Supporting Information

Development of Peptidomimetics with a Vinyl Sulfone Warhead as Irreversible Falcipain-2 Inhibitors

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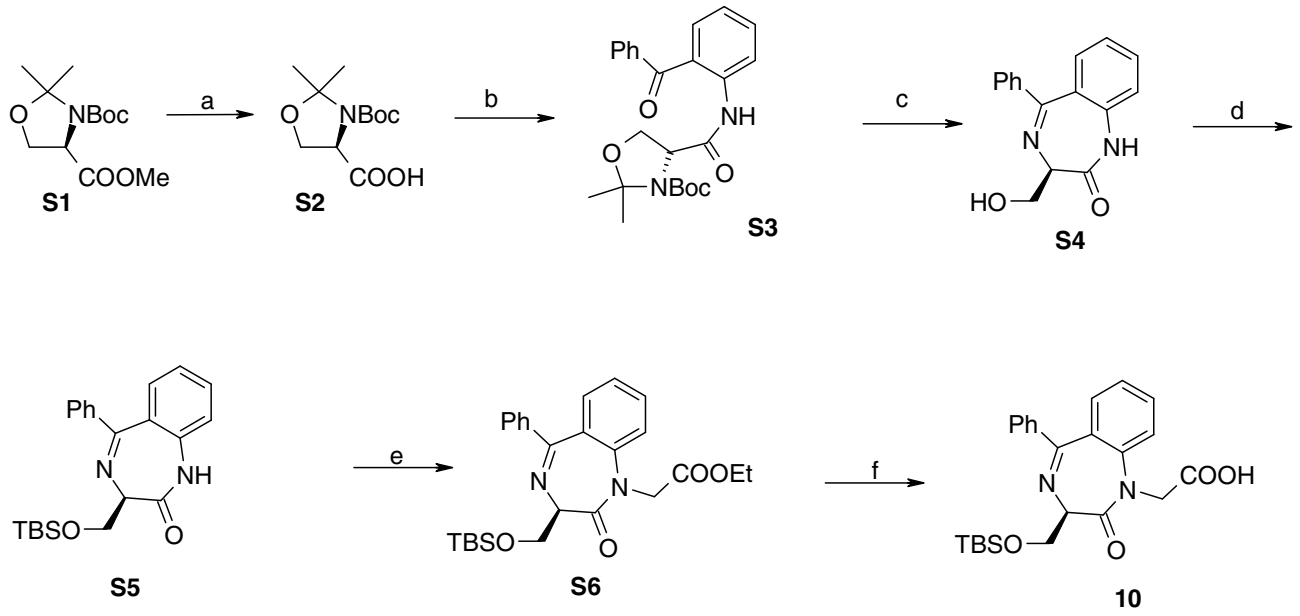
Contents: Experimental details for the synthesis of compound **10**.
Elemental analyses for final compounds **2a-2d and 3a-3d**.

Scheme[a]



[a]Reagents and conditions: (a) LiOH, MeOH, 0 °C-rt, 6 h; (b) *i*-BuOCOCl, NMM, CH_2Cl_2, 0 °C - rt, 30 min, then 2-aminobenzophenone, reflux, 20 min, rt, 12 h; (c) HCl/MeOH, reflux, 5 h, then $NaHCO_3$, MeOH, rt, 12 h; (d) TBS-Cl, imidazole, CH_2Cl_2, 0 °C - rt, 12 h; (e) NaH, $BrCH_2COOEt$, 0 °C - rt, 5 h; (f) LiOH, MeOH, 0 °C - rt, 6 h.

(*R*)-2,2-Dimethyl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester (S2). To a solution of (*R*)-2,2-dimethyloxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester (**S1**) (5g, 19 mmol) in a mixture methanol/water (1/1 v/v, 95 mL) at 0 ºC was added LiOH (910 mg, 38 mmol) and the resulting mixture was stirred at room temperature until disappearance of starting material (TLC monitoring). The solvent was concentrated under reduced pressure and a 10% aqueous solution of citric acid was added to the resulting residue until pH = 5. The aqueous layer was extracted with EtOAc (2 X 100 mL), the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the acid **S2** which was used for the next step without further purification (4.7 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.40-1.68 (m, 15H), 4.10-4.25 (m, 2H), 4.46 (m, 1H), 9.25 (bs, 1H).

(*R*)-4-(2-Benzoyl-phenylcarbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (S3). To a solution of acid **S2** (4.7 g, 19 mmol) in dry CH_2Cl_2 (95 mL) at 0 ºC was added *N*-methyl morpholine (2.31 mL, 21 mmol) followed by isobutyl chloroformate (2.72 mL, 21 mmol). After 30 min., a solution of 2-aminobenzophenone (3.74 g, 19 mmol) in CH_2Cl_2 (20 mL) was added to the refluxing reaction mixture dropwise over 20 min. After stirring for 12 h at room temperature, the reaction mixture was washed with with 0.1N HCl (100 mL), aqueous $NaHCO_3$ (100 mL), and

water (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by flash chromatography (petroleum ether/EtOAc 95/5) to give the product **S2** (6.4 g, 80%). RP-HPLC-MS: gradient D, retention time 3.95 min. MS (ESI^+) *m/z* 425.1 $[M + H]^+$ (100%). ^1H NMR (300 MHz, $CDCl_3$): 1.20-1.87 (m, 15H), 4.16-4.37 (m, 2H), 4.48 (m, 1H), 7.10 (m, 1H), 7.41-7.72 (m, 7H), 8.69 (m, 1H), 11.30 (bs, 1H) ^{13}C NMR (75 MHz, $CHCl_3$): 22.98, 23.98, 25.96, 26.91, 28.18, 66.73, 67.00, 121.41, 122.46, 128.16, 129.95, 132.35, 133.17, 133.88, 198.51.

(*R*)-3-Hydroxymethyl-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (S4). To a solution of **S3** (6.4 g, 15.2 mmol) in MeOH (70 mL) was added 6 N aq. HCl (12.5 mL, 75 mmol). The resulting mixture was refluxed for 5 h and the solvent was then removed under reduced pressure. The residue was partitioned between EtOAc (200 mL) and ss. $NaHCO_3$ (2 x 200 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was taken up in MeOH (70 mL) and stirred at room temperature until complete conversion into the desired product (12 h). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/petroleum ether 6/4), to give product as **S3** as a white solid (3.8 g, 95%). RP-HPLC-MS: gradient E, retention time 3.36 min. MS (ESI^+) *m/z* 267.1 $[M + H]^+$ (100%). ^1H NMR (300 MHz, $CDCl_3$): 2.88 (m, 1H), 3.82 (t, J = 6.5 Hz, 1H), 4.26 (m, 1H), 4.43 (m, 1H), 7.13-7.55 (m, 9H), 8.65 (bs, 1H). ^{13}C NMR (75 MHz, CD_3OD): 63.04, 65.98, 122.29, 124.45, 128.75, 129.26, 130.91, 131.27, 131.62, 132.23, 133.19, 140.26, 140.27, 172.07, 172.38.

(*R*)-3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one (S5). To a solution of alcohol **S4** (3.8 g, 14 mmol) in CH_2Cl_2 (140 mL) at 0 ºC were added imidazole (2.1 g, 31 mmol) and TBS-Cl (5.3 g, 35 mmol). After stirring for 12 h at room temperature the mixture was washed with water (2 x 150 mL), the organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether 1/9) to afford the title compound as an oil (5.3 g, 98%). RP-HPLC-MS: gradient E, retention time 7.18 min. MS (ESI^+) *m/z* 381.2 $[M + H]^+$ (100%).^1H NMR (300 MHz, $CDCl_3$): 0.17 (s, 3H), 0.19 (s, 3H), 0.99 (s, 9H), 3.76 (t, J = 6.3 Hz, 1H), 4.31 (dd, J = 10.0, 6.3 Hz, 1H), 4.62 (dd, J = 10.0,6.3 Hz, 1H), 7.12- 7.53(m, 9H), 9.60 (bs, 1H). ^{13}C NMR (75 MHz, $CHCl_3$): -5.18, 18.52, 25.99, 63.76, 65.25, 121.32, 123.22, 127.66, 128.10, 129.77, 130.17, 131.10, 131.51, 138.37, 139.27, 169.63, 171.01.

(*R*)-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-oxo-5-phenyl-2,3-dihydro-benzo[*e*][1,4]diazepin-1-yl]-acetic acid ethyl ester (S6). To a suspension of NaH (401 mg, 16.7 mmol) in dry DMF (40 mL) at 0 ºC was added a solution of **S5** (5.3 g, 13.9 mmol) in dry DMF (20 mL) and the resulting mixture was allowed to warm to room temperature over 1 h. Ethyl

bromoacetate (3.49g, 20 mmol) was then added dropwise *via* syringe over 5 min and the resulting mixture was further stirred for 12 h at room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (150 mL).The organic layer was separated, washed with water (2 x 150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether 2/8) to afford product **S6** as an oil (6.4 g, 99%). RP-HPLC-MS: gradient D, retention time 5.64 min. MS (ESI^+) *m/z* 467.2 $[M + H]^+$ (100%).^{1}H NMR (300 MHz, $CDCl_3$): 0.14 (s, 3H), 0.16 (s, 3H), 0.92 (s, 9H), 1.17 (t, *J* = 6.9 Hz, 3H), 3.85 (t, *J* = 6.3 Hz, 1H), 4.07-4.21 (m, 2H), 4.33 (dd, *J* = 10.0, 6.3 Hz, 1H), 4.54-4.61 (m, 3H), 7.18-7.65 (m, 9H). ^{13}C NMR (75 MHz, $CHCl_3$): -5.26, 13.95, 18.40, 25.90, 49.53, 61.42, 63.95, 65.07, 121.48, 124.34, 128.08, 129.58, 129.88, 130.21, 130.29, 131.42, 138.72, 142.32, 168.55, 168.90, 169.02.

(*R*)-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-oxo-5-phenyl-2,3-dihydro-benzo[*e*][1,4]diazepin-1-yl]-acetic acid (10). Title compound **10** (5.9 g, 99%) was obtained treating ester **S6** (6.4 g, 13 mmol) as described for compound **S2**. RP-HPLC-MS: gradient D, retention time 4.55 min. MS (ESI^+) *m/z* 439.2 $[M + H]^+$ (100%). ^{1}H NMR (300 MHz, $CDCl_3$): 0.12 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 3.83 (t, *J* = 6.3 Hz, 1H), 4.31 (dd, *J* = 10.0, 6.3 Hz, 1H), 4.49-4.60 (m, 3H), 6.60 (bs, 1H), 7.18-7.60 (m, 9H). ^{13}C NMR (75 MHz, $CHCl_3$): -5.23, 18.44, 25.93, 49.16, 63.83, 65.00, 121.58, 124.65, 128.16, 129.65, 130.03, 130.35, 130.44, 131.66, 138.66, 142.08, 169.14, 169.56, 173.12.

Elemental Analyses (C, H, N) of compounds **2a-2d** and **3a-3d**

2a	$C_{38}H_{34}ClF_3N_4O_6S$	Calcd	C	59.49	H	4.47	N	7.30
		Found	C	59.34	H	4.65	N	7.45
2b	$C_{39}H_{36}ClF_3N_4O_6S$	Calcd	C	59.96	H	4.64	N	7.17
		Found	C	60.15	H	4.47	N	7.05
2c	$C_{43}H_{36}ClF_3N_4O_6S$	Calcd	C	62.28	H	4.38	N	6.76
		Found	C	62.08	H	4.20	N	6.90
2d	$C_{44}H_{38}ClF_3N_4O_7S$	Calcd	C	61.50	H	4.46	N	6.52
		Found	C	61.75	H	4.60	N	6.30
3a	$C_{30}H_{26}ClF_3N_4O_6S$	Calcd	C	54.34	H	3.95	N	8.45
		Found	C	54.44	H	3.85	N	8.54
3b	$C_{31}H_{28}ClF_3N_4O_6S$	Calcd	C	54.99	H	4.17	N	8.27
		Found	C	55.18	H	4.07	N	8.15
3c	$C_{35}H_{28}ClF_3N_4O_6S$	Calcd	C	57.97	H	3.89	N	7.73
		Found	C	57.85	H	3.78	N	7.96
3d	$C_{36}H_{30}ClF_3N_4O_7S$	Calcd	C	57.26	H	4.00	N	7.42
		Found	C	57.07	H	4.09	N	7.65