The Development of an Aryloxazole Class of Hepatitis C Virus Inhibitors Targeting the Entry Stage of the Viral Replication Cycle

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SUPPORTING INFORMATION

Table S.1. NIAID viral screening panel results S-2

Table S.2. Structures of diamine fragments **6** S-4

Table S.3. Structures of oxazole carboxylic acid fragments **5**, **12** and **17** S-5

General synthesis and analysis experimental details S-6

Synthesis and sourcing of diamine fragments **6** S-6

Synthesis of oxazole carboxylic acid fragments **5**, **12** and **17** S-15

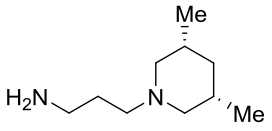
Table S1. NIAID antiviral screen of CCZ against 13 viruses. The antiviral screen of lead compound **7nn** against 13 viruses using the non-clinical and preclinical services program offered by the National Institute of Allergy and Infectious Diseases (NIAID).

viral assay	assay activity for **7nn**			assay activity for control compound[a]		
	EC_{50} (µg/mL)[b]	CC_{50} (µg/mL)[c]	selectivity index	EC_{50} (µg/mL)[b]	CC_{50} (µg/mL)[c]	selectivity index
Dengue virus 2[d] (visual)	3.2	3.6	1.1	0.00032	>0.1	>320
Dengue virus 2[d] (neutral red)	3.2	5.1	1.6	0.00031	>0.1	>320
Influenza A virus H_1N_1[e] (visual)	15	32	2.1	13	>320	>25
Influenza A virus H_1N_1[e] (neutral red)	13	19	1.5	7.5	>320	>43
Polio virus 3[f] (visual)	10	10	1	0.32	>10	>31
Polio virus 3[f] (neutral red)	>8	8	0	0.25	>10	>40
Respiratory syncytial virus[g] (visual)	15	32	2.1	14	>1,000	>71
Respiratory syncytial virus[g] (neutral red)	15	32	2.1	14	>1,000	>71
Rift Valley fever virus[h] (visual)	>19	19	0	9.2	>1,000	>110
Rift Valley fever virus[h] (neutral red)	>17	17	0	8.6	>1,000	>120
SARS coronavirus[i] (visual)	3.2	32	10	0.5	>100	>200
SARS coronavirus[i] (neutral red)	3.2	34	11	0.14	>100	>710
Tacaribe virus[j] (visual)	>10	10	0	7	>1,000	>140
Tacaribe virus[j] (neutral red)	>11	11	0	7.6	>1,000	>130

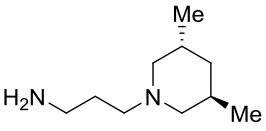
Venezuelan equine encephalitis virus[k] (visual)	32	32	1	0.000032	>0.01	>310
Venezuelan equine encephalitis virus[k] (neutral red)	>19	19	0	0.000045	>0.01	>220
Hepatitis B virus[l] (DNA hybridization, virion/neutral red, toxicity)	40[q]	48[q]	1.2	0.037[q]	2,128[q]	57,514
Hepatitis C virus[m] (luciferase reporter, replicon/Cyto Tox-1, toxicity)	3.41[q]	8.87[q]	3	0.07[r]	>2[r]	>29
Herpes simplex virus 1[n] (crystal violet)	>12[q]	50.13[q]	<4	2.39[q]	>300[q]	>126
Human cytomegalovirus[o] (crystal violet)	>2.4[q]	11.4[q]	<5	1.91[q]	>300[q]	>157
Vaccinia virus[p] (crystal violet)	>60[q]	74.27[q]	<1	4.85[q]	>300[q]	>39

[a] for control used, see viral assay details; [b] cytopathic effect; [c] toxicity; [d] strain: New Guinea C, cell line: Vero76; control: infergen; [e] strain: California/07/2009, cell line: MDCK; control: ribavirin; [f] strain: WM-3, cell line: Vero76; control: Pirodavir; [g] strain: A2, cell line: MA-104; control: ribavirin; [h] strain: MP-12, cell line: Vero76; control: ribavirin; [i] strain: Urbani, cell line: Vero76; control: M128533; [j] strain: TRVL 11573, cell line: Vero; control: ribavirin; [k] strain: TC-83, cell line: Vero76; control: infergen; [l] strain: ayw, cell line: 2.2.15; control: lamivudine; [m] strain: CON-1 (genotype 1b), cell line: Huh-Luc/Neo ET; control: IFNα-2b; [n] strain: E-377, cell line: HFF; control: acyclovir; [o] strain: AD169, cell line: HFF; control: ganciclovir; [p] strain: Copenhagen, cell line: HFF; control: cidofovir; [q] results reported in µM; [r] results reported in IU/mL.

Table S2. Structures of the diamine fragments **6**.



6a



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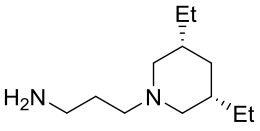

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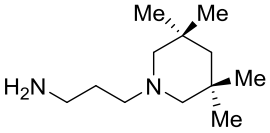

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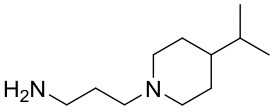

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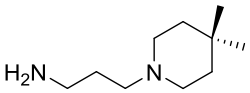

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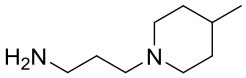

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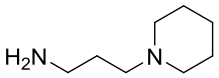

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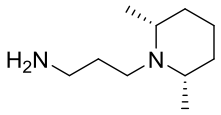

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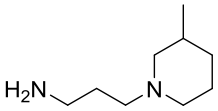

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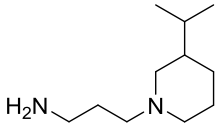

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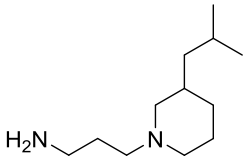

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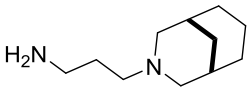

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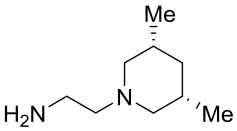

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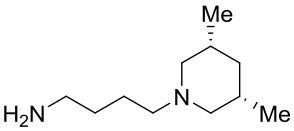

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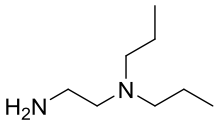

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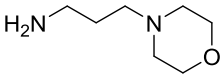

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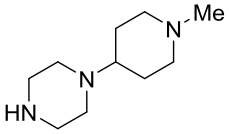
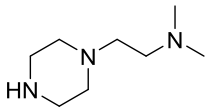
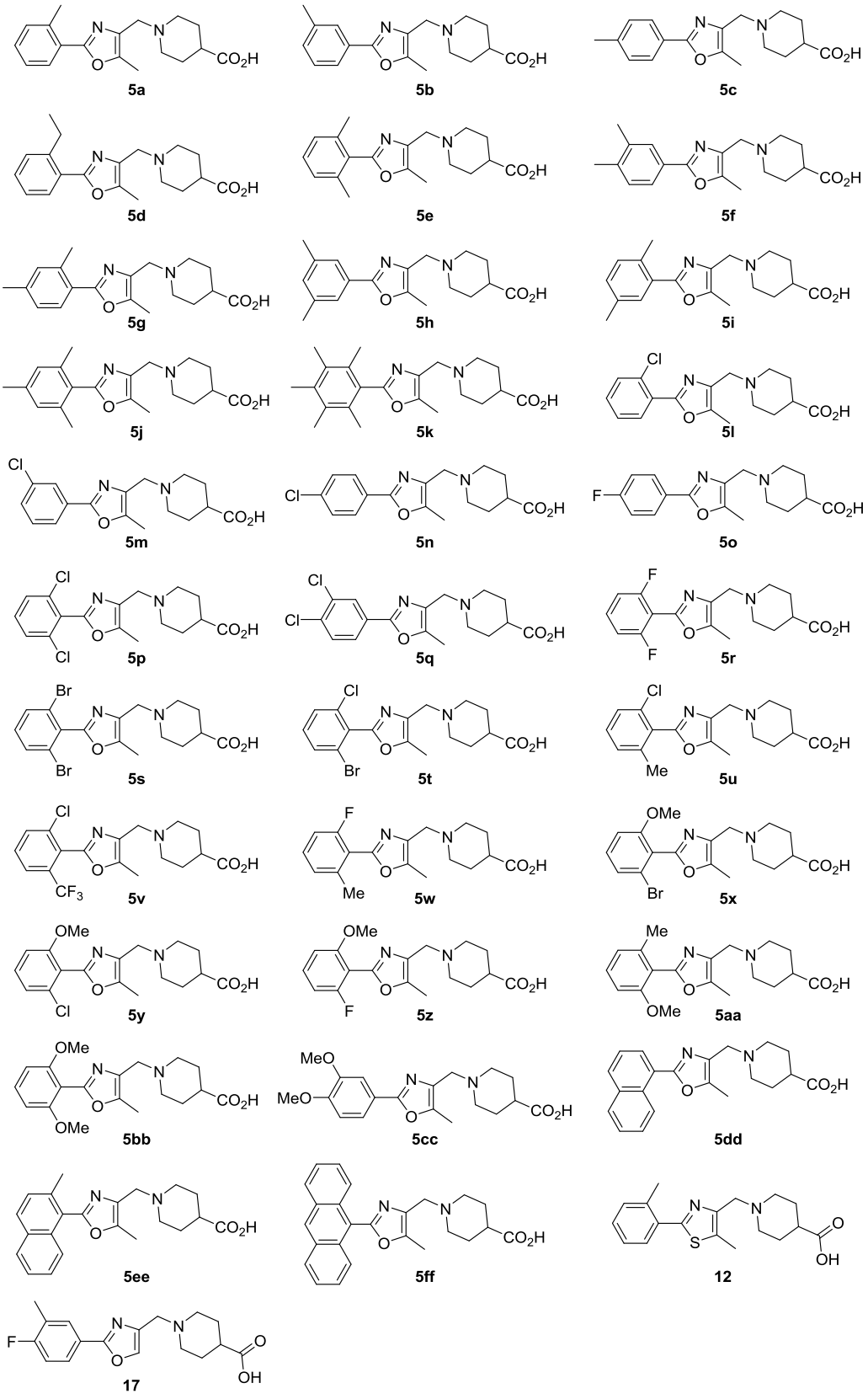


6r



6s

Table S.3. Structures of oxazole carboxylic acid fragments **5**.

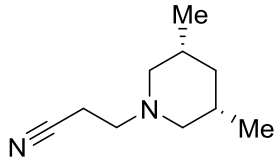


General synthesis and analysis experimental details: All reagents were used as received from the following suppliers: Alfa Aesar, Ark Pharm, Aldrich, and Fisher Scientific. Acetonitrile and THF were purified using the Innovative Technology PureSolv solvent purification system. The ^{1}H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz or 500 MHz spectrometer. Chemical shifts are reported in parts per million and were referenced to residual proton solvent signals. ^{13}C multiplicities were determined with the aid of an APT pulse sequence, differentiating the signals for methyl (CH_3) and methyne (CH) carbons as "d" from methylene (CH_2) and quarternary (C) carbons as "u". The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a Thermo Scientific Nicolet iS5 FT-IR spectrometer and the absorbtion frequencies are reported in cm^{-1}. Microwave syntheses were conducted in a Biotage Initiator constant temperature microwave synthesizer. Flash column chromatography separations were performed using the Teledyne Isco CombiFlash R_F using RediSep R_F silica gel columns. TLC was performed on Analtech UNIPLATE silica gel GHLF plates (gypsum inorganic hard layer with fluorescence). TLC plates were developed using iodine vapor. Automated preparative RP HPLC purification was performed using an Agilent 1200 Mass-Directed Fractionation system (Prep Pump G1361 with gradient extension, make-up pump G1311A, pH modification pump G1311A, HTS PAL autosampler, UV-DAD detection G1315D, fraction collector G1364B, and Agilent 6120 quadrapole spectrometer G6120A). The preparative chromatography conditions included a Waters X-Bridge C_{18} column (19 × 150 mm, 5 µm, with 19 × 10-mm guard column), elution with a water and acetonitrile gradient, which increases 20% in acetonitrile content over 4 min at a flow rate of 20 mL/min (modified to pH 9.8 through addition of NH_4OH by auxiliary pump), and sample dilution in DMSO. The preparative gradient, triggering thresholds, and UV wavelength were selected according to the analytical RP HPLC analysis of each crude sample. The analytical method used an Agilent 1200 RRLC system with UV detection (Agilent 1200 DAD SL) and mass detection (Agilent 6224 TOF). The analytical method conditions included a Waters Aquity BEH C_{18} column (2.1 × 50 mm, 1.7 µm) and elution with a linear gradient of 5% acetonitrile in pH 9.8 buffered aqueous ammonium formate to 100% acetonitrile at 0.4 mL/min flow rate. Compound purity was measured on the basis of peak integration (area under the curve) from UV/Vis absorbance (at 214 nm), and compound identity was determined on the basis of mass analysis.

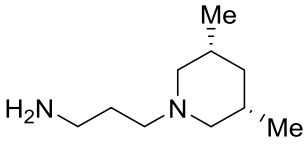
SYNTHESIS AND SOURCING OF DIAMINE FRAGMENTS

General procedure A: amine addition to acrylonitrile. To a mixture of acrylonitrile and water (0.01 mL/mmol) cooled in an ice/water bath was added portionwise a mixture of amine (0.5 equiv.) and formamide (0.5 equiv.). The reaction was stirred for 15 h, slowly warming to rt. The reaction was partitioned between brine and ethyl ether (two portions), the combined organics dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by silica chromatography to afford the propionitrile product.

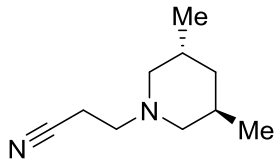
General procedure B: nitrile hydrogenation. To a Parr reactor containing a solution of nitrile in MeOH (50 mL) was added methanolic ammonia (7 M, 8 mL) followed by Raney nickel (0.5 g). The reactor was sealed, the vessel purged with hydrogen and then stirred under a hydrogen atmosphere (200 psi) for 16 h at rt. The reaction was filtered, rinsed with methanol and the solvent removed in vacuo to afford the diamine product, which was used without further purification.



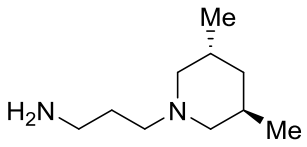
3-(*cis*-3,5-Dimethylpiperidin-1-yl)propanenitrile S1a. *cis*-3,5-Dimethylpiperidine (8.37 g, 73.9 mmol) was reacted accorded to general procedure A to afford the product as a colorless oil (6.71 g, 40.4 mmol, 55% yield). R_f = 0.16 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.47 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 6H), 1.55 (t, *J* = 10.8 Hz, 2H), 1.62–1.74 (m, 3H), 2.50 (t, *J* = 7.6 Hz, 1H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.76–2.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.5, 31.1; u (C, CH_2): 15.6, 41.9, 53.6, 60.9, 119.0; IR 1459, 2912, 2246, 2950 cm^{-1}.



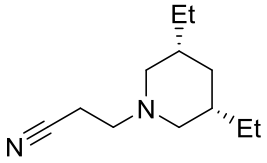
3-(*cis*-3,5-Dimethylpiperidin-1-yl)propan-1-amine 6a. 3-(*cis*-3,5-Dimethylpiperidin-1-yl)propanenitrile (976 mg, 5.87 mmol) was reacted according to general procedure B to afford the diamine product as a green-colored oil (930 mg, 5.46 mmol, 93% yield). To obtain satisfactory NMR characterization, a sample of the diamine (157 mg, 0.92 mmol) was dissolved in ethyl ether (12 mL) and treated with HCl solution in ethyl ether (1.38 mL, 2 M, 2.77 mmol, 3.0 equiv.). The solids were filtered, washed with ethyl ether and recrystallized from MeOH/MeCN to afford the dihydrochloride salt as a white solid (186 mg, 0.77 mmol, 83% yield). ^{1}H NMR (400 MHz, D_2O) δ 0.76 (q, *J* = 12.6 Hz, 1H), 0.83 (d, *J* = 6.5 Hz, 6H), 1.70–1.85 (m, 3H), 1.99–2.07 (m, 2H), 2.42 (t, *J* = 12.2 Hz, 2 H), 2.96 (t, *J* = 7.8 Hz, 2H), 3.06–3.10 (m, 2H), 3.33 (td, *J* = 2.0, 11.9 Hz, 2H); ^{13}C NMR (101 MHz, D_2O, APT pulse sequence) δ d (CH, CH_3): 17.5, 29.0; u (C, CH_2): 21.7, 36.6, 38.3, 53.6, 58.1; IR 1457, 2909, 2948 cm^{-1}; HRMS calcd. for $C_{10}H_{23}N_2$ $[M + H]^+$ 171.1856, found 171.1854.



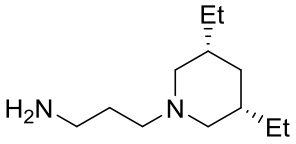
(±)-3-(*trans*-3,5-Dimethylpiperidin-1-yl)propanenitrile S1b. *trans*-3,5-Dimethylpiperidine (1.82 g, 16.1 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (1.06 g, 6.4 mmol, 40% yield). R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.82 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 7.6 Hz, 3H) 1.26 (dt, *J* = 4.7, 13.2 Hz, 1H), 1.51–1.58 (m, 1H), 1.93–2.11 (m, 3H), 2.16–2.24 (m, 1H), 2.46 (t, *J* = 12.1 Hz, 1H), 2.92–2.99 (m, 3H), 3.04–3.11 (m, 2H), 3.22–3.27 (m, 1H), 3.31 (td, *J* = 2.0, 12.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.0, 27.3; u (C, CH_2): 15.9, 38.8, 53.8, 60.4, 119.1; IR 1466, 2252, 2911, 2951 cm^{-1}.



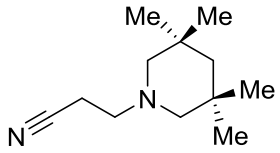
(±)-3-(*trans*-3,5-Dimethylpiperidin-1-yl)propan-1-amine 6b. 3-(*trans*-3,5-Dimethylpiperidin-1-yl)propanenitrile (980 mg, 5.89 mmol) was reacted according to general procedure B to afford the diamine product as a green-colored oil (946 mg, 5.56 mmol, 94% yield). To obtain satisfactory NMR characterization, a sample of the diamine (477 mg, 2.80 mmol) was dissolved in ethyl ether (20 mL) and treated with HCl solution in ethyl ether (4.2 mL, 2 M, 8.40 mmol, 3.0 equiv.). The solids were filtered, washed with ethyl ether and recrystallized from MeOH/MeCN to afford the dihydrochloride salt as a white solid (375 mg, 1.54 mmol, 55% yield). ^{1}H NMR (400 MHz, D_2O) δ 1.13 (d, *J* = 6.2 Hz, 6 H), 1.19–1.35 (m, 3H), 1.56–1.60 (m, 2H), 1.64–1.69 (m, 1H), 2.39 (t, *J* = 7.5 Hz, 2 H), 2.37 (m, 2 H), 3.14 (t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (101 MHz, D_2O, APT pulse sequence) δ d (CH, CH_3): 16.3, 17.8, 23.9, 26.5; u (C, CH_2): 21.6, 35.1, 36.6, 54.1, 57.3, 58.9; IR 1465, 2910, 2948 cm^{-1}.



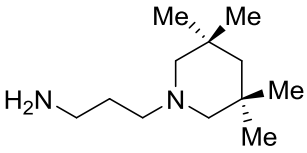
3-(*cis*-3,5-Diethylpiperidin-1-yl)propanenitrile S1c. *cis*-3,5-Diethylpiperidine (911 mg, 6.45 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (588 mg, 3.03 mmol, 47% yield). R_f = 0.30 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.43 (q, *J* = 12.6 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 6H), 1.10–1.28 (m, 4H), 1.38–1.50 (m, 2H), 1.57 (t, *J* = 10.8 Hz, 2H), 1.81–1.86 (m, 1H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.84–2.87 (m, 2H); HRMS calcd. for $C_{12}H_{23}N_2$ $[M + H]^+$ 195.1856, found 195.1875.



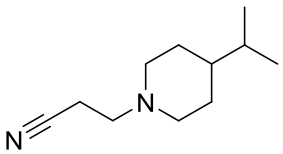
3-(*cis*-3,5-Diethylpiperidin-1-yl)propan-1-amine 6c. 3-(*cis*-3,5-Diethylpiperidin-1-yl)propanenitrile (238 mg, 1.23 mmol) was reacted according to general procedure B to afford the diamine product as a light greenish oil (241 mg, 1.22 mmol, 99% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.47 (q, *J* = 12.4 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 6H), 1.24 (q, *J* = 7.2 Hz, 4H), 1.46–1.53 (m, 3H), 1.72 (t, *J* = 7.4 Hz, 2H), 1.85–1.90 (m, 2H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.98 (dd, *J* = 1.0, 8.4 Hz, 2H); HRMS calcd. for $C_{12}H_{27}N_2$ $[M + H]^+$ 199.2169, found 199.2180.



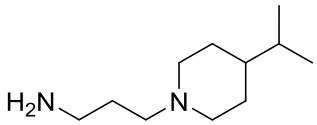
3-(3,3,5,5-Tetramethylpiperidin-1-yl)propanenitrile S1d. 3,3,5,5-Tetramethylpiperidine (227 mg, 1.61 mmol) was reacted accorded to general procedure A to afford the nitrile product as a white solid (157 mg, 0.81 mmol, 50% yield). R_f = 0.30 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.96 (s, 12H), 1.10 (s, 2H), 2.06 (s, 4H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.63 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 29.5; u (C, CH_2): 16.3, 31.7, 50.8, 53.5, 66.2, 119.0; HRMS calcd. for $C_{12}H_{23}N_2$ $[M + H]^+$ 195.1856, found 195.1869.



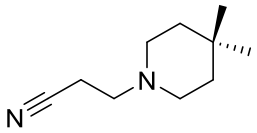
3-(3,3,5,5-Tetramethylpiperidin-1-yl)propan-1-amine 6d. 3-(3,3,5,5-Tetramethylpiperidin-1-yl)propanenitrile (100 mg, 0.52 mmol) was reacted according to general procedure B to afford the diamine product as a light greenish oil (102 mg, 0.52 mmol, quantitative yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.93 (s, 12H), 1.08 (s, 2H), 1.40–1.85 (m, 4H), 1.96 (s, 4H), 2.22–2.41 (m, 2H), 2.88 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 29.7; u (C, CH_2): 27.0, 31.5, 51.0, 56.8, 66.9, 67.0; HRMS calcd. for $C_{12}H_{27}N_2$ $[M + H]^+$ 199.2169, found 199.2174.



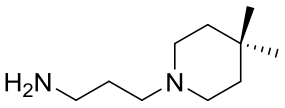
3-(4-Isopropylpiperidin-1-yl)propanenitrile S1e. 4-Isopropylpiperidine (565 mg, 4.99 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (831 mg, 4.61 mmol, 93% yield). R_f = 0.26 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 6H), 0.95–1.06 (m, 1H), 1.27 (dq, *J* = 3.5, 12.6 Hz, 2H), 1.43 (sept, *J* = 6.6 Hz, 1H), 1.64–1.68 (m, 2H), 2.00 (dt, *J* = 2.4, 11.5 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.88–2.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.8, 32.4, 42.2; u (C, CH_2): 15.7, 29.2, 53.82, 53.84, 119.0.



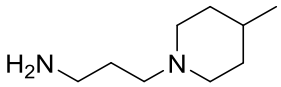
3-(4-Isopropylpiperidin-1-yl)propan-1-amine 6e. 3-(4-Isopropylpiperidin-1-yl)propanenitrile (643 mg, 3.57 mmol) was reacted according to general procedure B to afford the diamine product as a light green-yellow oil (617 mg, 3.35 mmol, 94% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 6H), 1.19–1.32 (m, 4H), 1.42 (sept, *J* = 6.6 Hz, 1H), 1.63–1.93 (complex, 6H), 2.32–2.38 (m, 2H), 2.92–3.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.7, 32.4, 42.4; u (C, CH_2): 29.3, 54.3, 54.4, 57.1, 57.3.



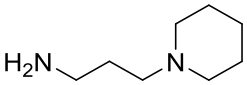
3-(4,4-Dimethylpiperidin-1-yl)propanenitrile S1f. 4,4-Dimethylpiperidine (565 mg, 4.99 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (808 mg, 4.86 mmol, 94% yield). R_f = 0.32 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.92 (s, 6H), 1.40 (t, *J* = 5.6 Hz, 4H), 2.44 (t, *J* = 5.7 Hz, 4H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9, 28.1, 28.3, 38.5, 49.6, 53.8, 119.0.



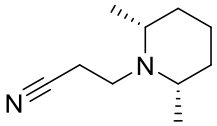
3-(4,4-Dimethylpiperidin-1-yl)propan-1-amine 6f. 3-(4,4-Dimethylpiperidin-1-yl)propanenitrile (489 mg, 2.94 mmol) was reacted according to general procedure B to afford the diamine product as a light blue-green oil (472 mg, 2.77 mmol, 94% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.87 (s, 6H), 1.35 (t, *J* = 5.5 Hz, 4H), 1.68–1.77 (m, 2H), 2.28–2.43 (m, 4H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.0, 28.4, 38.6, 38.7, 41.1, 50.1, 57.4. ^{1}H NMR data are consistent with those previously reported.[1]



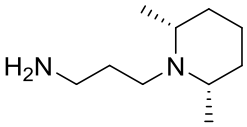
3-(4-Methylpiperidin-1-yl)propan-1-amine 6g. Purchased from Combi-Blocks Inc.



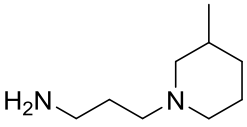
3-(Piperidin-1-yl)propan-1-amine 6h. Purchased from Sigma-Aldrich Co. LLC.



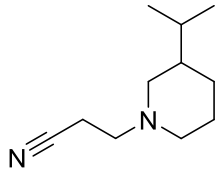
3-(*cis*-2,6-Dimethylpiperidin-1-yl)propanenitrile S1i. *cis*-2,6-Dimethylpiperidine (2.92 g, 25.8 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (0.96 g, 5.76 mmol, 22% yield). R_f = 0.43 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.13 (d, *J* = 6.2 Hz, 6H), 1.19–1.35 (m, 3H), 1.56–1.60 (m, 2H), 1.64–1.69 (m, 1H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.37 (m, 2H), 3.14 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 21.2, 55.3; u (C, CH_2): 13.0, 24.4, 34.6, 43.9, 119.2.



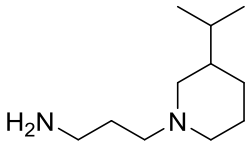
3-(*cis*-2,6-Dimethylpiperidin-1-yl)propan-1-amine 6i. 3-(*cis*-2,6-Dimethylpiperidin-1-yl)propanenitrile (938 mg, 5.64 mmol) was reacted according to general procedure B to afford the diamine product as a faintly blue oil (768 mg, 4.51 mmol, 80% yield). To obtain satisfactory NMR characterization, a sample of the diamine (104 mg, 0.61 mmol) was dissolved in ethyl ether (20 mL) and treated with HCl solution in ethyl ether (0.92 mL, 2 M, 1.83 mmol, 3.0 equiv.). The solids were filtered, washed with ethyl ether and recrystallized from MeOH/MeCN to afford the dihydrochloride salt as a white solid (139 mg, 0.57 mmol, 94% yield). ^{1}H NMR (400 MHz, D_2O) δ 1.25 (d, *J* = 6.4 Hz, 6 H), 1.40–1.50 (m, 3H), 1.57–1.69 (m, 1H), 1.84–2.03 (complex, 4H), 2.97–3.04 (m, 2 H), 3.22–3.28 (complex, 4H); ^{13}C NMR (101 MHz, D_2O, APT pulse sequence) δ d (CH, CH_3): 17.5, 59.2; u (C, CH_2): 19.5, 21.7, 31.9, 36.5, 44.6.



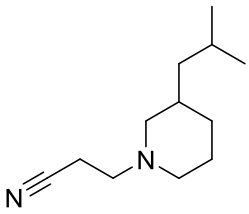
(±)-3-(3-Methylpiperidin-1-yl)propan-1-amine 6j. Purchased from Oakwood Products Inc.



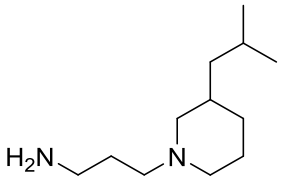
(±)-3-(3-Isopropylpiperidin-1-yl)propanenitrile S1k. 3-Isopropylpiperidine (109 mg, 0.86 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (84 mg, 0.47 mmol, 54% yield). R_f = 0.30 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.91 (dd, *J* = 1.0, 6.8 Hz, 6H), 0.94 (dq, *J* = 3.0, 12.7 Hz, 1H), 1.30–1.40 (m, 1H), 1.45 (sept, *J* = 6.7 Hz, 1H), 1.55 (tq, *J* = 3.9, 12.3 Hz, 1H), 1.68–1.82 (complex, 3H), 1.98 (dt, *J* = 2.4, 11.5 Hz, 1H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.67–2.76 (m, 2H), 2.82–2.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.8, 31.0, 42.4; u (C, CH_2): 15.7, 25.5, 27.5, 53.7, 54.1, 57.7, 119.0.



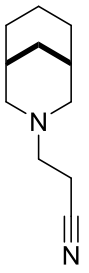
(±)-3-(3-Isopropylpiperidin-1-yl)propan-1-amine 6k. 3-(3-Isopropylpiperidin-1-yl)propanenitrile (76 mg, 0.42 mmol) was reacted according to general procedure B to afford the diamine product as a greenish oil (77 mg, 0.41 mmol, 99% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.90 (dd, *J* = 1.0, 6.7 Hz, 6H), 0.93 (dq, *J* = 3.7, 12.3 Hz, 1H), 1.28–1.40 (m, 1H), 1.45 (sept, *J* = 6.7 Hz, 1H), 1.51–1.93 (complex, 8H), 2.33–2.49 (m, 2H), 2.69–2.99 (m, 3H).



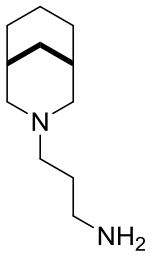
(±)-3-(3-Isobutylpiperidin-1-yl)propanenitrile S1l. 3-Isobutylpiperidine (1.12 g, 7.93 mmol) was reacted accorded to general procedure A to afford the nitrile product as a colorless oil (503 mg, 2.59 mmol, 33% yield). R_f = 0.32 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.73–0.83 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 2H), 1.44–1.73 (complex, 6H), 1.94 (dt, *J* = 2.9, 11.1 Hz, 1H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.61–2.67 (m, 2H), 2.71–2.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 22.6, 23.0, 24.7, 33.7; u (C, CH_2): 15.6, 25.3, 30.9, 43.8, 53.7, 54.0, 60.2, 119.0.



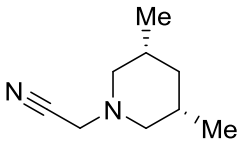
(±)-3-(3-Isobutylpiperidin-1-yl)propan-1-amine 6l. 3-(3-Isobutylpiperidin-1-yl)propanenitrile (302 mg, 1.55 mmol) was reacted according to general procedure B to afford the diamine product as a light yellow oil (296 mg, 1.49 mmol, 96% yield). To obtain satisfactory NMR characterization, a sample of the diamine (147 mg, 0.74 mmol) was dissolved in ethyl ether (15 mL) and treated with HCl solution in ethyl ether (1.1 mL, 2 M, 2.22 mmol, 3.0 equiv.). The solids were filtered, washed with ethyl ether and recrystallized from MeOH/MeCN to afford the dihydrochloride salt as a white solid (95 mg, 0.74 mmol, 47% yield). ^{1}H NMR (400 MHz,D_2O) δ 0.73 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.93–1.07 (m, 3H), 1.49–1.66 (m, 2H), 1.69–1.88 (m, 3H), 1.98–2.07 (m, 2H), 2.51 (t, *J* = 12.1 Hz, 1H), 2.76 (dt *J* = 2.6, 12.5 Hz, 1H), 2.96 (t, *J* = 7.9 Hz, 2H), 3.05–3.09 (m, 2H), 3.30–3.37 (m, 1H), 3.40–3.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 21.5, 22.0, 23.8, 31.9; u (C, CH_2): 21.7, 22.7, 27.8, 36.6, 41.9, 53.1, 53.8, 58.0.



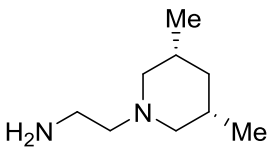
3-(3-Azabicyclo[3.3.1]nonan-3-yl)propanenitrile S1m. Acrylonitrile (0.17 mL, 2.52 mmol, 2.0 equiv.) was added portionwise to a mixture of 3-azabicyclo[3.3.1]nonane hydrochloride (204 mg, 1.26 mmol), K_2CO_3 (174 mg, 1.26 mmol) and formamide (57 mg, 1.26 mmol) in water (1 mL) cooled in an ice/water bath. The reaction was stirred for 17 h, slowly warming to rt. The reaction was partitioned between brine and ethyl ether (two portions), the combined organics dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by silica chromatography to afford the nitrile product as a colorless oil (209 mg, 1.17 mmol, 93% yield). R_f = 0.74 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.41–1.52 (m, 2H), 1.54–1.68 (m, 3H), 1.76 (tdd, *J* = 1.2, 4.4, 12.2 Hz, 2H), 1.79–1.86 (m, 2H), 2.30 (td, *J* = 2.1, 10.7 Hz, 2H), 2.47–2.64 (complex, 5H), 2.89 (qd, *J* = 0.9, 10.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 29.4; u (C, CH_2): 16.0, 22.0, 31.4, 33.9, 54.1, 59.1, 119.1; IR 1447, 1496, 2250, 2852, 2909 cm^{-1}.



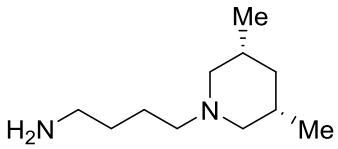
3-(3-azabicyclo[3.3.1]nonan-3-yl)propan-1-amine 6m. 3-(3-Azabicyclo[3.3.1]nonan-3-yl)propanenitrile (503 mg, 2.82 mmol) was reacted according to general procedure B to afford the diamine product as a yellow oil (452 mg, 2.48 mmol, 88% yield). To obtain satisfactory NMR characterization, a sample of the diamine (99 mg, 0.54 mmol) was dissolved in ethyl ether (15 mL) and treated with HCl solution in ethyl ether (0.82 mL, 2 M, 1.63 mmol, 3.0 equiv.). The solids were filtered, washed with ethyl ether and recrystallized from MeOH/MeCN to afford the dihydrochloride salt as a white solid (78 mg, 0.31 mmol, 56% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.48–1.74 (complex, 8H), 2.01–2.10 (m, 4H), 2.95 (t, *J* = 7.8 Hz, 2H), 3.01–3.11 (m, 4H), 3.52 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (101 MHz, D_2O, APT pulse sequence) δ d (CH, CH_3): 27.1; u (C, CH_2): ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 27.1; u (C, CH_2): 16.0, 22.0, 31.4, 33.9, 54.1, 59.1, 119.1; IR 1443, 1459, 2846, 2892 cm^{-1}.



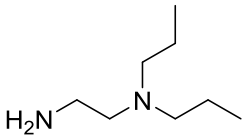
2-(*cis*-3,5-Dimethylpiperidin-1-yl)acetonitrile S1n. 2-Chloroacetonitrile (1.97 mL, 31.2 mmol, 1.1 equiv.) was added to a mixture of *cis*-3,5-dimethylpiperidine (3.21 g, 28.4 mmol), potassium iodide (4.71 g, 28.4 mmol) and K_2CO_3 (7.84 g, 56.7 mmol, 2.0 equiv.) in MeCN (50 mL) and the reaction stirred at rt for 16 h. The reaction was partitioned between water and ethyl ether (two portions), the combined organics dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by silica chromatography to afford the nitrile product as a light yellow oil (2.05 g, 13.5 mmol, 47% yield). R_f = 0.21 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.51–0.61 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 6H), 1.65–1.76 (m, 3H), 1.84 (t, *J* = 10.8 Hz, 2H), 2.70 (td, *J* = 1.8, 10.0 Hz, 2H), 3.52 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.4, 31.1; u (C, CH_2): 41.0, 46.4, 59.8, 114.8.



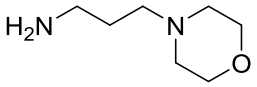
2-(*cis*-3,5-Dimethylpiperidin-1-yl)ethan-1-amine 6n. **2**-(*cis*-3,5-Dimethylpiperidin-1-yl)acetonitrile (1.20 g, 7.88 mmol) was reacted according to general procedure B to afford the diamine product as a yellow oil (0.80 g, 5.12 mmol, 65% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.51 (q, *J* = 11.2 Hz, 1H), 0.84 (d, *J* = 6.5 Hz, 6H), 1.44 (t, *J* = 11.0 Hz, 2H), 1.60–1.72 (complex, 4H), 2.37 (t, *J* = 6.4 Hz, 2H), 2.78–2.82 (complex, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 19.6, 31.1; u (C, CH_2): 39.1, 42.2, 61.5, 61.9.



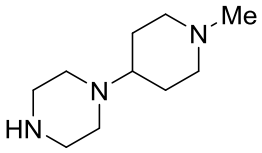
4-(*cis*-3,5-Dimethylpiperidin-1-yl)butan-1-amine 6o. Purchased from Enamine LLC.



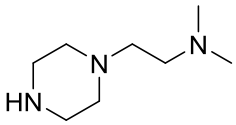
***N*^{1},*N*^{1}-Dipropylethane-1,2-diamine 6p**. Purchased from Combi-Blocks Inc.



3-Morpholinopropan-1-amine 6q. Purchased from Sigma-Aldrich.



1-(1-Methylpiperidin-4-yl)piperazine 6r. Purchased from Sigma-Aldrich.



***N*,*N*-Dimethyl-2-(piperazin-1-yl)ethan-1-amine 6s**. Purchased from Sigma-Aldrich.

SYNTHESIS OF OXAZOLE CARBOXYLIC ACID FRAGMENTS

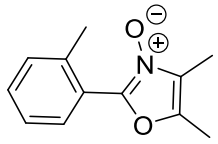
General procedure C: synthesis of 2-aryl-4,5-dimethyloxazole-3-oxides 3. According to the literature method for oxazole synthesis,[2] a mixture of 2,3-butanedione monoxime **2** and aldehyde **1** (1.1 equiv.) in acetic acid (6 mL/mmol) was cooled to 0 ^{o}C and a solution of HCl (4.0 M in dioxane, 1.5 equiv.) was added. The reaction mixture was allowed to

warm to room temperature and stirred for 16 h, diluted with methyl *tert*-butyl ether and filtered. The solid was collected, washed with ethyl ether and dried to afford the oxazole oxide product, which was used without further purification.

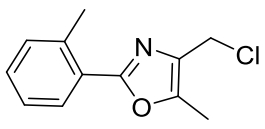
General procedure C-2: synthesis of 2-aryl-4,5-dimethyloxazole-3-oxides 3. To a mixture of 2,3-butanedione monoxime **2** and aldehyde **1** (1.1 equiv.) in acetic acid (6 mL/mmol) at 0 ^{o}C, was bubbled HCl gas until the solution was saturated (ca. 5 mins). The reaction mixture was allowed to warm to room temperature and stirred for 16 h, diluted with ethyl ether and filtered. The solid was collected, washed with ethyl ether and dried to afford the oxazole oxide product, which was used without further purification.

General procedure D: synthesis of 2-aryl-4-(chloromethyl)-5-methyloxazoles 4. To a solution of 2-aryl-4,5-dimethyloxazole-3-oxide **3** (789 mg, 3.32 mmol) in DCE (8 mL/mmol), was added $POCl_3$ (1.1 equiv.). The reaction was heated at reflux for 30 min, then cooled to rt, carefully quenched with water and extracted with DCM (2 x 20.0 mL). The evaporated residue was purified via silica gel chromatography to afford the chloromethyl oxazole product.

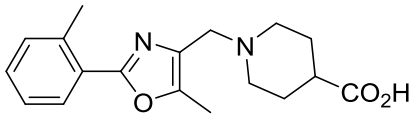
General procedure E: synthesis of 1-((5-Methyl-2-aryloxazol-4-yl)methyl)piperidine-4-carboxylic acids 5. To a solution of piperidine-4-carboxylic acid (1.5 equiv.) and potassium hydroxide (3 equiv.) in ethanol (3 mL/mmol of oxazole substrate), was added 2-(aryl)-4-(chloromethyl)-5-methyloxazole **4** in EtOH (5 mL). The mixture was stirred at rt for 16 h. Solvent was removed *in vacuo* and the residue was purified via C-18 functionalized silica gel chromatography (MeCN/water eluents) to afford the carboxylic acid product.



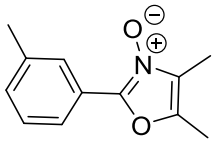
4,5-Dimethyl-2-(*o*-tolyl)oxazole 3-oxide 3a. *o*-Tolylaldehyde (1.20 g, 9.96 mmol) was reacted according to general procedure C to afford the oxazole product[2] as a white solid (1.63 g, 6.80 mmol, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (d, J = 0.8 Hz, 3H), 2.45 (s, 3H), 2.46 (s, 3H),7.41–7.46 (m, 2H), 7.57 (dt, J = 1.1, 7.6 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.8, 11.0, 20.6, 126.6, 130.2, 132.0, 133.2; u (C, CH_2): 120.3, 126.9, 138.9, 145.7, 152.2; IR 1443, 1602, 1627, 2001 cm^{-1}.



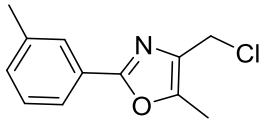
4-(Chloromethyl)-5-methyl-2-(*o*-tolyl)oxazole 4a. 4,5-Dimethyl-2-(*o*-tolyl)oxazole 3-oxide (1.03 g, 5.07 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product[2] as a colorless oil (0.75 g, 3.38 mmol, 67% yield). R_f = 0.52 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.42 (s, 3H), 2.66 (s, 3H), 4.56 (s, 2H), 7.22–7.33 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 21.9, 125.9, 128.7, 129.8, 131.5; u (C, CH_2): 37.5, 126.3, 132.6, 137.3, 146.1, 160.4; IR 1499, 2342, 2364 cm^{-1}.



1-((5-Methyl-2-(o-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 5a. 4-(Chloromethyl)-5-methyl-2-(o-tolyl)oxazole (2.20 g, 9.92 mmol) was reacted according to general procedure E to afford the carboxylic acid product as an off-white solid (1.60 g, 5.09 mmol, 51% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.43 (q, *J* = 10.6 Hz, 2H), 1.63–1.66 (m, 3H), 1.91 (t, *J* = 10.4 Hz, 2H), 2.34 (s, 3H), 2.58 (s, 3H), 2.75 (d, *J* = 11.0 Hz, 2H), 3.30 (s, 2H), 7.27–7.35 (m, 3H), 7.83 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 21.5, 44.3, 126.1, 127.9, 129.6, 131.6; u (C, CH_2): 29.8, 53.5, 126.2, 132.6, 136.2, 145.5, 158.4, 177.9; IR 1557, 2342, 2360, 3280 cm^{-1}.

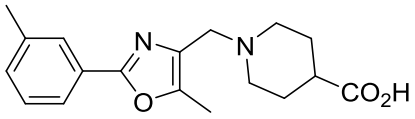


4,5-Dimethyl-2-(*m*-tolyl)oxazole 3-oxide 3b. *m*-Tolylaldehyde (2.17 g, 18.1 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (1.60 g, 7.87 mmol, 48% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (d, *J* = 0.5 Hz, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 7.29–7.50 (m, 2H), 8.08 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.6, 11.0, 21.4, 123.2, 126.1, 129.6, 132.9; u (C, CH_2): 122.1, 128.3, 139.1, 144.2, 148.6. HRMS (m/z): calcd for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1019; found 204.1020.

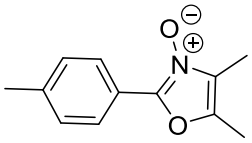


4-(Chloromethyl)-5-methyl-2-(*m*-tolyl)oxazole 4b. 4,5-Dimethyl-2-(*m*-tolyl)oxazole 3-oxide (1.42 g, 6.99 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (1.20 g, 5.41 mmol, 77% yield). R_f = 0.48 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.36 (s, 6H), 4.52 (s, 2H), 7.20 (d,

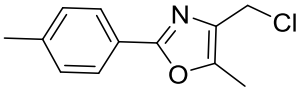
J = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 21.3, 123.3, 126.7, 128.6, 131.1; u (C, CH_2): 37.3, 127.1, 132.8, 138.4, 146.4, 160.2.



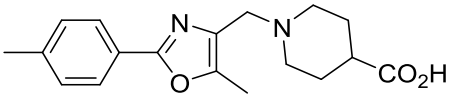
1-((5-Methyl-2-(*m*-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 5b. 4-(Chloromethyl)-5-methyl-2-(m-tolyl)oxazole (255 mg, 1.15 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (254 mg, 0.811 mmol, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (dq, *J* = 3.6, 11.4 Hz, 2H), 1.68 (dd, *J* = 2.6, 13.1 Hz, 2H), 1.76–1.89 (m, 1H), 1.94 (dt, *J* = 2.0, 11.3 Hz, 2H), 2.37 (s, 3H), 2.38 (s, 3H), 2.73–2.79 (m, 2H), 3.31 (s, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 20.8, 29.3, 43.9, 53.2, 53.3, 122.6, 125.9, 127.0, 128.9, 130.7, 132.7, 138.3, 146.0, 158.2, 177.4; HRMS (m/z): calcd for $C_{18}H_{22}N_2O_3$ $[M + H]^+$ 315.1703; found 315.1647.



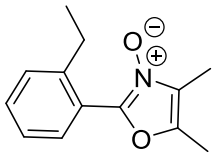
4,5-Dimethyl-2-(*p*-tolyl)oxazole 3-oxide 3c. *p*-Tolylaldehyde (1.73 g, 14.4 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (1.25 g, 6.15 mmol, 47% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.17 (s, 3H), 2.39 (s, 3H), 2.40 (s, 3H), 7.43 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.6, 10.9, 21.7, 126.4, 130.3; u (C, CH_2): 119.0, 127.8, 143.2, 144.2, 149.8.



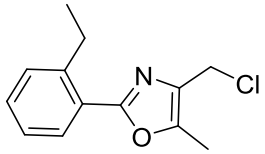
4-(Chloromethyl)-5-methyl-2-(*p*-tolyl)oxazole 4c. 4,5-Dimethyl-2-(*p*-tolyl)oxazole 3-oxide (1.25 g, 6.15 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (0.90 g, 4.06 mmol, 66% yield). R_f = 0.49 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.37 (s, 3H), 2.39 (s, 3H), 4.52 (s, 2H), 7.22 (d, *J* = 8.0 Hz, 2H7.88 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 21.5, 126.1, 129.4; u (C, CH_2): 37.4, 124.5, 132.7, 140.5, 146.2, 160.2.



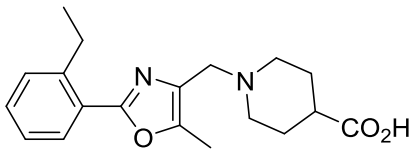
1-((5-Methyl-2-(*p*-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 5c. 4-(Chloromethyl)-5-methyl-2-(p-tolyl)oxazole (216 mg, 0.97 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (270 mg, 0.86 mmol, 88% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.44 (dq, *J* = 3.4, 11.4 Hz, 2H), 1.60 (dd, *J* = 2.7, 13.1 Hz, 2H), 1.71–1.77 (m, 1H), 1.92 (dt, *J* = 1.5, 11.2 Hz, 2H), 2.35 (s, 6H), 2.75 (d, *J* = 11.0 Hz, 2H), 3.29 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 20.9, 29.4, 43.8, 53.3, 53.4, 124.5, 125.4, 129.6, 132.6, 139.8, 145.7, 158.2, 177.5; HRMS (m/z): calcd for $C_{18}H_{22}N_2O_3$ $[M + H]^+$ 315.1703; found 315.1631.



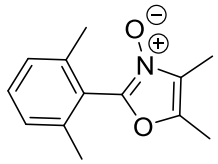
2-(2-Ethylphenyl)-4,5-dimethyloxazole 3-oxide 3d. 2-Ethylbenzaldehyde (0.93 g, 6.93 mmol) was reacted according to general procedure C to afford the oxazole product as a light orange solid (0.90 g, 4.15 mmol, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, *J* = 7.4 Hz, 3H), 2.27 (s, 3H), 2.46 (s, 3H), 2.75 (q, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.8, 11.0, 15.9, 126.7, 130.4, 130.7, 133.6; u (C, CH_2): 26.6, 119.5, 126.9, 145.0, 146.1, 152.6; HRMS (m/z): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1174.



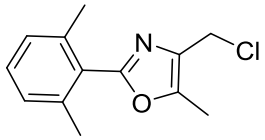
4-(Chloromethyl)-5-methyl-2-(2-ethylphenyl)oxazole 4d. 2-(2-Ethylphenyl)-4,5-dimethyloxazole 3-oxide (0.90 g, 4.15 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (0.15 g, 0.653 mmol, 16% yield). R_f = 0.53 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.5 Hz, 3H), 2.41 (s, 3H), 3.08 (q, *J* = 7.5 Hz, 2H), 4.56 (s, 2H), 7.23–7.39 (complex, 3H), 7.88 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 15.4, 125.9, 129.1, 129.9, 130.1; u (C, CH_2): 27.3, 37.5, 125.8, 132.7, 143.6, 146.2, 160.2.



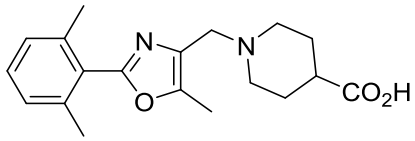
1-((2-(2-Ethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5d. 4-(Chloromethyl)-5-methyl-2-(2-ethylphenyl)oxazole (110 mg, 0.467 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (101 mg, 0.308 mmol, 66% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.14 (t, J = 7.5 Hz, 3H), 1.45 (dq, J = 3.5, 11.5 Hz, 2H), 1.66 (dd, J = 2.6, 13.2 Hz, 2H), 1.70–1.76 (m, 1H), 1.95 (dt, J = 1.6, 11.3 Hz, 2H), 2.37 (s, 3H), 2.38 (s, 3H), 2.78 (d, J = 11.2 Hz, 2H), 3.05 (q, J = 7.5 Hz, 2H), 3.35 (s, 2H), 7.29–7.42 (complex, 3H), 7.81 (dd, J = 1.2, 7.8 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 15.5, 26.7, 29.5, 43.8, 53.2, 53.3, 125.6, 126.1, 128.3, 129.9, 130.1, 132.5, 142.6, 145.5, 158.0, 177.4; HRMS (m/z): calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$ 329.1860; found 329.1867.



2-(2,6-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide 3e. 2,6-Dimethylbenzaldehyde (1.74 g, 12.97 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (2.28 g, 10.49 mmol, 89% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.20 (s, 6H), 2.26 (s, 3H), 2.45 (s, 3H), 7.25 (d, J = 7.7 Hz, 2H), 7.45–7.49 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.8, 11.1, 19.7, 128.3, 133.0; u (C, CH_2): 120.7, 126.8, 140.0, 147.1, 152.0.

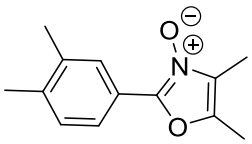


4-(Chloromethyl)-5-methyl-2-(2,6-dimethylphenyl)oxazole 4e. 2-(2,6-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide (1.12 g, 5.16 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (0.35 g, 1.46 mmol, 28% yield). R_f = 0.58 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 2.38 (s, 3H), 4.55 (s, 2H), 7.07 (d, J = 7.5 Hz, 2H), 7.19–7.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.2, 20.3, 127.6, 129.8; u (C, CH_2): 37.4, 127.9, 132.0, 138.4, 146.3, 159.4.

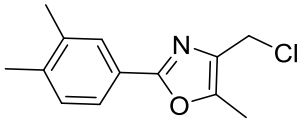


1-((2-(2,6-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5e. 4-(Chloromethyl)-5-methyl-2-(2,6-dimethylphenyl)oxazole (280 mg, 1.19 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a

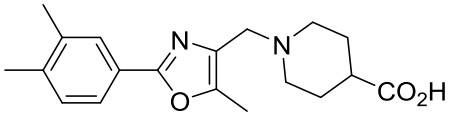
viscous, colorless oil (313 mg, 0.953 mmol, 80% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.46 (dq, J = 2.9, 11.4 Hz, 2H), 1.69 (d, J = 10.9 Hz, 2H), 1.78–1.66 (m, 1H), 1.96 (t, J = 9.9 Hz, 2H), 2.17 (s, 6H), 2.34 (s, 3H), 2.78 (d, J = 11.0 Hz, 2H), 3.38 (s, 2H), 7.15 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.9, 19.8, 29.3, 43.2, 52.8, 53.0, 127.6, 128.2, 129.6, 131.3, 137.6, 145.6, 157.3, 177.4.



2-(3,4-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide 3f. 3,4-Dimethylbenzaldehyde (420 mg, 3.13 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (562 mg, 2.59 mmol, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.18 (d, J = 0.6 Hz, 3H), 2.29 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 7.38 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H), 8.04 (dd, J = 1.7, 8.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.6, 10.9, 19.8, 20.1, 124.2, 127.1, 130.7; u (C, CH_2): 119.1, 127.7, 138.0, 142.3, 144.2, 150.0; HRMS (m/z): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1176.

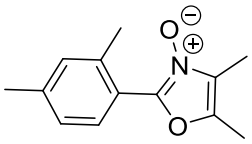


4-(Chloromethyl)-5-methyl-2-(3,4-dimethylphenyl)oxazole 4f. 2-(3,4-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide (485 mg, 2.23 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as an amorphous white solid (508 mg, 2.16 mmol, 97% yield). R_f = 0.68 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 4.54 (s, 2H), 7.18 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 19.8, 123.7, 127.3, 130.0; u (C, CH_2): 37.4, 124.8, 132.6, 137.1, 139.3, 146.1, 160.4.

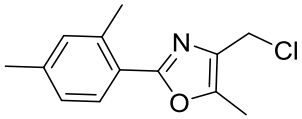


1-((2-(3,4-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5f. 4-(Chloromethyl)-5-methyl-2-(3,4-dimethylphenyl)oxazole (105 mg, 0.445 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (78 mg, 0.238 mmol, 53% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43–1.53 (m, 2H), 1.72 (d, J = 12.1 Hz, 2H), 1.93–2.07 (m, 3H), 2.24 (s, 3H), 2.24 (s, 3H), 2.33 (s, 3H), 2.76 (d, J = 11.3 Hz, 2H), 3.31 (s, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H),

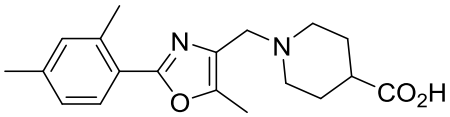
7.68 (s, 1H) ; ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.5, 19.7, 19.8, 41.7, 123.4, 126.8, 130.5; u (C, CH_2): 28.9, 53.0, 53.6, 125.3, 132.9, 137.5, 139.1, 146.1, 158.8, 177.3.



2-(2,4-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide 3g. 2,4-Dimethylbenzaldehyde (1.00 g, 7.45 mmol) was reacted according to general procedure C to afford the oxazole product as an orange, amorphous solid (1.37 g, 6.31 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.49 (s, 6H), 2.50 (s, 3H), 7.20 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.3, 11.0, 20.8, 21.7, 127.6, 131.2, 132.6; u (C, CH_2): 115.5, 127.3, 138.9, 144.8, 145.2, 156.0; HRMS (m/z): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1181.

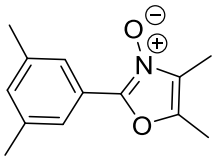


4-(Chloromethyl)-5-methyl-2-(2,4-dimethylphenyl)oxazole 4g. 2-(2,4-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.84 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (222 mg, 0.933 mmol, 51% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.33 (s, 3H), 2.55 (s, 3H), 4.49 (s, 2H), 6.97–7.01 (m, 2H), 7.74 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 21.3, 126.6, 128.7, 132.3; u (C, CH_2): 37.6, 123.6, 132.5, 137.2, 140.0, 145.8, 160.6; HRMS (m/z): calcd for $C_{13}H_{15}ClNO_2$ $[M + H]^+$ 236.0837; found 236.0835.

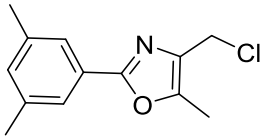


1-((2-(2,4-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5g. 4-(Chloromethyl)-5-methyl-2-(2,4-dimethylphenyl)oxazole (201 mg, 0.853 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (264 mg, 0.804 mmol, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, *J* = 9.9 Hz, 2H), 1.64–1.76 (m, 3H), 1.94 (t, *J* = 9.9 Hz, 2H), 2.31 (s, 3H), 2.35 (s, 3H), 2.57 (s, 3H), 2.78 (d, *J* = 10.9 Hz, 2H), 3.32 (s, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 20.7, 21.4, 44.0, 126.7, 127.9, 132.1; u (C, CH_2): 29.6, 53.4, 53.5, 123.5, 132.4,

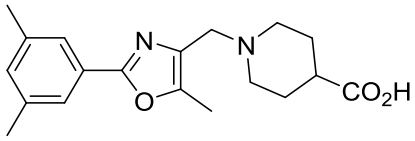
136.0, 139.1, 145.1, 158.5, 177.8; HRMS (m/z): calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$ 329.1860; found 329.1862.



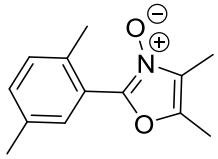
2-(3,5-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide 3h. 3,3-Dimethylbenzaldehyde (1.00 g, 7.45 mmol) was reacted according to general procedure C to afford the oxazole product as a light orange, amorphous solid (1.36 g, 6.25 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 6H), 2.45 (s, 3H), 2.46 (s, 3H), 7.29 (s, 1H), 7.91 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.2, 10.9, 21.3, 125.9, 136.6; u (C, CH_2): 119.1, 127.9, 139.5, 144.4, 154.3; HRMS (m/z): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1182.



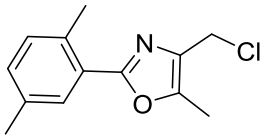
4-(Chloromethyl)-5-methyl-2-(3,5-dimethylphenyl)oxazole 4h. 2-(3,5-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.84 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (255 mg, 1.08 mmol, 59% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 2.34 (s, 3H), 4.47 (s, 2H), 6.99 (s, 1H), 7.56 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 21.2, 124.0, 132.1; u (C, CH_2): 37.3, 126.9, 132.7, 138.4, 146.3, 160.4; HRMS (m/z): calcd for $C_{13}H_{15}ClNO_2$ $[M + H]^+$ 236.0837; found 236.0835.



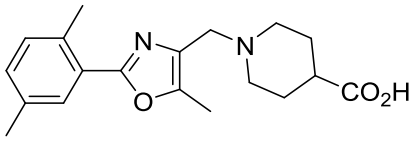
1-((2-(3,5-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5h. 4-(Chloromethyl)-5-methyl-2-(3,5-dimethylphenyl)oxazole (201 mg, 0.853 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (264 mg, 0.804 mmol, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, J = 10.1 Hz, 2H), 1.64–1.75 (m, 3H), 1.92 (t, J = 10.1 Hz, 2H), 2.33 (s, 6H), 2.35 (s, 3H), 2.76 (d, J = 10.9 Hz, 2H), 3.29 (s, 2H), 7.10 (s, 1H), 7.53 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 20.7, 44.1, 123.1, 131.4; u (C, CH_2): 29.6, 53.4, 53.5, 127.0, 132.8, 145.8, 158.2, 177.9; HRMS (m/z): calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$ 329.1860; found 329.1862.



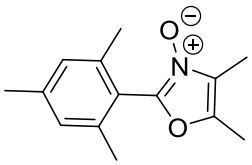
2-(2,5-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide 3i. 2,5-Dimethylbenzaldehyde (1.06 g, 7.89 mmol) was reacted according to general procedure C to afford the oxazole product as a light orange, amorphous solid (1.31 g, 6.04 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.45 (s, 3H), 2.47 (s, 6H), 7.20 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.3, 11.0, 20.3, 20.8, 131.3, 131.7, 134.9; u (C, CH_2): 118.1, 127.3, 136.0, 136.6, 145.2, 156.0; HRMS (m/z): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1183.



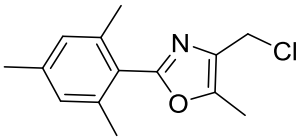
4-(Chloromethyl)-5-methyl-2-(2,5-dimethylphenyl)oxazole 4i. 2-(2,5-Dimethylphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.84 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (253 mg, 1.08 mmol, 58% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.34 (s, 3H), 2.53 (s, 3H), 4.48 (s, 2H), 7.00–7.10 (m, 2H), 7.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 20.8, 21.4, 129.2, 130.7, 131.5; u (C, CH_2): 37.5, 126.0, 132.5, 134.2, 135.4, 146.1, 160.7; HRMS (m/z): calcd for $C_{13}H_{15}ClNO_2$ $[M + H]^+$ 236.0837; found 236.0833.



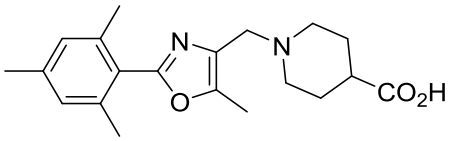
1-((2-(2,5-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5i. 4-(Chloromethyl)-5-methyl-2-(2,5-dimethylphenyl)oxazole (220 mg, 0.933 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (295 mg, 0.899 mmol, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (q, *J* = 11.5 Hz, 2H), 1.62–1.77 (m, 3H), 1.94 (t, *J* = 11.3 Hz, 2H), 2.32 (s, 3H), 2.37 (s, 3H), 2.56 (s, 3H), 2.78 (d, *J* = 11.1 Hz, 2H), 3.33 (s, 2H), 7.13–7.25 (m, *2*H), 7.69 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 20.4, 21.1, 44.1, 128.2, 130.2, 131.5; u (C, CH_2): 29.7, 53.4, 53.5, 125.9, 132.5, 133.1, 135.1, 145.3, 158.4, 177.7; HRMS (m/z): calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$ 329.1860; found 329.1861.



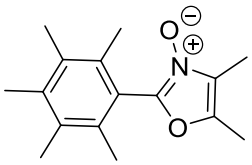
2-(2,4,6-Trimethylphenyl)-4,5-dimethyloxazole 3-oxide 3j. 2,4,6-Trimethylbenzaldehyde (1.13 g, 7.59 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.46 g, 6.32 mmol, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 9H), 2.33 (s, 3H), 2.35 (s, 3H), 6.95 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 6.5, 11.2, 19.7, 21.3, 128.5; u (C, CH_2): 119.6, 127.7, 139.6, 141.4, 142.9.



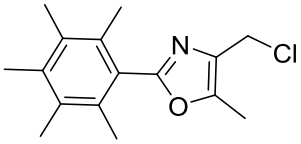
4-(Chloromethyl)-5-methyl-2-(2,4,6-trimethylphenyl)oxazole 4j. 2-(2,4,6-Trimethylphenyl)-4,5-dimethyloxazole 3-oxide (207 mg, 0.895 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (113 mg, 0.454 mmol, 51% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 6H), 2.34 (s, 3H), 2.43 (s, 3H), 4.60 (s, 2H), 6.93 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 20.3, 21.2, 128.5; u (C, CH_2): 37.4, 125.0, 131.8, 138.3, 139.7, 146.2, 159.7.



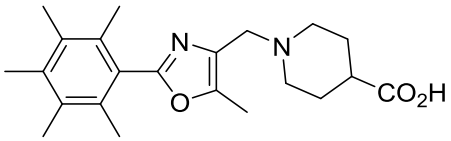
1-((2-(2,4,6-Trimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5j. 4-(Chloromethyl)-5-methyl-2-(2,4,6-trimethylphenyl)oxazole (105 mg, 0.420 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (133 mg, 0.388 mmol, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, J = 10.2 Hz, 2H), 1.61–1.73 (m, 3H), 1.94 (t, J = 11.5 Hz, 2H), 2.14 (s, 6H), 2.28 (s, 3H), 2.33 (s, 3H), 2.77 (d, J = 11.0 Hz, 2H), 3.35 (s, 2H), 6.97 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 19.8, 20.7, 44.3, 128.3; u (C, CH_2): 29.7, 53.2, 53.3, 125.4, 131.4, 137.5, 138.9, 145.4, 157.5, 178.0.



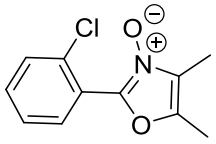
2-(2,3,4,5,6-Pentamethylphenyl)-4,5-dimethyloxazole 3-oxide 3k. 2,3,4,5,6-Pentamethylbenzaldehyde (1.22 g, 6.92 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.16 g, 4.48 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H), 2.23 (s, 6H), 2.29 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.4, 11.1, 16.2, 17.3, 18.4; u (C, CH_2): 117.0, 126.9, 133.8, 134.5, 141.2, 146.0, 158.1.



4-(Chloromethyl)-5-methyl-2-(2,3,4,5,6-pentamethylphenyl)oxazole 4k. 2-(2,3,4,5,6-Pentamethylphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.54 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (88 mg, 0.315 mmol, 20% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.25 (s, 6H), 2.30 (s, 3H), 2.44 (s, 3H), 4.62 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 16.3, 16.9, 18.0; u (C, CH_2): 37.5, 126.4, 131.7, 132.6, 133.6, 137.1, 146.2, 161.2.

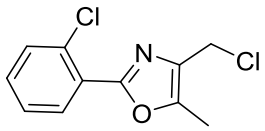


1-((2-(2,3,4,5,6-Pentamethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5k. 4-(Chloromethyl)-5-methyl-2-(2,3,4,5,6-pentamethylphenyl)oxazole (83 mg, 0.420 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (101 mg, 0.274 mmol, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44 (q, J = 10.2 Hz, 2H), 1.56–1.73 (m, 3H), 1.91–1.96 (complex, 8H), 2.18 (s, 6H), 2.23 (s, 3H), 2.33 (s, 3H), 2.77 (d, J = 10.6 Hz, 2H), 3.36 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 16.0, 16.6, 17.6, 44.5; u (C, CH_2): 29.8, 53.2, 53.3, 126.9, 131.1, 132.1, 132.8, 136.3, 145.2, 159.1, 177.4.

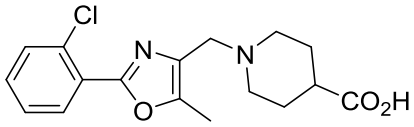


2-(2-Chlorophenyl)-4,5-dimethyloxazole 3-oxide 3l. 2-Chlorobenzaldehyde (3.07 g, 21.87 mmol) was reacted according to general procedure C to afford the oxazole product as a light yellow solid (3.07 g, 13.73 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (d, J = 0.6 Hz, 3H), 2.42 (s, 3H), 7.57 (dt, J = 1.2, 7.6 Hz, 1H), 7.63 (dt, J = 1.7, 7.4 Hz, 1H), 7.70 (dd, J = 1.1, 8.1 Hz, 1H), 8.28 (dd, J = 1.6, 7.8 Hz, 1H); ^{13}C NMR (101 MHz,

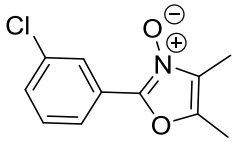
$CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 6.7, 11.1, 127.9, 131.2, 131.6, 133.9; u (C, CH_2): 121.0, 127.9, 132.1, 145.6, 146.9; HRMS (m/z): calcd for $C_{11}H_{11}ClNO_2$ $[M + H]^+$ 224.0473; found 224.0469.



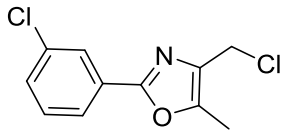
4-(Chloromethyl)-5-methyl-2-(2-chlorophenyl)oxazole 4l. 2-(2-Chlorophenyl)-4,5-dimethyloxazole 3-oxide (1.12 g, 5.01 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (0.59 g, 2.43 mmol, 49% yield). R_f = 0.46 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.58 (s, 2H), 7.30–7.37 (m, 2H), 7.45–7.48 (m, 1H), 7.92–7.98 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 126.8, 130.9, 131.0, 131.1; u (C, CH_2): 37.2, 126.2, 132.3, 132.9, 147.2, 157.9.



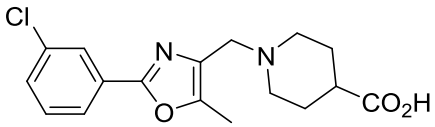
1-((2-(2-Chlorolphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5l. 4-(Chloromethyl)-5-methyl-2-(2-chlorophenyl)oxazole (168 mg, 0.694 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white, amophorous solid (171 mg, 0.511 mmol, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (q, J = 9.8 Hz, 2H), 1.69–1.79 (m, 2H), 1.98–2.04 (m, 3H), 2.39 (s, 3H), 2.80 (d, J = 11.2 Hz, 2H), 3.38 (s, 2H), 7.45–7.55 (m, *2*H), 7.56–7.65 (m, 1H), 7.86–7.99 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 28.7, 41.8, 52.6, 53.1, 125.9, 127.5, 130.6, 130.8, 131.0, 131.4, 132.7, 146.7, 156.0, 176.9; HRMS (m/z): calcd for $C_{17}H_{20}ClN_2O_3$ $[M + H]^+$ 335.1157; found 335.1161.



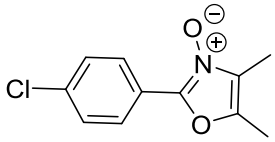
2-(3-Chlorophenyl)-4,5-dimethyloxazole 3-oxide 3m. 3-Chlorobenzaldehyde (1.51 g, 10.77 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (1.78 g, 7.96 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 3H), 2.38 (s, 3H), 7.57–7.60 (m, 2H), 8.12–8.17 (m, 1H), 8.44 (d, J = 0.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 6.5, 11.1, 123.6, 124.3, 131.0, 131.5; u (C, CH_2): 124.4, 129.0, 134.2, 144.5, 145.9; HRMS (m/z): calcd for $C_{11}H_{11}ClNO_2$ $[M + H]^+$ 224.0473; found 224.0470.



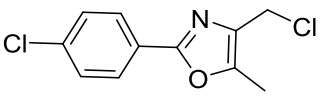
4-(Chloromethyl)-5-methyl-2-(3-chlorophenyl)oxazole 4m. 2-(3-Chlorophenyl)-4,5-dimethyloxazole 3-oxide (1.52 g, 6.80 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (0.39 g, 1.59 mmol, 23% yield). R_f = 0.51 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.52 (s, 2H), 7.28–7.38 (m, 2H), 7.83 (td, *J* = 1.6, 7.1 Hz, 1H), 7.94–7.96 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 124.1, 126.1, 130.0, 130.2; u (C, CH_2): 37.1, 128.7, 133.2, 134.8, 147.1, 158.6.



1-((2-(2,5-Dimethylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5m. 4-(Chloromethyl)-5-methyl-2-(2,5-dimethylphenyl)oxazole (360 mg, 1.49 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (400 mg, 1.19 mmol, 80% yield). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 1.45 (dq, *J* = 3.5, 11.3 Hz, 2H), 1.67 (dd, *J* = 2.9, 13.2 Hz, 2H), 1.76 (tt, *J* = 3.9, 11.2 Hz, 1H), 1.93 (dt, *J* = 1.8, 11.1 Hz, 2H), 2.38 (s, 3H), 2.75 (d, *J* = 11.1 Hz, 2H), 3.32 (s, 2H), 7.53–7.55 (m, *2*H), 7.86–7.89 (m, 2H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 10.0, 29.4, 43.6, 53.3, 124.0, 124.9, 128.9, 129.8, 131.1, 133.2, 133.7, 146.8, 156.7, 177.3; HRMS (m/z): calcd for $C_{17}H_{20}ClN_2O_3$ $[M + H]^+$ 335.1157; found 335.1197.

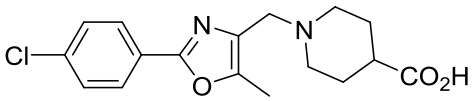


2-(4-Chlorophenyl)-4,5-dimethyloxazole 3-oxide 3n. 4-Chlorobenzaldehyde (1.65 g, 11.74 mmol) was reacted according to general procedure C to afford the oxazole product as a white solid (1.37 g, 6.11 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.34 (s, 3H), 7.44 (d, *J* = 8.8 Hz, 2H), 8.40 (d, *J* = 8.8 Hz, 2H), 7.97 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 6.3, 11.1, 126.1, 129.0; u (C, CH_2): 121.6, 129.4, 136.1, 142.1, 146.0.

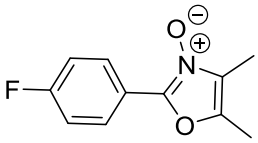


4-(Chloromethyl)-5-methyl-2-(4-chlorophenyl)oxazole 4n. 2-(4-Chlorophenyl)-4,5-dimethyloxazole 3-oxide (1.32 g, 5.01 mmol) was reacted according to general procedure

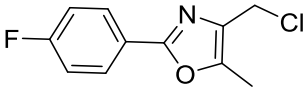
D to afford the chloromethyloxazole product as a white solid (0.71 g, 2.92 mmol, 50% yield). R_f = 0.56 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.53 (s, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 127.4, 129.0; u (C, CH_2): 37.2, 125.7, 133.1, 136.3, 146.8, 159.1.



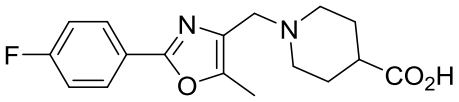
1-((2-(4-Chlorolphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5n. 4-(Chloromethyl)-5-methyl-2-(4-chlorophenyl)oxazole (318 mg, 1.31 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (409 mg, 1.22 mmol, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44 (q, *J* = 11.0 Hz, 2H), 1.63–1.71 (m, 3H), 1.93 (t, *J* = 9.7 Hz, 2H), 2.37 (s, 3H), 2.75 (d, *J* = 10.9 Hz, 2H), 3.31 (s, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 29.6, 44.0, 53.4, 53.5, 125.9, 127.2, 129.2, 133.1, 134.6, 146.5, 157.2, 177.3; HRMS (m/z): calcd for $C_{17}H_{20}ClN_2O_3$ $[M + H]^+$ 335.1157; found 335.1171.



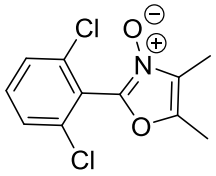
2-(4-Fluorophenyl)-4,5-dimethyloxazole 3-oxide 3o. 4-Fluorobenzaldehyde (1.12 g, 8.98 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.69 g, 8.16 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.46 (s, 3H), 7.20–7.32 (m, 2H), 8.30–8.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.1, 11.0, 117.2 (d, *J* = 22.7 Hz), 131.2 (d, *J* = 9.7 Hz); u (C, CH_2): 115.8 (d, *J* = 3.4 Hz), 128.0, 144.8, 153.1, 166.1 (d, *J* = 260.5 Hz); HRMS (m/z): calcd for $C_{11}H_{11}FNO_2$ $[M + H]^+$ 208.0768; found 208.0781.



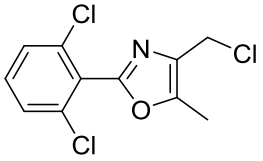
4-(Chloromethyl)-5-methyl-2-(4-fluorophenyl)oxazole 4o. 2-(4-Fluorophenyl)-4,5-dimethyloxazole 3-oxide (480 mg, 2.32 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (359 mg, 1.59 mmol, 69% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.56 (s, 2H), 7.09–7.20 (m, 2H), 7.96–8.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 115.9 (d, *J* = 22.2 Hz), 128.3 (d, *J* = 8.7 Hz); u (C, CH_2): 37.2, 123.6 (d, *J* = 3.2 Hz), 132.9, 146.6, 162.7, 165.2; HRMS (m/z): calcd for $C_{11}H_{10}ClFNO$ $[M + H]^+$ 226.0429; found 226.0450.



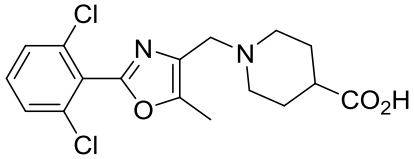
1-((2-(4-Fluorophenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5o. 4-(Chloromethyl)-5-methyl-2-(4-fluorophenyl)oxazole (200 mg, 0.886 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (282 mg, 0.886 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (q, J = 8.8 Hz, 2H), 1.69 (d, J = 13.1 Hz, 2H), 1.78–1.94 (m, 1H) 1.94 (t, J = 11.1 Hz, 2H), 2.36 (s, 3H), 2.76 (d, J = 11.1 Hz, 2H), 3.31 (s, 2H), 7.28–7.39 (m, 2H), 7.90–8.01 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 43.3, 53.4, 116.1 (d, J = 22.3 Hz), 127.8 (d, J = 8.8 Hz); u (C, CH_2): 29.3, 53.2, 53.3, 123.8 (d, J = 3.0 Hz), 132.8, 146.2, 157.3, 163.0 (d, J = 248.6 Hz), 177.6; HRMS (m/z): calcd for $C_{17}H_{20}FN_2O_3$ $[M + H]^+$ 319.1452; found 319.1468.



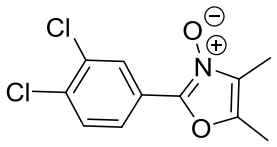
2-(2,6-Dichlorophenyl)-4,5-dimethyloxazole 3-oxide 3p. 2,6-Dichlorobenzaldehyde (1.00 g, 5.71 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.08 g, 4.18 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.40 (s, 3H), 7.40–7.51 (complex, 3H); HRMS (m/z): calcd for $C_{11}H_{10}Cl_2NO_2$ $[M + H]^+$ 258.0083; found 258.0090.



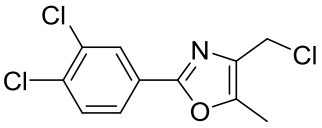
4-(Chloromethyl)-5-methyl-2-(2,6-dichlorophenyl)oxazole 4p. 2-(2,6-Dichlorophenyl)-4,5-dimethyloxazole 3-oxide (423 mg, 1.64 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (186 mg, 0.674 mmol, 41% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 4.52 (s, 2H), 7.23–7.37 (complex, 3H).



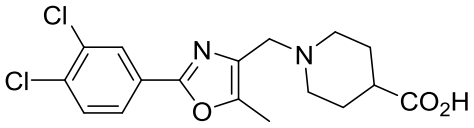
1-((2-(2,6-Dichlorophenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5p. 4-(Chloromethyl)-5-methyl-2-(2,6-dichlorophenyl)oxazole (196 mg, 0.71 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (260 mg, 0.70 mmol, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39–1.49 (m, 2H), 1.58–1.71 (m, 3H), 1.94 (t, J = 10.1 Hz, 2H), 2.37 (s, 3H), 2.76 (d, J = 11.0 Hz, 2H), 3.38 (s, 2H), 7.57–7.68 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.4, 127.4, 132.2, 135.1; u (C, CH_2): 29.8, 53.3, 53.1, 127.4, 132.2, 135.1, 146.8, 152.8, 177.5; HRMS (m/z): calcd for $C_{17}H_{19}Cl_2N_2O_3$ $[M + H]^+$ 369.0767; found 369.0779.



2-(3,4-Dichlorophenyl)-4,5-dimethyloxazole 3-oxide 3q. 3,4-Dichlorobenzaldehyde (1.00 g, 5.71 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.26 g, 4.87 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (d, J = 1.0 Hz, 3H), 2.50 (d, J = 1.0 Hz, 3H), 7.68 (d, J = 8.6 Hz, 1H), 8.25 (dd, J = 2.1, 8.6 Hz, 1H), 8.38 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.1, 11.1, 126.9, 129.3, 131.8; u (C, CH_2): 119.2, 128.7, 134.4, 139.2, 145.6, 151.4; HRMS (m/z): calcd for $C_{11}H_{10}Cl_2NO_2$ $[M + H]^+$ 258.0083; found 258.0088.

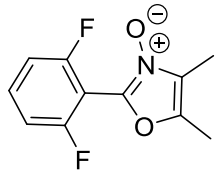


4-(Chloromethyl)-5-methyl-2-(3,4-dichlorophenyl)oxazole 4q. 2-(3,4-Dichlorophenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.55 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (253 mg, 0.915 mmol, 59% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.56 (s, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 2.0, 8.4 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 125.2, 127.9, 130.9; u (C, CH_2): 37.0, 127.0, 133.2, 133.4, 134.5, 147.3, 158.0; HRMS (m/z): calcd for $C_{11}H_9Cl_3NO$ $[M + H]^+$ 277.9715; found 277.9719.

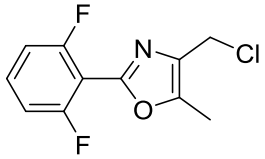


1-((2-(3,4-Dichlorophenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5q. 4-(Chloromethyl)-5-methyl-2-(3,4-dichlorophenyl)oxazole (218 mg, 0.79 mmol) was

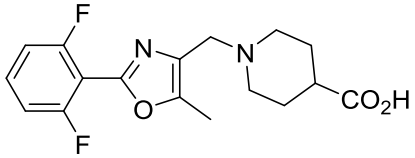
reacted according to general procedure E to afford the carboxylic acid product as a white solid (261 mg, 0.71 mmol, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (dt, J = 3.4, 11.3 Hz, 2H), 1.69 (dd, J = 2.7, 13.1 Hz, 2H), 1.83 (tt, J = 3.8, 11.1 Hz, 1H), 1.95 (dt, J = 1.6, 11.1 Hz, 2H), 2.38 (s, 3H), 2.76 (d, J = 11.0 Hz, 2H), 3.32 (s, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 2.0, 8.4 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 43.1, 125.4, 126.9, 131.4; u (C, CH_2): 29.2, 53.1, 53.2, 127.4, 131.9, 132.5, 133.4, 147.1, 156.0, 177.4; HRMS (m/z): calcd for $C_{17}H_{19}Cl_2N_2O_3$ $[M + H]^+$ 369.0767; found 369.0778.



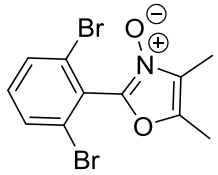
2-(2,6-Difluorophenyl)-4,5-dimethyloxazole 3-oxide 3r. 2,6-difluorobenzaldehyde (1.00 g, 7.04 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (1.09 g, 4.84 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.39 (s, 3H), 7.01–7.11 (m, 1H), 7.48–7.55 (m, 2H); HRMS (m/z): calcd for $C_{11}H_{10}F_2NO_2$ $[M + H]^+$ 226.0674; found 226.0673.



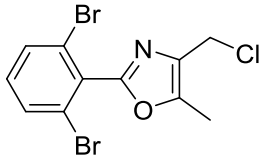
4-(Chloromethyl)-5-methyl-2-(2,6-difluorophenyl)oxazole 4r. To a solution of 2-(2,6-difluorophenyl)-4,5-dimethyloxazole 3-oxide (1.09 g, 4.84 mmol) in $CHCl_3$ (17 mL) was added $SOCl_2$ (0.39 mL, 5.32 mmol, 1.1 equiv) and the reaction heated at reflux for 18 h. After cooling to rt, the reaction was quenched with brine (25 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with Na_2SO_4, evaporated and purified by flash chromatography to afford the chloromethyloxazole product as a white solid (454 mg, 1.87 mmol, 39% yield). R_f = 0.50 (33% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 4.62 (s, 2H), 6.99–7.10 (m, 2H), 7.39–7.47 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.4, 37.0, 106.3 (t, J = 16.1 Hz), 112.2 (dd, J = 4.4, 25.4 Hz), 131.9 (t, J = 10.5 Hz), 133.1, 147.7, 151.3 (t, J = 2.9 Hz), 160.7 (dd, J = 5.6, 257.6 Hz); HRMS (m/z): calcd for $C_{11}H_9ClF_2NO$ $[M + H]^+$ 244.0335; found 244.0333.



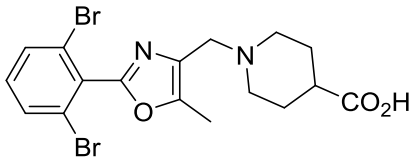
1-((2-(2,6-Difluorolphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5r. 4-(Chloromethyl)-5-methyl-2-(2,6-difluorophenyl)oxazole (305 mg, 1.25 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a colorless, sticky oil (421 mg, 1.25 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (q, J = 9.8 Hz, 2H), 1.65–1.76 (m, 3H) 1.93 (t, J = 11.2 Hz, 2H), 2.37 (s, 3H), 2.77 (d, J = 11.0 Hz, 2H), 3.34 (s, 2H), 7.29 (t, J = 8.5 Hz, 2H), 7.59–7.66 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.0, 112.5 (d, J = 25.0 Hz), 132.7 (t, J = 10.6 Hz); u (C, CH_2): 29.6, 53.2, 53.4, 133.0, 147.1, 149.2, 158.4 (d, J = 5.9 Hz), 160.9 (d, J = 5.8 Hz), 177.9; HRMS (m/z): calcd for $C_{17}H_{19}F_2N_2O_3$ [M + H]$^+$ 337.1358; found 337.1367.



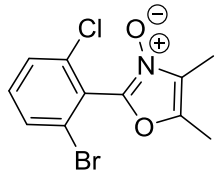
2-(2,6-Dibromophenyl)-4,5-dimethyloxazole 3-oxide 3s. 2,6-Dibromobenzaldehyde (0.988 g, 3.74 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (0.860 g, 2.48 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.57 (s, 3H), 7.46 (t, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.5, 11.3, 132.1, 135.8; u (C, CH_2): 123.4, 125.6, 127.8, 147.7, 152.8; HRMS (m/z): calcd for $C_{11}H_{10}Br_2NO_2$ [M + H]$^+$ 347.9053; found 347.9050.



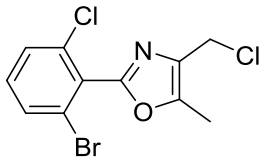
4-(Chloromethyl)-5-methyl-2-(2,6-dibromophenyl)oxazole 4s. 2-(2,6-Dibromophenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.15 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (50 mg, 0.14 mmol, 12% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.61 (s, 2H), 7.22 (t, J = 8.1 Hz, 1H), 7.63 (d, J = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 131.7, 132.5; u (C, CH_2): 37.0, 125.2, 131.6, 132.4, 147.3, 157.0; HRMS (m/z): calcd for $C_{11}H_9Br_2ClNO$ [M + H]$^+$ 365.8714; found 365.8706.



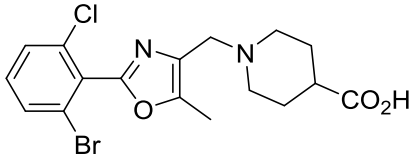
1-((2-(2,6-Dibromophenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5s. 4-(Chloromethyl)-5-methyl-2-(2,6-dibromophenyl)oxazole (48 mg, 0.13 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (60 mg, 0.13 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (q, J = 11.5 Hz, 2H), 1.56–1.69 (m, 3H) 1.95 (dt, J = 0.7, 11.6 Hz, 2H), 2.37 (s, 3H), 2.76 (d, J = 10.8 Hz, 2H), 3.35 (s, 2H), 7.45 (t, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.9, 29.8, 44.3, 53.1, 53.2, 124.6, 131.4, 131.88, 131.91, 133.6, 146.4, 155.4, 177.1; HRMS (m/z): calcd for $C_{17}H_{19}Br_2N_2O_3$ $[M + H]^+$ 458.9737; found 458.9725.



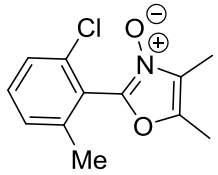
2-(2-Bromo-6-chlorophenyl)-4,5-dimethyloxazole 3-oxide 3t. 2-Bromo-6-chlorobenzaldehyde (0.98 g, 4.47 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light yellow solid (0.79 g, 2.60 mmol, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.56 (s, 3H), 7.48–7.62 (m, *2*H), 7.68 (dd, J = 2.0, 7.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.5, 11.3, 129.1, 131.7, 135.6; u (C, CH_2): 121.3, 125.5, 127.9, 137.3, 148.0, 151.8; HRMS (m/z): calcd for $C_{11}H_{10}BrClNO_2$ $[M + H]^+$ 303.9558; found 303.9552.



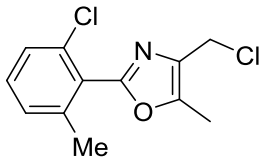
4-(Chloromethyl)-5-methyl-2-(2-bromo-6-chlorophenyl)oxazole 4t. 2-(2-Bromo-6-chlorophenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.32 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (62 mg, 0.19 mmol, 15% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.60 (s, 2H), 7.29 (t, J = 8.1 Hz, 1H), 7.45 (dd, J = 1.1, 8.1 Hz, 1H), 7.59 (dd, J = 1.1, 8.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 128.6, 131.2, 132.2; u (C, CH_2): 37.0, 125.3, 129.7, 132.5, 136.3, 147.5, 155.9; HRMS (m/z): calcd for $C_{11}H_9BrCl_2NO$ $[M + H]^+$ 321.9219; found 321.9205.



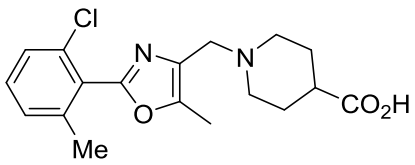
1-((2-(2-Bromo-6-chlorophenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5t. 4-(Chloromethyl)-5-methyl-2-(2-bromo-6-chlorophenyl)oxazole (60 mg, 0.19 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a colorless oil (68 mg, 0.16 mmol, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, *J* = 11.0 Hz, 2H), 1.63–1.69 (m, *3*H), 1.95 (t, *J* = 11.0 Hz, 2H), 2.37 (s, 3H), 2.77 (d, *J* = 11.0 Hz, 2H), 3.38 (s, 2H), 7.53 (t, *J* = 8.1 Hz, 1H), 7.69 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.80 (dd, *J* = 1.1, 8.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.3, 128.9, 131.6, 133.3; u (C, CH_2): 29.8, 53.1, 53.2, 124.6, 129.4, 132.0, 135.0, 146.6, 154.1, 177.6; HRMS (m/z): calcd for $C_{17}H_{19}BrClN_2O_3$ $[M + H]^+$ 415.0242; found 415.0297.



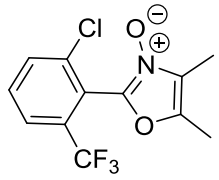
2-(2-Chloro-6-methylphenyl)-4,5-dimethyloxazole 3-oxide 3u. 2-Chloro-6-methylbenzaldehyde (0.702 g, 4.54 mmol) was reacted according to general procedure C to afford the oxazole product as a tan-colored solid (0.797 g, 3.35 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.53 (s, 6H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.4, 11.2, 20.4, 127.3, 129.3, 134.5; u (C, CH_2): 118.9, 127.6, 135.2, 143.0, 147.5, 153.8; HRMS (m/z): calcd for $C_{12}H_{13}ClNO_2$ $[M + H]^+$ 238.0635; found 238.0627.



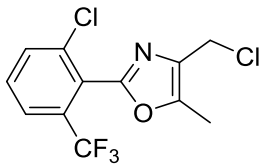
4-(Chloromethyl)-5-methyl-2-(2-chloro-6-methylphenyl)oxazole 4u. 2-(2-Chloro-6-methylphenyl)-4,5-dimethyloxazole 3-oxide (789 mg, 3.32 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (327 mg, 1.28 mmol, 39% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.42 (s, 3H), 4.58 (s, 2H), 7.11–7.21 (m, 1H), 7.21–7.33 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 20.3, 127.0, 128.5, 131.0; u (C, CH_2): 37.2, 127.7, 132.2, 134.8, 141.0, 147.0, 156.9; HRMS (m/z): calcd for $C_{12}H_{12}Cl_2NO$ $[M + H]^+$ 256.0296; found 256.0288.



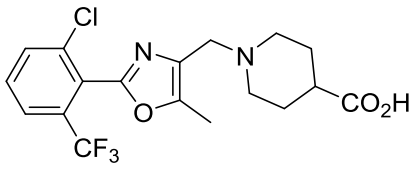
1-((2-(2-Chloro-6-methylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5u. 4-(Chloromethyl)-5-methyl-2-(2-chloro-6-methylphenyl)oxazole (130 mg, 0.51 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a colorless oil (113 mg, 0.32 mmol, 64% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46–1.56 (m, 2H), 1.74 (dd, J = 2.8, 13.1 Hz, 2H), 2.02 (t, J = 11.1 Hz, 2H), 2.02–2.08 (m, 1H), 2.19 (s, 3H), 2.36 (s, 3H), 2.80 (d, J = 11.4 Hz, 2H), 3.42 (s, 2H), 7.31–7.40 (m, 1H), 7.40–7.50 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.9, 19.7, 28.6, 41.5, 52.3, 52.7, 126.9, 127.7, 128.9, 131.4, 131.5, 133.4, 140.7, 146.4, 155.0, 176.8; HRMS (m/z): calcd for $C_{18}H_{22}ClN_2O_3$ $[M + H]^+$ 349.1319; found 349.1340.



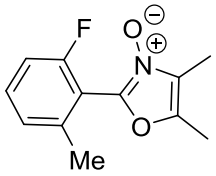
2-(2-Chloro-6-(trifluoromethyl)phenyl)-4,5-dimethyloxazole 3-oxide 3v. 2-Chloro-6-(trifluoromethyl)benzaldehyde (1.52 g, 7.29 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (0.914 g, 3.13 mmol, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.58 (s, 3H), 7.79–7.91 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.4, 11.2, 125.5 (q, J = 4.5 Hz), 133.9, 135.2; u (C, CH_2): 117.0, 122.0 (q, J = 275.5 Hz), 128.3, 133.3 (q, J = 32.9 Hz), 138.1, 148.3, 149.5; HRMS (m/z): calcd for $C_{12}H_{10}ClF_3NO_2$ $[M + H]^+$ 292.0347; found 292.0346.



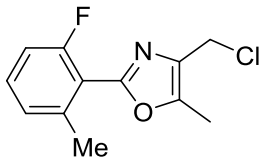
4-(Chloromethyl)-5-methyl-2-(2-chloro-6-(trifluoromethyl)phenyl)oxazole 4v. 2-(2-chloro-6-(trifluoromethyl)phenyl)-4,5-dimethyloxazole 3-oxide (360 mg, 1.23 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (29 mg, 0.094 mmol, 8% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.46 (s, 3H), 4.60 (s, 2H), 7.57–7.61 (m, 1H), 7.68–7.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 124.7 (q, J = 4.9 Hz), 131.5, 133.1; u (C, CH_2): 36.9, 122.7 (q, J = 275.3 Hz), 130.0, 132.5, 132.8, 137.1, 147.8, 153.7; HRMS (m/z): calcd for $C_{12}H_9Cl_2F_3NO$ $[M + H]^+$ 310.0008; found 309.9993.



1-((2-(2-Chloro-6-(trifluoromethyl)phenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5v. 4-(Chloromethyl)-5-methyl-2-(2-chloro-6-(trifluoromethyl)phenyl)oxazole (22 mg, 0.071 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (28 mg, 0.070 mmol, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (dq, J = 0.8, 12.3, 2H), 1.62–1.71 (m, 3H), 1.94 (t, J = 10.3 Hz, 2H), 2.37 (s, 3H), 2.74 (d, J = 10.6 Hz, 2H), 3.39 (s, 2H), 7.84 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 9.8, 29.7, 44.0, 52.85, 52.93, 122.7 (q, J = 274.7 Hz), 125.4 (q, J = 5.0 Hz), 126.05, 126.07, 130.9 (q, J = 31.0 Hz), 132.3, 132.8, 133.8, 147.1, 151.8, 177.1; HRMS (m/z): calcd for $C_{18}H_{19}ClF_3N_2O_3$ $[M + H]^+$ 403.1031; found 403.1058.

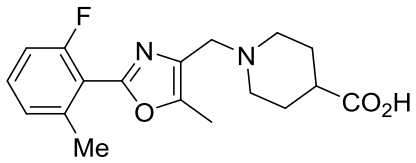


2-(2-Fluoro-6-methylphenyl)-4,5-dimethyloxazole 3-oxide 3w. 2-Fluoro-6-methylbenzaldehyde (1.00 g, 7.24 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light yellow solid (1.41 g, 6.35 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.53 (s, 6H), 7.11 (t, J = 8.9 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H) 7.55–7.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.4, 11.3, 20.2 (d, J = 1.1 Hz), 113.6 (d, J = 13.8 Hz), 126.8 (d, J = 3.2 Hz), 135.6 (d, J = 9.5 Hz); u (C, CH_2): 107.8 (d, J = 13.8 Hz), 127.9, 142.3, 147.6, 151.9, 161.0 (d, J = 257.5 Hz); HRMS (m/z): calcd for $C_{12}H_{13}FNO_2$ $[M + H]^+$ 222.0925; found 222.0918.

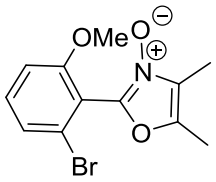


4-(Chloromethyl)-5-methyl-2-(2-fluoro-6-methylphenyl)oxazole 4w. To a solution of 2-(2- fluoro-6-methylphenyl)-4,5-dimethyloxazole 3-oxide (0.40 g, 1.81 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (85 mg, 0.36 mmol, 20% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.47 (s, 3H), 4.60 (s, 2H), 6.96–7.05 (m, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.29–7.35 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d

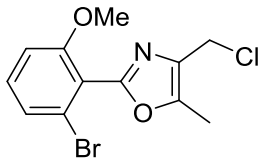
(CH, CH_3): 10.3, 20.5 (d, *J* = 2.5 Hz), 37.2, 113.3 (d, *J* = 22.1 Hz), 126.2 (d, *J* = 3.2 Hz), 131.2 (d, *J* = 9.4 Hz); u (C, CH_2): 116.0 (d, *J* = 13.4 Hz), 132.5, 140.7 (d, *J* = 1.4 Hz), 147.0, 155.2, 161.2 (d, *J* = 252.9 Hz); HRMS (m/z): calcd for $C_{12}H_{12}ClFNO$ $[M + H]^+$ 240.0586; found 240.0584.



1-((2-(2-Fluoro-6-methylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5w. 4-(Chloromethyl)-5-methyl-2-(2-fluoro-6-methylphenyl)oxazole (72 mg, 0.30 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a colorless, sticky oil (100 mg, 0. 30 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, *J* = 10.2 Hz, 2H), 1.64–1.72 (m, 3H) 1.94 (t, *J* = 9.8 Hz, 2H), 2.36 (s, 3H), 2.37 (s, 3H), 2.78 (d, *J* = 11.0 Hz, 2H), 3.36 (s, 2H), 7.16–7.22 (m, 2H), 7.42–7.48 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 19.9 (d, *J* = 2.5 Hz), 44.2, 113.2 (d, *J* = 21.9 Hz), 126.5, 131.5 (d, *J* = 9.5 Hz); u (C, CH_2): 29.7, 53.2, 53.4, 115.9 (d, *J* = 13.9 Hz), 132.3, 140.1 (d, *J* = 1.5 Hz), 146.3, 153.1, 160.2 (d, *J* = 250.1 Hz), 177.8; HRMS (m/z): calcd for $C_{18}H_{22}FN_2O_3$ $[M + H]^+$ 333.1609; found 333.1624.

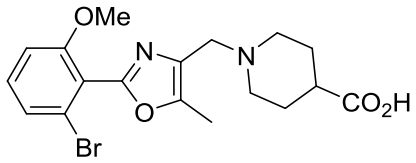


2-(2-Bromo-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide 3x. 2-Bromo-6-methoxybenzaldehyde (0.86 g, 4.00 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light orange oil (0.68 g, 2.28 mmol, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 6H), 3.91 (s, 3H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.3, 11.2, 56.9, 110.7, 125.0, 135.9; u (C, CH_2): 110.8, 124.6, 127.5, 146.9, 151.4, 160.7; HRMS (m/z): calcd for $C_{12}H_{13}BrNO_3$ $[M + H]^+$ 298.0073; found 298.0072.

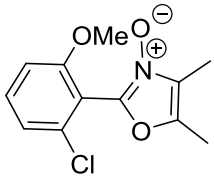


4-(Chloromethyl)-5-methyl-2-(2-bromo-6-methoxyphenyl)oxazole 4x. 2-(2-Bromo-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.34 mmol) was reacted

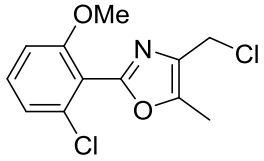
according to general procedure D to afford the chloromethyloxazole product as a white solid (51 mg, 0.16 mmol, 12% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.80 (s, 3H), 4.61 (s, 2H), 6.93 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.21–7.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 56.3, 110.0, 124.7, 132.4; u (C, CH_2): 37.3, 119.6, 125.1, 132.2, 147.2, 155.9, 159.9; HRMS (m/z): calcd for $C_{12}H_{12}BrClNO_2$ $[M + H]^+$ 315.9734; found 315.9734.



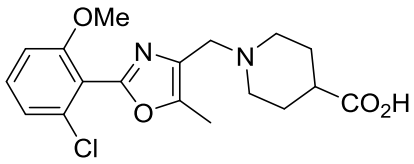
1-((2-(2-Bromo-6-methoxyphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5x. 4-(Chloromethyl)-5-methyl-2-(2-bromo-6-methoxyphenyl)oxazole (50 mg, 0.16 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (62 mg, 0.15 mmol, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, *J* = 10.6 Hz, 2H), 1.60–1.70 (m, *3*H), 1.93 (t, *J* = 10.5 Hz, 2H), 2.33 (s, 3H), 2.77 (d, *J* = 10.1 Hz, 2H), 3.33 (s, 2H), 3.76 (s, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.4, 56.2, 111.0, 124.2, 132.9; u (C, CH_2): 29.8, 53.3, 53.4, 99.5, 119.4, 131.9, 146.0, 154.1, 159.6, 177.4; HRMS (m/z): calcd for $C_{18}H_{22}BrN_2O_4$ $[M + H]^+$ 409.0757; found 409.0777.



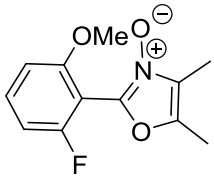
2-(2-Chloro-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide 3y. 2-Chloro-6-methoxybenzaldehyde (0.96 g, 5.63 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light orange oil (1.04 g, 4.10 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.51 (s, 3H), 3.94 (s, 3H), 6.99 (dd, *J* = 0.9, 8.7 Hz, 1H), 7.13 (dd, *J* = 0.9, 8.0 Hz, 1H), 7.56 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.4, 11.2, 56.9, 110.2, 121.9, 135.7; u (C, CH_2): 108.6, 127.6, 136.0, 147.0, 151.2, 160.7; HRMS (m/z): calcd for $C_{12}H_{13}ClNO_3$ $[M + H]^+$ 254.0578; found 254.0573.



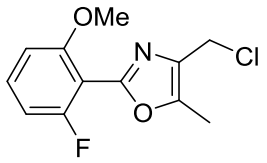
4-(Chloromethyl)-5-methyl-2-(2-chloro-6-methoxyphenyl)oxazole 4y. 2-(2-Chloro-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide (430 mg, 1.70 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (120 mg, 0.44 mmol, 26% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.81 (s, 3H), 4.61 (s, 2H), 6.89 (dd, *J* = 0.9, 8.5 Hz, 1H), 7.08 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.37 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 56.3, 109.4, 121.7, 132.0; u (C, CH_2): 37.3, 117.5, 132.3, 135.9, 147.3, 154.8, 159.8; HRMS (m/z): calcd for $C_{12}H_{12}Cl_2NO_2$ $[M + H]^+$ 272.0240; found 272.0233.



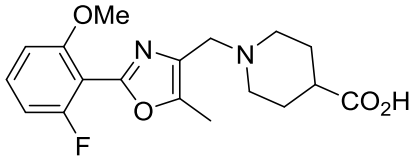
1-((2-(2-Chloro-6-methoxyphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5y. 4-(Chloromethyl)-5-methyl-2-(2-chloro-6-methoxyphenyl)oxazole (110 mg, 0.40 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (145 mg, 0.40 mmol, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (q, *J* = 10.9 Hz, 2H), 1.64–1.77 (m, *3*H), 1.94 (t, *J* = 10.5 Hz, 2H), 2.33 (s, 3H), 2.78 (d, *J* = 10.0 Hz, 2H), 3.34 (s, 2H), 3.77 (s, 3H), 7.17 (t, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.0, 56.3, 110.6, 121.2, 132.6; u (C, CH_2): 29.6, 53.26, 53.29, 117.3, 132.0, 134.4, 146.2, 152.9, 159.5, 177.7; HRMS (m/z): calcd for $C_{18}H_{22}ClN_2O_4$ $[M + H]^+$ 365.1263; found 365.1287.



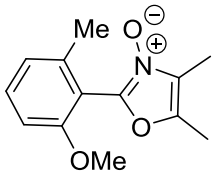
2-(2-Fluoro-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide 3z. 2-Fluoro-6-methoxybenzaldehyde (1.00 g, 6.49 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light orange oil (1.11 g, 4.68 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.52 (s, 3H), 3.96 (s, 3H), 6.79–6.91 (m, 2H), 7.59–7.64 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.6, 11.3, 57.1, 107.8 (d, *J* = 2.9 Hz), 108.2 (d, *J* = 20.2 Hz), 136.9 (d, *J* = 11.0 Hz); u (C, CH_2): 97.6 (d, *J* = 16.0 Hz), 127.8, 147.4, 149.9, 160.0 (d, *J* = 4.4 Hz), 161.4 (d, *J* = 258.7 Hz); HRMS (m/z): calcd for $C_{12}H_{13}FNO_3$ $[M + H]^+$ 238.0874; found 238.0873.



4-(Chloromethyl)-5-methyl-2-(2-fluoro-6-methoxyphenyl)oxazole 4z. 2-(2-Fluoro-6-methoxyphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.69 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (112 mg, 0.44 mmol, 26% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.75 (s, 3H), 4.50 (s, 2H), 6.64–6.74 (m, 2H), 7.25–7.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.3, 56.4, 106.9 (d, *J* = 3.1 Hz), 108.2 (d, *J* = 22.1Hz), 132.2 (d, *J* = 10.9 Hz); u (C, CH_2): 37.3, 106.3 (d, *J* = 16.5 Hz), 132.5, 147.3, 152.9, 159.4 (d, *J* = 5.7 Hz), 161.6 (d, *J* = 253.0 Hz); HRMS (m/z): calcd for $C_{12}H_{12}ClFNO_2$ $[M + H]^+$ 256.0535; found 256.0531.

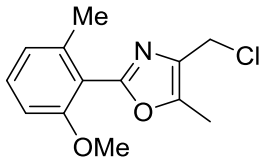


1-((2-(2-Fluoro-6-methoxyphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5z. 4-(Chloromethyl)-5-methyl-2-(2-fluoro-6-methoxyphenyl)oxazole (100 mg, 0.39 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (135 mg, 0.39 mmol, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (q, *J* = 10.8 Hz, 2H), 1.64–1.74 (m, *3*H), 1.93 (t, *J* = 10.2 Hz, 2H), 2.34 (s, 3H), 2.77 (d, *J* = 10.8 Hz, 2H), 3.32 (s, 2H), 3.81 (s, 3H), 6.93–6.97 (m, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.51–7.57 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 9.9, 44.1, 56.4, 107.8 (d, *J* = 17.5 Hz), 107.9, 132.6 (d, *J* = 10.9 Hz); u (C, CH_2): 29.6, 53.4, 106.2 (d, *J* = 17.0 Hz), 132.4, 146.4, 150.7, 159.0 (d, *J* = 5.8 Hz), 160.6 (d, *J* = 249.2 Hz), 177.7; HRMS (m/z): calcd for $C_{18}H_{22}FN_2O_4$ $[M + H]^+$ 349.1558; found 349.1572.

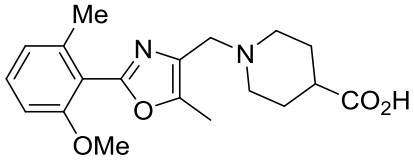


2-(2-Methoxy-6-methylphenyl)-4,5-dimethyloxazole 3-oxide 3aa. 2-Methoxy-6-methylbenzaldehyde (0.229 g, 1.52 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a white solid (0.313 g, 1.34 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.47 (q, *J* = 1.0 Hz, 3H), 2.52 (q, *J* = 1.0 Hz, 3H), 3.87 (s, 3H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.93 (td, *J* = 0.8, 7.7 Hz, 1H), 7.49 (dd, *J* = 7.7, 8.5

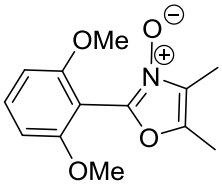
Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.5, 11.1, 19.9, 56.3, 108.9, 122.9, 135.0; u (C, CH_2): 108.1, 127.3, 141.5, 146.6, 154.6, 159.3; HRMS (m/z): calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1125; found 234.1120.



4-(Chloromethyl)-5-methyl-2-(2-methoxy-6-methylphenyl)oxazole 4aa. 2-(2-Methoxy-6-methylphenyl)-4,5-dimethyloxazole 3-oxide (278 mg, 1.19 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (84 mg, 0.33 mmol, 28% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 4.60 (s, 2H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* =7.7 Hz, 1H), 7.31 (dd, *J* = 7.7, 8.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 20.0, 55.9, 108.4, 122.5, 131.0; u (C, CH_2): 37.5, 117.4, 132.0, 140.4, 146.7, 157.3, 158.8; HRMS (m/z): calcd for $C_{13}H_{15}ClNO_2$ $[M + H]^+$ 252.0786; found 252.0776.

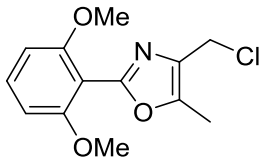


1-((2-(2-Methoxy-6-methylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5aa. 4-(Chloromethyl)-5-methyl-2-(2-methoxy-6-methylphenyl)oxazole (71 mg, 0.28 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (97 mg, 0.28 mmol, quantitative yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 1.44 (q, *J* = 10.6 Hz, 2H), 1.62–1.70 (m, 3H), 1.93 (t, *J* = 10.5 Hz, 2H), 2.12 (s, 3H), 2.32 (s, 3H), 2.77 (d, *J* = 10.9 Hz, 2H), 3.33 (s, 2H), 3.73 (s, 3H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, APT pulse sequence) δ d (CH, CH_3): 9.9, 19.3, 44.3, 55.7, 108.9, 122.1, 131.0; u (C, CH_2): 29.8, 53.3, 53.4, 117.6, 126.9, 131.6, 139.4, 145.5, 155.3, 158.2, 177.4.

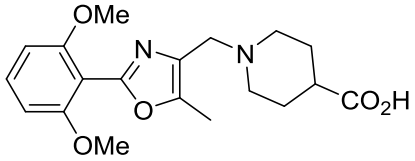


2-(2,6-Dimethoxyphenyl)-4,5-dimethyloxazole 3-oxide 3bb. 2,6-Dimethoxybenzaldehyde (1.00 g, 6.02 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light orange oil (1.14 g, 4.55 mmol, 83% yield). ^{1}H

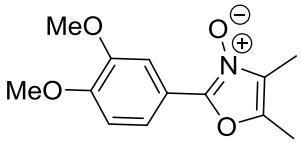
NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.52 (s, 3H), 3.88 (s, 6H), 6.63 (d, *J* = 8.5 Hz, 2H), 7.54 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.5, 11.1, 56.4, 103.9, 136.4; u (C, CH_2): 97.1, 127.1, 146.4, 152.6, 160.2; HRMS (m/z): calcd for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1074; found 250.1069.



4-(Chloromethyl)-5-methyl-2-(2,6-dimethoxyphenyl)oxazole 4bb. 2-(2,6-Dimethoxyphenyl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.61 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a white solid (129 mg, 0.48 mmol, 30% yield). R_f = 0.50 (20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.78 (s, 6H), 4.60 (s, 2H), 6.60 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 56.1, 103.8, 132.1; u (C, CH_2): 37.5, 106.5, 132.0, 147.0, 155.1, 159.7; HRMS (m/z): calcd for $C_{13}H_{15}ClNO_3$ $[M + H]^+$ 268.0735; found 268.0733.

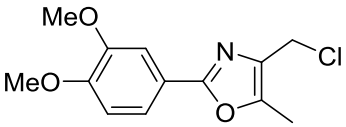


1-((2-(2,6-Dimethoxyphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5bb. 4-(Chloromethyl)-5-methyl-2-(2,6-dimethoxyphenyl)oxazole (120 mg, 0.448 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (160 mg, 0.444 mmol, 99% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 1.46 (dq, *J* = 2.1, 11.7 Hz, 2H), 1.65–1.78 (m, 3H), 1.92 (dt, *J* = 1.4, 11.2 Hz, 2H), 2.30 (s, 3H), 2.78 (d, *J* = 11.0 Hz, 2H), 3.29 (s, 2H), 3.71 (s, 6H), 6.75 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 44.0, 55.8, 104.0, 132.1; u (C, CH_2): 29.6, 53.5, 106.7, 131.8, 145.5, 153.1, 159.1, 177.8; HRMS (m/z): calcd for $C_{19}H_{25}N_2O_5$ $[M + H]^+$ 361.1758; found 361.1768.

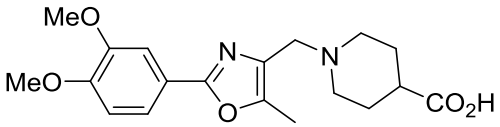


2-(3,4-Dimethoxyphenyl)-4,5-dimethyloxazole 3-oxide 3cc. 3,4-Dimethoxybenzaldehyde (3.09 g, 18.60 mmol) was reacted according to general procedure C to afford the oxazole product as a bright yellow solid (3.75 g, 13.12 mmol, 78% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.43 (s, 3H), 3.96 (s, 3H), 3.97 (s,

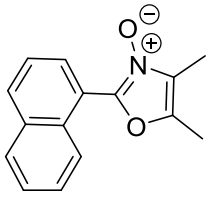
3H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 1.7 Hz, 1H), 7.94 (dd, *J* = 1.7, 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.1, 10.9, 56.3, 56.5, 110.3, 111.4, 123.2; u (C, CH_2): 111.5, 127.51, 143.5, 149.5, 154.2, 154.5; IR 1420, 1518, 1595, 1925 cm^{-1}.



4-(Chloromethyl)-5-methyl-2-(3,4-dimethoxyphenyl)oxazole 4cc. 2-(3,4-Dimethoxyphenyl)-4,5-dimethyloxazole 3-oxide (2.11 g, 7.38 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a tan solid (1.72 g, 6.44 mmol, 87% yield). R_f = 0.45 (33% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.94 (s, 3H), 4.01 (s, 3H), 4.69 (s, 2H), 6.94 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.8, 56.2, 56.8, 110.3, 111.2, 121.5; u (C, CH_2): 34.4, 115.3, 128.7, 147.5, 149.6, 153.4, 160.3; IR 1462, 1508, 1605 cm^{-1}.

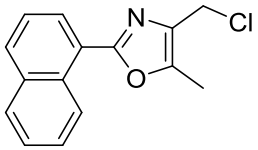


1-((2-(3,4-dimethoxy-6-methylphenyl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5cc. 4-(Chloromethyl)-5-methyl-2-(3,4-dimethoxy-6-methylphenyl)oxazole (558 mg, 4.32 mmol) was reacted according to general procedure E to afford the carboxylic acid product as an off-white solid (900 mg, 2.50 mmol, 87% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (dq, *J* = 3.4, 11.6 Hz, 2H), 1.58–1.73 (m, 3H), 1.86 (dt, *J* = 2.0, 11.2 Hz, 2H), 2.30 (s, 3H), 2.71 (d, *J* = 11.2 Hz, 2H), 3.23 (s, 2H), 3.77 (s, 63H), 3.79 (s, 3H), 7.02 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 2.0, 8.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.5, 44.6, 55.9, 56.0, 108.9, 112.2, 119.0; u (C, CH_2): 30.0, 53.85, 53.89, 120.3, 132.9, 145.9, 149.3, 150.8, 158.7, 178.6; IR 1501, 1553, 2835, 2947, 3450 cm^{-1}.

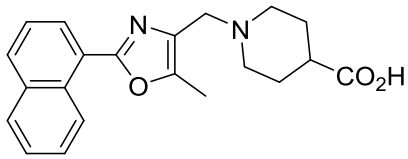


2-(Naphthalen-1-yl)-4,5-dimethyloxazole 3-oxide 3dd. 1-Naphthaldehyde (1.00 g, 6.40 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light yellow solid (1.39 g, 5.81 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s,

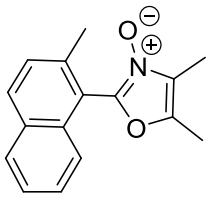
3H), 2.46 (s, 3H), 7.52–7.67 (m, 3H), 7.89–7.96 (m, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 8.37–8.45 (m, 1H), 8.88 (dd, *J* = 1.2, 7.4 Hz, 1H).



4-(Chloromethyl)-5-methyl-2-(naphthalen-1-yl)oxazole 4dd. 2-(Naphthalen-1-yl)-4,5-dimethyloxazole 3-oxide (1.39 g, 5.81 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a light yellow oil (0.88 g, 3.41 mmol, 59% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.55 (s, 2H), 7.39–7.50 (m, 2H), 7.56 (ddd, *J* = 1.4, 6.8, 8.5 Hz, 1H), 7.77–7.82 (m, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.06 (dd, *J* = 1.2, 7.3 Hz, 1H), 9.15–9.18 (m, 1H).

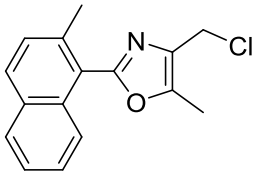


1-((5-Methyl-2-(naphthalene-1-yl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 5dd. 4-(Chloromethyl)-5-methyl-2-(naphthalen-1-yl)oxazole (305 mg, 1.18 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a colorless oil (385 mg, 1.10 mmol, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.48 (dq, *J* = 2.1, 11.3 Hz, 2H), 1.66–1.80 (m, 3H), 1.99 (dt, *J* = 1.7, 11.1 Hz, 2H), 2.44 (s, 3H), 2.83 (d, *J* = 11.0 Hz, 2H), 3.42 (s, 2H), 7.58–7.67 (m, 2H), 7.70 (dd, *J* = 6.8, 8.5 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.15 (dd, *J* = 1.2, 7.3 Hz, 1H), 9.28 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.0, 29.5, 43.9, 53.4, 53.5, 123.2, 125.3, 125.8, 126.4, 127.0, 127.5, 128.6, 129.1, 130.7, 132.8, 133.5, 145.9, 157.8, 177.6; HRMS (m/z): calcd for $C_{21}H_{23}N_2O_3$ $[M + H]^+$ 351.1703; found 351.1712.

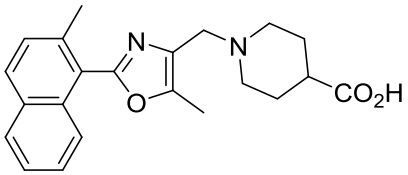


4,5-Dimethyl-2-(2-methylnaphthalen-1-yl)-oxazole 3-oxide 3ee. 2-Methyl-1-naphthaldehyde (0.93 g, 5.45 mmol) was reacted according to general procedure C-2 to afford the oxazole product as a light orange oil (1.24 g, 4.90 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 6H), 2.57 (s, 3H), 7.36–7.46 (m, 2H), 7.49–7.59 (m, 2H), 7.85–7.92 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.5, 11.3, 20.8, 123.6, 126.5, 128.3, 128.60, 128.63, 133.9; u

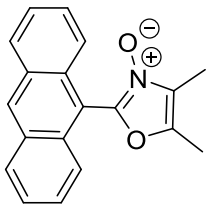
(C, CH_2): 114.6, 127.7, 131.46, 131.47, 140.8, 147.2, 156.0; HRMS (m/z): calcd for $C_{16}H_{16}NO_2$ $[M + H]^+$ 254.1176; found 254.1174.



4-(Chloromethyl)-5-methyl-2-(2-methylnaphthalen-1-yl)oxazole 4ee. 4,5-Dimethyl-2-(2-methylnaphthalen-1-yl)-oxazole 3-oxide (400 mg, 1.58 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a colorless oil (70 mg, 0.256 mmol, 16% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.51 (s, 3H), 4.69 (s, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.45–7.92 (m, 3H), 7.79–9.18 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 10.4, 20.8, 125.0, 125.4, 127.1, 128.0, 128.5, 130.3; u (C, CH_2): 37.4, 124.0, 131.8, 132.3, 132.6, 137.3, 147.0, 158.9; HRMS (m/z): calcd for $C_{16}H_{15}ClNO$ $[M + H]^+$ 272.0837; found 272.0832.

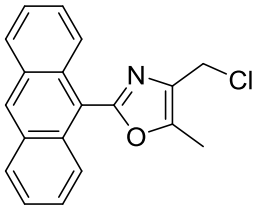


1-((5-Methyl-2-(2-methylnaphthalene-1-yl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 5ee. 4-(Chloromethyl)-5-methyl-2-(2-methylnaphthalen-1-yl)oxazole (57 mg, 0.21 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (75 mg, 0.21 mmol, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (q, *J* = 10.6 Hz, 2H), 1.65–1.73 (m, 3H), 2.00 (t, *J* = 10.5 Hz, 2H), 2.39 (s, 3H), 2.42 (s, 3H), 2.87 (d, *J* = 10.6 Hz, 2H), 3.44 (s, 2H), 7.49–7.56 (m, 3H), 7.64–7.67 (m, 1H), 7.96–7.99 (m, 1H), 8.01 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.0, 20.2 44.4, 124.6, 125.5, 127.1, 128.0, 128.5, 129.9; u (C, CH_2): 29.8, 53.36, 53.44, 124.2, 131.3, 131.87, 131.89, 136.6, 146.1, 156.7, 177.5; HRMS (m/z): calcd for $C_{22}H_{25}N_2O_3$ $[M + H]^+$ 365.1860; found 365.1872.

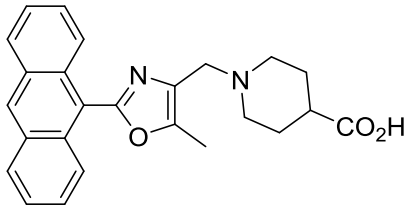


2-(Anthracen-9-yl)-4,5-dimethyloxazole 3-oxide 3ff. Anthracene-9-carbaldehyde (1.00 g, 4.85 mmol) was reacted according to general procedure C-2 to afford the oxazole

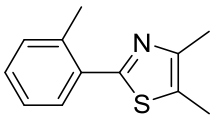
product as a light green solid (0.87 g, 3.02 mmol, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 2.72 (s, 3H), 7.58 (dd, *J* = 6.5, 8.0 Hz, 2H), 7.69 (dd, *J* = 6.5, 8.9 Hz, 2H), 7.73–7.82 (m, 2H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.80 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 7.8, 11.4, 124.0, 126.2, 129.2, 129.3, 134.5; u (C, CH_2): 110.6, 128.2, 130.7, 131.6, 147.5, 155.9; HRMS (m/z): calcd for $C_{19}H_{16}NO_2$ $[M + H]^+$ 290.1176; found 290.1182.



2-(Anthracen-9-yl)-4-(chloromethyl)-5-methyloxazole 4ff. 2-(Anthracen-9-yl)-4,5-dimethyloxazole 3-oxide (400 mg, 1.38 mmol) was reacted according to general procedure D to afford the chloromethyloxazole product as a yellow solid (114 mg, 0.37 mmol, 27% yield). R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.76 (s, 2H), 7.51–7.58 (complex, 4H), 8.03–8.09 (complex, 4H), 8.63 (s, 1H); HRMS (m/z): calcd for $C_{19}H_{15}ClNO$ $[M + H]^+$ 308.0837; found 308.0832.

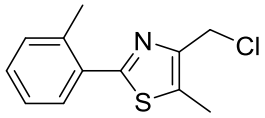


1-((2-(Anthracen-9-yl)-5-methyloxazol-4-yl)methyl)piperidine-4-carboxylic acid 5ff. 2-(Anthracen-9-yl)-4-(chloromethyl)-5-methyloxazole (114 mg, 0.37 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (116 mg, 0.29 mmol, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (q, *J* = 10.7 Hz, 2H), 1.69–1.78 (m, 3H), 2.05 (t, *J* = 10.4 Hz, 2H), 2.49 (s, 3H), 2.90 (d, *J* = 10.7 Hz, 2H), 3.52 (s, 2H), 7.58–7.64 (complex, 4H), 7.89–7.95 (m, 2H), 8.18–8.24 (m, 2H), 8.85 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 10.1, 44.4, 125.1, 125.7, 127.3, 128.6, 129.8; u (C, CH_2): 29.9, 53.5, 53.6, 121.7, 130.4, 130.6, 132.4, 146.9, 156.2, 177.6; HRMS (m/z): calcd for $C_{25}H_{25}N_2O_3$ $[M + H]^+$ 401.1860; found 401.1878.

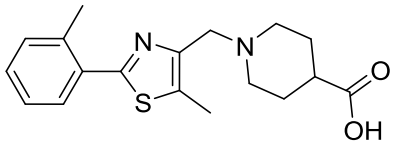


4,5-Dimethyl-2-(o-tolyl)thiazole 10. To a solution of 2-methylbenzothioamide (445 mg, 2.94 mmol) in isopropanol (3 mL) was added 3-chlorobutan-2-one (314 mg, 2.94 mmol). The reaction

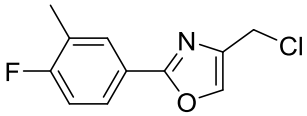
was heated under microwave irradiation at 120 °C for 1 h and cooled to rt, precipitating a tan sold. The solid was filtered, washed with ether then partitioned between CH_2Cl_2 and saturated, aqueous $NaHCO_3$. The organics were combined, dried (Na_2SO_3) and evaporated to afford the thiazole product as a colorless gummy solid (386 mg, 1.90 mmol, 65% yield), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 6H), 2.56 (s, 3H), 7.21–7.31 (m, 3H), 7.65 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 11.3, 14.8, 21.3, 125.9, 128.9, 129.7, 131.2; u (C, CH_2): 127.0, 133.3, 136.2, 148.4, 162.8.



4-(Chloromethyl)-5-methyl-2-(o-tolyl)thiazole 11. According to the procedure of Yamane and coworkers,[3] to a solution of 4,5-dimethyl-2-(*o*-tolyl)thiazole (244 mg, 1.20 mmol) in MeCN (3 mL) was added *N*-chlorosuccinimide (160 mg, 1.20 mmol). The reaction was heated at 60 °C for 2 h and cooled to rt. Solvent was removed in vacuo and the residue purified by silica chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.58 (s, 3H), 4.74 (s, 2H), 7.22–7.33 (m, 3H), 7.67 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence) δ d (CH, CH_3): 11.2, 21.4, 126.0, 129.3, 129.7, 131.4; u (C, CH_2): 39.0, 132.7, 132.9, 136.4, 147.9, 164.2.

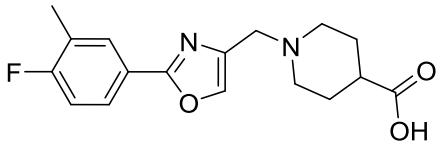


1-((5-Methyl-2-(o-tolyl)thiazol-4-yl)methyl)piperidine-4-carboxylic acid 12. 4-(Chloromethyl)-5-methyl-2-(o-tolyl)thiazole (247 mg, 1.04 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (267 mg, 0.81 mmol, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42–1.53 (m, 2H), 1.70 (d, *J* = 10.9 Hz, 2H), 1.96–2.05 (m, 3H), 2.42 (s, 3H), 2.48 (s, 3H), 2.78 (d, *J* = 11.1 Hz, 2H), 3.54 (s, 2H), 7.23–7.31 (m, 3H), 7.62 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6, APT pulse sequence) δ d (CH, CH_3): 11.4, 21.6, 40.8, 126.7, 129.5, 129.6, 131.9; u (C, CH_2): 29.2, 53.1, 55.8, 131.3, 133.0, 135.9, 149.7, 162.0, 177.9.



4-(Chloromethyl)-2-(4-fluoro-3-methylphenyl)oxazole 16. 4-Fluoro-3-methylbenzamide (6.12 g, 40.0 mmol) and dichloroacetone (6.09 g, 48.0 mmol, 1.2 equiv.) were slurried in toluene (50 mL) in a pressure vessel. The reaction was sealed and heated at 140 °C for 5 h. The reaction was evaporated in vacuo, the residue dissolved

in CH_2Cl_2 and purified by silica gel chromatography (eluents: 0 to 30% EtOAc in hexanes) to afford the oxazole product as an off-white solid (5.10 g, 22.6 mmol, 57% yield). R_f = 0.53 (25% EtOAc in hexanes); ^{1}H NMR (400MHz,$CDCl_3$)δ2.33 (s, 3H), 4.56 (s,2H),7.07 (t, *J* = 8.9 Hz, 1H), 7.67 (t, *J* = 0.8 Hz, 1H), 7.80–7.84 (m, 1H),7.90 (dd, *J* = 1.5, 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, APT pulse sequence)δ d (CH, CH_3): 14.5 (d, *J* = 3.5 Hz), 115.6 (d, *J* = 23.4 Hz), 125.9 (d, *J* = 8.8 Hz), 130.0 (d, *J* = 5.9 Hz), 136.1; u (C, CH_2): 37.0, 123.0, 125.7 (d, *J* = 18.2 Hz), 138.7, 161.8 (d, *J* = 1.1 Hz), 162.9 (d, *J* = 251.1 Hz); IR 1491, 1591 cm^{-1}.



1-((2-(4-Fluoro-3-methylphenyl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid 17. 4-(Chloromethyl)-2-(4-fluoro-3-methylphenyl)oxazole (2.41 g, 10.68 mmol) was reacted according to general procedure E to afford the carboxylic acid product as a white solid (3.15 g, 9.89 mmol, 93% yield). ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.37–1.47 (m, 2H), 1.58–1.67 (m, 3H), 1.89 (t, *J* = 10.3 Hz, 2H), 2.36 (s, 3H), 2.75 (d, *J* = 11.0 Hz, 2H), 3.31 (s, 2H), 7.24 (t, *J* = 9.0 Hz, 1H), 7.73–7.78 (m, 1H), 7.84–7.88 (m, 1H), 7.95 (s, 1H); ^{13}C NMR (101 MHz, DMSO-D_6, APT pulse sequence) δ d (CH, CH_3): 14.5, 44.7, 116.2 (d, *J* = 23.2 Hz), 126.0 (d, *J* = 8.9 Hz), 129.8 (d, *J* = 6.3 Hz), 137.6; u (C, CH_2): 30.2, 54.1, 54.3, 123.8, 125.8 (d, *J* = 18.8 Hz), 139.4, 160.0 (d, *J* = 1.0 Hz), 162.3 (d, *J* = 248.6 Hz), 178.1; ^{19}F NMR 376 MHz, DMSO-D_6) δ -114.3; IR 1569, 2894, 2925, 3422 cm^{-1}.

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[3] Yamane, T.; Mitsudera, H.; Shundoh, T. *Tetrahedron Lett.* **2004**, *45*, 69–73.