SUPPLEMENTARY NOTE

1. Photochemistry of PA-Nic

Byproducts from Photolysis of PA-Nic. Initial LC-MS experiments on the photolysis of compound **6** (PA-Nic) showed that the compound released nicotine (**1**) and two byproducts from the coumarin cage, presumably dialkylcoumarin **13** (~20%) and monoalkylcoumarin **12** (~80%); these same two products were also observed upon photolysis of model compound **10** (**Fig. SN1a**). As further evidence, we measured the absorption spectrum before and after exhaustive photolysis of PA-Nic (**6**). We observed a 44 nm hypsochromic shift, (λ_{max} = 359 nm, **Fig SN1b**), consistent with a monoalkylated coumarin as the major photoproduct. To confirm the identity of these products we compared these products with authentic samples synthesized in our laboratory. Compound **13** was synthesized by alkylation of coumarin **15** followed by deprotection as previously described;[1] compound **12** is a byproduct in this reaction due to incomplete alkylation (**Fig. SN1a**). Analysis by LC–MS confirmed the identity of **12** and **13** (**Fig. SN1c**) and the ^{1}H NMR spectrum of **12** prepared by alkylation of **15** or by photolysis of **10** were identical (**Fig. SN1d**).

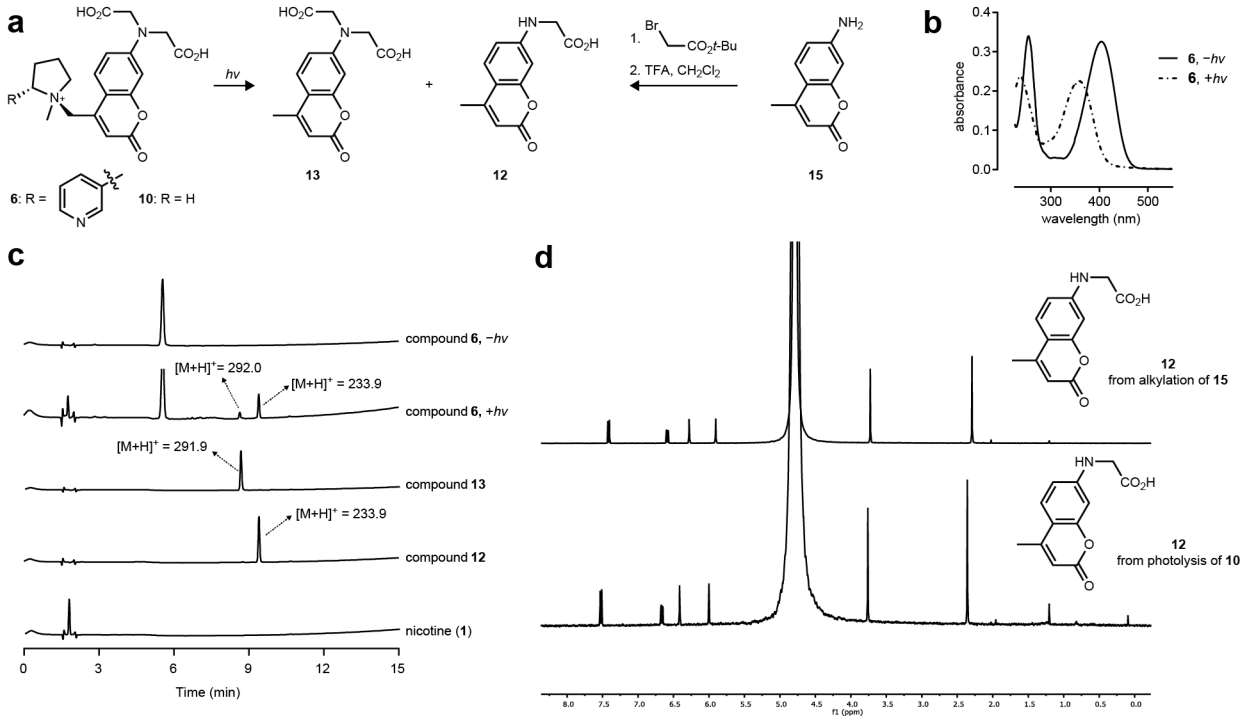


Fig SN1. Identification of byproducts from PA-Nic photolysis. (**a**) Photolysis of PA-Nic (**6**) or model compound **10** results in two coumarin byproducts **12** and **13**. Authentic samples of **12** and **13** could be prepared by alkylation of coumarin **15**. (**b**) Absorption of spectra of PA-Nic (**6**, 20 μM) in PBS pH 7.4 before and after photolysis (80 s illumination with 405 nm LED light). (**c**) LC–MS traces of PA-Nic (**6**) before and after 10 sec illumination with 405 nm LED light and authentic samples of released products **12**, **13**, and nicotine (**1**). (**d**) ^{1}H-NMR spectra of byproduct **12** prepared by alkylation of **15** (*i.e.*, 'authentic sample'; top) and from purified from photolysis of **10** (bottom).

Photochemical Reaction Mechanism. The presence of the 4-methylcoumarin byproducts **12** and **13** suggest a radical cleavage mechanism as previously proposed by Giese and coworkers for coumarin-caged secondary amines.[2] This could occur via two modes (**Fig. SN2**). In Pathway 1, excitation of **6** followed by intramolecular electron abstraction could yield a diradical species. Release of nicotine (**1**), followed by H· migration could yield an iminium species. Attack by water and release of glyoxylic acid, would give coumarin byproduct **12**. In Pathway 2, excitation of **6** followed by intermolecular electron abstraction from solvent could give a radical species. Release of nicotine (**1**), followed by H· abstraction from solvent could yield byproduct **13**. We note that compound **12** could also arise from photobleaching of **13**, although compound **12** is observed throughout the photolysis reaction of **6**.

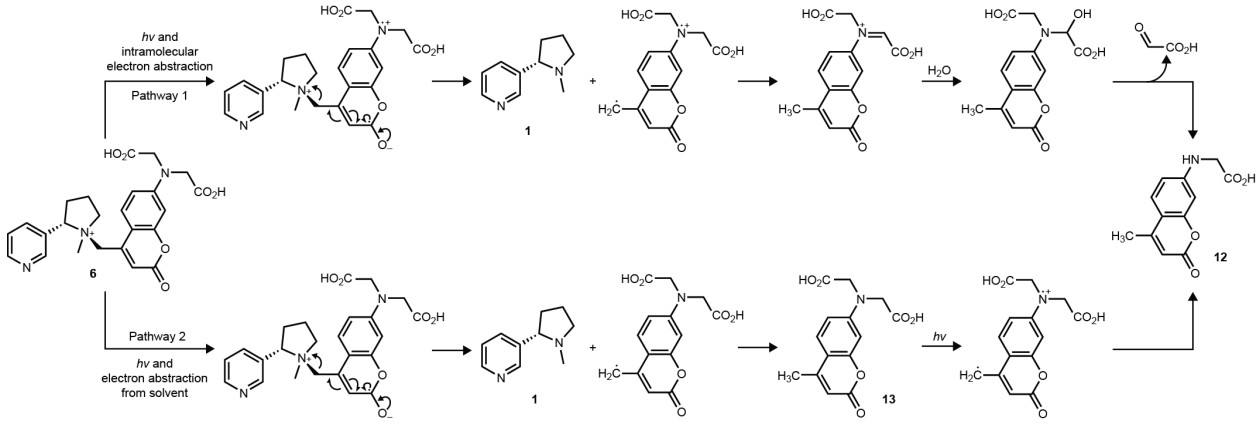


Figure SN2. Possible mechanisms of PA-Nic photolysis to yield byproducts **12** and **13**.

2. Synthesis and photochemical properties of photoactivatable drugs

Introduction. Synthesis of all the photoactivatable (PA) drugs was accomplished using the same general procedure (**Fig. SN3**). Alkylation of the drugs with iminodiacetic acid-substituted coumarin bromide (**5**)[1] afforded the quaternary nitrogen center. The desired PA drug compounds were obtained after deprotection of *tert*-butyl groups with TFA. Alkylation of nicotine (**1**) and fentanyl (**3**) produced two or more isomers, which were separable on HPLC and distinguished by 2D NOESY spectra. Alkylation of nicotine yielded three isomers: two diastereomers (compounds **6** and **19**) and another regioisomer (compound **20**) with the coumarin attached to the pyridine nitrogen. Photochemical quantum yield (Φ_{pc}) of two diastereomers of PA-Nic is similar and an order of magnitude higher than the pyridinium compound **20** (**Table SN1**). Similarly, alkylation of fentanyl (**3**) synthesis gave two diastereomers, compounds **8** and **24**, with compound **8** (PA-Fen) showing a higher Φ_{pc} than compound **24**.

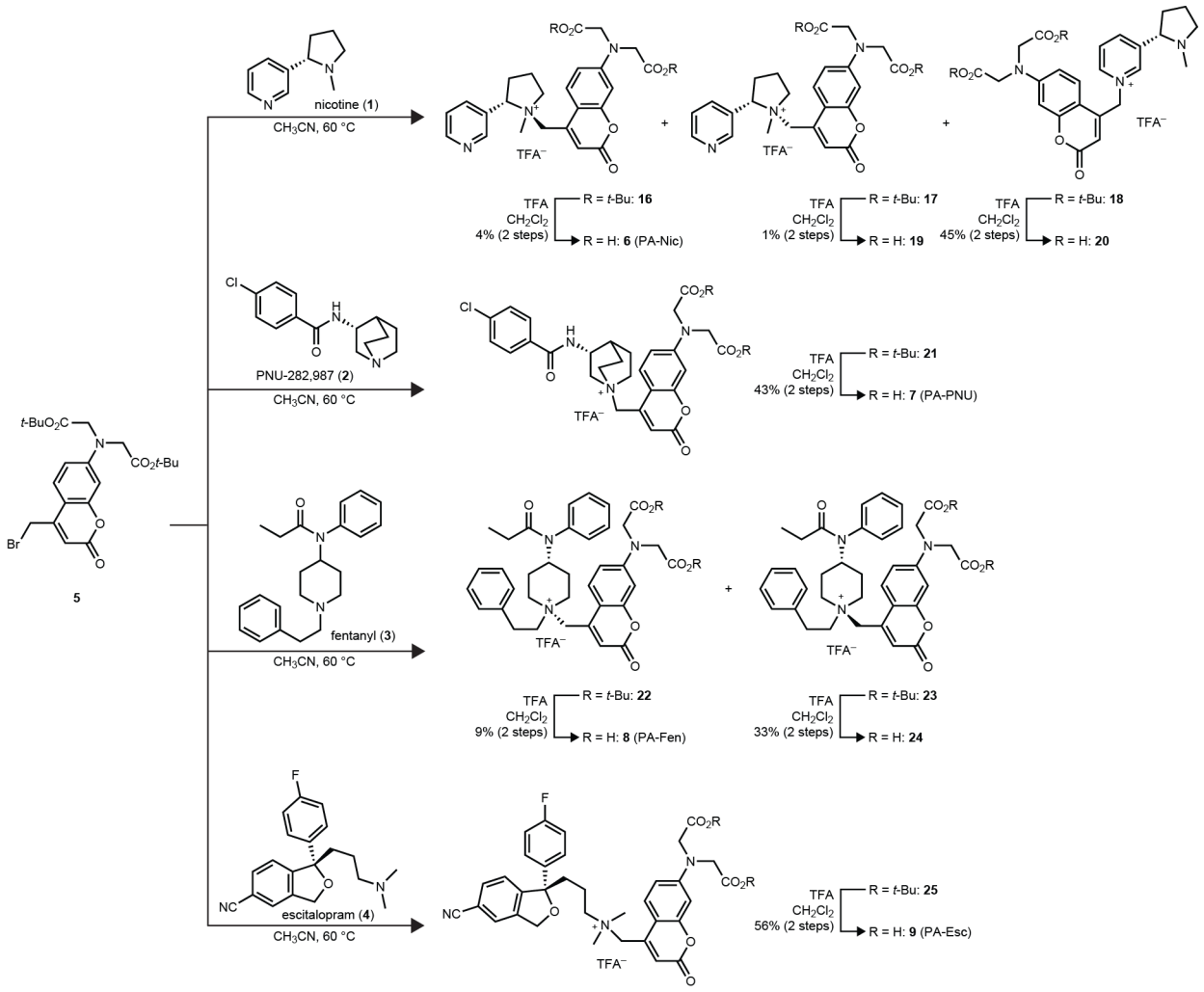


Figure SN3. Synthesis of photoactivatable drugs.

Compound	λ_{max} (nm)	ε (M^{-1} cm^{-1})	Φ_{pc}
6 (PA-Nic)	404	17400	7.4×10^{-3}
7 (PA-PNU)	407	14700	8.7×10^{-3}
8 (PA-Fen)	410	14500	5.5×10^{-3}
9 (PA-Esc)	406	19600	5.1×10^{-3}
19 (PA-Nic isomer-2)	404	14300	7.6×10^{-3}
20 (PA-Nic isomer-3)	388	17200	0.5×10^{-3}
24 (PA-Fen isomer-2)	407	17500	3.0×10^{-3}

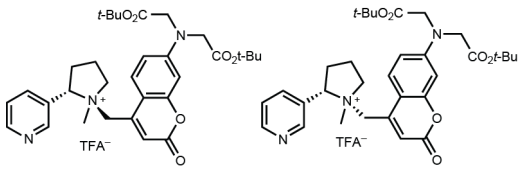
Table SN1. Spectral and photochemical properties of the photoactivatable drugs in PBS, pH 7.4.

General Experimental Information. Commercial reagents were obtained from reputable suppliers and used as received. All solvents were purchased in septum-sealed bottles stored under an inert atmosphere. All reactions were sealed with septa through which an argon atmosphere was introduced unless otherwise noted. Reactions were conducted in round-bottomed flasks containing Teflon-coated magnetic stir bars. Heating of reactions was accomplished with an aluminum reaction block on top of a stirring hotplate equipped with an electronic contact thermometer to maintain the indicated temperatures.

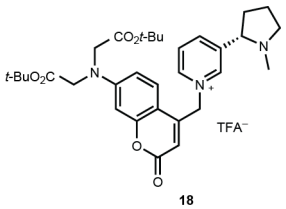
Reactions were monitored by thin layer chromatography (TLC) on precoated TLC glass plates (silica gel 60 F_{254} 250 μm thickness) or by LC/MS (4.6 mm × 150 mm 5 μm C18 column; 5 μL injection; 10–95% CH_3CN/H_2O, linear gradient, with constant 0.1% v/v TFA additive; 20 min run; 1 mL/min flow; ESI; positive ion mode; UV detection at 254 nm). TLC chromatograms were visualized by UV illumination or developed with $KMnO_4$ stain. Flash chromatography was performed on an automated purification system using pre-packed silica gel columns or by preparative HPLC (Phenomenex Gemini NX 30 × 150 mm 5 μm C18 column). High-resolution mass spectrometry was performed by the High Resolution Mass Spectrometry Center at the University of Iowa.

NMR spectra were recorded on a 400 MHz spectrometer. ^1H and ^{13}C chemical shifts (δ) were referenced to TMS or residual solvent peaks. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR spectra are reported by chemical shift (δ ppm) with hydrogen multiplicity (C, CH, CH_2, CH_3) information obtained from DEPT spectra.

General procedure for the reaction of drugs with coumarin-bromide: The following procedure for di-*tert*-butyl PA-Nic isomers (**16**–**18**) are representative. Nicotine **1** (303 mg, 1.87 mmol) was dissolved in 40 mL anhydrous CH_3CN. Coumarin bromide **5**[1] (900 mg, 1.87 mmol) was added and the reaction was heated to 60 °C and stirred for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. Purification by HPLC (5–50% v/v MeCN in H_2O, linear gradient, constant 0.1% v/v TFA additive) and lyophilization afforded the desired product as pale yellow powder. Compounds **16** and **17** are diastereomers and eluted as a single peak, inseparable at this step; obtained 82 mg (6%) as a 3:1 diastereomeric mixture. Both isomers were distinguished by 2D NOESY spectra. The regioisomer **18** (820 mg, 56%) is easily separable by HPLC and distinguished ^1H NMR.



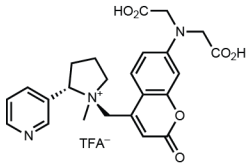
Compounds 16 and 17 (3:1 mixture). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.95 (s, 1H), 8.83 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 7.72 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.64 (d, *J* = 9.1 Hz, 0.7H), 7.52 (d, *J* = 9.1 Hz, 0.3H), 6.66 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.52 (d, *J* = 2.6 Hz, 1H), 6.39 (s, 0.7H), 6.36 (s, 0.3H) 5.28 – 5.20 (m, 1H), 4.41 (d, *J* = 13.1 Hz, 0.3H), 4.34 (d, *J* = 13.1 Hz, 0.7H), 4.19 (s, 4H), 4.02 (d, *J* = 13.2 Hz, 0.3H), 3.97 – 3.89 (m, 1H), 3.66 – 3.56 (m, 1H), 3.19 (s, 0.7H), 2.91 (s, 2.3H), 2.83 – 2.63 (m, 2H), 2.48 – 2.23 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (CD_3OD, 101 MHz) δ 170.7 (C), 162.0 (C), 161.9 (C), 157.5 (C), 157.3 (C), 153.6 (C), 152.6 (C), 143.9 (C), 143.7 (C), 141.2 (CH), 141.0 (CH), 127.1 (CH), 126.6 (CH), 118.2 (CH), 117.9 (CH), 111.0 (CH), 110.6 (C), 110.3 (C), 100.3 (CH), 83.4 (CH), 81.3 (CH), 79.8 (CH), 65.4 (CH_2), 63.3 (CH_2), 61.2 (CH_2), 55.6 (CH_2), 55.1 (CH_2), 50.3 (CH_3) 49.9 (CH_3), 42.9 (CH_3) 28.3 (CH_3), 27.4 (CH_2), 26.7 (CH_2), 20.8 (CH_2), 20.2 (CH_2). HRMS (ESI) calcd for $C_{32}H_{42}N_3O_6$ $[M]^+$ 564.3068, found 564.3074.



Compound 18. ^{1}H NMR (CD_3OD, 400 MHz) δ 9.45 (s, 1H), 9.22 (d, *J* = 6.2 Hz, 1H), 8.98 (d, *J* = 8.3 Hz, 1H), 8.35 (dd, *J* = 8.2, 6.2 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 6.69 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.53 (d, *J* = 2.6Hz, 1H), 6.19 (s, 2H), 5.63 (s, 1H), 4.75 (dd, *J* = 9.4, 8.4 Hz, 1H), 4.20 (s, 4H), 3.98 – 3.92 (m, 1H), 3.44 – 3.37 (m, 1H), 2.89 (s, 3H), 2.76 – 2-67 (m, 1H), 2.54 – 2.44 (m, 1H), 2.39 – 2.31 (m, 2H), 1.48 (s, 18H); ^{13}C NMR (CD_3OD, 101 MHz) δ 170.7 (C), 162.4 (C), 156.9 (C), 153.7 (C), 149.4 (C), 148.6 (CH), 148.2 (CH), 148.1 (CH), 136.6 (C), 130.5 (CH), 125.9 (CH), 111.1 (CH), 109.9 (CH), 108.6 (CH), 100.0 (CH), 83.4 (C), 69.5 (C), 61.7 (CH_2), 57.8 (CH_2),55.2 (CH_2), 39.6 (CH), 32.0 (CH_2), 28.3 (CH_3), 23.0 (CH_2). HRMS (ESI) calcd for $C_{32}H_{42}N_3O_6$ $[M]^+$ 564.3068, found 564.3072.

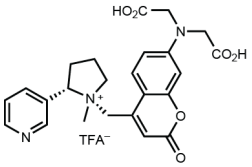
General procedure for deprotection of *tert*-butyl groups: The following procedure for PA-Nic (**6**) is representative. To deprotect the *tert*-butyl ester group, a mixture of diastereomers **16** and **17** (52 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (2.5 mL). Trifluoroacetic acid (TFA; 0.5 mL) was added and the

reaction was stirred at ambient temperature for 2 h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC (3% v/v CH_3CN in H_2O, isocratic gradient, constant 0.1% v/v TFA additive). Obtained 26 mg (59%) of PA-Nic (**6**; *S*,*S*-isomer) and 8 mg (18%) of compound **19** (*S*,*R*-isomer) as pale yellow powders. The two diastereomers were distinguished by 2D NOESY spectra.



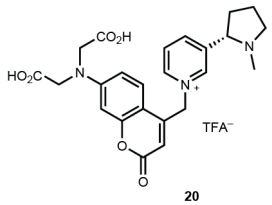
6

Compound 6 (PA-Nic). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.96 (s, 1H), 8.83 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.73 (s, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 6.69 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.38 (s, 1H), 5.27 (dd, *J* = 11.3, 8.4 Hz, 1H), 4.85 (d, *J* = 13.2 Hz, 1H), 4.32 (d, *J* = 13.2 Hz, 1H), 4.30 (s, 4H), 3.98 – 3.88 (m, 1H), 3.64 – 3.59 (m, 1H), 2.90 (s, 3H), 2.83 – 2.62 (m, 2H), 2.44 – 2.23 (m, 2H). ^{13}C NMR (CD_3OD, 101 MHz) δ 172.1 (C), 160.6 (C), 156.1 (C), 152.1 (C), 151.4 (CH), 142.4 (C), 139.8 (CH), 125.7 (CH), 116.5 (CH), 109.6 (CH), 108.9 (C), 98.9 (CH), 78.3 (CH), 63.9 (CH_2), 59.7 (CH_2), 52.7 (CH_2), 41.5 (CH_3), 25.2 (CH_2), 18.8 (CH_2). HRMS (ESI) calcd for $C_{26}H_{42}N_3O_6$ $[M]^+$ 452.1816, found 452.1841.



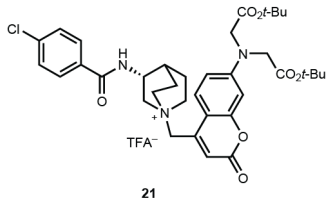
19

Compound 19. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.94 (s, 1H), 8.83 (s, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 7.72 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.49 (d, *J* = 9.1 Hz, 1H), 6.69 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.36 (s, 1H), 5.23 (dd, *J* = 9.7, 8.1 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 4.29 (s, 4H), 4.02 (d, *J* = 13.2 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.63 – 3.56 (m, 1H), 3.19 (s, 3H), 3.02 – 2.90 (m, 1H), 2.80 – 2.71 (m, 1H), 2.61 – 2.40 (m, 2H). ^{13}C NMR (CD_3OD, 101 MHz) δ 172.1 (C), 160.5 (C), 155.9 (C), 152.2 (C), 151.4 (CH), 151.3 (CH) 142.3 (C), 139.5 (CH), 125.1 (CH), 116.9 (CH), 109.6 (CH), 109.2 (C), 100.0 (C), 98.9 (CH), 79.9 (CH), 61.9 (CH_2), 54.1 (CH_2), 52.7 (CH_2), 48.9 (CH_3), 26.0 (CH_2), 19.4 (CH_2). HRMS (ESI) calcd for $C_{26}H_{42}N_3O_6$ $[M]^+$ 452.1816, found 452.1829.



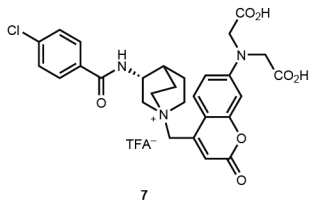
20

Compound 20: This compound was prepared from **18** according to the general procedure described above for compound **6**. Method for reverse phase HPLC: 05–40% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 80%, pale yellow powder. ^{1}H NMR (D_2O, 400 MHz) δ 9.25 (s, 1H), 9.16 (d, *J* = 6.1 Hz, 1H), 8.94 (d, *J* = 8.2 Hz, 1H), 8.37 (dd, *J* = 8.2, 6.2 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 6.72 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 6.18 (s, 2H), 5.72 (s, 1H), 4.35 (s, 4H), 3.95 (brs, 1H), 3.44 (brs, 1H), 2.86 (s, 3H), 2.78 – 2.69 (m, 1H), 2.48 – 2.31 (m, 3H). ^{13}C NMR (CD_3OD, 101 MHz) δ 173.9 (C), 162.4 (C), 156.9 (C), 153.5 (C), 149.2 (C), 148.6 (CH) 148.0 (CH), 147.9 (CH), 137.0 (C), 130.5 (CH), 126.0 (CH), 111.0 (CH), 110.1 (CH), 108.5 (C), 99.9 (CH), 69.4 (CH), 61.6 (CH_2), 57.7 (CH_2), 54.5 (CH_2), 39.6 (CH_3), 32.1 (CH_2), 23.0 (CH_2). HRMS (ESI) calcd for $C_{26}H_{42}N_3O_6$ $[M]^+$ 452.1816, found 452.1827.



21

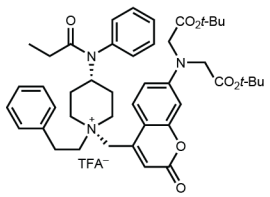
Di-*tert*-butyl PA-PNU (21): This compound was prepared according to the general procedure described above for compounds **16**–**18**. Method for reverse phase HPLC: 05–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: quantitative, pale yellow powder. ^{1}H NMR (CD_3CN, 400 MHz) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 6.68 – 6.59 (m, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.29 (s, 2H), 4.40 (s, 3H), 4.10 (s, 4H), 3.95 (t, *J* = 10.2 Hz, 1H), 3.54 (d, *J* = 36.4 Hz, 5H), 2.35 (s, 1H), 2.24 (brs, 1H), 2.05 (brs, 2H), 1.90 (brs, 1H), 1.45 (s, 18H). ^{13}C NMR (CD_3OD, 101 MHz) δ 170.7 (C), 169.5 (C) , 162.0 (C), 157.4 (C), 153.6 (C), 142.7 (C), 139.1(C), 133.5 (C), 130.3 (CH), 129.7 (CH), 127.5 (CH), 118.5 (CH), 111.2 (C), 110.7 (CH), 100.2 (CH), 83.4 (C), 62.9 (CH_2), 62.0 (CH_2), 56.8 (CH_2), 56.6 (CH_2), 55.1 (CH_2), 47.7 (CH), 30.7 (C), 28.3 (CH_3), 25.6 (CH), 23.9 (CH_2), 23.7 (C), 20.0 (CH_2). HRMS (ESI) calcd for $C_{36}H_{45}ClN_3O_7$ $[M]^+$ 666.2941, found 666.2953.



7

PA-PNU (7): This compound was prepared from **21** according to the general procedure described above for the compound **6**. Method for reverse phase HPLC: 05–30% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 43%, pale yellow powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.58 – 6.53 (m, 1H), 6.37 (s, 1H), 4.58 (s, 2H), 4.47 – 4.41 (m, 1H), 4.30 (s, 4H), 4.11 (t, *J* = 11.3 Hz, 1H), 3.63 (t, *J* = 7.9 Hz, 4H), 3.65 – 3.51 (m, 5H), 2.38 – 2.00 (m, 5H). ^{13}C NMR (CD_3OD, 101 MHz) δ 173.5 (C), 169.7 (C) , 162.0 (C), 157.5 (C), 153.6 (C), 142.6 (C), 139.2 (C), 133.5 (C), 130.3 (CH), 129.8 (CH), 127.3 (CH), 118.5 (CH), 111.1 (CH), 110.7 (CH), 100.2 (C), 62.9 (CH_2), 62.3 (CH_2), 56.7 (CH_2), 54.2 (CH_2), 47.8 (CH), 25.5 (CH), 23.9 (CH_2), 20.0 (CH_2). HRMS (ESI) calcd for $C_{36}H_{45}ClN_3O_7$ $[M]^+$ 554.1689, found 554.1693.

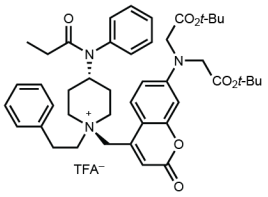
Di-*tert*-butyl PA-Fen isomers (22 and 23): These compounds were prepared from compound **3** according to the general procedure described above for compounds **16**–**18**. Method for reverse phase HPLC: 40–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 55% (22% of minor isomer (**22**) and 78% of major isomer (**23**)), pale yellow powders. Isomers distinguished by 2D NOESY spectra.



22

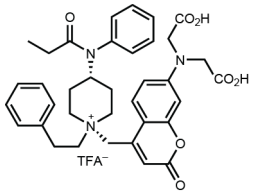
Di-*tert*-butyl PA-Fen minor isomer (22): ^{1}H NMR (CD_3OD, 400 MHz) δ 7.69 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.32 – 7.20 (m, 5H), 7.10 – 7.07 (m, 2H), 6.58 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.54 (d, *J* = 2.6 Hz, 1H), 6.26 (s, 1H), 4.71 (s, 2H), 4.69 – 4.62 (m, 1H), 4.21 (s, 4H), 3.72 (brs, 4H), 3.61 – 3.56 (m, 2H), 3.15 – 3.11 (m, 2H), 2.47 – 2.22 (m, 4H), 2.00 (q, *J* = 7.5 Hz, 2H), 1.48 (s, 18H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (CD_3OD, 101 MHz) δ 176.4 (C), 170.6 (C), 161.7 (C), 157.3 (C), 153.7 (C), 143.4 (C), 140.8 (C), 136.4 (C), 131.3 (CH), 130.8 (CH), 130.4 (CH), 130.1 (CH),129.9 (CH), 128.5 (CH), 126.9 (CH)

117.3 (CH), 111.0 (CH), 110.4 (CH), 100.4 (C), 83.4 (C), 66.1 (CH_2), 59.2 (CH_2), 55.8 (CH_2), 55.2 (CH_2), 51.2 (CH), 29.6 (CH_2), 29.5 (CH_2), 28.3 (CH), 25.4 (CH_2), 9.8 (CH). HRMS (ESI) calcd for $C_{44}H_{56}N_3O_7$ $[M]^+$ 738.4113, found 738.4132.



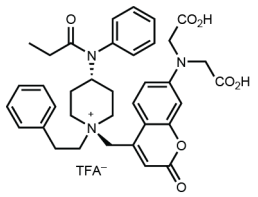
23

Di-*tert*-butyl PA-Fen major isomer (23): ^{1}H NMR (CD_3OD, 400 MHz) δ 7.84 (d, J = 9.1 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.35 – 7.25 (m, 5H), 7.14 – 7.08 (m, 2H), 6.71 (dd, J = 9.1, 2.6 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 6.45 (s, 1H), 4.80 (s, 2H), 4.53 (dt, J = 11.9, 6.3 Hz, 1H), 4.21 (s, 4H), 3.72 – 3.54 (m, 6H), 3.16 – 3.12 (m, 2H), 2.18 – 2.02 (m, 4H), 1.98 (q, J = 7.5 Hz, 2H), 1.48 (s, 18H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CD_3OD, 101 MHz) δ 176.3 (C), 170.7 (C), 161.9 (C), 157.4 (C), 153.6 (C), 142.7 (C), 140.5 (C), 136.5 (C), 131.2 (CH), 130.7 (CH), 130.3 (CH), 130.2 (CH),129.9 (CH), 128.6 (CH), 127.2 (CH) 119.0 (CH), 111.1 (CH), 100.9 (C), 100.3 (CH), 83.5 (C), 62.1 (CH_2), 59.1 (CH_2), 58.6 (CH_2), 55.1 (CH_2), 51.6 (CH), 29.5 (CH_2), 28.9 (CH_2), 28.3 (CH_3), 24.8 (CH_2), 9.8 (CH). HRMS (ESI) calcd for $C_{44}H_{56}N_3O_7$ $[M]^+$ 738.4113, found 738.4121.



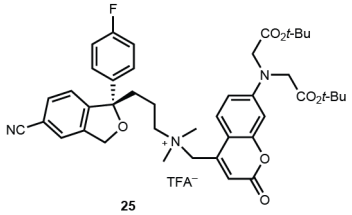
8

PA-Fen (8): This compound was prepared from **22** according to the general procedure described above for compound **6**. Method for reverse phase HPLC: 05–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 79%, pale yellow powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.59 (d, J = 8.7 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.34 – 7.25 (m, 4H), 7.27 – 7.20 (m, 1H), 7.15 – 7.06 (m, 2H), 6.59 – 6.57 (m, 2H), 6.25 (s, 1H), 4.75 – 4.71 (m, 1H),4.69 (s, 2H), 4.30 (s, 4H), 3.73 – 3.65 (m, 4H), 3.63 – 3.58 (m, 2H), 3.16 – 3.12 (m, 2H), 2.32 – 2.23 (m, 4H), 2.01 – 1.96 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR (CD_3OD, 101 MHz) δ 176.4 (C), 174.3 (C), 161.7 (C), 159.9 (C), 157.3 (C), 153.4 (C), 143.4 (C), 140.5 (C), 136.3 (C), 131.3 (CH), 130.9 (CH), 130.5 (CH), 130.1 (CH), 129.9 (CH), 128.5 (CH), 126.9 (CH), 117.3 (CH), 111.0 (CH), 100.4 (CH), 66.3 (C), 66.1 (CH_2), 59.3 (CH_2), 55.7 (CH_2), 55.1 (CH_2), 51.2 (CH), 29.6 (CH_2), 29.4 (CH_2), 25.5 (CH_2), 9.8 (CH). HRMS (ESI) calcd for $C_{36}H_{40}N_3O_7$ $[M]^+$ 626.2861, found 626.2865.



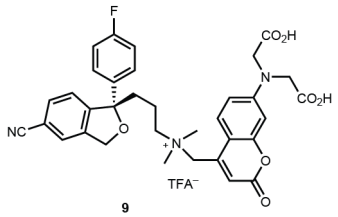
24

PA-Fen isomer-2 (24): This compound was prepared from **23** according to the general procedure described above for compound **6**. Method for reverse phase HPLC: 05–95% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 77 %, pale yellow powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.36 – 7.25 (m, 5H), 7.12 (d, *J* = 7.3 Hz, 2H), 6.75 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 6.45 (s, 1H), 4.79 (s, 2H), 4.57 – 4.48 (m, 1H), 4.31 (s, 4H), 3.70 – 3.53 (m, 6H), 3.16 – 3.11 (m, 2H), 2.15 – 1.96 (m, 6H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (CD_3OD, 101 MHz) δ 176.3 (C), 173.6 (C), 161.9 (C), 157.4 (C), 153.6 (C), 142.6 (C), 140.5 (C), 136.5 (C), 131.2 (CH), 130.7 (CH), 130.3 (CH), 129.9 (CH), 128.6 (CH), 127.2 (CH), 119.0 (CH), 111.1 (CH), 110.9, 100.3 (CH), 62.1 (CH_2), 59.1 (CH_2), 58.6 (CH_2), 54.2 (CH_2), 51.6 (CH), 29.5 (CH_2), 28.9 (CH_2), 24.8 (CH_2), 9.8 (CH). HRMS (ESI) calcd for $C_{36}H_{40}N_3O_7$ $[M]^+$ 626.2861, found 626.2863.



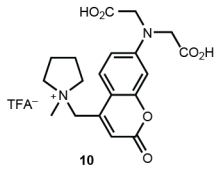
25

Di-*tert*-butyl PA-Esc (25): This compound was prepared from compound **4** according to the general procedure described above for compounds **16–18**. Method for reverse phase HPLC: 40–55% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 70%, pale yellow powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.67 (s, 1H) 7.61 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.13 – 7.02 (m, 2H), 6.70 (dd, *J* = 9.1, 2.7 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.35 (s, 1H), 5.25 – 5.06 (m, 2H), 4.70 – 4.55 (m, 2H), 4.22 (s, 4H), 3.61 – 3.38 (m, 2H), 3.09 (s, 3H), 3.05 (s, 3H), 2.42 – 2.29 (m, 1H), 2.21 – 2.06 (m, 1H), 1.95 – 1.69 (m, 2H), 1.48 (s, 19H). ^{13}C NMR (CD_3OD, 101 MHz) δ 170.7 (C), 162.0 (C), 157.4 (C), 153.6 (C), 150.2 (C), 143.3 (C), 141.7 (C), 140.4 (2C), 133.2 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.8 (CH), 124.1 (CH), 119.5 (C), 118.2 (CH), 116.5 (CH), 116.3 (CH), 113.1 (C), 111.0 (CH), 110.6 (C), 100.3 (CH), 91.8 (C), 83.4 (C), 72.4 (CH_2), 66.6 (CH_2), 63.2 (CH_2), 55.1 (CH_2), 51.5 (CH_3), 51.3 (CH_3), 38.2 (CH_2), 28.3 (CH_3), 19.3 (CH_2). HRMS (ESI) calcd for $C_{42}H_{49}FN_3O_7$ $[M]^+$ 726.3549, found 726.3565.



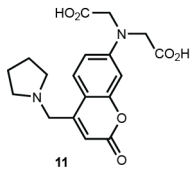
9

PA-Esc (9): This compound was prepared from **25** according to the general procedure described above for compound **6**. Method for reverse phase HPLC: 05–70% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive. Yield: 80%, pale yellow powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.76 (d, *J* = 9.1 Hz, 1H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.66 (s, 1H), 7.65 – 7.57 (m, 1H), 7.58 – 7.48 (m, 2H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.73 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.31 (s, 1H), 5.25 – 5.05 (m, 2H), 4.59 (s, 2H), 4.32 (s, 4H), 3.58 – 3.41 (m, 2H), 3.09 (s, 3H), 3.04 (s, 3H), 2.40 – 2.33 (m, 1H), 2.18 – 2.11 (m, 1H), 1.94 – 1.68 (m, 2H). ^{13}C NMR (CD_3OD, 101 MHz) δ 173.5 (C), 164.8 (C), 162.4 (C), 161.9 (C) , 157.4 (C), 153.5 (C), 150.3 (C), 143.2 (C), 141.6 (C), 140.4 (2C), 133.2 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 126.8 (CH), 124.1 (CH), 119.5 (C), 118.3 (CH), 116.5 (CH), 116.3 (CH), 113.0 (C), 111.0 (CH), 110.6 (C), 100.2 (CH), 91.8 (C), 72.4 (CH_2), 66.6 (CH_2), 63.1 (CH_2), 54.1 (CH_2), 51.5 (CH_3), 51.3 (CH_3), 38.2 (CH_2), 19.3 (CH_2). HRMS (ESI) calcd for $C_{34}H_{33}FN_3O_7$ $[M]^+$ 614.2297, found 614.2305.



10

Compound 10. Coumarin bromide (**5**, 20 mg, 41.5 μmol) was dissolved in 3 mL anhydrous CH_3CN. *N*-methylpyrrolidine (18 mg, 207 μmol) was added and the reaction mixture was heated to 60 °C and stirred for 30 min. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. This crude mixture was used directly in the TFA-mediated deprotection of *tert*-butyl group as described above for the compound **6** and purified by reverse phase HPLC (05–50% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive). ^{1}H NMR (D_2O, 400 MHz) δ 7.61 (d, *J* = 9.2 Hz, 1H), 6.60 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H) 6.25 (s, 1H), 4.60 (s, 2H), 4.00 (s, 4H), 3.65 – 3.53 (m, 4H), 2.98 (s, 3H), 2.26 – 2.16 (m, 4H). ^{13}C NMR (D_2O+1 drop CH_3OH, 101 MHz) δ 177.5 (C), 163.6 (C), 160.2 (C), 155.7 (C), 152.6 (C), 143.8 (C), 125.9 (CH), 113.9 (CH), 110.2 (CH), 108.4 (C), 97.9 (CH), 64.5 (CH_2), 60.2 (CH_2), 55.6 (CH_2), 48.4 (CH_3), 20.6 (CH_2). HRMS (ESI) calcd for $C_{19}H_{23}N_2O_6$ $[M]^+$ 375.1551, found 375.1567.



11

Comound 11: Coumarin bromide (**5**, 20 mg, 41.5 μmol) was dissolved in 3 mL anhydrous CH_3CN. Pyrrolidine (29.5 mg, 415 μmol) was added and the reaction mixture was heated to 60 °C and stirred for 30 min. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. This crude mixture was used directly in the TFA-mediated deprotection of *tert*-butyl group as described above for the compound **6** and purified by reverse phase HPLC (05–50% MeCN/H_2O, linear gradient, with constant 0.1% v/v TFA additive). ^{1}H NMR (D_2O, 400 MHz) δ 7.68 (d, J = 9.1 Hz, 1H), 6.76 (dd, J = 9.0, 2.6 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 6.40 (s, 1H), 4.63 (s, 2H), 4.38 (s, 4H), 3.75 (brs. 2H), 3.32 (brs, 2H) 2.23 (brs, 2H), 2.08 (brs, 2H). ^{13}C NMR (D_2O, 101 MHz) δ 175.9 (C), 163.6 (C), 155.5 (C), 151.5 (C), 146.3 (C), 125.6 (CH), 111.5(CH), 109.9 (CH), 108.3 (C), 98.8 (CH), 55.1 (CH_2), 54.2 (CH_2), 52.9 (CH_2), 22.6 (CH_2). HRMS (ESI) calcd for $C_{18}H_{21}N_2O_6$ $[M+H]^+$ 361.1394, found 361.1408.

References

1. Hagen, V., Dekowski, B., Nache, V. et al., *Angew. Chem. Int. Ed.* **44**, 7887-7891 (2005).
2. Schoenleber, R.O. and Giese, B., *Synlett* **2003**, 501-504 (2003).