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Discovering hitherto unknown impurities of well-established drugs by UV-light induced decomposition reactions

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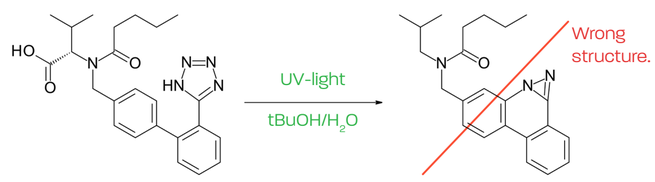
What we found surprised us

Valsartan is a Top200 drug that is used as an AT_1-antagonist to treat hypertension.[1]
We wanted to develop a new reference standard based on compound **A**, a postulated degradation product of Valsartan.[2] UV-light induced stressing was expected to provide the desired compound. **But analytical data did not match.**

We not only discovered that the postulated structure of compound **A** was wrong. Two hitherto unknown impurities were formed. These results help us to provide valuable information as well as unrivaled new products to our customers.



Valsartan
(Active Pharmaceutical Ingredient).

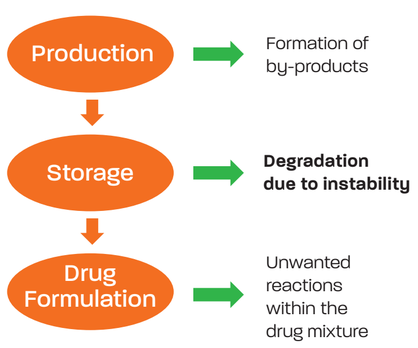
Compound A
(Postulated Impurity).

1. Drugs & their impurities

Impure pharmaceuticals can have severe additional side effects compared to their pure counterparts. Prior to the release of a drug, it is therefore mandatory to check the active pharmaceutical ingredient (API) for known impurities by comparison with certified reference standards.

Degradation products are the most frequently requested category by our customers. Providing a complete set of impurities that ideally encompasses all possible degradation pathways is therefore of particular value.

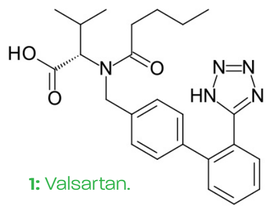
Possible sources of impurities:



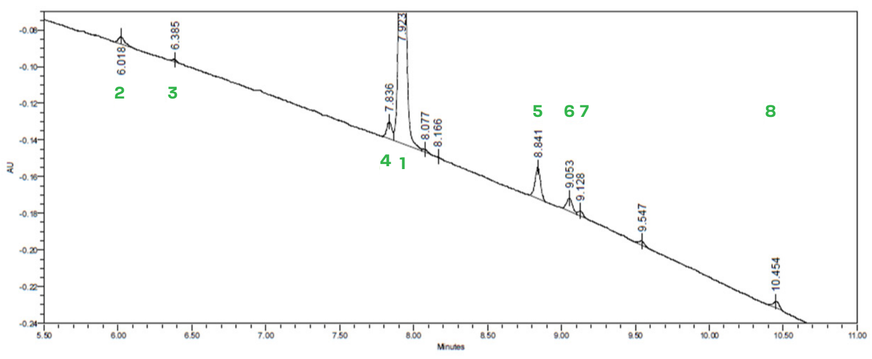
2. Degradation of Valsartan 1

As a model substance for photochemical degradation, Valsartan **1** was selected to identify its structural weak points under the influence of light.

Valsartan is of particular interest as API family due to a recent *N*-nitrosodimethylamine impurity related retraction of large amounts of formulated sartane products in Europe.[3] Based on UPLC-HRMS analysis of stressed samples, a variety of degradation products were observed (**table 1**).[4]



1: Valsartan.



Chromatogram of sunlight-stressed Valsartan solution.

Table 1: retention time, HRMS and Area% of impurities formed during stability studies.

no.	rt [min]	compound	composition	Difference to 1	calc. $[M+H]^+$	found $[M+H]^+$	Δ [ppm]	Area%[a]
1	7.92	1 (API)	$C_{24}H_{30}N_5O_5$	---	436.23432	436.23470	0.9	90.03
2	6.02	2	$C_{13}H_{11}N_4$	- $C_{11}H_{19}O_3$	223.09782	223.09789	0.3	0.77
3	6.38	3	$C_{19}H_{22}N_5O$	- $C_5H_8O_2$	336.18189	336.18171	0.5	0.35
4	7.83	4	$C_{20}H_{22}N_5O_2$	- C_4H_8O	364.17680	364.17681	0.0	2.13
5	8.84	5	$C_{24}H_{28}N_5O_3$	- H_2	434.21867	434.21901	0.8	1.57
6	9.04	6	$C_{23}H_{30}N_5O$	-CO_2	392.24449	392.24463	0.4	2.49
7	9.12	7	$C_{20}H_{20}N_5O_2$	- $C_4H_{10}O$	362.16115	362.16114	0.0	0.23
8	10.45	8	$C_{23}H_{28}N_5O$	- CO_2, - H_2	390.22884	390.22859	0.6	0.44
A	---	A	$C_{23}H_{28}N_3O$	- CO_2, - N_2, - H_2	362.22269	---	---	Not observed
Total decomposition (including unidentified degradants):								9.97

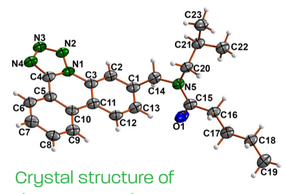
[a]Average of two runs with two independently stressed samples. Analyzed at 200 nm.

3. Structural Re-evaluation

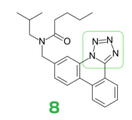
After identification of target compounds from stressing the API, Valsartan was irradiated in a UV-light lab reactor. Impurities are formed much faster under these conditions which allows for the isolation of sufficient material to develop new catalogue products.

Chromatographic separation gave several impurities, of which one was remarkable. Phenanthridine **8** matched the 2D NMR data of literature known[2] degradation product **A** in all aspects. Surprisingly UPLC-HRMS measurements suggest an intact tetrazole moiety rather than the previously published diazirine. Re-evaluation of the analytical data led us to the proposal of **8** as the correct structure, which was then confirmed by crystal structure analysis. This is in accordance with similar cyclizations without ring diminishment that have been described in the literature for Valsartan.[5,6]

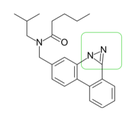
Setup for light-induced degradation reactions.



Crystal structure of degration product 8.



8

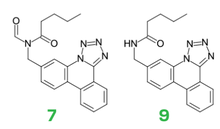


Compound A
Not observed.

4. Degradation in the presence of oxygen

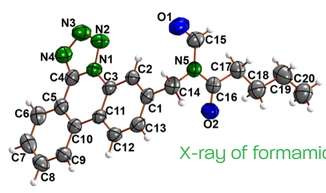
When the valsartan mixture was irradiated in the presence of oxygen, two other, previously unknown structures were isolated. Based on 2D NMR spectra and UPLC-HRMS and in case of **7** via X-ray structure determination, they were assigned as formamide **7** and amide **9**.

Mechanistically, formation of **7** is believed to progress via radical-based stepwise oxidation towards the enamine, followed by a formal 1,2-addition/oxidative cleavage cascade with O_2. Oxidative C-C bond cleavage under irradiation in α-position to amines is a common degradation process, which has been extensively studied and supported by theoretical calculations.[7]

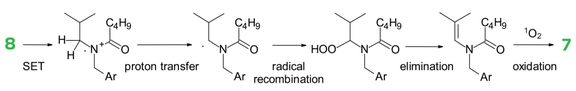


7 **9**

Degration products additionally formed in the presence of oxygen.



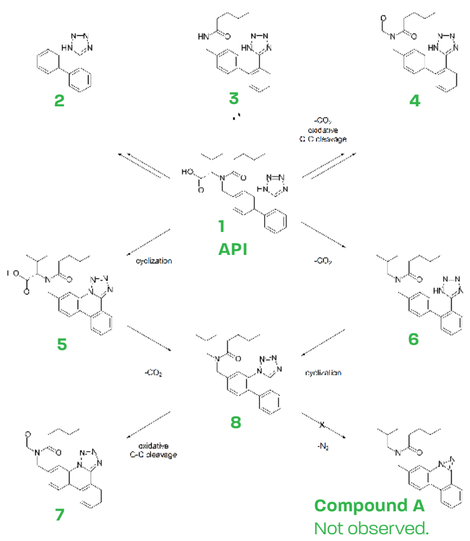
X-ray of formamide **7**.



Mechanistic rationale for formation of formamide **7**.

5. Formulation of degradation pathways for 1

Based on UPLC-HRMS data analysis and structure elucidation of isolated deterioration products, the following degradative pathways are proposed, which seem to proceed independently from each other. Decarboxylation of **1** is the fastest degradative process, followed by cyclization. Stepwise decomposition of the isobutyl fragment seems to require longer irradiation times and the presence of oxygen to proceed. Ring diminishment of the tetrazole unit was not observed in any case.



Compound A
Not observed.

Proposed degradation pathways of Valsartan under the influence of light.

Summary

Three previously unknown Valsartan degradation products were isolated and characterised. Structural elucidation based on 2D-NMR, UPLC-HRMS and X-ray analysis helped to prove the misassignment of **8** in the literature. These information helped to identify Valsartan' s structural weak points under the influence of light. Development of new materials based on photo degradation of similar pharmaceuticals will be performed in the future. This paves the way for a range of new interesting reference standards made by our team in Luckenwalde.

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(4) T. Kurzawa, S. Fazzani, R. Tempel, H. Helmboldt, C. Bleschke, A. Kohlmann, A. Hagenbach j. Mol. Struct. 2023, 134599.
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(6) K. Kumaraswamy etal. Asian J. Chem. 2020, 32, 1064-1068.
(7) J. Zhou, S. Wang, W. Duan, Q. Lina, W. Wei Green Chem. 2021, 3261-3267.