Supplementary Materials

Thiazolidinone Derivatives as Competitive Inhibitors of Protein Tyrosine Phosphatase 1B (PTP1B)

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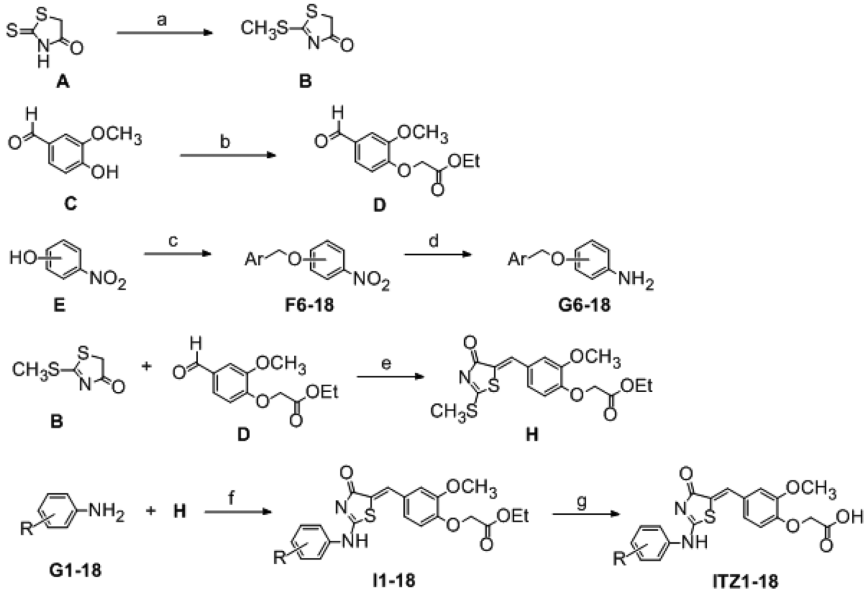
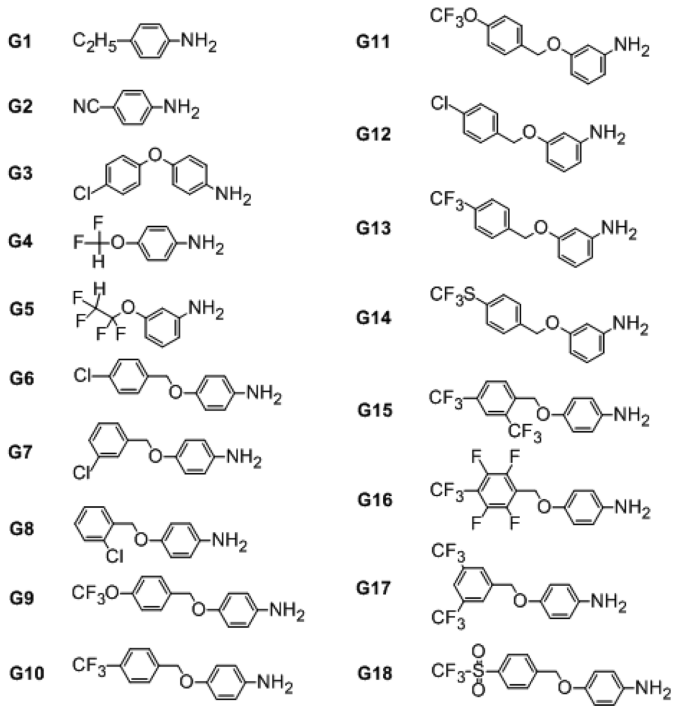
Synthesis of **ITZ1-18**





Synthesis of B

A solution of rhodanine (1.332 g, 10 mmol), *N*,*N*-diisopropyl ethylamine (1.422 g, 11 mmol), and methyl iodide (1.6 g, 11 mmol) in ethanol (30 mL) was stirred at rt for 4 h. After evaporation of ethanol from the reaction mixture, H_2O (20 mL) was added and the whole mixture was extracted with CH_2Cl_2 (25 mL × 3). Combined organic layer was washed with saturated $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL), successively. It was then dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography to obtain compound **B** (0.87 g, 59% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.80 (bs, 3H), 3.07 (bs, 2H).

Synthesis of D

To a mixture of vanillin (0.152 g, 1 mmol) and anhydrous K_2CO_3 (0.207 g, 1.5 mmol) in dry acetone (6 mL) was added ethyl α-bromoacetate (0.251 g, 1.5 mmol) at r.t. The mixture was heated to reflux for 4 h. After evaporation of the solvent under reduced pressure, H_2O (50 mL) was added and the resulting mixture was extracted with ethyl acetate (2 × 50 mL). Combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain compound **D** (0.225 g, 94% yield) as yellow oil, which solidified on standing at rt for 2 days. It was pure enough to be used for the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.94 (s, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.77 (s, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 9.84 (s, 1H).

General Procedure for the Synthesis of F6-18

To a solution of *m*- or *p*-nitrophenol (2.0 mmol) in dry DMF (4 mL) was added appropriate derivatives of benzyl chloride or benzyl bromide (2.2 mmol) and K_2CO_3 (10 mmol). The mixture was heated at 65-70 ºC for 1-2 h. After aqueous workup, the crude product was purified by column chromatography.

F6: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.13 (s, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 7.38 (bs, 4H), 8.21 (d, *J* = 9.2 Hz, 2H).

F7: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.14 (s, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 7.30-7.44 (m, 4H), 8.22 (d, *J* = 9.2 Hz, 2H).

F8: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.27 (s, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 7.26-7.36 (m, 2H), 7.42-7.54 (m, 2H), 8.23 (d, *J* = 9.2 Hz, 2H).

F9: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.21 (s, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 8.27 (d, *J* = 9.0 Hz, 2H).

F10: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (s, 2H), 7.11 (d, *J* = 9.2 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 8.30 (d, *J* = 9.2 Hz, 2H).

F11: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.20 (s, 2H), 7.30-7.38 (m, 3H), 7.46-7.56 (m, 3H), 7.86-7.94 (m, 2H).

F12: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.16 (s, 2H), 7.30-7.50 (m, 6H), 7.84-7.92 (m, 2H).

F13: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.27 (s, 2H), 7.32-7.94 (m, 8H).

F14: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.27 (s, 2H), 7.10 (d, *J* = 9.2 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 9.2 Hz, 2H).

F15: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.49 (s, 2H), 7.12 (d, *J* = 9.2 Hz, 2H), 7.94-8.06 (m, 4H), 8.32 (d, *J* = 9.2 Hz, 2H).

F16: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (s, 2H), 7.13 (d, *J* = 9.2 Hz, 2H), 8.33 (d, *J* = 9.2 Hz, 2H).

F17: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (s, 2H), 7.15 (d, *J* = 9.2 Hz, 2H), 7.98 (bs, 3H), 8.34 (d, *J* = 9.2 Hz, 2H).

F18: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.38 (s, 2H), 7.13 (d, *J* = 9.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 8.2 Hz, 2H), 8.32 (d, *J* = 9.2 Hz, 2H).

G1-5 were purchased from Aldrich or TCI and used for reactions without purification.

General Procedure for the Synthesis of G6-18

To a solution of **F6-18** (0.10 mmol) in 50% aqueous MeOH (25 mL) was added concentrated HCl (1.0 mL). Zinc powder (2.0 mmol) was then added while the solution was stirred vigorously. Additional concentrated HCl (2.0 mL) was added dropwise and the reaction was continued at r.t. for 30 min. NaOH solution was added to the reaction mixture until zincate was formed as white precipitate. The mixture was extracted with $CHCl_3$ (20 mL × 2), and the combined organic layer was dried and concentrated to obtain **G6-18** in an essentially pure form in > 80% yield.

G6: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50 (bs, 2H, NH_2), 5.03 (s, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.42 (bs, 4H).

G7: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.96 (s, 2H), 6.64 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H), 7.20-7.30 (bs, 3H), 7.42 (bs, 1H).

G8: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.09 (s, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 7.23-7.40 (m, 3H), 7.53-7.58 (m, 1H).

G9: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.75 (bs, 2H, NH_2), 5.03 (s, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 2H).

G10: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.10 (s, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H).

G11: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (s, 2H), 6.57-6.61 (m, 3H), 7.16-7.32 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 2H).

G12: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.74 (bs, 2H, NH_2), 5.05 (s, 2H), 6.40-6.48 (m, 3H), 7.13-7.41 (m, 5H).

G13: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.15 (s, 2H), 6.60-6.64 (m, 3H), 7.18-7.26 (m, 1H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H).

G14: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50 (bs, 2H, NH_2), 5.10 (s, 2H), 6.82-6.93 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H).

G15: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.32 (s, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H). 7.90-8.10 (m, 4H).

G16: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (bs, 2H, NH_2), 5.18 (s, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H).

G17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.80-7.92 (m, 3H).

G18: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.0 Hz,

2H), 8.12 (d, J = 8.8 Hz, 2H).

Synthesis of H

A solution of **B** (1.50 g, 10 mmol) and **D** (2.38 g, 10 mmol) in 2-propanol (15 mL) was heated to 65-70 °C for 3 h. After cooling to r.t., the solvent was evaporated and the residue was purified by recrystallization in ethanol. The mother liquor was further purified by column chromatography to obtain additional product (1.58 g, 43% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3H), 2.90 (s, 3H), 4.01(s, 3H), 4.34 (q, J = 7.2 Hz, 2H), 4.82 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.11 (bs, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H).

Synthesis of I1-18

A solution of compound **H** (0.10 mmol) and amines (**G1-18**, 0.10 mmol) in ethanol (4.0 mL) was heated to reflux for 6 h. After cooling to rt, solvent was evaporated from the reaction mixture and the resulting solid was purified by column chromatography.

I1: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, J = 7.4 Hz, 6H), 2.73 (q, J = 7.4 Hz, 2H), 3.93 (s, 3H), 4.30 (q, J = 7.4 Hz, 2H), 4.76 (s, 2H), 6.85 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.20-7.33 (m, 4H), 7.72 (s, 1H).

I2: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 3.89 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 4.73 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.95-7.04 (m, 2H), 7.19-7.23 (m, 2H), 7.68-7.71 (m, 3H).

I3: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 3.90 (s, 3H), 4.27 (q, J = 7.0 Hz, 2H), 4.73 (s, 2H), 6.80-7.34 (m, 11H), 7.68 (s, 1H).

I4: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 3.96 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 4.79 (s, 2H), 6.87-7.34 (m, 7H), 7.75 (s, 1H).

I5: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 3.94 (s, 3H), 4.32 (q, J = 7.2 Hz, 2H), 4.79 (s, 2H), 5.72-6.26 (m, 1H) 6.88 (d, J = 8.4 Hz, 1H), 7.04-7.16 (m, 5H), 7.45-7.49 (m, 1H), 7.77 (s, 1H).

I6: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H), 3.89 (s, 3H), 4.26 (q, J = 7.0 Hz, 2H), 4.72 (s, 2H), 5.06 (s, 2H), 6.79-7.39 (m, 11H), 7.67 (s, 1H).

I7: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 3.89 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 4.72 (s, 2H), 5.07 (s, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.98-7.04 (m, 4H), 7.18-7.27 (m, 3H), 7.34 (bs, 2H), 7.47 (bs, 1H), 7.68 (s, 1H).

I8: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 3.88 (s, 3H), 4.26 (q, J = 7.0 Hz, 2H), 4.72 (s, 2H), 5.20 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.98-7.07 (m, 4H), 7.19-7.41 (m, 5H), 7.57-7.60 (m, 1H), 7.68 (s, 1H).

I9: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 3.92 (s, 3H), 4.31 (q, J = 7.0 Hz, 2H), 4.77 (s, 2H), 5.12 (s, 2H), 6.86 (d, J = 8.0 Hz, 1H), 7.02-8.00 (m, 4H), 7.29-7.33 (m, 4H), 7.46-7.56 (m, 2H), 7.73 (s, 1H).

I10: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 3.94 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.78 (s, 2H), 5.21 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.03-7.11 (m, 4H), 7.26-7.32 (m, 2H), 7.61-7.77 (m, 5H).

I11: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H), 3.93 (s, 3H), 4.31 (q, J = 7.0 Hz, 2H), 4.77 (s, 2H), 5.12 (s, 2H), 6.84-7.52 (m, 11H), 7.75 (s, 1H).

I12: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 3.90 (s, 3H), 4.29 (q, J = 7.2 Hz, 2H), 4.76 (s, 2H), 5.06 (s, 2H), 6.82-7.05 (m, 7H), 7.30-7.38 (m, 4H), 7.72 (s, 1H).

I13: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 3.93 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 4.78 (s, 2H), 5.18 (s, 2H), 6.84-7.10 (m, 6H), 7.32-7.38 (m, 1H), 7.56-7.76 (m, 5H).

I14: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 3.95 (s, 3H), 4.33 (q, J = 7.2 Hz, 2H), 4.78 (s, 2H), 5.19 (s, 2H), 6.88-7.11 (m, 5H), 7.31 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.74-7.87 (m, 3H).

I15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 3H), 3.87 (s, 3H), 4.25 (q, J = 7.3 Hz, 2H), 4.71 (s, 2H), 5.34 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.96-7.03 (m, 4H), 7.22 (d, J = 8.4 Hz, 2H), 7.66 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.93-7.98 (m, 2H).

I16: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 3.88 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 4.70 (s, 2H), 5.20 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.97-7.00 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 7.67 (bs, 1H).

I17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 3.88 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.71 (s, 2H), 5.18 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.97-7.07 (m, 4H), 7.18-7.28 (m, 2H) 7.67 (bs, 1H), 7.80-7.92 (m, 3H).

I18: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 3.88 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.71 (s, 2H), 5.32 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.97-7.07 (m, 4H), 7.15-7.25 (m, 3H) 7.67 (bs, 1H), 7.77 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H).

General procedure for the synthesis of ITZ1-18

A solution of the esters **I1-18** (0.052 mmol) in THF (1 mL) and 2 M aqueous NaOH (0.030 mL) was heated to reflux for 1.5 h. The reaction mixture was cooled to rt and acidified using 1 M HCl. After evaporation of the solvent under reduced pressure, the solid was washed with H_2O (2 mL × 5) and dried under high vacuum to be used as inhibitors without purification.