SUPPORTING INFORMATION

Defining the mechanism of action of S1QELs, specific suppressors of superoxide production in quinone-reaction site in mitochondrial complex I

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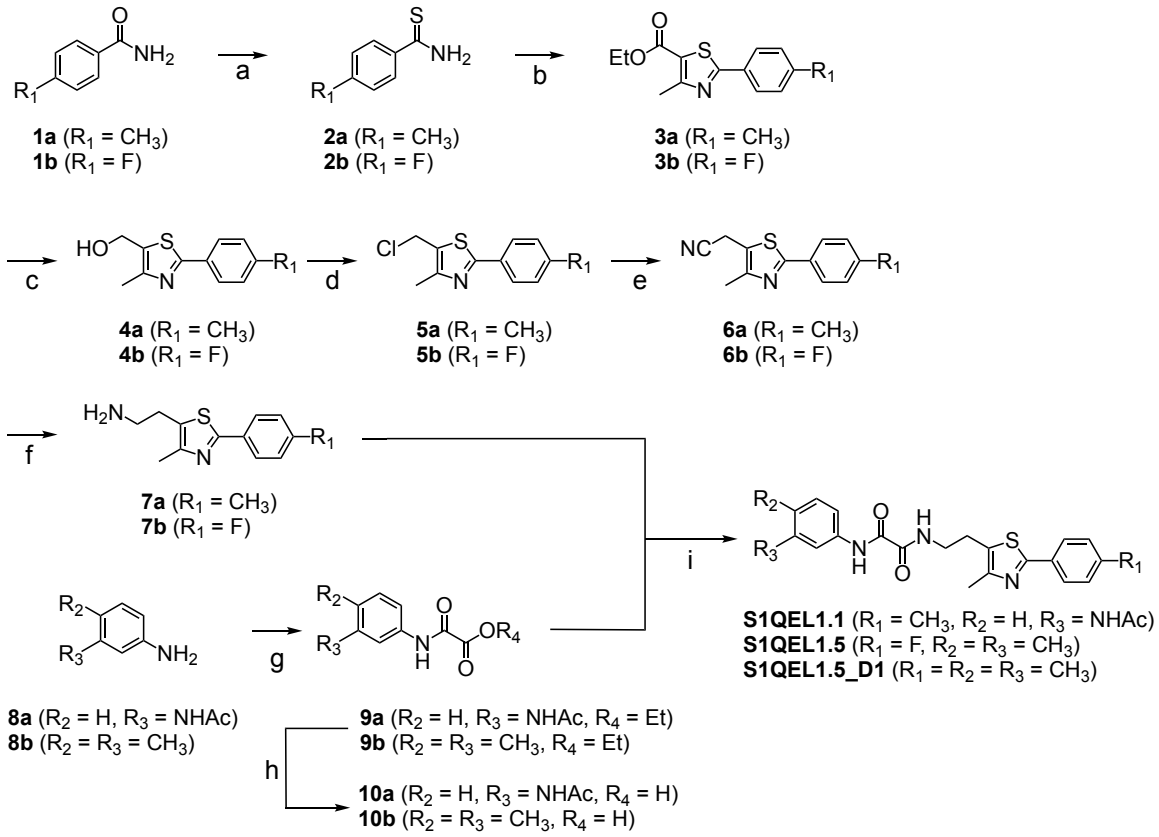
General synthetic methods

All moisture- and air-sensitive reactions were performed in oven-dried glassware under nitrogen or argon atmosphere with dry solvents under anhydrous conditions using standard syringe septum techniques. ^{1}H-NMR spectra were recorded at 400 or 500 MHz with Bruker AVANCE III 400 or 500 spectrometers, respectively, using tetramethylsilane (TMS) as the internal standard. ^{13}C-NMR spectra were recorded at 100 or 125 MHz, respectively. Chemical shifts (δ) were given in ppm relative to TMS with coupling constants (J) in Hz. The mass spectra were recorded on a Shimadzu LCMS-8040 with ESI source. Thin-layer chromatography (TLC) was performed on Merk TLC plate Silica-gel 60F254, and the spot was detected by iodine, anis, phosphomolybdic acid, or UV absorbance. Dry solvents were either used as purchased or freshly distilled using common practices where appropriate. HPLC purification was carried out with a Shimadzu LC-10 AS. Elution profiles were monitored at 254 nm with a Shimadzu SPD-10A.

Abbreviations

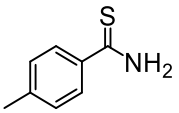
Ac_2O, acetic acid anhydride; AcOH, acetic acid; Boc, *tert*-butoxycarbonyl; chloramine T, sodium *p*-toluenesulfonchloramide trihydrate; DIBAL-H, diisobutylaluminium hydride; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; Et_3N, triethylamine; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate *N*-oxide; LAH, lithium aluminium hydride; Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione; MS, mass spectrometry; NBS, *N*-bromosuccinimide; rt, rt; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography.

Scheme 1[a]



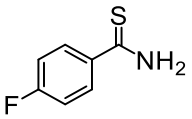
[a] **Synthesis of S1QEL1.1, S1QEL1.5, and S1QEL1.5_D1.**

Reagents and conditions: (a) Lawesson's reagent, THF, reflux, 4 h, 81% and 92% (for **2a** and **2b**); (b) ethyl 2-chloroacetoacetate, EtOH, reflux, 4 h, 91% and 78% (for **3a** and **3b**); (c) $LiAlH_4$, THF, 0 °C to rt, 1 h, 88% and 85% (for **4a** and **4b**); (d) $SOCl_2$, DMF, CH_2Cl_2, 40 °C, 4 h; (e) NaCN, DMF, rt, 16 h, 87% and 50% (for **6a** and **6b**, 2 steps); (f) $BH_3 \cdot Me_2S$, THF, reflux, 4 h; (g) ethyl chloroglyoxylate, Et_3N, THF, reflux, 1 h, 91% and 88% (for **9a** and **9b**); (h) 6.0 M NaOH aq., MeOH/THF, rt, overnight, 88% and 83% (for **10a** and **10b**); (i) HATU, *N*-methylmorpholine, DMF, rt,16 h, 30%, 48% and 43% (for **S1QEL1.1**, **S1QEL1.5**, and **S1QEL1.5_D1**, 2 steps).



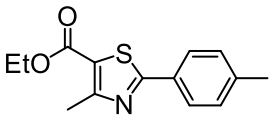
***p*-Methylbenzothioamide (2a)**

To a solution of *p*-toluamide (**1a**) (1.7 g, 13 mmol) in anhydrous THF (40 mL) was added Lawesson's reagent (5.1 g, 13 mmol) under an argon atmosphere, and the mixture was refluxed for 4 h (ref. *1*). The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$) to afford **2a** (1.5 g, 10 mmol, 81%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.9, 136.2, 129.1 (2C), 127.0 (2C), 21.4; ESI-MS (*m/z*) 125.0 $[M+H]^+$.



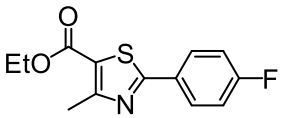
***p*-Fluorobenzothioamide (2b)**

2b was prepared from *p*-fluorobenzamide (**1b**) according to the procedure described for **2a**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$) to afford **2a** (1.7 g, 11 mmol, 92%): ^{1}H-NMR (400 MHz, CDCl3) δ 7.93-7.90 (m, 2H), 7.07 (t, J = 8.6 Hz, 2H), 2.30 (s, 2H); ^{13}C-NMR (100 MHz, CDCl3) δ 166.5, 164.0, 135.5, 129.7, 129.6, 115.6, 115.4; ESI-MS (*m/z*) 156.0 $[M+H]^+$.



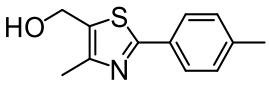
Ethyl 4-methyl-2-(*p*-tolyl)thiazole-5-carboxylate (3a)

To a solution of **2a** (2.0 g, 13 mmol) in ethanol (20 mL) was added ethyl 2-chloroacetoacetate (2.6 g, 16 mmol), and the mixture was refluxed for 4 h (ref. *1*). Then, the reaction mixture was cooled 0 ˚C and stirred for 16 h to form white precipitate. The precipitate was collected by filtration, washed with ice-cooled ethanol, and dried *in vacuo* to afford pure **3a** (3.2 g, 12.1 mmol, 91%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 2.60 (s, 3H), 2.29 (s, 3H), 1.23 (t, J = 7.1, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 169.7, 161.9, 160.7, 142.0, 130.4, 130.0 (2C), 127.0 (2C), 121.2, 61.63, 21.5, 17.7, 14.6; ESI-MS (*m/z*) 262.1 $[M+H]^+$.



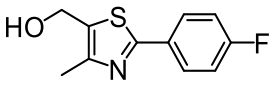
Ethyl 2-(*p*-fluorophenyl)-4-methylthiazole-5-carboxylate (3b)

3b was prepared from **2b** according to the procedure described for **3a** to afford **3b** (1.3 g, 5.0 mmol, 78%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.14 (t, J = 8.7 Hz, 2H), 4.36(q, J = 7.2 Hz, 2H), 2.77 (s, 3H), 1.39 (t, J = 7.1, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.8, 165.9, 162.4, 161.2, 129.6, 129.1, 129.0, 122.1, 116.5, 116.3, 61.5, 26.4, 17.7, 14.5; ESI-MS (*m/z*) 266.1 $[M+H]^+$.



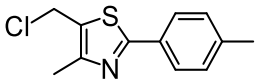
(4-Methyl-2-(*p*-tolyl)thiazol-5-yl)methanol (4a)

To an ice-cooled suspension of $LiAlH_4$ (1.7 g, 46 mmol) in anhydrous THF (60 mL) was added **3a** (3.0 g, 12 mmol) in THF (20 mL) under a nitrogen atmosphere, and the mixture was warmed up to the room temperature and stirred for further 1 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% MeOH/$CHCl_3$) to afford **4a** (2.2 g, 10 mmol, 88%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 4.80 (s, 2H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 150.3, 140.2, 131.0, 130.5, 130.0 (2C), 126.3 (2C), 56.9, 21.4, 21.5, 15.1; ESI-MS (*m/z*) 220.1 $[M+H]^+$.



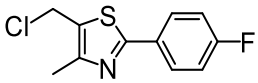
(2-(*p*-Fluorophenyl)-4-methylthiazol-5-yl)methanol (4b)

4b was prepared from **3b** according to the procedure described for **4a**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% MeOH/$CHCl_3$) to afford **4b** (932 mg, 4.17 mmol, 85%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.10 (t, J = 8.5 Hz, 2H), 4.80 (s, 2H), 2.42 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.2, 162.8, 150.5, 131.4, 130.2, 128.5, 128.4, 116.3, 116.1, 57.0, 26.4, 15.3; ESI-MS (*m/z*) 224.1 $[M+H]^+$.



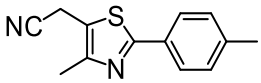
5-(Chloromethyl)-4-methyl-2-(*p*-tolyl)thiazole (5a)

To a solution of **4a** (2.0 g, 9.1 mmol) in anhydrous dichloromethane (50 mL) were added thionyl chloride (6.5 g, 55 mmol) and DMF (1 drop) at room temperature under nitrogen atmosphere. After stirring at 40 ˚C for 3 h, the solvent was removed in vacuo to afford crude product of **5a**, which was subjected to the next reaction without further purification: ESI-MS (*m/z*) 238.1 $[M+H]^+$.



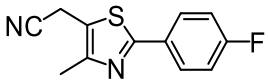
5-(Chloromethyl)-2-(*p*-fluorophenyl)-4-methylthiazole (5b)

5b was prepared from **4b** according to the procedure described for **5a**. The crude **5b** was subjected to the next reaction without further separation: ESI-MS (*m/z*) 242.1 $[M+H]^+$.



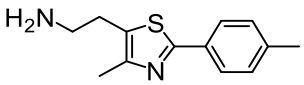
2-(4-Methyl-2-(*p*-tolyl)thiazol-5-yl)acetonitrile (6a)

To a solution of **5a** (2.0 g) in anhydrous DMF (60 mL) was added sodium cyanide (1.3 g, 27 mmol) at room temperature under nitrogen atmosphere, and the mixture was stirred for 16 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine and dried over $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, $CHCl_3$) to afford **6a** (1.8 g, 7.9 mmol, 81%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 9.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 3.84(s, 2H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.5, 151.7, 140.7, 130.5, 129.7 (2C), 126.4, 126.3 (2C), 117.9, 21.4, 15.3, 15.1; ESI-MS (*m/z*) 229.1 $[M+H]^+$.



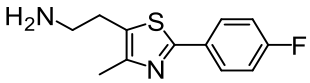
2-(2-(*p*-Fluorophenyl)-4-methylthiazol-5-yl)acetonitrile (6b)

6b was prepared from **5b** according to the procedure described for **6a**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, $CHCl_3$) to afford **6a** (469 mg, 2.02 mmol, 50%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (m, 2H), 7.12 (t, J = 8.6 Hz, 2H), 3.85(s, 2H), 2.45 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3, 162.8, 152.1, 129.7, 128.6, 128.5 (2C), 118.8, 116.4, 116.2, 15.5, 15.3; ESI-MS (*m/z*) 233.1 $[M+H]^+$.



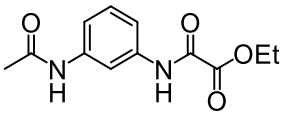
2-(4-Methyl-2-(*p*-tolyl)thiazol-5-yl)ethan-1-amine (7a)

To a solution of **6a** (200 mg, 0.88 mmol) in anhydrous THF (20 mL) was added borane-dimethyl sulfide complex (2.0 M in THF, 1.76 mL, 3.52 mmol) at room temperature under nitrogen atmosphere, and the mixture was refluxed for 4 h. The reaction was carefully quenched by the addition of methanol, followed by the extraction of the mixture with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 to give **7a** as a crude product, which was subjected to the next step without further purification: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H), 2.89(t, J = 6.4 Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.5, 149.5, 139.7, 131.2, 129.5 (2C), 128.8, 126.0 (2C), 43.3, 30.7, 21.4, 15.2; ESI-MS (*m/z*) 233.1 $[M+H]^+$.



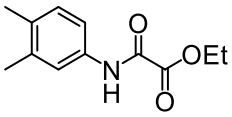
2-(2-(*p*-Fluorophenyl)-4-methylthiazol-5-yl)ethan-1-amine (7b)

7b was prepared from **6b** according to the procedure described for **7a**. The crude product **7b** was subjected to the next reaction without further purification: ESI-MS (*m/z*) 237.1 $[M+H]^+$.



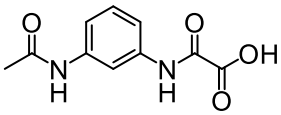
Ethyl *N*-(*m*-acetamidophenyl)-oxamate (9a)

To an ice-cooled solution of *m*-aminoacetanilide (**8a**) (500 mg, 3.33 mmol) in anhydrous THF (14 mL) were added triethylamine (741 mg, 7.32 mmol) and ethyl chloroglyoxylate (500 mg, 3.66 mmol) at room temperature under nitrogen atmosphere, and the mixture was refluxed for 1 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$ to afford pure **9a** (758 mg, 3.03 mmol, 91%): ^{1}H-NMR (400 MHz, MeOD) δ 8.00 (d, J = 2.0 Hz, 1H), 7.43-7.39 (m, 2H), 7.30 (t, J = 8.1 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.40 (t, J = 7.1 Hz,, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.9, 161.9, 157.4, 140.6, 138.9, 130.3, 118.3, 117.7, 113.9, 64.3, 24.0, 14.4; ESI-MS (*m/z*) 251.1 $[M+H]^+$.



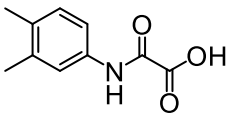
Ethyl *N*-(3,4-dimethylphenyl)oxamate (9b)

9b was prepared from 3,4-dimethylaniline (**8b**) according to the procedure described for **8a** (640 mg, 2.9 mmol, 91%): ^{1}H-NMR (400 MHz, MeOD) δ 7.46 (d, J = 1.8 Hz, 1H), 7.43 (dd, J = 8.1, 2.3 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.39(q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 1.41 (t, J = 7.1 Hz,, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0, 157.2, 138.4, 136.2, 135.1, 131.0, 123.1, 120.0, 64.2, 20.1, 19.4, 14.4; ESI-MS (*m/z*) 222.1 $[M+H]^+$.



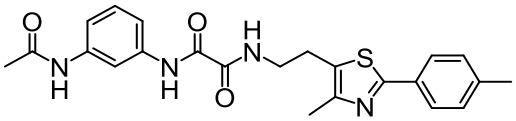
***N*-(*m*-Acetamidophenyl)oxamic acid (10a)**

To a solution of **9a** (400 mg, 1.60 mmol) in a mixture of methanol/THF (12 mL/4 mL) was added 6.0 M aqueous NaOH (0.8 mL). After stirring at room temperature for 16 h, the mixture was acidified with 1.0 M HCl to pH 4 ~ 5, followed by the removal of organic solvent *in vacuo*. The residue was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. The removal of the organic solvent gave **10a** (313 mg, 1.41 mmol, 88%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 10.12 (s, 1H), 7.99 (s, 1H), 7.33 (t, J = 10.0, 2H), 7.18 (t, J = 8.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 168.4, 164.2, 162.7, 139.6, 138.5, 128.7, 114.6, 110.7, 24.0; ESI-MS (*m/z*) 221.1 $[M-H]^-$.



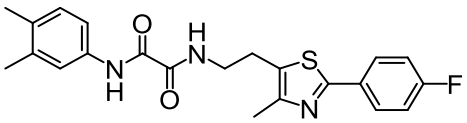
***N*-(3,4-Dimethylphenyl)oxamic acid (10b)**

10b was prepared from 3,4-dimethylaniline (**9b**) according to the procedure described for **10a** (530 mg, 2.75 mmol, 83%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.5 (s, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.45 (dd, J = 8.2, 2.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 2.19 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 162.3, 156.7, 136.4, 135.4, 132.5, 129.6, 121.5, 117.9, 19.7, 18.9; ESI-MS (*m/z*) 192.1 $[M-H]^-$.



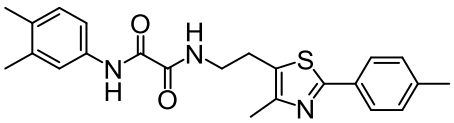
***N*-(*m*-Acetamidophenyl)-*N'*-(2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)oxamide (S1QEL1.1)**

To a solution of **7a** (200 mg) and **10a** (250 mg, 1.08 mmol) in DMF (2.0 mL) were added *N*-methylmorpholine (455 mg, 4.50 mmol) and HATU (513 mg, 1.35 mmol) sequentially under nitrogen atmosphere. After stirring at room temperature for 16 h, the reaction was quenched with brine, extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 10% MeOH/$CHCl_3$), which was further purified by recrystallization from $CHCl_3$ to afford pure **S1QEL1.1** (118 mg, 0.27 mmol, 30%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.97 (s, 1H), 9.13 (t, J = 6.1 Hz, 1H), 8.07 (s, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 14.3 Hz, 1H), 7.37 (d, J = 15.2 Hz, 1H), 7.27-7.21 (m, 3H), 3.43 (q, J = 6.5 Hz,, 2H), 3.03 (t, J = 6.9 Hz, 2H), 2.33(s, 3H), 2.03 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 168.4, 163.2, 160.1, 158.4, 149.6, 139.5, 137.8, 130.7, 129.7, 128.8, 128.4, 125.6, 115.5, 111.4, 25.5, 24.0, 20.9, 14.8; ESI-MS (*m/z*) 437.2 $[M+H]^+$.



***N*-(3,4-Dimethylphenyl)-*N'*-(2-(2-(*p*-fluorophenyl)-4-methylthiazol-5-yl)ethyl)oxamide (S1QEL1.5)**

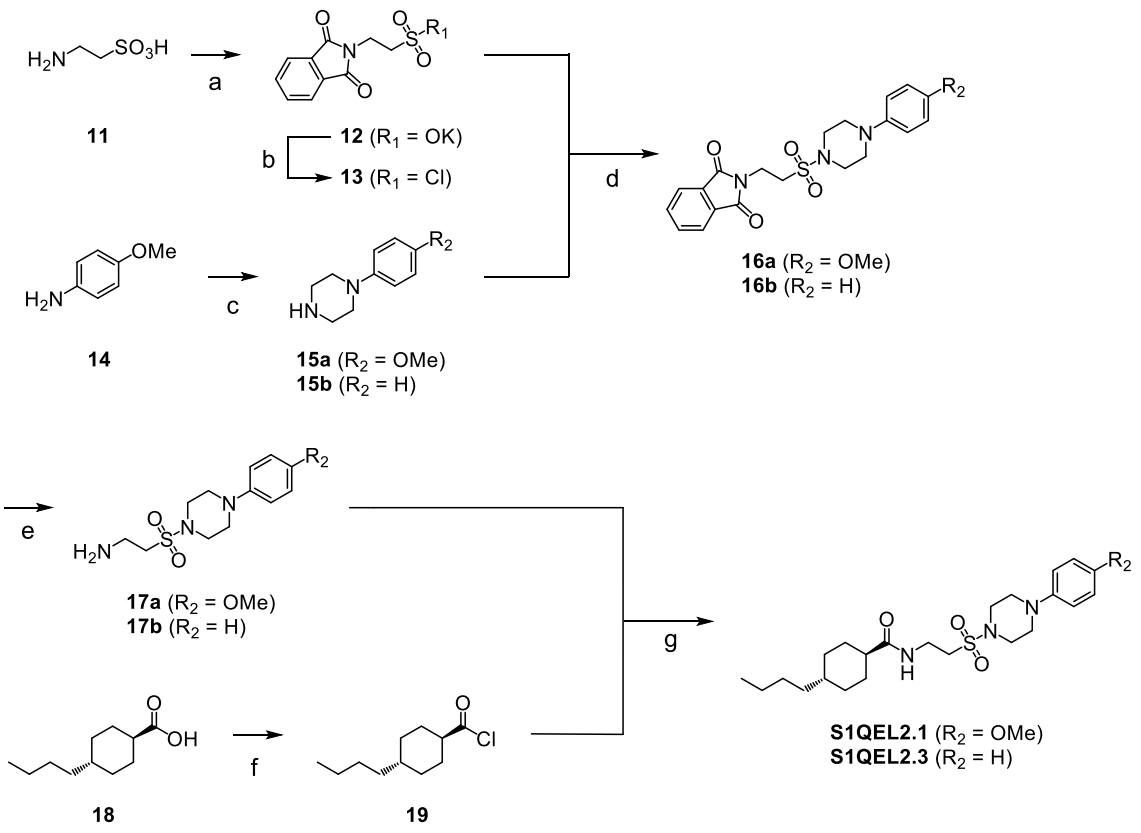
S1QEL1.5 was prepared from **7b** and **10b** according to the procedure described for **S1QEL1.1**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 10% MeOH/$CHCl_3$), which was further purified by recrystallization from ethanol to afford **S1QEL1.5** (138 mg, 0.34 mmol, 48%, 2 steps from **6b**): ^{1}H-NMR (400 MHz/ $CDCl_3$) δ 9.13 (s, 1H), 7.86-7.84 (m, 2H), 7.77 (d, J = 1.3, 1H), 7.40 (d, J = 1.9, 1H), 7.36 (dd, J = 8.1, 2.2 Hz, 1H), 7.13-7.07 (m, 3H), 3.63 (q, J = 6.7 Hz, 2H), 3.07 (t, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.03 (s, 3H); ^{13}C-NMR (100 MHz/ $CDCl_3$) δ 163.9, 160.5 (2C), 157.1, 150.6, 137.8, 134.2 (2C), 130.4 (2C), 128.4, 128.3, 127.7, 121.2, 117.5, 116.2, 116.0, 41.1, 26.6, 20.1, 19.5, 15.3; ESI-MS (*m/z*) 412.3 $[M+H]^+$.



***N*-(3,4-Dimethylphenyl)-*N'*-(2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)oxamide (S1QEL1.5_D1)**

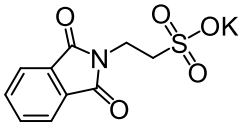
S1QEL1.5_D1 was prepared from **7a** and **10b** according to the procedure described for **S1QEL1.1**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 10% MeOH/$CHCl_3$), which was further purified by recrystallization from ethanol to afford **S1QEL1.5_D1** (255 mg, 0.62 mmol, 43%, 2 steps from **6a**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.83 (t, J = 6.1 Hz, 1H), 7.76 (d, J = 6.4 Hz, 2H), 7.40 (d, J = 2.0 Hz, 1H), 7.36 (dd, J = 8.2, 2.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.1 Hz, 1H) 3.62 (q, J = 6.8 Hz, 2H), 3.06 (t, J = 6.9 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3, 160.5, 157.2, 150.4, 140.1, 137.8, 134.2, 130.4, 129.7 (2C), 127.1, 126.4 (2C), 121.2, 117.4, 41.1, 26.6, 21.6, 20.1, 19.5, 15.3; ESI-MS (*m/z*) 408.3 $[M+H]^+$.

Scheme 2[b]



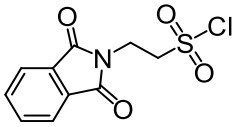
[b] **Synthesis of S1QEL.2.1 and S1QEL2.3.**

Reagents and conditions: (a) phthalic anhydride, AcOK, AcOH, reflux, 3 h, 82%; (b) PCl_5, toluene, reflux, 3 h, 87%; (c) bis(2-chloroethyl)amine hydrochloride, 2-(2-methoxyethoxy)ethanol, 150 °C, 16 h, 52%; (d) Et_3N, CH_2Cl_2, rt, 5 h, 62% and 86% (for **16a** and **16b**); (e) $H_2NN_2H \cdot H_2O$, EtOH, reflux, 7 h, 73% and 92% (for **17a** and **17b**); (f) $SOCl_2$, toluene, 75 °C, 5 h; (g) Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 63% and 41% (for **S1QEL2.1** and **S1QEL2.3**, 2 steps).



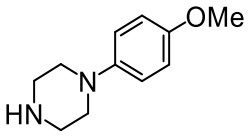
Potassium 2-(1,3-dioxoisoindolin-2-yl)ethane-1-sulfonate (12)

To a solution of 2-aminoethanesulfonic acid (**11**) (2.0 g, 16 mmol) in acetic acid (8.0 mL) was added potassium acetate (1.4 g, 14 mmol) at room temperature. The mixture was refluxed for 10 min, followed by the addition of phthalic anhydride (2.6 g, 18 mmol). After stirring the mixture under reflux for further 3 h, the reaction mixture was cooled to 0 °C to form white precipitate. The precipitate was collected by filtration, washed with ice-cooled ethanol, and dried *in vacuo* to afford pure **12** (3.9g, 13 mmol, 82%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.86-7.81 (m, 4H), 3.86-3.82 (m, 2H), 2.78-2.74 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 167.7, 134.3, 131.8, 122.9, 48.7, 34.5; ESI-MS (*m/z*) 294.2 $[M+H]^+$.



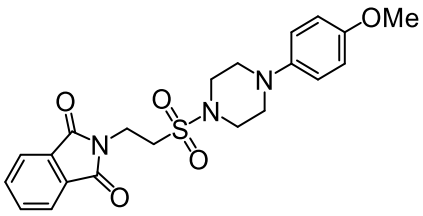
2-(1,3-Dioxoisoindolin-2-yl)ethane-1-sulfonyl chloride (13)

To a solution of **12** (1.6 g, 5.5 mmol) in anhydrous toluene (8.0 mL) was added phosphorus pentachloride (1.0 g, 4.9 mmol) in one portion. After stirring the mixture under reflux for 1 h, additional phosphorous pentachloride (1.0 g, 4.9 mmol) was added, and the resulting mixture was refluxed for further 1 h. The mixture was concentrated *in vacuo*, then the residue was washed with ice-cooled water to afford **13** (1.3 g, 4.8 mmol, 87%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 2H), 7.79-7.76 (m, 2H), 4.36 (t, J = 6.5 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.5 (2C), 134.7 (2C), 131.8 (2C), 124.0 (2C), 61.6, 33.0; ESI-MS (*m/z*) 274.5 $[M+H]^+$.



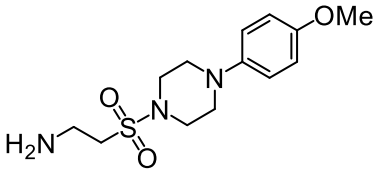
1-(*p*-Methoxyphenyl)piperazine (15a)

To a solution of *p*-anisidine (**14**) (500 mg, 4.06 mmol) in 2-(2-methoxyethoxy)ethanol (1.5 mL) was added bis(2-chloroethyl)amine hydrochloride (725 mg, 4.06 mmol), and the mixture was stirred at 150 °C for 16 h. The mixture was cooled to room temperature, and it was diluted with diethyl ether (150 mL) to form brown solid. The solid was collected by filtration and dried *in vacuo* to afford **15a** (402 mg, 2.09 mmol, 52%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H), 3.48 (d, J = 6.7 Hz, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 124.9, 120.3, 115.0 (4C), 55.8, 49.0 (2C), 43.6 (2C); ESI-MS (*m/z*) 193.2 $[M-H]^-$.



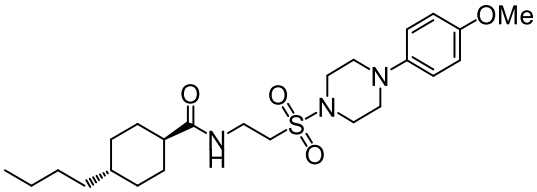
2-(2-((4-(*p*-Methoxyphenyl)piperazin-1-yl)sulfonyl)ethyl)isoindoline-1,3-dione (16a)

To a solution of (**15a**) (400 mg, 2.08 mmol) and triethylamine (442 mg, 4.38 mmol) in dichloromethane (10 mL) was added **13** (627 mg, 2.30 mmol) in small portions, and the mixture was stirred at room temperature for 5 h. The reaction was quenched with 1.0 M aqueous HCl, extracted with dichloromethane, and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 10% MeOH/$CHCl_3$) to afford **16a** (555 mg, 1.3 mmol, 62%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.75-7.73(m, 2H), 6.90-6.83 (m, 4H), 4.17 (t, J = 7.0 Hz, 2H), 3.77 (s, 3H) 3.47 (t, J = 4.9 Hz, 4H), 3.38 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 4.9 Hz, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.9 (2C), 154.8, 134.5 (2C), 132.1 (2C), 124.0, 123.8 (2C), 119.5 (2C), 114.8 (2C), 55.8, 51.3 (2C), 46.9 46.1 (2C), 32.6; ESI-MS (*m/z*) 430.2 $[M+H]^+$.



2-((4-(*p*-Methoxyphenyl)piperazin-1-yl)sulfonyl)ethan-1-amine (17a)

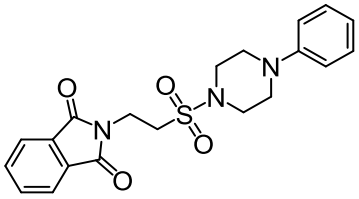
To a solution of **16a** (550 mg, 1.28 mmol) in ethanol (10 mL) was added hydrazine monohydrate (78 mg, 1.54 mmol), and the mixture was heated under reflux for 1 h. The reaction was quenched by the addition of 1.0 M aqueous HCl, followed by the removal of insoluble material by filtration. The filtrate was basified with 2.0 M aqueous NaOH, then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 to afford **17a** (353 mg, 1.18 mmol, 92%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 9.1 Hz, 2H), 6.83(t, J = 9.1 Hz, 2H), 3.77 (s, 3H) 3.31-3.26 (m, 6H), 3.06 (t, J = 4.7 Hz, 4H), 2.98 (t, J = 7.1 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 153.6, 144.9, 118.3 (2C), 114.4 (2C), 55.3, 49.9 (2C), 49.6 45.3 (2C), 35.5; ESI-MS (*m/z*) 360.2 $[M+H]^+$.



(1*S*,4*R*)-4-Butyl-*N*-(2-((4-(*p*-methoxyphenyl)piperazin-1-yl)sulfonyl)ethyl)cyclohexane-1-carboxamide (S1QEL2.1)

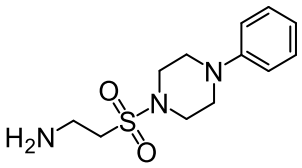
To a solution of **18** (300 mg, 1.6 mmol) in toluene (3.0 mL) was added thionyl chloride (213 mg, 1.89 mmol) and DMF (1 drop), and the mixture was stirred at 75 °C for 5 h. The mixture was concentrated *in vacuo* to provide a crude acyl chloride **19**.

To a solution of **17a** (200 mg, 0.67 mmol), triethylamine (135 mg, 1.34 mmol), and *N,N*-dimethyl-4-aminopyridine (4 mg, 0.03 mmol) in anhydrous dichloromethane (5.0 mL) was added **19** in dichloromethane (1.0 mL), and the mixture was stirred at room temperature for 3 h. The reaction was quenched with water, extracted with dichloromethane, dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, /$CHCl_3$) to afford **16a** (129 mg, 0.28 mmol, 41%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.92-6.84 (m, 4H), 6.25 (t, J = 6.8 Hz, 1H), 3.78-3.74 (m, 5H), 3.42 (t, J = 4.9 Hz, 4H) 3.15-3.09 (m, 6H), 2.05 (tt, J = 12.2, 3.5 Hz, 1H), 1.90 (d, J = 13.8 Hz, 2H), 1.82 (d, J = 12.6 Hz, 2H), 1.82 (m, 2H), 1.28-1.18 (m, 7H), 0.92-0.87 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.7, 154.9, 145.2, 119.5 (2C), 114.8 (2C), 55.8, 51.2 (2C), 46.1 (2C), 45.6, 37.1 (2C), 33.8, 32.7 (2C), 29.7 (2C), 29.3 (2C), 23.2, 14.3; ESI-MS (*m/z*) 466.4 $[M+H]^+$.



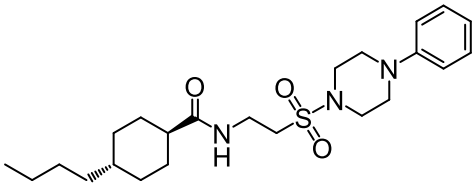
2-(2-((4-Phenylpiperazin-1-yl)sulfonyl)ethyl)isoindoline-1,3-dione (16b)

16b was prepared from **15b** according to the procedure described for **16a**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$) to afford **16b** (456 mg, 1.14 mmol, 86%):^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.75-7.72(m, 2H), 7.28 (t, J = 8.1 Hz, 2H), 6.94-6.91 (m, 3H), 4.18 (t, J = 7.1 Hz, 2H), 3.47 (t, J = 5.0 Hz, 4H), 3.38 (t, J = 7.0 Hz, 2H), 3.24 (t, J = 5.0 Hz, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.7 (2C), 150.6, 134.6 (2C), 132.1 (2C), 129.5 (2C), 123.8 (2C), 117.2 (2C), 121.0 , 49.6 (2C), 45.8, 45.6 (2C), 32.4; ESI-MS (*m/z*) 400.1 $[M+H]^+$.



2-((4-phenylpiperazin-1-yl)sulfonyl)ethan-1-amine (17b)

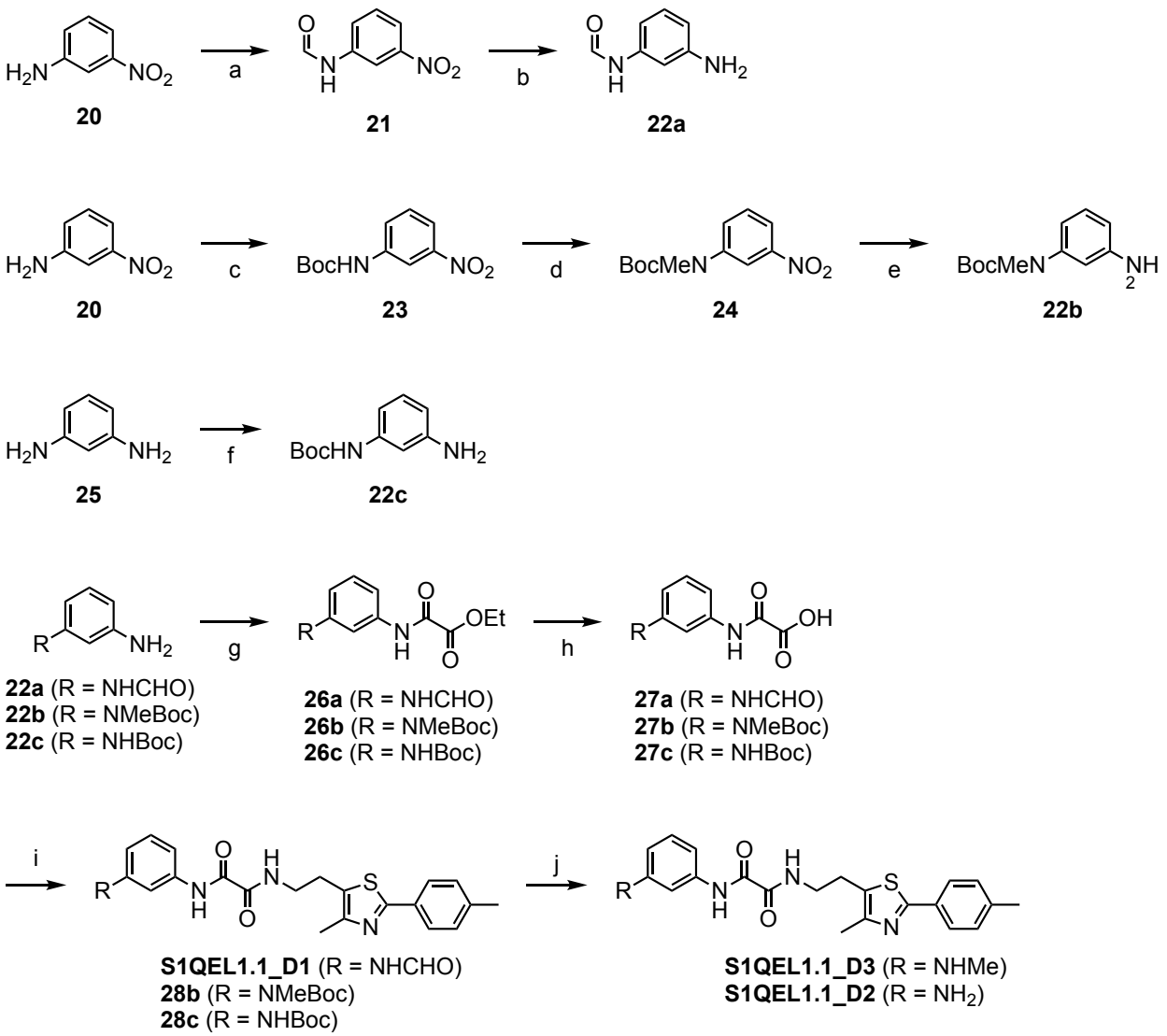
17b was prepared from **16b** according to the procedure described for **17a** (147 mg, 0.55 mmol, 73%): ^{1}H-NMR (400 MHz, MeOD) δ 7.74 (d, J = 8.1 Hz, 2H), 7.52-7.43(m, 3H), 3.84 (t, J = 4.7 Hz, 4H), 3.75 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 6.8 Hz, 2H), 3.37 (t, J = 6.7 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.6, 130.3 (2C), 121.8, 118.3 (2C), 51.6, 51.0 (2C), 47.0 (2C), 37.1; ESI-MS (*m/z*) 270.1 $[M+H]^+$.



(1*S*,4*R*)-4-butyl-*N*-(2-((4-phenylpiperazin-1-yl)sulfonyl)ethyl)cyclohexane-1-carboxamide (S1QEL2.3)

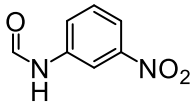
S1QEL2.3 was prepared from **17b** and **19** according to the procedure described for **S1QEL2.1**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, $CHCl_3$), which was further purified by recrystallized from $CHCl_3$ to afford **S1QEL2.3** (203 mg, 0.47 mmol, 63%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 6.3 Hz, 4H), 6.24 (t, J = 5.7 Hz, 1H), 3.76 (q, J = 5.8 Hz, 2H),3.43 (t, J = 5.0 Hz, 4H), 3.26 (t, J = 5.0 Hz, 4H) 3.10 (t, J = 5.8 Hz, 2H), 2.05 (tt, J = 12.2, 3.5 Hz, 1H), 1.90 (d, J = 13.8 Hz, 2H), 1.82 (d, J = 12.5 Hz, 2H), 1.82 (m, 2H), 1.28-1.18 (m, 7H), 0.96-0.88 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.5, 150.7, 129.3 (2C), 121.0, 117.1 (2C), 49.6 (2C), 45.7 (2C), 45.5, 36.9 (2C), 33.6, 32.4 (2C), 29.5 (2C), 29.1 (2C), 23.0, 14.1; ESI-MS (*m/z*) 436.3 $[M+H]^+$.

Scheme 3[c]



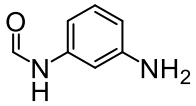
[c]**Synthesis of S1QEL1.1_D1, S1QEL1.1_D2, and S1QEL1.1_D3.**

Reagents and conditions: (a) HCOOH, reflux, 16 h, 71%; (b) H_2, Pd/C, EtOH, rt, 2 h, quant.; (c) Boc_2O, Et_3N, THF, rt, 16 h, 84%; (d) NaH, MeI, DMF, rt, 2 h, 45%; (e) H_2, Pd/C, EtOH, rt, 2 h, 90%; (f) Boc_2O, Et_3N, THF, rt, 16 h, 68%; (g) ethyl chloroglyoxylate, Et_3N, THF, reflux, 1 h, 92%, 81%, and quant. (for **27a**, **27b**, and **27c**); (h) 6.0 M aq. NaOH, MeOH/THF, rt, 16 h, 46%, 97%, and quant. (for **28a**, **28b**, and **28c**); (i) **7a**, HATU, *N*-methylmorphorine, DMF, rt, 4 h, 1.8% (for **S1QEL1.1_D4**); (j) TFA, CH_2Cl_2, rt, 3 h, 9.1% and 8.3% (for **S1QEL1.1_D3** and **S1QEL1.1_D2**, 2 steps).



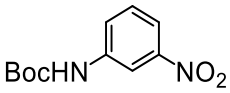
***N*-(*m*-Nitrophenyl)formamide (21)**

A mixture of *m*-nitroaniline (**20**) (1.38 g, 10.0 mmol) and formic acid (15 mL) was heated under reflux for 16 h. The mixture was concentrated *in vacuo*. The crude product was purified by recrystallization from methanol to afford **21** (1.18 g, 7.08 mmol, 71%) as a mixture of rotamers (84:16 on ^{1}H-NMR): ^{1}H-NMR (400 MHz, DMSO-d_6, major rotamer) δ 10.68 (br, 1H), 8.61 (t, J = 2.1 Hz, 1H), 8.37 (s, 1H), 7.95-7.86 (m, 2H), 7.69-7.58 (m, 1H); ^{1}H-NMR (400 MHz, DMSO-d_6, minor rotamer) δ 10.68 (br, 1H), 8.94 (s, 1H), 8.02 (t, J = 1.9 Hz, 1H), 7.95-7.86 (m, 1H), 7.69-7.58 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 160.5, 148.1, 139.3, 130.5, 125.2, 118.3, 113.5.



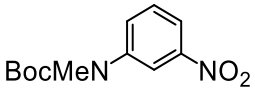
***N*-(*m*-Aminophenyl)formamide (22a)**

A solution of **21** (332 mg, 2.01 mmol) in anhydrous ethanol (16 mL) was stirred with 10% palladium on carbon (56 mg) under hydrogen atmosphere. After stirring at room temperature for 2 h, the mixture was filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to afford **22a** (272 mg, 2.01 mmol, quant.) as a mixture of rotamers (68:32 on ^{1}H-NMR): ^{1}H-NMR (400 MHz, DMSO-d_6, major rotamer,) δ 9.85 (br s, 1H), 8.15 (d, J = 1.9 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 6.88 (t, J = 2.0 Hz, 1H), 6.65 (dd, J = 7.9, 0.9 Hz, 1H), 6.29 (dd, J = 8.0, 1.4 Hz, 1H), 5.04 (br s, 1H); ^{1}H-NMR (400 MHz, DMSO-d_6, minor rotamer) δ 9.90 (br s, 1H), 8.62 (d, J = 11.1 Hz, 1H), 6.93 (t, J = 7.9 Hz, 1H), 6.34-6.29 (m, 3H), 5.10 (br s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6, major rotamer) δ 159.7, 149.3, 138.98, 129.5, 110.2, 107.5, 105.2;^{13}C-NMR (100 MHz, DMSO-d_6, minor rotamer) δ 162.7, 149.9, 139.02, 130.2, 110.3, 105.7, 103.4; ESI-MS (*m/z*) 136.2 $[M+H]^+$.



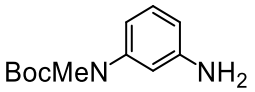
***tert*-Butyl (*m*-nitrophenyl)carbamate (23)**

To an ice-cooled solution of *m*-nitroaniline (**20**) (1.4 g, 10 mmol) and di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) in anhydrous THF (50 mL) was added *N*,*N*-dimethyl-4-aminopyridine (1.3 g, 11 mmol) under a nitrogen atmosphere. After stirring at room temperature for 16 h, the reaction mixture was diluted with water, followed by the removal of organic solvent under reduced pressure. The residue was extracted with ethyl acetate, washed with brine, and the organic layer was dried over $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 0-10% methanol/chloroform) to afford **24** (2.0 g, 8.4 mmol, 84%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (t, J = 2.2 Hz, 1H), 7.88 (ddd, J = 8.2, 2.2, 0.8 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 4.1 Hz, 1H), 6.83 (br s, 1H), 1.54 (s, 9H); ^{13}C-NMR (100 MHz, CDCl3) δ 152.5, 148.9, 139.9, 129.9, 124.1, 117.8, 113.3, 81.8, 28.4 (3C); ESI-MS (*m/z*) 239.1 $[M+H]^+$.



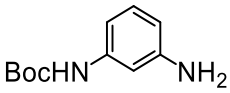
***tert*-Butyl methyl(*m*-nitrophenyl)carbamate (24)**

To an ice-cooled solution of **23** (1.7 g, 7.0 mmol) in anhydrous DMF (14 mL) was added NaH (336 mg, 8.40 mmol, 60% in mineral oil), and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled with ice-bath, then iodomethane (1.5 g, 11 mmol) was added, followed by the stirring of the mixture for further 2h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 0-10% methanol/chloroform) to afford **25** (790 mg, 3.13 mmol, 45%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (t, J = 2.2 Hz, 1H), 8.01 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.63 (dd, J = 8.1, 1.2 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 3.33 (s, 3H), 1.49 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.2, 148.5, 145.0, 131.1, 129.3, 120.0, 119.9, 81.7, 37.1, 28.5 (3C); ESI-MS (*m/z*) 253.1 $[M+H]^+$.



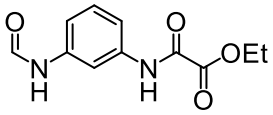
***tert*-Butyl (*m*-aminophenyl)(methyl)carbamate (22b)**

22b was prepared from **24** according to the procedure described for **22a** (624 mg, 2.81 mmol, 90%): ^{1}H-NMR (400 MHz, CDCl3) δ 7.10 (t, J = 7.9 Hz, 1H), 6.66-6.62 (m, 2H), 6.55-6.52 (m, 1H), 3.52 (br s, 2H), 3.21 (s, 3H), 1.45 (s, 9H); ^{13}C-NMR (100 MHz, CDCl3) δ 155.0, 146.2, 145.0, 129.5, 116.4, 113.0, 112.9, 80.3, 37.5, 28.5 (3C); ESI-MS (*m/z*) 223.1 $[M+H]^+$.



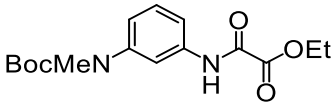
***tert*-butyl (*m*-aminophenyl)carbamate (22c)**

To an ice-cooled solution of *m*-phenylenediamine (**26**) (400 mg, 3.71 mmol) and triethylamine (374 mg, 3.71 mmol) in anhydrous THF (20 mL) was added di-*tert*-butyldicarbonate (808 mg, 3.71 mmol) under nitrogen atmosphere. After stirring at room temperature for 16 h, the mixture was concentrated *in vacuo*. The residue was resuspended in toluene, washed with brine, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 30% ethyl acetate/*n*-hexane) to afford **22c** (523 mg, 2.51 mmol, 68%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.03 (t, J = 8.0 Hz, 1H), 6.97 (br s, 1H), 6.55-6.52 (m, 1H), 6.40 (br s, 1H), 6.37-6.34 (m, 1H), 3.66 (br s, 2H), 1.51 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.3, 139.5, 129.8, 110.0, 108.7, 105.2, 80.5, 28.5 (3C); ESI-MS (*m/z*) 209.1 $[M+H]^+$.



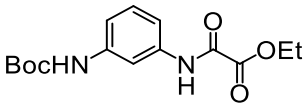
Ethyl *N*-(*m*-formamidophenyl)oxamate (26a)

To an ice-cooled solution of **22a** (272 mg, 2.00 mmol) in anhydrous THF (7 mL) were added triethylamine (405 mg, 4.00 mmol) and ethyl chloroglyoxylate (300 mg, 2.20 mmol) under a nitrogen atmosphere. After refluxed for 1 h, the mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$ to afford **26a** (287 mg, 1.21 mmol, 61%) as a mixture of rotamers (77:23 on ^{1}H-NMR):^{1}H-NMR (500 MHz, MeOD, major rotamer) δ 8.27 (s, 1H), 8.03 (t, J = 2.0 Hz, 1H), 7.47-7.42 (m, 2H), 7.33 (t, J = 8.1 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{1}H-NMR (500 MHz, MeOD, minor rotamer) δ 8.72 (s, 1H), 7.65 (s, 1H), 7.47-7.42 (1H, m), 7.34 (t, J = 8.1 Hz, 1H), 7.02-6.99 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (125 MHz, MeOD, including rotamic pairs) δ 163.2, 160.3, 160.2, 155.9, 138.1, 137.5, 129.7, 129.0, 116.6, 116.5, 112.1, 62.8, 12.8; ESI-MS (*m/z*) 237.1 $[M+H]^+$.



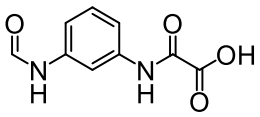
ethyl *N*-(*m*-((*tert*-butoxycarbonyl)(methyl)amino)phenyl)oxamate (26b)

26b was prepared from **22b** according to the procedure described for **26a** (587 mg, 1.82 mmol, 81%): ^{1}H-NMR (400 MHz, CDCl3) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 7.65 (t, J = 2.1 Hz, 1H), 7.40 (dd, J = 8.2, 0.9 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.08 (ddd, J = 8.0, 1.9, 0.9 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.27 (s, 3H), 1.47 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, CDCl3) δ 161.1, 154.8, 154.1, 144.9, 136.7, 129.4, 122.6, 117.2, 116.8, 80.9, 64.0, 37.4, 28.5 (3C), 14.2; ESI-MS (*m/z*) 323.4 $[M+H]^+$.



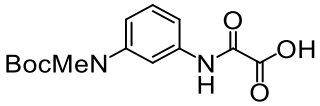
ethyl *N*-(*m*-((*tert*-Butoxycarbonyl)amino)phenyl)oxamate (26c)

26c was prepared from **22c** according to the procedure described for **26a** (677 mg, 2.20 mmol, quant.): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.85 (br s, 1H), 7.76 (t, J = 2.1 Hz, 1H), 7.42-7.39 (m, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.14-7.11 (m, 1H), 6.54 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.52 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 154.0, 152.7, 139.4, 137.1, 129.9, 115.4, 114.4, 109.8, 81.0, 63.9, 28.5 (3C), 14.1; ESI-MS (*m/z*) 309.1 $[M+H]^+$.



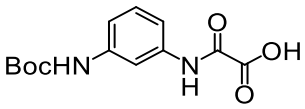
***N*-(*m*-Formamidophenyl)oxamic acid (27a)**

To a solution of **26a** (278 mg, 1.18 mmol) in methanol (7.5 mL) and THF (2.5 mL) was added 6.0 M aqueous NaOH (0.6 mL). After stirring at room temperature for 16 h, the reaction mixture was acidified with aqueous 6.0 M HCl to pH 1~2. The removal of organic solvent *in vacuo* gave **27a** as a white precipitate, which was collected by filtration (116 mg, 0.56 mmol, 46%). **27a** was immediately subjected to the next reaction without further purification: ESI-MS (*m/z*) 207.1 $[M-H]^-$.



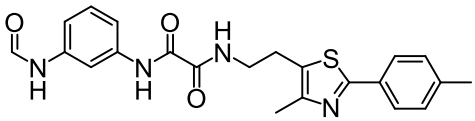
***N*-(*m*-((*tert*-Butoxycarbonyl)(methyl)amino)phenyl)oxamic acid (27b)**

27b was prepared from **26b** according to the procedure described for **27a**. (514 mg, 1.82 mmol, 97%): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.78 (br s, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.03 (dd, J = 8.1, 1.1 Hz, 1H), 3.11 (s, 3H), 1.33 (s, 9H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 162.3, 154.1, 153.1, 144.1, 137.8, 129.1, 122.0, 117.9, 117.8, 80.2, 37.2, 28.2 (3C); ESI-MS (*m/z*) 293.1 $[M-H]^-$.



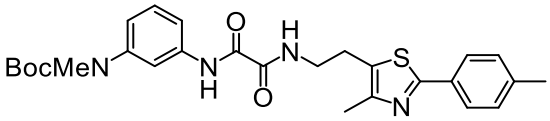
***N*-(*m*-((*tert*-Butoxycarbonyl)amino)phenyl)oxamic acid (27c)**

27c was prepared from **26c** according to the procedure described for **27a** (561 mg, 2.00 mmol, quantitatively): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 9.32 (s, 1H), 7.86 (s, 1H), 7.30 (dt, J = 8.2, 1.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.14 (dt, J = 8.2, 1.5 Hz, 1H), 1.43 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 164.9, 162.1, 153.1, 140.1, 137.6, 129.1, 115.6, 115.3, 111.5, 79.5, 28.4 (3C); ESI-MS (*m/z*) 279.2 $[M-H]^-$.



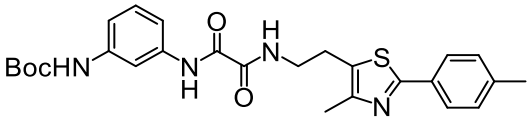
***N*-(*m*-Formamidophenyl)-*N'*-(2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)oxamide (S1QEL1.1_D1)**

S1QEL1.1_D4 was prepared from **7a** and **27a** according to the procedure described for **S1QEL1.1**. The crude product was purified by recrystallization from ethanol to afford **S1QEL1.1_D1** (3.1 mg, 0.0073 mmol, 1.8%) as a mixture of rotamers (75:25 on ^{1}H-NMR): ^{1}H-NMR (400 MHz, MeOD/$CDCl_3$ = 1:1, major rotamer) δ 8.24 (s, 1H), 7.98 (s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.44-7.37 (m, 2H), 7.29 (t, J = 8.1 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 3.57 (t, J = 7.0 Hz, 2H), 3.07 (t, J = 7.0 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{1}H-NMR (400 MHz, MeOD/$CDCl_3$ = 1:1, minor rotamer) δ 8.68 (s, 1H) 7.70 (d, J = 8.1 Hz, 2H) 7.67-7.64 (m, 2H), 7.44-7.37 (m, 1H), 7.31 (t, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 3.57 (t, J = 7.0 Hz, 2H), 3.07 (t, J = 7.0 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C-NMR (100 MHz, MeOD/$CDCl_3$ (1:1), including rotamic pairs) δ 166.9, 164.4, 161.6, 161.4, 159.0, 150.6, 141.3, 139.2, 138.4, 131.7, 131.0, 130.5 (2C), 130.3, 129.1, 127.1 (2C), 117.6, 117.5, 117.3, 115.9, 112.9, 111.2, 41.9, 29.9, 21.6, 14.9; ESI-MS (*m/z*) 423.1 $[M+H]^+$.



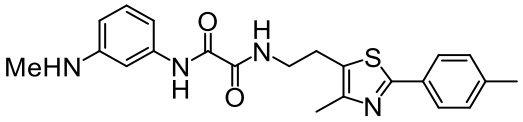
***tert*-Butyl methyl(*m*-(2-((2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)amino)-2-oxoacetamido)phenyl) carbamate (28b)**

28b was prepared from **7a** and **27b** according to the procedure described for **S1QEL1.1**. The crude **29b** was subjected to the next reaction without further purification: ESI-MS (*m/z*) 509.2 $[M+H]^+$.



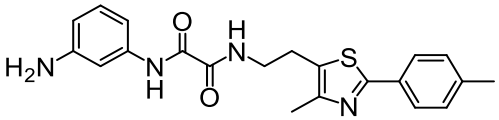
***tert*-Butyl (*m*-(2-((2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)amino)-2-oxoacetamido)phenyl) carbamate (28c)**

28b was prepared from **7a** and **27b** according to the procedure described for **S1QEL1.1**. The crude **29c** was used in next reaction without further purification: ESI-MS (*m/z*) 495.2 $[M+H]^+$.



***N*-(2-(4-Methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)-*N'*-(*m*-(methylamino)phenyl)oxamide (S1QEL1.1_D3)**

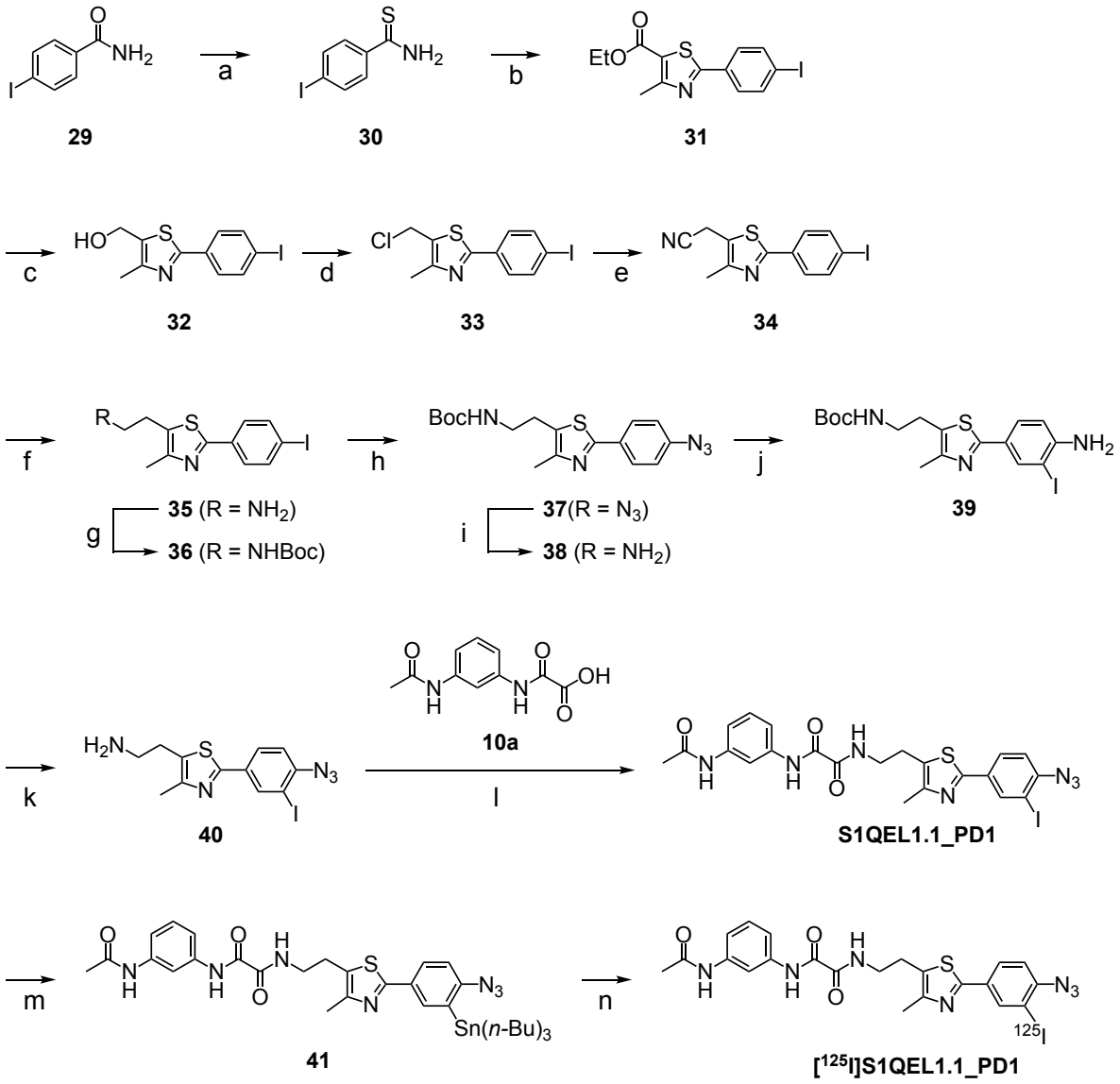
To a solution of crude **28b** in anhydrous dichloromethane (2.0 mL) was added trifluoroacetic acid (0.2 mL), and the mixture was stirred at room temperature for 16 h. The reaction was quenched with water, extracted with dichloromethane, and dried over anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 30% ethyl acetate/*n*-hexane) to afford **S1QEL1.1_D3** (23 mg, 0.056 mmol, 9.1%, 2 steps from **7a**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.77 (dt, J = 8.2, 1.8 Hz, 2H), 7.72 (m, 1H), 7.21 (dd, J = 8.5, 0.5 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.03 (t, J = 2.1 Hz, 1H), 6.84 (ddd, J = 7.9, 2.0, 0.8 Hz, 1H), 6.43 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 3.83 (br s, 1H), 3.63 (q, J = 6.8 Hz, 2H), 3.07 (t, J = 6.9 Hz, 2H), 2.84 (s, 3H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3, 160.5, 157.2, 150.4, 150.3, 140.2, 137.5, 131.2, 130.1, 129.8 (2C), 127.1, 126.4 (2C), 109.8, 108.8, 103.7, 41.2, 30.8, 26.6, 21.6, 15.3; ESI-MS (*m/z*) 409.2 $[M+H]^+$.



***N*-(*m*-aminophenyl)-*N'*-(2-(4-methyl-2-(*p*-tolyl)thiazol-5-yl)ethyl)oxamide (S1QEL1.1_D2)**

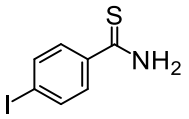
S1QEL1.1_D2 was prepared from **28c** according to the procedure described for **S1QEL1.1_D3**. The crude product was purified by reverse-phase HPLC using acetonitrile/water system as an eluent to afford pure **S1QEL1.1_D2** (12 mg, 0.031 mmol, 8.3% for 2 steps): ^{1}H-NMR (400 MHz, MeOD) δ 8.07 (t, J = 2.0 Hz, 1H), 7.74 (dt, J = 8.2, 1.8 Hz, 2H), 7.67 (ddd, J = 8.3, 2.0, 0.9 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 8.0 Hz, J 2H), 7.15 (ddd, J = 7.9, 2.1, 0.9 Hz, 1H), 3.59 (dt, J = 8.7, 3.4 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, MeOD) δ 167.6, 161.7, 150.1, 142.5, 140.5, 133.3, 131.8, 131.2, 131.0 (2C), 130.3, 127.5 (2C), 121.4, 119.9, 115.6, 41.7, 27.0, 21.5, 14.5; ESI-MS (*m/z*) 395.1 $[M+H]^{+}$.

Scheme 4[d]



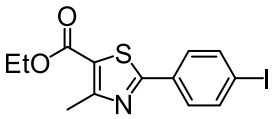
[d] **Synthesis of S1QEL1.1_PD1 and [^{125}I]S1QEL1.1_PD1.**

Reagents and conditions: (a) Lawesson's reagent, 1,4-dioxane, reflux, 0.5 h, quant.; (b) ethyl 2-chloroacetoacetate, EtOH, reflux, 3 h, 75% (2 steps); (c) DIBAL-H, THF, -78 to 0 °C, 7 h, 82%; (d) $SOCl_2$, DMF, CH_2Cl_2, 40 °C, 4 h, crude; (e) NaCN, DMF, rt, 16 h, 95% (2 steps); (f) $BH_3 \cdot Me_2S$, THF, reflux, 4 h; (g) Boc_2O, DMAP, THF, rt, 16 h, 57% (2 steps); (h) sodium L-ascorbate, CuI, *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine, NaN_3, rt to reflux, 15 min; (i) $LiAlH_4$, THF, -40 ˚C, 1 h, 90% (2 steps); (j) ICl, $NaHCO_3$, MeOH / CH_2Cl_2, rt, 4 h, 52%; (k) i) $NaNO_2$, 6.0 M HCl, 0 °C, 0.5 h, ii) NaN_3, rt, 2 h, 27%; (l) **10a**, HATU, *N*-methylmorpholine, DMF, rt, 16 h, 20%; (m) bis(tributyltin), $Pd(PPh_3)_4$, 1,4-dioxane, 50 °C, 16 h, 17%; (n) [^{125}I]NaI, chloramine T, 0.2 M Aq. KH_2PO_4, rt, 10 min, 13%.



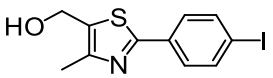
***p*-Iodobenzothioamide (30)**

To a solution of *p*-iodobenzamide (**29**) (4.0 g, 16 mmol) in 1,4-dioxane (40 mL) was added Lawesson's reagent (3.9 g, 9.7 mmol), and the mixture was heated under reflux for 30 min. The reaction mixture was concentrated in vacuo. The residue was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$) to afford **30** (4.2 g, 16 mmol): ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.76 (dt, J = 8.6, 2.1 Hz, 2H), 7.59 (dt, J = 8.6, 2.1 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.1, 138.7, 137.9 (2C), 128.6 (2C), 99.4; ESI-MS (*m/z*) 263.9 $[M+H]^+$.



Ethyl 2-(*p*-iodophenyl)-4-methylthiazole-5-carboxylate (31)

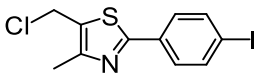
To a solution of **30** (4.9 g, 16 mmol) in ethanol (20 mL) was added ethyl 2-chloroacetoacetate (3.2 g, 19.4 mmol), and the mixture was refluxed for 4 h. Then, the reaction mixture was cooled to 0˚C and the stirring was continued for 16 h to provide white precipitate. The precipitate was collected by filtration, washed with ice-cooled ethanol, and dried *in vacuo* to afford **31** (4.5 g, 12 mmol, 75%): ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.79 (dt, J = 8.6, 2.0 Hz, 2H), 7.69 (dt, J = 8.6, 2.0 Hz, 2H), 4.36(q, J = 7.1 Hz, 2H), 2.77 (s, 3H), 1.39 (t, J = 7.1, 3H); ^{13}C-NMR (100MHz, DMSO-d_6) δ 168.7, 162.3, 161.2, 138.3 (2C), 132.6, 128.3 (2C), 122.3, 97.6, 61.5, 17.6, 14.5; ESI-MS (*m/z*) 373.9 $[M+H]^+$.



(2-(*p*-Iodophenyl)-4-methylthiazol-5-yl)methanol (32)

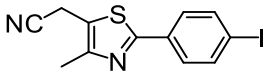
To a solution of **31** (4.5 g, 12 mmol) in THF was added DIBAL-H (1.0 M in THF, 30 mL, 30 mmol) at -78 °C under nitrogen atmosphere, and the reaction mixture was allowed to warm up to -50 ˚C for 7 h with stirring. The reaction was quenched with saturated aqueous Rochelle salt, followed by vigorous stirring until the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% MeOH/$CHCl_3$) to afford **32** (3.2 g, 9.8 mmol, 82%): ^{1}H-NMR (400MHz, MeOH/$CDCl_3$ = 1:1) δ 7.79 (dt, J = 8.6, 2.1 Hz, 2H), 7.62 (d, J = 8.6, 2.1 Hz,

2H), 4.76 (s, 2H), 2.44 (s, 3H); ^{13}C-NMR (100MHz, MeOH/$CDCl_3$ = 1:1) δ 165.9, 150.3, 138.8 (2C), 133.6, 128.4 (2C), 108.3, 96.4, 56.4, 14.8; ESI-MS (*m/z*) 331.9 $[M+H]^+$.



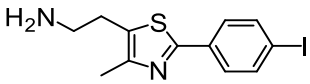
5-(Chloromethyl)-2-(*p*-iodophenyl)-4-methylthiazole (33)

To a solution of **32** (3.2 g, 9.7 mmol) in anhydrous dichloromethane (19 mL) were added thionyl chloride (6.9 g, 58 mmol) and DMF (1 drop) under nitrogen atmosphere, and the mixture was stirred at 40 °C for 3 h. The mixture was concentrated under reduced pressure to afford crude **33**, which was subjected to the next reaction without further purification; ESI-MS (*m/z*) 349.9 $[M+H]^+$.



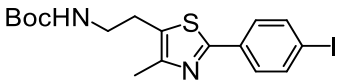
2-(2-(*p*-Iodophenyl)-4-methylthiazol-5-yl)acetonitrile (34)

To a solution of **33** (3.2 g) in DMF (22 mL) was added sodium cyanide (1.4 g, 29 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, $CHCl_3$) to afford **34** (3.1 g, 9.1 mmol, 95%, 2 steps): ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.78 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.61 (dt, *J* = 8.6, 2.1 Hz, 2H), 3.85 (s, 2H), 2.46 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 165.1, 152.1, 138.1, 132.6, 127.8, 118.9 (2C), 116.1 (2C), 96.5, 15.1, 14.2; ESI-MS (*m/z*) 340.9 $[M+H]^+$.



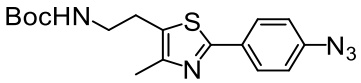
2-(2-(*p*-Iodophenyl)-4-methylthiazol-5-yl)ethan-1-amine (35)

To a solution of **34** (1.5 g, 4.3 mmol) in anhydrous THF (34 mL) was added borane-dimethyl sulfide complex (2.0 M in THF, 8.7 mL, 17 mmol) under nitrogen atmosphere, and the mixture was heated under reflux for 30 min. The reaction was quenched by the addition of methanol and water, extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4. The crude amine **35** was subjected to the next reaction without further purification; ESI-MS (*m/z*) 345.1 $[M+H]^+$.



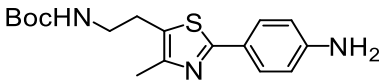
tert-Butyl (2-(2-(*p*-iodophenyl)-4-methylthiazol-5-yl)ethyl)carbamate (36)

To a solution of crude amine **35** (1.4 g) in anhydrous THF (25 mL) were added di-*tert*-butyldicarbonate (1.9 mg, 8.7 mmol) and *N,N*-dimethyl-4-aminopyridine (53 mg, 0.43 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water, extracted with ethyl acetate, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, $CHCl_3$) to afford **36** (1.1 g, 2.49 mmol, 57%, 2 steps): ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.74 (dt, J = 8.6, 2.1 Hz, 2H), 7.61 (dt, J = 8.6, 2.1 Hz, 2H), 3.36 (q, J = 6.2 Hz, 2H), 2.97 (t, J = 6.5 Hz, 2H), 2.40 (s, 3H), 1.44 (s, 9H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 163.5, 155.9, 150.8, 138.2 (2C), 133.5, 129.4, 127.9 (2C), 95.8, 63.1, 41.9, 28.6 (3C), 27.3, 15.2; ESI-MS (*m/z*) 445.1 $[M+H]^+$.



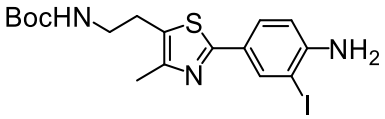
***tert*-Butyl (2-(2-(*p*-azidophenyl)-4-methylthiazol-5-yl)ethyl)carbamate (37)**

To a solution **36** (1.1 g, 2.5 mmol) in ethanol (21 mL) and water (9.0 mL) were added sodium ascorbate (50 mg, 0.25 mmol), copper(I) iodide (95 mg, 0.50 mmol), *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine (105 mg, 0.74 mmol), and sodium azide (483 mg, 7.43 mmol), and the mixture was heated under reflux for 15 min. Then, the reaction was quenched with water, extracted with ethyl acetate, washed with brine, and the organic layer was dried over $MgSO_4$. The azide **37** was immediately subjected to the next reaction without further purification: ESI-MS (*m/z*) 360.2 $[M+H]^+$.



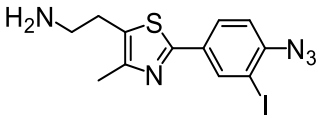
***tert*-Butyl (2-(2-(*p*-aminophenyl)-4-methylthiazol-5-yl)ethyl)carbamate (38)**

To a suspension of $LiAlH_4$ (94 mg, 2.5 mmol) in anhydrous THF (15 mL) was added dropwise a solution of **37** (900 mg) in THF (10 mL) at -40 °C under nitrogen atmosphere. After stirring the mixture at -40 ˚C for 1 h, the reaction was quenched with the addition of saturated aqueous Rochelle salt. The resulting mixture was extracted with ethyl acetate, washed with brine, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% MeOH, $CHCl_3$) to afford **38** (741 mg, 2.2 mmol, 90%, 2 steps): ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.68 (dt, J = 8.6, 2.3 Hz, 2H), 6.68 (dt, J = 8.6, 2.3 Hz, 2H), 4.67 (br s, 1H), 3.86 (br s, 2H), 3.35(q, J = 5.8 Hz, 2H), 2.93 (t, J = 6.5 Hz, 2H), 2.37 (s, 3H), 1.44 (s, 9H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 165.4, 156.0, 149.7, 148.2, 133.3, 127.8 (2C), 124.7, 115.1 (2C), 79.7, 42.0, 28.6 (3C), 27.2, 15.2; ESI-MS (*m/z*) 334.2 $[M+H]^+$.



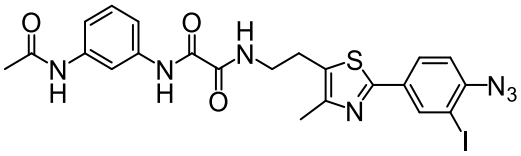
***tert*-Butyl (2-(2-(4-amino-3-iodophenyl)-4-methylthiazol-5-yl)ethyl)carbamate (39)**

To a solution of **38** (1.8 g, 5.5 mmol) and sodium bicarbonate (898 mg, 5.53 mmol) in methanol (20 mL) was added iodine monochloride (929 mg, 11.1 mmol) in dichloromethane. After stirring at room temperature for 4 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$, extracted with ethyl acetate and washed with brine, and the organic layer was dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$) to afford **39** (1.3 g, 2.9 mmol, 52%): ESI-MS (*m/z*) 460.1 $[M+H]^+$.



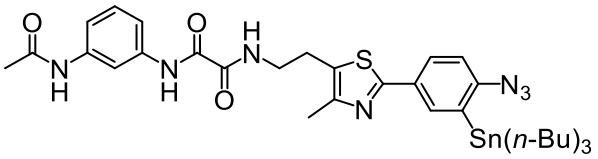
2-(2-(4-Azido-3-iodophenyl)-4-methylthiazol-5-yl)ethan-1-amine (40)

To a solution of **39** (285 mg, 0.62 mmol) in 6.0 M aqueous HCl (6.0 mL) was added sodium nitrite (103 mg, 1.49 mmol) in water at 0 °C, and the mixture was stirred at 0 °C for 30 min. Then, sodium azide (121 mg, 1.86 mmol) was added to the mixture at 0˚C, followed by the stirring at room temperature for further 2 h. The reaction mixture was diluted with ethyl acetate, basified with 6.0 M aqueous NaOH. The aqueous layer was again extracted with ethyl acetate, and the combined organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by preparative reverse-phase HPLC using MeOH/water system as an eluent to afford **40** (65 mg, 0.17 mmol, 27%): ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.32 (t, J = 1.8 Hz, 1H), 7.88 (dt, J = 8.4, 2.2 Hz, 1H), 7.14 (dd, J = 8.4, 2.2 Hz, 1H), 3.00 (q, J = 6.6 Hz, 2H), 2.91 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 161.6, 150.3, 142.7, 137.5, 132.3, 130.4, 118.6, 88.3, 43.5, 30.9, 15.3; ESI-MS (*m/z*) 386.0 $[M+H]^+$.



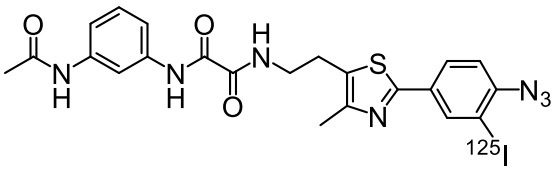
***N*-(3-Acetamidophenyl)-*N*'-(2-(2-(4-azido-3-iodophenyl)-4-methylthiazol-5-yl)ethyl)oxamide (S1QEL1.1_PD1)**

S1QEL1.1_PD1 was prepared from **40** and **10a** according to the procedure described for **S1QEL1.1**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% MeOH/$CHCl_3$), followed by the recrystallization from ethanol to afford **S1QEL1.1_PD1** (20 mg, 0.03 mmol, 20%): ^{1}H-NMR (400MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.32 (d, J = 1.9 Hz, 1H), 7.92 (s, 1H), 7.88 (dd, J = 8.4, 2.0 Hz, 1H), 7.69 (t, J = 6.4 Hz, 1H), 7.38-7.29 (m, 3H), 7.20 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 3.64 (q, J = 6.7 Hz, 2H), 3.09 (t, J = 6.9, 2H), 2.42(s, 3H), 2.18 (s, 3H); ^{13}C-NMR (100MHz, MeOD) δ 170.2 (2C), 163.2, 160.5, 157.5, 139.1, 137.6 (2C), 136.8, 129.7, 129.5, 129.3, 127.6 (2C), 118.7 (2C), 111.7, 88.0, 40.4, 29.5, 23.4, 13.7; ESI-MS (*m/z*) 590.1 $[M+H]^+$.



***N*-(3-Acetamidophenyl)-*N*'-(2-(2-(4-azido-3-(tributylstannyl)phenyl)-4-methylthiazol-5-yl)ethyl)oxamide (41)**

To a solution **S1QEL1.1_PD1** (18 mg, 0.031 mmol) in anhydrous 1,4-dioxane (1 mL) were added bis(tributyltin) (89 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (0) (3.5 mg, 0.0030 mmol) under argon atmosphere. After stirred at room temperature for 16 h, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Wako gel® C-200, 2% MeOH/$CHCl_3$), followed by further purification by preparative reverse-phase HPLC using MeOH/water system as an eluent to afford **41** (3.9 mg, 0.0051 mmol, 17%): ^{1}H-NMR (400MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.90-7.85 (m, 3H), 7.69 (t, J = 6.1 Hz, 1H), 7.37-7.29 (m, 3H), 7.20 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 3.64 (q, J = 6.7 Hz, 2H), 3.08 (t, J = 7.0, 2H), 2.42(s, 3H), 2.18 (s, 3H), 1.57-1.50 (m, 6H), 1.38-1.29 (m, 6H), 1.15-1.11 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ^{13}C-NMR (125MHz, $CDCl_3$) δ 168.5 (2C), 164.8, 160.2, 157.4, 150.7, 138.9, 135.6 (2C), 130.3, 130.1, 128.1, 127.3, 117.4 (2C), 116.7, 115.6, 111.1, 40.4, 29.5, 23.4, 13.7; ESI-MS (*m/z*) 754.3 $[M+H]^+$ (maximum peak for ^{120}Sn-isotope).

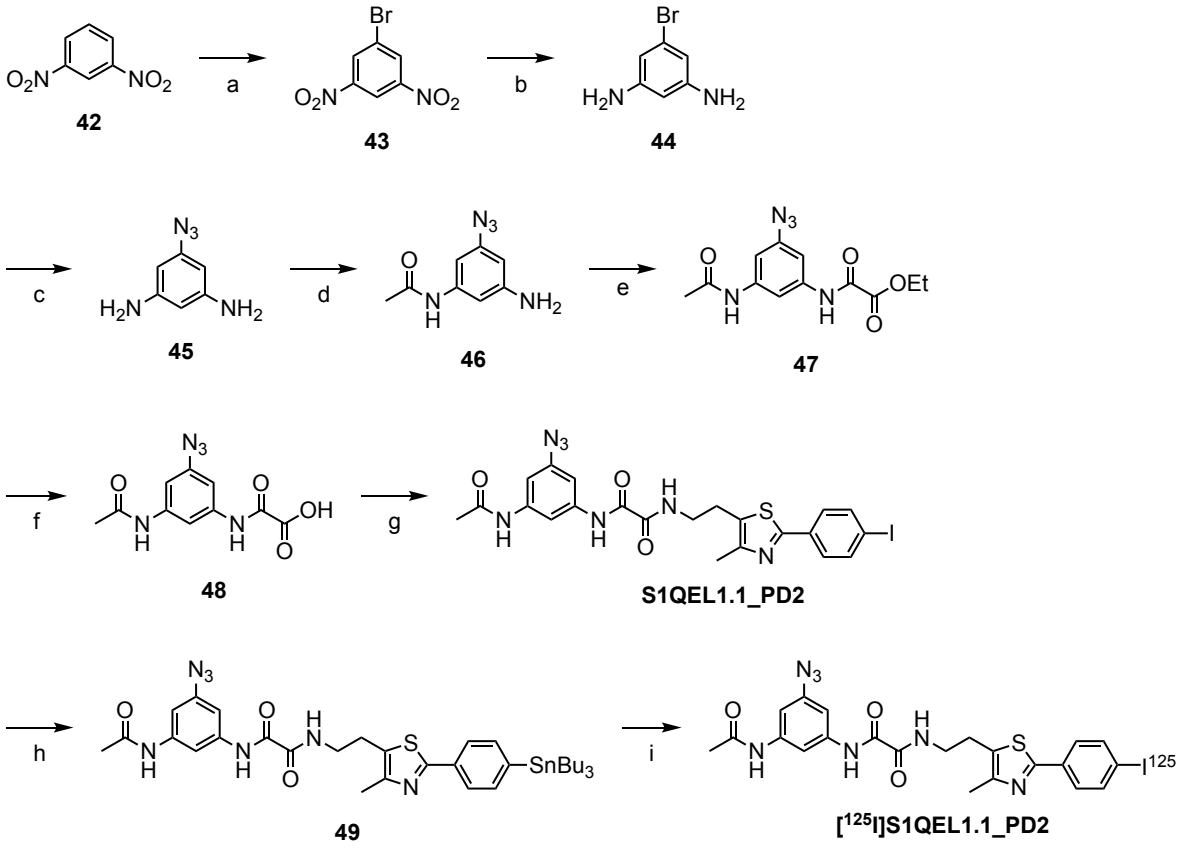


[^{125}I]S1QEL1.1_PD1

To a solution of the tin-precursor **41** (1.0 mM, in ethanol, 20 μL) in screw-capped 1.5mL plastic-tube was added [^{125}I]NaI (PerkinElmer, NEZ033A, 1 mCi, 2000 Ci/mmol, 10 μL). The radio-iodination was initiated by adding freshly prepared aqueous chloramine T (3.0 mM in KPi buffer, pH 7.4, 20 μL), and the mixture was incubated at room temperature for 10 min (Ref. *2*). The reaction was quenched with 5% aqueous $NaHSO_3$ (100 μL), and the resulting mixture was extracted with chloroform (100 μL x 3). The combined organic layer was concentrated using vacuum-centrifugal evaporator. The crude product was dissolved in methanol (50 μL), and subjected to HPLC (Shimazu LC-10 AS) purification using a C18 column (COSMOSIL 5C18-MS-II, 4.6 x 150 mm, Nacalai Tesque) at a flow rate of 0.8 mL/min with methanol/water system as an eluent.

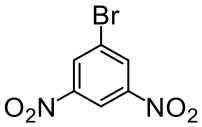
The column was eluted with isocratic 10% methanol in 5 min, then isocratic 90% methanol in 15 min. The fraction was collected every 30 s (~400 μL) and the radioactivity was measured by γ-counting system (COBRATMII, Packard). The strong radioactive fractions corresponding to the retention time of **[^{125}I]S1QEL1.1_PD1** (14.5 min) were combined and the solvent was evaporated by vacuum-centrifugal concentrator. **[^{125}I]S1QEL1.1_PD1** was stored as an ethanolic solution (1 mCi/mL) at -18 °C. The radiochemical yield of **[^{125}I]S1QEL1.1_PD1** from the initial [^{125}I]NaI was 13%. The radiochemical purity and the specific activity were >99% and 2000 Ci/mmol, respectively (judged from HPLC and TLC analyses).

Scheme 5[e]



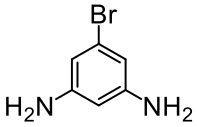
[e]**Synthesis of S1QEL1.1_PD2 and [^{125}I]S1QEL1.1_PD2.**

Reagents and conditions: (a) *N*-bromosuccinimide, conc. H_2SO_4, 60 °C, 16 h, 96%; (b) Fe, NH_4Cl, MeOH/water, 60 ˚C, 4 h, 82%; (c) sodium L-ascorbate, CuI, *N*,*N*'-dimethylethylenediamine, NaN_3, EtOH/H_2O, reflux, 1 h, 87%; (d) Ac_2O, Et_3N, CH_2Cl_2, rt, 5 h, 25%; (e) ethyl chloroglyoxylate, Et_3N, THF, reflux, 1 h, 88%; (f) 6.0 M aq. NaOH, MeOH/THF, rt, 15 min, quant.; (g) **36**, HATU, *N*-methylmorphorine, DMF, rt, 3 h, 15%; (h) bis(tributyltin), $Pd(PPh_3)_4$, 1,4-dioxane, 50 °C, 1 d, 12%; (i) [^{125}I]NaI, chloramine T, 0.2 M aq. KH_2PO_4, rt, 10 min, 34%.



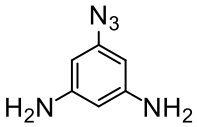
1-Bromo-3,5-dinitrobenzene (43)

A solution of *m*-dinitrobenzene **42** (3.03 g, 18.0 mmol) in concentrated sulfuric acid (50 mL) was heated at 60 ˚C, followed by the addition of *N*-bromosuccinimide (3.84 g, 21.6 mmol) in several portions. After stirring at 60 ˚C for 16 h, the reaction mixture was cooled to room temperature and poured into crushed ice. The mixture was extracted with dichloromethane and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% ethyl acetate / *n*-hexane) to afford **43** (4.26 g, 17.2 mmol, 96%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.01 (t, J = 2.0 Hz, 1H), 8.71 (d, J = 2.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.02, 132.21 (2C), 124.02, 117.56 (2C).



5-Bromobenzene-1,3-diamine (44)

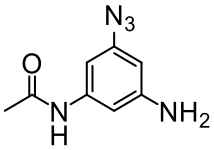
To a solution of **43** (4.26 g, 17.2 mmol) in methanol (20 mL) and water (20 mL) were added ammonium chloride (7.38 g, 138 mmol) and iron powder (4.82 g, 86 mmol). After stirring at 60 ˚C for 4 h, the mixture was filtered through a pad of Celite®, followed by the removal of methanol under reduced pressure. The resulting aqueous solution was extracted with dichloromethane, and the organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 30% ethyl acetate/*n*-hexane) to afford **44** (2.64 g, 14.1 mmol, 82%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.25 (d, J = 2.0 Hz, 2H), 5.90 (t, J = 2.0 Hz, 1H), 3.60 (br s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.7 (2C), 123.7, 108.9 (2C), 100.2; ESI-MS (m/z) 187.0 $[M+H]^+$ (for ^{79}Br-isotope), 189.0 $[M+H]^+$ (for ^{81}Br-isotope).



5-Azidobenzene-1,3-diamine (45)

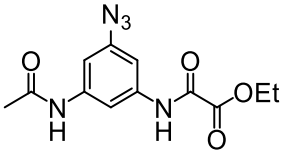
To a solution of **44** (1.87 g, 10.0 mmol) in ethanol (25 mL) and water (25 mL) were added sodium ascorbate (200 mg, 1.01 mmol), copper(I) iodide (381 mg, 2.0 mmol), *N*,*N*'-dimethylethylenediamine (264 mg, 3.02 mmol) and sodium azide (1.30 g, 20.4 mmol), and the mixture was heated under reflux for 15 min. Then, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica-gel column chromatography (Wako

gel® C-200, 2% methanol/chloroform) to afford **45** (1.30 g, 8.72 mmol, 87%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.79 (s, 3H), 3.64 (br s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.8 (2C), 142.1, 98.5, 96.6 (2C); ESI-MS (*m/z*) 150.1 $[M+H]^+$.



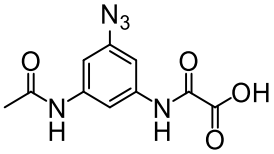
***N*-(3-Amino-5-azidophenyl)acetamide (46)**

To an ice-cooled solution of **45** (1.30 g, 8.72 mmol) in anhydrous dichloromethane (50 mL) were added triethylamine (1.06 g, 10.5 mmol) and acetic anhydride (0.89 g, 8.72 mmol) under nitrogen atmosphere. After stirring the mixture at room temperature for 5 h, it was concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 5% ethyl acetate/*n*-hexane) to afford **46** (416 mg, 2.18 mmol, 25%): ^{1}H-NMR (400 MHz, MeOD) δ 6.73 (t, J = 1.7 Hz, 1H), 6.65 (t, J = 1.8 Hz, 1H), 6.14 (t, J = 1.9 Hz, 1H), 2.08 (s, 3H); ^{13}C-NMR (100 MHz, MeOD) δ 171.7, 151.1, 142.4, 141.9, 104.3, 102.1, 101.0, 23.9; ESI-MS (*m/z*) 192.1 $[M+H]^+$.



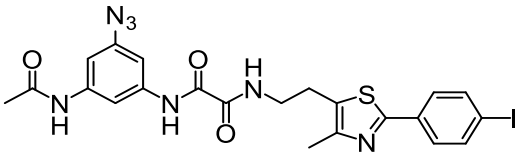
Ethyl *N*-(3-acetamido-5-azidophenyl)oxamate (47)

To an ice-cooled solution of **46** (416 mg, 2.18 mmol) in anhydrous THF (10 mL) were added triethylamine (440 mg, 4.35 mmol) and ethyl chloroglyoxylate (327 mg, 2.39 mmol) under nitrogen atmosphere, and the mixture was refluxed for 1h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$ to afford **46** (560 mg, 1.92 mmol, 88%): ^{1}H-NMR (400 MHz, MeOD) δ 7.72 (t, J = 1.8 Hz, 1H), 7.30 (t, J = 1.9 Hz, 1H), 7.23 (t, J = 1.9 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.12 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, MeOD) δ 172.9, 161.5, 157.3, 142.6, 141.9, 140.2, 109.5, 64.2, 23.9, 14.2; ESI-MS (*m/z*) 292.1 $[M+H]^+$.



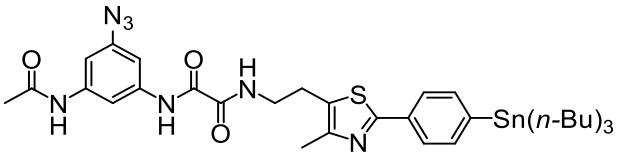
***N*-(3-Acetamido-5-azidophenyl)oxamic acid (48)**

To a solution of **47** (58.3 mg, 0.20 mmol) in methanol (1.5 mL) and THF (0.5 mL) was added 6.0 M aqueous NaOH (0.1 mL), and the mixture was stirred at room temperature for 16 h. The mixture was acidified with 6.0 M HCl to pH 1~2, followed by the removal of organic solvent *in vacuo*. The resulting aqueous solution was extracted with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$ to afford **48** (52.6 mg, 0.20 mmol, quant): ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 10.16 (s, 1H), 7.79 (t, J = 1.5 Hz, 1H), 7.27 (t, J = 1.7 Hz, 1H), 7.20 (t, J = 1.8 Hz, 1H), 2.03 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 169.4, 162.2, 157.6, 141.1, 140.4, 139.5, 107.8, 105.9, 102.0, 24.3; ESI-MS (*m/z*) 262.1 $[M-H]^-$.



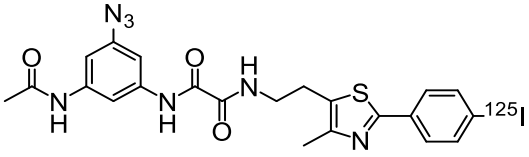
***N*-(3-Acetamido-5-azidophenyl)-*N'*-(2-(2-(4-iodophenyl)-4-methylthiazol-5-yl)ethyl)oxamide (S1QEL1.1_PD2)**

S1QEL1.1_PD2 was prepared from **35** and **48** according to the procedure described for **S1QEL1.1**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 30-50% ethyl acetate/*n*-hexane) to afford **S1QEL1.1_PD2** (15.4 mg, 0.026 mmol, 15%): ^{1}H-NMR (400 MHz, MeOD/$CDCl_3$ =1/1) δ 7.78 (dt, J = 8.6, 2.1 Hz, 2H), 7.62-7.58 (m, 3H), 7.30 (t, J = 2.0 Hz, 1H), 7.24 (t, J = 1.9 Hz, 1H), 3.60 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 2.43 (s, 3H), 2.14 (s, 3H); ^{13}C-NMR (100 MHz, MeOD/$CDCl_3$ =1/1) δ 171.2, 165.0, 161.0, 158.5, 150.9, 142.1, 141.1, 139.0, 138.7 (2C), 133.4, 129.6, 128.3 (2C), 108.4, 107.6, 106.8, 96.3, 41.2, 24.0, 14.8; ESI-MS (*m/z*) 590.1 $[M+H]^+$.



***N*-(3-Acetamido-5-azidophenyl)-*N'*-(2-(4-methyl-2-(4-(tributylstannyl)phenyl)thiazol-5-yl)ethyl)oxamide (49)**

49 was prepared from **S1QEL1.1_PD2** according to the procedure described for **41**. The crude product was purified by silica-gel column chromatography (Wako gel® C-200, 30-50% ethyl acetate/*n*-hexane) to afford **50** (1.2 mg, 0.0016 mmol, 12%): ^{1}H-NMR (400 MHz, MeOD/$CDCl_3$ = 1/1) δ 7.78 (d, J = 8.1 Hz, 2H), 7.62 (s, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 1.9 Hz, 1H), 7.26 (t, J = 1.9 Hz, 1H), 3.60 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 2.43 (s, 3H), 2.14 (s, 3H), 1.61-1.53 (m, 6H), 1.40-1.30 (m, 6H), 1.13-1.08 (m, 6H), 0.90 (t, J = 7.3 Hz, 9H); ^{13}C-NMR (400 MHz, MeOD/$CDCl_3$ = 1/1) δ 171.1, 166.8, 161.0, 158.6, 150.5, 146.0, 142.1, 141.1, 139.1, 137.6 (2C), 133.4, 128.9, 126.0 (2C), 108.5, 107.6, 106.8, 41.3, 29.7 (3C), 27.9 (3C), 26.6, 24.0, 14.8, 13.9 (3C), 10.1 (3C); ESI-MS (*m/z*) 754.3 $[M+H]^+$ (maximum peak for ^{120}Sn isotope).



***N*-(3-Acetamido-5-azidophenyl)-*N'*-(2-(2-(4-[^{125}I]iodophenyl)-4-methylthiazol-5-yl)ethyl)oxamide ([^{125}I]S1QEL1.1_PD2)**

[^{125}I]S1QEL1.1_PD2 was prepared from **49** according to the same procedure described for **[^{125}I]S1QEL1.1_PD1**. The radiochemical yield from the initial [^{125}I]NaI was 34%. The radiochemical purity and the specific activity were >99% and 2,000 Ci/mmol, respectively (judged from HPLC and radio-TLC). **^{125}I]S1QEL1.1_PD2** was stored as an ethanoic solution (1 mCi/mL) at 4 ˚C.

References (for synthetic procedures)

1. Li, Z., Qiu, Q., Xu, X., Wang, X., Jiao, L., Su, X., Pan, M., Huang, W., and Qian, H. (2016) Design, synthesis and structure-activity relationship studies of new thiazole-based free fatty acid receptor 1 agonists for the treatment of type 2 diabetes. *Eur. J. Med. Chem.* 113, 246-257.
2. Uno, S., Kimura, H., Murai, M., and Miyoshi, H. (2019) Exploring the quinone/inhibitor-binding pocket in mitochondrial respiratory complex I by chemical biology approaches. *J. Biol. Chem.* 294, 679-696.

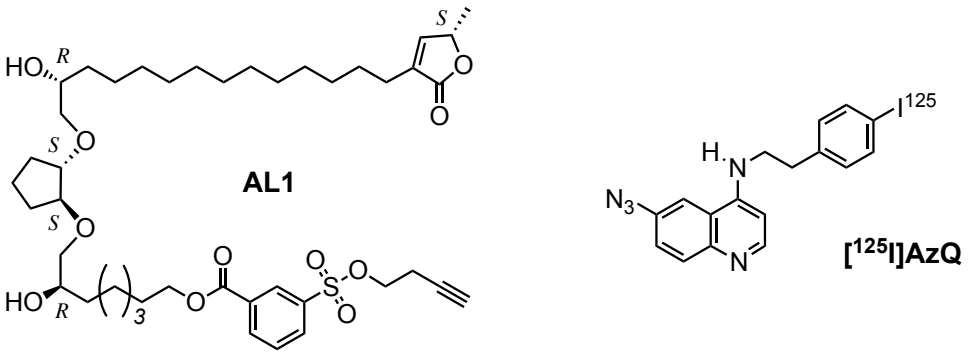


Figure S1

Structures of AL1 and [^{125}I]AzQ used in the present study.

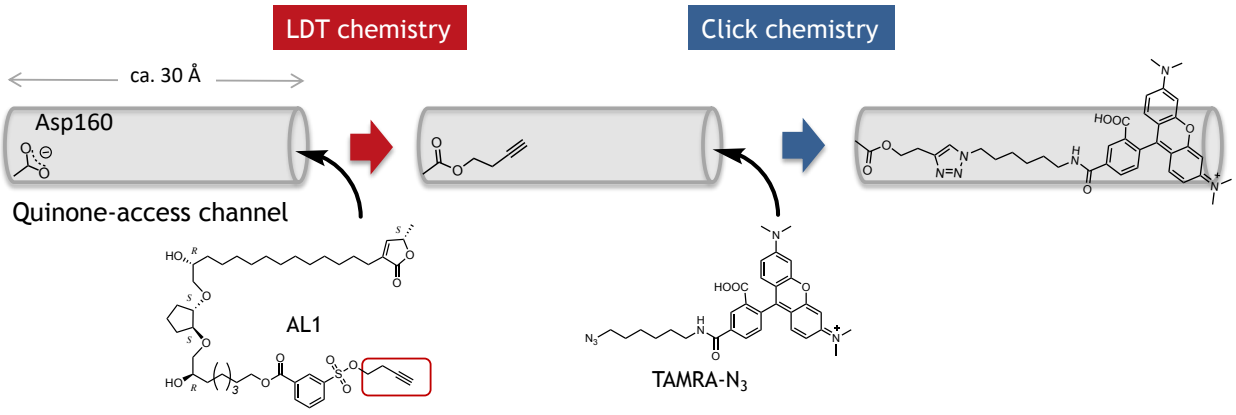


Figure S2

Schematic diagram of the pinpoint chemical modification of the 49 kDa Asp160. The 49 kDa Asp160 can be modified by an externally added TAMRA-N_3 through the two-step conjugation procedure, LDT and click chemistry (see refs. *31*, *32*).

Table S1. Proteins identified by MALDI-TOF MS

Protein name (Swiss Prot accession No.)	Matched peptides	MOWSE score [a] (Sequence coverage)	Matched in-gel triptic digests				
			Observed *m/z* (MH^+)	Mr		Peptide sequence	Residues
				Expected	Calculated		
Complex I-ND1 subunit (P03887)	7	51 (15%)	979.544	978.5367	978.5321	VLGYMQLR	27-34
			1107.639	1106.6320	1106.6270	VLGYMQLRK	27-35
			2050.167	2049.1601	2049.1622	KGPNVVGPYGLLQPIADAIK	35-54
			1922.077	1921.0701	1921.0673	GPNVVGPYGLLQPIADAIK	36-54
			876.526	875.5187	875.5229	YALIGALR	127-134
			1649.860	1648.8535	1648.8548	FRYDQLMHLLWK	280-291
			1346.698	1345.6908	1345.6853	YDQLMHLLWK	282-291
ADP/ATP carrier (P02722)	12	72 (48%)	1219.737	1218.7297	1218.6608	DFLAGGVAAAISK	11-23
			1169.605	1168.5977	1168.5655	EQGFLSFWR	64-72
			856.507	855.4997	855.4926	GNLANVIR	73-89
			1446.790	1445.7827	1445.7343	YFPTQALNFAFK	81-92
			1004.563	1003.5557	1003.5451	QIFLGGVDR	97-105
			2796.347	2795.3397	2795.3377	YFAGNLASGGAAGATSLCFVYPLDFAR +carbamidomethyl (C)	112-138
			1927.115	1926.1077	1926.0363	GLYQGFNVSVQGIIIYR	172-188
			1205.615	1204.6077	1204.5764	AAYFGVYDTAK	189-199
			1644.763	1643.7557	1643.7072	GADIMYTGTVDCWR +carbamidomethyl (C)	246-259
			1660.796	1659.7617	1659.7021	GADIMYTGTVDCWR +carbamidomethyl (C) ; oxidation (M)	246-259
			902.496	901.4887	901.4770	GAWSNVLR	273-280
			1739.973	1738.9657	1738.9328	GMGGAFVLVLYDEIKK	281-296

[a]MOWSE score is -10*logP, where P is the probability that the observed match is a random event. Scores greater than 54 are significant ($p<0.05$).