# Supporting Information

## Discovery of *N*-substituted 3-amino-4-(3-boronopropyl)pyrrolidine-3-carboxylic acids as highly potent third generation inhibitors of human arginase I and II

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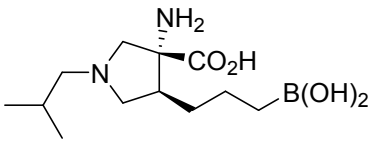
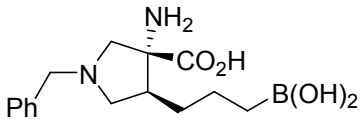
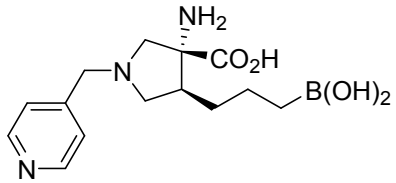
# $^{1}$H NMR, $^{13}$C NMR and ESI-LCMS Summary Data for Target Compounds 30-49



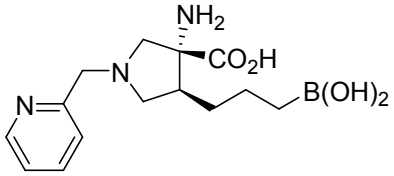

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-isobutylpyrrolidine-3-carboxylic acid dihydrochloride (30).** $^{1}$H NMR (600 MHz, $D_2O$): δ 4.05 - 3.94 (m, 3 H), 3.26 (t, *J* = 12.3 Hz, 1 H), 3.21 - 3.10 (m, 2 H), 2.71 - 2.62 (m, 1 H), 2.06 - 1.97 (m, 1 H), 1.69 - 1.61 (m, 1 H), 1.42 - 2.21 (m, 3 H), 0.93 (d, *J* = 6.1 Hz, 6 H), 0.76 - 0.65 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.38, 64.81, 63.42, 59.56, 57.58, 45.55, 28.94, 24.72, 22.03, 19.02, 13.98, 10.47. MS (CI): *m/z* for $C_{12}H_{25}BN_2O_4$: expected 272.2; found: 297.3 (M+i-PrOH-2$H_2O$+1), 255.2 (M-$H_2O$+1), 237.2 (M-2$H_2O$+1).



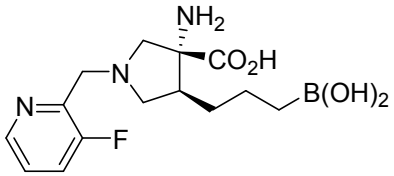

**(3R,4S)-3-amino-1-benzyl-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (31).** $^{1}$H NMR (600 MHz, $CDCl_3$): δ 7.54 -7.47 (m, 5 H), 4.57 (d, *J* =12.9 Hz, 1 H), 4.48 (d, *J* = 12.9 Hz, 1 H), 4.12 - 3.99 (m, 1 H), 3.92 - 3.75 (m, 1 H), 3.79 (dd, $J_1$ = 11.7 Hz, $J_2$ = 7.5Hz, 1 H), 3.50 - 3.27 (m, 1 H), 2.75 - 2.49 (m, 1 H), 1.72 - 1.63 (m, 1 H), 1.42 - 1.24 (m, 3 H), 0.80 - 0.67 (m, 2 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 170.46, 130.37, 130.20, 129.33, 129.18, 64.69, 59.34, 58.62, 56.60, 45.41, 29.01, 21.94, 13.92. MS (CI): *m/z* for $C_{15}H_{23}BN_2O_4$: expected 306.2; found: 331.2 (M+i-PrOH-2$H_2O$+1), 289.1 (M-$H_2O$+1), 271.1 (M-2$H_2O$+1).



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(pyridin-4-ylmethyl)pyrrolidine-3-carboxylic acid dihydrochloride (32).** $^{1}$H NMR (600 MHz, $D_2O$): δ 8.93 (d, $J$ = 6.8 Hz, 1 H), 8.27 (d, $J$ = 6.8 Hz, 1 H), 4.97 (d, $J$ = 14.1 Hz, 1 H), 4.89 (d, $J$ = 14.0 Hz, 1 H), 4.14 (d, $J$ = 13.1 Hz, 1 H), 3.98 - 3.92 (m, 2 H), 3.57 (t, $J$ = 11.7 Hz, 1 H), 2.80 - 2.73 (m, 1 H), 1.74 - 1.67 (m, 1 H), 1.43 - 1.28 (m, 3 H), 0.81 - 0.69 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.22, 149.53, 142.25, 128.39, 64.65, 59.37, 57.84, 57.30, 44.87, 29.19, 21.98, 13.95. MS (CI): *m/z* for $C_{14}H_{22}BN_3O_4$: expected 307.2; found: 332.2 (M+i-PrOH-2$H_2O$+1), 290.2 (M-$H_2O$+1), 272.1 (M-2$H_2O$+1).

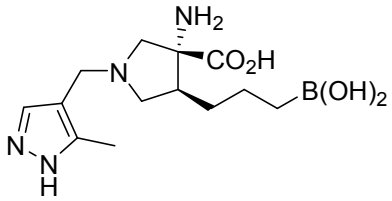



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(pyridin-2-ylmethyl)pyrrolidine-3-carboxylic acid dihydrochloride (33).** $^{1}$H NMR (600 MHz, $D_2O$): δ 8.79 (dd, $J_1$ = 5.6 Hz, $J_2$ = 1.6 Hz, 1 H), 8.46 (td, $J_1$ = 7.9 Hz, $J_2$ = 1.6 Hz, 1 H), 8.04 (d, $J$ = 8.0 Hz, 1 H), 7.95 (m, 1 H), 4.83 (d, $J$ = 14.7 Hz, 1 H), 4.76 (d, $J$ = 14.6 Hz, 1 H), 4.03 (d, $J$ = 12.9 Hz, 1 H), 3.89 - 383 (m, 2 H), 3.37 (t, $J$ = 11.4 Hz, 1 H), 2.74 - 2.66 (m, 1 H), 1.74 - 1.62 (m, 1 H), 1.42 - 1.26 (m, 3 H), 0.80 - 0.66 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.26, 146.08, 145.38, 144.64, 127.60, 127.14, 64.95, 59.33, 57.62, 55.94, 45.33, 29.43, 21.96, 13.91. MS (CI): *m/z* for $C_{14}H_{22}BN_3O_4$: expected 307.2; found: 332.2 (M+i-PrOH-2$H_2O$+1), 290.2 (M-$H_2O$+1), 272.1 (M-2$H_2O$+1).

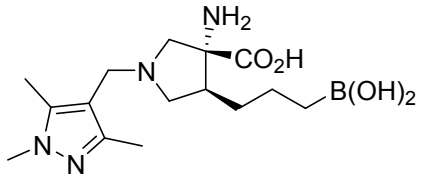



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-((3-fluoropyridin-2-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (34).** $^{1}$H NMR (600 MHz, $D_2O$): δ 8.43 (dt, $J_1$ = 4.8 Hz, $J_2$ = 1.3 Hz, 1 H), 7.70 (ddd, $J_1$ = 9.6 Hz, $J_2$ = 8.4 Hz, $J_3$ = 1.3 Hz, 1 H), 7.54 (dt, $J_1$ = 8.8 Hz, $J_2$ = 4.6 Hz, 1 H), 4.19 (d, $J$ = 13.5 Hz, 1 H), 4.06 - 3.93 (m, 2 H), 3.56 (t, $J$ =11.9 Hz, 1 H), 2.84 - 2.71 (m, 1 H), 1.74 - 1.67 (m, 1 H), 1.43 - 1.27 (m, 3 H), 0.80 - 0.67 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$):

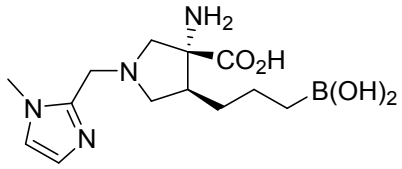
δ 169.97, 158.56, 156.85, 145.45, 145.42, 137.36, 137.26, 126.83, 126.80, 125.11, 124.99, 64.59, 59.04, 57.44, 53.97, 44.83, 29.07, 21.95, 13.89. MS (CI): *m/z* for $C_{14}H_{21}BFN_3O_4$: expected 325.2; found: 350.2 (M+i-PrOH-2$H_2O$+1), 308.2 (M-$H_2O$+1), 290.1 (M-2$H_2O$+1).



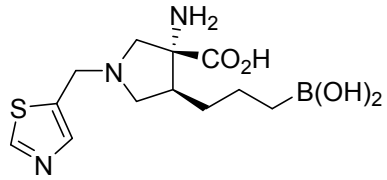

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-((5-methyl-1H-pyrazol-4-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (35).** $^1$H NMR (400 MHz, $D_2O$): δ 8.19 (s, 1 H), 4.55 (q, *J* = 14.2 Hz, 2 H), 4.07 (d, *J* = 13.2 Hz, 1 H), 3.88 (dd, $J_1$ = 11.5 Hz, $J_2$ = 7.6 Hz, 1 H), 3.90 - 3.76 (m, 1 H), 3.43 (t, *J* = 11.7 Hz, 1 H), 2.75 - 2.63 (m, 1 H), 2.47 (s, 3 H), 1.75 - 1.64 (m, 1 H), 1.47 - 1.26 (m, 3 H), 0.84 - 0.67 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 172.78, 148.26, 138.52, 111.27, 67.19, 60.66, 58.87, 50.36, 47.48, 31.71, 24.54, 16.48, 11.55. MS (CI): *m/z* for $C_{13}H_{23}BN_4O_4$: expected 310.2; found: 335.2 (M+i-PrOH-2$H_2O$+1), 293.2 (M-$H_2O$+1), 275.2 (M-2$H_2O$+1).



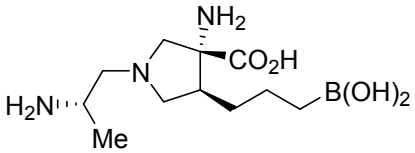

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-((1,3,5-trimethyl-1H-pyrazol-4-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (36).** $^1$H NMR (400 MHz, $D_2O$): 4.55 (d, *J* = 14.5 Hz, 1 H), 4.48 (d, *J* = 14.5 Hz, 1 H), 4.01 (d, *J* = 13.0 Hz, 1 H), 3.92 - 3.78 (m, 2 H), 3.87 (s, 3 H), 3.36 (t, *J* = 11.5 Hz, 1 H), 2.73 - 2.54 (m, 1 H), 2.43 (s, 3 H), 2.40 (s, 3 H), 1.76 - 1.64 (m, 1 H), 1.49 - 1.26 (m, 3 H), 0.85 - 0.69 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.31, 146.31, 146.01, 107.82, 64.63, 58.41, 56.32, 47.09, 45.08, 35.18, 29.12, 22.00, 13.93, 9.51, 9.35. MS (CI): *m/z* for $C_{15}H_{27}BN_4O_4$: expected 338.2; found: 361.2 (M+Na), 339.2 (M+1), 321.2 (M-2$H_2O$+1).



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-((1-methyl-1H-imidazol-2-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (37).** $^{1}$H NMR (400 MHz, $D_2O$): 7.53 - 7.41 (m, 2 H), 4.44 (q, *J* = 15.6 Hz, 2 H), 3.91 (s, 3 H), 3.61 - 3.44 (m, 3 H), 2.79 (t, *J* = 10.1 Hz, 1 H), 2.56 - 2.43 (m, 1 H), 1.68 - 1.52 (m, 1 H), 1.49 - 1.26 (m, 3 H), 0.77 (d, *J* = 8.9 Hz, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.59, 138.36, 124.99, 119.68, 65.47, 59.73, 57.86, 46.23, 46.00, 34.76, 29.83, 22.01, 13.92. MS (CI): *m/z* for $C_{13}H_{23}BN_4O_4$: expected 310.2; found: 335.2 (M+i-PrOH-2$H_2O$+1), 293.2 (M-$H_2O$+1), 275.1 (M-2$H_2O$+1).

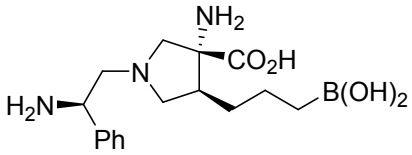


**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(thiazol-2-ylmethyl)pyrrolidine-3-carboxylic acid dihydrochloride (38).** $^{1}$H NMR (600 MHz, $D_2O$): 9.69 - 9.55 (m, 1 H), 8.40 - 8.29 (m, 1 H), 4.96 (d, *J* = 14.4 Hz, 1 H), 4.91 (d, *J* = 14.4 Hz, 1 H), 4.13 (d, *J* = 13.3 Hz, 1 H), 3.92 (dd, $J_1$ = 11.6 Hz, $J_2$ = 7.7 Hz, 1 H), 3.87 (d, *J* = 13.3 Hz, 1 H), 3.56 - 3.45 (m, 1 H), 2.80 - 2.67(m, 1 H), 1.73 - 1.62 (m, 1 H), 1.41 - 1.24 (m, 3 H), 0.77 - 0.64 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 169.70, 159.96, 141.44, 128.03, 64.46, 58.23, 56.73, 49.94, 44.87. MS (CI): *m/z* for $C_{12}H_{20}BN_3O_4S$: expected 313.1; found: 338.6 (M+i-PrOH-2$H_2O$+1), 296.5 (M-$H_2O$+1), 278.4 (M-2$H_2O$+1).

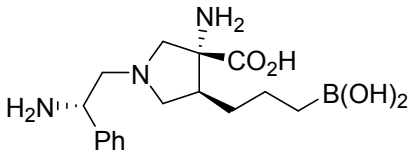


**(3R,4S)-3-amino-1-((S)-2-aminopropyl)-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (39).** $^{1}$H NMR (600 MHz, $D_2O$): δ 4.17 (d, *J* = 13.2 Hz, 1 H), 4.07 (dd, $J_1$ =11.6 Hz, $J_2$ = 7.8 Hz, 1 H), 4.00 (d, *J* = 13.3 Hz, 1 H), 3.85 (h, *J* = 6.7 Hz, 1 H), 3.72 (dd, $J_1$ =13.4 Hz,

$J_2$ = 5.9 Hz, 1 H), 3.64 (dd, $J_1$ = 13.5 Hz, $J_2$ = 7.2 Hz, 1 H), 3.51 (t, $J$ =11.8 Hz, 1 H), 2.84 - 2.76 (m, 1 H), 1.72 - 1.65 (m, 1 H), 1.44 (d, $J$ = 6.7 Hz, 3 H), 1.43 - 1.24 (m, 3 H), 0.81 - 0.66 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.13, 64.63, 59.96, 58.11, 58.09, 45.03, 43.89, 28.99, 21.96, 16.49, 13.92. MS (CI): *m/z* for $C_{11}H_{24}BN_3O_4$: expected 273.19; found 298.6 (M+i-PrOH-2$H_2O$+1), 281.6 (M+i-PrOH-2$H_2O$-NH2+1), 256.5 (M-$H_2O$+1), 238.5 (M-2$H_2O$+1), 221.4 (M-2$H_2O$-$NH_2$+1).

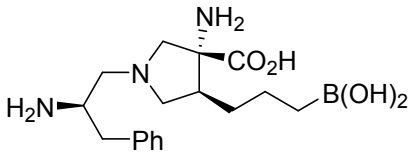



**(3R,4S)-3-amino-1-((R)-2-amino-2-phenylethyl)-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (40).** $^1$H NMR (600 MHz, $D_2O$): δ 7.61 - 7.54 (m, 5 H), 4.86 (dd, $J_1$ = 10.2 Hz, $J_2$ = 4.9 Hz, 1 H), 4.13 (dd, $J_1$ = 13.1 Hz, $J_2$ = 10.2 Hz, 1 H), 4.08 (dd, $J_1$ = 13.1 Hz, $J_2$ = 4.9 Hz, 1 H), 4.03 (d, $J$ = 12.9 Hz, 1 H), 3.79 (d, $J$ = 12.7 Hz, 1 H), 3.74 (dd, $J_1$ = 11.5 Hz, $J_2$ = 7.9 Hz, 1 H), 3.30 (t, $J$ =11.5 Hz, 1 H), 2.63 - 2.56 (m, 1 H), 1.66 - 1.56 (m, 1 H), 1.32 - 1.22 (m, 2 H), 1.22 - 1.13 (m, 1 H), 0.74 - 0.63 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.27, 131.18, 131.12, 130.14, 127.81, 64.31, 59.39, 58.73, 56.78, 51.11, 44.44, 29.26, 21.87, 13.86. MS (CI): *m/z* for $C_{16}H_{26}BN_3O_4$: expected 335.20; found 343.7 (M+i-PrOH-2$H_2O$-$NH_2$+1), 318.6 (M-$H_2O$+1), 301.6 (M-$H_2O$-$NH_2$+1), 283.5. (M-2$H_2O$-$NH_2$+1).

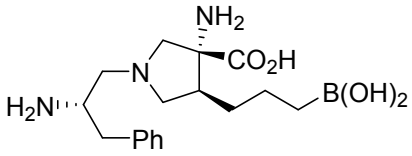



**(3R,4S)-3-amino-1-((S)-2-amino-2-phenylethyl)-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (41**). $^1$H NMR (600 MHz, $D_2O$): δ 7.65 - 7.52 (m, 5 H), 4.85 (dd, $J_1$ = 10.7 Hz, $J_2$ = 4.6 Hz, 1 H), 4.18 (dd, $J_1$ = 12.9 Hz, $J_2$ = 10.8 Hz, 1 H), 4.08 (dd, $J_1$ = 13.0 Hz, $J_2$ = 4.6 Hz, 1 H), 3.95 - 3.86 (m, 2 H), 3.73 (d, $J$ = 13.1 Hz, 1 H), 3.46 (t, $J$ =11.7 Hz, 1 H), 2.63 - 2.52 (m, 1 H), 1.69 - 1.60 (m, 1 H), 1.41 - 1.20 (m, 3 H), 0.78 - 0.65 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.14, 131.18, 130.86, 130.17, 127.87, 64.39, 60.43, 57.74, 56.87, 50.89, 44.71, 29.16, 21.95,

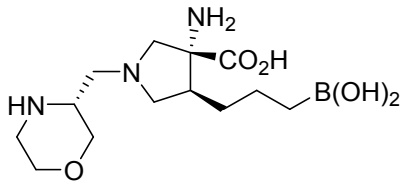
13.94. MS (CI): *m/z* for $C_{16}H_{26}BN_3O_4$: expected 335.20; found 343.7 (M+i-PrOH-$2H_2O$-$NH_2$+1), 318.6 (M-$H_2O$+1), 301.6 (M-$H_2O$-$NH_2$+1), 283.5 (M-$2H_2O$-$NH_2$+1).



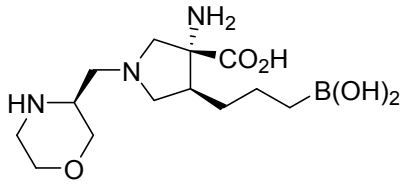

**(3R,4S)-3-amino-1-((R)-2-amino-3-phenylpropyl)-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (42).** $^1$H NMR (600 MHz, $D_2O$): δ 7.49 - 7.39 (m, 3 H), 7.39 - 7.30 (m, 2 H), 4.02 - 3.87 (m, 2 H), 3.87 - 3.77 (m, 1 H), 3.75 - 3.56 (m, 3 H), 3.11 (d, *J* = 7.4 Hz, 2 H), 3.04 (t, *J* = 10.9 Hz, 1 H), 2.64 - 2.52 (m, 1 H), 1.69 - 1.57 (m, 1 H), 1.40 - 1.26 (m, 2 H), 1.26 - 1.11 (m, 1 H), 0.76 (t, *J* = 7.5 Hz, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.05, 133.57, 129.54, 129.39, 128.17, 64.44, 59.69, 57.95, 57.18, 49.24, 44.64, 36.76, 29.21, 21.92, 13.90. MS (CI): *m/z* for $C_{17}H_{28}BN_3O_4$: expected 349.22; found 374.7 (M+i-PrOH-$2H_2O$+1), 332.6 (M-$H_2O$+1), 314.6 (M-$2H_2O$+1), 297.5 (M-$2H_2O$-$NH_2$+1).



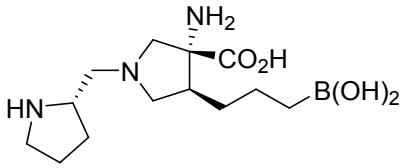

**(3R,4S)-3-amino-1-((S)-2-amino-3-phenylpropyl)-4-(3-boronopropyl)pyrrolidine-3-carboxylic acid dihydrochloride (43).** $^1$H NMR (600 MHz, $D_2O$): δ 7.46 - 7.41 (m, 2 H), 7.40 - 7.37 (m, 1 H), 7.36 (d, *J* = 7.5 Hz, 2 H), 3.98 (qd, $J_1$ = 7.4 Hz, $J_2$ = 3.9 Hz, 1 H), 3.92 (d, *J* = 12.8 Hz, 1 H), 3.78 (dd, $J_1$ = 14.2 Hz, $J_2$ = 6.8 Hz, 2 H), 3.66 (dd, $J_1$ = 14.3 Hz, $J_2$ = 3.9 Hz, 1 H), 3.62 (brs, 1 H), 3.43 (t, *J* = 11.5 Hz, 1 H), 3.11 (d, *J* = 7.5 Hz, 2 H), 2.70 - 2.58 (m, 1 H), 1.68 - 1.59 (m, 1 H), 1.39 - 1.18 (m, 3 H), 0.76 - 0.64 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.08, 133.51, 129.47, 129.40, 128.22, 64.41, 59.71, 57.64, 57.07, 49.40, 44.20, 36.62, 29.22, 21.94, 13.84. MS (CI): *m/z* for $C_{17}H_{28}BN_3O_4$: expected 349.22; found 374.8 (M+i-PrOH-$2H_2O$+1), 332.7 (M-$H_2O$+1), 314.6 (M-$2H_2O$+1), 297.6 (M-$2H_2O$-$NH_2$+1).



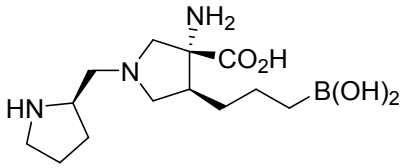

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((R)-morpholin-3-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (44).** $^{1}$H NMR (400 MHz, $D_2O$): δ 4.18 (dd, $J_1$ = 13.0 Hz, $J_2$ = 3.3 Hz, 1 H), 4.05 (dt, $J_1$ = 13.2 Hz, $J_2$ = 3.7 Hz, 1 H), 3.96 - 3.82 (m, 4 H), 3.77 (dd, $J_1$ = 12.9 Hz, $J_2$ = 8.8 Hz, 2 H), 3.65 - 3.56 (m, 2 H), 3.47 (dt, $J_1$ = 13.5 Hz, $J_2$ = 3.3 Hz, 1 H), 3.42 - 3.28 (m, 2 H), 2.71 - 2.56 (m, 1 H), 1.73 - 1.60 (m, 1 H), 1.49 - 1.25 (m, 3 H), 0.87 - 0.69 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 172.74, 68.07, 67.07, 65.71, 62.59, 60.54, 56.00, 52.50, 47.35, 45.16, 31.90, 24.55, 16.51. MS (CI): *m/z* for $C_{13}H_{26}BN_3O_5$: expected 315.20; found 340.7 (M+i-PrOH_2$H_2O$+1), 298.5 (M-$H_2O$+1), 280.5 (M-2$H_2O$+1).



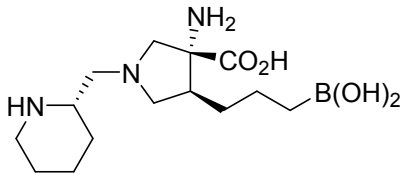

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((S)-morpholin-3-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (45**). $^{1}$H NMR (400 MHz, $D_2O$): δ 4.17(dd, $J_1$ = 13.0 Hz, $J_2$ = 3.3 Hz, 1 H), 4.05 (dt, $J_1$ = 13.2 Hz, $J_2$ = 3.7 Hz, 1 H), 3.99 - 3.80 (m, 4 H), 3.80 - 3.66 (m, 2 H), 3.65 - 3.51 (m, 2 H), 3.46 (dt, $J_1$ = 13.3 Hz, $J_2$ = 3.3 Hz, 1 H), 3.38 - 3.20 (m, 2 H), 2.68 - 2.55 (m, 1 H), 1.72 - 1.60 (m, 1 H), 1.48 - 1.26 (m, 3 H), 0.86 - 0.69 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 172.69, 68.20, 67.28, 65.70, 62.10, 61.14, 56.03, 52.60, 47.37, 45.17, 31.82, 24.55, 16.49. MS (CI): *m/z* for $C_{13}H_{26}BN_3O_5$: expected 315.20; found 340.6 (M+i-PrOH-2$H_2O$+1), 298.5 (M-$H_2O$+1), 280.5 (M-2$H_2O$+1.



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((S)-pyrrolidin-2-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (46).** $^1$H NMR (400 MHz, $D_2O$): δ 4.10 (d, $J$ = 12.7 Hz, 1 H), 4.07 - 3.99 (m, 2 H), 3.94 - 3.84 (m, 2 H), 3.80 (dd $J_1$ = 13.7 Hz, $J_2$ = 6.2 Hz, 1 H), 3.56 (t, $J$ = 11.3 Hz, 1 H), 3.45 (dd $J_1$ = 8.3 Hz, $J_2$ = 6.5 Hz, 2 H), 2.78 - 2.67 (m, 1 H), 2.48 - 2.38 (m, 1 H), 2.25 - 2.00 (m, 2 H), 1.96 - 1.83 (m, 1 H), 1.79 - 1.67 (m, 1 H), 1.53 - 1.27 (m, 3 H), 0.90 - 0.72 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.33, 64.51, 59.74, 57.75, 56.07, 55.56, 46.14, 44.69, 29.27, 28.75, 22.75, 22.00, 13.97. MS (M+i-PrOH-2$H_2O$+1): 324.5, (M-$H_2O$+1): 282.4, (M-2$H_2O$+1): 264.3.

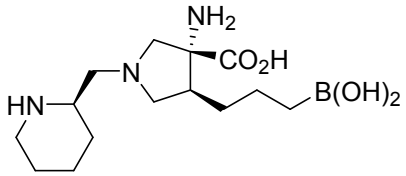



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((R)-pyrrolidin-2-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (47).** $^1$H NMR (400 MHz, $D_2O$): δ 4.12 (d, $J$ = 12.6 Hz, 1 H), 4.09 - 4.00 (m, 2 H), 3.94 - 3.84 (m, 2 H), 3.80 (dd $J_1$ = 13.8 Hz, $J_2$ = 5.7 Hz, 1 H), 3.54 (t, $J$ = 11.4 Hz, 1 H), 3.49 - 3.42 (m, 2 H), 2.77 - 2.68 (m, 1 H), 2.47 - 2.38 (m, 1 H), 2.23 - 2.02 (m, 2 H), 1.94 - 1.82 (m, 1 H), 1.78 - 1.67 (m, 1 H), 1.52 - 1.28 (m, 3 H), 0.88 - 0.72 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.19, 64.56, 59.47, 58.20, 56.16, 55.52, 46.19, 44.78, 29.16, 28.87, 22.69, 22.00, 13.97. MS (M+i-PrOH-2$H_2O$+1): 324.5, (M-$H_2O$+1): 282.4, (M-2$H_2O$+1): 264.3.



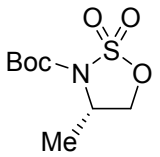

**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((S)-piperidin-2-yl)methyl)pyrrolidine-3-carboxylic acid dihydrochloride (48).** $^1$H NMR (400 MHz, $D_2O$): δ 4.10 (d, $J$ = 12.8 Hz, 1H), 4.04 (dd, $J_1$ = 11.3 Hz, $J_2$ = 7.8 Hz, 1 H), 3.98 (d, $J$ = 12.9 Hz, 1 H), 3.80 - 3.60 (m, 3 H), 3.56 - 3.46 (m, 2 H), 3.08 (td, $J_1$ = 12.6 Hz, $J_2$ = 3.1 Hz, 1 H), 2.83 - 2.72(m, 1 H), 2.18 - 2.07 (m, 1 H), 1.98 - 1.87 (m, 2 H), 1.79 - 1.55 (m, 4 H), 1.52 - 1.29 (m, 3 H), 0.88 - 0.72 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ

170.15, 64.50, 59.92, 57.96, 57.36, 52.19, 45.07, 44.72, 29.19, 26.52, 21.98, 21.10, 20.75, 13.93. MS (CI): *m/z* for $C_{14}H_{28}BN_3O_4$: expected 313.21; found 338.5 (M+i-PrOH-$2H_2O$+1), 296.2 (M-$H_2O$+1), 278.2 (M-$2H_2O$+1).

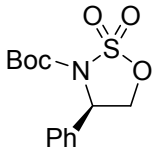



**(3R,4S)-3-amino-4-(3-boronopropyl)-1-(((R)-piperidin-2-yl)methyl)pyrrolidine-3-carboxylic acid (49).** $^1$H NMR (400 MHz, $D_2O$): δ 4.09 (d, $J$ = 12.6 Hz, 1 H), 4.02 (dd, $J_1$ = 11.3 Hz, $J_2$ = 7.9 Hz, 1 H), 3.85 (d, $J$ = 12.5 Hz, 1 H), 3.77 - 3.57 (m, 3 H), 3.49 (dd, $J_1$ = 12.5 Hz, $J_2$ = 11.3 Hz, 2 H), 3.08 (td, $J_1$ =12.6 Hz, $J_2$ = 3.0 Hz, 1 H), 2.76 - 2.64 (m, 1 H), 2.18 - 2.07 (m, 1 H), 1.98 - 1.88 (m, 2 H), 1.78 - 1.56 (m, 4 H), 1.52 - 1.29 (m, 3 H), 0.89 - 0.73 (m, 2 H); $^{13}$C NMR (600 MHz, $D_2O$): δ 170.27, 64.66, 59.36, 58.72, 57.55, 52.22, 45.10, 44.63, 29.23, 26.67, 22.00, 21.10, 20.75, 13.96. MS (CI): *m/z* for $C_{14}H_{28}BN_3O_4$: expected 313.21; found 338.5 (M+i-PrOH-$2H_2O$+1), 296.2 (M-$H_2O$+1), 278.2 (M-$2H_2O$+1).

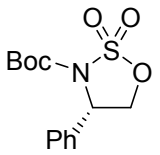
# $^{1}$H NMR, $^{13}$C NMR and LC/MS Summary Data for sulfamate Intermediates




***tert*-Butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide**. $^{1}$H NMR (600 MHz, $CDCl_3$): δ 4.66 (dd, $J_1$ = 9.1 Hz, $J_2$ = 6.0 Hz, 1 H), 4.41 (d, $J_1$ = 6.3 Hz, $J_2$ = 2.9 Hz, 1 H), 4.19 (dd, $J_1$ = 9.1 Hz, $J_2$ = 2.9 Hz, 1 H), 1.55 (s, 9 H), 1.50 (d, $J$ = 6.4 Hz, 3 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 148.59, 85.52, 71.44, 53.94, 28.09, 18.47. Anal. Calcd for $C_8H_{15}NO_5S$: C 40.50; H, 6.37; N, 5.90. Found C, 40.77; H, 6.36; N, 5.96.

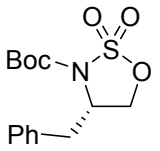



***tert*-Butyl (R)-4-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide.** $^{1}$H NMR (600 MHz, $CDCl_3$): δ 7.44 - 7.40 (m, 4 H), 7.40 - 7.36 (m, 1 H), 5.29 (dd, $J_1$ = 6.7 Hz, $J_2$ = 4.2 Hz, 1 H), 4.87 (dd, $J_1$ = 9.3 Hz, $J_2$ = 6.7 Hz, 1 H), 4.40 (dd, $J_1$ = 9.3 Hz, $J_2$ = 4.2 Hz, 1 H), 1.43 (s, 9 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 148.39, 137.06, 129.38, 129.27, 126.28, 85.71, 71.93, 60.89, 27.95. Anal. Calcd for $C_{13}H_{17}NO_5S$: C 52.16; H, 5.72; N, 4.68. Found C, 52.24; H, 5.83; N, 4.72.

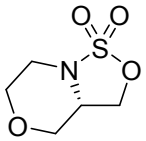



***tert*-Butyl (S)-4-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide.** $^{1}$H NMR (600 MHz, $CDCl_3$): δ 7.44 -7.40 (m, 4 H), 7.40 -7.36 (m, 1 H), 5.29 (dd, $J_1$ = 6.7 Hz, $J_2$ = 4.3 Hz, 1 H), 4.87 (dd, $J_1$ = 9.3 Hz, $J_2$ = 6.7 Hz, 1 H), 4.40 (dd, $J_1$ = 9.3 Hz, $J_2$ = 4.3 Hz, 1 H), 1.43 (s, 9 H); $^{13}$C NMR

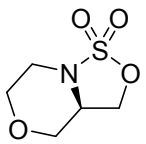
(600 MHz, $CDCl_3$): δ 148.39, 137.06, 129.38, 129.27, 126.28, 85.71, 71.93, 60.89, 27.95. Anal. Calcd for $C_{13}H_{17}NO_5S$: C 52.16; H, 5.72; N, 4.68. Found C, 52.19; H, 5.70; N, 4.69.



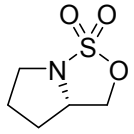

**tert-Butyl (S)-4-benzyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide.** $^1$H NMR (600 MHz, $CDCl_3$): δ 7.35 (dd, $J_1$ = 8.0 Hz, $J_2$ = 6.7 Hz, 2 H), 7.31 - 7.27 (m, 1 H), 7.23 (dd, $J_1$ = 7.0 Hz, $J_2$ = 1.7 Hz, 2 H), 4.50 - 4.39 (m, 2 H), 4.32 (d, $J$ = 7.7 Hz, 1 H), 3.41 - 3.32 (m, 1 H), 2.92 (dd, $J_1$ = 13.5 Hz, $J_2$ = 10.0 Hz, 1 H), 1.56 (s, 9 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 148.61, 135.25, 129.58, 129.23, 127.64, 85.75, 77.16, 68.85, 58.69, 37.97, 28.08. Anal. Calcd for $C_{14}H_{19}NO_5S$: C 53.66; H, 6.11; N, 4.47. Found C, 53.71; H, 6.05; N, 4.52.



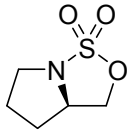

**(S)-tetrahydro-3H-[1,2,3]oxathiazolo[4,3-c][1,4]oxazine 1,1-dioxide.** $^1$H NMR (600 MHz, CDCl3): δ 4.58 (dd, $J_1$ = 8.1 Hz, $J_2$ = 6.4 Hz, 1H), 4.30 (dd, $J_1$ = 9.3 Hz, $J_2$ = 8.1 Hz, 1 H), 4.01 (dd, $J_1$ = 11.6 Hz, $J_2$ = 3.4 Hz, 1 H), 3.87 (dt, $J_1$ = 11.9 Hz, $J_2$ = 3.7 Hz, 1 H), 3.82 (dddd, $J_1$ = 9.5 Hz, $J_2$ = 7.7 Hz, $J_3$ = 6.4 Hz, $J_4$ = 3.4 Hz, 1 H), 3.74 (ddd, $J_1$ = 12.0 Hz, $J_2$ = 9.0 Hz, $J_3$ = 3.2 Hz, 1 H), 3.60 (dd, $J_1$ = 11.6 Hz, $J_2$ = 7.8 Hz, 1 H), 3.36 (dt, $J_1$ = 12.0 Hz, $J_2$ = 3.7 Hz, 1 H), 3.15 (ddd, $J_1$ = 12.2 Hz, $J_2$ = 9.0 Hz, $J_3$ = 3.3 Hz, 1 H); $^{13}$C NMR (600 MHz, CDCl3): δ 69.88, 66.65, 64.79, 54.31, 43.56. Anal. Calcd for $C_5H_9NO_4S$: C 33.51; H, 5.06; N, 7.82. Found C, 33.75; H, 5.05; N, 7.81.



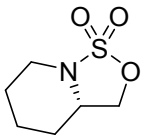
**(R)-tetrahydro-3H-[1,2,3]oxathiazolo[4,3-c][1,4]oxazine 1,1-dioxide.** $^1$H NMR (600 MHz, $CDCl_3$): δ 4.58 (dd, $J_1$ = 8.1 Hz, $J_2$ = 6.4 Hz, 1 H), 4.30 (dd, $J_1$ = 9.3 Hz, $J_2$ = 8.1 Hz, 1 H), 4.01 (dd, $J_1$ = 11.6 Hz, $J_2$ = 3.4 Hz, 1 H), 3.87 (dt, $J_1$ = 11.9 Hz, $J_2$ = 3.7 Hz, 1 H), 3.82 (dddd, $J_1$ = 9.5 Hz, $J_2$ = 7.7 Hz, $J_3$ = 6.4 Hz, $J_4$ = 3.4 Hz, 1 H), 3.74 (ddd, $J_1$ = 12.0 Hz, $J_2$ = 9.0 Hz, $J_3$ = 3.2 Hz, 1 H), 3.60 (dd, $J_1$ = 11.6 Hz, $J_2$ = 7.8 Hz, 1 H), 3.36 (dt, $J_1$ = 12.0 Hz, $J_2$ = 3.7 Hz, 1 H), 3.15 (ddd, $J_1$ = 12.2 Hz, $J_2$ = 9.0 Hz, $J_3$ = 3.3 Hz, 1 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 69.88, 66.65, 64.79, 54.31, 43.56. Anal. Calcd for $C_5H_9NO_4S$: C 33.51; H, 5.06; N, 7.82. Found C, 33.79; H, 4.91; N, 7.94.



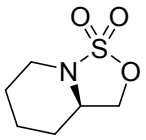

**(S)-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxathiazole 1,1-dioxide.** $^1$H NMR (600 MHz, $CDCl_3$): δ 4.55(dd, $J_1$ = 8.7 Hz, $J_2$ = 6.9 Hz, 1 H), 4.30 - 4.25 (m, 1 H), 4.04 (dd, $J_1$ = 8.8 Hz, $J_2$ = 6.0 Hz, 1 H), 3.67 (dt, $J_1$ = 11.5 Hz, $J_2$ = 6.3 Hz, 1 H), 3.26 (dt, $J_1$ = 11.2 Hz, $J_2$ = 7.1 Hz, 1 H), 2.22 - 2.13 (m, 1 H), 2.00 - 1.90 (m, 2 H), 1.86 - 1.77 (m, 1 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 71.88, 62.57, 51.17, 31.35, 25.21.




**(R)-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]oxathiazole 1,1-dioxide**. $^1$H NMR (600 MHz, $CDCl_3$): δ 4.54 (dd, $J_1$ = 8.7 Hz, $J_2$ = 6.9 Hz, 1 H), 4.30 - 4.24 (m, 1 H), 4.04 (dd, $J_1$ = 8.8 Hz, $J_2$ = 6.0 Hz, 1 H), 3.67 (dt, $J_1$ = 12.0 Hz, $J_2$ = 6.3 Hz, 1 H), 3.26 (dt, $J_1$ = 11.1 Hz, $J_2$ = 7.1 Hz, 1 H), 2.22 - 2.14 (m, 1 H), 2.00 - 1.89 (m, 2 H), 1.85 - 1.78 (m, 1 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 71.88, 62.56, 51.16, 31.32, 25.19.



**(S)-hexahydro-[1,2,3]oxathiazolo[3,4-a]pyridine 1,1-dioxide**. $^{1}$H NMR (600 MHz, $CDCl_3$): δ 4.57(t, $J$ = 6.8 Hz, 1 H), 4.18 (ddd, $J_1$ = 9.7 Hz, $J_2$ = 7.7 Hz, $J_3$ = 1.8 Hz, 1 H), 3.56 (brd, $J$ = 11.2 Hz, 1 H), 3.49 - 3.42 (m, 1 H), 2.77 (td, $J_1$ = 11.9 Hz, $J_1$ = 2.7 Hz, 1 H), 1.95 - 1.88 (m, 2 H), 1.83 (brd, $J$ = 13.6 Hz, 1 H), 1.68 - 1.59 (m, 1 H), 1.49 - 1.40 (m, 1 H), 1.40 - 1.31 (m, 1 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 73.73, 57.27, 43.77, 27.87, 23.49, 22.02.



**(R)-hexahydro-[1,2,3]oxathiazolo[3,4-a]pyridine 1,1-dioxide**. $^{1}$H NMR (600 MHz, $CDCl_3$): δ 4.57(t, $J$ = 6.8 Hz, 1 H), 4.18 (ddd, $J_1$ = 9.7 Hz, $J_2$ = 7.7 Hz, $J_3$ = 1.8 Hz, 1 H), 3.56 (brd, $J$ = 11.2 Hz, 1 H), 3.49 - 3.42 (m, 1 H), 2.77 (td, $J_1$ = 11.9 Hz, $J_1$ = 2.7 Hz, 1 H), 1.95 - 1.88 (m, 2 H), 1.83 (brd, $J$ = 13.6 Hz, 1 H), 1.68 - 1.59 (m, 1 H), 1.49 - 1.40 (m, 1 H), 1.40 - 1.31 (m, 1 H); $^{13}$C NMR (600 MHz, $CDCl_3$): δ 73.73, 57.27, 43.77, 27.87, 23.49, 22.02.

# Analytical Purity: HPLC Summary Data

Analytical purity was determined using a Gilson 215 robotic liquid handler equipped with a Gilson ELSD detector and an Agilent Eclipse XDB-Phenyl analytical HPLC column (3.5 μm; 4.6 x 150 mm). The standard methods used water (Phase A) with acetonitrile (Phase B), each containing 0.1% TFA for the specified gradient. The measured purities, retention times and method used for each test compound are listed in the table 1 below. Chromatograms are provided in pages S5-S19.

**Table S1**

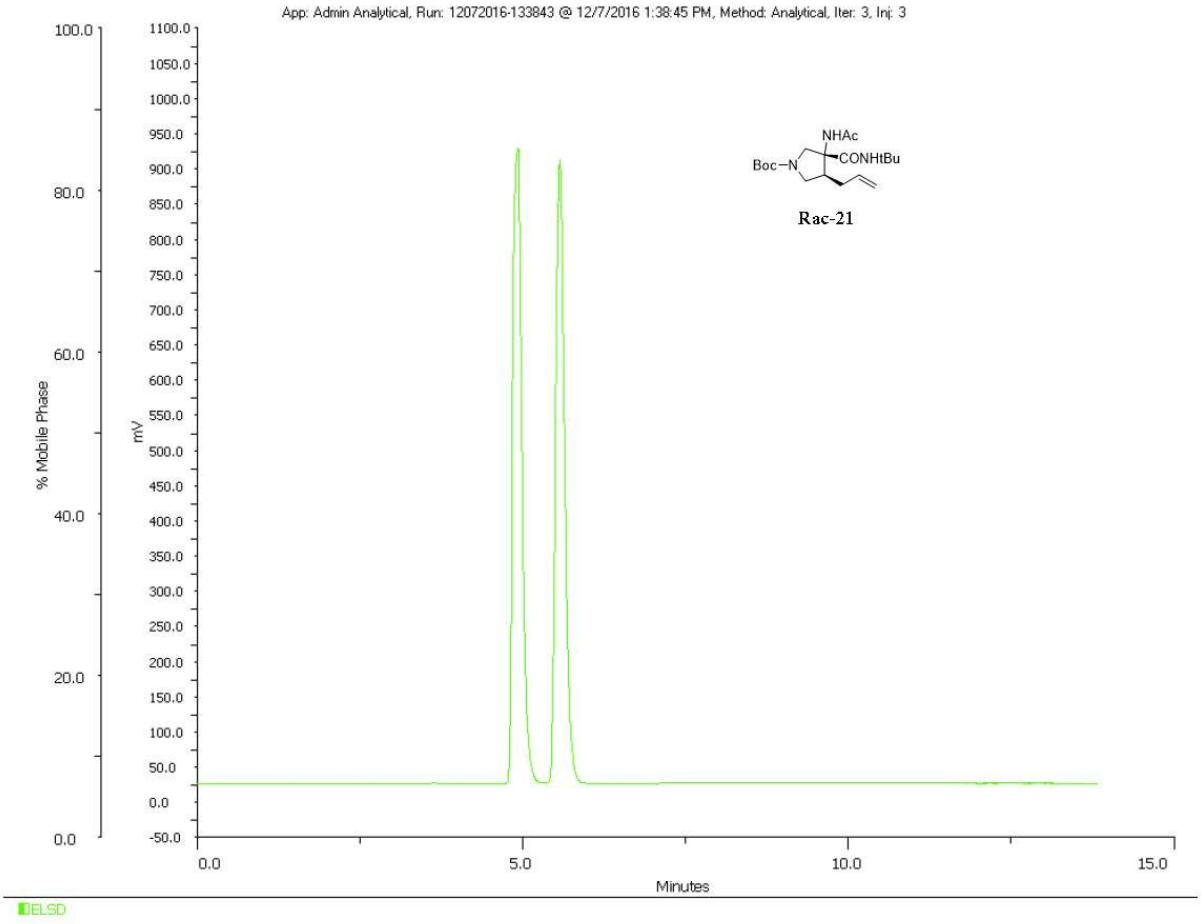
| Compound | Purity | Retention Time (min) | Method |
|---|---|---|---|
| 8 | 99.7% | 5.08 | D |
| 9 | 100.0% | 5.07 | D |
| 13 | 95.0% | 5.16 | D |
| 15 | 99.2% | 4.5 | A |
| 23 | 99.9% | 2.73 | B |
| 26 | 99.9% | 2.68 | B |
| 29 | 100.0% | 3.12 | A |
| 30 | 99.8% | 2.98 | B |
| 31 | 100.0% | 5.58 | C |
| 32 | 99.9% | 2.67 | B |
| 33 | 99.7% | 2.89 | B |
| 34 | 99.9% | 2.95 | B |
| 35 | 99.9% | 2.78 | B |
| 36 | 99.9% | 2.86 | B |
| 37 | 99.7% | 2.83 | B |
| 38 | 100.0% | 2.84 | A |
| 39 | 100.0% | 3.14 | A |
| 40 | 99.8% | 3.44 | A |
| 41 | 99.9% | 3.13 | A |
| 42 | 99.4% | 6.03 | A |
| 43 | 99.2% | 10.14 | A |
| 44 | 99.8% | 3.24 | A |
| 45 | 99.8% | 3.24 | A |
| 46 | 100.0% | 2.73 | B |
| 47 | 100.0% | 2.74 | B |
| 48 | 100.0% | 2.77 | B |
| 49 | 100.0% | 2.79 | B |

*Method A*: 20% to 80% B over 5 min, then holding at 80% for an additional 2 min
*Method B*: 25% to 95% B over 5 min, then holding at 95% for an additional 2 min
*Method C*: 25% to 100% B over 5 min, then holding at 100% for an additional 2 min
*Method D*: 10% to 60% B over 5 min, then holding at 60% for an additional 2 min

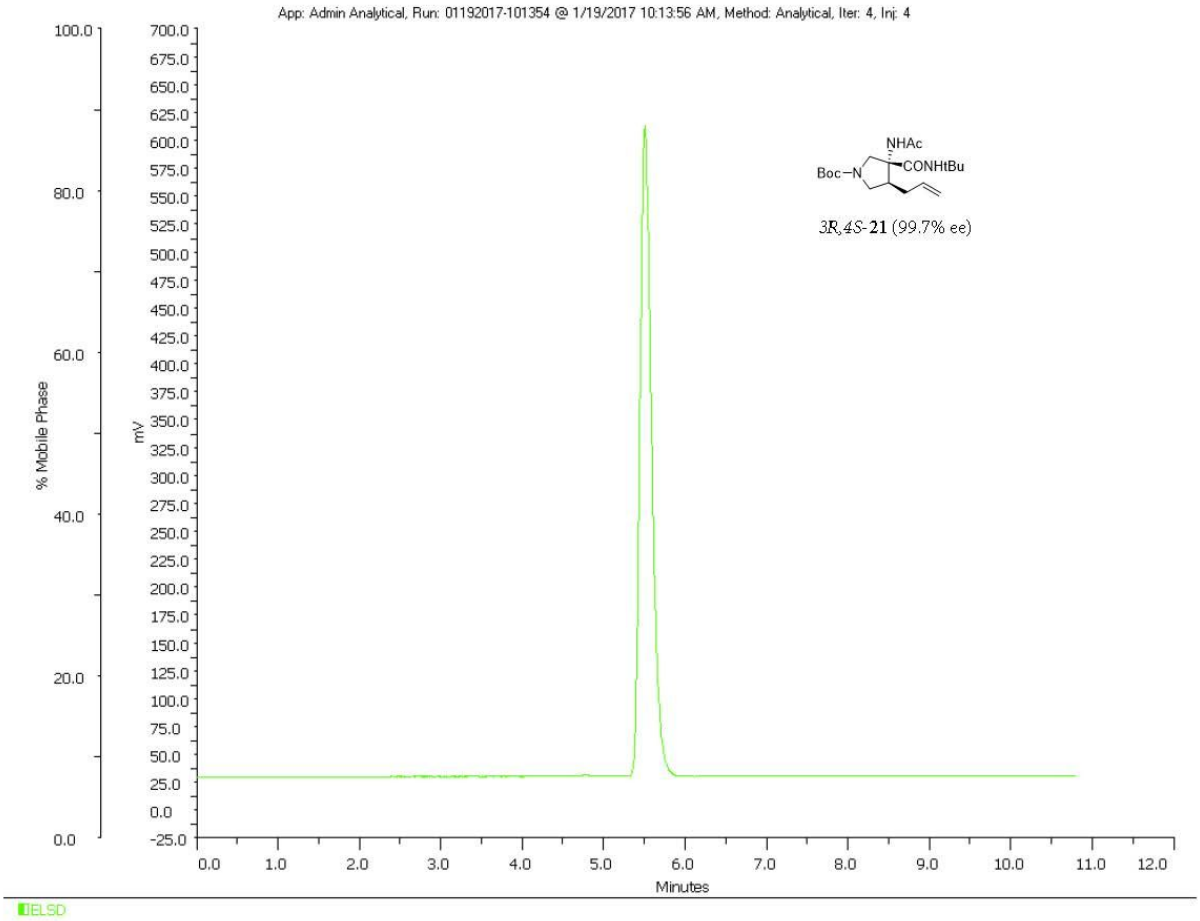
# Optical Purity Determination

The optical purity of intermediate **21** was determined by HPLC using a Gilson 215 Liquid Handler equipped with a PrepELS II Detector, Daicel Corporation Chiralpak IB 5µm (4.6 mm x 250 mm) column using 10% ethanol/ hexane (isocratic) over 12 minutes with a flow rate of 1 mL/min.

***HPLC Chromatogram of racemic 21***



***HPLC Chromatogram of resolved 21***



# Example arginase inhibition $IC_{50}$ curves

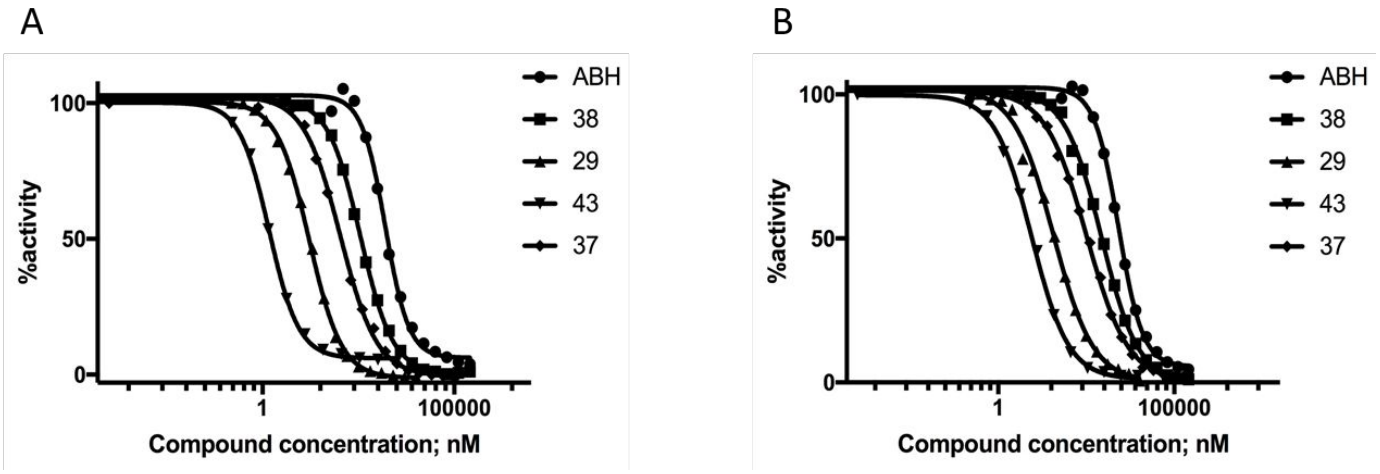



Figure S1. Representative dose-response curves for example compounds. (A) Against Arginase 1. (B) Against Arginase 2. Each point represents the average of duplicate measurements.

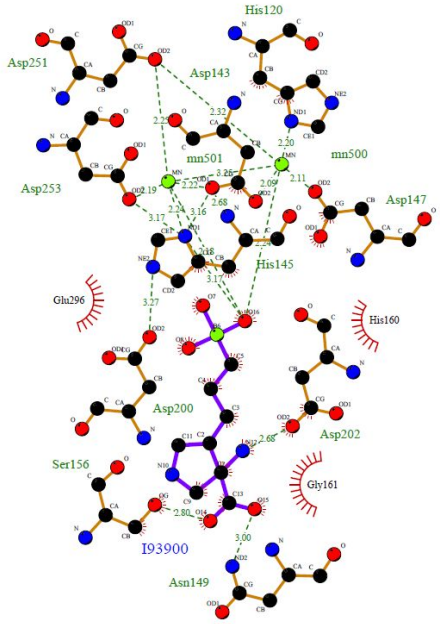
# X-ray crystallography data collection and refinement statistics

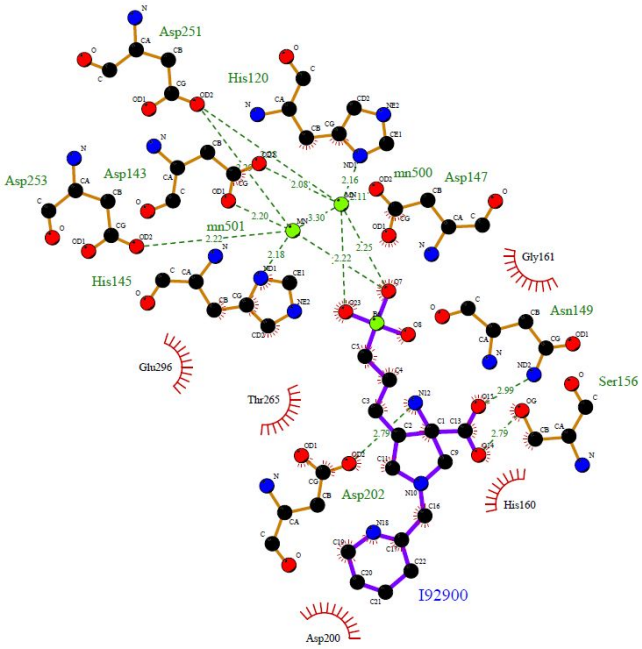
**Table S2.** Data Collection and Refinement Statistics. Values in parentheses are for the highest resolution shell

| | **Example 23** | **Example 49** |
|---|---|---|
| | **Data collection** | |
| PDB entry | 6Q37 | 6Q39 |
| X-ray source | Home source | Home source |
| Wavelength (Å) | 1.5418 | 1.5418 |
| Space group | $P4_22_12$ | $P4_22_12$ |
| Unit-cell parameters | a=b= 128.16 Å c= 158.98Å | a=b= 128.30 Å c= 159.15Å |
| Resolution range (Å) | 50.0 – 2.20 (2.28 – 2.20) | 50.0 – 2.20 (2.28 – 2.20) |
| No. of observations | 747 806 | 589 289 |
| No. of unique reflections | 63 433 | 61 688 |
| Multiplicity | 11.8 (10.2) | 9.6 (8.8) |
| Completeness (%) | 93.8 (60.5) | 91.3 (55.4) |
| $R_{sym}$ (%) | 7.9 (28.5) | 12.6 (44.7) |
| Mean $I/\sigma(I)$ | 30.7 (7.9) | 16.1 (4.7) |
| | **Refinement** | |
| Refinement resolution range (Å) | 26.49-2.21 | 29.91-2.21 |
| $R_{work}$ (%) | 14.82 | 16.23 |
| $R_{free}$ (%) | 18.94 | 20.98 |
| No. of reflections for refinement | 63 100 | 61 552 |
| $RMSD_{bonds}$ (Å) | 0.008 | 0.008 |

| | | |
|---|---|---|
| $RMSD_{angles}$ (°) | 1.064 | 1.105 |
| Protein Atoms in A.U. | 7152 | 7152 |
| Water molecules | 849 | 579 |
| Ramachandran plot favored (%) | 97.81 | 97.70 |
| Ramachandran plot allowed (%) | 1.86 | 1.97 |
| Ramachandran plot outliers (%) | 0.33 | 0.33 |

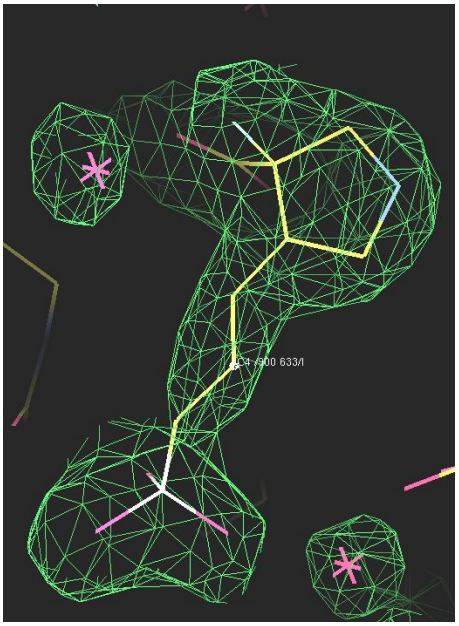
# Example 2D diagrams of contacts

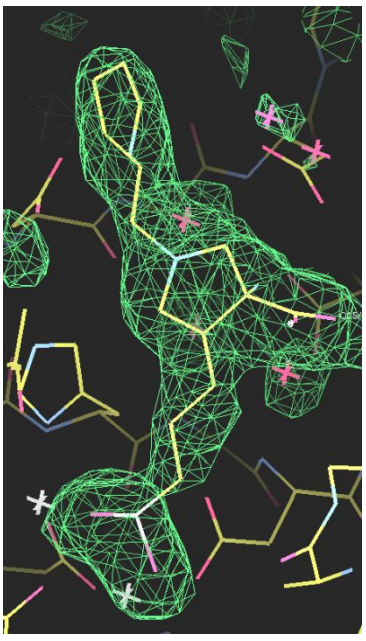



**Example 23** **Example 49**

Details of inhibitor signal. The signal of the inhibitors appeared very strongly in the electron density maps, as shown in the figures below, which superpose the inhibitor model with the initial difference maps, calculated with the protein model alone and averaged over the three monomers in the asymmetric unit, contoured at the 5.0 σ level.





**Example 23** **Example 49**