Supporting Information

Solid-Phase Synthesis of 2-Aminoimidazolones

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Experimental Section

General. All the reagents used are available from commercial sources, and were used without further purification. Rink Amide MBHA resin and Fmoc-NCS were purchased from Novabiochem. All NMR spectra (400 MHz) were recorded on a Varian Instruments Gemini-400 spectrometer. Analytical work employed a Rainin Microsorb-MV C_{18} column (water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 1.5 mL/min flow-rate). Preparative HPLC work utilized a Dynamax-60A C18 column (water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 21 mL/min flow-rate). All HPLC solutions contained 0.1% TFA. Yields of all compounds reported in Table 1 and 2 are of purified material and were based upon the loading levels of the starting resins. Purities of crude compounds were estimated from integrated peak areas of HPLC chromatographs generated at 254 nm. Mass spectral analysis was performed by M-Scan, Inc., West Chester, PA.

General Procedure for Rink Amide MBHA Resin Modification

Rink Amide MBHA resin (1g, 0.68 mmol) was placed into a plastic syringe and swollen with DMF (10 mL, 5 min, 3 x). The resin was treated with 20% piperidine in DMF (10 mL, 20 min, 2 x), and washed with DMF (10 mL, 30 s, 3 x). A DMF solution of

HOBT/HBTU/NMM/Fmoc protected amino acid (1:1:2:1) was applied to the resin in 5 equiv. excess (4 h, 1 x). The resin was washed with DMF (10 mL, 30s, 5 x) and used directly in the next reaction sequence.

General Procedure for the Synthesis of 2-Aminoimidazalones 1a-h.

Rink Amide MBHA resin (0.5 g, 0.34 mmol) was placed into a plastic syringe and swollen with DMF (10 mL, 5 min, 3 x). The resin was treated with 20% piperidine in DMF, and washed with DMF (10 mL, 30 s, 3 x), MeOH (10 mL, 30 s, 3 x) and DCM (10 mL, 30s, 3 x). FmocNCS in DCM (0.25 M, 10 mL, 2 h) was added to the resin followed by DCM (10 mL, 30s, 3 x) and DMF (10 mL, 30s, 3 x) washes. 20% piperidine in DMF (10 mL, 20 min, 2 x) was added, the resin washed with DMF (10 mL, 30 s, 3 x), and a DMF solution of CH_3I (0.5 M, 7 mL, 1 h, 3 x) was added. The resin was washed with DMF (10 mL, 30 s, 3x), and 17 mL of a DMF solution of HOBT(0.1M)/HBTU(0.1M)/ NMM(0.2M) was added followed by the Fmoc-protected amino acid (5 equiv.) and the resin was agitated for 4 hours. The resin was washed with DMF (10 mL, 30s, 5x) and treated with 20% piperidine in DMF (10 mL, 20 min., 2x), followed by a DMF wash (10 mL, 30s, 5 x). DMSO (10 mL) was added, and the resin was heated at 80 °C for 24 h. After cooling to room temperature, the resin was washed with DMF (10 mL, 30 s, 3 x), MeOH (10 mL, 30 s, 3 x) and DCM (10 mL, 1 min, 5 x). The resin was dried under nitrogen for 10 min. and cleaved with 95% aqueous TFA at 60 °C for 4 h. The cleavage eluant was collected and the resin washed with 95% aqueous TFA (5 mL, 1 x) and MeOH (5 mL, 2 x). The eluant and washes were combined and dried with a Speedvac. The compound was purified with preparative HPLC, Dynamax-60A C18 column (0.1% solutions of TFA, water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 21 mL/min flow rate).

Compound 1a

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.02 (s, 1H), 0.95 (s, 9H).

^{13}C NMR (400 MHz, DMSO-d_6) δ 173.88, 158.17, 66.88, 34.52, 25.0.

HR-MS FAB *m/z* for $C_7H_{13}N_3O$ calcd 156.1137 ($M + H^+$), obsd 156.1137.

Compound 1b

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28-7.31 (m, 2H), 7.18-7.23 (m, 3H), 4.23 (dd, J = 8, 5 Hz, 1H), 2.68 (t, J = 8 Hz, 2H), 2.00-2.07 (m, 1H), 1.93-1.99 (m, 1H).

^{13}C NMR (400 MHz, DMSO-d_6) δ 175.14, 158.14, 140.35, 128.63, 128.42, 126.36, 58.26, 32.16, 30.19.

HR-MS FAB *m/z* for $C_{11}H_{13}N_3O$ calcd 204.1137 (M + H^+), obsd 204.1131.

Compound 1c

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21-7.27 (m, 4H), 3.39 (d, *J* = 17 Hz, 2H), 3.25 (d, *J* = 17 Hz, 2H).

^{13}C NMR (400 MHz, DMSO-d_6) δ 177.58, 157.18, 139.07, 127.33, 124.47, 69.22, 42.88.

HR-MS FAB *m/z* for $C_{11}H_{11}N_3O$ calcd 202.0980 (M + H^+), obsd 202.0965.

Compound 1d

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 4.61 (t, *J* = 5 Hz, 1H), 3.11 (dd, *J* = 14, 5 Hz, 1H), 3.02 (dd, *J* = 14, 5 Hz, 1H).

^{13}C NMR (400 MHz, DMSO-d_6) δ 174.35, 157.93, 133.68, 132.08, 131.53, 128.42, 59.43, 34.91.

HR-MS FAB *m/z* for $C_{10}H_{10}ClN_3O$ calcd 224.0591 (M + H^+), obsd 224.0587.

Compound 1e

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, *J* = 9 Hz, 2H), 7.49 (d, *J* = 9 Hz, 2H), 4.69 (t, *J* = 6 Hz, 1H), 3.26 (dd, *J* = 14, 5 Hz, 1H), 3.18 (dd, *J* = 14, 6 Hz, 1H).

^{13}C NMR (400 MHz, DMSO-d_6) δ 174.26, 158.10, 146.84, 143.26, 131.05, 123.49, 59.15, 35.47.

HR-MS FAB *m/z* for $C_{10}H_{10}N_4O_3$ calcd 235.0831 (M + H^+), obsd 235.0842.

Compound 1f

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.13 and 4.09 (2 x s, 2H), 3.07 (d, *J* = 6 Hz, 2H), 2.03 (t, *J* = 12 Hz, 1H), 1.74 (d, *J* = 11 Hz, 4H), 1.42-1.50 (bm, 1H), 1.24-1.32 (m, 2H), 0.87-0.95 (m, 2H).

HR-MS FAB *m/z* for $C_{11}H_{18}N_4O_2$ calcd 239.1508 (M + H^+), obsd 239.1504.

Compound 1g

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H), 4.67 and 4.60 (2 x t, *J* = 5 Hz, 1H), 2.95-3.11 (bm, 4H), 1.96-2.05 (m, 1H), 1.67-1.76 (m, 2H), 1.52-1.60 (bm, 2H), 1.36-1.41 (bm, 1H), 1.18-1.32 (m, 2H), 0.67-0.88 (bm, 2H).

HR-MS FAB *m/z* for $C_{18}H_{23}ClN_4O_2$ calcd 363.1588 (M + H^+), obsd 363.1566.

Compound 1h

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 4.69 (bs, 1H), 3.73-3.93 (bm, 2H), 3.18-3.24 (m, 2H). 3.02-3.09 (m, 2H), 2.41-2.46 (m, 1H), 1.73-1.98 (bm, 2H), 1.53-1.63 (bm, 2H).

HR-MS FAB m/z for $C_{18}H_{19}ClN_4O_2$ calcd 335.1275 (M + H$^+$), obsd 335.1287.

General Procedure for the Synthesis of 2-Aminoimidazalones 2a-e.

The resin bound S-methyl isothiourea **4** was treated with oxazolone (**9**, 0.25 M, 7 mL) and sodium methoxide (0.2 M, 3.4 mL) at 100 °C for 12 h. The resin was cooled to room temperature, and washed with DMF (10 mL, 30 s, 3 x), MeOH (10 mL, 30 s, 3 x) and DCM (10 mL, 1 min, 5 x). The resin was dried under nitrogen for 10 min. and cleaved with 95% aqueous TFA at 60 °C for 4 h. The cleavage eluant was collected and the resin washed with 95% aqueous TFA (5 mL, 1 x) and MeOH (5 mL, 2 x). The eluant and washes were combined and dried with a Speedvac. The compound was purified with preparative HPLC, Dynamax-60A C18 column (0.1% solutions of TFA, water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 21 mL/min flow rate).

Compound 2a

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94-7.98 (m, 1H), 7.64-7.70 (m, 1H), 7.40-7.49 (m, 3H), 6.85 (s, 1H), 6.80 (s, 1H), 3.35-3.38 (m, 1H), 3.17-3.25 (m, 2H), 2.03 (bt, J = 13 Hz, 1H), 1.75-1.78 (bm, 4H), 1.45-1.60 (bm, 1H), 1.30 (bq, J = 13 Hz, 2H), 0.99 (bq, J = 12 Hz, 2H).

HR-MS FAB m/z for $C_{18}H_{22}N_4O_2$ calcd 327.1821 (M + H$^+$), obsd 327.1814.

Compound 2b

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80-8.00 (bm, 5H), 7.42-7.56 (bm, 5H), 4.68 (s, 2H).

HR-MS FAB m/z for $C_{18}H_{16}N_4O_2$ calcd 321.1352 (M + H$^+$), obsd 321.1358.

Compound 2c

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7 Hz, 1H), 7.48-7.52 (m, 1H), 7.32-7.41 (m, 2H), 6.93 (s, 1H), 6.63 (s, 1H).

HR-MS FAB m/z for $C_{10}H_8ClN_3O$ calcd 222.0434 (M + H$^+$), obsd 222.0441.

Compound 2d

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (dd, J = 18, 8 Hz, 1H), 7.52 (t, J = 6 Hz, 1H), 7.33-7.39 (bm, 2H), 6.96 (s, 1H), 6.94 (s, 1H), 3.20 (t, J = 8 Hz, 2H), 2.02-2.08 (bm, 1H), 1.79 (t, J = 12 Hz, 4H), 1.51-1.58 (bm, 1H), 1.29-1.36 (bm, 2H), 0.88-1.01 (bm, 2H).

HR-MS FAB *m/z* for $C_{18}H_{21}ClN_4O_2$ calcd 361.1431 ($M + H^+$), obsd 361.1428.

Compound 2e

^1H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.13 (dd, J = 8, 2 Hz, 2H), 7.68 (t, J = 8 Hz, 1H), 6.66 (s, 1H).

HR-MS FAB *m/z* for $C_{10}H_8N_4O_3$ calcd 233.0675 ($M + H^+$), obsd 233.0678.