# Supporting Information

# Crystal Structures and Structure-activity Relationships of Imidazothiazole Derivatives as IDO1 Inhibitors

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## Table of contents

**1) Supplementary figures** **S2**

**2) Synthetic procedures and characterization** **S5**

**3) Purification method of recombinant IDO1 protein** **S16**

**4) Biological assay method** **S16**

**5) X-ray crystallography** **S17**

**6) Reference** **S19**

## 1) Supplementary figures

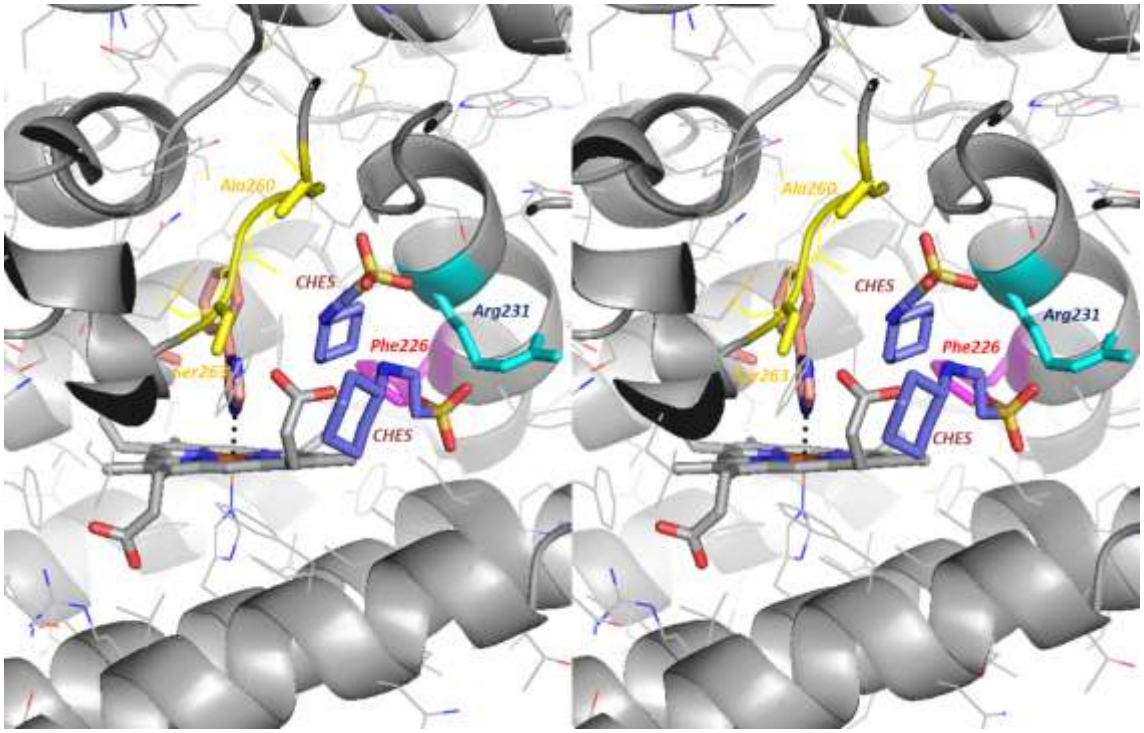



Figure S1. Stereoview of IDO1/PI (purple) complex (PDB:2DOT). CHES is colored in blue. Main chain Ala260-Ser263 (yellow), Phe226 (pink), and Arg231 (cyan) are showing.

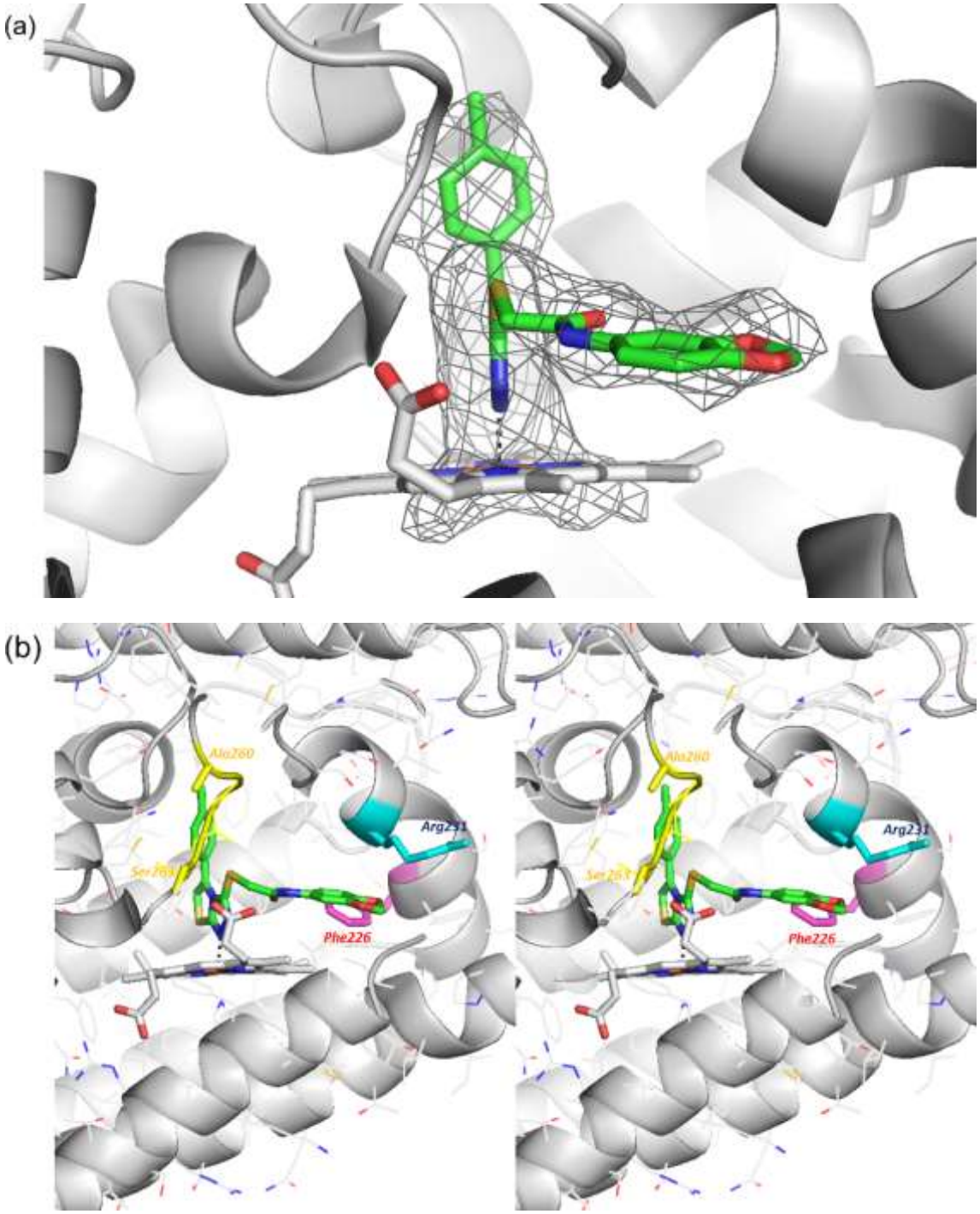



Figure S2. Crystal structure of IDO1/Amg-1 (green) complex (PDB:4PK5). (a) Omit map (contoured 2.0sigma) of Amg-1 in the active site. (b) Stereoview of Amg-1. Main chain Ala260-Ser263 (yellow), Phe226 (pink), and Arg231 (cyan) are showing in (a) and (b).

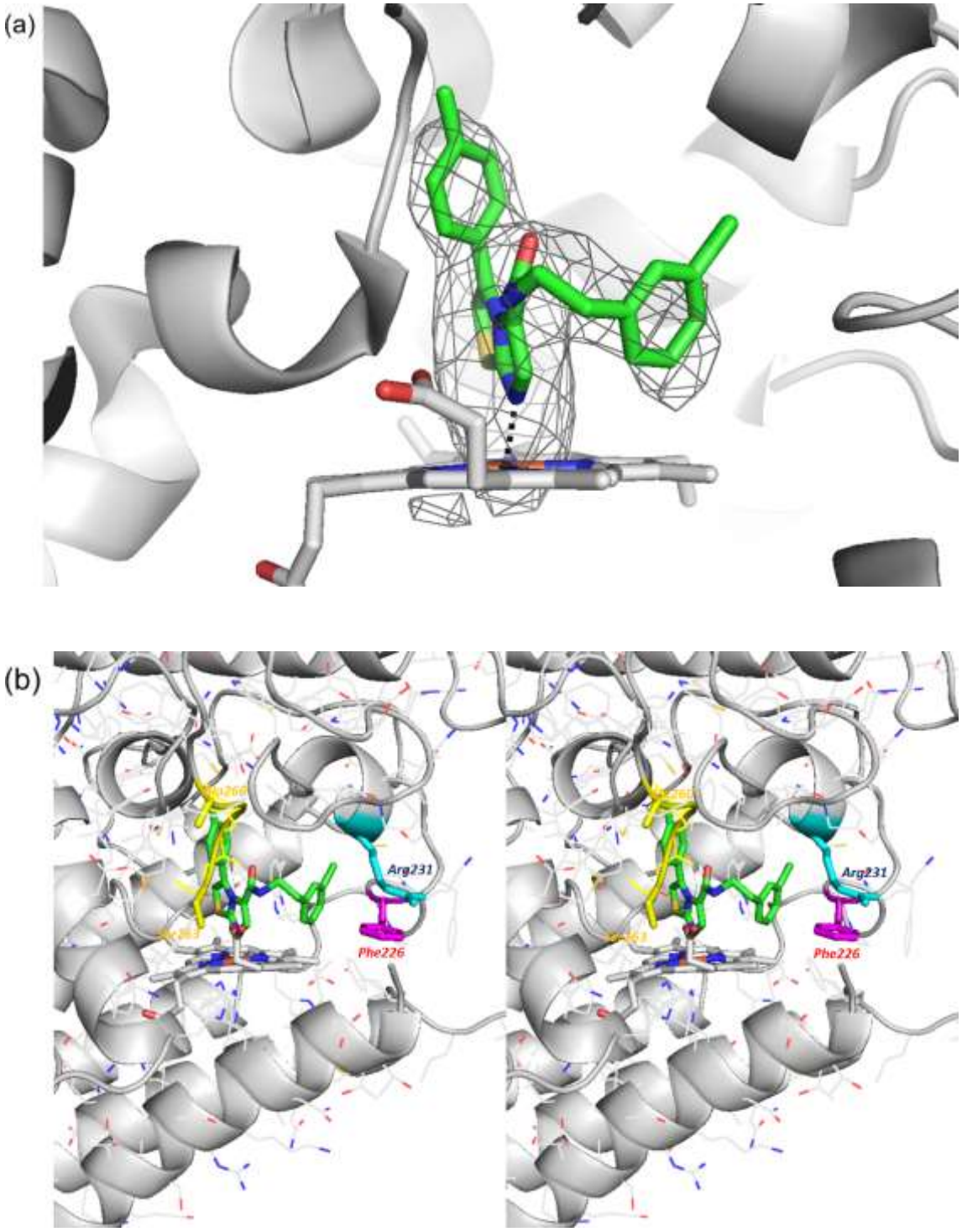


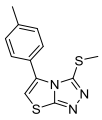

Figure S3. Crystal structure of IDO1/**13b** (green) complex (PDB:4PK6). (a) Omit map (contoured 2.0sigma) of **13b** in the active site. (chain b) (b) Main chain Ala260-Ser263 (yellow), Phe226 (pink), and Arg231 (cyan) are showing in (a) and (b).

## 2) Synthetic procedures and characterization

### General information

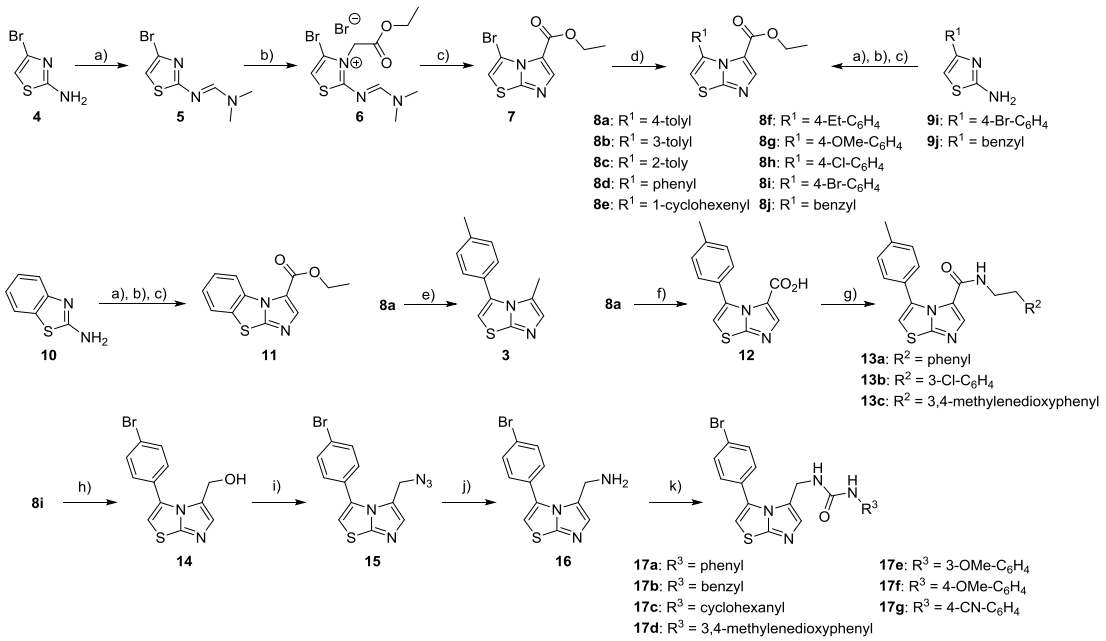
Melting points were determined on a Stanford Research Systems *Opti Meit*. NMR spectra were recorded on a JEOL *JNM-LA300* spectrometer. Splitting patterns were designated as "s, d, t, q, m, and br" indicating "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. Chemical shifts (δ) are reported with DMSO (δ = 2.49 ppm) or $CHCl_3$ (δ = 7.24 ppm) as internal standard. All *J* values are given in Hz. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ Orbitrap Discovery MS equipment. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out using a Yamazen *W-prep* system, and performed using pre-packed silica-gel ($SiO_2$) or amino silica-gel (amino $SiO_2$) columns. Reaction progress was monitored by TLC analysis on a silica-gel or amino silica-gel coated glass plate. Visualization was done with UV light (254 nm) or iodine. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned. HPLC was performed using a SHIMADZU *Prominence UFLC*$^{TM}$ system. The sample was dissolved in acetonitrile or methanol solution, applied on a Phenomenex® Kinetex® C18 column (3.0 mm × 75 mm, 2.5 μm), and eluted at 1 mL/min with a 8.5 min gradient (from 10% B to 90% B), where solvent A is water (0.1% TFA solution) and solvent B is acetonitrile (0.1% TFA solution). The purity of all new compounds was determined by UPLC and was > 97%.

### 3-(Methylthio)-5-(4'-tolyl)thiazolo[2,3-*c*][1,2,4]triazole (2)



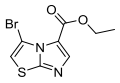
To a solution of 5-(4'-tolyl)thiazolo[2,3-c][1,2,4]triazole-3-thiol (62.3 mg, 0.252 mmol) in DMF (2 ml) were added $K_2CO_3$ (104.2 mg, 0.754 mmol) and MeI (0.031 ml, 0.498 mmol) at room temperature. After stirring at the same temperature for 1 h, the reaction was quenched by sat. $NaHCO_3$ aq. (15 ml), the aq. layer was extracted with ethyl acetate (20 ml x 2). The organic layer was washed with brine (50 ml), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography ($SiO_2$, chloroform / MeOH) to give compound **2** (64.9 mg, 99%) as white solids. mp 188-190 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.48 (2H, d, *J* = 8.1 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.28 (1H, s), 2.47 (3H, s), and 2.38 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.0, 142.7, 139.9, 130.4, 129.6, 128.9, 124.6, 114.7, 21.0, and 15.2; HRMS (ESI) *m/z*, calcd. for $C_{12}H_{12}N_3S_2$ $(M+H)^+$: 262.0467, found 262.0467 (Δ = –0.05 mmu); HPLC purity = 99.2% (Rt = 4.40 min).

Scheme S1. Synthesis of the imidazothiazole compounds[a]




[a]Reagents and conditions: (a) *N*,*N*-dimethylformamide dimethyl acetal, DMF, 80 °C; (b) ethyl bromoacetate, 80 °C; (c) DBU, DMF, 60 °C; (d) $R^1B(OH)_2$ or $R^1BPin$, $Pd(PPh_3)_4$, $K_2CO_3$, 1,4-dioxane-$H_2O$ (3:1), 100 °C; (e) $LiAlH_4$, $AlCl_3$, THF, reflux (15%); (f) 1N NaOH, MeOH-THF (99%); (g) $R^2CH_2CH_2NH_2$, WSC•HCl, HOBt, *i*-$Pr_2NEt$, DMF; (h) DIBAL-H, THF, 0 °C (94%); (i) DPPA, DBU, DMF, 60 °C (75%); (j) $PPh_3$, $H_2O$, THF, 45 °C (90%); (k) $R^3NCO$, *i*-$Pr_2NEt$, THF.

**Ethyl 3-bromoimidazo[2,1-*b*]thiazole-5-carboxylate (7)**



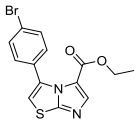
To a solution of **4** (5.00 g, 27.9 mmol) in DMF (50 ml) was added *N*,*N*-dimethylformamide dimethyl acetal (7.44 ml, 55.8 mmol) at room temperature. After stirring at 70 °C for 1 h, the reaction mixture was diluted with water (500 ml), and the aq. layer was extracted with ethyl acetate (250 ml x 2). The organic layer was washed with brine (500 ml), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography ($SiO_2$, hexane / ethyl acetate) to give compound **5** (5.50 g, 84%) as brown solids. $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s), 6.65 (1H, s), 3.10 (3H, s), and 3.07 (3H, s).

To a solution of ethyl bromoacetate (50 ml, 451 mmol) was added **5** (5.30 g, 22.6 mmol) at room temperature. After stirring at 80 °C for 15 h, the reaction mixture was cooled to 0 °C and diluted with ethyl acetate (200 ml). The generated precipitates were filtered and washed with ethyl acetate to afford the bromide **6** (7.60 g, 84%) as white solids. $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.75 (1H, s), 7.02

(1H, s), 4.94 (2H, s), 4.26 (2H, q, *J* = 7.2 Hz), 3.63 (3H, s), and 1.28 (3H, t, *J* = 7.2 Hz).

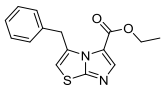
To a solution of **6** (1.23 g, 3.07 mmol) in DMF (20 ml) was added DBU (1.37 ml, 9.20 mmol) at room temperature. After stirring at 60 °C for 9 h, the reaction mixture was diluted with water (100 ml), and the aq. layer was extracted with ethyl acetate (100 ml x 2). The organic layer was washed with brine (200 ml), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residue was subjected to flash column chromatography ($SiO_2$, hexane / ethyl acetate) provided imidazothiazole compound **7** (780 mg, 92%) as white solids. mp 80-81 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.96 (1H, d, *J* = 1.1 Hz), 6.93 (1H, d, *J* = 1.1 Hz), 4.34 (2H, q, *J* = 7.2 Hz), and 1.37 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.4, 154.3, 143.4, 121.0, 113.2, 101.1, 60.9, and 14.3; HRMS (ESI) *m/z*, calcd. for $C_8H_8O_2N_2BrS$ $(M+H)^+$: 274.9484, found 274.9483 (Δ = –0.10 mmu); HPLC purity = 99.4% (Rt = 3.87 min).

**Ethyl 3-(4-bromophenyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8i)**



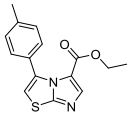

Synthetic procedure was followed as described for compound **7**. The crude material was purified by flash column chromatography ($SiO_2$, hexane / ethyl acetate) to afford compound **8i** (3.41 g, 53% in 3 steps) as white solids. mp 127-128 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.01 (1H, s), 7.58-7.53 (2H, m), 7.31-7.23 (2H, m), 6.83 (1H, s), 4.02 (2H, q, *J* = 7.2 Hz), and 1.09 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.3, 154.7, 141.9, 134.3, 131.3, 129.8, 129.6, 123.7, 120.4, 112.9, 60.8, and 14.0; HRMS (ESI) *m/z*, calcd. for $C_{14}H_{12}O_2N_2BrS$ $(M+H)^+$: 350.9797, found 350.9796 (Δ = –0.15 mmu); HPLC purity = 99.7% (Rt = 5.45 min).

**Ethyl 3-benzylimidazo[2,1-*b*]thiazole-5-carboxylate (8j)**



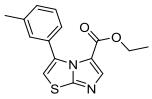

Synthetic procedure was followed as described for compound **7**. The crude material was purified by flash column chromatography ($SiO_2$, hexane / ethyl acetate) to afford compound **8j** (970 mg, 65% in 3 steps) as white solids. mp 108-109 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.92-7.89 (1H, m), 7.35-7.15 (5H, m), 6.87-6.83 (1H, m), 4.52 (2H, s), 4.21 (2H, q, *J* = 7.0 Hz), and 1.22 (3H, t, *J* = 7.0 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.7, 155.4, 142.8, 136.9, 134.7, 128.7, 128.5, 126.7, 120.1, 112.1, 60.4, 34.5, and 14.2; HRMS (ESI) *m/z*, calcd. for $C_{15}H_{15}O_2N_2S$ $(M+H)^+$: 287.0849, found 287.0844 (Δ = –0.43 mmu); HPLC purity = 99.8% (Rt = 5.37 min).

**Ethyl 3-(4'-tolyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8a)**



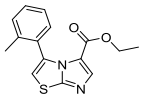
To a solution of **7** (2.10 g, 7.63 mmol) in 1,4-dioxane (40 ml) and water (8 ml) were added 4-tolylboronic acid (1.24 g, 9.15 mmol), $Pd(PPh_3)_4$ (441 mg, 0.382 mmol) and potassium carbonate (3.18 g, 23.0 mmol). After stirring at 100 °C for 4 h, the reaction mixture was diluted with sat. $NaHCO_3$ aq. (50 ml), and the aq. layer was extracted with chloroform (50 ml x 2). The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to give compound **8a** (2.03 g, 93%) as white solids. mp 137-139 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.94 (1H, s), 7.28-7.23 (2H, m), 7.19-7.15 (2H, m), 6.68 (1H, s), 3.92 (2H, q, *J* = 7.2 Hz), 2.36 (3H, s), and 0.98 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.7, 155.0, 142.8, 139.3, 135.4, 128.7, 128.2, 127.7, 120.4, 111.3, 60.5, 21.4, and 13.8; HRMS (ESI) *m/z*, calcd. for $C_{15}H_{14}O_2N_2NaS$ $(M+Na)^+$: 309.0668, found 309.0667 (Δ = –0.14 mmu); HPLC purity = 99.8% (Rt = 5.07 min).

**Ethyl 3-(3'-tolyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8b)**



Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8b** (55.6 mg, 82%) as white solids. mp 99-101 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.95 (1H, s), 7.39-7.23 (5H, m), 3.81 (2H, q, *J* = 7.2 Hz), 2.33 (3H, s), and 0.86 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.2, 154.4, 142.3, 137.3, 134.3, 130.9, 129.7, 128.0, 128.0, 124.6, 119.9, 113.2, 60.1, 20.9, and 13.5; HRMS (ESI) *m/z*, calcd. for $C_{15}H_{14}O_2N_2NaS$ $(M+Na)^+$: 309.0668, found 309.0668 (Δ = 0.01 mmu); HPLC purity = 99.7% (Rt = 5.07 min).

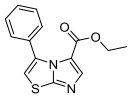
**Ethyl 3-(2'-tolyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8c)**



Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8c** (53.5 mg, 81%) as white solids. mp 99-101 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.96 (1H, s), 7.41-7.23 (5H, m), 3.83-3.67 (2H, m), 2.03 (3H, s), and 0.90 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.0, 154.3, 142.5, 137.3, 133.8, 131.0, 129.8, 129.5, 129.3, 125.5, 120.1, 113.8, 59.9, 19.2, and 13.7; HRMS (ESI) *m/z*, calcd. for $C_{15}H_{14}O_2N_2NaS$ $(M+Na)^+$: 309.0668, found 309.0670 (Δ = 0.14

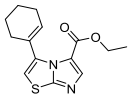
mmu); HPLC purity = 99.7% (Rt = 4.97 min).

**Ethyl 3-phenylimidazo[2,1-*b*]thiazole-5-carboxylate (8d)**



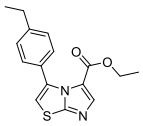
Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8d** (70.3 mg, 86%) as white solids. mp 150-151 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.96 (1H, s), 7.50-7.40 (5H, m), 7.39 (1H, s), 3.80 (2H, q, *J* = 7.2 Hz), and 0.85 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.1, 154.5, 142.5, 134.2, 131.0, 129.0, 128.1, 127.6, 119.9, 113.4, 60.1, and 13.5; HRMS (ESI) *m/z*, calcd. for $C_{14}H_{12}O_2N_2NaS$ $(M+Na)^+$: 295.0512, found 295.0504 (Δ = –0.72 mmu); HPLC purity = 99.9% (Rt = 4.54 min).

**Ethyl 3-(cyclohex-1-en-1-yl)imidazo[2,1-*b*]thiazole-5-carboxylate (8e)**



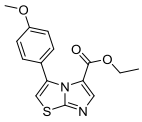
Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8e** (73.8 mg, 89%) as white solids. mp 115-117 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.92 (1H, s), 7.13 (1H, s), 5.92 (1H, brs), 4.23 (2H, q, *J* = 6.8 Hz), 2.10-2.03 (4H, m), 1.74-1.56 (4H, m), and 1.26 (3H, t, *J* = 6.8 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.3, 154.6, 142.5, 136.8, 129.3, 128.78, 119.7, 111.4, 60.3, 27.8, 24.8, 21.4, 21.2, and 14.2; HRMS (ESI) *m/z*, calcd. for $C_{14}H_{17}O_2N_2S$ $(M+H)^+$: 277.1005, found 277.1004 (Δ = –0.12 mmu); HPLC purity = 99.2% (Rt = 5.38 min).

**Ethyl 3-(4'-ethylphenyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8f)**



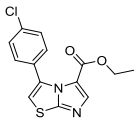
Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8f** (51.6 mg, 71%) as a colorless amorphous. $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.97 (1H, d, *J* = 1.1 Hz), 7.31 (2H, d, *J* = 7.9 Hz), 7.23 (2H, d, *J* = 7.9 Hz), 6.71 (1H, d, *J* = 1.1 Hz), 3.91 (2H, q, *J* = 7.2 Hz), 2.69 (2H, q, *J* = 7.6 Hz), 1.24 (3H, t, *J* = 7.6 Hz), and 0.95 (3H, t, *J* = 7.2 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.8, 155.0, 145.6, 143.1, 135.5, 128.6, 127.8, 127.6, 120.4, 111.3, 60.5, 28.7, 15.4, and 13.8; HRMS (ESI) *m/z*, calcd. for $C_{16}H_{17}O_2N_2S$ $(M+H)^+$: 301.1005, found 301.1007 (Δ = 0.15 mmu); HPLC purity = 99.9% (Rt = 5.60 min).

**Ethyl 3-(4'-methoxyphenyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8g)**



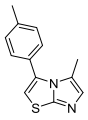
Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8g** (45.0 mg, 82%) as white solids. mp 112-113 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.95 (1H, s), 7.39 (2H, d, *J* = 8.4 Hz), 7.28 (1H, s), 6.99 (2H, d, *J* = 8.4 Hz), 3.85 (2H, q, *J* = 7.2 Hz), 3.80 (3H, s), and 0.90 (2H, t, *J* = 7.2 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 159.8, 158.1, 154.4, 142.48, 134.2, 129.1, 123.3, 119.9, 113.4, 112.3, 60.1, 55.3, and 13.6; HRMS (ESI) *m/z*, calcd. for $C_{15}H_{15}O_3N_2S$ $(M+H)^+$: 303.0798, found 303.0798 (Δ = 0.04 mmu); HPLC purity = 99.9% (Rt = 4.56 min).

**Ethyl 3-(4'-chlorophenyl)imidazo[2,1-*b*]thiazole-5-carboxylate (8h)**



Synthetic procedure was followed as described for compound **8a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **8h** (53.6 mg, 72%) as white solids. mp 156-157 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.98 (1H, s), 7.54-7.47 (4H, m), 7.44 (1H, s), 3.90 (2H, q, *J* = 7.0 Hz), and 0.95 (3H, t, *J* = 7.0 Hz); $^{13}$C-NMR (DMSO-*d6*, 75 MHz) δ 158.0, 154.6, 142.7, 133.7, 133.0, 129.9, 129.8, 128.0, 119.9, 114.2, 60.1, and 13.6; HRMS (ESI) *m/z*, calcd. for $C_{14}H_{11}O_2N_2ClNaS$ $(M+Na)^+$: 329.0122, found 329.0122 (Δ = 0.04 mmu); HPLC purity = 99.4% (Rt = 5.29 min).

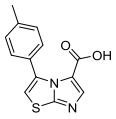
**5-Methyl-3-(4'-tolyl)imidazo[2,1-*b*]thiazole (3)**



To a solution of **8a** (100 mg, 0.349 mmol) in THF (5 ml) were added $AlCl_3$ (56.0 mg, 0.420 mmol) and $LiAlH_4$ (60.0 mg, 1.39 mmol) at 0 °C. After stirring at reflux for 1 day, the reaction was quenched by 4N NaOH (0.06 ml) at 0 °C. The resultant mixture was diluted with water (0.24 ml) and 4N NaOH (0.24 ml), filtered through a celite pad, and the filtrate was concentrated. The residue was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to give compound **3** (12.0 mg, 15%) as white solids. mp 108-110 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.46 (2H, d, *J* = 7.9 Hz), 7.31 (2H, d, *J* = 7.9 Hz), 7.05 (1H, s), 6.95 (1H, brs), 2.38 (3H, s), and 1.92 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 147.8, 139.2, 132.8, 132.5, 129.7, 128.9, 126.5, 122.9, 109.6, 20.9, and 11.0; HRMS (ESI) *m/z*, calcd. for $C_{13}H_{13}N_2S$ $(M+H)^+$: 229.0794, found 229.0795 (Δ =

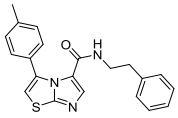
0.07 mmu); HPLC purity = 99.7% (Rt = 3.22 min).

**3-(4'-Toly)limidazo[2,1-*b*]thiazole-5-carboxylic acid (12)**



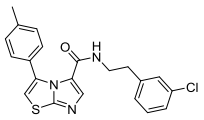
To a solution of **8a** (384 mg, 1.34 mmol) in THF (6 ml) and MeOH (6 ml) was added 1N NaOH (9 ml), and the mixture was stirred at room temperature for 13 h. The reaction mixture was concentrated, the residue was diluted with water (10 ml) and acidified with 1N HCl until pH 4. The resultant precipitates were filtered and washed with water and ether to give the acid **12** (342 mg, 99%) as white solids. mp 196-198 °C; $^{1}$H-NMR (DMSO-$d_6$, 300 MHz) δ 12.49 (1H, brs), 7.39 (1H, s), 7.32 (2H, d, *J* = 7.8 Hz), 7.29 (1H, s), 7.21 (2H, d, *J* = 7.8 Hz), and 2.34 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 159.2, 154.3, 142.0, 138.2, 134.5, 128.4, 128.1, 127.7, 120.8, 112.5, and 21.0; HRMS (ESI) *m/z*, calcd. for $C_{13}H_{11}O_2N_2S$ $(M+H)^+$: 259.0536, found 259.0540 (Δ = 0.38 mmu); HPLC purity = 99.5% (Rt = 3.14 min).

***N*-Phenethyl-3-(4'-tolyl)imidazo[2,1-*b*]thiazole-5-carboxamide (13a)**



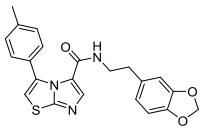
To a solution of **12** (64.8 mg, 0.251 mmol) in DMF (2 ml) were added HOBt (34.0 mg, 0.252 mmol), *i*-$Pr_2$NEt (0.151 ml, 0.876 mmol) and WSC·HCl (71.9 mg, 23.0 mmol). After stirring at room temperature overnight, the reaction mixture was quenched by sat. $NaHCO_3$ aq. (20 ml), and the aq. layer was extracted with ethyl acetate (30 ml x 2). The organic layer was washed with brine (50 ml), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography ($SiO_2$, chloroform / MeOH) to give compound **13a** (82.1 mg, 91%) as a colorless amorphous. $^{1}$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.40 (1H, t, *J* = 5.1 Hz), 7.57 (1H, s), 7.33-7.24 (5H, m), 7.23-7.18 (5H, m), 3.17 (2H, dt, *J* = 5.1, 7.3 Hz), 2.61 (2H, t, *J* = 7.3 Hz), and 2.33 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.4, 151.6, 139.4, 138.3, 136.5, 133.7, 128.6, 128.5, 128.3, 127.7, 126.9, 126.1, 124.0, 111.2, 79.2, 34.9, and 20.9; HRMS (ESI) *m/z*, calcd. for $C_{21}H_{20}ON_3S$ $(M+H)^+$: 362.1322, found 362.1325 (Δ = 0.32 mmu); HPLC purity = 99.4% (Rt = 4.50 min).

***N*-(3''-Chlorophenethyl)-3-(4'-tolyl)imidazo[2,1-*b*]thiazole-5-carboxamide (13b)**



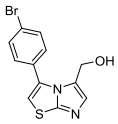
Synthetic procedure was followed as described for compound **13a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **13b** (82.4 mg, 77%) as a colorless amorphous. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.40 (1H, t, *J* = 5.5 Hz), 7.57 (1H, s), 7.35-7.22 (6H, m), 7.24-7.13 (3H, m), 3.19 (2H, dt, *J* = 5.5, 7.0 Hz), 2.63 (2H, d, *J* = 7.0 Hz), and 2.33 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.4, 151.6, 142.1, 138.2, 136.6, 133.7, 132.9, 130.1, 128.5, 128.5, 127.7, 127.5, 126.9, 126.1, 123.9, 111.3, 34.4, and 20.9; HRMS (ESI) *m/z*, calcd. for $C_{21}H_{18}ON_3ClNaS$ $(M+Na)^+$: 418.0751, found 418.0753 (Δ = 0.16 mmu); HPLC purity = 98.4% (Rt = 5.02 min).

**_N_-(2”-(Benzo[_d_][1”,3”]dioxol-5”-yl)ethyl)-3-(4’-tolyl)imidazo[2,1-_b_]thiazole-5-carboxamide (13c)**



Synthetic procedure was followed as described for compound **13a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **13c** (86.5 mg, 86%) as a colorless amorphous. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.35 (1H, t, *J* = 5.5 Hz), 7.57 (1H, s), 7.27 (2H, d, *J* = 7.7 Hz), 7.25 (1H, s), 7.19 (2H, d, *J* = 7.8 Hz), 6.82 (1H, d, *J* = 7.7 Hz), 6.74 (1H, s), 6.61 (1H, d, *J* = 7.8 Hz), 5.95 (2H, s), 3.13 (2H, dt, *J* = 5.5, 7.3 Hz), 2.52 (2H, t, *J* = 7.3 Hz), and 2.33 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 158.4, 151.6, 147.2, 145.5, 138.3, 136.5, 133.7, 133.2, 128.5, 127.7, 126.9, 124.0, 121.5, 111.3, 109.0, 108.1, 100.6, 34.6, and 20.9; HRMS (ESI) *m/z*, calcd. for $C_{22}H_{19}O_3N_3NaS$ $(M+Na)^+$: 428.1039, found 428.1040 (Δ = 0.07 mmu); HPLC purity = 99.2% (Rt = 4.40 min).

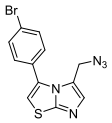
**{3-(4’-bromophenyl)imidazo[2,1-_b_]thiazol-5-yl}methanol (14)**



To a solution of **8i** (3.30 g, 9.39 mmol) in THF (90 ml) was added DIBAL-H (31.5 ml, 1.02 M in hexane solution, 32.1 mmol) at 0 °C. After stirring at the same temperature for 3.5 h, the reaction mixture was quenched by sat. Rochelle salts aq. (100 ml), and the mixture was stirred at room temperature overnight. The aq. layer was extracted with chloroform (150 ml x 2). The organic layer was washed with brine (200 ml), dried over $Na_2SO_4$ and concentrated. The residue was suspended in ethyl acetate (30 ml). The suspension was stirred at reflux for 1 h and cooled to 0 °C. The generated precipitates were filtered and washed with ethyl acetate to afford the alcohol **14** (2.74 g, 94%) as white solids. mp 202-203 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.68 (2H, d, *J* = 8.1 Hz), 7.59 (2H, d, *J* = 8.1 Hz), 7.20 (1H, t, *J* = 0.6 Hz), 7.16 (1H, s), 4.78 (1H, dt, *J* = 0.6, 5.1 Hz), and 4.23 (2H, d, *J*

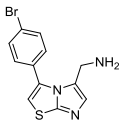
= 5.1 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 149.2, 134.0, 132.0, 131.3, 131.2, 129.0, 128.2, 123.0, 111.1, and 52.8; HRMS (ESI) *m/z*, calcd. for $C_{12}H_9ON_2BrNaS$ $(M+Na)^+$: 330.9511, found 330.9509 (Δ = –0.17 mmu); HPLC purity = 98.8% (Rt = 2.64 min).

**5-(azidomethyl)-3-(4'-bromophenyl)imidazo[2,1-*b*]thiazole (15)**



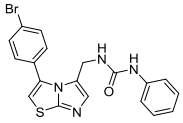
To a solution of **14** (999 mg, 3.23 mmol) in DMF (30 ml) were added DBU (0.964 ml, 6.46 mmol), and DPPA (1.45 ml, 6.46 mmol) at room temperature. After stirring at 60 °C for 6 h, the reaction mixture was quenched by sat. $NaHCO_3$ aq. (150 ml), and the aq. layer was extracted with ethyl acetate (100 ml x 2). The organic layer was washed with brine (150 ml), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography ($SiO_2$, chloroform / MeOH) to give compound **15** (812 mg, 75%) as white solids. mp 156-158 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.73 (2H, d, *J* = 8.4 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.34 (1H, s), 7.28 (1H, s), and 4.33 (2H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 150.6, 135.9, 131.6, 131.6, 131.5, 128.3, 123.5, 121.5, 115.2, 111.9, and 43.8; HRMS (ESI) *m/z*, calcd. for $C_{12}H_9N_5BrS$ $(M+H)^+$: 333.9757, found 333.9757 (Δ = 0.04 mmu); HPLC purity = 99.1% (Rt = 3.85 min).

**{3-(4'-bromophenyl)imidazo[2,1-*b*]thiazol-5-yl}methanamine (16)**



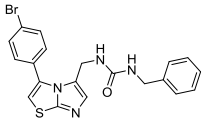
To a solution of **15** (350 mg, 1.05 mmol) in THF (10 ml) and water (0.189 ml, 10.5 mmol) was added $PPh_3$ (550 mg, 2.10 mmol) at room temperature. After stirring at 45 °C for 8.5 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography (amino $SiO_2$, chloroform / MeOH) to give compound **16** (290 mg, 90%) as white solids. mp 141-143 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.71 (2H, d, *J* = 8.3 Hz), 7.59 (2H, d, *J* = 8.3 Hz), 7.17 (1H, s), 7.10 (1H, s), 3.44 (2H, s), and 1.29 (2H, brs); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 148.3, 132.2, 131.5, 131.5, 131.4, 130.3, 129.0, 123.2, 110.8, and 36.5; HRMS (ESI) *m/z*, calcd. for $C_{12}H_{10}N_3BrNaS$ $(M+Na)^+$: 329.9671, found 329.9670 (Δ = –0.12 mmu); HPLC purity = 99.4% (Rt = 1.90 min).

**1-[{3'-(4''-bromophenyl)imidazo[2,1-*b*]thiazol-5'-yl}methyl]-3-phenylurea (17a)**



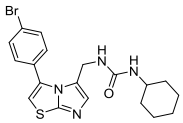
To a solution of **16** (40.0 mg, 0.13 mmol) in THF (1.0 ml) were added *i*-$Pr_2NEt$ (0.028 ml, 0.17 mmol) and PhNCO (0.017 ml, 0.16 mmol) at room temperature. After stirring at the same temperature for 2 h, the reaction mixture was quenched by sat. $NaHCO_3$ aq. (10 ml), and the aq. layer was extracted with ethyl acetate (20 ml x 2). The organic layer was washed with brine (20 ml), dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography ($SiO_2$, chloroform / MeOH) to give compound **17a** (52.9 mg, 96%) as white solids. mp 225-227 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.22 (1H, s), 7.64 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 7.5 Hz), 7.21-7.14 (4H, m), 6.87 (1H, dd, *J* = 7.1, 7.3 Hz), 6.15 (1H, t, *J* = 5.0 Hz), 4.02 (2H, d, *J* = 5.0 Hz), and 2.49 (1H, dd, *J* = 1.7, 1.8 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 154.4, 148.9, 140.1, 133.3, 131.5, 131.3, 128.6, 128.5, 125.4, 123.3, 121.2, 117.8, 111.3, and 34.4; HRMS (ESI) *m/z*, calcd. for $C_{19}H_{16}ON_4BrS$ $(M+H)^+$: 427.0223, found 427.0222 (Δ = –0.02 mmu); HPLC purity = 98.5% (Rt = 3.99 min).

**1-benzyl-3-[{3'-(4''-bromophenyl)imidazo[2,1-*b*]thiazol-5'-yl}methyl]urea (17b)**



Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17b** (57.7 mg, 100%) as white solids. mp 233-235 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.66 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 7.33-7.26 (2H, m), 7.24-7.15 (4H, m), 7.07 (1H, s), 6.23 (1H, t, *J* = 6.0 Hz), 6.02 (1H, t, *J* = 5.1 Hz), 4.12 (2H, d, *J* = 6.0 Hz), and 3.93 (2H, d, *J* = 5.1 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 157.3, 148.7, 140.7, 133.0, 131.5, 131.5, 131.3, 128.6, 128.2, 126.9, 126.6, 126.0, 123.2, 111.2, 42.8, and 34.8; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{17}ON_4BrNaS$ $(M+Na)^+$: 463.0199, found 463.0199 (Δ = 0.00 mmu); HPLC purity = 98.7% (Rt = 3.96 min).

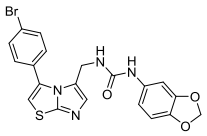
**1-[{3'-(4''-bromophenyl)imidazo[2,1-*b*]thiazol-5'-yl}methyl]-3-cyclohexylurea (17c)**



Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17c** (52.7 mg, 94%) as white solids. mp 227-229 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 7.66 (2H, d, *J* = 7.9 Hz), 7.53 (2H, d, *J* = 7.9 Hz), 7.20 (1H, s), 7.06 (1H, s), 5.71 (1H, t, *J* = 4.8 Hz), 5.54 (1H, d, *J* = 7.7 Hz), 3.91 (2H, d, *J* = 4.8 Hz), 3.28-3.13 (1H, m), 1.71-1.54 (4H, m), 1.54-1.43 (1H, m), and 1.30-0.92 (5H, m); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 156.5, 148.7, 133.1, 131.6, 131.5, 131.3, 128.6,

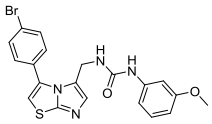
125.9, 123.2, 111.1, 47.7, 34.6, 33.2, 25.3, and 24.4; HRMS (ESI) *m/z*, calcd. for $C_{19}H_{21}ON_4BrNaS$ $(M+Na)^+$: 455.0512, found 455.0516 (Δ = 0.46 mmu); HPLC purity = 99.4% (Rt = 4.10 min).

**1-(benzo[*d*][1,3]dioxol-5'-yl)-3-[{3''-(4'''-bromophenyl)imidazo[2,1-*b*]thiazol-5''-yl}methyl]urea (17d)**



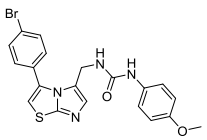
Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17d** (59.4 mg, 96%) as white solids. mp 228-230 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.10 (1H, s), 7.64 (2H, d, *J* = 8.3 Hz), 7.55 (2H, d, *J* = 8.3 Hz), 7.21 (1H, s), 7.13 (1H, s), 7.06 (1H, brs), 6.74 (1H, d, *J* = 8.3 Hz), 6.55 (1H, brd, *J* = 8.3 Hz), 6.07 (1H, t, *J* = 4.8 Hz), 5.91 (2H, s), and 4.00 (2H, d, *J* = 4.8 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 154.5, 148.9, 147.1, 141.5, 134.6, 133.3, 131.5, 131.5, 131.3, 128.5, 125.4, 123.3, 111.3, 110.4, 107.9, 100.7, 100.6, and 34.4; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{16}O_3N_4BrS$ $(M+H)^+$: 471.0121, found 471.0121 (Δ = 0.09 mmu); HPLC purity = 99.1% (Rt = 3.86 min).

**1-((3''-(4'''-bromophenyl)imidazo[2,1-*b*]thiazol-5''-yl)methyl)-3-(3'-methoxyphenyl)urea (17e)**



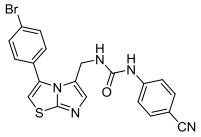
Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17e** (58.9 mg, 99%) as white solids. mp 194-196 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.26 (1H, s), 7.65 (2H, d, *J* = 8.3 Hz), 7.56 (2H, d, *J* = 8.3 Hz), 7.21 (1H, s), 7.14 (1H, s), 7.09 (1H, d, *J* = 8.3 Hz), 7.06-7.03 (1H, m), 6.76 (1H, brd, *J* = 8.3 Hz), 6.48-6.43 (1H, m), 6.16 (1H, t, *J* = 4.8 Hz), 4.01 (2H, d, *J* = 4.8 Hz), 3.68 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 159.6, 154.3, 148.9, 141.4, 133.2, 131.5, 131.3, 129.3, 128.5, 125.4, 123.3, 111.3, 110.1, 106.7, 103.4, 54.8, and 34.4; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{17}O_2N_4BrNaS$ $(M+Na)^+$: 479.0148, found 479.0149 (Δ = 0.10 mmu); HPLC purity = 99.3% (Rt = 4.05 min).

**1-((3''-(4'''-bromophenyl)imidazo[2,1-*b*]thiazol-5''-yl)methyl)-3-(4'-methoxyphenyl)urea (17f)**



Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17f** (53.3 mg, 90%) as white solids. mp 231-233 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.03 (1H, s), 7.65 (2H, d, *J* = 8.3 Hz), 7.55 (2H, d, *J* = 8.3 Hz), 7.21-7.13 (4H, m), 6.79 (2H, d, *J* = 8.3 Hz), 6.04 (1H, t, *J* = 5.0 Hz), 4.00 (2H, brd, *J* = 5.0 Hz), and 3.67 (3H, s); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 154.6, 154.0, 148.8, 133.2, 131.5, 131.3, 128.5, 125.6, 123.3, 119.6, 113.8, 111.2, 55.1, and 34.4; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{17}O_2N_4BrNaS$ $(M+Na)^+$: 479.0148, found 479.0152 (Δ = 0.38 mmu); HPLC purity = 99.3% (Rt = 3.88 min).

**1-((3”-(4”’-bromophenyl)imidazo[2,1-*b*]thiazol-5”-yl)methyl)-3-(4’-cyanophenyl)urea (17g)**




Synthetic procedure was followed as described for compound **17a**. The crude material was purified by flash column chromatography (amino $SiO_2$, hexane / ethyl acetate) to afford compound **17g** (59.8 mg, 100%) as white solids. mp 206-208 °C; $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ 8.68 (1H, s), 7.66-7.58 (4H, m), 7.54 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.6 Hz), 6.37 (1H, t, *J* = 4.6 Hz), and 4.06 (2H, d, *J* = 4.6 Hz); $^{13}$C-NMR (DMSO-$d_6$, 75 MHz) δ 153.7, 149.1, 144.6, 133.6, 133.1, 131.6, 131.5, 131.3, 128.5, 124.8, 123.3, 119.5, 117.6, 111.3, 102.5, and 34.4; HRMS (ESI) *m/z*, calcd. for $C_{20}H_{15}ON_5BrS$ $(M+H)^+$: 452.0175, found 452.0175 (Δ = –0.03 mmu); HPLC purity = 99.0% (Rt = 3.96 min).

**2) Purification method of recombinant IDO1 protein**

Human IDO1 was cloned into pET-28a vector (Novagen), expressed and purified by the published procedures[1)] except for using LB medium containing 0.75mM δ-aminolaevulinic acid. The level of heme incorporation achieved was ~78% based on an A406/A280 ratio of 2.2 for fully heme-incorporated IDO1[1)].

**3) Biological assay method**

IDO1 enzyme assay were performed as described before[2)] with some modifications. Briefly, test compounds were added to 150 μL of reaction mixture containing 50 nM recombinant IDO1, 100 μM L-Trp, 20 mM ascorbate, 10 μM methylene blue and 100 μg/mL catalase in 50 mM potassium phosphate buffer (pH 6.7). After incubation at room temperature for 30 min, the reactions were stopped by adding 30μL of 30% (w/v) trichloroacetic acid. Reaction mixtures were incubated at 65 °C for 15 min to convert *N*-formylkynurenine to kynurenine and then mixed with 180 μL of 2% (w/v) *para*-dimethylaminobenzaldehyde in acetic acid. The yellow color generated from the reaction

with kynurenine was measured at 480 nm using SPECTRA MAX M2 (Molecular Devices).

**4) X-ray crystallography**

Prior to crystallization with compounds, the sample buffer was exchanged to buffer C (25 mM MES pH 6.5, 25 mM NaCl, 2 mM compound) using a PD-10 Desalting Column (GE Healthcare) and concentrated by centrifugation. This exchange procedure to remove buffer contained TCEP and add compound at the same time was essential for IDO1-compound complex crystallization. IDO1 was concentrated to 20-40 mg/ml in a buffer containing 10 mM MES (pH 6.5), 25 mM NaCl, and 2 mM compound. Crystals of IDO1–compound complex were obtained by vapor diffusion method using reservoir solution (10% polyethylene glycol 20,000, 2% Dioxane, 100 mM Bicine, pH 9.0). Crystals were grown in a few days at 20°C in the space group $P2_12_12_1$. The crystals were cryoprotected by soaking in the reservoir with 30% xylitol. Diffraction data sets were collected using BL41XU beamline at SPring-8 (Hyogo, Japan) or PXI beamline at SLS (Villigen, Swiss). The data were reduced and scaled with HKL2000[3)] or iMosflm[4)] and SCALA[5)] of the CCP4 program suites[6)]. The X-ray crystal structures were solved by molecular replacement method with Molrep[7)] of the CCP4 program suites[6)] using the phenyl imidazole complex of IDO1 (PDB ID: 2D0T) as the search model. The structures were refined through an iterative procedure utilizing REFMAC[8)] followed by model building in COOT[9)]. The dictionary files for the ligands were prepared using AFITT (OpenEye Scientific Software, USA). Data collection and refinement statistics are shown in Table S1. All structural figures were prepared with PyMOL[10)].

Table S1. Crystallographic statistics.

| | Amg-1/IDO1 | **13b**/IDO1 |
|---|---|---|
| Data Collection | | |
| Beamline Synchrotron | BL41XU/SPring-8 | PXI/SLS |
| Resolution (Å) | 74.56-2.80(2.85-2.80) | 91.12-3.45(3.64-3.45) |
| Space Group | $P2_12_12_1$ | $P2_12_12_1$ |
| a, b, c (Å) | 84.81, 90.41, 131.76 | 84.08, 91.12, 135.69 |
| No. of reflections (total/unique) | 171317/25711 | 83106/14275 |
| Completeness (>0σ) (%) | 99.8(98.2) | 100.0(99.4) |
| I/σ | 15.0(2.1) | 3.0(2.2) |
| Rmerge | 0.113(0.698) | 0.096(0.245) |
| Average redundancy | 6.7(4.1) | 5.8(6.1) |
| Refinement | | |
| Resolution (Å) | 2.79 | 3.45 |
| Rcryst/Rfree (%) | 18.5/25.6 | 19.0/25.6 |
| No. of atoms | | |
| Non-hydrogen Protein | 5912 | 5912 |
| Non-hydrogen Hetero | 144 | 140 |
| Solvent | 8 | 0 |
| RMSD | | |
| Bond lengths (Å) | 0.012 | 0.005 |
| Bond angle (deg.) | 1.725 | 1.183 |
| PDB entry ID | 4PK5 | 4PK6 |
| Ramachandran analysis (%) | | |
| favored | 93.0 | 92.7 |
| allowed | 6.5 | 6.8 |
| outlier | 0.5 | 0.5 |

The values in parentheses are for the highest-resolution shell. *R*merge is $\Sigma |<I>- I |/\Sigma | I |$. *R*cryst is $\Sigma |Fo - Fc|/ \Sigma Fo$, where *F*o and *F*c are the observed and calculated amplitude, respectively; *R*free is the same statistic calculated over a subset, 5%, of all the data that have not been used for refinement. Ramachandran statistics as defined by RAMPAGE[11)]

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