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Oxazole light triggered protecting groups: synthesis and photolysis of fused heteroaromatic conjugates

Ana M.S. Soares, Susana P.G. Costa, M. Sameiro T. Gonçalves *

Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

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ABSTRACT

Fused oxazole derivatives were synthesized and evaluated as new light triggered protecting groups by using amino acids as model bifunctional molecules. The photosensitivity of ester conjugates was tested under irradiation at 254, 300, and 350 nm. Oxazole conjugates were readily photolyzed with complete release of the amino acid, the best results obtained for naphtho[2,3-*d*]oxazole at 254 and 300 nm, being the first reported application of this type of heterocycles as photocleavable protecting groups for carboxylic acids.

1. Introduction

The need for protecting groups represents a deviation from the concept of an ideal organic synthesis, which should be as fast and efficient as possible from readily available reagents in a simple, safe, and environmentally friendly process. Although very interesting examples of protecting group-free syntheses have been accomplished in recent years,[1] most of the synthetic work is still performed by using classical protecting group chemistry, with its inherent drawbacks. To overcome these limitations, several strategies have been proposed from which light activated protecting groups stand out as an attractive option as no additional reagents are required for deprotection. This feature is appealing in solution and solid phase organic synthesis for the masking of aldehydes and ketones,[2] carboxylic acids,[3] alcohols,[4] thiols,[5] and amines,[6] and especially in biomedical research for the caging of biomolecules.[7–10] There are also reports for the application of photolabile groups and linkers in nanotechnology and materials sciences.[11–15] Numerous types of structures have been proposed with particular emphasis on aromatics, such as 2-nitrobenzyl,[16] benzoin,[17] phenacyl,[18] cinnamyl,[19] 3-nitro-2-naphthalenemethanol,[20] anthracene-9-methanol,[21] phenanthren-9-ylmethoxycarbonyl,[22] anthraquinon-2-ylmethoxycarbonyl,[22] 2-(1′-hydroxyethyl)-anthraquinon,[23] anthraquinon-2-ylethyl-1′,2′-diol,[24] pyren-1-ylmethyl,[25] pyren-1-ylmethoxycarbonyl,[22] and heteroaromatics like acylnitroindolines,[26] xanthones,[6] coumarins (trivial designation for 2-oxo-2*H*-benzopyrans),[27] benzocoumarins,[28] quinolines,[29] and quinolones.[30] Attempts to improve and tune the photolability of the above mentioned groups have been achieved through synthetic tailoring in terms of substituents present in the structure. Recent research by the authors has been focused on the synthesis and application of novel oxygen and nitrogen heterocycles as photolabile protecting groups for the carboxylic and amine functions of amino acids, as well as neurotransmitters.[28,30–34] Bearing these facts in mind, the present work intends to evaluate the use of oxazole as the basis for a novel and alternative protecting group for carboxylic acids, a type of heterocycle, which has never been reported for photriggering applications, to the best of our knowledge. It is now presented the synthesis of novel ester conjugates based on benzo[*d*]oxazole, naphtho[2,3-*d*]oxazole, and oxobenzopyrano[6,7-*d*]oxazole, the latter having the linkage between the heterocycle and the bifunctional model molecule through the oxazole or the oxopyran moieties. The stability of the ester bond to irradiation was evaluated in a photochemical reactor at 254, 300, and 350 nm and photocleavage kinetic data was obtained.

2. Results and discussion

The synthesis of bromomethylated benzo[*d*]oxazole (Box-Br) **1** and naphtho[2,3-*d*]oxazole (Nox-Br) **2** was achieved by condensation reaction between 2-aminophenol and 3-aminonaphthalen-2-ol, respectively, and bromoacetic acid, mediated by polyphosphoric acid (PPA). 4-Aminobenzene-1,3-diol was reacted with ethyl acetoacetate or ethyl 4-chloroacetoacetate through a Pechmann reaction, catalyzed by sulfuric acid at room temperature, yielding the

* Corresponding author. Tel.: + 351 253 604372; fax: +351 253 604382; e-mail address: msameiro@quimica.uminho.pt (M.S.T. Gonçalves).

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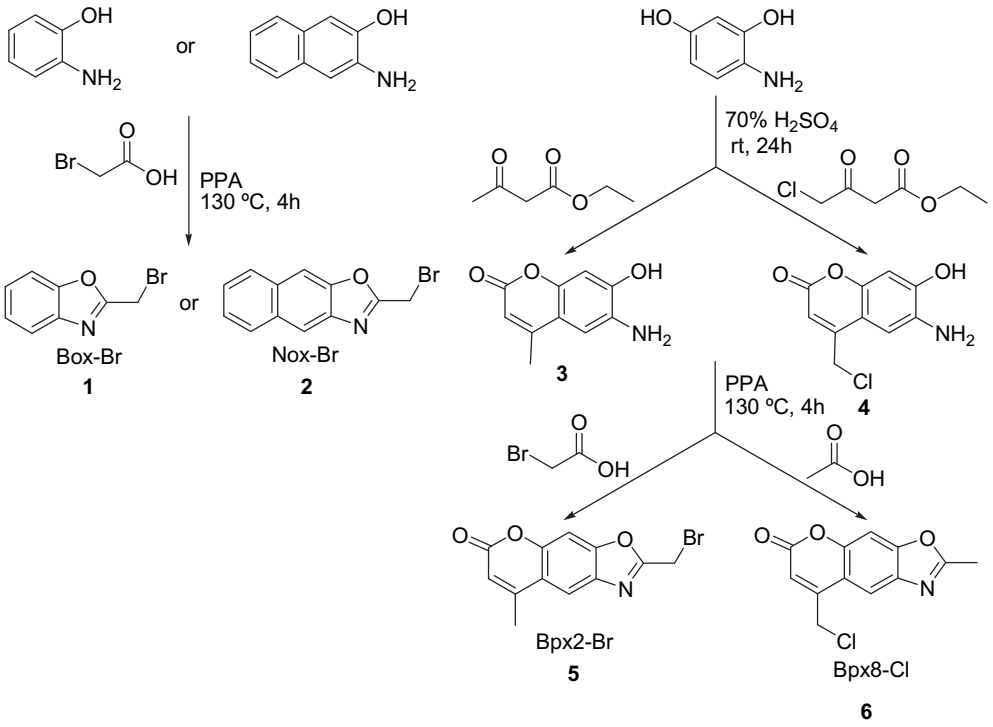
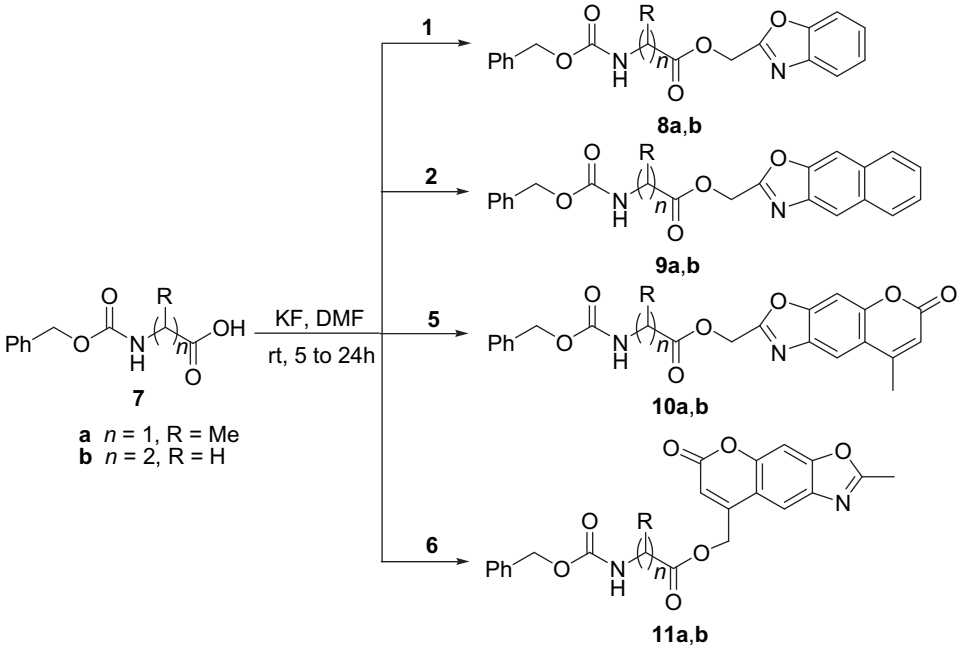
corresponding 6-amino-7-hydroxy-4-methyl-2-oxo-2*H*-benzopyran **3** and 6-amino-4-(chloromethyl)-7-hydroxy-2-oxo-2*H*-benzopyran **4**. Cyclization of compounds **3** and **4** with bromoacetic acid or acetic acid afforded the fused oxazole derivatives 2-(bromomethyl)-8-methyl-6-oxo-6*H*-benzopyrano[6,7-*d*]oxazole (Bpx2-Br) **5** and 8-(chloromethyl)-2-methyl-6-oxo-6*H*-benzopyrano[6,7-*d*]oxazole (Bpx8-Cl) **6** (Scheme 1).

The latter compounds were linked to the model bifunctional moieties either through the oxazole or the oxopyran, allowing the evaluation of the influence of the adjacent heterocycle in the photocleavage process. Compounds **1**, **2**, **5**, and **6**, bearing a reactive halomethyl group, were used in the derivatization at the C-terminus of *N*-benzyloxycarbonyl-protected alanine (**7a**) and β-alanine (**7b**) in the presence of potassium fluoride in DMF, at room temperature,[35] resulting in the model ester conjugates **8**–**11** (Scheme 2). All compounds synthesized were fully characterized by high resolution mass spectrometry, IR, ^{1}H, and ^{13}C NMR spectroscopy.

Considering that the present work involved the evaluation of oxazoles as new photocleavable protecting groups, UV–visible spectroscopic characterization was carried out to obtain the



Scheme 1. Synthesis of functionalized fused oxazoles **1**–**6**.



Scheme 2. Synthesis of model amino acid ester conjugates **8**–**11**.

parameters needed for monitorization during photolysis. Absorption spectra of degassed 10^{-5} M solutions in absolute ethanol and in a methanol/HEPES buffer (80:20) solution of conjugates **8**–**11**, in comparison with precursors **1**–**6** were measured, absorption maxima and molar absorptivities are reported (Table 1). By comparison of the absorption maxima for all compounds in both solvents, no significant changes were observed, being for conjugates **8**–**11** in the range 269–325 nm. Furthermore, upon linkage of benzoxazole **1** and naphthoxazole **2** to amino acids, an hypsochromic shift of ca. 20 or 30 nm (in ethanol and methanol/HEPES buffer) was observed for conjugates **8a**,**b** and **9a**,**b**, respectively. The evaluation of heterocycles **1**,**2**,**5**, and **6** as photolabile protecting groups was carried out by photolysis studies of the corresponding alanine and β-alanine conjugates **8**–**11** under irradiation at different wavelengths. Concerning the amino acid moiety, both are suitable as models for bifunctional compounds whose application on protecting group-free syntheses is not straightforward and that could benefit from a photolytic deprotection strategy.

Table 1
Yields and UV/vis data in ethanol and methanol/HEPES buffer (80:20) solutions for compounds **1**–**6** and **8**–**11**

Compound	Yield (%)	Ethanol		Methanol/HEPES buffer (80:20)	
		λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
1	58	290	3.73	286	3.71
2	13	334	3.67	334	3.60
3	99	318	3.54	359	3.75
4	63	315	3.45	342	3.65
5	23	325	3.80	325	3.54
6	34	326	3.98	325	3.94
8a	56	270	3.60	270	3.64
8b	49	270	3.64	269	366
9a	99	302	3.95	303	3.95
9b	90	301	4.04	301	3.63
10a	53	323	4.01	323	4.08
10b	95	323	4.01	322	3.80
11a	86	325	3.95	325	3.95
11b	98	324	3.95	324	3.94

Solutions of the mentioned compounds (1×10^{-4} M) in methanol/HEPES buffer (80:20) solution were irradiated in a Rayonet RPR-100 reactor at 254, 300, and 350 nm in order to determine the most favorable cleavage conditions. The course of the photocleavage reaction was followed by reverse phase HPLC with UV detection. The plots of peak area (A) of the starting material versus irradiation time were obtained for each compound, at the considered wavelengths. Peak areas were determined by HPLC, which revealed a gradual decrease with time, and were the average of three runs. The determined irradiation time represents the time necessary for the consumption of the starting materials until less than 5% of the initial area was detected (Table 2). For each compound and based on HPLC data, the plot of ln A versus irradiation time showed a linear correlation for the disappearance of the starting material, which suggested a first order reaction, obtained by the linear least squares methodology for a straight line, with good correlation coefficients. The corresponding rate constants (k) were calculated and are presented in Table 2.

Table 2
Irradiation times (t_{Irr}, min) and rate constants (k, $\times10^{-2}$ min^{-1}) for the photolysis of conjugates **8**–**11**, at different wavelengths in methanol/HEPES buffer (80:20) solution

Compound	254 nm		300 nm		350 nm	
	t_{Irr}	k	t_{Irr}	k	t_{Irr}	k
8a Z-Ala-OBox	0.7	391.2	17.4	17.3	—	—
8b Z-β-Ala-OBox	3.4	86.8	88.5	3.4	—	—
9a Z-Ala-ONox	1.3	228.7	2.3	127.9	1127	0.3
9b Z-β-Ala-ONox	4.8	63.0	5.3	54.6	3731	0.1
10a Z-Ala-OBpx2	58.5	5.3	53.3	5.7	4973	0.06
10b Z-β-Ala-OBpx2	27.8	10.8	37.0	8.2	7545	0.04
11a Z-Ala-OBpx8	35.4	8.3	18.9	16.1	244	1.3
11b Z-β-Ala-OBpx8	27.6	11.3	19.3	16.0	242	1.2

As mentioned earlier, 2-oxo-2*H*-benzopyran (coumarin) derivatives are among the well-established light activable protecting groups, and in addition to evaluate for the first time the potential for the applicability of oxazoles as a photolabile protecting groups, it was intended to assess the influence of the combination of 2-oxo-2*H*-benzopyran and oxazole in a fused system on the photorelease properties. It was found that conjugates **8** and **9** bearing a benzo[*d*]oxazole (Box) and naphtho[2,3-*d*]oxazole (Nox), cleaved readily at 254 and 300 nm. Having in mind that for practical applications longer irradiation wavelengths are preferable, the best results at 300 nm were obtained for the naphtho[2,3-*d*]oxazole conjugates **9a**,**b**, occurring quantitative release of alanine and β-alanine within 2 and 5 min, respectively. The presence of oxobenzopyrano[6,7-*d*]oxazole (Bpx2 and Bpx8) in conjugates **10** and **11**, which makes them suitable for the evaluation of the effect of replacement of a benzenic ring by an oxopyran, in the photorelease process, was also studied. Furthermore, in these conjugates the linkage to the amino acid was performed by either through the oxazole or the oxopyran, being possible to assess the influence of the adjacent heterocycle on the lability of the ester bond. The results indicated that the presence of the oxopyran fused to the benzoxazole increased the irradiation time in conjugates **10a** (53 min) and **10b** (37 min), which were linked by the oxazole as in the case of naphtho[2,3-*d*]oxazoles **9**, thus suggesting that this structural change was not advantageous. For conjugates **11**, there was also an increase in the irradiation times when compared to **9**, but in this case the ester bond to the amino acid was through the oxopyran. However, in the latter the observed increase was not so marked as for conjugates **10**. Photocleavage at 350 nm was also carried out for all conjugates, and although they possessed much lower sensitivity to irradiation at this wavelength, conjugates **11a**,**b** (linked through the oxopyran) presented the shorter irradiation times (at about 240 min, 4 h), which is in agreement with our previously reported results concerning the use of oxobenzobenzopyrans as protecting groups, being appealing for the photorelease at 350 nm.[28,34]

Benzo[*d*]oxazole, naphtho[2,3-*d*]oxazole, and oxobenzopyrano[6,7-*d*]oxazole linked through the oxazole (conjugates **8**, **9**, and **10**, respectively) do not cleave or cleave very slowly at 350 nm, thus suggesting the feasibility of selective photodeprotection at this wavelength, if used in the presence of oxobenzopyrano[6,7-*d*]oxazole linked though the oxopyran (conjugate **11**). As reported before, the *N*-benzyloxycarbonyl group was stable in the tested conditions, no cleavage being detected.[31]

In addition, the photolysis process at 300 nm was also monitorized by ^{1}H NMR in a methanol-d_4/D_2O (80:20) solution for all conjugates in a concentration of 9.0×10^{-3} M, which is several times larger than the concentration used in the experiments followed by HPLC, leading to an increase in the photolysis time for the complete release of the amino acid. During irradiation, the signals related to the linked amino acid decreased gradually, with concomitant increase of its signals in the released form, as well as signals due to aromatic by-products related to the protecting group. Depending on the structure of the conjugate (amino acid and/or heterocycle), variable irradiation times were required for the quantitative release of the caged amino acid (see Fig. 1 for conjugate **9b**).

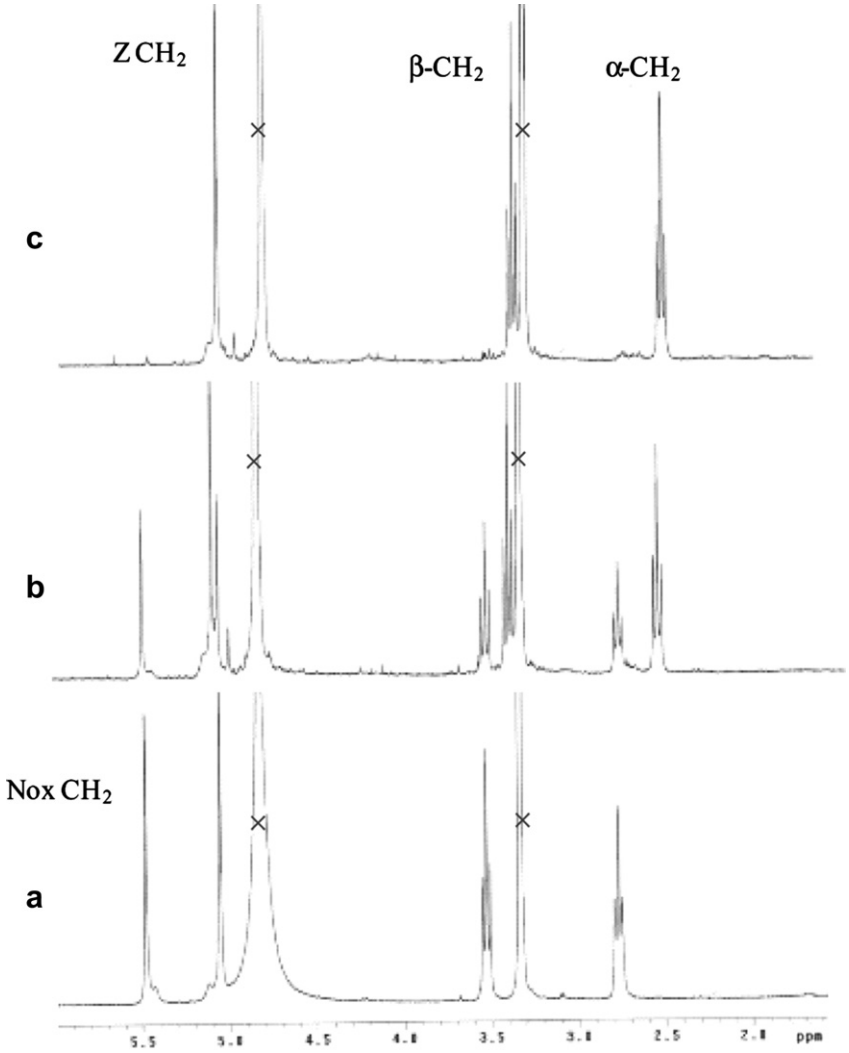


Figure 1. ^{1}H NMR spectra (aliphatic region) in methanol-d_4/D_2O (80:20) solutions of the photolysis of conjugate Z-β-Ala-ONox **9b** (C=9.0×10^{-3} M) at 300 nm: (a) before irradiation; (b) after irradiation for 90 min; (c) after irradiation for 270 min.

3. Conclusions

In summary, the evaluation of oxazole derivatives, obtained by simple one- or two-step syntheses, as new light triggered protecting groups, was carried out by submitting the corresponding model ester conjugates to irradiation at 254, 300, and 350 nm in methanol/HEPES buffer (80:20) solution. The oxazole conjugates required short irradiation times for the quantitative release of the amino acids at 254 and 300 nm, the best results obtained for naphtho[2,3-*d*]oxazole (1–5 min). At 350 nm, only oxobenzopyrano[6,7-*d*]oxazole linked through the oxopyran showed a practical irradiation time, a feature that may be exploited in a selective photodeprotection strategy in presence of the remaining oxazoles. Overall, these results suggest that the studied oxazole derivatives may be considered as promising alternatives as photocleavable protecting groups for carboxylic acids.

4. Experimental section

4.1. General

All melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F_{254}) and spots were visualised under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230–240 mesh). IR spectra were determined on a BOMEM MB 104 spectrophotometer. UV/visible absorption spectra (200–800 nm) were obtained using a Shimadzu UV/2501PC spectrophotometer. NMR spectra were obtained on a Varian Unity Plus Spectrometer at an operating frequency of 300 MHz for ^{1}H NMR and 75.4 MHz for ^{13}C NMR or a Bruker Avance III 400 at an operating frequency of 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR using the solvent peak as internal reference at 25 °C. All chemical shifts are given in ppm using δ_H Me_4Si=0 ppm as reference and *J* values are given in hertz. Assignments were made by comparison of chemical shifts, peak multiplicities, and *J* values and were supported by spin decoupling-double resonance and bidimensional heteronuclear HMBC and HMQC correlation techniques. Low and high resolution mass spectrometry analyses were performed at the 'C.A.C.T.I. – Unidad de Espectrometria de Masas', at University of Vigo, Spain. Commercially available reagents were used as received.

4.2. Synthetic procedures for precursors 1–6

4.2.1. Synthesis of 2-(bromomethyl)benzo[d]oxazole ***1****.* To a mixture of 2-aminophenol (0.250 g, 2.29 mmol) in polyphosphoric acid (2.29 g), bromoacetic acid (0.478 g, 3.44 mmol) was added and stirred at 130 °C for 4 h. The reaction mixture was poured into ice water and stirred for 1 h to give a fine brown precipitate. The solid

was collected by filtration, washed with cold water, and dried in a vacuum oven. The compound **1** was obtained as a brown solid (0.279 g, 58%). Mp=119.2–120.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=4.61 (s, 2H, CH_2), 7.34–7.44 (m, 2H, H-5, and H-6), 7.54–7.59 (m, 1H, H-7), 7.73–7.77 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=20.59 (CH_2), 110.88 (C-7), 120.50 (C-4), 124.86 (C-6), 126.01 (C-5), 141.02 (C-3a), 151.13 (C-7a), 161.03 (C-2). IR (KBr 1%, cm^{-1}): ν=3039, 2972, 1681, 1611, 1568, 1538, 1479, 1467, 1452, 1432, 1346, 1289, 1242, 1226, 1215, 1192, 1173, 1145, 1124, 1106, 1000, 951, 863, 838, 762, 749, 734, 691, 666, 623. UV/vis (ethanol, nm): λ_{max} (log ε)=290 (3.73).

4.2.2. Synthesis of 2-(bromomethyl)naphtho[2,3-d]oxazole ***2****.* Starting from 3-aminonaphthalen-2-ol (0.300 g, 1.88 mmol) in polyphosphoric acid (1.88 g) and bromoacetic acid (0.262 g, 1.88 mmol), following the same procedure as described before for the synthesis of compound **1**, a fine greenish precipitate was obtained. Purification by dry flash chromatography, using ethyl acetate/*n*-hexane, mixtures of increasing polarity as the eluent gave compound **2** as a pink solid (0.062 g, 13%). Mp=133.1–133.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=4.63 (s, 2H, CH_2), 7.48–7.58 (m, 2H, H-6, and H-7), 7.94 (s, 1H, H-9), 7.96 (dd, *J* 6.8 and 2.7 Hz, 1H, H-8), 8.01 (dd, *J* 6.9 and 2.7 Hz, 1H, H-5), 8.19 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=20.62 (CH_2), 106.78 (C-9), 118.17 (C-4), 124.96 (C-7), 125.94 (C-6), 127.95 (C-8), 128.61 (C-5), 131.38 (C-8a), 131.99 (C-4a), 140.81 (C-3a), 149.80 (C-9a), 163.25 (C-2). IR (KBr 1%, cm^{-1}): ν=3395, 3355, 3166, 1659, 1622, 1604, 1590, 1547, 1485, 1455, 1420, 1357, 1250, 1233, 1218, 1158, 1019, 971, 879, 864, 747, 715, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=334 (3.67). HRMS (EI): calcd for $C_{12}H_8NO^{79}Br$ [M^+]: 260.9789; found: 260.9786; calcd for $C_{12}H_8NO^{81}Br$ [M^+]: 262.9769; found: 260.9786.

4.2.3. Synthesis of 6-amino-7-hydroxy-4-methyl-2-oxo-2H-benzopyran ***3****.* To a solution of 4-aminobenzene-1,3-diol (0.040 g, 0.248 mmol) in 70% aqueous sulfuric acid (2 mL), ethyl acetoacetate (0.1 mL, 0.744 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was poured into ice water and stirred for 20 min to give a fine gray precipitate. The solid was collected by filtration, washed with cold water, and dried in a vacuum oven. The compound **3** was obtained as a gray solid (0.047 g, 99%). Mp=243.6–244.2 °C. ^{1}H NMR (DMSO-d_6, 300 MHZ): δ=2.32 (d, *J* 1.2 Hz, 3H, CH_3), 6.15 (d, *J* 1.2 Hz, 1H, H-3), 6.78 (s, 1H, H-8), 7.24 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 75.4 MHZ): δ=18.15 (CH_3), 102.21 (C-8), 110.89 (C-3), 111.92 (C-4a), 113.64 (C-5), 125.79 (C-6), 149.92 (C-8a), 151.41 (C-7), 152.98 (C-4), 160.30 (C-2). IR (KBr 1%, cm^{-1}): ν=3646, 3390, 3065, 2928, 2623, 1731, 1639, 1622, 1577, 1537, 1515, 1454, 1395, 1370, 1353, 1281, 1251, 1233, 1215, 1174, 1139, 1120, 1060, 976, 929, 892, 854, 745, 708, 686, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=318 (3.54). HRMS (EI): calcd for $C_{12}H_9NO_3$ [M^+]: 191.0582; found: 191.0589.

4.2.4. Synthesis of 6-amino-4-(chloromethyl)-7-hydroxy-2-oxo-2H-benzopyran ***4****.* Starting from 4-aminobenzene-1,3-diol (0.050 g, 0.309 mmol) in 70% aqueous sulfuric acid (2 mL) and ethyl chloroacetoacetate (0.70 mL, 0.464 mmol), following the same procedure as described before for the synthesis of compound **3** gave compound **4** as a gray solid (0.044 g, 63%). Mp=173.1–174.5 °C. ^{1}H NMR (DMSO-d_6, 400 MHZ): δ=4.88 (s, 2H, CH_2), 6.46 (s, 1H, H-3), 6.84 (s, 1H, H-8), 7.36 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6, 100.6 MHZ): δ=41.40 (CH_2), 102.58 (C-8), 109.27 (C-4a), 111.95 (C-3), 114.15 (C-5 and C-6), 150.31 (C-8a), 150.85 (C-7), 152.10 (C-4), 160.06 (C-2). IR (KBr 1%, cm^{-1}): ν=3457, 3085, 2927, 2637, 1738, 1704, 1642, 1622, 1549, 1519, 1448, 1399, 1381, 1352, 1288, 1258, 1174, 1135, 1062, 1031, 977, 946, 897, 877, 839, 806, 779, 742, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=315 (3.45). HRMS (ESI): calcd for $C_{10}H_9NO_3{}^{35}Cl$ [M^++1]: 226.02655; found: 226.02623. calcd for $C_{10}H_9NO_3{}^{37}Cl$ [M^++1]: 228.02360; found: 228.02333.

4.2.5. Synthesis of 2-(bromomethyl)-8-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole ***5****.* Starting from 6-amino-7-hydroxy-4-methyl-2-oxo-2*H*-benzopyrane **3** (0.100 g, 0.524 mmol) in polyphosphoric acid (0.524 g) and bromoacetic acid (0.109 g, 0.785 mmol), following the same procedure as described before for the synthesis of compound **1** (stirring time 5 h), a fine pink precipitate was obtained. Purification by dry flash chromatography, using ethyl acetate/*n*-hexane, mixtures of increasing polarity as eluent gave compound **5** as a white solid (0.036 g, 23%). Mp=220.1–221.4 °C. ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=2.53 (d, *J* 1.2 Hz, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.34 (d, *J* 1.2 Hz, 1H, H-7), 7.52 (s, 1H, H-4), 7.96 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=19.22 (CH_3), 20.03 (CH_2), 99.68 (C-4), 114.35 (C-7), 115.78 (C-9), 118.08 (C-8a), 137.98 (C-9a), 152.24 (C-4a), 152.31 (C-8), 152.57 (C-3a), 160.31 (C-6), 162.73 (C-2). IR (KBr 1%, cm^{-1}): ν=3400, 3083, 3029, 2969, 2924, 2854, 1739, 1698, 1635, 1598, 1571, 1470, 1438, 1386, 1349, 1297, 1265, 1227, 1208, 1139, 1055, 1037, 945, 931, 894, 878, 864, 816, 754, 742, 698, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=325 (3.80). HRMS (EI): calcd for $C_{12}H_8NO_3{}^{79}Br$ [M^+]: 292.9688; found: 292.9691; calcd for $C_{12}H_8NO_3{}^{81}Br$ [M^+]: 294.9667; found: 294.9679.

4.2.6. Synthesis of 8-(chloromethyl)-2-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole ***6****.* Starting from 6-amino-4-(chloromethyl)-7-hydroxy-2-oxo-2*H*-benzopyrane **4** (0.033 g, 0.146 mmol) in polyphosphoric acid (0.150 g) and acetic acid (0.1 mL, 7.75 mmol), following the same procedure as described before for the synthesis of compound **1** (stirring time 5 h), a fine gray precipitate was obtained. Purification by dry flash chromatography, using ethyl acetate/*n*-hexane, mixtures of increasing polarity as eluent gave compound **6** as a white solid (0.012 g, 34%). Mp=134.4–135.1 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=2.7 (s, 3H, CH_3), 4.73 (d, *J* 1.2 Hz, 2H, CH_2), 6.60 (s, 1H, H-7), 7.51 (s, 1H, H-4), 7.95 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=14.62 (CH_3), 41.60 (CH_2), 99.62 (C-4), 114.22 (C-9), 114.48 (C-8a), 114.74 (C-7), 138.80 (C-9a), 149.79 (C-8), 151.81 (C-4a), 152.81 (C-3a), 160.16 (C-6), 166.04 (C-2). IR (KBr 1%, cm^{-1}): ν=3077, 3048, 3010, 2928, 1723, 1722, 1642, 1606, 1578, 1477, 1437, 1430, 1394, 1382, 1354, 1283, 1273, 1253, 1218, 1149, 1131, 1037, 1016, 962, 915, 901, 879, 869, 814, 734, 699, 681, 609. UV/vis (ethanol, nm): λ_{max} (log ε)= 326 (3.98). HRMS (ESI): calcd for $C_{12}H_9NO_3{}^{35}Cl$ [M^++1]: 250.02655; found: 250.02628; calcd for $C_{12}H_9NO_3{}^{37}Cl$ [M^++1]: 252.02360; found: 252.02341.

4.3. General procedure for the synthesis of conjugates 8–11

The bromo- or chloromethyloxazole **1**, **2**, **5** or **6** (1 equiv) was dissolved in dry DMF (2 or 3 mL), potassium fluoride (3 equiv) and the corresponding amino acid, Z-Ala-OH **7a** or Z-β-Ala-OH **7b** (1 equiv) was added. The reaction mixture was stirred at room temperature for 5 or 24 h. The solvent was removed by rotary evaporation under reduced pressure and the crude residue was purified by column chromatography using mixtures of ethyl acetate and *n*-hexane as eluent.

4.3.1. N-(Benzyloxycarbonyl)-L-alanine (benzo[d]oxazole) methyl ester ***8a****.* Compound **1** (0.100 g, 0.472 mmol), DMF (4 mL), potassium fluoride (0.082 g, 1.42 mmol), and Z-Ala-OH **7a** (0.106 g, 0.472 mmol) were used and the reaction time was 24 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent, to give compound **8a** as a yellow solid (0.094 g, 56%). Mp=83.3–84.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=1.50 (d, *J* 6.0 Hz, 3H, CH_3 Ala), 4.50–4.52 (m, 1H, α-CH Ala), 5.12 (s, 2H, CH_2 Z), 5.35–5.50 (m, 3H, CH_2, and α-NH Ala), 7.28–7.41 (m, 7H, H-5, H-6, and 5×Ar–H Z), 7.51–7.56 (m, 1H, H-7), 7.72–7.77 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=18.44 (CH_3 Ala), 49.57 (α-CH Ala), 58.82 (CH_2), 66.95 (CH_2 Z), 110.80 (C-7), 120.41 (C-4), 124.68 (C-6), 125.69 (C-5), 128.03 (Ar–C), 128.12 (2×Ar–C), 128.45 (2×Ar–C), 136.11 (Ar–C), 140.63 (C-3a) 150.82 (C-7a), 155.56 (C=O urethane), 159.86 (C-2), 172.25 (C=O ester). IR (KBr 1%, cm^{-1}):

ν=3343, 2924, 2853, 1754, 1743, 1687, 1527, 1455, 1359, 1310, 1263, 1241, 1180, 1168, 1121, 1076, 937, 833, 749, 698, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=270 (3.60). HRMS (ESI): calcd for $C_{19}H_{19}N_2O_5$ [M^++1]: 355.12885; found: 355.12853.

4.3.2. N-(Benzyloxycarbonyl)-β-alanine (benzo[d]oxazole) methyl ester ***8b***. Compound **1** (0.193 g, 0.910 mmol), DMF (3 mL), potassium fluoride (0.159 g, 2.73 mmol), and Z-β-Ala-OH **7b** (0.216 g, 0.910 mmol) were used and the reaction time was 24 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent to give compound **8b** as a yellow oil (0.159 g, 49%). ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=2.72 (t, *J* 6.0 Hz, 2H, α-CH_2 β-Ala), 3.57–3.63 (m, 2H, β-CH_2 β-Ala), 5.12 (s, 2H, CH_2 Z), 5.40 (s, 2H, CH_2), 6.01 (br s, 1H, NH), 7.28–7.36 (m, 7H, H-5, H-6, and 5×Ar–H Z), 7.50 (dd, *J* 7.2 Hz, 1H, H-7), 7.62 (d, *J* 7.8 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=34.63 (α-CH_2 β-Ala), 36.70 (β-CH_2 β-Ala), 58.13 (CH_2), 66.77 (CH_2 Z), 110.73 (C-7), 120.33 (C-4), 124.69 (C-6), 125.56 (C-5), 128.09 (Ar–C), 128.18 (2×Ar–C), 128.48 (2×Ar–C), 136.42 (Ar–C), 140.41 (C-3a) 150.78 (C-7a), 156.44 (C=O urethane), 160.51 (C-2), 171.36 (C=O ester). IR (cm^{-1}): ν=3332, 3064, 3034, 2950, 2894, 1954, 1747, 1721, 1617, 1577, 1526, 1455, 1401, 1367, 1241, 1162, 1106, 1077, 1003, 936, 884, 832, 747, 698, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=270 (3.64). HRMS (ESI): calcd for $C_{19}H_{18}N_2O_5$ [M^++1]: 355.12885; found: 355.12999.

4.3.3. N-(Benzyloxycarbonyl)-L-alanine (naphtho[2,3-d]oxazole) methyl ester ***9a***. Compound **2** (0.080 g, 0.305 mmol), DMF (3 mL), potassium fluoride (0.053 g, 0.916 mmol), and Z-Ala-OH **7a** (0.068 g, 0.305 mmol) were used and the reaction time was 5 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent, to give compound **9a** as a white solid (0.123 g, 99%). Mp=138.7–139.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=1.55 (d, *J* 7.2 Hz, 3H, CH_3 Ala), 4.60 (t, *J* 4.0 Hz, 1H, α-CH Ala), 5.08–5.20 (m, 2H, CH_2 Z), 5.37–5.56 (m, 3H, CH_2, and α-NH Ala), 7.27–7.39 (m, 5H, 5×Ar–H Z), 7.47–7.56 (m, 2H, H-6, and H-7), 7.92 (s, 1H, H-9) 7.95 (d, *J* 8.2 Hz, 1H, H-8), 8.0 (d, *J* 8.4 Hz, 1H, H-5), 8.19 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=18.52 (CH_3 Ala), 49.63 (α-CH Ala), 58.93 (CH_2), 67.03 (CH_2 Z), 106.78 (C-9), 118.05 (C-4), 124.91 (C-7), 125.84 (C-6), 127.92 (C-8), 128.02 (Ar–C), 128.07 (Ar–C), 128.17 (Ar–C), 128.50 (Ar–C), 128.53 (Ar–C), 128.58 (C-5), 131.31 (C-8a), 131.79 (C-4a), 136.12 (Ar–C), 140.39 (C-3a), 149.49 (C-9a), 155.59 (C=O urethane), 162.20 (C-2), 172.28 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3339, 2943, 1764, 1685, 1619, 1578, 1528, 1463, 1409, 1386, 1365, 1308, 1262, 1243, 1209, 1167, 1149, 1123, 1078, 1046, 1029, 961, 931, 914, 882, 870, 864, 846, 785, 699. UV/vis (ethanol, nm): λ_{max} (log ε)=302 (3.95). HRMS (ESI): calcd for $C_{23}H_{21}N_2O_5$ [M^++1]: 405.14450; found: 405.14408.

4.3.4. N-(Benzyloxycarbonyl)-β-alanine (naphtho[2,3-d]oxazole) methyl ester ***9b***. Compound **2** (0.031 g, 0.120 mmol), DMF (2 mL), potassium fluoride (0.021 g, 0.361 mmol), and Z-β-Ala-OH **7b** (0.028 g, 0.120 mmol) were used and the reaction time was 5 h. Mixtures of increasing polarity of ethyl acetate/*n*-hexane were used as the dry flash chromatography eluent, to give compound **9b** as a yellow solid (0.044 g, 90%). Mp=105.6–106.9 °C. ^{1}H NMR ($CDCl_3$, 300 MHZ): δ=2.76 (t, *J* 5.7 Hz, 2H, α-CH_2 β-Ala), 3.55–3.75 (m, 2H, β-CH_2 β-Ala), 5.15 (s, 2H, CH_2 Z), 5.45 (s, 2H, CH_2), 6.15 (br s, 1H, NH), 7.30–7.42 (m, 5H, 5×Ar–H Z), 7.43–7.60 (m, 2H, H-6, and H-7), 7.80–8.00 (m, 3H, H-9, H-8, and H-5), 8.07 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75.4 MHZ): δ=34.74 (α-CH_2 β-Ala), 36.80 (β-CH_2 β-Ala), 58.18 (CH_2), 66.78 (CH_2 Z), 106.73 (C-9), 117.03 (C-4), 124.86 (C-7), 125.80 (C-6), 127.60 (Ar–C), 127.90 (Ar–C), 128.06 (Ar–C), 128.11 (C-8), 128.24 (Ar–C), 128.53 (Ar–C), 128.61 (C-5), 131.28 (C-8a), 131.68 (C-4a), 136.47 (Ar–C), 140.06 (C-3a), 149.48 (C-9a), 156.53 (C=O urethane), 162.94 (C-2), 171.34 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3305, 3066, 2958, 2921, 2850, 1750, 1724, 1715, 1638, 1620, 1577, 1546, 1506, 1457, 1426, 1409, 1382, 1366, 1278, 1254, 1245, 1231, 1202, 1179, 1165, 1140, 1080, 1046, 1025, 971, 911, 888, 869, 778, 751, 697. UV/vis (ethanol, nm): λ_{max} (log ε)=301 (4.04). HRMS (ESI): calcd for $C_{23}H_{20}N_2O_5$ [M^++1]: 405.1444; found: 405.1445.

4.3.5. N-(Benzyloxycarbonyl)-L-alanine (8-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole) methyl ester ***10a***. Compound **5** (0.100 g, 0.340 mmol), DMF (3 mL), potassium fluoride (0.059 g, 9.25 mmol), and Z-Ala-OH **7a** (0.076 g, 0.340 mmol) were used and the reaction time was 5 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent to give compound **10a** as a white solid (0.078 g, 53%). Mp=124.2–125.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=1.53 (d, *J* 7.2 Hz, 3H, CH_3 Ala), 2.51 (d, *J* 0.4 Hz, 3H, CH_3) 4.56 (m, 1H, α-CH Ala), 5.10–5.20 (m, 2H, CH_2 Z), 5.34 (d, *J* 6.8 Hz, 1H, α-NH Ala), 5.39–5.50 (m, 2H, CH_2), 6.33 (d, *J* 1.6 Hz, 1H, H-7), 7.28–7.40 (m, 5H, 5×Ar–H Z), 7.51 (s, 1H, H-4), 7.96 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=18.48 (CH_3 Ala), 19.19 (CH_3), 49.59 (α-CH Ala), 58.56 (CH_2), 67.07 (CH_2 Z), 99.67 (C-4), 114.32 (C-7), 115.74 (C-9), 117.96 (C-8a), 128.07 (Ar–C), 128.21 (2×Ar–C), 128.52 (2×Ar–C), 136.07 (Ar–C), 137.62 (C-9a), 152.06 (C-4a), 152.30 (C-8), 152.33 (C-3a), 155.56 (C=O urethane), 160.33 (C-6), 161.64 (C-2), 172.23 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3307, 3065, 2986, 2957, 1723, 1716, 1694, 1634, 1577, 1538, 1440, 1391, 1342, 1291, 1259, 1206, 1170, 1133, 1095, 1071, 1055, 1028, 977, 956, 932, 887, 842, 813, 778, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=323 (4.01). HRMS (ESI): calcd for $C_{23}H_{21}N_2O_7$ [M^++1]: 437.13433; found: 437.13406.

4.3.6. N-(Benzyloxycarbonyl)-β-alanine (8-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole) methyl ester ***10b***. Compound **5** (0.030 g, 0.102 mmol), DMF (2 mL), potassium fluoride (0.018 g, 3.07 mmol), and Z-β-Ala-OH **7b** (0.024 g, 0.102 mmol) were used and the reaction time was 5 h. Mixtures of increasing polarity of ethyl acetate/*n*-hexane were used as the dry flash chromatography eluent to give compound **10b** as a yellow solid (0.042 g, 95%). Mp=114.6–115.4 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=2.40 (s, 3H, CH_3), 2.74 (t, *J* 6.0 Hz, 2H, α-CH_2 β-Ala), 3.58–3.63 (m, 2H, β-CH_2 β-Ala), 5.13 (s, 2H, CH_2 Z), 5.41 (s, 2H, CH_2), 5.82 (br s, 1H, NH), 6.31 (d, *J* 0.8 Hz, 1H, H-7), 7.25–7.40 (m, 5H, 5×Ar–H Z), 7.50 (s, 1H, H-4), 7.89 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=19.08 (CH_3), 34.55 (α-CH_2 β-Ala), 36.72 (β-CH_2 β-Ala), 57.91 (CH_2), 66.72 (CH_2 Z), 99.66 (C-4), 114.27 (C-7), 115.60 (C-9), 117.94 (C-8a), 127.91 (Ar–C), 128.12 (Ar–C), 128.30 (Ar–C), 128.55 (2×Ar–C), 136.42 (Ar–C), 137.42 (C-9a), 151.98 (C-4a), 152.26 (C-8), 152.39 (C-3a), 156.40 (C=O urethane), 160.37 (C-6), 162.29 (C-2), 171.30 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3366, 3060, 3047, 2958, 2927, 2852, 1742, 1716, 1691, 1631, 1600, 1576, 1535, 1498, 1455, 1441, 1418, 1394, 1347, 1324, 1311, 1289, 1261, 1211, 1166, 1133, 1081, 1069, 1030, 1013, 975, 938, 920, 894, 884, 816, 784, 739, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=323 (4.01). HRMS (ESI): calcd for $C_{23}H_{21}N_2O_7$ [M^++1]: 437.1353; found: 437.1343.

4.3.7. N-(Benzyloxycarbonyl)-L-alanine (8-methyl-2-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole) methyl ester ***11a***. Compound **6** (0.077 g, 0.308 mmol), DMF (3 mL), potassium fluoride (0.054 g, 0.925 mmol), and Z-Ala-OH **7a** (0.069 g, 0.308 mmol) were used and the reaction time was 24 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent to give compound **11a** as a light pink solid (0.116 g, 86%). Mp=159.4–160.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=1.50 (d, *J* 7.2 Hz, 3H, CH_3 Ala), 2.68 (s, 3H, CH_3), 4.53 (t, *J* 7.2 Hz, 1H, α-CH Ala), 5.04–5.19 (m, 2H, CH_2 Z), 5.33–5.50 (m, 3H, α-NH Ala, and CH_2), 6.50 (s, 1H, H-7), 7.30–7.40 (m, 5H, 5×Ar–H Z), 7.49 (s, 1H, H-4), 7.78 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=14.56 (CH_3), 18.26 (CH_3 Ala), 49.72 (α-CH Ala), 62.20 (CH_2), 67.13 (CH_2 Z), 99.60 (C-4), 112.44 (C-7), 113.42 (C-9), 114.15 (C-8a), 127.99 (Ar–C), 128.13 (Ar–C), 128.20 (Ar–C), 128.46 (Ar–C), 128.50 (Ar–C), 136.04 (Ar–C), 138.66 (C-9a), 148.65 (C-8), 151.57 (C-4a), 152.68 (C-3a), 155.68 (C=O urethane), 160.10 (C-6), 166.03 (C-

2), 172.32 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3321, 1740, 1725, 1687, 1634, 1605, 1575, 1538, 1454, 1442, 1382, 1348, 1331, 1257, 1205, 1151, 1134, 1116, 1075, 1025, 987, 951, 916, 893, 874, 815, 758, 695, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=325 (3.95). HRMS (ESI): calcd for $C_{23}H_{21}N_2O_7$ [M^++1]: 437.13433; found: 437.13392.

4.3.8. N-(Benzyloxycarbonyl)-β-alanine (8-methyl-2-methyl-6-oxo-6H-benzopyrano[6,7-d]oxazole) methyl ester ***11b****.* Compound **6** (0.060 g, 0.240 mmol), DMF (3 mL), potassium fluoride (0.042 g, 0.721 mmol), and Z-β-Ala-OH **7b** (0.057 g, 0.240 mmol) were used and the reaction time was 24 h. Ethyl acetate/*n*-hexane 1:1 was used as column chromatography eluent to give compound **11b** as a yellow solid (0.103 g, 98%). Mp=174.5–175.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ=2.68 (s, 3H, CH_3), 2.73 (t, *J* 6.0 Hz, 2H, α-CH_2 β-Ala), 3.50–3.60 (m, 2H, β-CH_2 β-Ala), 5.11 (s, 2H, CH_2 Z), 5.29 (br s, 1H, α-NH Ala), 5.36 (s, 2H, CH_2), 6.47 (s, 1H, H-7), 7.26–7.40 (m, 5H, 5×Ar–H Z), 7.49 (s, 1H, H-4), 7.77 (s, 1H, H-9). ^{13}C NMR ($CDCl_3$, 100.6 MHZ): δ=14.59 (CH_3), 34.36 (α-CH_2 β-Ala), 36.46 (β-CH_2 β-Ala), 61.62 (CH_2), 66.85 (CH_2 Z), 99.60 (C-4), 112.40 (C-7), 113.43 (C-9), 114.22 (C-8a), 128.13 (Ar–C), 128.16 (2×Ar–C), 128.51 (2×Ar–C), 136.32 (Ar–C), 138.76 (C-9a), 148.95 (C-8), 151.58 (C-4a), 152.73 (C-3a), 156.26 (C=O urethane), 160.17 (C-6), 166.01 (C-2), 171.50 (C=O ester). IR (KBr 1%, cm^{-1}): ν=3315, 3092, 3035, 1737, 1727, 1688, 1637, 1605, 1561, 1455, 1440, 1417, 1387, 1367, 1322, 1283, 1268, 1256, 1243, 1214, 1175, 1147, 1134, 1088, 1042, 1006, 983, 948, 922, 892, 838, 816, 774, 693, 666. UV/vis (ethanol, nm): λ_{max} (log ε)=324 (3.95). HRMS (ESI): calcd for $C_{23}H_{21}N_2O_7$ [M^++1]: 437.13433; found: 437.13400.

4.4. Photolysis general

Photolyses were carried out using a Rayonet RPR-100 chamber reactor equipped with 10 lamps of 254 (35 W), 300 (21 W), and 350 (24 W) nm. HPLC analyses were performed using a Licrospher 100 RP18 (5 μm) column in a JASCO HPLC system composed by a PU-2080 pump and a UV-2070 detector with ChromNav software.

4.4.1. General photolysis procedure. A 1×10^{-4} M methanol/HEPES buffer (80:20) solution of conjugates **8**–**11** (5 mL) were placed in a quartz tube and irradiated in the reactor at the desired wavelength. The lamps used for irradiation were of 254, 300, and 350±10 nm. HEPES buffer solution was prepared in distilled water with HEPES (4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid) (10 mM), NaCl (120 mM), KCl (3 mM), $CaCl_2$ (1 mM), and $MgCl_2$ (1 mM) and pH adjusted to 7.2. Aliquots of 100 μL were taken at regular intervals and analysed by RP-HPLC. The eluent was acetonitrile/water, 3:1, at a flow rate of 0.8 mL/min, for all compounds, previously filtered through a Millipore, type HN 0.45 μm filter and degassed by ultra-sound for 30 min. The chromatograms were traced by detecting UV absorption at the wavelength of maximum absorption for each conjugate (retention time: **8a**, 4.4; **8b**, 4.1; **9a**, 6.0; **9b**, 6.2; **10a**, 4.1; **10b**, 4.1; **11a**, 4.1; **11b**, 4.0 min).

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