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## SUPPLEMENTARY INFORMATION

### Initial development of a cytotoxic amino-*seco*-CBI warhead for delivery by prodrug systems

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#### Synthetic methods for 31-33,37

**Naphthalene-1,4-dione (14).** KNO<sub>3</sub> (35.5 mg, 0.35 mmol) was added to **13** (67.6 mg, 0.35 mmol) in CF<sub>3</sub>CO<sub>2</sub>H (10 mL) at -20°C. The mixture was stirred at -20°C for 35 min and poured onto ice. Extraction (EtOAc), drying and chromatography (CH<sub>2</sub>Cl<sub>2</sub> / EtOAc 3:2) gave **14** (41.4 mg, 75%) as a pale buff solid: mp 124-126°C (lit.<sup>1</sup> 125-127°C); <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) (COSY) δ 7.14 (2 H, s, 2,3-H<sub>2</sub>), 7.93 (2 H, m, 6,7-H<sub>2</sub>), 8.04 (2 H, m, 5,8-H<sub>2</sub>); <sup>13</sup>C NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 125.83 (5,8-C<sub>2</sub>), 131.53 (4a,8a-C<sub>2</sub>), 134.18 (6,7-C<sub>2</sub>), 138.70 (2,3-C<sub>2</sub>), 184.80 (1,4-C<sub>2</sub>); MS *m/z* 159.0446 (M + H)<sup>+</sup> (C<sub>10</sub>H<sub>7</sub>O<sub>2</sub> requires 159.0446).

**4-Amino-2-nitronaphthalen-1-ol (16).** SnCl<sub>2</sub>·2H<sub>2</sub>O (15.0 g, 67 mmol) in EtOH (20 mL) was added to **15** (5.04 g, 22 mmol) in aq. HCl (9 M, 20 mL) and EtOH (10 mL) during 1 h at < 35°C. The mixture was stirred for 17 h at 20°C. The suspension was filtered and the solid was washed with EtOH / aq. HCl (9 M) (3:2). The yellow solid was partitioned between EtOAc and water. The aqueous layer was extracted (EtOAc, 3×). The combined extracts were washed (brine) and dried. Evaporation and chromatography (CH<sub>2</sub>Cl<sub>2</sub>) gave **16** (3.11 g, 71%) as a pale pink solid: mp 160-161°C (lit.<sup>2</sup> mp 160°C); IR *v*<sub>max</sub> 3418, 3337 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 3.98 (2 H, s, NH<sub>2</sub>), 7.26 (1 H, s, 3-H), 7.64 (1 H, dd, *J* = 8.1, 7.0 Hz, 7-H), 7.74 (1 H, dd, *J* = 8.3, 6.9 Hz, 6-H), 7.83 (1 H, d, *J* = 8.4 Hz, 5-H), 8.53 (1 H, dd, *J* = 8.3, 0.6 Hz, 8-H), 11.92 (1 H, s, OH); <sup>13</sup>C NMR δ 100.54 (3-C), 121.42 (5-C), 125.65 (8a-C), 125.92 (8-C), 127.15 (7-C), 127.90 (2-C), 129.56 (4a-C), 130.87 (6-C), 135.18 (4-C), 150.11 (1-C); MS *m/z* 203.0466 (M - H)<sup>-</sup> (C<sub>10</sub>H<sub>7</sub>N<sub>2</sub>O<sub>3</sub> requires 203.0457).

**4-Amino-2-nitronaphthalen-1-yl 1,1-dimethylethyl carbonate (17).** Compound **16** (54 mg, 0.26 mmol) was stirred with Boc<sub>2</sub>O (60 mg, 0.28 mmol) and 4-dimethylaminopyridine (25 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (17 mL) for 30 min under N<sub>2</sub>. The mixture was washed (water, brine) and dried. Evaporation and chromatography (CH<sub>2</sub>Cl<sub>2</sub>) gave **17** (14 mg, 17%) as a yellow solid, which decomposed on heating: <sup>1</sup>H NMR δ 1.60 (9 H, s, Bu<sup>t</sup>), 4.34 (2 H, s, NH<sub>2</sub>), 7.29 (1 H, s, 3-H), 7.62-7.66 (2 H, m, 6,7-H<sub>2</sub>), 7.81 (1 H, m, 5-H), 8.15 (1 H, m, 8-H); <sup>13</sup>C NMR δ 27.60 (CMe<sub>3</sub>), 84.87 (CMe<sub>3</sub>), 102.48 (3-C), 121.22 (5-C), 124.15 (8-C), 126.12 (4a-C), 128.14 (6-C), 128.20 (8a-C), 128.67 (7-C), 133.79 (4-C), 137.91 (2-C), 141.07 (1-C), 150.94 (C=O).

**1,1-Dimethylethyl (4-hydroxy-3-nitronaphthalen-1-yl)carbamate (18).** Compound **16** (560 mg, 2.7 mmol) was stirred with Boc<sub>2</sub>O (3.04 g, 14 mmol) in dry THF (25 mL) under N<sub>2</sub> under reflux for 20 h. The mixture was cooled. The evaporation residue, in CH<sub>2</sub>Cl<sub>2</sub>, was washed (water, brine). Drying, evaporation and chromatography (petroleum ether / EtOAc 9:1) gave **18** (740 mg, 89%) as an orange solid: mp 175-177°C; IR *v*<sub>max</sub> 3338, 3259, 1687, 1525 cm<sup>-1</sup>; <sup>1</sup>H NMR (NOESY) δ 1.55 (9 H, s, Bu<sup>t</sup>), 6.59 (1 H, br s, NH), 7.65 (1 H, ddd, *J* = 8.2, 7.0, 1.1 Hz,

6-H), 7.77 (1 H, ddd,  $J = 8.2, 6.9, 1.2$  Hz, 7-H), 7.87 (1 H, d,  $J = 8.4$  Hz, 8-H), 8.33 (1 H, s, 2-H), 8.56 (1 H, dd,  $J = 8.4, 0.5$  Hz, 5-H), 12.11 (1 H, s, OH);  $^{13}\text{C}$  NMR  $\delta$  28.31 ( $\text{CMe}_3$ ), 81.31 ( $\text{CMe}_3$ ), 112.82 (2-C), 121.46 (8-C), 125.45 (8a-C), 125.83 (4-C), 125.91 (4a-C), 127.25 (6-C), 127.55 (3-C), 131.56 (7-C), 152.98 (4-C), 153.50 (C=O); MS  $m/z$  327.0966 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{15}\text{H}_{16}\text{N}_2\text{NaO}_5$  requires 327.0957).

#### **4-(1,1-Dimethylethoxycarbonylamino)-2-nitronaphthalen-1-yl**

**trifluoromethanesulfonate (19).** ( $\text{F}_3\text{CSO}_2$ ) $_2\text{O}$  (1.20 g, 4.2 mmol) was added dropwise during 45 min to **18** (808 mg, 2.7 mmol) in dry pyridine (20 mL) under  $\text{N}_2$  at  $0^\circ\text{C}$  and the mixture was stirred for 30 min at  $0^\circ\text{C}$ . The mixture was then warmed to  $20^\circ\text{C}$  during 10 min. Water was added and the mixture was extracted (EtOAc). Drying, evaporation and chromatography ( $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2 / \text{EtOAc}$  1:1  $\rightarrow$  EtOAc) gave **19** (942 mg, 81%) as a yellow solid: mp  $110\text{--}111^\circ\text{C}$ ; IR  $\nu_{\text{max}}$  3435, 1737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (NOESY)  $\delta$  1.59 (9 H, s,  $\text{Bu}^t$ ), 7.19 (1 H, s, NH), 7.78–7.82 (2 H, m, 6,7- $\text{H}_2$ ), 7.96 (1 H, d,  $J = 8.0$  Hz, 5-H), 8.29 (1 H, d,  $J = 8.2$  Hz, 8-H), 8.73 (1 H, s, 3-H);  $^{13}\text{C}$  NMR  $\delta$  28.20 ( $\text{CMe}_3$ ), 82.54 ( $\text{CMe}_3$ ), 110.52 (3-C), 118.42 (q,  $J = 321.2$  Hz,  $\text{CF}_3$ ), 121.34 (5-C), 125.19 (8-C), 127.13 (8a-C), 127.51 (4a-C), 129.35 (6-C or 7-C), 130.12 (7-C or 6-C), 132.72 (2-C), 134.61 (4-C), 143.02 (1-C), 152.20 (C=O).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -72.55 (s,  $\text{CF}_3$ ); MS  $m/z$  459.0484 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{NaO}_7\text{S}$  requires 459.0450).

**1,1-Dimethylethyl N-(3-amino-4-oxonaphthalen-1-ylidene)carbamate (21).** Compound **18** (66 mg, 0.22 mmol) was stirred vigorously with Pd/C (36.5 mg) in MeOH (20 mL) under  $\text{H}_2$  for 1.5 h. Filtration (Celite $^{\text{®}}$ ) and evaporation gave **21** (51 mg, 84%) as a dark buff solid: mp  $155\text{--}156^\circ\text{C}$ ; IR  $\nu_{\text{max}}$  3331, 1704  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.61 (9 H, s,  $\text{Bu}^t$ ), 5.06 (2 H, s,  $\text{NH}_2$ ), 6.10 (1 H, s, 2-H), 7.58 (1 H, t,  $J = 7.2$  Hz, 6-H), 7.65 (1 H, t,  $J = 6.9$  Hz, 7-H), 8.09 (1 H, d,  $J = 7.6$  Hz, 5-H), 8.29 (1 H, d,  $J = 7.7$  Hz, 8-H);  $^{13}\text{C}$  NMR  $\delta$  28.23 ( $\text{CMe}_3$ ), 82.26 ( $\text{CMe}_3$ ), 99.01 (2-C), 125.78 (8-C), 126.33 (5-C), 130.41 (4a-C), 131.27 (6-C), 133.62 (7-C), 134.84 (8a-C), 144.84 (3-C), 157.13 (1-C), 162.94 (Boc C=O), 180.70 (4-C); MS  $m/z$  567.2262 ( $2\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{30}\text{H}_{32}\text{N}_4\text{NaO}_6$  requires 567.2220), 295.1052 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{15}\text{H}_{16}\text{N}_2\text{NaO}_3$  requires 295.1059).

**1,1-Dimethylethyl N-(4-oxo-3-(2,2,2-trifluoroacetamido)naphthalen-1-ylidene)carbamate (22).**  $\text{K}_2\text{CO}_3$  (178 mg, 1.3 mmol) and  $\text{Na}_2\text{S}_2\text{O}_4$  (198 mg, 1.1 mmol) in water (4.0 mL) were added dropwise to **18** (75 mg, 0.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (8.0 mL) and water (1.0 mL) under  $\text{N}_2$ . Stirring was continued for 16 h at  $35^\circ\text{C}$ . The organic phase was separated, dried and filtered. The filtrate was cooled to  $0^\circ\text{C}$ .  $\text{Pr}^i_2\text{NEt}$  (580 mg, 4.5 mmol) was added, followed by dropwise addition of ( $\text{F}_3\text{CCO}$ ) $_2\text{O}$  (315 mg, 1.5 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 15 min then at  $20^\circ\text{C}$  for 2 h, before being washed with (water, brine) and dried. Evaporation and chromatography (petroleum ether / EtOAc 9:1) gave **22** (39 mg, 42%) as a yellow solid: mp  $122\text{--}123^\circ\text{C}$ ; IR  $\nu_{\text{max}}$  3290, 3097, 1744  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.66 (9 H, s,  $\text{Bu}^t$ ), 7.71 (1 H, ddd,  $J = 9.0, 7.7, 1.9$  Hz, 6-H), 7.78 (1 H, ddd,  $J = 8.9, 7.4, 1.5$  Hz, 7-H), 8.13 (1 H, s, 2-H), 8.19 (1 H, dd,  $J = 7.7, 1.1$  Hz, 5-H), 8.36 (1 H, dd,  $J = 7.8, 0.9$  Hz, 8-H), 9.17 (1 H, s, NH);  $^{13}\text{C}$  NMR  $\delta$  28.13 ( $\text{CMe}_3$ ), 84.22 ( $\text{CMe}_3$ ), 114.57 (2-C), 114.72 (q,  $J = 288.4$  Hz,  $\text{CF}_3$ ), 126.11 (8-C), 127.12 (5-C), 129.40 (4a-C), 132.45 (6-C), 133.67 (3-C), 134.80 (7-C), 135.00 (8a-C), 155.28 (Boc C=O), 155.57 (q,  $J = 39.2$  Hz,  $\text{CF}_3\text{C=O}$ ), 161.36 (1-C), 178.63 (4-C);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -75.76 (s,  $\text{CF}_3$ ); MS  $m/z$  367.0941 ( $\text{M} - \text{H}$ ) $^-$  ( $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_4$  requires 367.0906).

**Ethyl 5-hydroxyindole-2-carboxylate (31).** 5-Hydroxyindole-2-carboxylic acid **30** (1.53 g, 8.6 mmol) was boiled under reflux in EtOH (100 mL) saturated with HCl under  $\text{N}_2$  for 4 h. The evaporation residue, EtOAc, was washed (water, brine). Drying, evaporation and chromatography ( $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2 / \text{EtOAc}$  4:1) gave **31** (1.64 g, 92%) as a white solid: mp

152-154°C (lit.<sup>3</sup> 146-148°C); IR  $\nu_{\max}$  3316, 3209, 1696  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  1.38 (3 H, t,  $J = 7.1$  Hz, Me), 4.37 (2 H, q,  $J = 7.1$  Hz,  $\text{CH}_2$ ), 6.86 (1 H, dd,  $J = 8.8, 2.4$  Hz, 6-H), 6.97 (1 H, d,  $J = 2.3$  Hz, 4-H), 7.00 (1 H, dd,  $J = 2.1, 0.8$  Hz, 3-H), 7.32 (1 H, d,  $J = 8.8$  Hz, 7-H), 8.93 (1 H, s, OH), 11.60 (1 H, s, NH).  $^{13}\text{C NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  14.29 (Me), 60.17 ( $\text{CH}_2$ ), 104.43 (4-C), 106.66 (3-C), 113.07 (7-C), 116.15 (6-C), 127.36 (2-C or 3a-C), 127.44 (3a-C or 2-C), 132.21 (7a-C), 151.34 (5-C), 161.30 (C=O).

**Ethyl 5-(2-Dimethylaminoethoxy)indole-2-carboxylate (32).**  $\text{Me}_2\text{N}(\text{CH}_2)_2\text{Cl}\cdot\text{HCl}$  (1.77 g, 12 mmol),  $\text{K}_2\text{CO}_3$  (3.40 g, 25 mmol) and water (8 mL) were added to **31** (1.68 g, 8.2 mmol) in  $\text{CHCl}_3$  (40 mL). The stirred solution was placed in an oil bath at 65°C. The temperature was slowly raised to 80°C during 65 min and the mixture was stirred for 16 h at 80°C. The organic phase was separated and the solvent was evaporated to 25% of its original volume. This solution was combined with the aqueous phase and diluted with water and toluene. The organic layer was separated, washed with water and extracted with aq. HCl (1.0 M). The acidic phase was washed (toluene), cooled to 0°C, basified (~pH 12) by addition of aq. NaOH (4.0 M) and extracted (toluene). The extract was washed (water, brine) and dried. Evaporation gave **32** (1.81 g, 80%) as a white solid: mp 108-109 (lit.<sup>3</sup> mp 110°C); IR  $\nu_{\max}$  3315, 1687;  $^1\text{H NMR}$   $\delta$  1.39 (3 H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.35 (6 H, s,  $\text{NMe}_2$ ), 2.76 (2 H, t,  $J = 5.8$  Hz,  $\text{Me}_2\text{NCH}_2\text{CH}_2$ ), 4.10 (2 H, t,  $J = 5.8$  Hz,  $\text{Me}_2\text{NCH}_2\text{CH}_2$ ), 4.39 (2 H, q,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 6.99 (1 H, dd,  $J = 8.9, 2.4$  Hz, 6-H), 7.07 (1 H, d,  $J = 2.4$  Hz, 4-H), 7.12 (1 H, dd,  $J = 2.1, 0.8$  Hz, 3-H), 7.28 (1 H, d,  $J = 8.9$  Hz, 7-H), 9.30 (1 H, s, NH);  $^{13}\text{C NMR}$   $\delta$  14.32 ( $\text{OCH}_2\text{CH}_3$ ), 45.83 ( $\text{NMe}_2$ ), 58.38 ( $\text{Me}_2\text{NCH}_2\text{CH}_2$ ), 60.82 ( $\text{OCH}_2\text{CH}_3$ ), 66.57 ( $\text{Me}_2\text{NCH}_2\text{CH}_2$ ), 103.67 (4-C), 108.13 (3-C), 112.69 (7-C), 117.37 (6-C), 127.74 (2-C), 127.89 (3a-C), 132.42 (7a-C), 153.83 (5-C), 162.01 (C=O).

**Ethyl 5-(2-Dimethylaminoethoxy)indole-2-carboxylate (33).** Ester **32** (609 mg, 2.2 mmol) was heated with  $\text{Cs}_2\text{CO}_3$  (2.50 g, 7.7 mmol) in MeOH (12 mL) and water (6 mL) at reflux for 2 h. The evaporation residue, in water, was adjusted to pH 6.5 with aq. HCl (1.0 M). The mixture was cooled to 4°C for 18 h. The crystals were collected by filtration, washed (ice-cold water, acetone) to give **33** (419 mg, 77%) as white crystals. A sample of the product was treated with HCl in 1,4-dioxane (4.0 M) and EtOAc. Filtration gave **33**.HCl as a white solid: mp 238-239°C (lit.<sup>4</sup> mp 237-239°C); IR  $\nu_{\max}$  3380, 3240, 1593  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  2.37 (6 H, s,  $\text{NMe}_2$ ), 2.81 (2 H, t,  $J = 5.7$  Hz,  $\text{NCH}_2$ ), 4.12 (2 H, t,  $J = 5.8$  Hz,  $\text{OCH}_2$ ), 6.91 (1 H, dd,  $J = 8.9, 2.4$  Hz, 6-H), 6.95 (1 H, d,  $J = 1.5$  Hz, 3-H), 7.14 (1 H, d,  $J = 2.3$  Hz, 4-H), 7.35 (1 H, d,  $J = 8.9$  Hz, 7-H), 11.50 (1 H, s, NH);  $^{13}\text{C NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  45.04 ( $\text{NMe}_2$ ), 57.39 ( $\text{NCH}_2$ ), 65.66 ( $\text{OCH}_2$ ), 103.18 (4-C), 106.06 (3-C), 113.21 (7-C), 115.50 (6-C), 127.27 (3a-C), 130.33 (2-C), 132.39 (7a-C), 152.69 (5-C), 163.30 (C=O).

**S-Oxiran-2-ylmethyl 4-nitrobenzenesulfonate (37).** 4-Nitrobenzenesulfonyl chloride (3.16 g, 14 mmol) was added portionwise to  $\text{Et}_3\text{N}$  (2.3 mL, 1.67 g, 16 mmol) and *R*-oxiranylmethanol **36** (1.00 g, 14 mmol) in toluene at 0°C. The mixture was stirred at 20°C for 30 min. The suspension was filtered (Celite<sup>®</sup>). The evaporation residue, in  $\text{CH}_2\text{Cl}_2$ , was washed (aq.  $\text{H}_2\text{SO}_4$  (2%), sat. aq.  $\text{NaHCO}_3$ , brine). Drying, evaporation and recrystallisation (toluene / hexane) gave **37** (1.69 g, 40%) as a white solid: mp 82-83°C (lit.<sup>5</sup> mp 84-86°C);  $[\alpha]_D^{18}$  ( $c = 6.5$ ,  $\text{CHCl}_3$ ) + 33.3° (lit.<sup>6</sup>  $[\alpha]_D^{25}$  + 26.5° ( $c = 2.45$ ,  $\text{CHCl}_3$ , 82% e.e.));  $^1\text{H NMR}$   $\delta$  2.60 (1 H, dd,  $J = 4.7, 2.5$  Hz, 3-H), 2.83 (1 H, t,  $J = 4.4$  Hz, 3-H), 3.20 (1 H, m, 2-H), 4.02 (1 H, dd,  $J = 11.6, 6.4$  Hz, SOCH), 4.46 (1 H, dd,  $J = 11.6, 2.9$  Hz, SOCH), 8.12 (2 H, m, Ph 2,6- $\text{H}_2$ ), 8.40 (2 H, m, Ph 3,5- $\text{H}_2$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  44.42 (3-C), 48.61 (2-C), 71.62 (SOCH<sub>2</sub>), 124.43 (Ph 3,5- $\text{C}_2$ ), 129.24 (Ph 2,6- $\text{C}_2$ ), 141.59 (Ph 1-C), 150.84 (Ph 4-C).

**1,1-Dimethylethyl N-(*R*-1-iodo-2-(*N*-(oxiranylmethyl)-2,2,2-trifluoroacetamido)naphthalen-4-yl)carbamate (diastereomeric atropisomers **38A** & **38B**).** Compound **29** (21 mg, 43  $\mu\text{mol}$ ) was stirred with **37** (17 mg, 66  $\mu\text{mol}$ ) and  $\text{K}_2\text{CO}_3$  (26 mg, 0.19 mmol) in acetone (20 mL) at 50°C under  $\text{N}_2$  for 3 d. Sat. aq.  $\text{NaHCO}_3$  was added to the mixture, which was extracted with EtOAc. The extract was washed (brine) and dried. Evaporation and chromatography (petroleum ether / EtOAc 19:1  $\rightarrow$  9:1) gave **38A** (7.8 mg, 34%) as a yellow oil:  $^1\text{H}$  NMR (NOESY)  $\delta$  1.56 (5.4 H, s,  $\text{Bu}'$  rotamer **a**), 1.56 (3.6 H, s,  $\text{Bu}'$  rotamer **b**), 2.45 (0.4 H, dd,  $J = 4.6, 2.4$  Hz, oxirane 3-C rotamer **b**), 2.56 (0.6 H, dd,  $J = 4.8, 2.5$  Hz, oxirane 3-H rotamer **a**), 2.84 (1 H, m, oxirane 3-H rotamers **a,b**), 3.17 (0.6 H, dd,  $J = 14.3, 7.1$  Hz,  $\text{CHNCOCF}_3$  rotamer **a**), 3.34 (0.4 H, m, oxirane 2-H rotamer **b**), 3.38 (0.4 H, dd,  $J = 13.6, 5.8$  Hz,  $\text{CHNCOCF}_3$  rotamer **b**), 3.44 (0.6 H, m, oxirane 2-H rotamer **a**), 4.55 (0.4 H, dd,  $J = 13.8, 4.6$  Hz,  $\text{CHNCOCF}_3$  rotamer **b**), 4.63 (0.6 H, dd,  $J = 14.3, 3.9$  Hz,  $\text{CHNCOCF}_3$  rotamer **a**), 6.99 (1 H, s, NH rotamers **a,b**), 7.63-7.67 (2 H, m, 6,7- $\text{H}_2$  rotamers **a,b**), 7.86 (1 H, m, 5-H rotamers **a,b**), 8.06 (0.4 H, s, 3-H rotamer **b**), 8.18 (0.6 H, s, 3-H rotamer **a**), 8.31 (1 H, m, 8-H rotamers **a,b**);  $^{13}\text{C}$  NMR  $\delta$  28.30 ( $\text{CMe}_3$  rotamer **b**), 28.33 ( $\text{CMe}_3$  rotamer **a**), 45.67 (oxirane 3-C rotamer **a**), 46.70 (oxirane 3-C rotamer **b**), 48.02 (oxirane 2-C rotamer **b**), 49.31 (oxirane 2-C rotamer **a**), 53.29 ( $\text{CH}_2\text{NCOCF}_3$  rotamer **b**), 54.66 ( $\text{CH}_2\text{NCOCF}_3$  rotamer **a**), 81.64 ( $\text{CMe}_3$  rotamer **a**), 81.68 ( $\text{CMe}_3$  rotamer **b**), 99.03 (1-C rotamer **a**), 99.45 (1-C rotamer **b**), 115.88 (q,  $J = 288.4$  Hz,  $\text{CF}_3$  rotamers **a,b**), 118.47 (3-C rotamers **a,b**), 120.55 (5-C rotamer **b**), 120.59 (5-C rotamer **a**), 125.80 (4a-C rotamers **a,b**), 128.05 (6-C rotamer **a**), 128.13 (6-C rotamer **b**), 128.78 (7-C rotamer **a**), 128.86 (7-C rotamer **b**), 134.42 (8-C rotamer **a**), 134.55 (8-C rotamer **b**), 135.06 (8a-C rotamer **a**), 135.09 (4-C rotamers **a,b**), 135.11 (8a-C rotamer **b**), 140.32 (2-C rotamer **b**), 140.80 (2-C rotamer **a**), 152.43 (Boc C=O rotamers **a,b**), 157.09 (q,  $J = 36.5$  Hz,  $\text{F}_3\text{CC}=\text{O}$  rotamer **a**), 157.20 (q,  $J = 38.1$  Hz,  $\text{F}_3\text{CC}=\text{O}$  rotamer **b**);  $^{19}\text{F}$  NMR  $\delta$  -68.40 (0.4 F, s,  $\text{CF}_3$  rotamer **b**), -68.52 (0.6 F, s,  $\text{CF}_3$  rotamer **a**); MS  $m/z$  537.0504 ( $\text{M} + \text{H}^+$ ) ( $\text{C}_{20}\text{H}_{21}\text{F}_3\text{IN}_2\text{O}_4$  requires 537.0498). Further elution gave **38B** (9.1 mg, 39%) as a pale yellow oil:  $^1\text{H}$  NMR (NOESY)  $\delta$  1.55 (9 H, s,  $\text{Bu}'$ ), 2.78 (1 H, dd,  $J = 4.7, 2.6$  Hz, oxirane 3-H), 2.95 (1 H, t,  $J = 4.5$  Hz, oxirane 3-H), 3.49 (1 H, m, oxirane 2-H), 4.30 (1 H, dd,  $J = 12.2, 6.2$  Hz,  $\text{CHNCOCF}_3$ ), 4.71 (1 H, dd,  $J = 12.2, 2.8$  Hz,  $\text{CHNCOCF}_3$ ), 6.70 (1 H, s, NH), 7.47 (1 H, t,  $J = 7.7$  Hz, 6-H), 7.57 (1 H, m, 7-H), 7.63 (1 H, s, 3-H), 7.76 (1 H, d,  $J = 8.4$  Hz, 5-H), 8.19 (1 H, d,  $J = 8.5$  Hz, 8-H);  $^{13}\text{C}$  NMR  $\delta$  28.29 ( $\text{CMe}_3$ ), 44.85 (oxirane 3-C), 48.89 (oxirane 2-C), 69.29 ( $\text{CH}_2\text{NCOCF}_3$ ), 81.25 ( $\text{CMe}_3$ ), 85.75 (1-C), 110.89 (3-C), 115.72 (q,  $J = 284.6$  Hz,  $\text{CF}_3$ ), 120.33 (5-C), 123.42 (4a-C), 125.48 (6-C), 128.25 (7-C), 132.53 (8-C), 134.43 (4-C), 134.95 (8a-C), 145.08 (2-C), 152.71 (C=O Boc);  $^{19}\text{F}$  NMR  $\delta$  -75.62 (s,  $\text{CF}_3$ ); MS  $m/z$  537.0504 ( $\text{M} + \text{H}^+$ ) ( $\text{C}_{20}\text{H}_{21}\text{F}_3\text{IN}_2\text{O}_4$  requires 537.0498).

**1,1-Dimethylethyl S-N-(1-iodo-2-(oxiran-2-ylmethylamino)naphthalen-4-yl)carbamate (40).** MeLi in  $\text{Et}_2\text{O}$  (1.6 M, 0.24 mL, 0.39 mmol) was added dropwise ( $\sim 5$  min) to a stirred suspension of CuCN (17.4 mg, 0.19 mmol) in dry THF (0.6 mL) at -78°C under  $\text{N}_2$  and the mixture was stirred for 5 min. The mixture was brought to 40°C and stirred for 30 min. After being cooled to -78°C, compound **38** (65.6 mg, 0.12 mmol) in dry THF (0.6 mL) was added dropwise and stirring was continued at -78°C. The mixture was stirred at 25°C for 3 d. Water was added. The mixture was extracted (EtOAc). The extract was washed (brine). Drying, evaporation and chromatography (petroleum ether / EtOAc 9:1) gave **40** (39 mg, 73%) as a yellow solid: mp 127-128°C; IR  $\nu_{\text{max}}$  3389, 3336, 3082, 1699  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (NOESY)  $\delta$  1.56 (9 H, s,  $\text{Bu}'$  conformers **A,B**), 2.77 (0.45 H, d,  $J = 2.6$  Hz, oxirane 3-H conformer **B**), 2.78 (0.55 H, d,  $J = 2.7$  Hz, oxirane 3-H conformer **A**), 2.84 (0.45 H, d,  $J = 2.6$  Hz, oxirane 3-H conformer **B**), 2.86 (1 H, d,  $J = 4.0$  Hz, oxirane 3-H conformer **A**), 3.27 (1 H, m, oxirane 2-H conformers **A,B**), 3.51 (0.55 H, dd,  $J = 6.2, 4.6$  Hz,  $\text{NCHH}$  conformer **A**), 3.55 (0.45 H, dd,  $J = 6.2, 4.6$  Hz,  $\text{NHCHH}$  conformer **B**), 3.71 (0.45 H, dd,  $J = 5.7, 3.5$  Hz,  $\text{NHCHH}$  conformer

**B**), 3.75 (0.55 H, dd,  $J = 5.7, 3.5$  Hz, NCHH conformer **A**), 4.87 (1 H, t,  $J = 5.8$  Hz, NHCH<sub>2</sub> conformers **A,B**), 6.93 (1 H, s, Boc NH conformers **A,B**), 7.26 (1 H, ddd,  $J = 8.1, 6.8, 1.1$  Hz, 6-H conformers **A,B**), 7.45 (1 H, ddd,  $J = 8.1, 6.8, 1.2$  Hz, 7-H conformers **A,B**), 7.62 (1 H, d,  $J = 8.2$  Hz, 5-H conformers **A,B**), 7.74 (1 H, s, 3-H conformers **A,B**), 7.99 (1 H, dd,  $J = 8.6, 0.6$  Hz, 8-H conformers **A,B**); <sup>13</sup>C NMR δ 28.32 (CMe<sub>3</sub>), 45.38 (NCH<sub>2</sub>), 45.44 (oxirane 3-C), 50.82 (oxirane 2-C), 78.88 (1-C), 80.91 (CMe<sub>3</sub>), 105.08 (3-C), 120.13 (5-C), 120.74 (4a-C), 122.63 (6-C), 128.10 (7-C rotamer **a**), 131.02 (8-C), 135.03 (4-C), 135.59 (8a-C), 145.84 (2-C), 152.84 (C=O); MS  $m/z$  463.0522 (M + Na)<sup>+</sup> (C<sub>18</sub>H<sub>21</sub>IN<sub>2</sub>NaO<sub>3</sub> requires 463.0495).

**1,1-Dimethylethyl N-(1-iodo-2-(N-(prop-2-enyl)-2,2,2-trifluoroacetamido)naphthalene-4-yl)-N-(prop-2-enyl)carbamate (41)**. Compound **29** (99.4 mg, 0.21 mmol), K<sub>2</sub>CO<sub>3</sub> (119 mg, 0.83 mmol) and 3-bromopropene (84 mg, 0.69 mmol) in acetone (15 mL) were stirred at 50°C under N<sub>2</sub> for 16 h. Sat. aq. NaHCO<sub>3</sub> was added and mixture was extracted (EtOAc). Washing (brine), drying and evaporation gave **41** (115 mg, 99%) as a yellow oil: IR  $\nu_{\max}$  1698 cm<sup>-1</sup>; <sup>1</sup>H NMR (COSY) δ 1.23 (0.6 H, br, Bu<sup>t</sup> conformers **A,B**), 3.71 (0.6 H, dd,  $J = 14.4, 8.3$  Hz, CF<sub>3</sub>CONCH conformer **A**), 3.76 (0.4 H, dd,  $J = 14.4, 8.0$  Hz, CF<sub>3</sub>CONCH conformer **B**), 3.83 (0.6 H, dd,  $J = 14.9, 7.4$  Hz, BocNCH conformer **A**), 3.95 (0.4 H, dd,  $J = 14.7, 7.1$  Hz, BocNCH conformer **B**), 4.53 (0.4 H, m, BocNCH conformer **B**), 4.64 (0.6 H, m, BocNCH conformer **A**), 4.98-5.21 (5 H, m, 2 × propenyl 3-H, CF<sub>3</sub>CONCH conformers **A,B**), 5.85-5.94 (2 H, m, 2 × propenyl 2-H conformers **A,B**), 7.11 (1 H, s, 3-H conformers **A,B**), 7.61-7.68 (2 H, m, 6,7-H<sub>2</sub> conformers **A,B**), 7.83 (1 H, m, 5-H conformers **A,B**), 8.31 (1 H, m, 8-H conformers **A,B**); <sup>13</sup>C NMR δ 27.88 (CMe<sub>3</sub> conformer **A**), 28.11 (CMe<sub>3</sub> conformer **B**), 52.45 (BocNCH<sub>2</sub> conformers **A,B**), 53.69 (CF<sub>3</sub>CONCH<sub>2</sub> conformer **A**), 80.78 (CMe<sub>3</sub> conformers **A,B**), 105.48 (1-C conformers **A,B**), 115.94 (q,  $J = 289.4$  Hz, CF<sub>3</sub> conformers **A,B**), 118.46 (BocNCH<sub>2</sub>CHCH<sub>2</sub> conformers **A,B**), 120.92 (CF<sub>3</sub>CONCH<sub>2</sub>CHCH<sub>2</sub> conformers **A,B**), 123.42 (5-C conformer **B**), 123.57 (5-C conformer **A**), 127.79 (3-C conformer **B**), 128.11 (3-C conformer **A**), 128.52 (6-C or 7-C conformers **A,B**), 128.91 (7-C or 6-C conformers **A,B**), 130.31 (CF<sub>3</sub>CONCH<sub>2</sub>CHCH<sub>2</sub> conformers **A,B**), 130.99 (4a-C conformers **A,B**), 133.37 (BocNCH<sub>2</sub>CHCH<sub>2</sub> conformers **A,B**), 133.87 (8-C conformers **A,B**), 135.71 (8a-C conformers **A,B**), 139.39 (2-C conformers **A,B**), 139.86 (4-C conformers **A,B**), 154.53 (Boc C=O conformers **A,B**), 156.42 (q,  $J = 36.0$  Hz, CF<sub>3</sub>C=O conformer **B**); 156.50 (q,  $J = 35.0$  Hz, CF<sub>3</sub>C=O conformer **A**); <sup>19</sup>F NMR δ -68.58 (1.2 F, s, CF<sub>3</sub> conformer **B**), -68.65 (1.8 F, s, CF<sub>3</sub> conformer **A**); MS  $m/z$  583.0804 (M + Na)<sup>+</sup> (C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>IN<sub>2</sub>NaO<sub>3</sub> requires 583.0681).

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