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Disarming antibiotics with a flash of light: LED-illuminated NMR and MS analysis

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Antibiotic resistance is a growing global problem that continues to accelerate, driven, amongst other things, by the presence of antibiotics in the environment, excreted after treatment, unchanged and still bioactive. The rational design of antibiotics with a built-in light-triggered self-destruction mechanism that is activated during already existing wastewater treatment strategies (human use) or by sunlight (veterinary use) would significantly contribute to combating the development of multidrug-resistant bacteria. To ensure that such antibiotics would degrade rapidly, efficiently, and safely, it is crucial to understand their photodegradation and identify the resulting degradation products. In this LED-illuminated NMR and MS study, we investigated the photodegradation of compounds containing three structurally related functional groups susceptible to light-induced degradation: oxazolidine, dioxazepine, and ethanolamine. Both oxazolidine and dioxazepine were found to converge to a common degradation intermediate, ethanolamine, which subsequently decomposes into two major products: aniline and dioxane bishemiacetal. The high sensitivity of MS provided additional insights by revealing nine minor degradation products formed during photolysis. Elucidating the degradation pathways of these model compounds establishes a predictive framework for understanding light-induced degradation and may facilitate the rational design of more sustainable drug candidates.

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Sustainability spotlight

Imagine an antibiotic designed with an inherent light-triggered self-destruct mechanism that activates after excretion during organized wastewater treatment (for human applications) or upon exposure to sunlight (for veterinary applications). Our goal is to identify functional group(s) that can be incorporated into active pharmaceutical molecules to enable their rapid, effective, and safe degradation after use. To achieve this, we investigate photodegradation mechanisms in detail and identify the resulting breakdown products, thereby minimizing the risk of forming secondary pollutants. Through this research, we aim to contribute to the fight against antimicrobial resistance, in alignment with the United Nations Sustainable Development Goals, particularly Good Health and Well-Being and Responsible Consumption and Production.

1 Introduction

Bacterial mutations drive the development of antibiotic resistance.^{1,2} The emergence of bacterial resistance is not new; Alexander Fleming, the discoverer of penicillin, highlighted this issue in his Nobel lecture.³ The lifesaving capability of antibiotics is under attack by the overuse in both human

medicine and in livestock. One factor contributing to resistance development is the presence of antibiotics in the sewage system and in the environment⁴ since many antibiotics are poorly metabolized in the body and are excreted unchanged and remain as biologically active as they were when they entered the patient.⁵ Some of these compounds exhibit long half-lives in the environment, providing bacteria with ample opportunity to develop resistance, which explains why they are included in the European Commission JRC Selection of substances for the 4th Watch List under the Water Framework Directive.⁶ A long half-life is also common for a range of other pharmaceuticals^{7,8} resulting in accumulation in the environment where they have unknown long-term effects on non-target organisms.⁹

There is an urgent need for designing greener pharmaceuticals,^{10,11} a task that our research group has been engaged in for some time by developing antimicrobial agents capable of

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degradation by exposure to light^{12–14} after excretion from the patient. This is achieved by incorporating a functionality in the compound that facilitates photodecomposition upon exposure to light, which can be controlled so that it only occurs after the pharmaceutical has been excreted from the patient. The ethanolamine moiety was identified as suitable for this purpose resulting in compounds with promising antimicrobial activity, exemplified by minimum inhibition activity (MIC) of 6.3 μM for ethanolamine **1** towards *S. agalactiae* (Scheme 1a), and the ability to undergo photodegradation within 24 hours under illumination from a medium-pressure mercury lamp resulting in products with no antimicrobial activity.^{12,14} Building on this proof of concept, we found that converting the ethanolamine to the corresponding oxazolidine **2** (Scheme 1a) reduced the time required for full decomposition to two hours under the same conditions. However, this enhanced degradation rate was accompanied by a reduction in the antimicrobial activity (MIC 25 μM towards *S. agalactiae*) (Scheme 1a).¹⁵ The improvement in degradation speed in addition to the fact that the structurally related oxazolidinone ring system is found in several antibiotics such as linezolid and tedizolid¹⁶ prompted the synthesis of a series of oxazolidines including compound **4** derived from ethanolamine **3** (Scheme 1b).

Although we have not yet succeeded in enhancing the antimicrobial activity of the oxazolidine-based compounds beyond a MIC of 25 μM (as observed for compound **2**) the improved decomposition rate warranted a more in-depth investigation of the photodegradation process and mechanism by LED-illuminated NMR.^{17–19} For this mechanistic study we chose to use oxazolidine **4** as a model compound since it was readily available in our laboratories and, based on our previous photodecomposition studies, the oxazolidines as a class undergoes degradation through bond cleavage at the oxazolidine group, irrespective of their substituents. This study was aimed at discovering details of that cleavage and identifying pathways forward which would be applicable to the whole class. The accumulated NMR in combination with MS data enabled the

elucidation of the photodecomposition products and their mechanism of formation.

2 Materials and methods

2.1 General

All chemicals were obtained from Sigma-Aldrich/Merck (Reading, NJ, USA) or VWR (Radnor, PA, USA) and used as supplied. When specified, solvents were dried by storing over 4 Å molecular sieves. For petroleum ether (pet. ether), the 40–60 °C fraction was used. All reactions were carried out under a nitrogen or argon atmosphere, unless otherwise specified. Thin-layer chromatography (TLC) was carried out with silica gel (60 F254) on aluminium sheets with solvent systems consisting of various mixtures of pet. ether, ethyl acetate, and dichloromethane (DCM). Visualization was achieved with either UV light (254 and/or 365 nm), or a potassium permanganate stain. Flash chromatography was performed with a hand pump and 230–400 mesh silica gel.

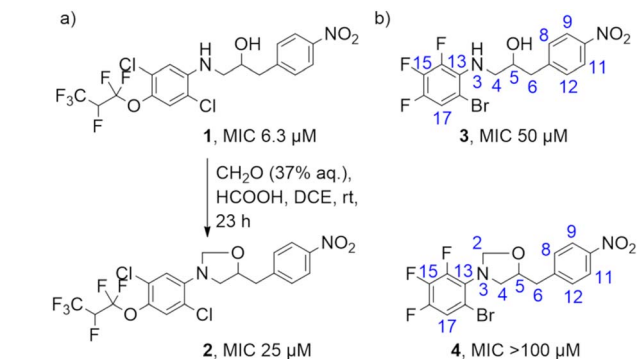
IR spectra were recorded on an Agilent Cary 630 FT-IR spectrophotometer equipped with an attenuated total reflectance attachment. Samples were analysed neat on a ZnSe crystal, and the absorption frequencies are given in wave numbers (cm^{-1}).

Deuterated solvents for NMR spectroscopy were purchased from EurIsotop (Saint Aubin, France). All NMR spectra were recorded at 25 °C using standard pulse sequences on the Bruker Ascend 400 and Bruker Avance AV600 spectrometers (Bruker, Billerica, MA, USA). The structures were elucidated using 1D and 2D NMR spectra (¹H, APT, COSY, HSQCe and HMBC) as shown in Fig. S1–S30. Proton–proton and carbon–fluorine coupling constants (*J*) from proton and carbon spectra, respectively, are given in Hz, and the multiplicity is reported as singlet (s), doublet (d), triplet (t), quartet (q), sextet (s), multiplet (m), and broad singlet (bs). Chemical shifts are reported in ppm in the order downfield to upfield, and calibration is performed using the residual solvent signals for ACN-*d*₃ (¹H 1.94 ppm; ¹³C 1.32 ppm).²⁰ All acquired NMR spectra were processed using Bruker TopSpin 4.3.0. (Bruker, Billerica, MA, USA) and ACD/Labs Spectrus Processor v2021 (ACD Systems, Victoria, BC, Canada) software.

Acetonitrile and formic acid were MS grade and were purchased from Carlo Erba (Milano, Italy). Ultrapure water was obtained from a Milli-Q Advantage A10 purification system from Merck KGaA (Darmstadt, Germany). All LC-HRMS analyses (Fig. S31–S80) were performed using Agilent 1290 Infinity II UHPLC coupled with Agilent 6550 iFunnel Q-TOF (Agilent Technologies, Santa Clara, CA, USA). LC-UV analyses (Fig. S81 and S82) were performed on Agilent 1290 Infinity II UPLC-DAD (Agilent Technologies, Santa Clara, CA, USA), while UV-vis spectrum of oxazolidine **4** (Fig. S83) was recorded using Genesys 50 UV/vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

2.2 Synthesis

2.2.1 Synthesis of 3-(6-bromo-2,3,4-trifluorophenyl)-5-(4-nitrobenzyl)oxazolidine (**4**). Formaldehyde (0.03 mL, 0.76 mmol)



Scheme 1 (a) Synthesis of oxazolidine **2** from the corresponding ethanolamine **1** and antimicrobial activity against *S. agalactiae*; (b) structure of ethanolamine **3** and antimicrobial activity against *S. agalactiae* and the structure of oxazolidine **4**. Compound numbering shown for compounds **3** and **4**.

and formic acid (0.01 mL, 0.21 mmol) was added to a stirred solution of 1-((6-bromo-2,3,4-trifluorophenyl)amino)-3-(4-nitrophenyl)propan-2-ol (78 mg, 0.19 mmol) in 1,2-dichloroethane (4 mL). The resulting reaction mixture was stirred at room temperature for 38 h before the reaction was quenched with H₂O (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL) and the combined organic fractions were washed with brine (1 × 10 mL) and dried over MgSO₄. Filtration and concentration gave the crude product which was purified by silica-gel column chromatography (DCM:pet. ether 7:3 → 8:2). Isolation of the relevant fractions (*R*_f = 0.5, DCM:pet. ether 8:2) gave the title compound **4** as a colourless oil (32 mg, 42%). IR (neat): λ_{max} (film) 1927, 1501, 1343, 1190 cm⁻¹; UV: λ_{max} (EtOAc) 288 nm, ε 7054 M⁻¹ cm⁻¹; ¹H NMR (600 MHz, CD₃CN:D₂O, 7:3): δ = 8.11 (d, *J* = 8.1 Hz, 2H, 9, 11), 7.47 (d, *J* = 8.8 Hz, 2H, 8, 12), 7.41 (ddd, *J* = 2.6, 7.9, 10.1 Hz, 1H, 17), 4.77 (d, *J* = 4.8 Hz, 1H, 2'), 4.63 (d, *J* = 4.8 Hz, 1H, 2''), 4.36 (quin, *J* = 6.6 Hz, 1H, 5), 3.57 (dd, *J* = 6.6, 10.5 Hz, 1H, 4'), 3.12 (dd, *J* = 7.0, 10.5 Hz, 1H, 4''), 3.02 (d, *J* = 6.6 Hz, 2H, 6); ¹³C NMR (151 MHz, CD₃CN:D₂O, 7:3): δ = 147.2 (dd, *J* = 2.4, 258.3 Hz, 1C, 16), 147.2 (dd, *J* = 3.6, 237.9 Hz, 1C, 14), 146.2 (1C, 10), 146.1 (1C, 7), 139.3 (dt, *J* = 16.1, 251.4 Hz, 1C, 15), 132.3 (d, *J* = 9.6 Hz, 1C, 13), 130.0 (2C, 8, 12), 122.9 (2C, 9, 11), 116.5 (1C, 18), 115.5 (d, *J* = 20.4 Hz, 1C, 17), 82.8 (d, *J* = 6.0 Hz, 1C, 2), 76.9 (1C, 5), 55.3 (d, *J* = 3.6 Hz, 1C, 4), 38.49 (1C, 6); although oxazolidine **4** produces a large chromatographic peak at RT = 12.50 (Fig. S81) in LC-DAD, the peak of matching intensity is not observed in any of the recorded LC-HRMS spectra. The small peak present at RT 12.5 in ESI⁻ does not have a corresponding interpretable HRMS spectrum underneath, likely due to the compound's low ionization efficiency.

2.2.2 Synthesis of 1-amino-3-(4-nitrophenyl)propan-2-ol (9). 2-(4-Nitrobenzyl)oxirane (100 mg, 0.52 mmol) was dissolved in 25% ammonia solution (10 mL). The mixture was stirred at rt for 17 h before being quenched with water (10 mL). The aqueous layer was extracted with CHCl₃ (3 × 10 mL) and the combined organic phases were dried over MgSO₄. Filtration and concentration under reduced pressure gave the crude product that was subjected to purification by silica-gel column chromatography (DCM/MeOH, 9:1). Concentration of the relevant fractions (*R*_f 0.1 in DCM:MeOH 9:1) gave a yellow solid that was recrystallized in EtOAc/hexane to yield the title compound **9** as a light-yellow solid (9 mg, 9%, mp 120–123 °C). IR (neat): λ_{max} 3355, 3280, 2843, 1907, 1511, 1340 cm⁻¹; ¹H NMR (400 MHz, CD₃CN): δ = 8.13 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 3.68–3.62 (m, 1H), 2.87 (dd, *J* = 13.6 Hz, 4.3 Hz, 1H), 2.75–2.68 (m, 2H), 2.48 (dd, *J* = 12.7 Hz, 7.3 Hz, 1H); ¹³C NMR (100 MHz, CD₃CN): δ = 149.1, 147.5, 131.4, 124.1, 73.7, 48.2, 41.6; HRMS: calculated for C₉H₁₂N₂O₃ M + H⁺, 197.0921; found 197.0925 (diff: 2.19 ppm).

2.3 Dioxazepine 5

Structure elucidation of dioxazepine **5** was performed in the mixture with oxazolidine **4**. The presence of the dioxazepine moiety in **5** was supported by a sequence of COSY correlations (H-6/H-5/H-4), as well as an extensive number of ¹H–¹³C HMBC correlations spanning the seven-membered ring and linking it

to the aromatic rings on both sides of the molecule (Fig. S15–S19). All proton and carbon NMR chemical shifts, as well as coupling constants, were consistent with the determined structure. ¹H NMR (600 MHz, CD₃CN:D₂O, 7:3): δ = 8.11 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 4.94 (d, *J* = 6.2 Hz, 1H), 4.87 (d, *J* = 5.9 Hz, 1H), 4.79 (d, *J* = 0.7 Hz, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 4.26–4.16 (m, 1H), 3.23 (d, *J* = 6.2 Hz, 2H), 2.94–2.89 (m, 1H), 2.88 (d, *J* = 5.1 Hz, 1H); ¹³C NMR (151 MHz, CD₃CN:D₂O): δ = 146.2 (s, 1C, 7), 133.3 (s, 1C, 13), 129.9 (s, 2C, 8, 12), 122.8 (s, 2C, 9, 11), 115.5 (d, *J* = 20.4 Hz, 1C, 17), 92.2 (s, 1C, 27), 81.5 (s, 1C, 2), 79.7 (s, 1C, 5), 57.6 (s, 1C, 4), 37.9 (s, 1C, 6); although a large chromatographic peak at RT = 12.50 (Fig. S82) is visible in the LC-DAD chromatogram of the oxazolidine **4** and dioxazepine **5** mixture, a peak of matching intensity is not observed in any of the recorded LC-HRMS spectra. The small peak present at RT 12.5 in ESI⁻ does not have a corresponding interpretable HRMS spectrum, likely due to the compound's low ionization efficiency. When compared to the pure oxazolidine **4**, both LC-DAD and LC-HRMS peaks of the mixture exhibit a shoulder, suggesting the presence of two different compounds eluting from the column almost simultaneously.

2.4 Degradation

To compare the influence of different decomposition triggers on the stability of oxazolidine **4** in an acetonitrile/water mixture, a total of 4.2 mg was dissolved in 1650 μL of ACN-*d*₃:D₂O (7:3). Aliquots of 550 μL were then transferred to three 5 mm NMR tubes: one was left unaltered to establish baseline, 0.55 μL of formic acid was added to the second, and the third was subjected to UV irradiation (310 nm). All three experiments were initiated simultaneously and monitored over a 14 day period at room temperature.

Photodegradation of pure oxazolidine **4** (9 mg), as well as the mixture (16 mg) of oxazolidine **4** (ca 75% molar content) and dioxazepine **5** (ca 25% molar content) was performed in 550 μL ACN-*d*₃:D₂O (7:3) at 25 °C. A series of ¹H spectra were recorded over a period of approximately three weeks.

The equipment for LED-illuminated NMR^{17–19} was purchased from ThorLabs GmbH (Bergkirchen, Germany). It included ThorLabs DC2200 LED driver, LED M310F1 and optical fibre. LED used in photodegradation experiments had wavelength of 310 nm and electrical power of 3 W.²¹ The optical fibre tip was modified¹⁷ to enable uniform light emission in all directions and was inserted into the sample inside the NMR tube using a quartz coaxial insert to prevent contamination. The LED output power measurement was performed at the sample (tip of the optical fibre) by integrated sphere with calibrated UV sensitive photodiode as detector. Output power of LED in our setup was measured to be around 0.5 mW. From this the photon flux at 310 nm was calculated to be 7.8 × 10¹⁴ photons per s.

2.5 HRMS analysis

The chromatographic separation was performed on Zorbax Eclipse Plus C18 RRHD (1.8 μm, 3.0 × 50 mm) column with the temperature set at 40 °C. The mobile phase consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

with the gradient elution profile as follows: 0 min 95% A; 10–13 min 5% A. The flow rate was set at 0.2 mL min⁻¹, and the injection volume was 1 μ L. HRMS analyses were performed by electrospray ionization in positive and negative mode ranging from m/z 50 to m/z 1500 with optimized parameters as indicated in Table S1. Collision-induced dissociation was performed using collision energies (CE): 5, 10, 20, 30, and 40 V.

3 Results and discussion

3.1 Photodegradation of a mixture of oxazolidine 4 and dioxazepine 5

Initially, we investigated the photochemistry of oxazolidine 4 using a sample that additionally contained 25% of dioxazepine 5, the unusual compound most likely formed *via* the process depicted in Scheme 2.²² The hydroxyl group in the imine intermediate reacts with an additional formaldehyde prior to cyclizing resulting in the formation of dioxazepine 5.

The 3 : 1 mixture of compound 4 and 5 showed a λ_{max} of 310 nm in acetonitrile (ACN), thus we commenced our studies by subjecting the mixture (16 mg) in ACN- d_3 : D₂O (7 : 3) to irradiation with 310 nm light. Water was included in the solvent to resemble environmental conditions while simultaneously keeping the concentration of the analytes at a level that facilitated acquisition of NMR data.

Since photodegradation was scheduled to begin only after NMR spectra for structure elucidation were acquired, the sample was inadvertently exposed to room temperature in the dark for three days before irradiation experiments commenced. During this period, oxazolidine 4 spontaneously began decomposing, yielding approximately 8% ethanolamine 3, while compound 5 remained stable (Fig. 1, 0 h). In this mixture, formation of the ethanolamine 3 was determined by proton chemical shift comparison to signals of an authentic compound

(Fig. S1–S5) synthesized following our previously reported procedure.¹²

Although the irradiation of this mixture lasted in total 417 hours (Fig. S20), the most interesting transformations occurred within the first 48 hours (Fig. 1). Under irradiation dioxazepine 5 undergoes degradation *via* the loss of methanediol, forming intermediate 6 (Fig. 1 and Scheme 3).

The structure of intermediate 6 was determined through detailed NMR analysis of the degradation mixture after 19.5 hours of irradiation (Fig. S21–S25), followed by LC-HRMS analysis in negative mode (Fig. S70–S72), where the product exhibited a retention time of 11.91 min. Characteristic ions included $[M + Cl]^-$ at m/z 468.9780 and $[M + HCOO]^-$ at m/z 479.0071. Additional signals at m/z 295.9531 and 136.0400 were identified as in-source fragments. MS/MS analysis of the $[M + HCOO]^-$ ion at m/z 479.0071 further confirmed the structure, and a possible fragmentation pathway was proposed. The concentration of intermediate 6 declines as it is converted into ethanolamine 3 through the loss of an additional methanediol unit (Scheme 3).

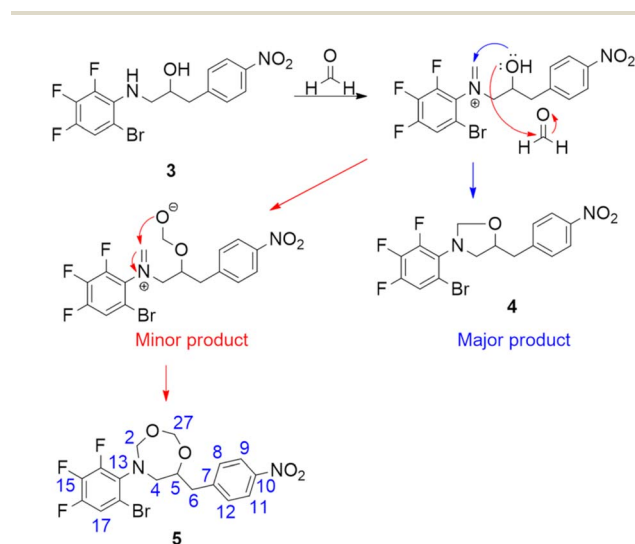
At this point the photodegradation pathways of oxazolidine 4 and dioxazepine 5 converge at formation of ethanolamine 3. Further degradation of ethanolamine 3 yields dimer 7 and aniline 8 (Scheme 3 and Fig. S20). The structures of both dimer 7 and aniline 8 were determined through NMR analysis of the degradation mixture after 417 hours of irradiation (Fig. S26–S30). The structure of dimer 7 was determined through the key ¹H–¹³C HMBC correlations shown in Fig. S30, along with characteristic chemical shifts of C-4 (92.7 ppm) and C-5 (75.6 ppm). The formation of aniline 8 was unambiguously confirmed by chemical shifts comparison with an authentic sample (Fig. S11–S14).

3.2 Photodecomposition of oxazolidine 4

A fresh batch of oxazolidine 4 was prepared and carefully purified by flash chromatography to obtain sufficient material for photodegradation. We first assessed the baseline stability under aqueous and acidic conditions (Fig. 2) since the findings with the mixture indicated stability issues for oxazolidine 4.

Aqueous conditions were examined due to the known susceptibility of oxazolidines to hydrolysis in water,²³ while acidic conditions were tested since formic acid, a predicted photodegradation product,¹² has been reported to induce ring-opening of oxazolidines.²⁴ To this end, three aliquots of compound 4 in ACN- d_3 : D₂O (7 : 3) solution were monitored at room temperature approximately three weeks by ¹H NMR spectroscopy while subjected to the following conditions: (1) shielded from light; (2) addition of 0.1% formic acid while shielded from light; and (3) irradiated at 310 nm. Although pure oxazolidine 4 had $\lambda_{\text{max}} = 288$ nm (Fig. S83), we decided to conduct the investigation with the same light source (310 nm) as in the previous experiments to facilitate data comparison.

The results depicted in Fig. 2a demonstrate that oxazolidine 4 in ACN- d_3 : D₂O (7 : 3) remains stable for at least 22 hours when kept in the dark at room temperature, and after three days less than 1% of the material had decomposed. This result was



Scheme 2 Mechanism for formation of the major product, oxazolidine 4, and formation of dioxazepine 5. Numbering used in the chemical shift assignment in NMR are inserted for compound 5.

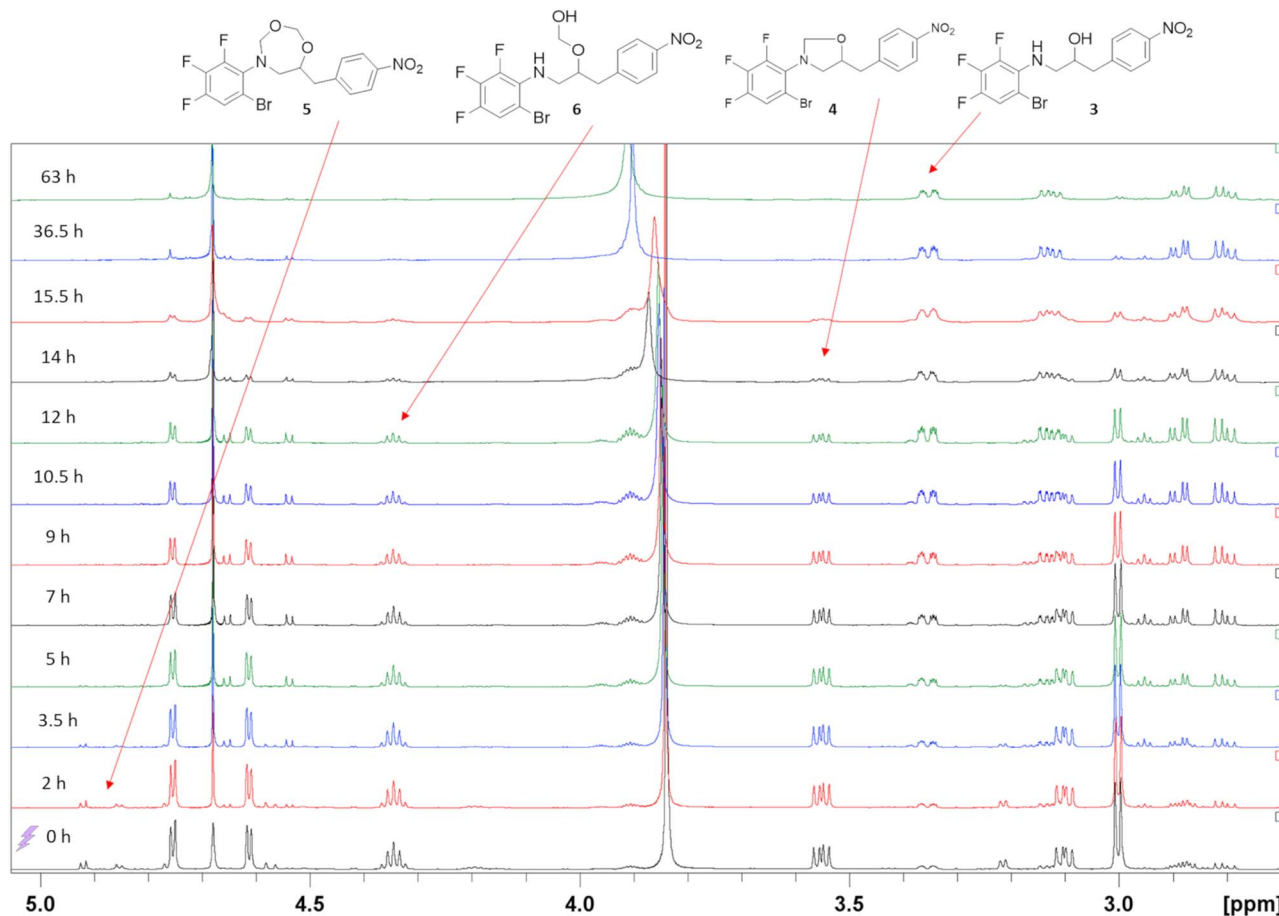


Fig. 1 The first 63 hours photodecomposition of compound 4 (75%) and 5 (25%) mixture in $\text{ACN-}d_3$: D_2O (7 : 3) at room temperature using UV light ($\lambda = 310$ nm).

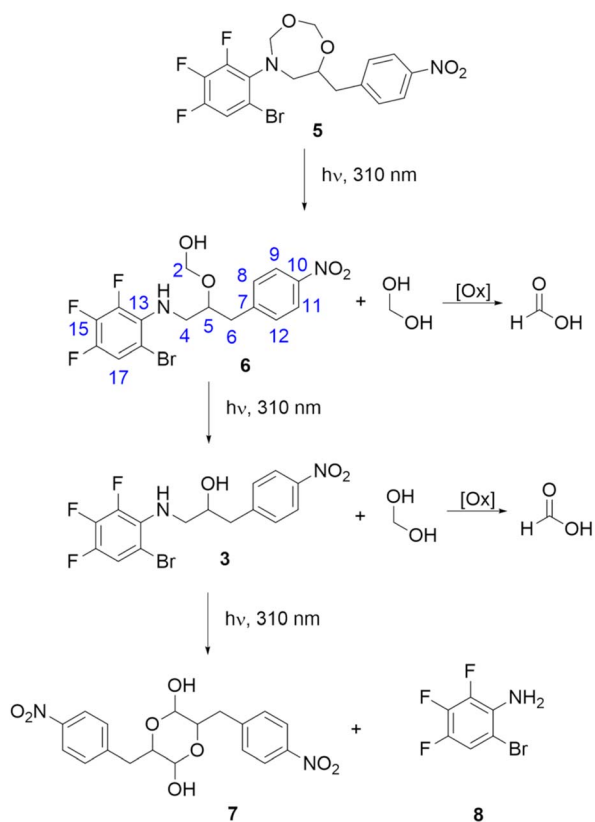
unexpected since oxazolidine 4 in the 3:1 mixture of compounds 4 and 5 under the exact same conditions underwent 8% decomposition. The most probable explanation for different degradation rates is the significantly higher (16 times) concentration of 4 in the previously analysed mixture.

The second aliquot showed that if formic acid is introduced under otherwise identical conditions, oxazolidine 4 undergoes complete decomposition to ethanolamine 3 in less than three hours. Based on the ^1H NMR data (Fig. 2b) this decomposition initiates almost immediately upon the addition of formic acid, as evident by the spectral data recorded after 48 min. The rapid conversion of compound 4 to the more stable ethanolamine 3 under mildly acidic conditions occurred more swiftly than expected. This rapid degradation would pose a challenge if oxazolidines were intended for use as oral drugs. However, this property also underscores the potential of oxazolidines as pro-drugs for potent ethanolamines, which can be an interesting ability given the higher antimicrobial activity of compound 1 compared to its corresponding oxazolidine 2 and ethanolamine 3 vs. oxazolidine 4.

The analysis of the third aliquot revealed that the effect of light is not as dramatic as the addition of formic acid, although it still accelerates the decomposition (Fig. S86 vs. Fig. 2b).

Oxazolidine 4 started to photodegrade to ethanolamine 3 ($\lambda_{\text{max}} = 311$ nm) which under further continuous irradiation at 310 nm eventually decomposes into several new compounds.

During this study it was observed that decomposition of oxazolidines occurs significantly faster (2 hours) when using 6 W medium-pressure mercury-vapor lamp filtered through Pyrex glass, compared to 3 W LED irradiation at a single wavelength, namely 310 nm. Considering that the oxazolidine concentration was of the same order of magnitude in both experiments (1.4 mg in 550 μL for the LED-illuminated *in situ* NMR experiment and 13 mg in 75 mL for the photoreactor experiment), the observed difference in reaction rate is unlikely to originate from differences in substrate concentration. Instead, it may be explained by the broader spectral output of the Pyrex-filtered medium-pressure mercury lamp, which emits several intense spectral lines between 300 and 365 nm and may therefore promote the reaction more effectively than the monochromatic LED. Furthermore, the LED used for the *in situ* NMR experiments had a lower electrical power (3 W vs. 6 W for the mercury lamp), and the photon flux reaching the sample was likely further reduced by transmission losses through the optical fibre.



Scheme 3 Photodegradation pathway for dioxazepine **5** exposed to light with wavelength 310 nm in ACN- d_3 :D $_2$ O (7 : 3) at room temperature. Numbering used in the chemical shift assignment in NMR are inserted for compound **6**.

3.3 Photodegradation products of oxazolidine **4**

To facilitate the structure elucidation of photodegradation products and discovery of the reaction pathway, 9 mg of pure oxazolidine **4** was dissolved in 550 μ L ACN- d_3 :D $_2$ O (7 : 3) and subjected to the same reaction conditions as before. In addition to monitoring the decomposition by NMR spectroscopy (Fig. 3), MS analysis (HRMS and MS/MS) monitoring was also performed at specific time points: before irradiation (0 hours) and after 7, 25, 49, 122, and 195 hours of irradiation at 310 nm.

As in previous experiments, oxazolidine **4** photodegrades to ethanolamine **3** by eliminating methanediol (observed as a singlet at 4.67 ppm), which, over time, undergoes further oxidation to formic acid (small singlet at 8.11 ppm) due to the presence of oxygen in the solution (as the solution was not degassed prior to the experiment to simulate real-life environmental conditions). Ethanolamine **3** was confirmed by LC-HRMS analysis (Fig. S31–S36) through the detection of a peak with retention time (RT) 11.45 min, corresponding to the observed accurate mass of the singly deprotonated ion at m/z 402.9908 (calculated m/z 402.9911, error -0.65 ppm). Further supporting evidence included characteristic ions such as $[M + Cl]^-$ at m/z 438.9690 (calculated m/z 438.9677, error 2.87 ppm) and $[M + HCOO]^-$ at m/z 448.9970 (calculated m/z 448.9965,

error 1.02 ppm). The MS spectrum also displayed signals at m/z 265.9439 and 136.0410, which were later assigned to in-source fragmentations based on detailed MS/MS analysis by collision-induced dissociation (CID). Using this data, a possible fragmentation pathway for ethanolamine **3** $[M - H]^-$ ion (m/z 402.9908) was proposed.

After 17 hours, no detectable traces of oxazolidine **4** remained in the 1H NMR spectra, while signals corresponding to photodecomposition products derived from ethanolamine **3** began to emerge. As before, two major photodegradation products of ethanolamine **3** were discovered to be: dimer **7** and aniline **8** (Scheme 4).

Aniline **8** can be formed *via* homolytic cleavage of ethanolamine **3** (Scheme 5a). Ethanolamine **3** can also undergo an oxidation to form the iminium **3a**. Through hydrolysis of the iminium, the α -hydroxy aldehyde **3b** is produced, which subsequently dimerizes to form the dioxane bishemiacetal **7** (Scheme 5b). Evidence for the formation of compound **3b** is derived from MS analysis (Table 1) while substrate **7** is deduced from the 1H NMR data.

3.4 Structure elucidation and degradation pathways for minor degradation products

The two major products, *viz.* compound **7** and **8**, are not the only chemical fate of ethanolamine **3**, as LC-HRMS analysis revealed the presence of several minor photodegradation products (Table 1). Their concentrations were too low for detection by NMR spectroscopy. None of these compounds were detected prior to irradiation, and most appeared at the first sampling point after 7 hours, suggesting that they are all photodegradation products. The structural elucidation of these compounds was conducted using a combination of HRMS data and MS/MS fragmentation pattern analysis and their mechanisms of formation are proposed (Scheme 6).

The HRMS spectrum of the degradation product **3b** (RT = 6.03 min) displayed a singly deprotonated ion at m/z 194.0460 (Fig. S37 and S38), while MS/MS analysis revealed the presence of a characteristic negatively charged 1-methyl-4-nitrobenzene ion at m/z 136 (Fig. S39 and S40), a feature consistently observed across degradation products where the nitro group remains intact. The identification of this compound within the degradation mixture supports the proposed degradation mechanism outlined in Scheme 5b.

Compound **9** was identified *via* LC-HRMS analysis at a retention time of 4.65 min, with an m/z 197.0912 for $[M + H]^+$ detected in positive mode. Its structure was unambiguously confirmed by comparing the LC-HRMS spectra with those of an authentic synthetic sample of ethanolamine **9** (Fig. S41–S42), which was prepared following a literature procedure²⁵ Mechanistically, ethanolamine **9** is likely formed through the homolytic cleavage of ethanolamine **3**, a process that also generates aniline **8**, as depicted in Scheme 5. The fact that ethanolamine **9** is detected only as a minor product suggests that it undergoes further degradation reactions.

The HRMS spectrum of degradation product **10** (RT = 7.15 min) exhibited a signal at m/z 257.0334, corresponding to the $[M$

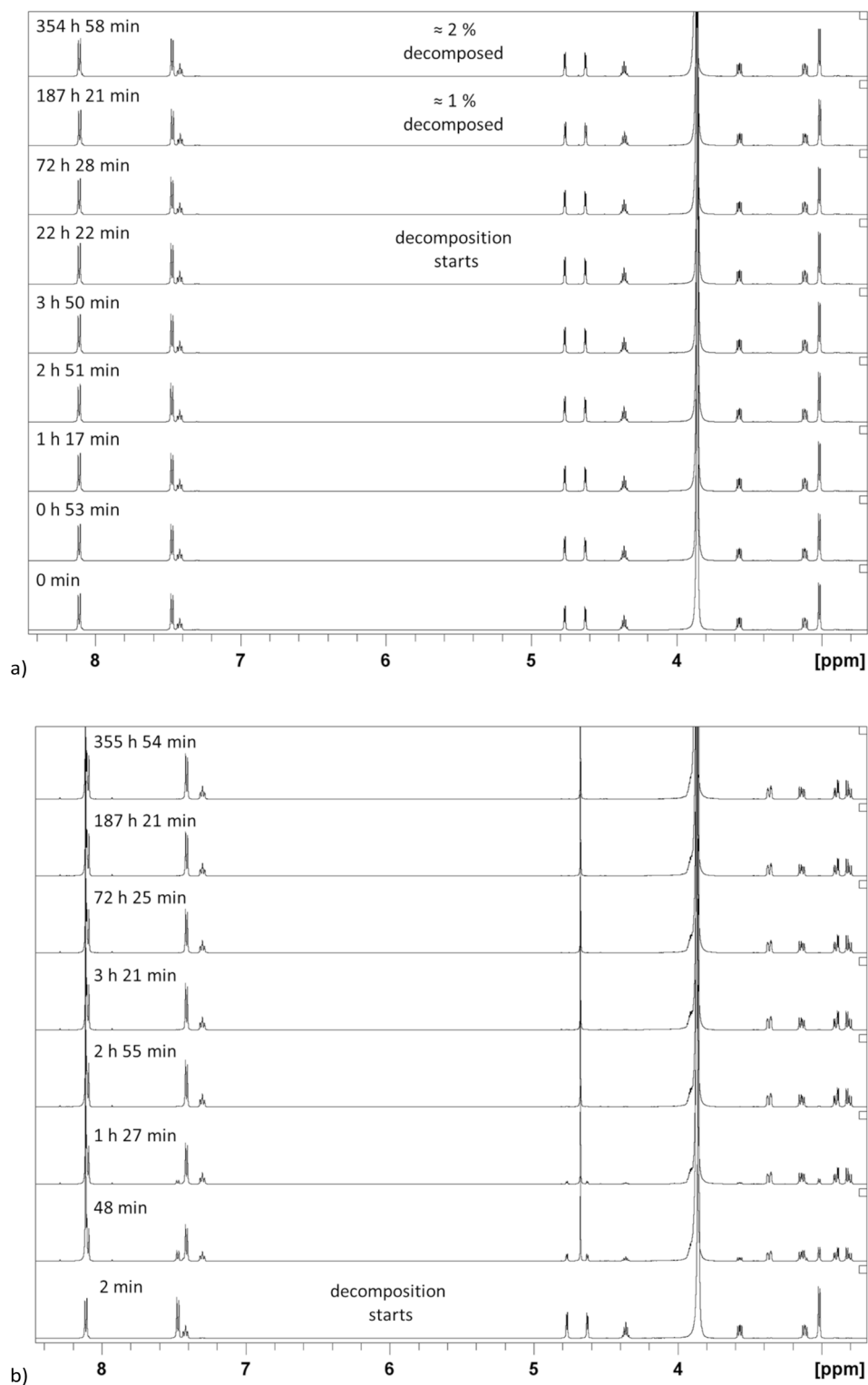


Fig. 2 Structural integrity of oxazolidine **4** in $\text{ACN-}d_3 : \text{D}_2\text{O}$ (7 : 3) during 14 days at room temperature: (a) shielded from light and (b) with 0.1% formic acid in the dark.

+ Cl^- adduct, and a signal at m/z 194.0459 (Fig. S44), which was assigned to an in-source fragment based on CID experiments (Fig. S45 and S46).

Degradation products **11** and **12** were observed at retention times of 9.59 and 10.51 min, respectively. Unexpectedly, their HRMS spectra were almost identical, each displaying only one characteristic signal at m/z 400.9954 (**11**) and m/z 400.9963 (**12**)

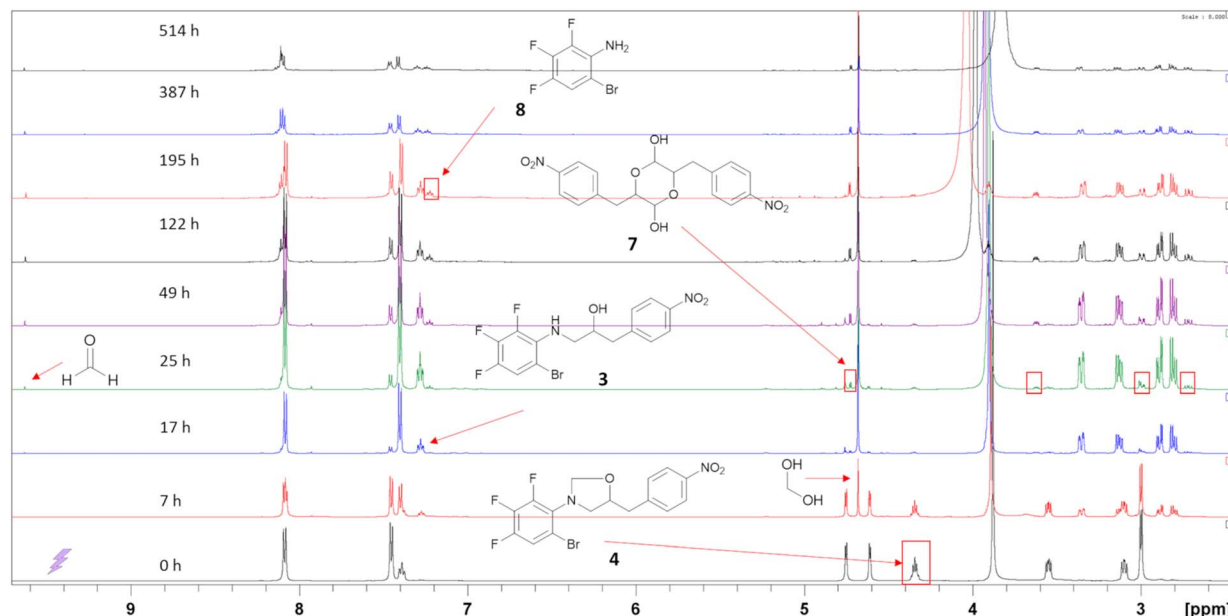
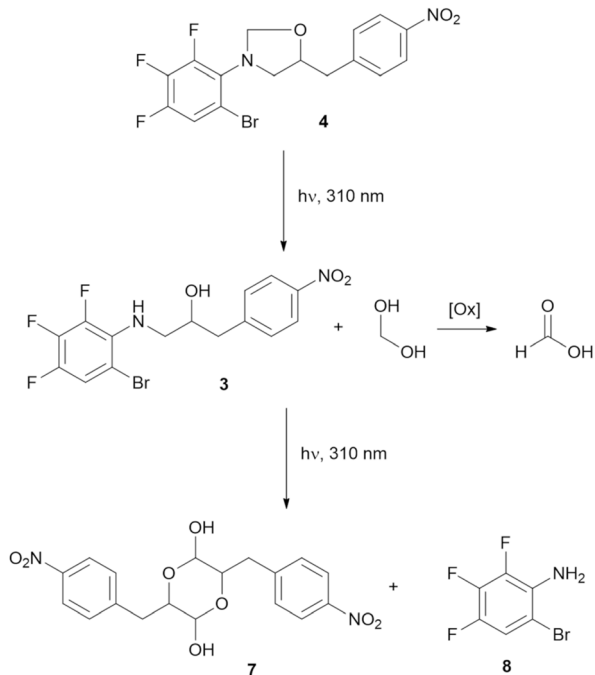


Fig. 3 Photodegradation of oxazolidine **4** through comparison of ^1H NMR spectra recorded during irradiation at 310 nm for the duration of 514 hours in $\text{ACN}-d_3:\text{D}_2\text{O}$ (7 : 3) at room temperature.

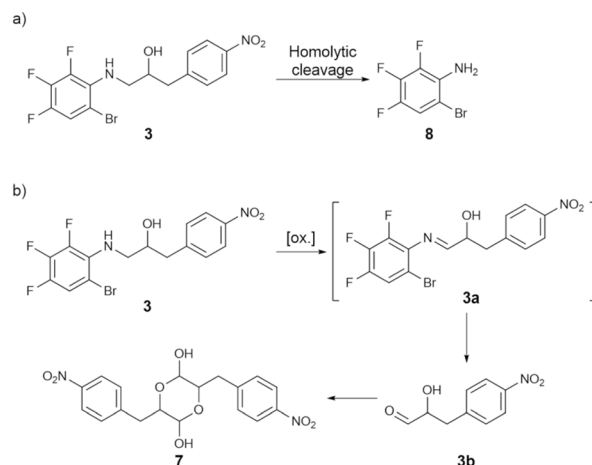
(Fig. S48 and S49). Both signals corresponded to a molecular formula of $\text{C}_{15}\text{H}_{13}\text{BrF}_2\text{N}_2\text{O}_4$, suggesting they are regioisomers resulting from either fluorine being substituted by a hydroxyl group. Examination of the isotopic pattern of the corresponding ions confirmed the presence of a Br atom in both regioisomers **11** and **12**, as evidenced by the characteristic $M + 2$ Da signal. A similar fluorine-to-hydroxyl substitution during photolysis was

recently reported^{26,27} during the photodegradation of Sitagliptin in aqueous media. The most plausible reaction mechanism for this photosubstitution (Scheme 6b) was proposed for fluoroquinolones.²⁸

The suggested mechanism involves the addition of water followed by the elimination of a fluoride anion *via* the triplet state, which was previously postulated³¹ for light-induced substitution reactions in other aromatic compounds. In that study, it was determined that position 5 in quinolone was preferred over position 6 for photosubstitution. In our case, three possible substitution positions were available, and although CID experiments revealed distinct fragmentation patterns (Fig. S50 and S52), the exact position of substitution could not be determined unambiguously (Fig. S51 and S53).

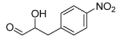
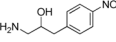
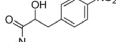
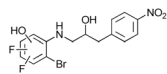
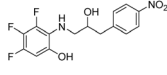
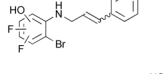
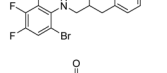
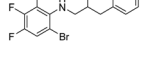


Scheme 4 Photodegradation pathway for oxazolidine **4** exposed to light with wavelength 310 nm in $\text{ACN}-d_3:\text{D}_2\text{O}$ (7 : 3) at room temperature.



Scheme 5 Photodegradation of ethanolamine **3** to give major degradation products: (a) aniline **8**; (b) dioxane bishemiacetal **7**.

Table 1 Minor degradation products of ethanolamine **3** discovered by LC-HRMS after irradiation with UV light (310 nm) in ACN-*d*₃: D₂O (7 : 3) at room temperature

DP	RT/min	Ion	Obs. <i>m/z</i>	Calc. <i>m/z</i>	Error/ppm	Suggested structure	<i>t</i> _{IRR} /h
3b	6.03	[M – H] [–]	194.0460	194.0459	0.61		7
9	4.64	[M + HCOO] [–]	240.0510	240.0514	–1.5		7
		[M + H] ⁺	197.0912	197.0921	–4.41		
10	7.15	[M + Cl] [–]	257.0334	257.0335	–0.23		7
		[M + HCOO] [–]	267.0618	267.0623	–1.72		
11 regioisomers	9.59	[M – H] [–]	400.9954	400.9954	0		7
12 regioisomers	10.51	[M + Cl] [–]	436.9732	436.9721	2.57		7
13	9.86	[M – H] [–]	400.9963	400.9954	2.24		7
		[M + H] [–]	341.0758	341.0755	0.98		
14 multiple isomers possible	10.28	[M + Cl] [–]	377.0507	377.0521	–3.83		25
		[M + HCOO] [–]	428.9908	428.9903	1.13		
15	11.57	[M – H] [–]	386.9947	386.9961	–0.13		7
		[M + Cl] [–]	422.9729	422.9728	0.17		
		[M + HCOO] [–]	433.0011	433.0016	–1.22		
16	11.86	[M – H] [–]	430.9857	430.9860	–0.64		7
		[M + Cl] [–]	466.9630	466.9627	0.74		
		[M + HCOO] [–]	476.9913	476.9915	–0.33		

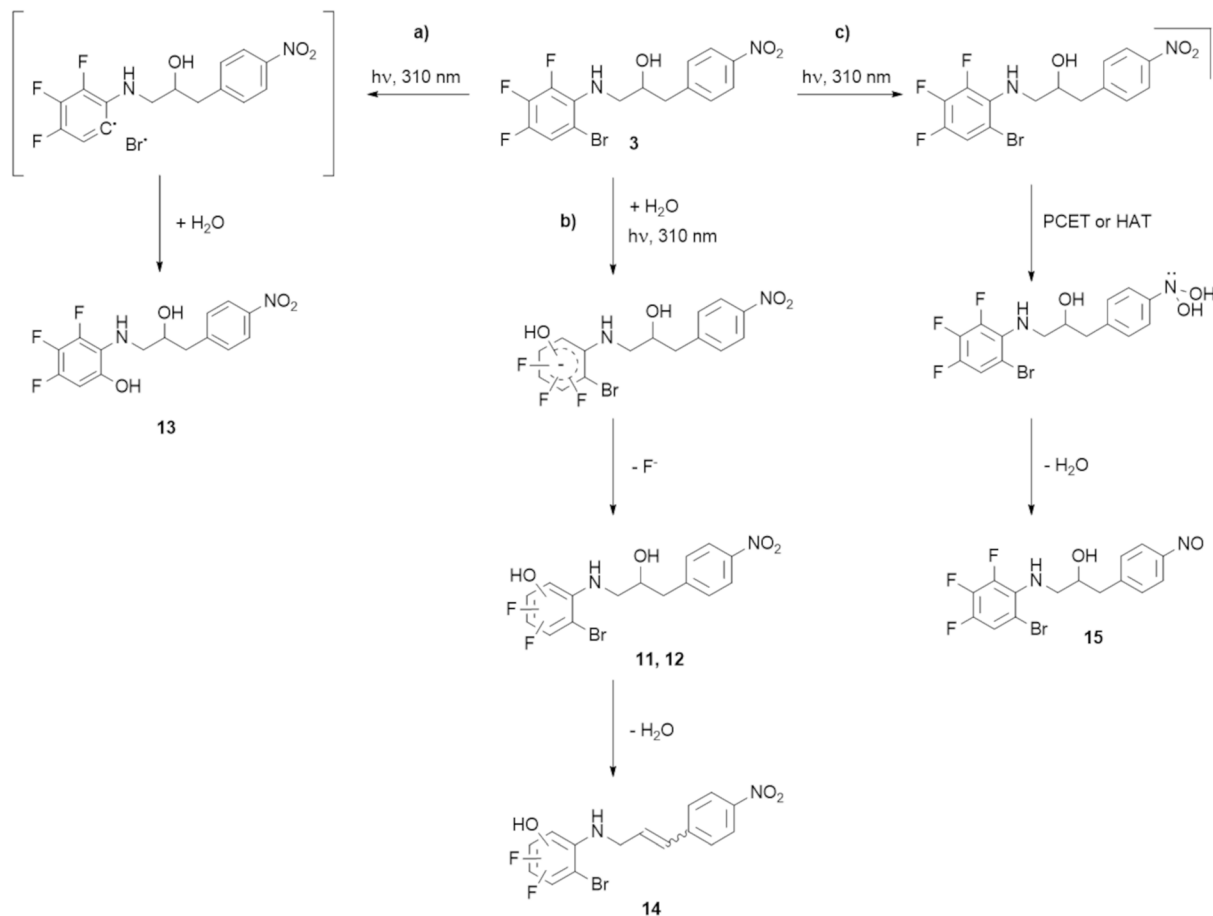
The HRMS signal at *m/z* 341.0758 (Fig. S54 and S55) for degradation product **13** (RT = 9.86 min) corresponded to the molecular formula C₁₅H₁₃F₃N₂O₄, indicating that bromine was substituted by a hydroxyl group. Careful examination of the isotopic pattern of *m/z* 341.0758 and its in-source fragment at *m/z* 323.0649 confirmed the absence of a bromine atom, as evident by the lack of the characteristic M + 2 Da signal. A degradation mechanism²⁹ leading to this outcome involves the formation of a radical pair following debromination, which then reacts with a water molecule to yield a stable hydroxy derivative (Scheme 6a). Similar mechanism was recently described for the pharmaceutical ambroxol³² and a series of bromophenols.³³

The degradation product **14** (RT = 10.28 min) was identified by a signal at *m/z* 428.9908, corresponding to the [M + HCOO][–] ion in the HRMS spectrum (Fig. S58 and S59) and matching the molecular formula C₁₅H₁₁BrF₃N₂O₃. This molecular formula, however, can correspond to at least three regioisomers and two double bond configurations (*E* and/or *Z* configuration), so this structure is tentative. Similar to degradation products **11** and **12**, the presence of a Br atom in degradation product **14** was readily confirmed by MS due to the characteristic ⁷⁹Br- and ⁸¹Br-isotope. Compared to the structure of ethanolamine **3**, this compound has undergone the loss of one water molecule, resulting in double bond formation, while one of its aromatic fluorine atoms has been substituted by a hydroxyl group. Compound **14** was the only degradation product detected at the second sampling time (25 h), suggesting that it may be a secondary degradation product. Given its structural similarity to compounds **11** and **12**, it is most likely derived from the dehydration of one of these compounds (Scheme 6b).

Additionally, MS/MS analysis (Fig. S60) revealed an interesting fragmentation pathway involving the loss of hydrogen bromide (Fig. S61) recently described in fragmentation of brominated aromatic compounds.³⁴

The HRMS signals at *m/z* 386.9947, 422.9729, and 433.0011 (Fig. S62 and S63) for degradation product **15** (RT 11.57) were assigned to [M – H][–], [M + Cl][–] and [M + HCOO][–] ions. MS/MS analysis (Fig. S64 and S65) did not yield the characteristic fragment *m/z* 136 (from 1-methyl-4-nitrobenzene). However, the presence of the fragment at *m/z* 120.0452 was observed, indicating reduction of the nitro group to the corresponding nitroso derivative. This degradation mode has previously been reported during photolysis of various nitroaromatic compounds in solid state^{35,36} and in solution.^{37,38} The possible mechanism was suggested³⁰ and involves proton-coupled electron transfer (PCET) or hydrogen atom transfer (HAT), formation of dihydroxylamine (–N(OH)₂) intermediate, followed by the loss of water (Scheme 6c).

Degradation product **16**, with an RT of 11.86 min, exhibited a complex HRMS spectrum (Fig. S67) characterized by distinguishing signals at *m/z* 430.9857 ([M – H][–]), 466.9630 ([M + Cl][–]), and 476.9913 ([M + HCOO][–]). MS/MS analysis of the [M + HCOO][–] ion (Fig. S68 and S69) revealed that the signals at *m/z* 364.9749 and 384.9812 in the native HRMS spectrum correspond to in-source fragments. Formic acid, which is generated in the mixture as a photodegradation product, can react with ethanolamine **3** to form esters such as degradation product **16**. The high acidity of formic acid allows it to self-catalyse esterification reactions.³⁹ However, due to steric hindrance around the hydroxyl



Scheme 6 Photodegradation of ethanolamine **3** to give degradation products through three previously described mechanisms: (a) ethanolamine **13**;²⁹ (b) compounds **11**, **12**, and **14**;²⁸ (c) nitroso **15**.³⁰

group, tertiary alcohols are less reactive than primary alcohols,⁴⁰ explaining why compound **16** is only a minor product.

Given that the solvent used in the degradation studies contained 30% D_2O , it is intriguing that water plays a crucial role in all described degradation mechanisms. Since the degradation reactions were conducted in an NMR tube, one might expect deuterium, rather than protons, to be detectable in the HRMS spectra. However, as only small aliquots (1 μL) of the deuterated degradation mixture were extracted and injected into the mobile phase containing protonated acetonitrile, water, and 0.1% formic acid, deuterium-proton exchange likely occurred, preventing the detection of deuterium in the MS analysis.

The comparison of the EIC areas measured at 7 hours and 195 hours (Fig. S73–S80) revealed that the majority of detected degradation products (**3b**, **9**, **10**, **11**, **12**, and **14**) were continuously formed throughout the irradiation period, as indicated by their increasing intensities over time. Compound **13** was the only degradation product that was exclusively generated during the first 7 hours and remained stable thereafter, as evident by its consistent EIC area. In contrast, degradation products **15** and **16** exhibited lower concentrations at 195 hours compared to the first sampling time, suggesting that these compounds may undergo further degradation at a faster rate than their formation.

4 Conclusions

This work follows our benign-by-design strategy for combating antibiotic resistance by developing antimicrobial scaffolds that intentionally photodegrade after use, reducing environmental persistence of bioactive compounds. In this study we have investigated the photodegradation of compounds containing three structurally related functional groups whose degradation could be triggered by light: oxazolidine **4**, dioxazepine **5** and ethanolamine **3**. Solid understanding of the chemical fate of these compounds after exposure to light is important in order to gain the knowledge required to successfully design pharmaceuticals following the strategy ‘benign by design’.^{10,11,41}

Oxazolidine **4** undergoes spontaneous decomposition into ethanolamine **3** at room temperature in $\text{ACN-}d_3:\text{D}_2\text{O}$ (7 : 3). This process is significantly accelerated by the addition of acid or irradiation with UV light ($\lambda = 310\text{ nm}$). Ethanolamine **3** subsequently undergoes homolytic cleavage, producing the major decomposition product aniline **8** and minor degradation product 1-amino-3-(4-nitrophenyl) propan-2-ol (**9**) (Table S1 and Fig. S41, S42). The formation of the second major product dioxane bishemiacetal **7** is believed to result from the oxidation of ethanolamine **3**, followed by hydrolysis and dimerization of

compound **3b**. However, the photodegradation of ethanolamine **3** is not limited to these, as, in addition to compound **9**, eight other minor degradation products were identified through LC-HRMS analysis, and their structures and mechanisms of formation proposed.

The second compound studied, dioxazepine **5**, does not appear to undergo spontaneous decomposition, as it remained stable for three days at room temperature during structure determination. However, immediately after the initiation of UV irradiation (310 nm), the formation of intermediate **6** was observed. Intermediate **6** was then hydrolysed into ethanolamine **3**.

Understanding the photodegradation mechanism of dioxazepine **5**, oxazolidine **4** and ethanolamine **3** enables us to predict the degradation behaviour of compounds with such structural motifs when exposed to UV light.

In conclusion, both oxazolidine and dioxazepine derivatives converge to a common degradation intermediate ethanolamine which further decomposes into two major products: aniline and dioxane bishemiacetal. This knowledge provides predictive framework for the design of greener drugs for future light-degradable pharmaceuticals with known, traceable breakdown products.

Author contributions

A. Čikoš: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, resources, software, supervision, visualization, writing – original draft, writing – review and editing. K. S. Håheim and David Klarić: data curation, formal analysis, investigation, methodology, writing – original draft, writing – review and editing. N. Galić: investigation, methodology, resources, supervision. M. Krznarić: data curation, formal analysis. L. N. Van Sang: data curation, formal analysis, writing – review and editing. S. Estopiña-Duran: data curation, formal analysis, investigation. M. O. Sydnès: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review and editing.

Conflicts of interest

The authors declare that they have no competing financial or non-financial interests, currently or previously.

Data availability

All data generated during this research is included in the submitted article and accompanying supplementary information (SI). Supplementary information: (Fig. S1–S86 and Table S1) contains experimental conditions for degradation, full analytical characterisation of each identified compound, MS spectra and fully assigned NMR spectra with extracted proton and carbon chemical shifts. See DOI: <https://doi.org/10.1039/d6su00265j>.

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Notes and references

- 1 Antibiotic Resistance Collaborators, *Lancet*, 2024, **404**, 1199–1226.
- 2 Antibiotic Resistance Collaborators, *Lancet*, 2022, **399**, 629–655.
- 3 A. Fleming, *Nobel Prize lecture*, 1945, <https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/>.
- 4 N. Hanna, A. J. Tamhankar and C. Stålsby Lundborg, *Lancet Planet. Health*, 2023, **7**, e45–e54.
- 5 M.-C. Danner, A. Robertson, V. Behrends and J. Reiss, *Sci. Total Environ.*, 2019, **664**, 793–804.
- 6 L. Gomez Cortes, D. Marinov, I. Sanseverino, A. Navarro Cuenca, M. Niegowska, E. Porcel Rodríguez, F. Stefanelli and T. Lettieri, *Selection of substances for the 4th Watch List under the Water Framework Directive*, Publications Office of the European Union, Luxembourg, 2022, DOI: [10.2760/01939](https://doi.org/10.2760/01939).
- 7 M. Patel, R. Kumar, K. Kishor, T. Mlsna, C. U. J. Pittman and D. Mohan, *Chem. Rev.*, 2019, **119**, 3510–3673.
- 8 J. L. Wilkinson, A. B. A. Boxall, D. W. Kolpin, K. M. Y. Leung, R. W. S. Lai, C. Galbán-Malagón, A. D. Adell, J. Mondon, M. Metian, R. A. Marchant, A. Bouzas-Monroy, A. Cuni-Sanchez, A. Coors, P. Carriquiriborde, M. Rojo, C. Gordon, M. Cara, M. Moermond, T. Luarte, V. Petrosyan, Y. Perikanyan, C. S. Mahon, C. J. McGurk, T. Hofmann, T. Kormoker, V. Iniguez, J. Guzman-Otazo, J. L. Tavares, F. Gildasio De Figueiredo, M. T. P. Razzolini, V. Dognon, G. Gbaguidi, O. Traoré, J. M. Blais, L. E. Kimpe, M. Wong, D. Wong, R. Nchantcho, J. Pizarro, G.-G. Ying, C.-E. Chen, M. Páez, J. Martínez-Lara, J.-P. Otamonga, J. Poté, S. A. Ifo, P. Wilson, S. Echeverría-Sáenz, N. Udikovic-Kolic, M. Milakovic, D. Fatta-Kassinos, L. Ioannou-Ttofa, V. Belušová, J. Vymazal, M. Cárdenas-Bustamante, B. A. Kassa, J. Garric, A. Chaumot, P. Gibba, I. Kunchulia,

- S. Seidensticker, G. Lyberatos, H. P. Halldórsson, M. Melling, T. Shashidhar, M. Lamba, A. Nastiti, A. Supriatin, N. Pourang, A. Abedini, O. Abdullah, S. S. Gharbia, F. Pilla, B. Chefetz, T. Topaz, K. M. Yao, B. Aubakirova, R. Beisenova, L. Olaka, J. K. Mulu, P. Chatanga, V. Ntuli, N. T. Blama, S. Sherif, A. Z. Aris, L. J. Looi, M. Niang, S. T. Traore, R. Oldenkamp, O. Ogunbanwo, M. Ashfaq, M. Iqbal, Z. Abdeen, A. O'Dea, J. M. Morales-Saldaña, M. Custodio, H. De La Cruz, I. Navarrete, F. Carvalho, A. B. Gogra, B. M. Koroma, V. Cerkvenik-Flajs, M. Gombač, M. Thwala, K. Choi, H. Kang, J. L. C. Ladu, A. Rico, P. Amerasinghe, A. Sobek, G. Horlitz, A. K. Zenker, A. C. King, J.-J. Jiang, R. Kariuki, M. Tumbo, U. Tezel, T. T. Onay, J. B. Lejju, Y. Vystavna, Y. Vergeles, H. Heinzen, A. Pérez-Parada, D. B. Sims, M. Figy, D. Good and C. Teta, *Proc. Natl. Acad. Sci. U. S. A.*, 2022, **119**, e2113947119.
- 9 L. Gunnarsson, J. R. Snape, B. Verbruggen, S. F. Owen, E. Kristiansson, L. Margiotta-Casaluci, T. Österlund, K. Hutchinson, D. Leverett, B. Marks and C. R. Tyler, *Environ. Int.*, 2019, **129**, 320–332.
- 10 K. S. Håheim, L. N. Van Sang and M. O. Sydnese, *ChemSusChem*, 2025, e2500788.
- 11 T. Brodin, M. G. Bertram, K. E. Arnold, A. B. A. Boxall, B. W. Brooks, D. Cervený, M. Jörg, K. A. Kidd, U. Lertxundi, J. M. Martin, L. T. May, E. S. McCallum, M. Michelangeli, C. R. Tyler, B. B. M. Wong, K. Kümmerer and G. Orive, *Nat. Sustainability*, 2024, **7**, 949–951.
- 12 V. Eikemo, B. Holmelid, L. K. Sydnese and M. O. Sydnese, *J. Org. Chem.*, 2022, **87**, 8034–8047.
- 13 G. A. Souto De Aquino, L. Nguyen Van Sang, R. Valery, M. Lanave, S. Estopiñá-Durán, K. S. Håheim, S. B. Ferreira and M. O. Sydnese, *RSC Adv.*, 2023, **13**, 29729–29734.
- 14 V. Eikemo, L. K. Sydnese and M. O. Sydnese, *RSC Adv.*, 2021, **11**, 32339–32345.
- 15 M. O. Sydnese and K. S. Håheim, WO2024079276A9, 2024.
- 16 G. F. S. Fernandes, C. B. Scarim, S.-H. Kim, J. Wu and D. Castagnolo, *RSC Med. Chem.*, 2023, **14**, 823–847.
- 17 C. Feldmeier, H. Bartling, E. Riedle and R. M. Gschwind, *J. Magn. Reson.*, 2013, **232**, 39–44.
- 18 A. Seegerer, P. Nitschke and R. M. Gschwind, *Angew. Chem., Int. Ed.*, 2018, **57**, 7493–7497.
- 19 Y. Ji, D. A. DiRocco, J. Kind, C. M. Thiele, R. M. Gschwind and M. Reibarkh, *ChemPhotoChem*, 2019, **3**, 984–992.
- 20 G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176–2179.
- 21 ThorLabs, Technical Information for M310F1, <https://media.thorlabs.com/globalassets/items/m/m3/m31/m310f1/mtn022604-s01.pdf?v=0116010427>, accessed June 20, 2026.
- 22 A. Schrey, F. Osterkamp, A. Straudi, C. Rickert, H. Wagner, U. Koert, B. Herrschaft and K. Harms, *Eur. J. Org. Chem.*, 1999, **1999**, 2977–2990.
- 23 G. P. Moloney, M. N. Iskander and D. J. Craik, *J. Pharm. Sci.*, 2010, **99**, 3362–3371.
- 24 T. H. Fife and J. E. C. Hutchins, *J. Org. Chem.*, 1980, **45**, 2099–2104.
- 25 T. Sugimoto and T. Tanikawa, *ACS Med. Chem. Lett.*, 2011, **2**, 234–237.
- 26 A. P. Bhat, W. C. K. Pomerantz and W. A. Arnold, *Environ. Sci. Technol.*, 2024, 3437–3448.
- 27 A. P. Bhat, T. F. Mundhenke, Q. T. Whiting, A. A. Peterson, W. C. K. Pomerantz and W. A. Arnold, *ACS Environ. Au*, 2022, **2**, 242–252.
- 28 A. Albini and S. Monti, *Chem. Soc. Rev.*, 2003, **32**, 238.
- 29 H.-I. Joschek and S. I. Miller, *J. Am. Chem. Soc.*, 1966, **88**, 3269–3272.
- 30 M. G. Kallitsakis, D. I. Ioannou, M. A. Terzidis, G. E. Kostakis and I. N. Lykakis, *Org. Lett.*, 2020, **22**, 4339–4343.
- 31 A. M. J. Van Eijk, A. H. Huizer, C. A. G. O. Varma and J. Marquet, *J. Am. Chem. Soc.*, 1989, **111**, 88–95.
- 32 L. Wang, H. Xu, J. Lu, J.-M. Chovelon and Y. Ji, *Water Res.*, 2022, **226**, 119275.
- 33 L. Fu, X. Peng, Q. Chen, Y. Ding and J. Jiang, *Sep. Purif. Technol.*, 2022, **280**, 119862.
- 34 W. M. A. Niessen, *Int. J. Mass Spectrom.*, 2021, **460**, 116496.
- 35 Y. Kawabe, H. Nakamura, E. Hino and S. Suzuki, *J. Pharm. Biomed. Anal.*, 2008, **47**, 618–624.
- 36 V. Marinkovic, D. Agbaba, K. Karljickovic-Rajic, J. Comor and D. Zivanov-Stakic, *Il Farmaco*, 2000, **55**, 128–133.
- 37 E. Fasani, D. Dondi, A. Ricci and A. Albini, *Photochem. Photobiol.*, 2006, **82**, 225.
- 38 Z. I. García-Berrios and R. Arce, *J. Phys. Chem. A*, 2012, **116**, 3652–3664.
- 39 B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Longman Group UK Limited, Harlow, UK, 5th edn, 1989.
- 40 C. G. Carlson, J. E. Hall, Y. Y. Huang, S. Kotila, A. Rauk and D. F. Tavares, *Can. J. Chem.*, 1987, **65**, 2461–2463.
- 41 K. Kümmerer, *Green Chem.*, 2007, **9**, 899–907.