09946	$C_{13}H_{19}N_3O_6S$	Oxidation	Probable

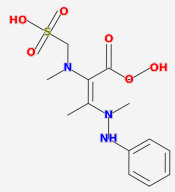
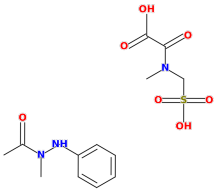
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CNN(C(=O)C(C(C)=O)N(C)CS(=O)(=O)O)c1ccccc1	DP-2-32	329.10454	$C_{13}H_{19}N_3O_5S$	Hydrolysis	Probable
 CNC1C(=O)N(c2ccccc2)N(C)C1(C)O.O=[SH]([O-])(O)CO	DP-2-33	235.13208 112.9914	$C_{12}H_{17}N_3O_2$ CH_5O_4S-	Hydrolysis	Probable
 CN(CO)C1C(=O)N(c2ccccc2)N(C)C1(C)O.O=S([O-])O	DP-2-34	265.14264 80.96519	$C_{13}H_{19}N_3O_3$ HO_3S-	Hydrolysis	Probable
 CN(CS(=O)(=O)O)C1OC(=O)N(c2ccccc2)N(C)C1(C)O	DP-2-35	345.09946	$C_{13}H_{19}N_3O_6S$	Oxidation	Expected

Degradation Step 2 - DP-1-7



Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CN(Nc1ccccc1)C1(C)OC1(C(=O)O)N(C)CS(=O)(=O)O	DP-2-36	345.09946	$C_{13}H_{19}N_3O_6S$	Oxidation	Expected
 C=O.CC(=C(NCS(=O)(=O)O)C(=O)O)N(C)Nc1ccccc1	DP-2-37	30.01056 315.08889	CH_2O $C_{12}H_{17}N_3O_5S$	Oxidation and Hydrolysis	Probable
 CNC(C(=O)O)=C(C)N(C)Nc1ccccc1.O=CS(=O)(=O)O	DP-2-38	235.13208 109.96738	$C_{12}H_{17}N_3O_2$ CH_2O_4S	Oxidation and Hydrolysis	Probable

Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CC(=C(C(=O)O)[N+](C)([O-])CS(=O)(=O)O)N(C)Nc1ccccc1	DP-2-39	345.09946	$C_{13}H_{19}N_3O_6S$	Oxidation	Probable
 CC(=O)N(C)Nc1ccccc1.CN(CS(=O)(=O)O)C(=O)C(=O)O	DP-2-40	164.09496 196.99941	$C_9H_{12}N_2O$ $C_4H_7NO_6S$	Oxidation	Expected
 CC(O)=C(C(=O)O)N(C)CS(=O)(=O)O	DP-2-41	225.03071	$C_6H_{11}NO_6S$	Hydrolysis	Probable
 CNC(C(=O)O)=C(C)N(C)Nc1ccccc1.O=[SH]([O-])(O)CO	DP-2-42	235.13208 112.9914	$C_{12}H_{17}N_3O_2$ CH_5O_4S-	Hydrolysis	Probable
 CC(=C(C(=O)O)N(C)CO)N(C)Nc1ccccc1.O=S([O-])O	DP-2-43	265.14264 80.96519	$C_{13}H_{19}N_3O_3$ HO_3S-	Hydrolysis	Probable

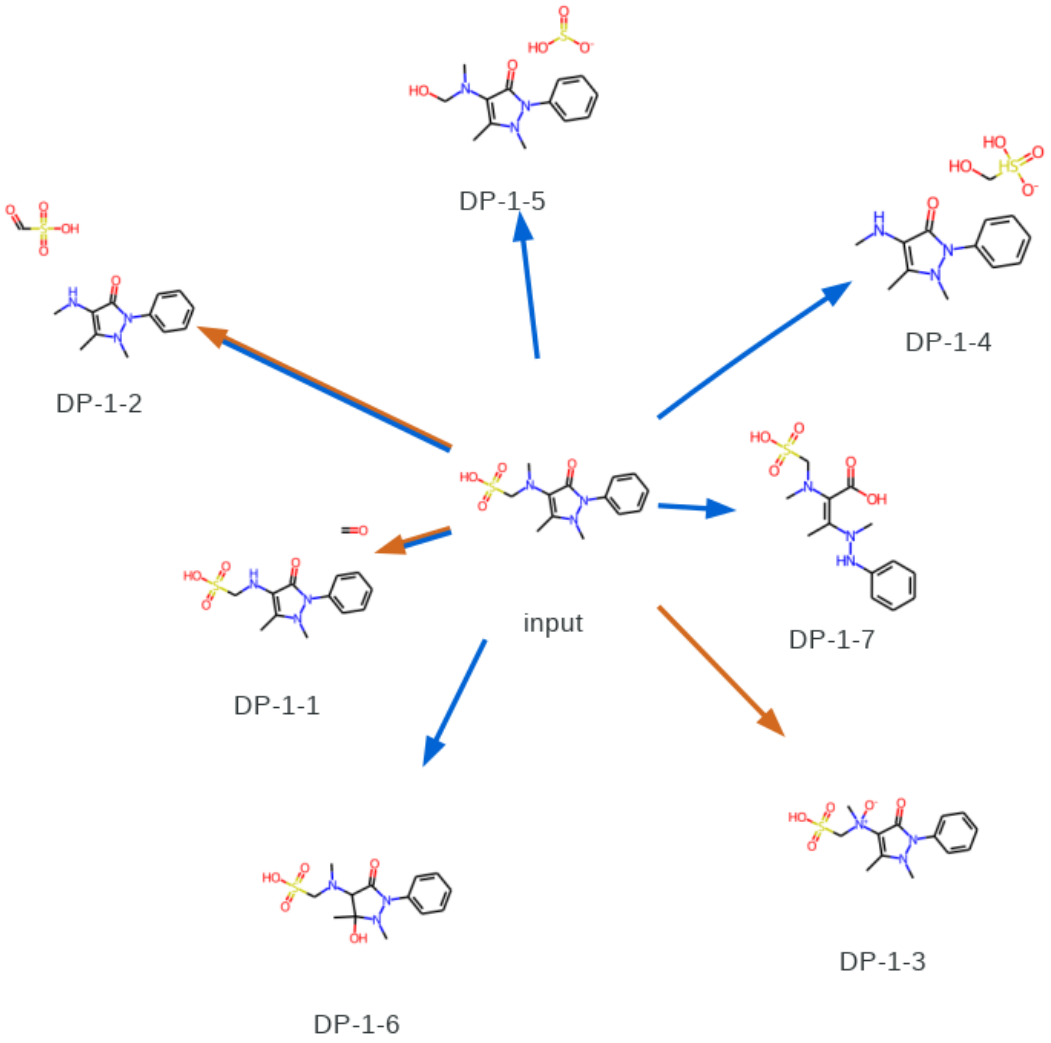
Product	Name	Mass	Formula	Condition	Reaction Likelihood
 CC(=C(C(=O)OO)N(C)CS(=O)(=O)O)N(C)Nc1ccccc1	DP-2-44	345.09946	$C_{13}H_{19}N_3O_6S$	Oxidation	Expected
 CC(=O)N(C)Nc1ccccc1.CN(CS(=O)(=O)O)C(=O)C(=O)O	DP-2-45	164.09496 196.99941	$C_9H_{12}N_2O$ $C_4H_7NO_6S$	Photolysis	Rare

Overview

The degradation plot provides an overview and indicates the possible degradation pathways through the use of a diagram and the colors of the arrow represent different types of reaction: orange, blue, red, and purple symbolize oxidation, hydrolysis, heat, and photolysis, respectively. Some products can be generated by two different reactions in the same step; for example, when hydrolysis and heat are combined, the color of the arrow will be a combination of blue and red; similarly, other combinations will follow the same concept.

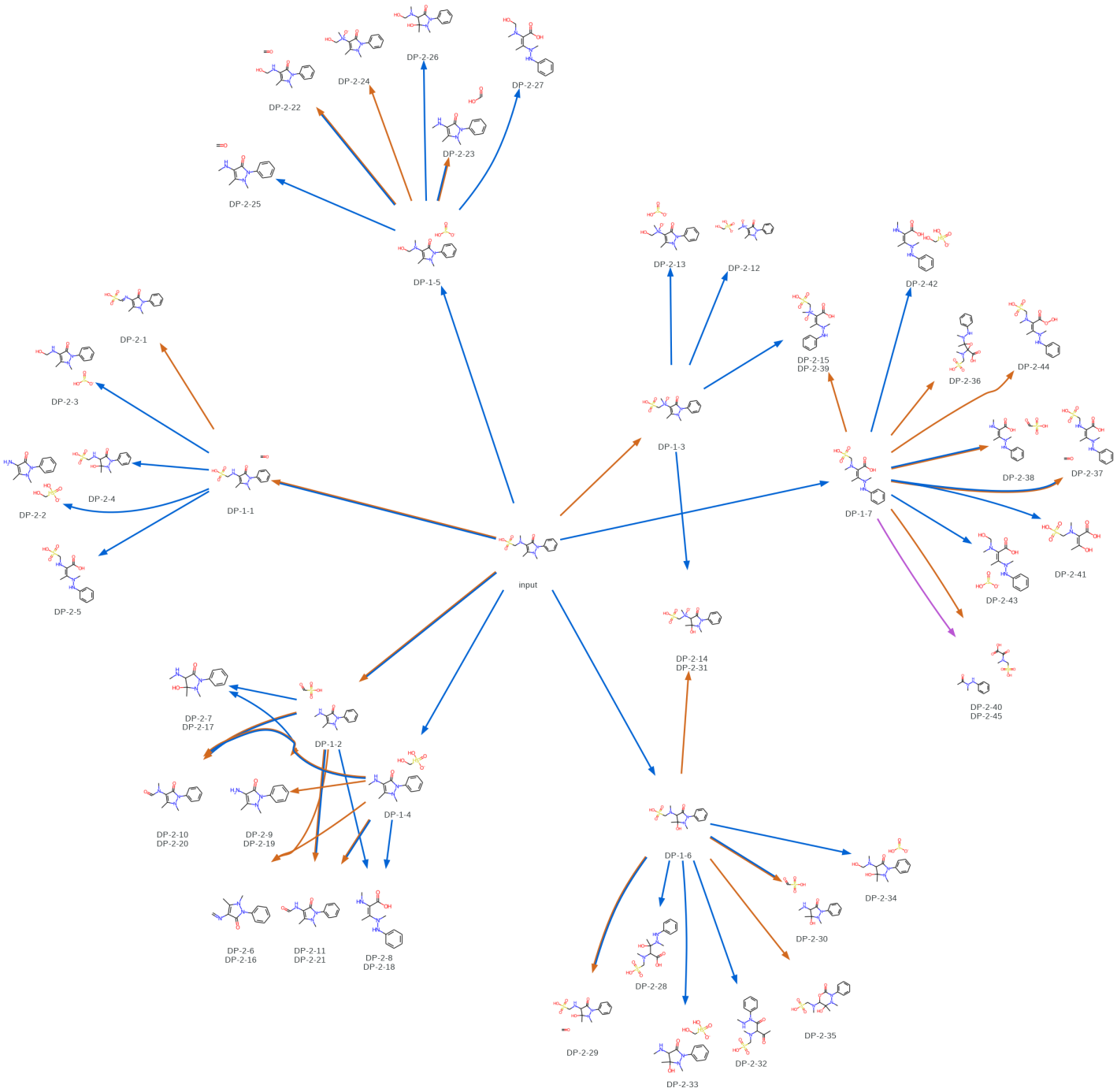
Legend:

- Hydrolysis
- Oxidation
- Photolysis
- Heat
- Hydrolysis and Heat
- Oxidation and Hydrolysis
- Heat and Photolysis
- Photolysis and Hydrolysis



Diagram

The image below shows the complete diagram for two degradation steps.



The image below shows the QRCode with the link to the complete diagram.

Also available here

References

1. Brittain, HG, ed. Analytical Profiles of Drug Substances and Excipients, Volume 22. San Diego. Academic Press, 1993: 86

2. Brittain, HG, ed. Analytical Profiles of Drug Substances and Excipients, Volume 26. San Diego. Academic Press, 1999: 312

3. Brittain, H. G. (Ed.) "Analytical Profiles of Drug Substances and Excipients." Academic Press, San Diego, Volume 26, p. 86 (1999)

4. Brittain, HG, ed. Analytical Profiles of Drug Substances and Excipients, Volume 21. San Diego. Academic Press, 1992: 151.Brittain, H. G. (Ed.) "Analytical Profiles of Drug Substances and Excipients." Academic Press, San Diego, Volume 28, p. 111 (2001).

5. Florey, K, ed. Analytical Profiles of Drug Substances, Volume 12. New York. Academic Press, 1983:122.

6. Joule, JA, Mills, K, Smith, GF. Heterocyclic Chemistry, Third Edition. Cheltenham, UK. Stanley Thornes (Publishers) Ltd., 1998: 101.

7. Benigni R, and Bossa C. Structure alerts for carcinogenicity, and the Salmonella assay system: A novel insight through the chemical relational databases technology. Mutation Research, 2008:659, 248-261.

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