SUPPLEMENTARY INFORMATION

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

Elvis A. Twum, Amit Nathubhai, Pauline J. Wood, Matthew D. Lloyd, Andrew S. Thompson and Michael D. Threadgill*

Medicinal Chemistry, Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK

Synthetic methods for 31-33,37

Naphthalene-1,4-dione (14). KNO_3 (35.5 mg, 0.35 mmol) was added to **13** (67.6 mg, 0.35 mmol) in CF_3CO_2H (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_2Cl_2 / EtOAc 3:2) gave **14** (41.4 mg, 75%) as a pale buff solid: mp 124-126°C (lit.[1] 125-127°C); ^{1}H NMR ($(CD_3)_2SO$) (COSY) δ 7.14 (2 H, s, 2,3-H_2), 7.93 (2 H, m, 6,7-H_2), 8.04 (2 H, m, 5,8-H_2); ^{13}C NMR ($(CD_3)_2SO$) δ 125.83 (5,8-C_2), 131.53 (4a,8a-C_2), 134.18 (6,7-C_2), 138.70 (2,3-C_2), 184.80 (1,4-C_2); MS *m/z* 159.0446 $(M + H)^+$ ($C_{10}H_7O_2$ requires 159.0446).

4-Amino-2-nitronaphthalen-1-ol (16). $SnCl_2.2H_2O$ (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_2Cl_2) gave **16** (3.11 g, 71%) as a pale pink solid: mp 160-161°C (lit.[2] mp 160°C); IR ν_{max} 3418, 3337 cm^{-1}; ^{1}H NMR δ 3.98 (2 H, s, NH_2), 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); ^{13}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 $(M - H)^-$ ($C_{10}H_7N_2O_3$ 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_2O (60 mg, 0.28 mmol) and 4-dimethylaminopyridine (25 mg, 0.20 mmol) in CH_2Cl_2 (17 mL) for 30 min under N_2. The mixture was washed (water, brine) and dried. Evaporation and chromatography (CH_2Cl_2) gave **17** (14 mg, 17%) as a yellow solid, which decomposed on heating: ^{1}H NMR δ 1.60 (9 H, s, Bu^t), 4.34 (2 H, s, NH_2), 7.29 (1 H, s, 3-H), 7.62-7.66 (2 H, m, 6,7-H_2), 7.81 (1 H, m, 5-H), 8.15 (1 H, m, 8-H); ^{13}C NMR δ 27.60 (C*Me*$_3$), 84.87 (*C*Me$_3$), 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_2O (3.04 g, 14 mmol) in dry THF (25 mL) under N_2 under reflux for 20 h. The mixture was cooled. The evaporation residue, in CH_2Cl_2, was washed (water, brine). Drying, evaporation and chromatography (petroleum ether / EtOAc 9:1) gave **18** (740 mg, 89%) as an orange solid: mp 175-177ºC; IR ν_{max} 3338, 3259, 1687, 1525 cm^{-1}; ^{1}H NMR (NOESY) δ 1.55 (9 H, s, Bu^t), 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}C NMR δ 28.31 (C*Me*$_3$), 81.31 (*C*Me$_3$), 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 (M + Na)$^+$ ($C_{15}H_{16}N_2NaO_5$ requires 327.0957).

4-(1,1-Dimethylethoxycarbonylamino)-2-nitronaphthalen-1-yl trifluoromethanesulfonate (19). $(F_3CSO_2)_2O$ (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 N_2 at 0°C and the mixture was stirred for 30 min at 0°C. The mixture was then warmed to 20°C during 10 min. Water was added and the mixture was extracted (EtOAc). Drying, evaporation and chromatography (CH_2Cl_2 → CH_2Cl_2 / EtOAc 1:1 → EtOAc) gave **19** (942 mg, 81%) as a yellow solid: mp 110-111°C; IR ν_{max} 3435, 1737 cm^{-1}; ^{1}H NMR (NOESY) δ 1.59 (9 H, s, Bu^t), 7.19 (1 H, s, NH), 7.78-7.82 (2 H, m, 6,7-H$_2$), 7.96 (1 H, d, *J* = 8.0 Hz, 5-H), 8.29 (1 H, d, *J* = 8.2 8-H), 8.73 (1 H, s, 3-H); ^{13}C NMR δ 28.20 (C*Me*$_3$), 82.54 (*C*Me$_3$), 110.52 (3-C), 118.42 (q, *J* = 321.2 Hz, 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}F NMR ($CDCl_3$) δ -72.55 (s, CF_3); MS *m/z* 459.0484 (M + Na)$^+$ ($C_{16}H_{15}F_3N_2NaO_7S$ 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 H_2 for 1.5 h. Filtration (Celite®) and evaporation gave **21** (51 mg, 84%) as a dark buff solid: mp 155-156°C; IR ν_{max} 3331, 1704 cm^{-1}; ^{1}H NMR δ 1.61 (9 H, s, Bu^t), 5.06 (2 H, s, 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}C NMR δ 28.23 (C*Me*$_3$), 82.26 (*C*Me$_3$), 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 M + Na)$^+$ ($C_{30}H_{32}N_4NaO_6$ requires 567.2220), 295.1052 (M + Na)$^+$ ($C_{15}H_{16}N_2NaO_3$ requires 295.1059).

1,1-Dimethylethyl N-(4-oxo-3-(2,2,2-trifluoroacetamido)naphthalen-1-ylidene)carbamate (22). K_2CO_3 (178 mg, 1.3 mmol) and $Na_2S_2O_4$ (198 mg, 1.1 mmol) in water (4.0 mL) were added dropwise to **18** (75 mg, 0.25 mmol) in CH_2Cl_2 (8.0 mL) and water (1.0 mL) under N_2. Stirring was continued for 16 h at 35°C. The organic phase was separated, dried and filtered. The filtrate was cooled to 0°C. Pr$^i_2$NEt (580 mg, 4.5 mmol) was added, followed by dropwise addition of $(F_3CCO)_2O$ (315 mg, 1.5 mmol). The mixture was stirred at 0°C for 15 min then at 20°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 122-123°C; IR ν_{max} 3290, 3097, 1744 cm^{-1}; ^{1}H NMR δ 1.66 (9 H, s, 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}C NMR δ 28.13 (C*Me*$_3$), 84.22 (*C*Me$_3$), 114.57 (2-C), 114.72 (q, *J* = 288.4 Hz, 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, CF_3C=O), 161.36 (1-C), 178.63 (4-C); ^{19}F NMR ($CDCl_3$) δ -75.76 (s, CF_3); MS *m/z* 367.0941 (M - H)$^-$ ($C_{17}H_{14}F_3N_2O_4$ 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 N_2 for 4 h. The evaporation residue, EtOAc, was washed (water, brine). Drying, evaporation and chromatography (CH_2Cl_2 → CH_2Cl_2 / EtOAc 4:1) gave **31** (1.64 g, 92%) as a white solid: mp

152-154°C (lit.[3] 146-148°C); IR ν_{max} 3316, 3209, 1696 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 1.38 (3 H, t, *J* = 7.1 Hz, Me), 4.37 (2 H, q, *J* = 7.1 Hz, 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}C NMR ($(CD_3)_2SO$) δ 14.29 (Me), 60.17 (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). $Me_2N(CH_2)_2Cl.HCl$ (1.77 g, 12 mmol), K_2CO_3 (3.40 g, 25 mmol) and water (8 mL) were added to **31** (1.68 g, 8.2 mmol) in $CHCl_3$ (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.[3] mp 110°C); IR ν_{max} 3315, 1687; ^1H NMR δ 1.39 (3 H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 2.35 (6 H, s, NMe_2), 2.76 (2 H, t, *J* = 5.8 Hz, $Me_2NC\mathit{H_2}CH_2$), 4.10 (2 H, t, *J* = 5.8 Hz, $Me_2NCH_2C\mathit{H_2}$), 4.39 (2 H, q, *J* = 7.1 Hz, $OC\mathit{H_2}CH_3$), 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}C NMR δ 14.32 ($OCH_2\mathit{C}H_3$), 45.83 (NMe_2), 58.38 ($Me_2N\mathit{C}H_2CH_2$), 60.82 ($O\mathit{C}H_2CH_3$), 66.57 ($Me_2NCH_2\mathit{C}H_2$), 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 Cs_2CO_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.[4] mp 237-239°C); IR ν_{max} 3380, 3240, 1593 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 2.37 (6 H, s, NMe_2), 2.81 (2 H, t, *J* = 5.7 Hz, NCH_2), 4.12 (2 H, t, *J* = 5.8 Hz, 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}C NMR ($(CD_3)_2SO$) δ 45.04 (NMe_2), 57.39 NCH_2), 65.66 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 Et_3N (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®). The evaporation residue, in CH_2Cl_2, was washed (aq. H_2SO_4 (2%), sat. aq. $NaHCO_3$, brine). Drying, evaporation and recrystallisation (toluene / hexane) gave **37** (1.69 g, 40%) as a white solid: mp 82-83ºC (lit.[5] mp 84-86°C); $[\alpha]^{18}_D$ (c = 6.5, $CHCl_3$) + 33.3º (lit.[6] $[\alpha]^{25}_D$ + 26.5° (c 2.45, $CHCl_3$, 82% e.e.)); ^1H NMR δ 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-H_2), 8.40 (2 H, m, Ph 3,5-H_2); ^{13}C NMR ($CDCl_3$) δ 44.42 (3-C), 48.61 (2-C), 71.62 ($SOCH_2$), 124.43 (Ph 3,5-C_2), 129.24 (Ph 2,6-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 μmol) was stirred with **37** (17 mg, 66 μmol) and K_2CO_3 (26 mg, 0.19 mmol) in acetone (20 mL) at 50°C under N_2 for 3 d. Sat. aq. $NaHCO_3$ 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 → 9:1) gave **38A** (7.8 mg, 34%) as a yellow oil: ^{1}H NMR (NOESY) δ 1.56 (5.4 H, s, Bu^t rotamer **a**), 1.56 (3.6 H, s, Bu^t 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, $CHNCOCF_3$ 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, $CHNCOCF_3$ 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, $CHNCOCF_3$ rotamer **b**), 4.63 (0.6 H, dd, *J* = 14.3, 3.9 Hz, $CHNCOCF_3$ rotamer **a**), 6.99 (1 H, s, NH rotamers **a,b**), 7.63-7.67 (2 H, m, 6,7-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}C NMR δ 28.30 (C*Me*$_3$ rotamer **b**), 28.33 (C*Me*$_3$ 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 (*C*H_2NCOCF$_3$ rotamer **b**), 54.66 (*C*H_2NCOCF$_3$ rotamer **a**), 81.64 (*C*Me$_3$ rotamer **a**), 81.68 (*C*Me$_3$ rotamer **b**), 99.03 (1-C rotamer **a**), 99.45 (1-C rotamer **b**), 115.88 (q, *J* = 288.4 Hz, 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, F_3C*C*=O rotamer **a**), 157.20 (q, *J* = 38.1 Hz, F_3C*C*=O rotamer **b**); ^{19}F NMR δ -68.40 (0.4 F, s, CF_3 rotamer **b**), -68.52 (0.6 F, s, CF_3 rotamer **a**); MS *m/z* 537.0504 $(M + H)^+$ ($C_{20}H_{21}F_3IN_2O_4$ requires 537.0498). Further elution gave **38B** (9.1 mg, 39%) as a pale yellow oil:^{1}H NMR (NOESY) δ 1.55 (9 H, s, Bu^t), 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, $CHNCOCF_3$), 4.71 (1 H, dd, *J* = 12.2, 2.8 Hz, $CHNCOCF_3$), 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}C NMR δ 28.29 (C*Me*$_3$), 44.85 (oxirane 3-C), 48.89 (oxirane 2-C), 69.29 (*C*H_2NCOCF$_3$), 81.25 (*C*Me$_3$), 85.75 (1-C), 110.89 (3-C), 115.72 (q, *J* = 284.6 Hz, 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}F NMR δ -75.62 (s, CF_3); MS *m/z* 537.0504 $(M + H)^+$ ($C_{20}H_{21}F_3IN_2O_4$ requires 537.0498).

1,1-Dimethylethyl *S*-N-(1-iodo-2-(oxiran-2-ylmethylamino)naphthalen-4-yl)carbamate (40). MeLi in Et_2O (1.6 M, 0.24 mL, 0.39 mmol) was added dropwise (~5 min) to a stirred suspension of CuCN (17.4 mg, 0.19 mmol) in dry THF (0.6 mL) at -78°C under 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 ν_{max} 3389, 3336, 3082, 1699 cm^{-1}; ^{1}H NMR (NOESY) δ 1.56 (9 H, s, Bu^t 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, NC*H*H conformer **A**), 3.55 (0.45 H, dd, *J* = 6.2, 4.6 Hz, NHC*H*H conformer **B**), 3.71 (0.45 H, dd, *J* = 5.7, 3.5 Hz, NHCH*H* conformer

B), 3.75 (0.55 H, dd, *J* = 5.7, 3.5 Hz, NCH*H* conformer **A**), 4.87 (1 H, t, *J* = 5.8 Hz, N*H*CH_2 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**); ^{13}C NMR δ 28.32 (C*Me*$_3$), 45.38 (NCH_2), 45.44 (oxirane 3-C), 50.82 (oxirane 2-C), 78.88 (1-C), 80.91 (*C*Me_3), 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 $(M + Na)^+$ ($C_{18}H_{21}IN_2NaO_3$ 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_2CO_3 (119 mg, 0.83 mmol) and 3-bromopropene (84 mg, 0.69 mmol) in acetone (15 mL) were stirred at 50°C under N_2 for 16 h. Sat. aq. $NaHCO_3$ was added and mixture was extracted (EtOAc). Washing (brine), drying and evaporation gave **41** (115 mg, 99%) as a yellow oil: IR ν_{max} 1698 cm^{-1}; ^{1}H NMR (COSY) δ 1.23 (0.6 H, br, Bu^t conformers **A,B**), 3.71 (0.6 H, dd, *J* = 14.4, 8.3 Hz, CF_3CONCH conformer **A**), 3.76 (0.4 H, dd, *J* = 14.4, 8.0 Hz, CF_3CONCH 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_3CONCH 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_2 conformers **A,B**), 7.83 (1 H, m, 5-H conformers **A,B**), 8.31 (1 H, m, 8-H conformers **A,B**); ^{13}C NMR δ 27.88 (C*Me*$_3$ conformer **A**), 28.11 (C*Me*$_3$ conformer **B**), 52.45 (BocN*C*H_2 conformers **A,B**), 53.69 (CF_3CONCH_2 conformer **A**), 80.78 (*C*Me_3 conformers **A,B**), 105.48 (1-C conformers **A,B**), 115.94 (q, *J* = 289.4 Hz, CF_3 conformers **A,B**), 118.46 ($BocNCH_2CHCH_2$ conformers **A,B**), 120.92 ($CF_3CONCH_2CHCH_2$ 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 ($CF_3CONCH_2CHCH_2$ conformers **A,B**), 130.99 (4a-C conformers **A,B**), 133.37 ($BocNCH_2CHCH_2$ 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_3C=O conformer **B**); 156.50 (q, *J* = 35.0 Hz, CF_3C=O conformer **A**); ^{19}F NMR δ -68.58 (1.2 F, s, CF_3 conformer **B**), -68.65 (1.8 F, s, CF_3 conformer **A**); MS *m/z* 583.0804 $(M + Na)^+$ ($C_{23}H_{24}F_3IN_2NaO_3$ requires 583.0681).

References for Supplementary Information

1. Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem*. **2011**, *9*, 2258.

2. Hodgson, H. H.; Smith, E. W. *J. Chem. Soc*. **1935**, 671.

3. Frecentese, F.; Fiorino, F.; Perissutti, E.; Severino, B.; Magli, E.; Esposito, A.; De Angelis, F.; Massarelli, P.; Nencini, C.; Viti, B.; Santagada, V.; Caliendo, G. *Eur. J. Med. Chem.* **2010,** *45*, 752.

4. Tercel, M.; Lee, H. H.; Yang, S.; Liyanage, H. D. S.; Mehta, S. Y.; Boyd, P. D. W.; Jaiswal, J. K.; Tan, K. L.; Pruijn, F. B. *ChemMedChem* **2011**, *6*, 1860.

5. Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem*. **1989**, *54*, 1295.

6. Yang, S.; Denny, W. A. *J. Org. Chem*. **2002**, *67*, 8958.