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Design and application of a new julolidine-based photolabile protecting group

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Photolabile protecting groups (PPGs) are invaluable tools for protecting a variety of functionalities and serve as alternatives to protecting groups that need chemical cleavage. PPGs are mainly classified into 3 categories namely, 2-nitrobenzyl type PPGs, coumarin-based PPGs, and benzyl type PPGs which have been designed by Wang and co-workers based on the *meta* effect and computational study observations. This work describes the design and synthesis of a julolidine-based benzyl type PPG **4** and the analysis of its reaction intermediates. The julolidine PPG **4** is applied for the protection of alcohols as carbonates, amines as carbamates, carboxylic acids as esters, and hydroxamic acid. Analysis of the photolyzed samples by HPLC has also been conducted.

Keywords: Benzyl type PPGs, *Meta* effect, Julolidine-based PPG, Mild condition, Deprotection

Photolabile protecting groups (PPGs) are indispensable tools used in organic chemistry[1-3]. PPGs are employed for fluorescence activation[4], caging of volatile compounds[5], and polymerization[6], and exploited within multiple scientific disciplines including developmental biology[7-8], biochemistry, and neurobiology. Wang and co-workers developed a new class of PPGs which are structurally simple and easy to install, and simple structural modification provides analogs with improved photochemical efficacy[9-21]. Advantageously, these newer PPGs are reactive under ambient photolysis conditions and possess remarkable dark stability[11]. Importantly, these PPGs have also demonstrated better chemical and photochemical (deprotection) yields compared to the first-generation 2-nitrobenzyl and coumarin-based PPGs[11,22]. Owing to their efficiency in protecting a wider range of functional groups, these PPGs have found widespread application in synthesis[23], caging[24] and materials science[25, 26].

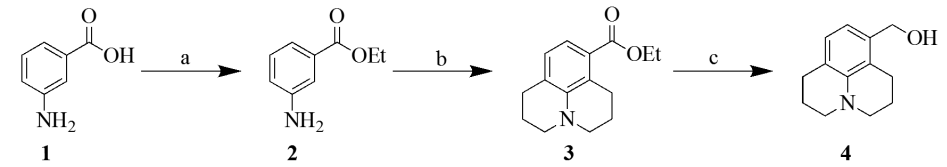
The current study describes the synthesis of synthesis, characterization and application of Julolidine-based PPG for the protection of various functional groups. It is envisioned that introduction of electron donating group at both *ortho* and *para* positions (methyl group in this case) would induce the bathochromic shift and absorb at higher wavelengths compared to the benzyl PPGs developed by Wang and co-workers. Also, it is intended to apply this novel PPG for the protection of hydroxamic acids along with alcohols as carbonates, amines as carbamates, and carboxylic acids as esters.

Materials

Unless otherwise mentioned all the commercially available chemicals were purchased from Sigma Aldrich Co. and AK Scientific Inc. Anhydrous solvents were prepared by the following procedures: THF distilled from Na/benzophenone; dry DMF purchased from Merck; EtOAc, hexane, acetone, methanol, ethanol, and dioxane are reagent grade and were used as supplied by Merck. Acetonitrile was chromatography grade and used as supplied.$CDCl_3$ and DMSO-d_6 were used for NMR spectroscopy as supplied by Cambridge Isotopes Laboratory.

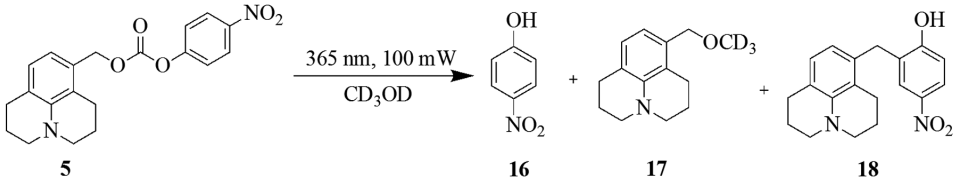
Synthesis of Julolidine-based PPG 4 and its derivatives

Julolidine-based PPG synthesis was achieved from commercially available 3-aminobenzoic acid **1** by treating with thionyl chloride in ethanol to generate ethyl 3-aminobenzoate **2** [27]. Subsequently, sodium carbonate was added to the solution of ethyl 3-aminobenzoate **2** dissolved in 1-bromo-3-chloropropane. The reaction temperature was gradually increased from 70°C to 160°C over 3 h and maintained at 160°C for 12 h. The julolidine ester **3** was isolated as a colorless liquid[28,29]. Subsequent reductions of julolidine ethyl ester **3** with lithium aluminum hydride ($LiAlH_4$) afforded the required julolidine PPG **4** (Scheme 1)[30].



Reagents and Reaction Conditions: (a) $SOCl_2$, EtOH, 50°C, 15 h, (b) 1-Bromo-3-chloropropane, Na_2CO_3, 70°C–160°C, 18 h, (c) $LiAlH_4$, THF, 3 h.

Scheme 1 — Synthesis of julolidine PPG **4**



Scheme 2 — Photolytic degradation of carbonate **5** in CD_3OD

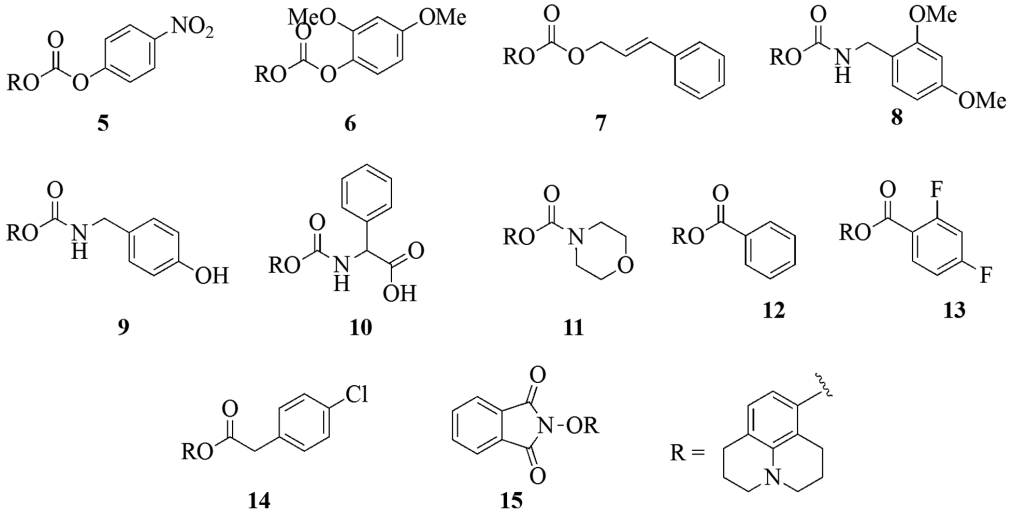


Fig. 1 — Application of julolidine PPG **4** for the protection of various functional groups

Derivatization of julolidine PPG 4

The julolidine PPG **4** was subsequently used for the protection of hydroxamic acid **15**, alcohols as carbonates (**5 - 7**), amines as carbamates (**8 – 11**), and carboxylic acids as esters (**12 – 14**). Julolidine 4-nitrophenyl carbonate **5** was used as an intermediate to synthesize the remaining carbonates (**6** and **7**) and carbamates (**8- 11**, Fig. 1).

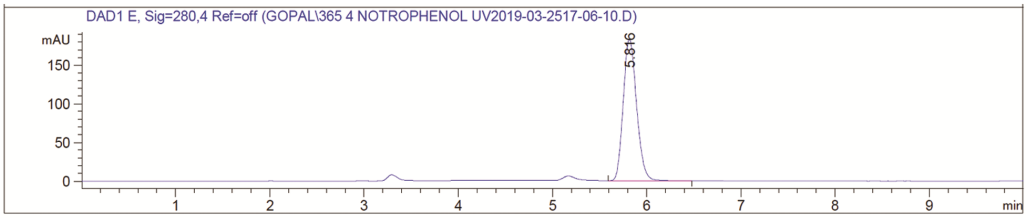
General procedure of photolysis

A 5.0 mM solution of Julolidine PPG derivatives (**5 – 15**) was prepared in CD_3OD (deuterated methanol) or CD_3CN/D_2O (deuterated acetonitrile and water) mixture and exposed to 365 nm and 100 mW intensity UV light for 60 min. The reaction mixture was analyzed by using HPLC and mass spectrometry to identify the photolytic fragments.

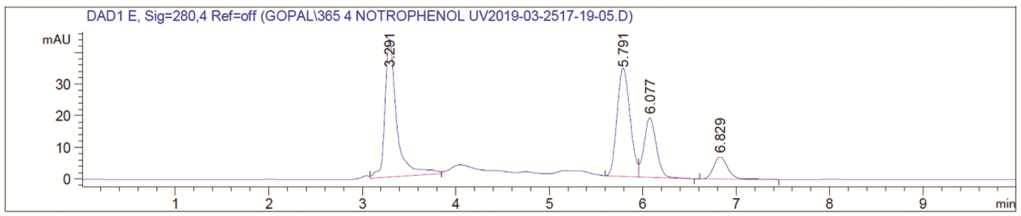
Results and Discussion

A 5.0 mM solution of julolidine 4-nitrophenyl carbonate **5** in CD_3OD (Peak at R_t = 5.816 min., Chromatogram A, Fig. 2) released the expected 4-nitrophenol **16** (Peak at R_t = 3.291 min., Chromatogram B, Fig. 2) and electrophilically substituted adduct **18** (Peak at R_t = 6.829 min., Chromatogram B, Fig. 2) (Scheme 2). Formation of julolidine substituted 4-nitrophenol **18** was accounted for by the electrophilic aromatic substitution of the julolidine carbocation, which is formed after the photolytic release of the required alcohol **16** (Fig. 2)[19].

The involvement of the radical mechanism for the formation of **18** is excluded due to the involvement of the *meta* effect[11,31-33]. Formation of julolidine substituted 4-nitrophenol **18** was confirmed by the

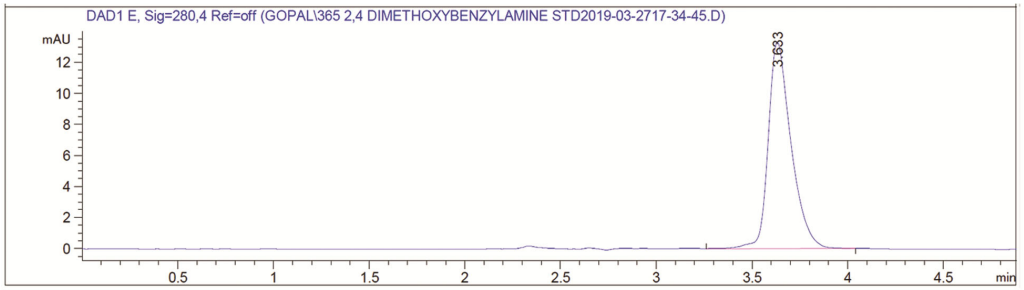


(a) Chromatogram of the julolidine 4-nitrophenyl carbonate **5** standard solutions

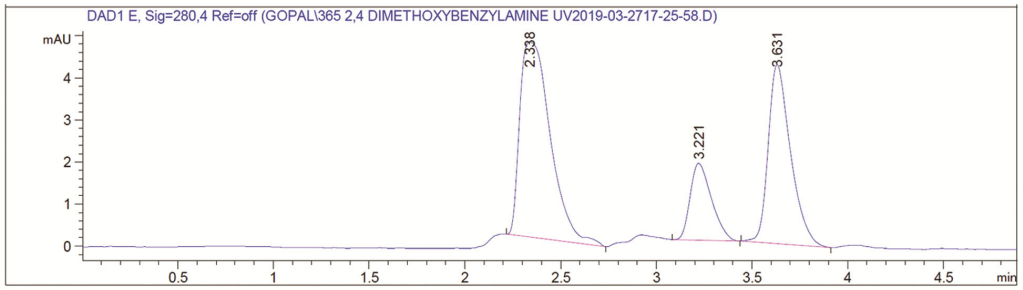


(b) Chromatogram after the photolysis of julolidine 4-nitrophenyl carbonate **5**

Fig. 2 — Photolysis of the julolidine 4-nitrophenyl carbonate **5**



(a) Chromatogram of 2,4-dimethoxybenzyl amine **8** standard solution



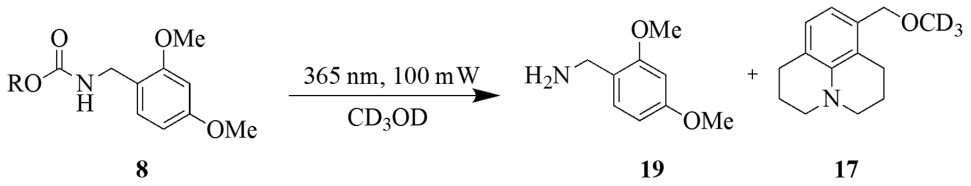
(b) Chromatogram of 2,4-dimethoxybenzyl amine **8** after photolysis

Fig. 3 — Photolysis of 2,4-dimethoxybenzyl amine **8**

LCMS analysis (*m/z* 324.1477, calculated for $(C_{19}H_{20}N_2O_3)^+$). The deuterated methyl ether **17** was observed as the major by-product. About 82% of the starting material underwent photolysis after 60 min of exposure as suggested by HPLC analysis of the samples after photolysis. Similar photolytic reaction conditions were applied to the photolysis of remaining carbonates (**6** and **7**) and as suggested HPLC analysis of the standard samples after photolysis, the starting materials showed near quantitative photolytic conversion.

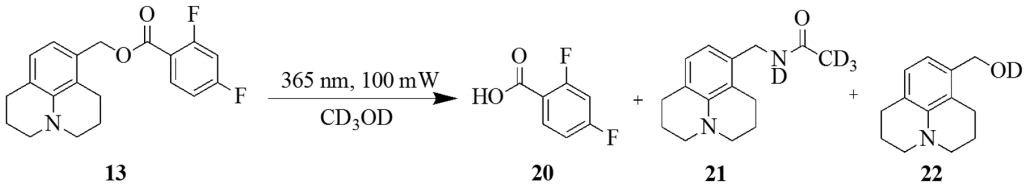
Analogous photolytic reaction conditions were next applied to the photolysis of carbamates (Scheme 3). Photolysis of a 5.0 mM solution of the 2,4-dimethoxybenzyl amine carbamate **8** at 365 nm and 100 mW liberated the desired 2,4-dimethoxybenzyl amine **19** (peak at R_t = 3.221 min., Chromatogram B, Fig. 3). After 60 min of exposure to UV light, 71% of the carbamate **8** (peak at R_t = 3.633 min., Chromatogram A, Fig. 3) underwent photolysis. Post-cleavage, the PPG was recovered as the deuterated methyl ether **17** (peak at R_t = 2.338 min., Chromatogram B, Fig. 3).

The photolytic release profile of julolidine-protected carboxylic acids (**12 - 14**) was studied in both CD_3OD and CD_3CN/D_2O solvent mixtures. A



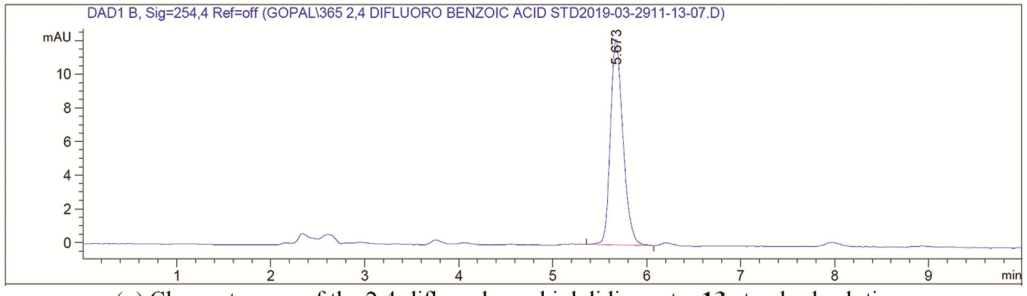
8 **19** **17**

Scheme 3 — Photolysis of 2,4-dimethoxy benzyl carbamate 8

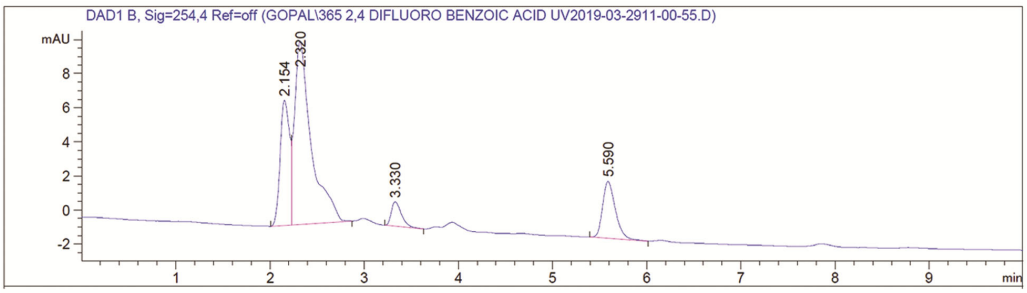


13 **20** **21** **22**

Scheme 4 — Photolysis of 2,4-difluorobenzyl julolidine ester 13



(a) Chromatogram of the 2,4-difluorobenzyl julolidine ester **13** standard solutions



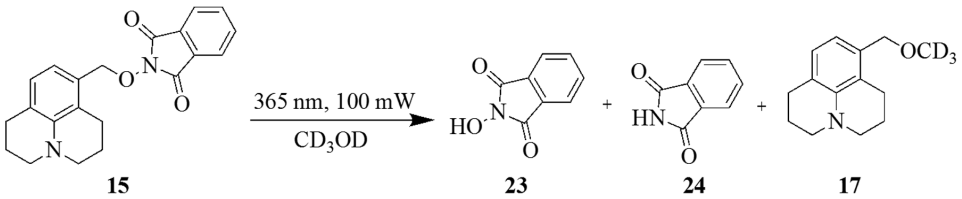
(b) Chromatogram of 2,4-difluorobenzyl julolidine ester **13** after photolysis

Fig. 4 — HPLC analysis of 2,4-difluorobenzoic acid **13** esters

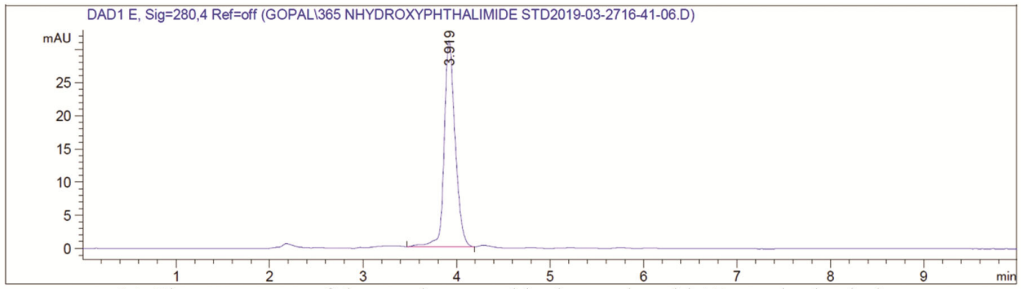
5.0 mM solution of julolidine 2,4-difluorobenzoate **13** was prepared in CD_3OD, and after 60 min of exposure to the 365 nm at 100 mV, approximately 50% of the starting material had undergone photolysis. Subsequently, repeating this photolysis reaction in CD_3CN/D_2O (9:1) under identical reaction conditions resulted in a 73% of conversion of the starting material (Scheme 4). The desired 2,4-difluorobenzoic acid **20** (Peak at R_t = 2.15 min., Chromatogram B, Fig. 4) was observed. Julolidine PPG **4** was mainly observed as **21** (*m/z* 248.1841, calculated for $(C_{15}H_{16}D_4N_2O)^+$) and deuterated alcohol **22** (*m/z* 204.1402, calculated for $(C_{13}H_{16}DNO)^+$). Optimized reaction conditions were applied for the photolytic release of remaining esters **12** and **14**. Analysis of the standard samples of esters **12** and **14** by HPLC revealed 70% and 98% conversion respectively after exposure to UV light for 60 min.

A 5.0 mM solution of caged hydroxamic acid **15** was prepared in CD_3OD (Scheme 5). Exposure of the sample to 365 nm and 100 mW intensity UV light for 60 min again resulted in the complete conversion of the starting material. The CD_3OD solvent facilitated effective photolysis, as evidenced by HPLC analysis of the reaction mixture (Fig. 5).

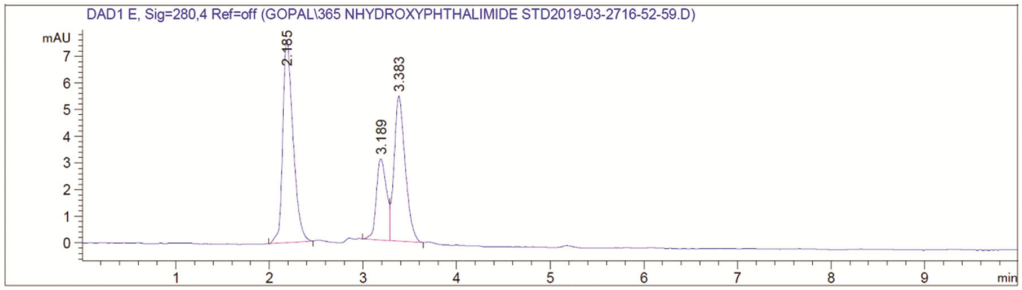
Post-irradiation, HPLC analysis of the sample revealed the formation of the desired N-hydroxy phthalimide **23** (from C-O bond cleavage) (Peak at



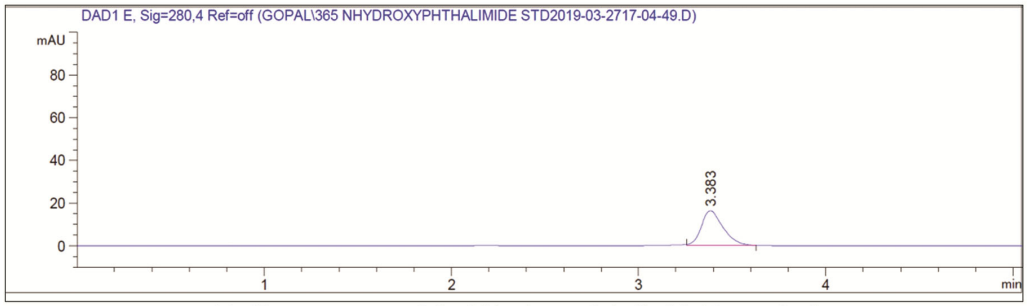
Scheme 5 — Photolysis of caged hydroxamic acid 15



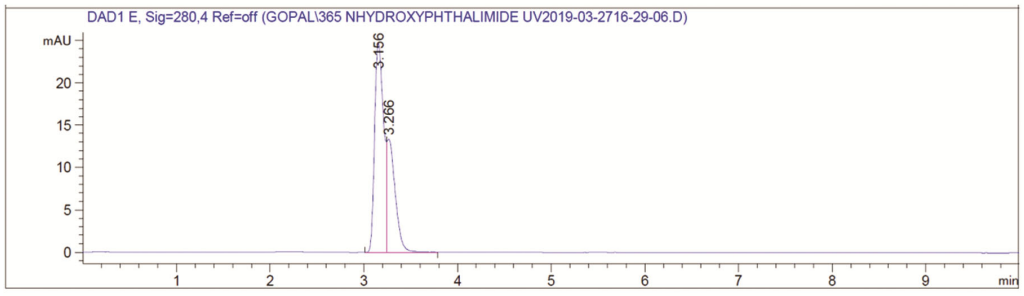
(a) Chromatogram of the starting caged hydroxamic acid **15** standard solution



(b) Chromatogram of the caged hydroxamic acid **15** standard solution after photolysis



(c) Chromatogram of the *N*-hydroxyphthalimide**23** standard



(d) Chromatogram of N-hydroxyphthalimide**23** and phthalimide **24** standard solution

Fig. 5 — HPLC analysis of caged hydroxamic acid 15 following photochemical irradiation at 365 nm

Table 1 — Protection/deprotection yields of julolidine PPG **4**

Compound	Protection Yield (%)	Photolytic cleavage after 60 min (%)
Julolidine 4-nitrophenyl carbonate **5**	100	82
2,4-Dimethoxybenzyl alcohol carbonate **6**	90	99
Cinnamyl alcohol carbonate **7**	89	98
2,4-Dimethoxy benzylamine carbamate **8**	92	71
4-Hydroxybenzylamine carbamate **9**	87	70
Phenyl glycine carbamate **10**	82	95
Morpholine carbamate **11**	90	80
Benzoyl julolidine ester **12**	80	70
2,4-Diflurobenzyl julolidine ester **13**	85	73
4-Chlorophenylacetate julolidine ester **14**	82	98
Caged hydroxamic acid **15**	70	100

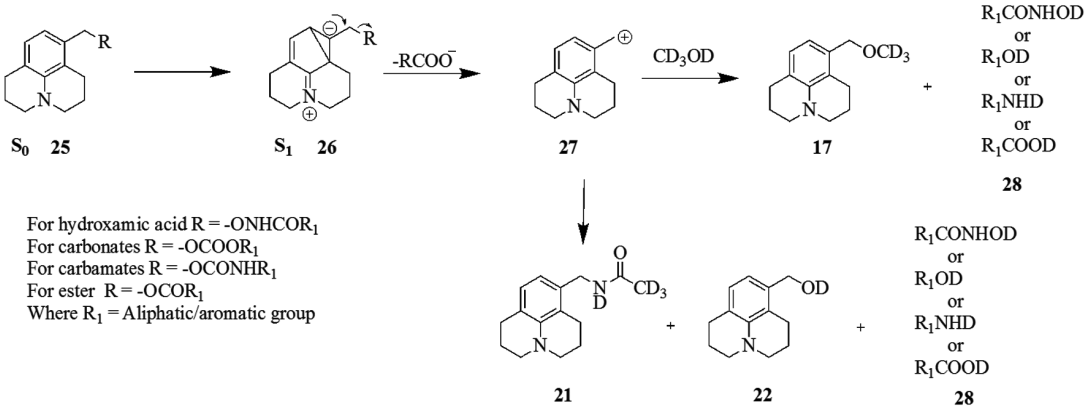


Fig. 6 — Plausible reaction mechanism for photolysis

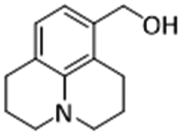
R_t = 3.383 min., Chromatogram B, Fig. 5) along with phthalimide **24** (arising from N-O bond cleavage) (Peak at R_t = 3.189 min., Chromatogram B, Fig. 5). Formation of both N-hydroxyphthalimide 23 (Peak at R_t = 3.383 min., Chromatogram C, Fig. 5) and phthalimide **24** was confirmed by injecting authentic samples of these products under identical analytical conditions (Chromatogram C and D, Fig. 5). Julolidine PPG **4** was mainly converted to the deuterated methyl ether **17** (Peak at R_t = 2.185 min., Chromatogram B, Fig. 5). Formation of the ether **17** was confirmed by the LCMS analysis (*m/z* 220.1705, calculated for $(C_{14}H_{16}D_3NO)^+$) of the standard sample after photolysis. The mechanism resulting in O-N bond cleavage and subsequent release of the undesired phthalimide **24** was not investigated in this study due to time constraints but is worthy of pursuit. The protection and photolytic conversion of each compound was tabulated below in Table 1.

The photo-release mechanism of julolidine-protected compounds

A plausible reaction mechanism for the photolysis of julolidine PPG **4** has been proposed based on previous literature reports (Fig. 6) [10,11,33]. Julolidine photolabile linker-protected model analog**25** upon exposure to UV (365 nm, 100 mW) is predicted to undergo a π-π* transition to generate the S_1 excited state intermediate **26** S_1. This intermediate **26** S_1 then collapsesto liberate the caged compound **28**and benzyl carbocation **27**, which is subsequently trapped by the solvent system (CD_3OD or CD_3CN/D_2O) to generate compounds **17**, **21**, and **22**.

Experimental Section

Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methanol, 4

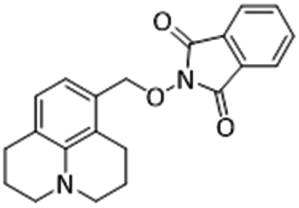


4

The Julolidine ester **3** (245 mg, 1.00 mmol) in THF (8 mL) was cooled to 0°C. Lithium aluminum hydride (60.0 mg, 1.50 mmol) was slowly added to the

reaction mixture in three portions and the reaction mixture was maintained at 0°C for 3 h. The reaction was monitored by TLC (EtOAc: hexane, 1:3) and upon completion was quenched with sat. aqueous Na_2SO_4 (10 mL). The reaction mixture was filtered through a celite bed and dried over anhyd. Na_2SO_4, filtered, and concentrated *in vacuo*. The crude isolate was purified by silica column chromatography (EtOAc: hexane, 3:7) to give the required Julolidine PPG **4** (160 mg, 80% yield) as light orange semi-solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 6.74 (d, J = 7.6, 1H), 6.58 (d, J = 7.6 Hz, 1H), 4.49 (s, 2H), 3.16 – 3.01 (m, 4H), 2.80 – 2.71 (m, 4H), 2.06 – 1.90 (m, 4H); ^{13}C NMR (101 MHz, Methanol-d_4): δ 143.0, 136.3, 126.0, 121.6, 120.0, 116.4, 62.2, 50.3, 49.6, 27.4, 23.2, 22.0, 21.8; IR (neat): 3248, 2935, 2916, 2822, 2370, 2322, 1596, 1578, 1490, 1437, 1422, 1394, 1353, 1300, 1231, 1212, 1185, 1153, 1120, 1064, 1042, 1008, 984, 924, 872, 799, 733 cm^{-1}; HRMS: Calcd for $(C_{13}H_{18}NO)^+$: *m/z* 204.1388. Found: 204.1368.

Synthesis of 2-((2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methoxy)isoindoline-1,3-dione, 15

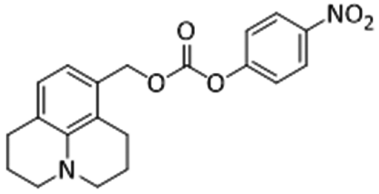


15

2,4,6-Trichloro-[1,3,5]triazine (TCT) (92.0 mg, 0.50 mmol) and DMF (0.10 mL) were reacted in an oven-dried round bottom flask at 25°C until a colorless solid formed in 15 min. After the complete conversion of the TCT by TLC (EtOAc: hexane, 1:1), DCM (5 mL) was added to the reaction mixture. Julolidine PPG **4** (100 mg, 0.50 mmol) dissolved in DCM (1 mL) was then added to the above-prepared reaction mixture and the reaction was stirred at RT for 4 h. After the complete conversion of the starting material, DCM was added (15 mL) to the reaction mixture. The reaction mixture was then washed with sat. sodium carbonate solution (10 mL), followed by 1N HCl (10 mL) and brine (10 mL). The organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated *in vacuo*. The isolated crude chloride **4a** was used in the next reaction without purification[34].

Crude chloride **4a** (97.0 mg, 0.43 mmol) and N-hydroxyphthalimide (84.0 mg, 0.52 mmol) were dissolved in DMF (5 mL). TEA (0.10 mL) was added to the mixture at RT and the reaction was stirred at 60°C for 12 h before being cooled to RT. Water (10 mL) was then added, and the mixture was extracted with EtOAc (3×20 mL). The combined organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated *in vacuo*. The crude compound was purified by silica column chromatography (EtOAc: hexane, 2:8) to obtain the required caged hydroxylamine **15** as an orange solid (107 mg, 70% yield). ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 7.82 (s, 4H), 6.72 (d, J = 7.5 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 5.08 (s, 2H), 3.20 -3.10 (m, 4H), 3.05 (t, J = 6.6 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.09 – 1.83 (m, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3): δ 164.2, 138.3, 135.7, 130.2, 129.6, 126.8, 124.0, 123.6, 122.8, 119.7, 78.6, 50.5, 50.0, 28.2, 24.2, 22.3, 22.2; IR (neat): 2952, 1844, 1783, 1734, 1723, 1578, 1475, 1444, 1377, 1310, 1237, 1204, 1181, 1132, 1079, 1042, 1012, 965, 923, 874, 789, 767, 728, 697 cm^{-1}; HRMS: Calcd for $(C_{21}H_{21}N_2O_3)^+$: *m/z* 349.1552. Found: 349.1529.

Synthesis of 4-nitrophenyl-((2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl)carbonate, 5



5

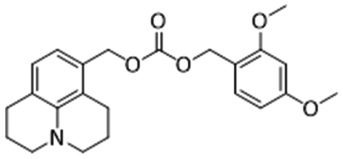
Julolidine PPG **4** (100 mg, 0.49 mmol) was dissolved in dry DCM (5 mL) and cooled to 0°C. Pyridine (79.00 µL, 0.735 mmol) was added and the reaction mixture was stirred for 5 min at 0°C before the addition of 4-nitrophenyl chloroformate (123 mg, 0.59 mmol). The reaction mixture was allowed to warm to RT and stir overnight. After the complete conversion of the starting material (determined by TLC), the reaction mixture was quenched by the addition of water (10 mL). The reaction mixture was extracted with DCM (3×10 mL), and the combined organic phase was dried over anhyd. Na_2SO_4 and filtered. The organic phase was concentrated *in vacuo* and the residue was purified by silica column chromatography (EtOAc: hexane, 2:8) to give julolidine 4-nitrophenyl carbonate 258 (181 mg, quant.) as an orange crystalline solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 8.54 – 8.12 (m, 2H), 7.65 – 7.22 (m, 2H), 6.79 (d, J = 7.6 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 5.20 (s, 2H), 3.43 – 2.94 (m, 4H), 2.77- 2.64

(m, 4H), 1.98 -1.81 (m, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3): δ 156.4, 153.0, 146.1, 144.1, 130.9, 127.1, 125.9, 123.6, 122.9, 121.3, 118.0, 70.3, 50.5, 49.8, 28.2, 24.2, 22.3, 22.2; IR (neat): 3077, 2938, 2813, 1763, 1615, 1515, 1491, 1454, 1400, 1381, 1342, 1307, 1244, 1207, 1184, 1162, 1110, 1076, 1035, 987, 954, 926, 862, 798, 754, 719, 685, 667 cm^{-1}; HRMS: Calcd for $(C_{20}H_{21}N_2O_5)^+$: *m/z* 369.1450. Found: 369.1450.

Representative Procedure A

In a typical reaction, julolidine 4-nitrophenyl carbonate **5** (36.8 mg, 0.10 mmol) was dissolved in DCM (6 mL) and the corresponding alcohol (0.12 mmol) was added. The reaction mixture was then cooled to 0°C before the addition of DMAP (12.2 mg, 0.10 mmol). The reaction mixture was stirred for 15 h at RT. After completion of the reaction (as determined by TLC), the solvent was removed *in vacuo* and the crude compound was purified by silica column chromatography (EtOAc: hexane, 2:8).

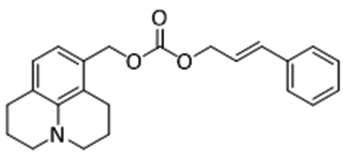
Synthesis of 2,4-dimethoxybenzyl-((2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ji]quinolin-8-yl)methyl)carbonate, 6



6

2,4-Dimethoxybenzyl carbonate **6** was synthesized according to Representative Procedure A from julolidine 4-nitrophenyl carbonate **5**. The required 2,4-dimethoxybenzyl carbonate **6** was obtained in 90% yield as a light orange semi-solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 7.25 (dd, J = 8.4, 1.7 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.64 – 6.40 (m, 3H), 5.09 (s, 2H), 5.04 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.24 – 2.99 (m, 4H), 2.79 – 2.63 (m, 4H), 2.03 – 1.92 (m, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3): δ 162.3, 159.7, 155.6, 133.5, 132.2, 131.9, 127.0, 123.2, 121.1, 116.6, 105.0, 98.9, 68.6, 65.4, 55.9, 55.7, 50.6, 49.8, 28.1, 24.1, 22.4, 22.2; HRMS: Calcd for $(C_{23}H_{28}NO_5)^+$: *m/z* 398.1967. Found: 398.1960.

Synthesis of cinnamyl-((2,3,6,7-tetrahydro-1*H*,5*H*-pyrido [3,2,1-ij] quinolin-8-yl)methyl)carbonate, 7



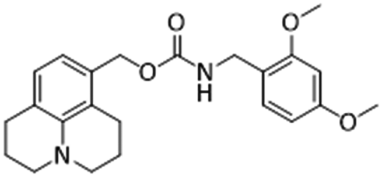
7

Cinnamyl alcohol carbonate **7** was synthesized according to Representative Procedure A from julolidine 4-nitrophenyl carbonate **5**. The target cinnamyl alcohol carbonate **7** was obtained in 89% yield as a light orange semi-solid. ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 7.52 – 7.20 (m, 5H), 6.86 – 6.64 (m, 2H), 6.53 (d, J = 7.6 Hz, 1H), 6.44 – 6.28 (m, 1H), 5.07 (s, 2H), 4.78 (dd, J = 6.3, 1.4 Hz, 2H), 3.19 – 3.05 (m, 4H), 2.70 - 2.60 (m, 4H), 1.93 - 180 (m, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3): δ 154.7, 146.1, 139.3, 135.9, 134.3, 129.2, 128.7, 127.1, 123.8, 123.2, 121.1, 68.8, 68.5, 50.5, 49.8, 28.9, 28.2, 22.4, 22.2; HRMS: Calcd for $(C_{23}H_{26}NO_3)^+$: *m/z* 364.1912. Found: 364.1886.

Representative Procedure B

In a typical reaction, julolidine 4-nitrophenyl carbonate **5** (36.8 mg, 0.1 mmol) and the corresponding amine (0.15 mmol) were dissolved in tetrahydrofuran (3 mL) and the mixture was cooled to 0°C. Pyridine (12 µL, 1.5 mmol) was added at 0°C and the reaction mixture was stirred for 15 h at RT [35]. After completion of the reaction (as determined by TLC), the solvent was removed *in vacuo* and the crude reaction mixture was purified by silica column chromatography (EtOAc: hexane, 2:8).

Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl(2,4-dimethoxybenzyl)carbamate, 8

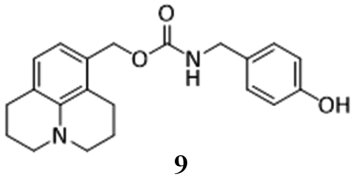


8

2,4-Dimethoxybenzylamine carbamate **8** was synthesized according to Representative Procedure B from julolidine 4-nitrophenyl carbonate **5**. The required 2,4-dimethoxybenzylamine carbamate **8** was obtained in 92% yield as a colorless semi-solid. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.41 (t, J = 6.1 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.50 (dd, J = 20.5, 5.2 Hz, 3H), 4.87 (s, 2H), 4.09 (d, J = 6.1 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.15 – 2.94 (m, 4H), 2.75 – 2.60 (m, 4H), 1.96 - 1.71 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 160.1, 157.9, 151.5, 143.5, 142.2, 128.7, 126.5, 121.8, 120.3, 119.8, 117.0, 104.7, 98.6, 55.8, 55.6, 50.2, 49.5, 27.8, 23.6, 22.1, 21.9; IR (neat): 3313, 2928, 2830, 1684, 1614, 1587, 1531, 1508, 1492, 1454, 1442, 1303,

1288, 1265, 1240, 1208, 1130, 1082, 1043, 1032, 993, 972, 956, 934, 879, 835, 800, 785, 761, 720 cm^{-1}; HRMS: Calcd for $(C_{23}H_{29}N_2O_4)^+$: *m/z* 397.2127. Found: 397.2115.

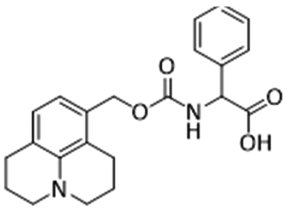
Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl (4-hydroxybenzyl)carbamate, 9



9

4-Hydroxybenzylamine carbamate **9** was synthesized according to Representative Procedure B from julolidine 4-nitrophenyl carbonate **5**. The required 4-hydroxybenzylamine carbamate **9** was obtained in 87% yield as a colorless semi-solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.02 (d, J = 8.1 Hz, 2H), 6.73 – 6.55 (m, 3H), 6.46 (d, J = 7.6 Hz, 1H), 4.88 (s, 2H), 4.11 (s, 2H), 3.01 (q, J = 7.9, 6.8 Hz, 4H), 2.65 (t, J = 6.6 Hz, 4H), 1.94 – 1.73 (m, 4H); ^{13}C NMR (101 MHz, Methanol-d_4): δ 156.9, 155.4, 142.3, 138.9, 129.2, 127.6, 125.4, 121.6, 119.7, 116.4, 114.1, 64.3, 49.4, 48.7, 43.0, 26.8, 22.7, 20.9; IR (neat): 3283, 2960, 2836, 1689, 1616, 1599, 1578, 1540, 1517, 1487, 1438, 1376, 1350, 1295, 1252, 1211, 1188, 1149, 1129, 1102, 1080, 1034, 1002, 984, 922, 891, 868, 851, 835, 822, 800, 778, 718, 670 cm^{-1}; HRMS: Calcd for $(C_{21}H_{25}N_2O_3)^+$: *m/z* 353.1865. Found: 353.1843.

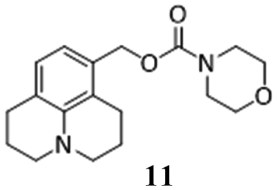
Synthesis of 2-phenyl-2-((((2,3,6,7-tetrahydro-1*H*,5*H*-pyrido [3,2,1-ij]quinolin-8-yl)methoxy)carbonyl)amino)acetic acid, 10



10

Phenyl glycine (12.0 mg, 0.08mmol) and 80 µL of aq. 2N NaOH solution was added to a solution of julolidine 4-nitrophenyl carbonate **5** (36.8 mg, 0.10 mmol) in tetrahydrofuran (2 mL)[36]. The reaction mixture was stirred at RT for 15 h. Water (10 mL) was then added, and the reaction mixture was washed with EtOAc (10 mL) to remove the unreacted carbonate, and the aqueous layer was acidified to *p*H 2 with 1 N HCl. The resultant solid was extracted into EtOAc (3×15 mL) and the combined organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated *in vacuo* to obtain the required carbamate **10** (25 mg, 82% yield) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.49 – 7.25 (m, 5H), 6.68 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 8.1 Hz, 1H), 4.88 (s, 2H), 3.10 - 3.03 (m, 4H), 2.69 -2.60 (m, 4H), 1.97 – 1.68 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.5, 156.3, 143.5, 137.9, 132.6, 128.8, 128.3, 128.1, 126.5, 121.9, 120.4, 117.1, 64.9, 58.6, 50.2, 49.4, 27.8, 23.6, 22.1, 21.9; IR (neat): 3351, 2940, 2871, 1686, 1581, 1513, 1496, 1444, 1351, 1300, 1242, 1209, 1183, 1111, 1076, 1043, 981, 937, 872, 842, 812, 767, 725 cm^{-1}; HRMS: Calcd for $(C_{22}H_{25}N_2O_4)^+$: *m/z* 381.1814. Found: 381.1792.

Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl morpholine-4-carboxylate, 11



11

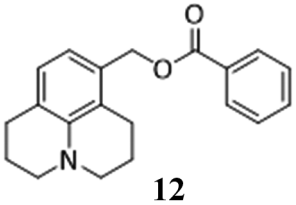
Morpholine carbamate **11** was synthesized according to Representative Procedure B from julolidine 4-nitrophenyl carbonate **5**. The target morpholine carbamate **11** was obtained in 90% yield as an off-white semi-solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 6.74 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 5.02 (s, 2H), 3.72 – 3.54 (m, 4H), 3.53 – 3.40 (m, 4H), 3.20 – 2.99 (m, 4H), 2.74 (td, J = 6.6, 1.9 Hz, 4H), 2.07 – 1.90 (m, 4H); ^{13}C NMR (101 MHz, Methanol-d_4): δ 155.7, 143.1, 131.6, 126.1, 122.5, 120.5, 117.2, 66.2, 66.0, 50.2, 49.5, 27.5, 23.6, 21.8, 21.7; IR (neat):2919, 2850, 2686, 2321, 1698, 1601, 1578, 1492, 1442, 1411, 1355, 1309, 1277, 1232, 1158, 1115, 1070, 1022, 984, 862, 815, 786, 768, 739, 722 cm^{-1}; HRMS: Calcd for $(C_{18}H_{25}N_2O_3)^+$: *m/z* 317.1865. Found: 317.1839.

Representative Procedure C

In a typical reaction, TEA (70 µL, 2.5 mmol) and DMAP (2.40 mg, 0.02 mmol) were added to a cooled solution (0°C) of alcohol (40.0 mg, 0.20 mmol) in DCM (5 mL).[17, 37] The corresponding acid chloride was then added to the reaction mixture, and the reaction mixture was heated to RT and stirred for 4 h. After complete consumption of the starting material (as determined by TLC), the reaction mixture was

diluted with DCM (10 mL) and quenched with sat. sodium bicarbonate (10 mL). The reaction mixture was extracted with DCM (3×10 mL) and the combined organic phase was dried over anhyd. Na_2SO_4, filtered, and the solvent was removed under vacuum. The crude compound was purified by silica column chromatography (EtOAc: hexane, 2:8).

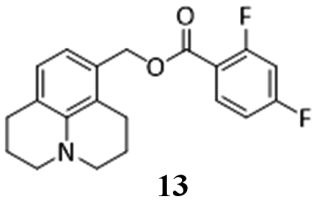
Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl benzoate, 12



12

Benzoyl ester **12** was synthesized according to Representative Procedure C from PPG **4**. The required benzoyl ester **12** was obtained in 80% yield as a red solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.07 – 7.98 (m, 2H), 7.66 – 7.56 (m, 1H), 7.52 – 7.44 (m, 2H), 6.77 (d, J = 7.6, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.25 (s, 2H), 3.16 -3.09 (m, 4H), 2.78 (dt, J = 18.6, 6.6 Hz, 4H), 2.06 -1.94 (m, 4H); ^{13}C NMR (151 MHz, Acetonitrile-d_3): δ 166.7, 144.0, 133.7, 132.3, 130.9, 129.8, 129.2, 128.5, 127.1, 123.1, 121.3, 66.1, 50.6, 49.9, 28.1, 24.2, 22.4, 22.2; IR (neat): 2931, 2775, 1738, 1580, 1490, 1445, 1429, 1374, 1345, 1303, 1209, 1187, 1146, 1081, 1044, 1013, 954, 926, 870, 800, 771, 733 cm^{-1}; HRMS: Calcd for $(C_{20}H_{22}NO_2)^+$: *m/z* 308.1650. Found: 308.1651.

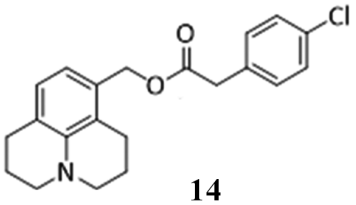
Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl 2,4-difluorobenzoate, 13



13

2,4-Difluorobenzoyl ester **13** was synthesized according to Representative Procedure C from julolidine PPG **4.** The required 2,4-difluorobenzoyl ester **13** was obtained in 85% yield as an orange semi-solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.60 – 7.47 (m, 1H), 7.17 – 6.96 (m, 2H), 6.76 (d, J = 7.6, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.27 (s, 2H), 3.13 (q, J = 5.3 Hz, 4H), 2.78 (dt, J = 19.5, 6.6 Hz, 4H), 2.13 – 1.81 (m, 4H); ^{13}C NMR (101 MHz, Methanol-d_4): δ 166.2, 143.2, 131.2, 130.1, 128.2, 126.2, 122.6, 120.6, 117.5, 64.9, 50.2, 49.5, 27.5, 23.5, 21.9, 21.7; IR (neat): 2927, 2840, 2113, 1716, 1654, 1620, 1578, 1492, 1460, 1425, 1372, 1355, 1288, 1255, 1226, 1186, 1155, 1112, 1065, 1101, 984, 926, 881, 802, 744, 718, 688 cm^{-1}; HRMS: Calcd for $(C_{20}H_{20}F_2NO_2)^+$: *m/z* 344.1457. Found: 344.1437.

Synthesis of (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-ij]quinolin-8-yl)methyl 2-(4-chlorophenyl)acetate, 14



14

4-Chlorophenylacetyl ester **14** was synthesized according to Representative Procedure C from julolidine PPG **4**. The target 4-chlorophenylacetyl ester **14** obtained in 82% yield as a red solid. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.38 – 7.20 (m, 4H), 6.71 (d, J = 7.6 Hz, 1H), 6.48 (d, J = 7.6 Hz, 1H), 5.00 (s, 2H), 3.65 (s, 2H), 3.18 – 2.98 (m, 4H), 2.74 (t, J = 6.6 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 2.06 – 1.79 (m, 4H); ^{13}C NMR (101 MHz, Methanol-d_4): δ 171.4, 143.1, 133.2, 132.6, 131.1, 130.6, 128.1, 126.1, 122.6, 120.8, 117.6, 65.4, 50.1, 49.4, 40.0, 27.5, 23.4, 21.9, 21.6; IR (neat): 3032, 2931, 2808, 2775, 1731, 1581, 1490, 1445, 1429, 1375, 1344, 1303, 1209, 1186, 1146, 1082, 1045, 1014, 953, 927, 870, 800, 772, 733, 684, 666 cm^{-1}; HRMS: Calcd for $(C_{21}H_{23}ClNO_2)^+$: *m/z* 356.1417. Found: 356.1404.

Conclusion

The novel Julolidine-based PPG **4** is active at 365nm UV light which is useful for biological and medicinal applications. All the PPG-caged compounds were prepared with excellent overall yields and exhibited efficient photolytic unmasking (Table 1). Caged hydroxamic acid **15** demonstrated 100% photochemical conversion however poor chemo selectivity was observed resulting in a mixture of N-hydroxyphthalimide **23** and phthalimide **24** due to C-O and O-N bond cleavage respectively. The mechanism leading to the undesired phthalimide **24** formation was not elucidated. Along with hydroxamic acid, alcohols, amines, and carboxylic acid were protected and released in good yields in deuterated methanol or acetonitrile/water mixtures (Table 1). Novel Julolidine-based PPG is easy to synthesize and

install on different functional groups and releases in good yields under mild conditions. Further studies for the biological application of this novel PPG are underway.

References

1 Albini A & Fagnoni M, *Handbook of synthetic photochemistry*, (John Wiley & Sons) 2009.
2 Schelhaas M & Waldmann H, *Ange Chemie Int Ed Eng,* 35 (1996) 2056.
3 Bochet C G, *J Chem Soc, Perkin Transactions,* 1 (2002) 125.
4 Li W-H & Zheng G, *Photochem Photobiol Sci*, 11 (2012) 460.
5 Herrmann A, *Angew Chemie Int Ed English,* 46 (2007) 5836.
6 Zhao H, Sterner E S, Coughlin E B & Theato P, *Macromolecules,* 45 (2012) 1723.
7 Kowalik L & Chen J K, *Nat Chem Bio,* 13 (2017) 587.
8 Courtney T & Deiters A, *Cur Opi Chem Bio,* 46 (2018) 99.
9 Ding X & Wang P, *J Org Chem,* 83 (2018) 10736.
10 Wang P, Hu H & Wang Y, *Organic Letters,* 9 (2007) 2831.
11 Wang P, *J Photochem Photobio A: Chem,* 335 (2007) 300.
12 Yang H, Zhang X, Zhou L & Wang P, *J Org Chem,* 76 (2011) 2040.
13 Zhou L, Yang H & Wang P, *J Org Chem,* 76 (2011) 5873.
14 Wang P, Zhou L, Zhang X & Liang X, *Chem Comm,* 46 (2010) 1514.
15 Yang H, Zhou L & Wang P, *Photochem & Photobio Sci,* 11 (2012) 514.
16 Wang P, Lu W, Devalankar D & Ding Z, *Organic Letters,* 17 (2015) 170.
17 Wang P, Lu W, Devalankar D A & Ding Z, *Organic Letters,* 17 (2015) 2114.
18 Ding X & Wang P, *J Org Chem,* 82 (2017) 7309.
19 Ding X & Wang P, *J Org Chem,* 83 (2018) 7459.
20 Wang P, Devalankar D A & Lu W, *J Org Chem,* 81 (2016) 6195.
21 Ding X & Wang P, *J Org Chem,* 83 (2018) 10736.
22 Wang P, *Asian J Org Chem,* 2 (2013) 452.
23 Kim J H, Huang F, Ly M & Linhardt R J, *J Org Chem,* 73 (2008) 9497.
24 Wang P, Mondal M & Wang Y, *Eur J Org Chem,* 2009 (2009) 2055.
25 Lu W, Tian C, Thogaripally P, Hu J & Wang P, *Chem Comm,* 49 (2013) 9636.
26 Sokolovskaya E, Barner L, Brase S & Lahann J, *Macromol Rapid Comm,* 35 (2014) 780.
27 Hradilová L, Poláková M, Dvořáková B, Hajdúch M & Petruš L, *Carbohydrate Research,* 361 (2012) 1.
28 Katayama H, Abe E & Kaneko K, *J Hetero Chem,* 19 (1982) 925.
29 Valenta Z, Deslongchamps P, Ellison R A & Wiesner K, *J Am Chem Soc,* 86 (1964) 2533.
30 Reinfelds M, Cosel J V, Falahati K, Hamerla C, Slanina T, Burghardt I & Heckel A, *Chem A Eur J,* 24 (2018) 13026.
31 Zimmerman H E, *J Am Chem Soc,* 117 (1995) 8988.
32 Zimmerman H E, *J Phys Chem A,* 102 (1998) 5616.
33 Zimmerman H E & Sandel V R, *J Am Chem Soc,* 85 (1963) 915.
34 De Luca L, Giacomelli G & Porcheddu A, *Organic Lett*, 4 (2002) 553.
35 Griffin R J, Evers E, Davison R, Gibson A E, Layton D & Irwin W J, *J Chem Soc*, *Perkin Trans 1*, 1205 (1996).
36 Chamberlin J W, *J Org Chem*, 31 (1966) 1658.
37 El Kazzouli S D, Berteina-Raboin S, Mouaddib A & Guillaumet G, *Tetrahedron Lett*, 44 (2003) 6265.