Supporting Information

Intramolecular Diels–Alder/1,3-Dipolar Cycloaddition Cascade of 1,3,4-Oxadiazoles

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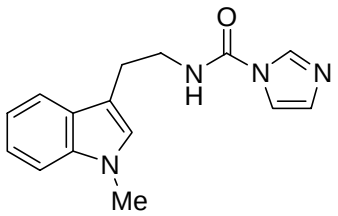
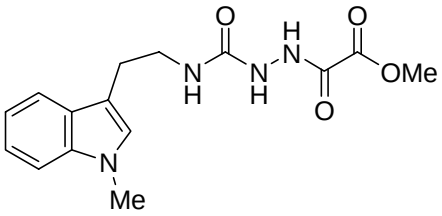
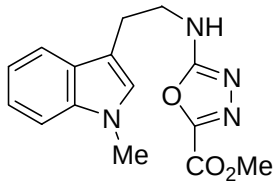


***N*^{1}-Methyl-*N*-carbonylimidazole Tryptamine (S1)**. Distilled N^1-methyl tryptamine (15.0 g, 86.2 mmol) in CH_2Cl_2 (500 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (20.95 g, 129.0 mmol) in THF (100 mL) under Ar cooled to 0 °C. The reaction mixture was allowed to stir and equilibrate to 23 °C overnight before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 5% MeOH–$CHCl_3$) provided **S1** (20.0 g, 74.9 mmol, 86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.02 (s, 1H), 6.92 (s, 1H), 5.90 (s, 1H), 3.76 (s, 3H), 3.72 (t, J = 6.5 Hz, 2H), 3.09 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.3, 137.1, 135.6, 128.9, 127.6, 127.0, 122.0, 119.2, 118.6, 116.3, 110.7, 109.5, 41.8, 32.7, 24.9; IR (film) ν_{max} 1727, 1603, 1528, 1511, 1471, 1415 cm^{-1}; FABHRMS (NBA/NaI) *m*/*z* 269.1410 ($C_{15}H_{16}N_4O + H^+$ requires 269.1402).

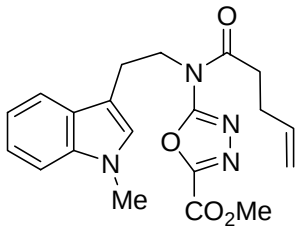


Methyl 2-{2-[2-(1-Methyl-1*H*-indol-3-yl)ethylcarbamoyl]hydrazinyl}-2-oxoacetate (S2). Methyl oxalylhydrazide[S1] (1.18 g, 10.1 mmol) was added to a solution of **S1** (2.70 g, 10.1 mmol) and AcOH (0.583 mL, 10.1 mmol) in THF (80 mL) under Ar and the reaction mixture was warmed at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 3% MeOH–EtOAc) provided **S2** (3.18 g, 9.4 mmol, 93%) as a white solid: mp 102–104 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (br s, 1H), 7.52 (d, J = 6.2 Hz, 1H), 7.24 (d, J = 5.7 Hz, 1H), 7.17 (t, J = 5.7

Hz, 1H), 7.07 (t, *J* = 6.2 Hz, 1H), 6.81 (s, 1H), 5.79 (br s, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 3.41 (m, 2H), 2.87 (t, *J* = 5.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 157.1, 154.7, 137.0, 127.7, 127.0, 121.6, 118.8, 118.7, 111.1, 109.2, 53.6, 40.6, 32.5, 25.4; IR (film) ν_{max} 3394, 1769, 1728, 1707, 1523, 1420 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 341.1220 ($C_{15}H_{18}N_4O_4 + Na^+$ requires 341.1233).

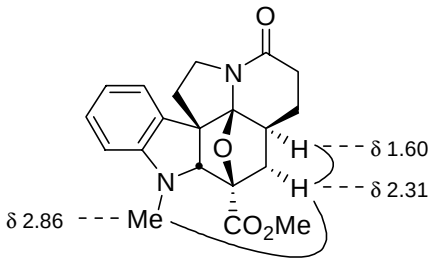


Methyl 5-[(2-(1-Methyl-1*H*-indol-3-yl)ethyl)amino]-1,3,4-oxadiazole-2-carboxylate (S3). Et_3N (19.5 mL, 140 mmol) was added to a stirring solution of **S2** (17.9 g, 56.0 mmol) and TsCl (10.75 g, 56.0 mmol) in CH_2Cl_2 (500 mL) under Ar at 23 °C. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexane) provided **S3** (10.9 g, 36.4 mmol, 65%; typically 60–85%) as white crystals: mp 144–146 °C (MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.24 (m, 1H), 7.11 (t, *J* = 7.7, Hz, 1H), 6.90 (s, 1H), 5.63 (s, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.73 (m, 2H), 3.10 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4, 154.8, 150.9, 137.2, 127.4, 127.3, 121.9, 119.1, 118.6, 110.0, 109.4, 53.2, 43.6, 32.7, 25.1; IR (film) ν_{max} 3421, 1743, 1619, 1537, 1473, 1155, 1068 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 301.1284 ($C_{15}H_{16}N_4O_3 + H^+$ requires 301.1295).



Methyl 5-{[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-(pent-4-enoyl)amino}-1,3,4-oxadiazole-2-carboxylate (1a). A solution of 4-pentenoic acid (0.05 mL, 0.5 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated with EDCI (98 mg, 0.5 mmol) followed by DMAP (2 mg, 0.02 mmol). Oxadiazole **S3** was added (50 mg, 0.17 mmol) and the mixture was allowed to stir at 23 °C for 16 h. The reaction mixture was concentrated in vacuo to 1 mL and diluted with 30 mL of EtOAc and 10 mL of 1 N aqueous HCl. The organic layer was separated and washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. PTLC (SiO_2, 50% EtOAc–hexanes) provided **1a** (49 mg, 0.13 mmol, 75%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.9 Hz,

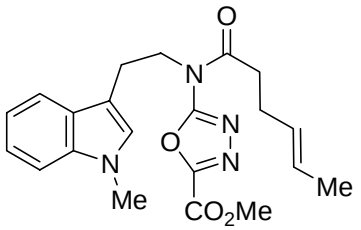
1H), 7.21 (dd, *J* = 7.0, 7.9 Hz, 1H), 7.12 (dd, *J* = 7.0, 7.5 Hz, 1H), 6.86 (s, 1H), 5.87–5.77 (m, 1H), 5.09–4.98 (m, 2H), 4.24 (t, *J* = 7.5 Hz, 2H), 4.06 (s, 3H), 3.72 (s, 3H), 3.12 (dd, *J* = 7.9, 8.5 Hz, 2H), 2.92 (dd, *J* = 7.9, 8.5 Hz, 2H), 2.45 (dt, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.9, 162.3, 154.2, 153.5, 137.2, 136.7, 127.8, 127.6, 121.9, 119.3, 119.1, 116.1, 110.1, 109.4, 53.9, 48.0, 35.8, 32.8, 28.9, 24.5; IR (film) ν_{max} 2923, 1749, 1702, 1567, 1442, 1328, 1153, 813, 743 cm^{-1}; MALDIFTMS (DHB) *m/z* 405.1536 ($C_{20}H_{22}N_4O_4$ + Na^+ requires 405.1533).



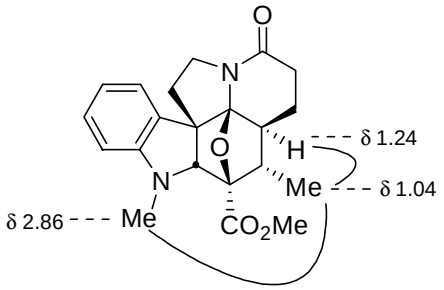
Solid curved lines represent nOe's observed in 1D ^{1}H–^{1}H GOESY ($CDCl_3$, 600 MHz)

Compound 1b (thermal). A solution of **1a** (15.0 mg, 0.039 mmol) in 10 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 3 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 55% EtOAc–hexanes) providing **1b** (12 mg, 0.034 mmol, 87%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz,) δ 7.09 (dt, *J* = 1.3, 7.9 Hz, 1H), 6.70 (dd, *J* = 0.9, 7.5 Hz, 1H), 6.58 (dt, *J* = 1.3, 7.9 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 4.02 (d, *J* = 1.3 Hz, 1H), 3.98 (dt, *J* = 9.2, 12.2 Hz, 1H), 3.76 (s, 3H), 3.75–3.70 (m, 2H), 2.86 (s, 3H), 2.35–2.27 (m, 2H), 2.23 (ddd, *J* = 2.2, 6.6, 8.8 Hz, 1H), 2.13 (ddd, *J* = 5.7, 6.1, 12.7 Hz, 1H), 1.74 (apparent dq, *J* = 5.2, 12.7 Hz, 1H), 1.62–1.57 (m, 1H), 1.49–1.45 (m, 1H), 1.38 (ddd, *J* = 3.1, 3.1, 12.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.6, 170.5, 153.2, 129.7, 129.0, 123.2, 118.1, 107.1, 105.8, 87.4, 81.9, 65.2, 52.9, 47.1 36.4, 34.93, 34.91, 33.9, 32.2, 26.7; IR (film) ν_{max} 2949, 1735, 1667, 1606, 1493, 1384, 1119 cm^{-1}; MALDIFTMS (DHB) *m/z* 355.1656 ($C_{20}H_{22}N_2O_4$ + H^+ requires 355.1652).

Compound 1b (microwave). A solution of **1a** (5.0 mg, 0.013 mmol) in 2.5 mL of anhydrous, degassed 1,2-dichlorobenzene was placed in a capped, silated microwave safe tube under Ar and irradiated for 30 min in a microwave (Personal Chemistry) at 250 ºC. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 55% EtOAc–hexanes) providing **1b** (3.2 mg, 0.009 mmol, 70%) as a white solid.



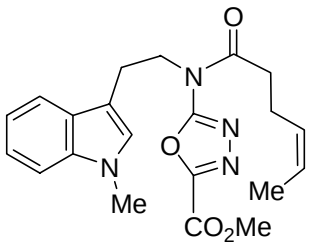
Methyl 5-{(*E*)-Hex-4-enoyl-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (2a). DMAP (107 mg, 0.88 mmol) was added to a solution of *trans*-4-hexenoic acid[S2] (100 mg, 0.88 mmol), **S3** (106 mg, 0.35 mmol), and EDCI (168 mg, 0.88 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) providing **2a** (110 mg, 0.28 mmol, 80%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 5.56–5.43 (m, 2H), 4.27 (t, *J* = 7.3 Hz, 2H), 4.03 (s, 3H), 3.74 (s, 3H), 3.15 (t, *J* = 7.3 Hz, 2H), 2.91 (t, *J* = 7.3 Hz, 2H), 2.41 (dt, *J* = 6.6, 7.0 Hz, 2H), 1.67 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 162.0, 154.0, 153.2, 136.9, 128.9, 127.5, 127.3, 126.5, 121.6, 119.0, 118.8, 109.8, 109.2, 53.6, 47.7, 36.2, 32.5, 27.7, 24.2, 17.9; IR (film) ν_{max} 2954, 1748, 1704, 1587, 1441, 1152 cm^{-1}; MALDIFTMS (DHB) *m/z* 419.1691 ($C_{21}H_{24}N_4O_4$ + Na^+ requires 419.1690).



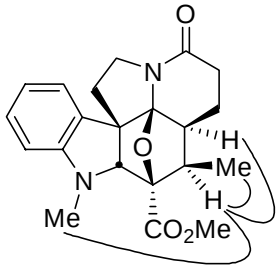
Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 2b. A solution of **2a** (30 mg, 0.076 mmol) in 15 mL of anhydrous degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 6 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 3% acetone–$CHCl_3$) providing **2b** (18 mg, 0.048 mmol, 65%) as a white solid: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.10 (dt, *J* = 1.2, 7.9 Hz, 1H), 6.69 (dd, *J* = 0.8, 7.2 Hz, 1H), 6.56 (dt, *J* = 0.8, 7.2 Hz, 1H), 6.30 (d, *J* = 7.9 Hz, 1H), 4.14 (d, *J* = 1.6 Hz, 1H), 4.04 (dt, *J* = 3.0, 11.7 Hz, 1H), 3.76 (s, 3H), 3.68 (dt, *J* = 2.8, 10 Hz, 1H), 2.86 (s, 3H), 2.38–2.22 (m, 3H), 2.08 (ddd, *J* = 5.6, 6.0, 7.8 Hz, 1H), 1.97–1.93 (m, 1H), 1.72–1.65

(m, 2H), 1.25 (dt, J = 5.2, 12.0 Hz, 1H), 1.04 (d, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.4, 152.4, 129.5, 128.5, 122.8, 117.3, 106.0, 105.1, 88.3, 81.4, 65.0, 52.5, 48.3, 46.4, 41.6, 37.0, 33.9, 31.7, 26.6, 12.6; IR (film) ν_{max} 2950, 1734, 1669, 1497, 1437, 1382, 1118 cm^{-1}; MALDIFTMS (DHB) *m/z* 369.1802 ($C_{21}H_{24}N_2O_4$ + H^+ requires 369.1809).



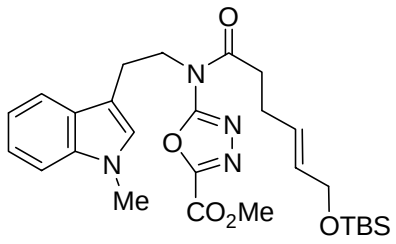
Methyl 5-{(*Z*)-Hex-4-enoyl-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (3a). DMAP (288 mg, 2.37 mmol) was added to a mixture of **S3** (285 mg, 0.95 mmol), *cis*-4-hexenoic acid (269 mg, 2.37 mmol) and EDCI (452 mg, 2.37 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 15 h before the reaction mixture was concentrated. Flash chromatography (SiO_2, 20% EtOAc–hexanes) provided **3a** (246 mg, 1.54 mmol, 65%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 6.8 Hz, 1H), 7.20 (dt, J = 1.1, 6.8 Hz, 1H), 7.10 (dt, J = 1.2, 7.9 Hz, 1H), 6.86 (s, 1H), 5.54–5.44 (m, 1H), 5.40–5.30 (m, 1H), 4.23 (d, J = 9.1 Hz, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 3.11 (t, J = 7.7 Hz, 2H), 2.86 (t, J = 7.3 Hz, 2H), 2.43 (q, J = 7.3 Hz, 2H), 1.63 (dd, J = 1.6, 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 162.0, 154.0, 153.2, 136.9, 128.0, 127.5, 127.4, 125.6, 121.6, 119.0, 118.8, 109.8, 109.2, 53.6, 47.7, 36.0, 32.6, 24.3, 22.3, 12.8; IR (film) ν_{max} 2954, 1749, 1705, 1566, 1474, 1441, 1409 cm^{-1}; HRESI-TOF *m/z* 397.1876 ($C_{21}H_{24}N_4O_4$ + H^+, requires 397.1870).



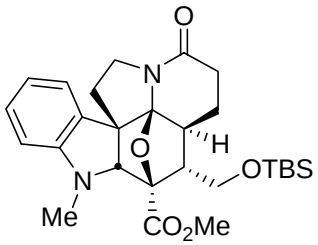
Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 3b. A solution of **3a** (30 mg, 0.076 mmol) in 1,2-dichlorobenzene (15 mL, passed through a pad of basic and neutral Al_2O_3 before use) was degassed for 0.5 h with Ar, then placed in an oil bath at 180 °C for 6 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes and **3b** was subsequently eluted with EtOAc. PTLC (SiO_2, 55% EtOAc–hexanes) gave **3b** (18 mg, 0.049 mmol, 65%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (dt, J = 1.1, 7.4 Hz, 1H), 6.75 (dd, J = 1.1, 7.4 Hz, 1H), 6.66 (t,

J = 7.4 Hz, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 4.10–4.15 (m, 1H), 4.01 (s, 1H), 3.87 (s, 3H), 3.78–3.83 (m, 1H), 3.02 (s, 3H), 2.73–2.78 (m, 1H), 2.52 (ddd, *J* = 1.8, 4.7, 17.9 Hz, 1H), 2.38–2.44 (m, 1H), 2.28–2.35 (m, 1H), 2.15 (ddd, *J* = 7.7, 12.9, 17.9 Hz, 1H), 1.92 (dt, *J* = 4.9, 13.1 Hz, 1H), 1.65–1.72 (m, 1H), 1.50–1.58 (m, 1H), 0.88 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 170.4, 152.8, 129.3, 128.4, 122.6, 117.9, 107.0, 104.6, 91.3, 81.5, 64.5, 52.2, 46.4, 38.2, 36.1, 35.2 (2C), 31.4, 19.7, 10.8; IR (film) ν_{max} 2951, 1754, 1731, 1667, 1606, 1493, 1433, 1397, 1381, 1317, 1271, 1246, 1156, 1115, 1089, 1006, 917, 874, 743 cm^{-1}; HRESI-TOF *m/z* 369.1810 ($C_{21}H_{24}N_2O_4$ + H^+ requires 369.1809).

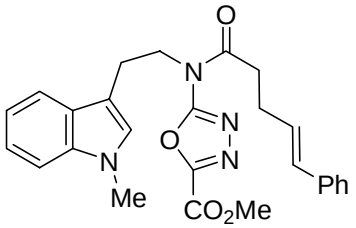


Methyl 5-{[6-*tert*-Butyldimethylsilyloxy)hex-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)-ethyl]amino}-1,3,4-oxadiazole-2-carboxylate ((*E*)-4a). Oxadiazole **S3** (121 mg, 0.40 mmol) was added in one portion to a solution of *trans*-6-(*tert*-butyldimethylsilyloxy)hex-4-enoic acid[S3] (295 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (5 mL) at 25 °C under Ar. The mixture was cooled to 0 °C and EDCI (232 mg, 1.21 mmol) was added. The resulting mixture was stirred for 5 min, before the addition of DMAP (147 mg, 1.21 mmol). The reaction mixture was stirred overnight at 23 °C before the solvent was removed in vacuo. Flash chromatography (SiO_2, 30% EtOAc–hexane) afforded (*E*)-**4a** (150 mg, 0.29 mmol, 71%) as an off-white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.24–7.08 (m, 3H), 6.84 (s, 1H), 5.97–5.50 (m, 2H), 4.20 (t, *J* = 7.3 Hz, 2H), 4.09–4.10 (m, 2H), 3.98 (s, 3H), 3.69 (s, 3H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.40 (dd, *J* = 7.0, 13.9 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 161.9, 154.0, 153.2, 136.9, 130.7, 128.5, 127.5, 127.3, 121.6, 119.0, 118.8, 109.8, 109.2, 63.6, 53.6, 47.7, 35.9, 32.5, 27.2, 25.9 (3C), 24.2, 18.4, –5.2 (2C); IR (film) ν_{max} 2954, 2855, 1749, 1707, 1567, 1442, 1252, 1152, 836 cm^{-1}; MALDIFTMS (DHB) *m/z* 549.2490 ($C_{27}H_{38}N_4O_5Si$ + Na^+ requires 549.2504).

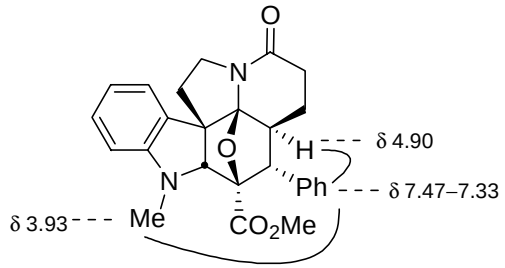


Compound 4b. A solution of (*E*)-**4a** (16.5 mg, 0.031 mmol) in 1,2-dichlorobenzene (6.3 mL, 0.005 M, passed through a column of basic alumina, degassed with Ar for 1 h while

protected from the light) was warmed to a gentle reflux in the absence of light for 24 h (16–24 h), at which time the solvent was removed in vacuo. Flash chromatography (SiO_2, 50% EtOAc–hexane) afforded **4b** (13.5 mg, 0.027 mmol, 86%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (t, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.0 Hz, 1H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.39 (d, *J* = 8.1 Hz, 1H), 4.15–4.06 (m, 2H), 3.85 (s, 3H), 3.82–3.61 (m, 4H), 2.98 (s, 3H), 2.25–2.16 (m, 6H), 1.88 (t, *J* = 2.9 Hz, 2H), 1.50–1.45 (m, 1H), 0.78 (s, 9H), –0.15 (s, 3H), –0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 170.6, 152.2, 129.6, 128.0, 122.7, 118.1, 106.7, 105.8, 88.3, 81.1, 64.9, 61.8, 56.5, 52.7, 46.3, 39.6, 36.7, 34.4, 31.5, 27.4, 25.8 (3C), 18.2, –5.5 (2C); IR (film) ν_{max} 2952, 2855, 1738, 1674, 1607, 1495, 1385, 1258, 1117, 1072, 1023, 837, 740 cm^{-1}; MALDIFTMS (DHB) *m/z* 521.2454 ($C_{27}H_{38}N_2O_5Si$ + Na^+ requires 521.2442).

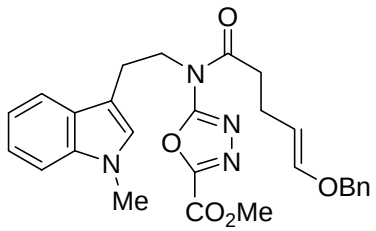


Methyl 5-{[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-((*E*)-5-phenylpent-4-enoyl)amino}-1,3,4-oxadiazole-2-carboxylate (5a). DMAP (34 mg, 0.28 mmol) was added to a solution of *trans*-5-phenylpent-4-enoic acid[S4] (50 mg, 0.28 mmol), **S3** (34 mg, 0.11 mmol), and EDCI (53 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) at 0 ºC. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) providing **5a** (42 mg, 0.099 mmol, 90%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.26–7.10 (m, 7H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.75 (s, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 7.0, 15.8 Hz, 1H), 4.18 (t, *J* = 7.3 Hz, 2H), 3.90 (s, 3H), 3.60 (s, 3H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.54 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 162.0, 154.0, 153.2, 137.2, 136.9, 131.2, 128.5 (2C), 128.2, 127.5, 127.3, 127.1, 126.0 (2C), 121.6, 119.0, 118.8, 109.8, 109.2, 53.6, 47.7, 36.0, 32.5, 28.2, 24.2; IR (film) ν_{max} 2953, 1747, 1703, 1564, 1440, 1409, 1327, 1150 cm^{-1}; MALDIFTMS (DHB) *m/z* 481.1840 ($C_{26}H_{26}N_4O_4$ + Na^+ requires 481.1846).

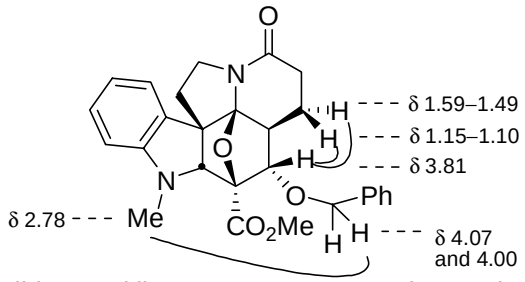


Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 5b. A solution of **5a** (9 mg, 0.019 mmol) in 3.8 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 178 °C for 14 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 55% EtOAc–hexanes) providing **5b** (5 mg, 0.012 mmol, 61%) as a white solid: ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.47–7.33 (m, 6H), 7.28 (dt, *J* = 1.1, 7.3 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 4.90 (d, *J* = 7.7 Hz, 1H), 4.71 (dd, *J* = 4.4, 8.1 Hz, 1H), 4.01 (dd, *J* = 3.0, 8.1 Hz, 1H), 3.93 (s, 3H), 3.71 (s, 3H), 3.57–3.51 (m, 2H), 3.00 (ddd, *J* = 5.1, 7.3, 8.5 Hz, 1H), 2.70–2.62 (m, 2H), 2.42–2.38 (m, 1H), 1.70–1.67 (m, 2H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 172.0, 169.0, 139.4, 138.2, 129.5 (2C), 128.0, 127.8 (2C), 127.5, 126.3, 123.2, 119.6, 119.0, 116.3, 109.6, 95.5, 82.2, 52.5, 49.5, 48.6, 37.8, 32.6, 27.3, 21.5, 17.4; IR (film) ν_{max} 2951, 2925, 1733, 1656, 1454, 1389, 1272, 1164 cm^{-1}; MALDIFTMS (DHB) *m/z* 431.1978 ($C_{26}H_{26}N_2O_4$ + H^+ requires 431.1965).

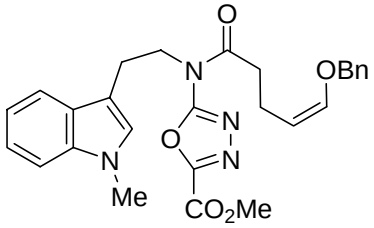


Methyl 5-{[(*E*)-5-(Benzyloxy)pent-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (6a). DMAP (94 mg, 0.80 mmol) was added to a solution of *trans*-5-(benzyloxy)pent-4-enoic acid (165 mg, 0.80 mmol), oxadiazole **S3** (96 mg, 0.32 mmol), and EDCI (153 mg, 0.80 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) afforded **6a** (122 mg, 0.25 mmol, 78%) as an amorphous solid: ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.36–7.24 (m, 6H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 6.40 (d, *J* = 12.3 Hz, 1H), 4.87 (dt, *J* = 12.3, 7.5 Hz, 1H), 4.69 (s, 2H), 4.19 (t, *J* = 7.5 Hz, 2H), 3.98 (s, 3H), 3.70 (s, 3H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.29 (dt, *J* = 7.0, 7.5 Hz, 2H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 171.9, 162.4, 154.6, 153.7, 147.5, 137.7, 137.4, 128.8, 128.8 (2C), 128.7 (2C), 128.1, 127.9, 127.8 (2C), 121.9, 119.2, 119.1, 110.3, 109.6, 103.0, 71.4, 48.0, 37.8, 32.8, 24.5, 23.6; IR (film) ν_{max} 2955, 2914, 1744, 1703, 1559, 1436, 1410, 1149 cm^{-1}; MALDIFTMS (DHB) *m/z* 489.2138 ($C_{27}H_{28}N_4O_5$ + H^+ requires 489.2132).



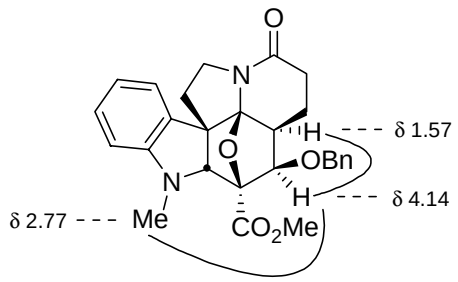
Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (C_6D_6, 400 MHz)

Compound 6b. A solution of **6a** (10 mg, 0.021 mmol) in 1,3,5-triisopropylbenzene (205 mL) was warmed at 230 °C for 6 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (100 mL). The product was eluted with EtOAc (25 mL) and concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **6b** (8.9 mg, 0.019 mmol, 94%) as an amorphous solid along with a trace amount of **12**: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.15–7.02 (m, 6H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.19 (d, *J* = 8.0 Hz, 1H), 4.39 (s, 1H), 4.10 (dt, *J* = 9.2, 12.1 Hz, 1H), 4.07 (d, *J* = 11.6 Hz, 1H), 4.00 (d, *J* = 11.6 Hz, 1H), 3.81 (t, *J* = 2.2 Hz, 1H), 3.67 (dt, *J* = 2.4, 12.2 Hz, 1H), 3.34 (s, 3H), 2.78 (s, 3H), 2.25–2.18 (m, 1H), 2.02 (dt, *J* = 9.9, 12.8 Hz, 1H), 1.92–1.82 (m, 2H), 1.59–1.49 (m, 2H), 1.15–1.10 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.8, 169.3, 152.8, 138.4, 129.8, 128.8, 128.7 (2C), 128.5, 128.3, 122.8, 116.9, 107.5, 105.6, 88.0, 86.4, 80.2, 73.9, 64.8, 53.7, 52.4, 47.1, 41.0, 36.7, 32.5, 31.9, 23.2; IR (film) ν_{max} 2954, 2892, 1733, 1667, 1605, 1497, 1385, 1262, 1113, 1204 cm^{-1}; MALDIFTMS (DHB) *m/z* 461.2068 ($C_{27}H_{28}N_2O_5$ + H^+ requires 461.2071).



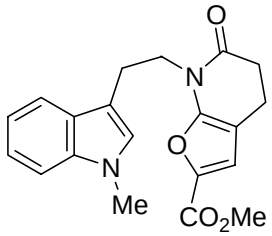
Methyl 5-{[(*Z*)-5-(Benzyloxy)pent-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (7a). DMAP (197 mg, 1.70 mmol) was added to a solution of a 1:1 mixture of *trans*- and *cis*-5-(benzyloxy)pent-4-enoic acid (250 mg, 1.20 mmol), oxadiazole **S3** (181 mg, 0.60 mmol), and EDCI (301 mg, 1.50 mmol) in CH_2Cl_2 (24 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) afforded a mixture of **6a** and **7a** (246 mg, 0.50 mmol, 83%) as an amorphous solid. The isomers were separated on a semipreparative Chiral Cel OD column (2 × 25 cm, 50% *i*-PrOH–hexanes, 10 mL/min flow rate) providing pure **7a** as an amorphous white solid: ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.37–7.24 (m, 6H), 7.18 (t, *J* = 7.4

Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.07 (d, *J* = 6.2 Hz, 1H), 4.78 (s, 2H), 4.43 (dt, *J* = 6.2, 6.9 Hz, 1H), 4.19 (t, *J* = 7.3 Hz, 2H), 3.99 (s, 3H), 3.70 (s, 3H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.45 (ddt, *J* = 1.5, 7.3, 7.3 Hz, 2H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 172.2, 162.5, 154.6, 153.7, 146.0, 138.1, 137.4, 128.8 (2C), 128.7, 128.2, 128.1, 127.9, 127.8 (2C), 121.9, 119.2, 119.1, 110.4, 109.5, 105.3, 74.1, 48.0, 36.6, 32.8, 24.5, 19.9; IR (film) ν_{max} 3029, 2935, 1747, 1700, 1563, 1149 cm^{-1}; MALDIFTMS (DHB) *m/z* 489.2138 ($C_{27}H_{28}N_4O_5$ + H^+ requires 489.2132).

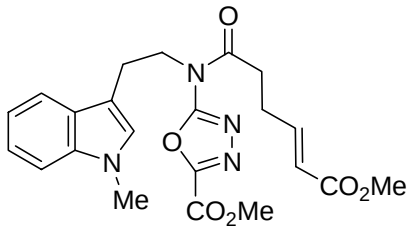


Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (C_6D_6, 400 MHz)

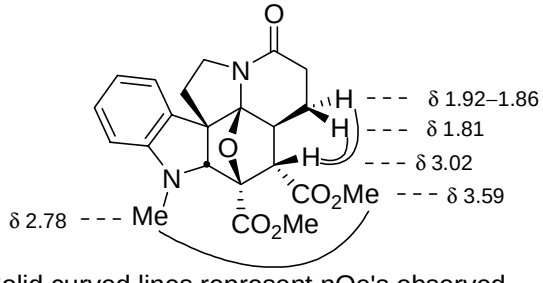
Compound 7b. A solution of **7a** (10 mg, 0.021 mmol) in 1,3,5-triisopropylbenzene (205 mL) was warmed at 230 °C for 38 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (100 mL). The product was eluted with EtOAc (50 mL) and concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **7b** (5.7 mg, 0.012 mmol, 61%) as an amorphous solid: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.15–7.02 (m, 6H), 6.62 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 6.28 (d, *J* = 7.9 Hz, 1H), 4.26 (d, *J* = 7.0 Hz, 1H), 4.14 (d, *J* = 11.4 Hz, 1H), 4.06 (dt, *J* = 9.2, 12.3 Hz, 1H), 3.98 (d, *J* = 11.4 Hz, 1H), 3.76 (t, *J* = 10.5 Hz, 1H), 3.66 (s, 1H), 3.40 (s, 3H), 2.77 (s, 3H), 2.32 (dd, *J* = 4.4, 13.6 Hz, 1H), 2.14 (ddt, *J* = 5.3, 13.1, 13.1 Hz, 1H), 1.95 (dt, *J* = 9.6, 12.7 Hz, 1H), 1.85 (ddd, *J* = 5.7, 7.9, 13.6 Hz, 1H), 1.72 (dd, *J* = 9.8, 10.1 Hz, 1H), 1.57 (m, 1H), 0.99 (dt, *J* = 7.0, 13.6 Hz, 1H); ^{13}C NMR (C_6D_6, 150 MHz) δ 170.0, 169.4, 153.0, 138.6, 129.6, 129.1, 128.6, 128.5, 128.1, 127.7, 127.6, 123.1, 118.8, 107.3, 104.3, 91.8, 80.6, 80.4, 74.3, 64.7, 51.7, 47.3, 41.1, 36.1, 35.2, 31.5, 19.0; IR (film) ν_{max} 2936, 2847, 1762, 1734, 1669, 1399, 1117 cm^{-1}; MALDIFTMS (DHB) *m/z* 461.2076 ($C_{27}H_{28}N_2O_5$ + H^+ requires 461.2071).



Methyl 7-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-6-oxo-4,5,6,7-tetrahydrofuro[2,3-*b*]pyridine-2-carboxylate (12). Mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 159.1, 151.8, 138.1, 137.1, 128.2, 127.2, 121.8, 120.0, 119.3, 119.1, 110.9, 109.3, 100.0, 51.8, 42.5, 32.8, 32.4, 24.4, 16.9; IR (film) ν_{max} 1718, 1682, 1631, 1533, 1472, 1431, 1323, 1190, 1154 cm^{-1}; MALDIFTMS (DHB) *m/z* 353.1488 ($C_{20}H_{20}N_2O_4$ + H^+ requires 353.1496).

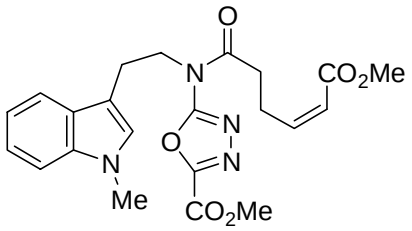


Methyl 5-{[(*E*)-5-(Methoxycarbonyl)pent-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (8a). EDCI (146 mg, 0.76 mmol) was added to a 1:1 solution of *trans*- and *cis*-hex-2-enedioic acid 1-methyl ester[S5] (100 mg, 0.63 mmol), oxadiazole **S3** (95 mg, 0.32 mmol), and DMAP (88 mg, 0.76 mmol) in CH_2Cl_2 (6.3 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 11 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) afforded a mixture of **8a** and **9a** (121 mg, 0.26 mmol, 83%) as a white solid. The isomers could be separated by PTLC with multiple elutions (SiO_2, 50% EtOAc–hexanes) providing a pure sample of **8a**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, *J* = 6.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 6.95 (dt, *J* = 6.6, 15.8 Hz, 1H), 6.85 (s, 1H), 5.87 (d, *J* = 15.8 Hz, 1H), 4.23 (t, *J* = 7.4 Hz, 2H), 3.99 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.10 (t, *J* = 7.4 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.58 (m, 2H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 170.9, 166.7, 161.8, 153.9, 153.2, 146.8, 136.9, 127.6, 127.3, 122.1, 121.7, 119.1, 118.8, 109.7, 109.3, 53.7, 51.5, 47.7, 34.7, 32.6, 27.0, 24.2; IR (film) ν_{max} 2943, 2902, 1743, 1707, 1701, 1562, 1436, 1149 cm^{-1}; MALDIFTMS (DHB) *m/z* 463.1582 ($C_{22}H_{24}N_4O_6$ + Na^+ requires 463.1588).

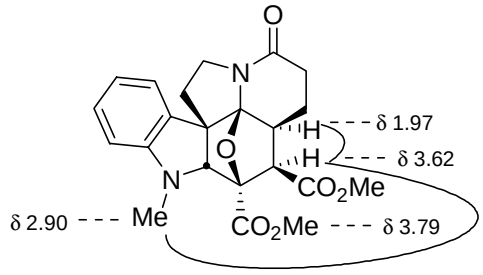


Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 8b. A solution of **8a** (13 mg, 0.028 mmol) in 1,3,5-triisopropylbenzene (3.7 mL) was warmed at 230 °C for 46 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (25 mL). The product was eluted with EtOAc (25 mL) and concentrated. PTLC (SiO_2, 60% EtOAc–hexanes) afforded **8b** (8.6 mg, 0.021 mmol, 71%) as a white solid: ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.19 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 4.39 (s, 1H), 4.08 (dt, *J* = 8.8, 12.2 Hz, 1H), 3.89 (s, 3H), 3.72 (dt, *J* = 2.4, 12.2 Hz, 1H), 3.59 (s, 3H), 3.02 (d, *J* = 4.9 Hz, 1H), 2.78 (s, 3H), 2.47–2.36 (m, 2H), 2.32 (ddd, *J* = 2.4, 9.2, 15.8 Hz, 1H), 2.21 (ddd, *J* = 5.5, 12.8, 15.8 Hz, 1H), 2.09 (dt, *J* = 4.9, 12.2 Hz, 1H), 1.92–1.86 (m, 1H), 1.81 (ddt, *J* = 5.5, 7.9, 13.4 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 170.1, 169.4, 168.8, 154.0, 129.6, 128.9, 122.8, 119.3, 108.8, 107.0, 89.3, 80.6, 65.0, 56.1, 53.8, 53.3, 51.9, 46.6, 36.1, 35.6, 31.8, 26.8; IR (film) ν_{max} 2943, 2912, 1739, 1662, 1487, 1384 cm^{-1}; MALDIFTMS (DHB) *m/z* 413.1699 ($C_{22}H_{24}N_2O_6$ + H^+ requires 413.1707).

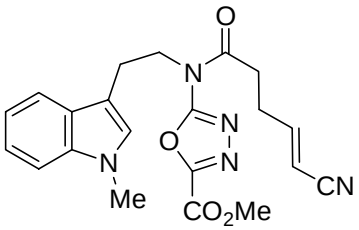


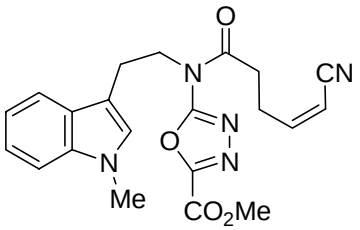
Methyl 5-{[(*Z*)-5-(Methoxycarbonyl)pent-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (9a). DMAP (67 mg, 0.57 mmol) was added to a solution of *cis*-hex-2-enedioic acid 1-methyl ester[S5] (75 mg, 0.47 mmol), oxadiazole **S3** (71 mg, 0.24 mmol), and EDCI (109 mg, 0.57 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 12 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) afforded **9a** (88 mg, 0.20 mmol, 85%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 6.85 (s, 1H), 6.22 (dt, *J* = 7.3, 11.4 Hz, 1H), 5.80 (d, *J* = 11.4 Hz, 1H), 4.22 (t, *J* = 7.3 Hz, 2H), 3.99 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.09 (t, *J* = 7.3 Hz, 2H), 3.05–2.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 166.4, 161.8, 154.0, 153.1, 147.8, 136.8, 127.5, 127.3, 121.6, 120.5, 119.0, 118.8, 109.7, 109.2, 53.6, 51.1, 47.6, 35.5, 32.5, 24.2, 24.1; IR (film) ν_{max} 2944, 2913, 1744, 1713, 1564, 1441, 1410, 1194, 1153 cm^{-1}; MALDIFTMS (DHB) *m/z* 463.1602 ($C_{22}H_{24}N_4O_6$ + Na^+ requires 463.1588).



Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

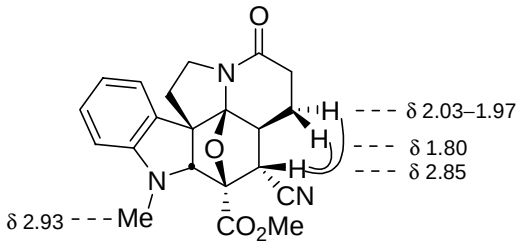
Compound 9b. A solution of **9a** (17 mg, 0.039 mmol) in 1,3,5-triisopropylbenzene (4.8 mL) was warmed at 230 °C for 60 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (25 mL). The product was eluted with EtOAc (25 mL) and concentrated. PTLC (SiO_2, 50% EtOAc–hexanes) afforded **9b** (9.9 mg, 0.024 mmol, 62%) as a white solid: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.18 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.04 (dt, *J* = 12.4, 9.2 Hz, 1H), 3.97 (s, 1H), 3.80 (dt, *J* = 2.4, 12.0 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 8.8 Hz, 1H), 3.59 (s, 3H), 2.90 (s, 3H), 2.45–2.35 (m, 2H), 2.29 (ddd, *J* = 2.4, 9.2, 12.8 Hz, 1H), 2.15 (ddd, *J* = 6.0, 9.2, 13.2 Hz, 1H), 1.97 (ddd, *J* = 4.4, 8.8, 13.2 Hz, 1H), 1.79 (ddt, *J* = 5.0, 5.2, 13.2 Hz, 1H), 1.50–1.42 (m, 1H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 170.6, 170.2, 169.5, 152.8, 129.6, 128.3, 122.9, 118.6, 107.7, 104.2, 87.8, 82.7, 64.9, 52.3, 51.8, 47.8, 46.8, 38.5, 36.4, 35.4, 31.1, 21.2; IR (film) ν_{max} 2943, 2892, 1764, 1733, 1666, 1487, 1431, 1385, 1194, 1113 cm^{-1}; MALDIFTMS (DHB) *m/z* 413.1710 ($C_{22}H_{24}N_2O_6$ + H^+ requires 413.1707).





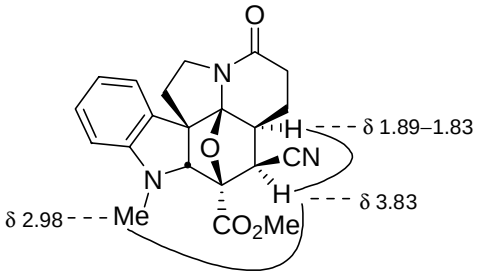
Methyl 5-{(5-Cyanopent-4-enoyl)-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (10a and 11a). DMAP (47 mg, 0.40 mmol) was added to a solution of a 1:1 mixture of *cis*- and *trans*-5-cyanopent-4-enoic acid (50 mg, 0.40 mmol), oxadiazole **S3** (40 mg, 0.13 mmol), and EDCI (77 mg, 0.40 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred for 14 h and gradually warmed to 25 °C. Saturated aqueous NH_4Cl (10 mL) was added and the organic layer was removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) afforded a mixture of **10a** and **11a** (51 mg, 0.12 mmol, 94%) as a white solid. The isomers could be separated by PTLC with multiple elutions (SiO_2, 50% EtOAc–hexanes). For **10a**, (*E*)-isomer: ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.68 (dt, *J* = 7.0, 16.2 Hz, 1H), 5.38 (d, *J* = 16.2 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 2H), 4.00 (s,

3H), 3.71 (s, 3H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.57 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 171.3, 162.6, 155.0, 154.5, 154.2, 137.9, 128.4, 128.3, 122.4, 119.8, 119.4, 118.1, 110.6, 110.2, 101.8, 54.5, 48.5, 35.2, 33.3, 28.9, 24.9; IR (film) ν_{max} 2933, 2851, 2226, 1749, 1702, 1564, 1441, 1410, 1136 cm^{-1}; MALDIFTMS (DHB) *m/z* 430.1478 ($C_{21}H_{21}N_5O_4$ + Na^+ requires 430.1486). For **11a**, (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 6.46 (dt, *J* = 7.5, 11.0 Hz, 1H), 5.35 (d, *J* = 11.0 Hz, 1H), 4.25 (t, *J* = 7.5 Hz, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 3.11 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.78 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.5, 161.7, 153.9, 153.2, 152.6, 136.9, 127.6, 127.3, 121.7, 119.1, 118.7, 115.6, 109.6, 109.3, 100.9, 53.7, 47.7, 34.9, 32.6, 26.8, 24.2; IR (film) ν_{max} 3046, 2933, 2205, 1744, 1703, 1564, 1441, 1419, 1149 cm^{-1}; MALDIFTMS (DHB) *m/z* 430.1476 ($C_{21}H_{21}N_5O_4$ + Na^+ requires 430.1486).



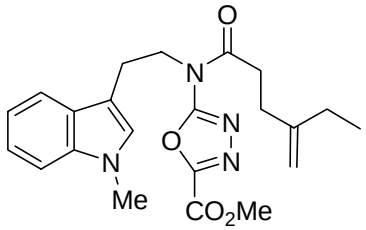
Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 10b. A solution of **10a** (13 mg, 0.032 mmol) in 1,3,5-triisopropylbenzene (4.0 mL) was warmed at 230 °C for 22 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (25 mL). The product was eluted with EtOAc (25 mL) and the eluent was concentrated. PTLC (SiO_2, 60% EtOAc–hexanes) afforded **10b** (9.6 mg, 0.025 mmol, 79%) as a white solid: ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 7.22 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.0 Hz, 1H), 6.71 (t, *J* = 7.0 Hz, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 4.38 (s, 1H), 4.11 (dt, *J* = 9.2, 12.3 Hz, 1H), 3.92 (s, 3H), 3.79 (ddd, *J* = 2.6, 7.0, 9.6 Hz, 1H), 2.93 (s, 3H), 2.85 (d, *J* = 4.4 Hz, 1H), 2.50–2.38 (m, 3H), 2.18 (ddd, *J* = 5.7, 4.3, 12.2 Hz, 1H), 2.03–1.97 (m, 1H), 1.91 (dt, *J* = 4.8, 12.3 Hz, 1H), 1.80 (ddd, *J* = 4.8, 7.9, 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.4, 168.8, 152.3, 130.3, 127.3, 122.7, 118.5, 117.1, 107.5, 106.7, 87.3, 81.3, 65.0, 53.6, 46.9, 39.9, 37.8, 35.7, 34.6, 31.4, 26.5; IR (film) ν_{max} 2954, 2902, 2236, 1738, 1667, 1605, 1487, 1436, 1385, 1113 cm^{-1}; MALDIFTMS (DHB) *m/z* 380.1598 ($C_{21}H_{21}N_3O_4$ + H^+ requires 380.1605).



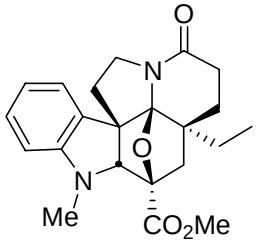
Solid curved lines represent nOe's observed in 2D ^{1}H–^{1}H ROESY (CD_2Cl_2, 400 MHz)

Compound 11b. A solution of **11a** (11.4 mg, 0.028 mmol) in 1,3,5-triisopropylbenzene (3.5 mL) was warmed at 230 °C for 22 h. After cooling to 25 °C, the solution was poured onto a plug of SiO_2 (2 × 8 cm) and the solvent was eluted with hexanes (25 mL). The product was eluted with EtOAc (25 mL) and concentrated. PTLC (SiO_2, 60% EtOAc–hexanes) afforded **11b** (7.9 mg, 0.021 mmol, 74%) as a white solid: ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 7.22 (t, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 6.4 Hz, 1H), 6.73 (t, *J* = 7.0 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 4.10 (s, 1H), 4.07 (dt, *J* = 9.2, 11.8 Hz, 1H), 3.93 (s, 3H), 3.83 (d, *J* = 7.8 Hz, 1H), 3.83 (t, *J* = 11.8 Hz, 1H), 2.98 (s, 3H), 2.59–2.52 (m, 1H), 2.42 (dt, *J* = 9.7, 13.2 Hz, 1H), 2.34 (ddd, *J* = 2.2, 4.4, 8.8 Hz, 1H), 2.23 (ddd, *J* = 5.7, 7.5, 13.2 Hz, 1H), 2.04 (ddt, *J* = 4.8, 9.2, 13.6 Hz, 1H), 1.89–1.83 (m, 2H); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 169.4, 168.4, 152.9, 130.1, 127.8, 123.1, 119.5, 116.8, 108.6, 105.1, 89.4, 82.1, 64.9, 53.3, 47.0, 37.2, 36.2, 36.1, 35.7, 31.3, 23.6; IR (film) ν_{max} 2954, 2902, 2236, 1759, 1733, 1667, 1487, 1390, 1118 cm^{-1}; MALDIFTMS (DHB) *m/z* 380.1599 ($C_{21}H_{21}N_3O_4$ + H^+ requires 380.1605).

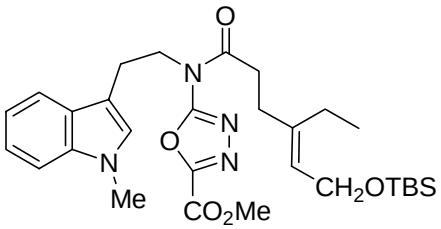


Methyl 5-{(4-Ethylpent-4-enoyl)-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-caboxylate (13a). Oxadiazole **S3** (552 mg, 1.84 mmol) was added in one portion to a solution of 4-ethyl-4-pentenoic acid[S6] (588 mg, 4.60 mmol) in anhydrous CH_2Cl_2 (5.0 mL) at 0 °C under Ar. The mixture was cooled to 0 °C and EDCI (881 mg, 4.60 mmol) was added. The resulting mixture was stirred for 5 min before the addition of DMAP (561 mg, 4.60 mmol). The reaction mixture was warmed to room temperature and stirred overnight at 23 °C, before the solvent was removed in vacuo. Flash chromatography (SiO_2, 50% EtOAc–hexanes) afforded **13a** (654 mg, 1.60 mmol, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.24–7.06 (m, 3H), 6.84 (s, 1H), 4.74 (s, 1H), 4.68 (s, 1H), 4.25–4.18 (m, 2H), 3.98 (s, 3H), 3.70 (s, 3H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.39 (t, *J* = 7.7 Hz, 2H), 2.01 (dd, *J* = 7.3, 14.6 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 162.0, 154.0, 153.2, 149.4, 136.9, 127.5, 127.4, 121.6, 119.0, 118.9, 109.8, 109.2, 108.3,

53.6, 47.8, 34.7, 32.6, 30.9, 28.9, 24.3, 12.3; IR (film) ν_{max} 2963, 1749, 1705, 1567, 1441, 1409, 1328, 1152, 742 cm^{-1}; MALDIFTMS (DHB) *m/z* 433.1860 ($C_{22}H_{26}N_4O_4$ + Na^+ requires 433.1846).

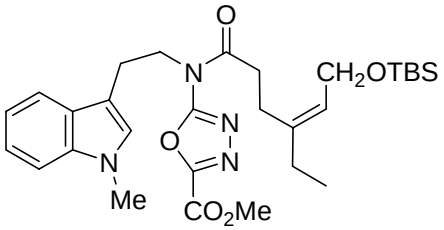


Compound 13b. A solution of **13a** (500 mg, 1.22 mmol) in 1,2-dichlorobenzene (40 mL) was added to refluxing 1,2-dichlorobenzene (80 mL, 0.010 M final concentration, passed through a column of basic alumina, degassed with Ar for 1 h while protected from the light) via syringe pump over 6.5 h and the resulting mixture was warmed at a gentle reflux in the absence of light for a total of 24 h, at which time the solvent was removed in vacuo. Flash chromatography (SiO_2, 20% Et_2O–CH_2Cl_2) afforded **13b** (346 mg, 0.91 mmol, 74%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.14 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 4.07 (s, 1H), 3.98–3.89 (m, 2H), 3.84 (s, 3H), 2.92 (s, 3H), 2.43 (m, 1H), 2.35 (dd, *J* = 4.8, 18.0 Hz, 1H), 2.27–2.13 (m, 4H), 1.72–1.68 (m, 2H), 0.91–0.84 (m, 1H), 0.58 (t, *J* = 7.4 Hz, 3H), 0.41–0.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 170.3, 153.1, 129.3, 128.5, 123.4, 118.0, 107.4, 106.3, 85.8, 82.4, 64.9, 52.6, 46.8, 43.6, 39.1, 37.5, 35.1, 29.1, 27.8, 22.4, 9.6; IR (film) ν_{max} 2954, 1737, 1667, 1606, 1493, 1440, 1397, 1270, 1120, 734 cm^{-1}; MALDIFTMS (DHB) *m/z* 383.1965 ($C_{22}H_{26}N_2O_4$ + H^+ requires 383.1965).

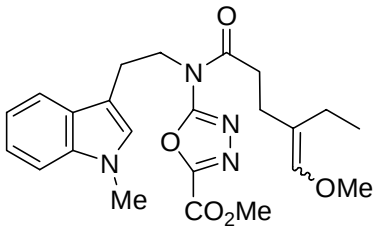


Methyl 5-{[(*E*)-6-(*tert*-Butyldimethylsilyloxy)-4-ethylhex-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate ((*E*)-14a). DMAP (87 mg, 0.75 mmol) was added to a solution of *trans*-6-(*tert*-butyldimethylsilyloxy)-4-ethyl-4-hexenoic acid (193 mg, 0.75 mmol), oxadiazole **S3** (112 mg, 0.38 mmol), and EDCI (144 mg, 0.75 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 20% EtOAc–hexanes) afforded (*E*)-**14a** (141 mg, 0.24 mmol, 70%) as a white solid: ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.21 (t, *J* = 7.0

Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 5.36 (t, *J* = 6.2 Hz, 1H), 4.23 (d, *J* = 6.2 Hz, 2H), 4.22 (t, *J* = 7.0 Hz, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 3.12 (t, *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 161.9, 153.9, 153.1, 140.5, 136.8, 127.4, 127.2, 124.9, 121.6, 119.0, 118.7, 109.7, 109.1, 59.8, 53.5, 47.6, 35.1, 32.5, 28.9, 25.9 (3C), 25.9, 24.2, 18.3, 12.3, –5.14 (2C); IR (film) ν_{max} 2944, 2851, 1749, 1703, 1564, 1441, 1410, 1154, 1082 cm^{-1}; MALDIFTMS (DHB) *m/z* 577.2809 ($C_{29}H_{42}N_4O_5Si$ + Na^+ requires 577.2817).

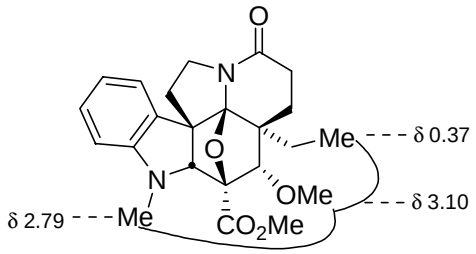


Methyl 5-{[(*Z*)-6-(*tert*-Butyldimethylsilyloxy)-4-ethylhex-4-enoyl]-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate ((*Z*)-14a). DMAP (76 mg, 0.65 mmol) was added to a solution of *cis*-6-(*tert*-butyldimethylsilyloxy)-4-ethyl-4-hexenoic acid (167 mg, 0.65 mmol), oxadiazole **S3** (97 mg, 0.33 mmol), and EDCI (125 mg, 0.65 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. Saturated aqueous NH_4Cl was added and the organic layer removed. The aqueous layer was washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 20% EtOAc–hexanes) afforded (*Z*)-**14a** (136 mg, 0.24 mmol, 78%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.86 (s, 1H), 5.28 (t, *J* = 6.2 Hz, 1H), 4.25 (m, 4H), 4.00 (s, 3H), 3.71 (s, 3H), 3.11 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.9 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.05 (q, *J* = 7.6 Hz, 2H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 161.9, 153.9, 153.1, 140.9, 136.8, 127.4, 127.3, 124.8, 121.5, 118.9, 118.8, 109.7, 109.1, 59.7, 53.5, 47.7, 34.8, 32.5, 31.0, 25.9 (3C), 24.2, 23.6, 18.3, 13.2, –5.2 (2C); IR (film) ν_{max} 2944, 2862, 1749, 1703, 1564, 1441, 1410, 1154, 1062 cm^{-1}; MALDIFTMS (DHB) *m/z* 577.2807 ($C_{29}H_{42}N_4O_5Si$ + Na^+ requires 577.2817).



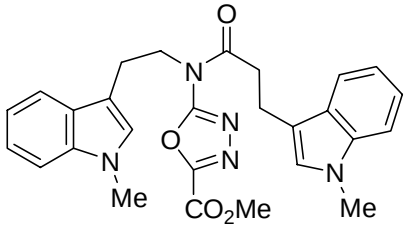
Methyl 5-{(4-Ethyl-5-methoxypent-4-enoyl)-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (15a). Oxadiazole **S3** (291 mg, 0.969 mmol) was added in one portion to a solution of 4-ethyl-5-methoxy-4-pentenoic acid

(459 mg, 2.91 mmol) in anhydrous CH_2Cl_2 (10 mL) at 25 °C under Ar. The mixture was cooled to 0 °C and EDCI (557 mg, 2.91 mmol) was added. The resulting mixture was stirred for 5 min, before the addition of DMAP (352 mg, 2.91 mmol). The reaction mixture was stirred at ambient temperature overnight, before the solvent was removed in vacuo. Flash chromatography (SiO_2, 30% EtOAc–hexane) afforded **15a** (300 mg, 0.68 mmol, 70%) as a yellow solid and as a mixture of (*E*)- and (*Z*)-stereoisomers: ^{1}H NMR ($CDCl_3$, 500 MHz; mixture, (*Z*)-**15a**) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.28–7.20 (m, 2H), 7.15–7.11 (m, 1H), 6.88 (s, 1H), 5.77 (s, 1H), 4.26–4.22 (m, 2H), 4.02 (s, 3H), 3.73 (s, 3H), 3.51 (s, 3H), 3.13 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.7 Hz, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 1.92 (q, *J* = 7.3 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{1}H NMR ($CDCl_3$, 500 MHz; mixture, (*E*)-**15a**, partial data) δ 6.88 (s, 1H), 5.81 (s, 1H), 3.55 (s, 1H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz; mixture, (*Z*)-**15a**) δ 172.3, 162.1, 154.0, 153.3, 142.5, 136.9, 127.5, 127.4, 121.6, 119.0, 118.9, 117.5, 109.9, 109.1, 59.2, 53.5, 47.8, 34.6, 32.5, 24.8, 24.2, 22.8, 13.1; IR (film) ν_{max} 2958, 2927, 1747, 1700, 1562, 1436, 1409, 1326, 1200, 1153, 1129, 1070 cm^{-1}; FABHRMS (NBA/NaI) *m/z* 441.2126 ($C_{23}H_{28}N_4O_5$ + H^+ requires 441.2138).

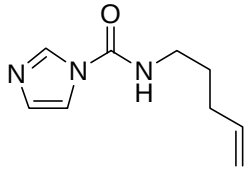


Solid curved lines represent nOe's observed in 1D ^{1}H–^{1}H GOESY ($CDCl_3$, 600 MHz)

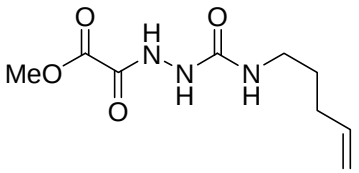
Compound 15b. A solution of (*E*)-**15a** (20 mg, 0.045 mmol) in 1,2-dichlorobenzene (9 mL, 0.005 M, passed through a column of basic alumina, degassed with Ar for 1 h while protected from the light) was warmed to a gentle reflux in the absence of light for 9 h (not optimized). The reaction mixture was cooled to 25 °C, and the solvent was removed in vacuo. Flash chromatography (SiO_2, 20% Et_2O–CH_2Cl_2) afforded **15b** (14 mg, 0.032 mmol, 70%) as a single diastereomer as a pale yellow oil which solidified upon standing: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.10 (t, *J* = 6.5 Hz, 1H), 6.60 (d, *J* = 6.5 Hz, 1H), 6.53 (t, *J* = 7.2 Hz, 1H), 6.18 (d, *J* = 7.9 Hz, 1H), 4.28 (s, 1H), 3.95–3.82 (m, 2H), 3.49 (s, 1H), 3.37 (s, 3H), 3.10 (s, 3H), 2.79 (s, 3H), 2.23 (ddd, *J* = 1.3, 5.3, 12.7 Hz, 1H), 2.15–1.99 (m, 3H), 1.78 (ddd, *J* = 1.3, 7.9, 12.3 Hz, 1H), 1.45 (ddd, *J* = 1.8, 5.7, 12.7 Hz, 1H), 0.92–0.86 (m, 1H), 0.69–0.62 (m, 1H), 0.37 (t, *J* = 7.4 Hz, 3H); IR (film) ν_{max} 1738, 1623, 1153, 897 cm^{-1}; FABHRMS (NBA/NaI) *m/z* 413.2087 ($C_{23}H_{28}N_2O_5$ + H^+ requires 413.2076).



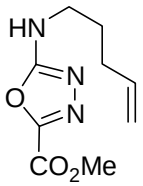
Methyl 5-{[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-[3-(1-methyl-1*H*-indol-3-yl)propionyl]amino}-1,3,4-oxadiazole-2-carboxylate (16a). A solution of 3-(1-methyl-1*H*-indol-3-yl)propionic acid (203 mg, 1.00 mmol) in 10 mL of anhydrous CH_2Cl_2 was treated with EDCI (191 mg, 1.00 mmol) and DMAP (12.2 mg, 0.10 mmol). Oxadiazole **S3** was added (100 mg, 0.30 mmol) and the reaction mixture was allowed to stir at 23 °C for 24 h. The reaction mixture was concentrated in vacuo to 2 mL and diluted with 50 mL of EtOAc and 10 mL of 1 N aqueous HCl. The organic layer was separated and washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. PTLC (SiO_2, 50% EtOAc–hexanes) provided **16a** (93 mg, 0.18 mmol, 64%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.26–7.24 (m, 2H), 7.21–7.18 (m, 2H), 7.12–7.06 (m, 2H), 6.87 (s, 1H), 6.79 (s, 1H), 4.18 (dd, *J* = 7.3, 7.5 Hz, 2H), 3.98 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.21 (dd, *J* = 6.6, 7.0 Hz, 2H), 3.15 (dd, *J* = 6.6, 8.5 Hz, 2H), 3.07 (dd, *J* = 7.5, 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.5, 162.2, 154.2, 153.3, 137.1, 128.5, 127.8, 127.6, 127.5, 127.0, 121.9, 121.8, 119.3, 119.1, 119.0, 118.9, 113.0, 110.1, 109.5, 109.4, 53.7, 48.0, 37.1, 32.8, 37.7, 24.5, 21.0; IR (film) ν_{max} 2933, 1749, 1697, 1583, 1441, 1323, 1151 cm^{-1}; MALDIFTMS (DHB) *m/z* 508.1955 ($C_{27}H_{27}N_5O_4$ + Na^+ requires 508.1952).



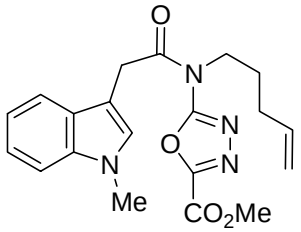
***N*-(Pent-4-enyl)-1*H*-imidazole-1-carboxamide (S4)**. 5-Amino-1-pentene hydrochloride[S7] (4.80 g, 35.0 mmol) was suspended in anhydrous CH_2Cl_2 (500 mL) under Ar. Carbonyldiimidazole (8.10 g, 50.0 mmol) was added in one portion followed by Et_3N (4.60 mL, 33.0 mmol). The reaction mixture was stirred for 16 h at 23 °C before solvent was removed under reduced pressure. Flash chromatography (SiO_2, 5% MeOH–$CHCl_3$) provided **S4** (5.50 g, 30.7 mmol, 89%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.90 (s, 1H), 7.40 (s, 1H), 7.07 (s, 1H), 5.78 (m, 1H), 5.10 (m, 2H), 3.41 (m, 2H), 2.13 (ddd, *J* = 7.6, 7.0, 6.8 Hz, 2H), 1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 137.4, 135.9, 129.5, 116.5, 115.5, 40.6, 31.0, 28.4; IR (film) ν_{max} 3448, 1727, 1528, 1510, 1477, 1315, 1275, 1057, 911 cm^{-1}; MALDIFTMS (DHB) *m/z* 180.1129 ($C_9H_{13}N_3O$ + H^+ requires 180.1131).



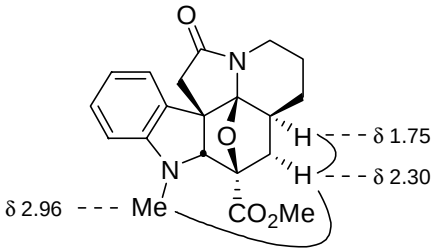
Methyl 2-Oxo-2-[2-(pent-4-enylcarbamoyl)hydrazinyl]acetate (S5). A solution of **S4** (5.50 g, 31.0 mmol) in THF (300 mL) and AcOH (3.6 mL, 64.0 mmol) under Ar was treated with methyl oxalylhydrazide[S1] (2.50 g, 31.0 mmol) and the reaction mixture was warmed at 40 °C for 16 h. The solvent was removed under reduced pressure and flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% $CHCl_3$) provided **S5** (3.10 g, 12.4 mmol, 42%) as a yellow solid: mp 97–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 8.05 (br s, 1H), 5.75 (m, 2H), 4.98 (m, 2H), 3.90 (s, 3H), 3.20 (dd, *J* = 4.8, 5.6 Hz, 2H), 2.06 (q, *J* = 5.6 Hz, 2H), 1.36 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 161.1, 160.5, 159.1, 139.4, 115.5, 53.9, 40.6, 32.2, 30.5; IR (film) ν_{max} 3374, 3282, 1730, 1697, 1543, 1435, 1292, 1230, 1143 cm^{-1}; MALDIFTMS (DHB) *m/z* 252.0960 $C_9H_{15}N_3O_4$ + Na^+ requires 252.0955).



Methyl 5-(Pent-4-enylamino)-1,3,4-oxadiazole-2-carboxylate (S6). TsCl (2.50 g, 13.0 mmol) was added to a solution of **S5** (3.00 g, 13.0 mmol) in anhydrous CH_2Cl_2 (160 mL) immediately followed by Et_3N (4.6 mL, 33.0 mmol). The reaction mixture was allowed to stir at 25 °C for 16 h before being concentrated in vacuo to 30 mL. The crude solution was diluted with EtOAc (150 mL) and the organic layer was washed with 1 N aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Chromatography (SiO_2, 5% MeOH–CH_2Cl_2) provided **S6** (2.50 g, 11.8 mmol, 91%) as a white solid: mp 92–93 °C (EtOAc–hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.50 (s, 1H), 5.85–5.71 (m, 1H), 5.08–4.95 (m, 2H), 3.98 (s, 3H), 3.43 (dt, *J* = 6.6, 7.0 Hz, 2H), 2.14 (dt, *J* = 8.3, 7.0 Hz, 2H), 1.79–1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.0, 155.1, 150.9, 137.4, 115.9, 53.5, 43.2, 30.9, 28.8; IR (film) ν_{max} 1738, 1634, 1549, 1444, 1365, 1266, 1205, 1167, 1060 cm^{-1}; MALDIFTMS (DHB) *m/z* 212.103 ($C_9H_{13}N_3O_3$ + H^+ requires 212.1029).



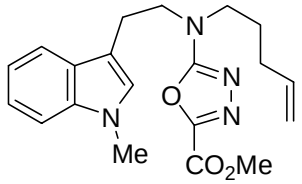
Methyl 5-{[2-(1-Methyl-1*H*-indol-3-yl)acetyl]-(pent-4-en-1-yl)amino}-1,3,4-oxadiazole-2-carboxylate (17a). A solution of 2-(1-methyl-1*H*-indol-3-yl)acetic acid (75 mg, 0.50 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated with EDCI (98 mg, 0.50 mmol) followed by DMAP (2 mg, 0.02 mmol). Oxadiazole **S6** was added (103 mg, 0.50 mmol) and the reaction mixture was allowed to stir at 23 °C for 24 h. The reaction mixture was concentrated in vacuo to 1 mL then diluted with 30 mL of EtOAc and 10 mL of 1 N aqueous HCl. The organic layer was separated and washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. PTLC (50% EtOAc–hexanes) provided **17a** (108 mg, 0.28 mmol, 57%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.23–7.15 (m, 2H), 7.09 (d, *J* = 7.0 Hz, 1H), 6.90 (s, 1H), 5.75–5.69 (m, 1H), 4.97–4.91 (m, 2H), 4.32 (s, 2H), 4.03 (s, 3H), 3.91 (t, *J* = 7.7, 7.3 Hz, 2H), 3.71 (s, 3H), 2.06–2.00 (m, 2H), 1.70 (dd, *J* = 7.7, 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 162.0, 154.3, 153.7, 137.0, 136.8, 128.0, 127.4, 121.9, 119.34, 119.30, 115.4, 109.3, 60.6, 53.8, 47.2, 33.3, 32.7, 30.5, 27.0; IR (film) ν_{max} 2932, 1749, 1703, 1567, 1442, 1159 cm^{-1}; FABHRMS (NBA/NaI) *m*/*z* 383.1711 ($C_{20}H_{22}N_4O_4$ + H^+ requires 383.1719).



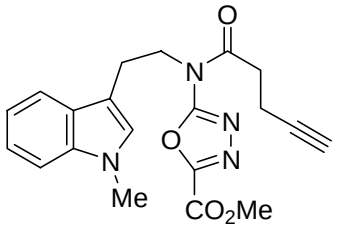
Solid curved lines represent nOe's observed in 1D ^{1}H–^{1}H GOESY ($CDCl_3$, 600 MHz)

Compound 17b. A solution of **17a** (11 mg, 0.029 mmol) in 1.5 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 160 °C for 6 h. The solution was concentrated under a stream of N_2 and the crude material was purified by PTLC (SiO_2, 40% EtOAc–CH_2Cl_2) providing **17b** (6.2 mg, 0.018 mmol, 61%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (dd, *J* = 7.3, 7.7 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.67 (dd, *J* = 7.7, 7.3 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.15 (s, 1H), 3.93 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.87 (s, 3H), 3.03 (dd, *J* = 13.2, 9.5 Hz, 1H), 2.96 (s, 3H), 2.94 (d, *J* = 13.5 Hz, 1H), 2.63 (d, *J* = 13.5 Hz, 1H), 2.30 (dd, *J* = 7.7, 4.7 Hz, 1H), 1.75 (d, *J* = 11.0 Hz, 1H), 1.69 (dd, *J* = 8.0, 4.3 Hz, 1H), 1.49 (m, 2H), 1.41 (dd, *J* = 11.1, 11.0 Hz, 1H), 1.28 (dd,

J = 8.0, 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7, 169.2, 152.1, 130.9, 129.5, 128.3, 122.6, 117.8, 106.7, 103.9, 86.1, 80.4, 59.4, 52.6, 45.1, 38.3, 34.6, 33.9, 28.0, 23.0; IR (film) ν_{max} 1707, 1584, 1420, 1343, 1164, 1092 cm^{-1}; FABHRMS (NBA/NaI) *m*/*z* 355.1652 ($C_{20}H_{22}N_2O_4$ + H^+ requires 355.1658).

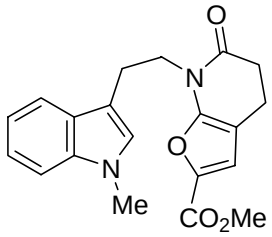


Methyl 5-{[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-(pent-4-en-1-yl)amino}-1,3,4-oxadiazole-2-carboxylate (18a). Oxadiazole **S3** (100 mg, 0.33 mmol) was dissolved in 2 mL of anhydrous DMF. The solution was cooled to 0 °C and Cs_2CO_3 (119 mg, 0.37 mmol) was added. After 30 min, 5-bromo-1-pentene (0.1 mL, 0.74 mmol) was added. The reaction mixture was allowed to warm to 23 °C and was stirred for 16 h. The mixture was diluted with 20 mL of Et_2O and the organic layer was washed with saturated aqueous NaCl (2 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. PTLC (SiO_2, 60% EtOAc–hexanes) provided **18a** (26 mg, 0.069 mmol, 21%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 7.0, 8.2 Hz, 1H), 7.14 (dd, *J* = 7.0, 7.9 Hz, 1H), 6.89 (s, 1H), 5.79–5.71 (m, 1H), 5.04–4.96 (m, 2H), 3.98 (s, 3H), 3.77–3.73 (m, 2H), 3.73 (s, 3H), 3.44 (t, *J* = 7.5 Hz, 2H), 3.11 (dd, *J* = 7.9, 7.5 Hz, 2H), 2.06 (dt, *J* = 7.5, 7.0 Hz, 2H), 1.72 (dt, *J* = 7.5, 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.2, 163.3, 155.2, 137.4, 137.3, 127.8, 127.2, 122.0, 119.3, 118.9, 115.7, 110.7, 109.6, 53.3, 50.3, 49.4, 32.9, 30.8, 27.0, 23.9; IR (film) ν_{max} 2933, 1739, 1615, 1436, 1328, 1150 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 369.1921 ($C_{20}H_{24}N_4O_3$ + H^+ requires 369.1921).

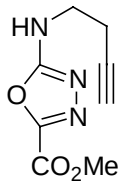


Methyl 5-{(Pent-4-ynoyl)-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-oxadiazole-2-carboxylate (19a). A solution of oxadiazole **S3** (15.0 mg, 0.050 mmol), 4-pentynoic acid (9.8 mg, 0.10 mmol), and EDCI (38.2 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) under Ar at 25 °C was treated with DMAP (12.2 mg, 0.10 mmol). The mixture was stirred at 25 °C for 18 h before the white slurry was concentrated. Chromatography (SiO_2, 2.5% MeOH–CH_2Cl_2) provided **19a** (18.2 mg, 0.048 mmol, 96%) as a white solid: mp 185–186 °C (EtOAc–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* =

7.6 Hz, 1H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.86 (s, 1H), 4.26 (t, *J* = 7.3 Hz, 2H), 4.01 (s, 3H), 3.72 (s, 3H), 3.11 (m, 4H), 2.60 (dt, *J* = 2.6, 7.0 Hz, 2H), 1.97 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 162.0, 154.2, 153.5, 137.2, 127.8, 127.6, 121.9, 119.3, 119.1, 110.0, 109.5, 82.6, 69.3, 53.9, 48.0, 35.7, 32.8, 24.5, 14.4; IR (film) ν_{max} 3260, 1739, 1714, 1573, 1438, 1414 cm^{-1}; MALDIFTMS (DHB) *m/z* 403.1381 ($C_{20}H_{20}N_4O_4$ + Na^+ requires 403.1377).

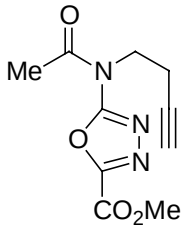


Methyl 7-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-6-oxo-4,5,6,7-tetrahydrofuro[2,3-*b*]pyridine-2-carboxylate (19b, see also **12)**. A solution of **19a** (7.0 mg, 0.017 mmol) in 1,2-dichlorobenzene (1.8 mL) was warmed in a sealed tube at 175 °C for 53 h. The solvent was removed by SiO_2 chromatography (hexanes) and the crude reaction mixture was eluted with EtOAc. Chromatography (SiO_2, 3.5% EtOAc–CH_2Cl_2) afforded **19b** (4.0 mg, 0.011 mmol, 63%) as an off-white solid: mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 159.1, 151.8, 138.1, 137.1, 128.2, 127.2, 121.8, 120.0, 119.3, 119.1, 110.9, 109.3, 100.0, 51.8, 42.5, 32.8, 32.4, 24.4, 16.9; IR (film) ν_{max} 1718, 1682, 1631, 1533, 1472, 1431, 1323, 1190, 1154 cm^{-1}; MALDIFTMS (DHB) *m/z* 353.1488 ($C_{20}H_{20}N_2O_4$ + H^+ requires 353.1496).

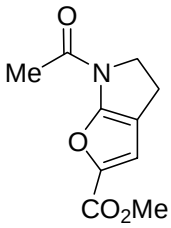


Methyl 5-(3-Butyn-1-yl)amino-1,3,4-oxadiazole-2-carboxylate (20a). Prepared from 1-amino-3-butyne according to the procedure reported for the preparation of **S6** and isolated as a white solid (41% over 3 steps): mp 151–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.91 (br s, 1H), 3.98 (s, 3H), 3.61 (dt, *J* = 6.3, 6.3 Hz, 2H), 2.57 (dt, *J* = 2.6, 6.3 Hz, 2H), 2.04 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6, 155.2, 151.6,

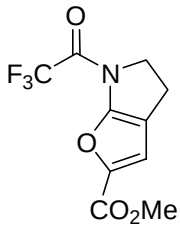
80.6, 71.4, 53.7, 42.4, 19.8; IR (film) ν_{max} 3234, 1741, 1626, 1549, 1442, 1205, 1159 cm^{-1}; MALDIFTMS (DHB) *m/z* 218.0535 ($C_8H_9N_3O_3 + Na^+$ requires 218.0536).



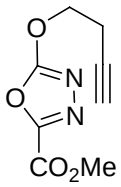
Methyl 5-(*N*-Acetyl-(but-3-yn-1-yl)amino)-1,3,4-oxadiazole-2-carboxylate (21a). A solution of **20a** (20 mg, 0.10 mmol) in 2 mL of acetic anhydride was treated with DMAP (6 mg, 0.051 mmol) and stirred at 25 °C for 18 h. The reaction mixture was concentrated under reduced pressure and subjected to flash chromatography (SiO_2, 2% MeOH–CH_2Cl_2) to provide **21a** (20 mg, 0.086 mmol, 84%) as a white solid: mp 85–86 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.15 (t, *J* = 7.0 Hz, 2H), 4.04 (s, 3H), 2.59 (dt, *J* = 2.6, 6.8 Hz, 2H), 2.55 (s, 3H), 1.91 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 162.3, 154.7, 154.0, 80.0, 71.1, 54.2, 45.7, 24.9, 18.5; IR (film) ν_{max} 3285, 2959, 1747, 1713, 1568, 1445, 1163, 814 cm^{-1}; MALDIFTMS (DHB) *m/z* 238.0819 ($C_{10}H_{11}N_3O_4 + H^+$ requires 238.0822).



Compound 21b. A solution of **21a** (10 mg, 0.042 mmol) in 8.5 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 18 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (50 mL) and then the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 55% EtOAc–hexanes) providing **21b** (6.5 mg, 0.031 mmol, 74%) as a yellow amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (s, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.84 (s, 3H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 158.6, 155.9, 142.6, 118.3, 109.3, 52.9, 51.6, 22.6, 20.5; IR (film) ν_{max} 1715, 1698, 1673, 1614, 1530 cm^{-1}; MALDIFTMS (DHB) *m/z* 210.0766 ($C_{21}H_{24}N_2O_4 + H^+$ requires 210.0761).



Methyl *N*-Trifluoroacetyl-5,6-dihydro-4*H*-furo[2,3-*b*]pyrrole-2-carboxylate (22b). A solution of **20a** (16.2 mg, 0.083 mmol) in 0.7 mL of trifluoroacetic anhydride was stirred at 25 °C for 20 h. The reaction mixture was concentrated under reduced pressure to afford the unstable trifluoroacetamide **22a** which was used immediately in subsequent reactions: ^{1}H NMR (1,2-$Cl_2C_6D_4$, 400 MHz) δ 4.04 (t, *J* = 6.8 Hz, 2H), 3.83 (s, 3H), 2.56 (dt, *J* = 2.6, 6.8 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H). A solution of **22a** in 0.5 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 165–170 °C for 18 h. The reaction mixture was cooled and loaded directly onto SiO_2 (1 × 8 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes, and the column was eluted with 1% MeOH–CH_2Cl_2 to provide **22b** (8.9 mg, 0.033 mmol, 71%) as a 2:1 mixture of trifluoroacetamide rotomers: mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) major rotomer δ 7.10 (s, 1H), 4.56 (t, *J* = 7.6 Hz, 2H), 3.85 (s, 3H), 2.96 (t, *J* = 7.6 Hz, 2H); minor rotomer δ 7.13 (s, 1H), 4.65 (t, *J* = 7.4 Hz, 2H), 3.85 (s, 3H), 3.05 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) major rotomer δ 158.7, 155.8, 152.6, 144.6, 117.6, 117.1, 113.0, 55.5, 52.4, 21.0; minor rotomer δ 158.9, 155.9, 152.6, 144.5, 117.6, 117.0, 113.0, 54.5, 52.4, 22.4; IR (film) ν_{max} 2954, 1726, 1690, 1140 cm^{-1}; MALDIFTMS (DHB) *m/z* 286.0291 ($C_{10}H_8NO_4F_3$ + Na^+ requires 286.0298).

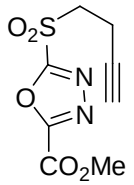


Methyl 5-(But-3-ynyloxy)-1,3,4-oxadiazole-2-carboxylate (23a, X = O). 3-Butyn-1-ol (1.52 g, 20.0 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (5.0 g, 30.8 mmol) in THF (200 mL) under Ar cooled to 0 °C. The reaction mixture was allowed to stir for 2 h at room temperature before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided but-3-ynyl 1*H*-imidazole-1-carboxylate (3.3 g, 100%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 7.40 (q, *J* = 1.6 Hz, 1H), 7.03 (t, *J* = 0.8 Hz, 1H), 4.46 (dt, *J* = 2.0, 6.8 Hz, 2H), 2.68–2.63 (m, 2H), 2.01 (dt, *J* = 0.8, 2.8 Hz, 1H).

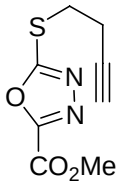
A solution of but-3-ynyl 1*H*-imidazole-1-carboxylate (3.2 g, 19.0 mmol) in CH_2Cl_2 (200 mL) was treated with hydrazine monohydrate (2 mL, 40.0 mmol). The reaction mixture was stirred at room temperature for 3 h before the solvent was removed under reduced pressure. The resulting crude product in CH_2Cl_2 (100 mL) under Ar at 0 °C was treated with Et_3N (3.5 mL, 27.4 mmol) followed by the dropwise addition of methyl oxalyl chloride (2.5 mL, 27.2 mmol). The reaction mixture was stirred for 2 h

before being quenched with the addition of H_2O. The organic layer was further washed with aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl, and dried over Na_2SO_4. Flash chromatography (SiO_2, 67% EtOAc–hexanes) provided but-3-ynyl 2-(2-methoxy-2-oxoacetyl)hydrazinecarboxylate (2.7 g, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68 (q, *J* = 6.8 Hz, 2H), 4.00 (s, 3H), 2.78 (dt, *J* = 6.0 Hz, 2H), 1.99–1.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 149.1, 140.9, 78.8, 71.0, 66.0, 54.3, 19.1.

Et_3N (2.9 mL, 22.0 mmol) was added to a stirring solution of but-3-ynyl 2-(2-methoxy-2-oxoacetyl)hydrazinecarboxylate (2.1 g, 10.0 mmol) and TsCl (2.86 g, 15.0 mmol) in CH_2Cl_2 (100 mL) under Ar at room temperature. The reaction mixture was stirred for 14 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided **23a** (X = O, 427 mg, 2.18 mmol, 22%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (q, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 2.47 (t, *J* = 2.8, 6.8 Hz, 2H), 2.05 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7, 156.5, 156.1, 79.8 70.2, 63.9, 53.6, 19.1; IR (film) ν_{max} 3282, 2944, 1744, 1590, 1446, 1374, 1302, 1205, 1148, 1087, 1015, 810, 646 cm^{-1}; HRESI-TOF *m*/*z* 197.0566 ($C_8H_8N_2O_4 + H^+$ requires 197.0557).



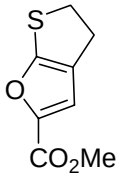
Methyl 5-(But-3-ynylsulfonyl)-1,3,4-oxadiazole-2-carboxylate (23a, X = SO_2). A solution of **24a** (318 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) was treated with *m*-CPBA (~70%, 820 mg, 3.3 mmol) at 0 °C. After the completion of the reaction as judged by TLC, the mixture was filtered and the filtrate was washed with saturated aqueous Na_2SO_3, H_2O, and saturated aqueous NaCl, and dried over Na_2SO_4. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **23a** (X = SO_2, 252 mg, 1.03 mmol, 69%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (s, 3H), 3.52–3.45 (m, 1H), 3.39–3.34 (m, 1H), 2.81–2.75 (m, 1H), 2.68–2.62 (m, 1H), 1.98 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.6, 163.3, 158.5, 79.3, 71.7, 55.2, 54.4, 11.5; IR (film) ν_{max} 3262, 2933, 1738, 1451, 1318, 1257, 1113, 1062, 815, 754 cm^{-1}.



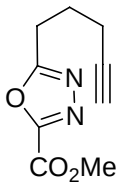
Methyl 5-(But-3-ynylthio)-1,3,4-oxadiazole-2-carboxylate (24a). A solution of methyl oxalylhydrazide (3.54 g, 30 mmol) in MeOH (40 mL) was treated with CS_2 (8 mL, 132 mmol) followed with KOH (1.68 g, 30 mmol). The reaction mixture was warmed at reflux for 24 h. The solvent was removed and the residue was re-dissolved in ice-water. The solution was then treated with 1 M aqueous HCl to achieve a pH 7 ~ 8. The resulting aqueous solution was extracted with EtOAc (100 mL × 3). The combined organic phase

was washed with saturated aqueous NaCl and dried over Na_2SO_4 and concentrated to give crude thione (2.5 g, 52%) as an oil.

A solution of the crude thione (640 mg, 4.0 mmol) in 20 mL of DMF was treated with Cs_2CO_3 (2.58 g, 8.0 mmol). The mixture was stirred at room temperature for 1 h before 4-bromo-1-butyne (1.33 g, 10.0 mmol) was added in one portion. The reaction mixture was stirred for additional 24 h before being quenched with the addition of H_2O, and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) provided **24a** (690 mg, 3.25 mmol, 82%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 3.45 (t, *J* = 6.8 Hz, 2H), 2.73 (dt, *J* = 2.8, 6.8 Hz, 2H), 2.03 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 157.7, 154.5, 80.9, 71.1, 54.0, 31.5, 19.5; IR (film) ν_{max} 3282, 2964, 1749, 1539, 1451, 1359, 1231, 1139, 1077, 1015, 949, 821, 769, 692, 636 cm^{-1}; HRESI-TOF *m/z* 213.0322 ($C_8H_8N_2O_3S + H^+$ requires 213.0328).



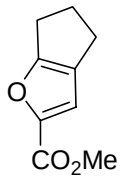
Methyl 4,5-Dihydrothieno[2,3-*b*]furan-2-carboxylate (24b). A solution of **24a** (22 mg, 0.10 mmol) in anhydrous, degassed 1,2-dichlorobenzene (20 mL) was warmed under Ar at 180 °C for 36 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes and subsequent elution with 25% EtOAc–hexanes gave **24b** (15 mg, 0.081 mmol, 81%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 3.85 (s, 3H), 3.81 (t, *J* = 8.0 Hz, 2H), 2.86 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 158.6, 148.5, 124.6, 117.2, 51.9, 40.6, 25.4; IR (film) ν_{max} 2933, 1692, 1574, 1487, 1410, 1302, 1241, 1185, 1082, 1057, 974, 903, 857, 754 cm^{-1}; HRESI-TOF *m/z* 185.0266 ($C_8H_8O_3S + H^+$ requires 185.0267).



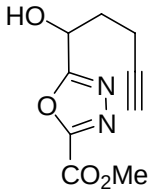
Methyl 5-(Pent-4-ynyl)-1,3,4-oxadiazole-2-carboxylate (25a). DMAP (122 mg, 1.0 mmol) was added to a solution of 5-hexynoic acid (0.60, 5.0 mmol), EDCI (1.92 g, 10.0 mmol) and methyl oxalyl hydrazide (1.18 g, 10.0 mmol) in CH_2Cl_2 (100 mL) under Ar at 0 °C. The reaction was stirred at room temperature for 10 h before being concentrated under reduce pressure. Flash chromatography (SiO_2, 67% EtOAc–hexanes) gave methyl 2-(2-hex-5-ynoylhydrazinyl)-2-oxoacetate (1.63 g, 77%) as a white solid: ^{1}H NMR

($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.25 (m, 2H), 1.96 (m, 1H), 1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 159.6, 152.8, 83.2, 69.7, 54.0, 47.3, 32.7, 19.4.

Et_3N (0.6 mL, 4.7 mmol) was added to a stirring solution of 2-(2-hex-5-ynoylhydrazinyl)-2-oxoacetate (850 mg, 4.0 mmol) and TsCl (900 mg, 4.7 mmol) in CH_2Cl_2 (40 mL) under Ar at room temperature. The reaction mixture was stirred for 10 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) provided **25a** (649 mg, 3.3 mmol, 84%) as an oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 2.97 (dt, *J* = 0.4, 7.6 Hz, 2H), 2.44 (dt, *J* = 2.8, 6.8 Hz, 2H), 1.98–1.90 (m, 2H), 1.89 (dt, *J* = 0.8, 2.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 156.8, 154.9, 82.4, 70.1, 53.9, 25.0, 24.4, 17.9; IR (film) ν_{max} 3292, 2944, 1749, 1559, 1436, 1395, 1262, 1200, 1154, 1031, 944, 805, 662 cm^{-1}; HRESI-TOF *m/z* 195.0762 ($C_9H_{10}N_2O_3 + H^+$ requires 195.0764).



Methyl 5,6-Dihydro-4*H*-cyclopenta[*b*]furan-2-carboxylate (25b). A solution of **25a** (21.5 mg, 0.11 mmol) in anhydrous, degassed 1,3,5-triisopropylbenzene (20 mL) was warmed under Ar at 230 °C for 44 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with hexanes and subsequent elution with 20% EtOAc–hexanes gave **25b** (16 mg, 0.096 mmol, 89%) as an solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.04 (s, 1H), 3.86 (s, 3H), 2.74 (t, *J* = 8.2 Hz, 2H), 2.60–2.56 (m, 2H), 2.49–2.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 159.4, 147.6, 128.0, 116.4, 51.7, 27.5, 24.8, 23.1; IR (film) ν_{max} 2933, 2861, 1702, 1600, 1513, 1444, 1333, 1282, 1205, 1179, 1077, 985, 918, 861, 764, 631 cm^{-1}; HRESI-TOF *m/z* 167.0701 ($C_9H_{10}O_3 + H^+$ requires 167.0703).



Methyl 5-(1-Hydroxypent-4-ynyl)-1,3,4-oxadiazole-2-carboxylate (S7). *n*-BuLi (2.5 M in hexanes, 11 mL, 27.5 mmol) was added slowly to a stirred solution of 5-hexynoic acid (1.51 g, 13.5 mmol) in THF (80 mL) at –78 °C under Ar. TMSCl (3.5 mL, 27.5 mmol) was added quickly to the white suspension. The reaction mixture was allowed to warm to 0 °C and quenched with the addition of aqueous HCl (1 M, 80 mL). CH_2Cl_2 (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The organic layers were combined and washed with saturated aqueous

NaCl and dried over Na_2SO_4. The solvents were removed to give crude 6-(trimethylsilyl)hex-5-ynoic acid. The crude acid was dissolved in Et_2O (40 mL) and treated with CH_2N_2 slowly. The reaction was quenched with the addition of HOAc (0.1 mL) and concentrated after the reaction was judged complete by TLC. Flash chromatography (SiO_2, 5% EtOAc–hexanes) provided methyl 6-(trimethylsilyl)hex-5-ynoate (1.3 g, 49%, 2 steps) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.87–1.79 (m, 2H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 105.9, 85.4, 51.6, 32.7, 23.7, 19.3, 0.1.

A solution of KHMDS (0.5 M in tolune, 15.8 mL, 7.9 mmol) was treated with a solution of above methyl ester (1.3 g, 6.6 mmol) in THF (60 mL) at –78 °C. The resulting mixture was stirred for 30 min before a solution of Davis oxaziridine (2.14 g, 8.2 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 4 h at –78 °C before being quenched with the addition of saturated NH_4Cl (80 mL). The aqueous layer was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4. Flash chromatography (SiO_2, 10% EtOAc–hexanes) provided methyl 2-hydroxy-6-(trimethylsilyl)hex-5-ynoate (720 mg, 51%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31–4.27 (m, 1H), 3.80 (s, 3H), 2.81 (d, *J* = 5.2 Hz, 1H), 2.41–2.37 (m, 2H), 2.06–2.00 (m, 1H), 1.87–1.80 (m, 1H), 0.14 (s, 9H).

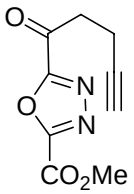
A concentrated solution of the α-hydroxyl methyl ester (720 mg, 3.3 mmol) and imidazole (320 mg, 4.7 mmol) in CH_2Cl_2 (2.5 mL) was treated with TBDMSCl (0.80 g, 6.0 mmol). The reaction mixture was stirred for 2 h before flash chromatography (SiO_2, 5% EtOAc–hexanes) which provided methyl 2-(*tert*-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-ynoate (1.02 g, 94%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (dd, *J* = 4.0, 8.8 Hz, 1H), 3.72 (s, 3H), 2.39–2.33 (m, 2H), 1.95–1.82 (m, 2H), 0.92 (s, 9H), 0.14 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

A solution of the methyl ester (950 mg, 2.89 mmol) in THF–MeOH–H_2O (3:1:1, 30 mL) was treated with $LiOH·H_2O$ (200 mg, 5.0 mmol) at 0 °C. After completion of the reaction as judged by TLC, the reaction mixture was neutralized by the addition of HCl (1 M, 5 mL). The reaction mixture was extracted by EtOAc (100 mL × 2). The organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4. The concentrated crude product was dissolved in CH_2Cl_2 (10 mL) together with methyl oxalyl hydrazide (448 mg, 4.0 mmol), EDCI (1.1 g, 6.0 mmol) and DMAP (112 mg, 1.0 mmol). The reaction mixture was stirred for 4 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 20% EtOAc–hexanes) provided methyl 2-(2-(2-(*tert*-butyldimethylsilyloxy)hex-5-ynoyl)hydrazinyl)-2-oxoacetate (326 mg, 35%, 2 steps) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40 (dd, *J* = 4.8, 7.2 Hz, 1H), 3.93 (s, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.01–1.95 (m, 2H), 0.96 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.14 (s, 9H).

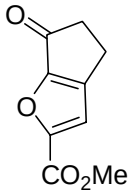
The solution of above hydrazide (307 mg, 0.90 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.2 mL, 1.5 mmol) followed by TsCl (270 mg, 1.5 mmol). The reaction mixture was stirred for 4 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 12% EtOAc–hexanes) provided methyl 5-(1-(*tert*-butyldimethylsilyloxy)-5-(trimethylsilyl)pent-4-ynyl)-1,3,4-oxadiazole-2-carboxylate (134 mg, 46%) as an oil.

A solution of the oxadiazole (47 mg, 0.15 mmol) in THF (1 mL) was treated with Bu_4NF (1 M in THF, 0.3 mL, 0.3 mmol) slowly. The reaction mixture was stirred for 15

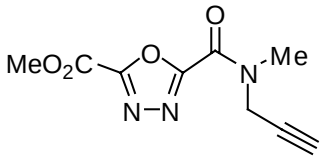
min before being concentrated. Flash chromatography (SiO_2, 40% EtOAc–hexanes) provided **S7** (14.2 mg, 0.067 mmol, 46%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.18 (dd, *J* = 4.8, 8.0 Hz, 1H), 4.00 (s, 3H), 2.46–2.39 (m, 2H), 2.18–2.12 (m, 2H), 1.93 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 157.0, 154.8, 82.3, 70.2, 64.8, 54.1, 33.4, 14.4; IR (film) ν_{max} 3385, 3282, 2933, 1754, 1549, 1446, 1384, 1154, 1051, 949, 821, 646 cm^{-1}; HRESI-TOF *m*/*z* 233.0536 ($C_9H_{10}N_2O_4$ + Na^+ requires 233.0533).



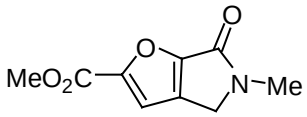
Methyl 5-Pent-4-ynoyl-1,3,4-oxadiazole-2-carboxylate (26a). A solution of **S7** (9.3 mg, 0.044 mmol) in CH_2Cl_2 (1 mL) was treated with Dess–Martin periodinane (20 mg, 0.047 mmol). The reaction mixture was stirred for 30 min before being concentrated. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **26a** (7.6 mg, 0.037 mmol, 82%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (s, 3H), 3.43 (t, *J* = 7.6 Hz, 2H), 2.67 (dt, *J* = 2.8, 7.2 Hz, 2H), 1.97 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.5, 161.0, 157.3, 154.1, 81.5, 70.0, 54.5, 39.4, 12.9; IR (film) ν_{max} 3292, 2953, 2913, 1754, 1713, 1600, 1523, 1451, 1400, 1359, 1277, 1200, 1164, 1072, 974, 810, 621 cm^{-1}; HRESI-TOF *m*/*z* 231.0375 ($C_9H_{10}N_2O_4$ + Na^+ requires 231.0376).



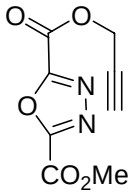
Methyl 6-Oxo-5,6-dihydro-4*H*-cyclopenta[*b*]furan-2-carboxylate(26b). A solution of **26a** (11 mg, 0.053 mmol) in anhydrous, degassed 1,3,5-triisopropylbenzene (10 mL) was warmed under Ar at 230 °C for 48 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with hexanes and the column was flushed with EtOAc. The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 33% EtOAc–hexanes) providing **26b** (6.5 mg, 0.036 mmol, 67%) as an oil:^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (s, 1H), 3.95 (s, 3H), 2.96–2.94 (m, 2H), 2.91–2.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.9, 159.0,156.9, 154.8, 153.0, 52.6, 40.6, 19.2; IR (film) ν_{max} 2913, 2814, 1728, 1692, 1431, 1354, 1267, 1205, 1082, 974, 923, 759 cm^{-1}; HRESI-TOF *m*/*z* 181.0495 ($C_9H_8O_4$ + H^+ requires 181.0495).



Methyl 5-(methyl(prop-2-ynyl)carbamoyl)-1,3,4-oxadiazole-2-carboxylate (27a). A stirring solution of dimethyl 1,3,4-oxadiazole-2,5-dicarboxylate (150 mg, 0.81 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was slowly added *N*-methylprop-2-yn-1-amine (73 μL, 0.89 mmol) followed by the addition of Et_3N (93 μL, 0.89 mmol). The solution was warmed to 23 °C overnight. Purification by column chromatography provided methyl 5-(methyl(prop-2-ynyl)carbamoyl)-1,3,4-oxadiazole-2-carboxylate (**27a**, 15 mg, 0.067 mmol, 8%) as a 3:2 mixture of rotamers as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (d, *J* = 2.5 Hz, 2H, minor), 4.42 (d, *J* = 2.5 Hz, 2H, major), 4.08 (s, 3H), 3.53 (s, 3H, major), 3.25 (s, 3H, minor), 2.35 (t, *J* = 2.5 Hz, 1H, minor), 2.33 (t, *J* = 2.5 Hz, 1H, major); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 158.9, 156.7, 156.6, 154.0, 153.9, 153.6, 153.2, 76.8, 75.6, 73.9, 73.4, 54.1, 40.5, 37.5, 36.0, 34.1; IR (film) ν_{max} 1720, 1695, 1506, 1356, 1195 cm^{-1}; MALDIFTMS (DHB) *m/z* 224.0666 ($C_9H_9NO_4$ + H^+ requires 224.0666).

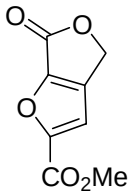


Methyl 5-methyl-6-oxo-5,6-dihydro-4*H*-furo[3,2-c]pyrrole-2-carboxylate (27b). A solution of **27a** (10 mg, 0.042 mmol) in 8.5 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 18 h. The reaction mixture was cooled to 25 °C and then to 0 °C. The resulting solid was collected and washed with cold hexanes providing methyl 5-methyl-6-oxo-5,6-dihydro-4*H*-furo[3,2-c]pyrrole-2-carboxylate (**27b**, 6.5 mg, 0.031 mmol, 84%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (s, 1H), 4.22 (s, 2H), 3.93 (s, 3H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 158.5, 153.6, 150.2, 133.9, 113.7, 52.4, 46.9, 30.6; IR (film) ν_{max} 1723, 1699, 1505, 1352, 1195 cm^{-1}; MALDIFTMS (DHB) *m/z* 196.0602 ($C_9H_9NO_4$ + H^+ requires 196.0604).

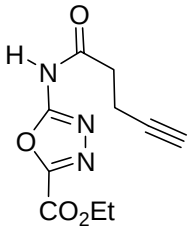


2-Methyl 5-Propargyl 1,3,4-oxadiazole-2,5-dicarboxylate (28a). NaOMe (20 mg, 0.38 mmol) was added to the solution of dimethyl 1,3,4-oxadiazole-2,5-dicarboxylate (372 mg, 2.0 mmol) and propargyl alcohol (0.46 mL, 8.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 10 min before being quenched by the addition of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were

washed with H_2O, saturated aqueous NaCl, and dried over Na_2SO_4. Flash chromatography (SiO_2, 50% Ether–hexanes) provided **28a** (119 mg, 0.57 mmol, 28%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.03 (t, *J* = 1.6 Hz, 2H), 4.07 (s, 3H), 2.59 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 157.1, 153.9, 152.9, 77.4, 75.5, 55.1, 54.5; IR (film) ν_{max} 3272, 2964, 2923, 1754, 1539, 1436, 1384, 1287, 1139, 1030, 815, 646 cm^{-1}; HRESI-TOF *m/z* 211.0352 ($C_8H_6N_2O_5$ + H^+ requires 211.0349).

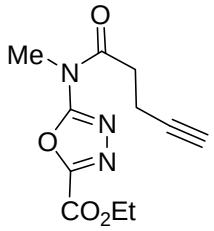


Methyl 6-Oxo-4,6-dihydrofuro[3,4-*b*]furan-2-carboxylate (28b). A solution of **28a** (15.2 mg, 0.07 mmol) in anhydrous, degassed 1,3,5-triisopropylbenzene (20 mL) was warmed under Ar at 230 °C for 34 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with hexanes and subsequent elution with 33% EtOAc–hexanes gave **28b** (11 mg, 0.06 mmol, 81%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (s, 1H), 5.22 (s, 2H), 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 158.2, 153.5, 147.6, 144.8, 113.1, 65.5, 52.8; IR (film) ν_{max} 2923, 1785, 1759, 1718, 1513, 1426, 1313, 1287, 1200, 1102, 1041, 954, 754 cm^{-1}; HRESI-TOF *m/z* 183.0287 ($C_8H_6O_5$ + H^+ requires 183.0288).

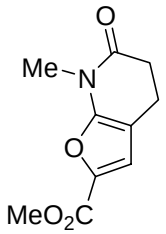


Ethyl 5-(Pent-4-ynoyl)amino-1,3,4-oxadiazole-2-carboxylate (29a). A solution of ethyl 5-amino-1,3,4-oxadiazole-2-carboxylate[S8] (50 mg, 0.32 mmol), EDCI (151 mg, 0.79 mmol) and pent-4-ynoic acid (78 mg, 0.79 mmol) was stirred at 25 °C for 18 h. The

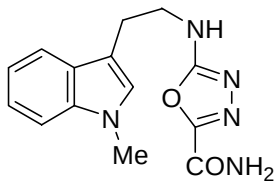
solvent was concentrated under reduced pressure, and the residue was subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **29a** (53 mg, 0.22 mmol, 70%) as mixture of rotamers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (br s, 1H), 5.41 (br s, 1H), 4.48 (q, *J* = 8.8 Hz, 4H), 3.14 (t, *J* = 8.8 Hz, 2H), 2.76 (t, *J* = 8.8 Hz, 2H), 2.66 (dt, *J* = 3.3, 9.2 Hz, 2H), 2.58 (dt, *J* = 3.3, 9.2 Hz, 2H), 2.02 (t, *J* = 3.3 Hz, 2H), 1.46 (t, *J* = 8.8 Hz, 6H); MALDIFTMS (DHB) *m/z* 260.0642 ($C_{10}H_{11}N_3O_4$ + Na^+ requires 260.0649).



Methyl 5-[(Pent-4-ynoyl)methylamino]-1,3,4-oxadiazole-2-carboxylate (30a). DMAP (96 mg, 0.79 mmol) was added to a solution of pent-4-ynoic acid (78 mg, 0.79 mmol), methyl 5-methylamino-1,3,4-oxadiazole-2-carboxylate[S8] (50 mg, 0.32 mmol), and EDCI (151 mg, 0.79 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C overnight (13 h). The solvent was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 2.5 × 20 cm, 30% EtOAc–hexanes) providing **30a** (66 mg, 0.28 mmol, 88%) as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 4.06 (s, 3H), 3.51 (s, 3H), 3.19 (t, *J* = 7.0 Hz, 2H), 2.62 (dt, *J* = 2.5, 7.0 Hz, 2H), 1.97 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 162.0, 154.2, 153.4, 82.4, 69.1, 53.8, 35.7, 33.4, 14.1; IR (film) ν_{max} 3281, 1748, 1705, 1575, 1443, 1339, 1210, 1147 cm^{-1}; MALDIFTMS (DHB) *m/z* 238.0823 ($C_{10}H_{11}N_3O_4$ + H^+ requires 238.0822).

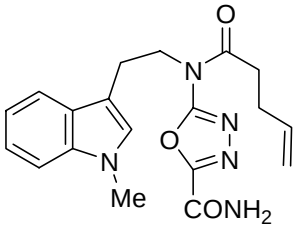


Methyl 7-Methyl-6-oxo-4,5,6,7-tetrahydrofuro[2,3-*b*]pyridine-2-carboxylate (30b). A solution of **30a** (10 mg, 0.042 mmol) in 8 mL of anhydrous degassed 1,2-dichlorobenzene was warmed under Ar at 178 °C for 22 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 55% EtOAc–hexanes) providing **30b** (5 mg, 0.024 mmol, 57%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (s, 1H), 3.87 (s, 3H), 3.35 (s, 3H), 2.78–2.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.9, 158.9, 151.8, 138.0, 120.0, 99.5, 51.6, 32.0, 27.7, 16.6; IR (film) ν_{max} 2954, 1714, 1694, 1630, 1537, 1439, 1332, 1319, 1165 cm^{-1}; MALDIFTMS (DHB) *m/z* 210.0765 ($C_{10}H_{11}NO_4$ + H^+ requires 210.0761).

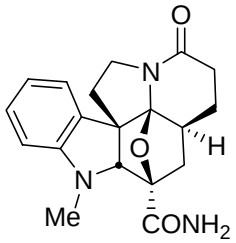


5-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxamide (S8). Ammonia was passed through a suspension of **S3** (224 mg, 0.75 mmol) in MeOH (4.0

mL) at 0 °C. A white precipitate was formed immediately. After bubbling NH_3 for 30 min, the white precipitate was collected by filtration, washed with MeOH, and dried to give **S8** (201 mg, 0.71 mmol, 94%): mp 200–204 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.19 (s, 1H), 8.16 (t, *J* = 5.9 Hz, 1H), 7.83 (s, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 3.49 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.3, 155.1, 152.9, 136.7, 136.6, 127.5, 127.4, 121.2, 118.5, 110.5, 109.6, 43.4, 32.3, 24.5; IR (film) ν_{max} 3316, 1668, 1620, 739 cm^{-1}; MALDIFTMS (DHB) *m/z* 308.1119 ($C_{14}H_{15}N_5O_2$ + Na^+ requires 308.1118).

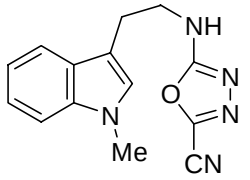


5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxamide (31a). DMAP (59.6 mg, 0.49 mmol) was added to a solution of 4-pentenoic acid (50.1 μL, 0.488 mmol), EDCI (93.6 mg, 0.49 mmol) and **S8** (55.6 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 40 h, the reaction was treated with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 20–50% EtOAc–hexanes gradient elution) provided **31a** (11.2 mg, 0.031 mmol, 18%, unoptimized) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.21 (dt, *J* = 1.1, 8.1 Hz, 1H), 7.12 (dt, *J* = 1.1, 8.1 Hz, 1H), 6.88 (s, 1H), 6.79 (br s, 1H), 6.05 (br s, 1H), 5.86–5.78 (m, 1H), 5.09–5.00 (m, 2H), 4.24 (t, *J* = 7.5 Hz, 2H), 3.72 (s, 3H), 3.12 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.44 (q, *J* = 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 162.5, 155.4, 154.2, 137.2, 136.7, 127.8, 127.6, 122.0, 119.3, 119.1, 116.1, 110.2, 109.4, 48.2, 35.7, 32.8, 28.9, 24.4; IR (film) ν_{max} 3369, 3195, 1708, 1686, 1568, 1434, 1175 cm^{-1}; MALDIFTMS (DHB) *m/z* 368.1722 ($C_{19}H_{21}N_5O_3$ + H^+ requires 368.1717).

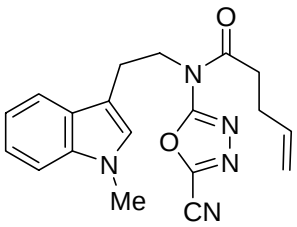


Compound 31b. A solution of **31a** (6.9 mg, 0.019 mmol) in 5.5 mL of anhydrous degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 5 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes and the column was flushed with 2.5%

MeOH–17.5% acetone–80% $CHCl_3$. The solution was concentrated and the residue was purified by PTLC (SiO_2, 2.5% MeOH–17.5% acetone–80% $CHCl_3$) providing **31b** (4.2 mg, 0.012 mmol, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (dt, *J* = 1.4, 7.7 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.47 (d, *J* = 7.7 Hz, 1H), 6.32 (br s, 1H), 5.41 (br s, 1H), 4.16 (dt, *J* = 9.2, 12.1 Hz, 1H), 4.00 (s, 1H), 3.85 (ddd, *J* = 3.3, 8.8, 12.1 Hz, 1H), 3.02 (s, 3H), 2.51–2.46 (m, 2H), 2.39–2.34 (m, 2H), 2.27–2.20 (m, 1H), 1.83–1.70 (m, 2H), 1.64–1.60 (m, 1H), 1.39–1.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 170.6, 152.7, 129.4, 127.7, 122.6, 117.4, 106.5, 105.0, 88.1, 80.9, 64.9, 46.8, 35.8, 34.4, 34.1, 33.7, 31.6, 26.3; IR (film) ν_{max} 3323, 3190, 1623, 1596, 1483, 1443, 1370 cm^{-1}; MALDIFTMS (DHB) *m/z* 340.1656 ($C_{19}H_{21}N_3O_3$ + H^+ requires 340.1656).

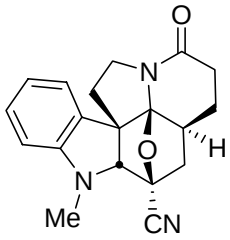


5-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carbonitrile (S9). Trifluoroacetic anhydride (310 μL, 2.21 mmol) was added dropwise to a solution of **S8** (572 mg, 2.01 mmol) in anhydrous dioxane (9 mL) and pyridine (341 μL, 4.22 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solution was recooled to 0 °C and a second equivalent of trifluroacetic anhydride (310 μL, 2.21 mmol) and pyridine (341 μL, 4.22 mmol) were added. The mixture was allowed to warm to room temperature and stirred for an additional 2 h. MeOH (10 mL) was added and the mixture was warmed at reflux for 0.5 h. The solution was concentrated and the residue was diluted with $CHCl_3$ (30 mL), washed with H_2O (2 × 10 mL) and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 20–50% EtOAc–hexanes gradient elution) provided **S9** (400 mg, 1.50 mmol, 75%) as a white solid: mp 138–140 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 5.59 (br s, 1H), 3.77 (s, 3H), 3.75 (dt, *J* = 6.5, 6.5 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4, 137.5, 137.4 136.0, 127.5, 122.3, 119.5, 118.7, 109.9, 109.8, 107.0, 44.1, 32.9, 25.2; IR (film) ν_{max} 3337, 3213, 2231, 1630, 1469, 1324, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 268.1193 ($C_{14}H_{14}N_5O$ + H^+ requires 268.1193).

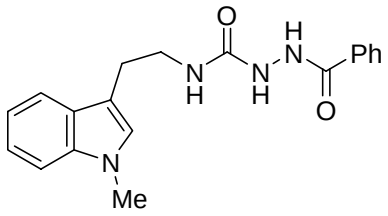


***N*-(5-Cyano-1,3,4-oxadiazol-2-yl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)pent-4-enamide (32a).** DMAP (133 mg, 1.09 mmol) was added to a solution of 4-pentenoic acid

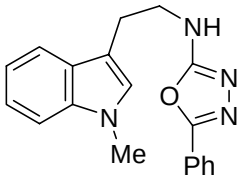
(0.122 mL, 1.09 mmol), EDCI (209 mg, 1.09 mmol) and **S9** (117 mg, 0.44 mmol) in CH_2Cl_2 (4.5 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 18 h, the reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 10–50% EtOAc–hexanes gradient elution) provided **32a** (97 mg, 0.28 mmol, 64%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.83 (s, 1H), 5.85 (m, 1H), 5.07 (d, *J* = 16.4 Hz), 5.01 (dd, *J* = 1.8, 10.3 Hz, 1H), 4.24 (t, *J* = 7.3 Hz, 2H), 3.73 (s, 3H), 3.12 (t, *J* = 6.9 Hz, 2H), 2.88 (t, *J* = 7.2 Hz), 2.44 (dt, *J* = 6.9, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 162.1, 138.2, 136.9, 136.2, 127.5, 127.1, 122.1, 119.3, 118.4, 116.0, 109.5, 109.4, 105.6, 48.0, 35.7, 32.6, 28.6, 24.2; IR (film) ν_{max} 2253, 1708, 1563, 1173, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 350.1618 ($C_{19}H_{19}N_5O_2$ + H^+ requires 350.1611).



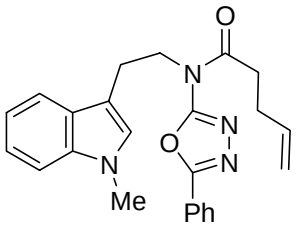
Compound 32b. A solution of **32a** (12.8 mg, 0.037 mmol) in 5.5 mL of anhydrous degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 3 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 40% EtOAc–hexanes) to yield **32b** (8.9 mg, 0.028 mmol, 75%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (dt, *J* = 1.1, 7.4 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.70 (dt, *J* = 1.1, 7.4 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 4.26 (s, 1H), 4.10 (dt, *J* = 9.1, 12.1 Hz, 1H), 3.86 (ddd, *J* = 2.4, 9.9, 12.1 Hz, 1H), 3.01 (s, 3H), 2.52 (ddd, *J* = 1.5, 5.2, 6.7 Hz, 1H), 2.46–2.33 (m, 3H), 2.23 (ddd, *J* = 6.25, 12.9, 18.7 Hz, 1H), 1.86 (ddt, *J* = 5.1, 12.8, 12.8, 1H), 1.75–1.70 (m, 1H), 1.64 (ddd, *J* = 1.5, 3.0, 12.8 Hz, 1H), 1.61–1.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 151.7, 129.7, 127.5, 122.8, 118.5, 118.0, 106.9, 106.7 83.0, 75.1, 64.2, 46.9, 35.7, 34.8, 34.2, 34.0, 31.4, 25.9; IR (film) ν_{max} 1673, 1606, 1489, 1388 cm^{-1}; MALDIFTMS (DHB) *m/z* 322.1552 ($C_{19}H_{19}N_3O_2$ + H^+ requires 322.1550).



2-Benzoyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)hydrazinecarboxamide (S10). Benzoylhydrazine (50.4 mg, 0.37 mmol) was added to a solution of **S1** (99.3 mg, 0.37 mmol) and acetic acid (21 μL, 0.37 mmol) in THF (3 mL) under Ar. The solution was warmed to 40 °C and stirred for 48 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (2.5% MeOH–17.5% CH_3COCH_3–80% $CHCl_3$) to give **S10** (107 mg, 0.32 mmol, 86%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.0 (s, 1H), 8.22 (s, 1H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.36–7.33 (m, 2H), 7.28–7.24 (m, 2H), 7.13–7.10 (m, 1H), 6.81 (s, 1H), 6.24 (s, 1H), 3.57 (s, 3H), 3.44 (dt, *J* = 6.7, 6.7 Hz, 2H), 2.89 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 159.0, 136.8, 132.0, 131.3, 128.4 (2C), 127.6, 127.5 (2C), 126.9, 121.4, 118.7, 118.6, 111.2, 109.1, 40.4, 32.2, 25.4; IR (film) ν_{max} 3429, 1639, 1482 cm^{-1}; MALDIFTMS (DHB) *m/z* 359.1488 ($C_{19}H_{19}N_4O_2$ + Na^+ requires 359.1488).

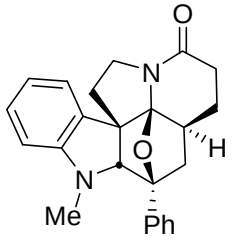


***N*-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-5-phenyl-1,3,4-oxadiazole (S11).** Et_3N (102 μL, 0.73 mmol) was added to a solution of **S10** (98 mg, 0.29 mmol) and TsCl (55.5 mg, 0.29 mmol) in CH_2Cl_2 under Ar at room temperature. The reaction mixture was stirred for 28 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexane) provided **S11** (58 mg, 0.18 mmol, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.86–7.85 (m, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.43–7.41 (m, 3H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.27–7.24 (m, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.94 (s, 1H), 5.25 (s, 1H), 3.76 (dt, *J* = 6.2, 6.2 Hz, 2H), 3.74 (s, 3H), 3.15 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.4, 158.9, 137.1, 130.4 (2C), 128.7, 127.5, 127.2, 125.7 (2C), 124.4, 121.8, 119.0, 118.7, 110.5, 109.3, 43.7, 32.6, 25.3; IR (film) ν_{max} 3231, 1627, 1587, 1560, 1472 cm^{-1}; MALDIFTMS (DHB) *m/z* 319.1556 ($C_{19}H_{19}N_4O$ + H^+ requires 319.1553).

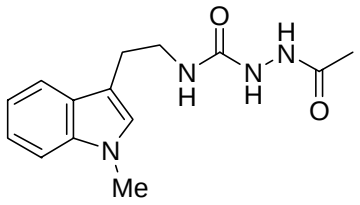


***N*-(2-(1-Methyl-1*H*-indol-3-yl)ethyl)-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)pent-4-enamide (33a).** DMAP (44 mg, 0.36 mmol) was added to a solution of 4-pentenoic acid (37 μL, 0.36 mmol), EDCI (69 mg, 0.36 mmol) and **S11** (29 mg, 0.091 mmol) in CH_2Cl_2 (1 mL) under Ar at 0 °C. The mixture was allowed to warm to room temperature. After stirring for 20 h, the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried with Na_2SO_4, filtered and concentrated. Flash

chromatography (SiO_2, 12–50% EtOAc–hexanes gradient elution) provided **33a** (29 mg, 0.073 mmol, 80%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74–7.76 (m, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.54–7.51 (m, 1H), 7.47–7.44 (m, 2H), 7.18–7.16 (m, 2H), 7.12–7.08 (m, 1H), 6.84 (s, 1H), 5.89–5.81 (m, 1H), 5.07 (dd, *J* = 1.8, 17.3 Hz, 1H), 5.01 (dd, *J* = 1.8, 10.3 Hz, 1H), 4.22 (t, *J* = 7.4 Hz, 2H), 3.65 (s, 3H), 3.16 (t, *J* = 7.4 Hz, 2H), 2.85 (t, *J* = 7.3 Hz, 2H), 2.46 (dt, *J* = 6.4, 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.8, 163.1, 162.4, 160.5, 136.9, 136.7, 131.7 (2C), 129.0, 127.6, 127.2 (2C), 126.4, 126.3, 123.2, 121.6, 119.0, 118.7, 115.6, 110.4, 109.3, 48.0, 35.0, 32.5, 28.9, 24.3; IR (film) ν_{max} 1695, 1593, 1574, 1547, 1485 1327, 1183 cm^{-1}; MALDIFTMS (DHB) *m/z* 423.1788 ($C_{24}H_{24}N_4O_2$ + Na^+ requires 423.1791).

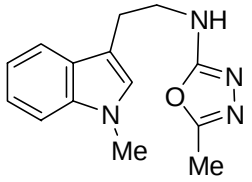


Compound 33b. A solution of **33a** (10.1 mg, 0.025 mmol) in 5.5 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 230 °C for 40 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (20 mL) and the column was flushed with EtOAc. The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 40% EtOAc–hexanes) to yield **33b** (6.5 mg, 0.017 mmol, 69%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46–7.40 (m, 4H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 4.15 (dt, *J* = 9.2, 9.2 Hz, 1H), 3.95 (dd, *J* = 10.1, 11.8 Hz, 1H), 3.82 (s, 1H), 2.74 (s, 3H), 2.69 (dd, *J* = 7.7, 12.1 Hz), 2.54–2.47 (m, 2H), 2.37 (ddd, *J* = 2.2, 8.8, 13.2 Hz, 1H), 2.25 (ddd**,** *J* = 5.7, 12.8, 18.2 Hz, 1H), 1.87–1.80 (m, 1H), 1.70–1.65 (m, 2H), 1.47 (dd, *J* = 1.3, 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.8, 152.8, 141.6, 129.2, 129.1, 128.6, 128.6, 127.6, 125.1, 125.1, 122.8, 117.8, 106.8, 104.3, 89.6, 86.5, 65.1, 46.9, 36.3, 35.5, 35.0, 34.8, 31.7, 26.3; IR (film) ν_{max} 1665, 1605, 1491, 1394, 1018, 733 cm^{-1}; MALDIFTMS (DHB) *m/z* 373.1908 ($C_{24}H_{24}N_2O_2$ + H^+ requires 373.1910).

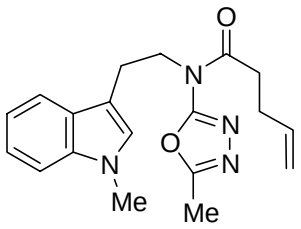


2-Acetyl-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]hydrazinecarboxamide (S12). Acetyl hydrazide (430 mg, 6.0 mmol) was added to a solution of **S1** (1.34 g, 5.0 mmol) and AcOH (0.35 mL, 5.0 mmol) in THF (50 mL) under Ar. The reaction mixture was

warmed at 60 °C for 20 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% CH_2Cl_2) provided **S12** (935 mg, 3.4 mmol, 68%) as a white foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.15–7.11 (m, 1H), 7.03–6.99 (m, 1H), 6.87 (s, 1H), 3.67 (s, 3H), 3.39 (t, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 6.8 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 159.4, 137.2, 127.9, 127.2, 121.6, 118.8, 118.7, 111.5, 109.3, 40.7, 32.3, 25.6, 20.1; IR (film) ν_{max} 3237, 1661, 1543, 1461, 1372, 1232 cm^{-1}; HRESI-TOF *m/z* 273.1363 ($C_{14}H_{18}N_4O_2$ + H^+ requires 273.1357).

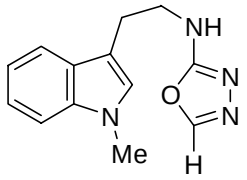


5-Methyl-2-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino-1,3,4-oxadiazole (S13). A solution of **S12** (900 mg, 3.3 mmol) in CH_2Cl_2 (30 mL) was treated with CBr_4 (1.16 g, 3.6 mmol) and PPh_3 (943 mg, 3.6 mmol). After 10 min, Et_3N (0.60 mL, 6.7 mmol) was added. The reaction mixture was stirred for 1 h before being quenched by the addition of H_2O (20 mL). The organic layer was washed with saturated aqueous NaCl and dried over Na_2SO_4. Flash chromatography (SiO_2, 2.5% MeOH–17.5% acetone–80% CH_2Cl_2) provided **S13** (126 mg, 0.49 mmol, 15%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.54 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.24–7.20 (m, 1H), 7.11–7.07 (m, 1H), 6.88 (s, 1H), 4.63 (br s, 1H), 3.73 (s, 3H), 3.62 (q, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.4, 132.3, 128.7, 127.8, 127.4, 122.1, 119.3, 119.0, 110.8, 109.6, 43.9, 32.9, 25.4, 11.2; IR (film) ν_{max} 3307, 3060, 2931, 1631, 1584, 1478, 1431, 1372, 1331, 1237, 1178, 1114, 1061, 732 cm^{-1}; HRESI-TOF *m/z* 257.1394 ($C_{14}H_{16}N_4O$ + H^+ requires 257.1397).

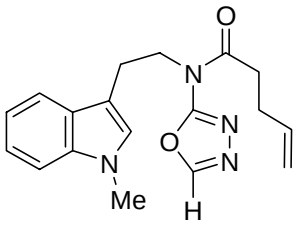


***N*-(5-Methyl-1,3,4-oxadiazol-2-yl)-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamide (34a).** DMAP (10 mg, 0.08 mmol) was added to a solution of 4-pentenoic acid (0.15 mL, 1.5 mmol), EDCI (192 mg, 1.0 mmol) and **S13** (74 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 20 h before being concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **34a** (20 mg, 0.043 mmol, 15%, unoptimized) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.20–7.16 (m, 1H), 7.11–7.06 (m, 1H), 6.81 (s, 1H), 5.81–5.71 (m, 1H), 5.04–4.94 (m, 2H), 4.09 (dt, *J* = 2.4, 7.6 Hz, 2H), 3.68 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.38 (q, *J* = 6.8 Hz, 2H), 2.27 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 137.2, 137.0, 127.8, 127.6, 121.9, 119.1, 119.0, 115.8, 110.5, 109.4, 47.8, 34.9, 32.8, 29.0, 24.5, 11.1; IR (film) ν_{max} 2919, 1731, 1614, 1542, 1449, 1331, 1190, 1143, 732 cm^{-1}; HRESI-TOF *m/z* 468.2131 ($C_{25}H_{29}N_3O_6$ + H^+ requires 468.2126).

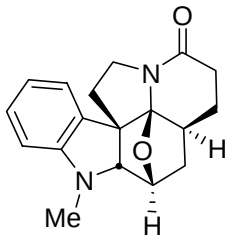


2-(1-Methyl-1*H*-indol-3-yl)ethylamino-1,3,4-oxadiazole (S14). Aqueous LiOH (1 M, 0.472 mL, 0.472 mmol) was added to a solution of **S3** (177 mg, 0.59 mmol) in THF–MeOH–H_2O (3:1:1, 21 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was acidified with aqueous HCl (1 M, 0.6 mL, 0.6 mmol) and the resulting solution was partitioned between EtOAc–H_2O (4:1, 30 mL). The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 2.5% MeOH–17.5% acetone–80% $CHCl_3$) provided **S14** (136 mg, 0.56 mmol, 95%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.86 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 4.77 (br s, 1H), 3.77 (s, 3H), 3.71 (dt, *J* = 6.3, 6.3 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.7, 147.0, 137.1, 127.6, 127.2, 121.8, 119.0, 118.7, 110.7, 109.4, 43.9, 32.6, 25.2; MALDIFTMS (DHB) *m/z* 243.1245 ($C_{13}H_{14}N_4O$ + H^+ requires 243.1246).

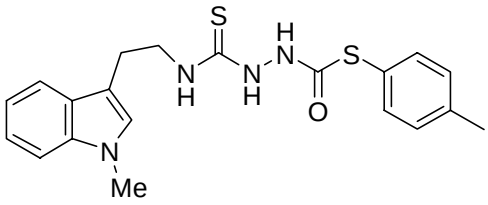


***N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-*N*-(1,3,4-oxadiazol-2-yl)pent-4-enamide (35a).** DMAP (148 mg, 1.21 mmol) was added to a solution of 4-pentenoic acid (0.13 mL, 1.21 mmol), EDCI (233 mg, 1.21 mmol) and **S14** (118 mg, 0.49 mmol) in CH_2Cl_2 (4.8 mL) under Ar at 0 °C. The mixture was warmed to room temperature. After stirring for 27 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$. The aqueous layers were extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 10–50% EtOAc–hexanes gradient elution) provided **35a** (88 mg, 0.27 mmol, 56%) as a viscous oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.22 (dt, *J* = 1.2, 7.0 Hz, 1H), 7.12 (ddd, *J* = 7.9, 6.8, 1.2 Hz, 1H), 6.87 (s, 1H), 5.86–5.76 (m, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.15 (dd, *J* = 6.2, 7.8 Hz, 2H), 3.72 (s, 3H), 3.10 (dd, *J* = 6.2, 7.8 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.42 (q, *J* = 7.0 Hz,

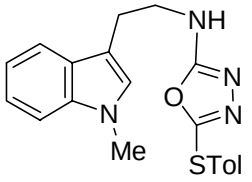
2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 171.7, 161.0, 150.3, 136.9, 136.6, 127.5, 127.2, 121.7, 119.0, 118.8, 115.7, 110.2, 109.2, 47.9, 35.0, 32.6, 28.7, 24.2; IR (film) ν_{max} 1691, 1640, 1579, 1517, 1170 cm^{-1}; MALDIFTMS (DHB) *m/z* 325.1668 ($C_{18}H_{20}N_4O_2$ + H^+ requires 325.1659).



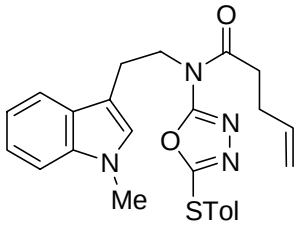
Compound 35b. A solution of **35a** (10.1 mg, 0.0204 mmol) in 5.5 mL of anhydrous, degassed 1,3,5-triisopropylbenzene (TIPB) was warmed under Ar at 210 °C for 15 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The TIPB was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was evaporated and the residue was purified by PTLC (SiO_2, 40% EtOAc–hexanes) to yield **35b** (trace): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.15 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.0 Hz, 1H), 6.61 (t, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 8.2 Hz, 1H), 4.70 (t, *J* = 5.1 Hz, 1H), 4.12–4.07 (m, 1H), 4.05 (d, *J* = 4.8 Hz, 1H), 3.83 (t, *J* = 10.7 Hz, 1H), 2.86 (s, 3H), 2.50–2.45 (m, 2H), 2.37–2.34 (m, 1H), 2.33–2.27 (m, 2H), 2.25–2.19 (m, 1H), 2.03–1.99 (m, 1H), 1.96 (dd, *J* = 12.7 and 8.3 Hz, 1H), 1.80–1.73 (m, 1H), 1.65–1.60 (m, 1H), 1.50–1.45 (m, 1H); MALDIFTMS (DHB) *m/z* 297.1599 ($C_{18}H_{20}N_2O_2$ + H^+ requires 297.1597).



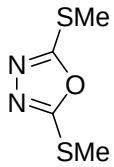
***S*-*p*-Tolyl 2-[2-(1-Methyl-1*H*-indol-3-yl)ethylcarbamothioyl]hydrazinecarbothioate (S15).** A mixture of 3-(2-isothiocyanatothyl)-1-methyl-1*H*-indole (1.08 g, 5.0 mmol) and *S*-*p*-tolyl hydrazinecarbothioate (920 mg, 5.0 mmol) in anhydrous 1,4-dioxane (10 mL) was warmed at reflux for 2 h. The reaction mixture was cooled and concentrated under reduced pressure. Flash chromatography (SiO_2, 5% acetone–CH_2Cl_2) gave **S15** (1.20 g, 3.02 mmol, 68%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.35–7.22 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.18–7.10 (m, 4H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.89 (s, 1H), 4.30–4.00 (m, 2H), 3.85 (br s, 2H), 3.61 (s, 3H), 3.03 (t, *J* = 6.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.2, 140.1, 137.3 (2C), 135.4 (2C), 130.1 (2C), 127.8, 127.3, 123.5, 121.8, 119.0, 118.9, 111.0, 109.4, 45.0, 32.6, 24.6, 21.2; IR (film) ν_{max} 3389, 2943, 2508, 1672, 1507, 1478, 1337, 1249, 1202, 732 cm^{-1}; HRESI-TOF *m/z* 399.1309 ($C_{20}H_{22}N_4OS_2$ + H^+ requires 399.1308).



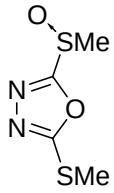
2-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]amino-5-(*p*-tolylthio)-1,3,4-oxadiazole (S16). A suspension of **S15** (920 mg, 2.3 mmol) in CH_2Cl_2 (20 mL) was treated with EDCI (890 mg, 4.6 mmol) and the reaction mixture was warmed at reflux for 2 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **S16** (392 mg, 1.1 mmol, 47%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 2.0, 6.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.21–7.19 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 4.84 (br s, 1H), 3.71 (s, 3H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.02 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3, 154.9, 139.5, 137.4, 132.7 (2C), 130.5 (2C), 127.7, 127.4, 125.7, 122.1, 119.3, 119.0, 110.6, 109.6, 43.8, 32.9, 25.3, 21.4; IR (film) ν_{max} 3425, 1625, 1478, 1132, 744 cm^{-1}; HRESI-TOF *m/z* 365.1433 ($C_{20}H_{20}N_4OS$+ H^+ requires 365.1431).



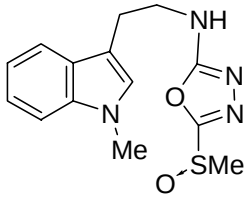
***N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-*N*-[5-(*p*-tolylthio)-1,3,4-oxadiazol-2-yl]pent-4-enamide (36a).** DMAP (24 mg, 0.20 mmol) was added to a solution of 4-pentenoic acid (0.10 mL, 1.0 mmol), EDCI (384 mg, 2.0 mmol) and **S16** (182 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2 h before being concentrated. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **36a** (187 mg, 0.42 mmol, 84%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.46–7.43 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.21–7.18 (m, 3H), 7.10 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.80 (s, 1H), 5.78–5.68 (m, 1H), 5.00–4.94 (m, 2H), 4.84 (br s, 1H), 4.06–4.02 (m, 2H), 3.70 (s, 3H), 3.12 (m, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.37–2.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 161.9, 161.3, 140.9, 137.1, 136.8, 134.4 (2C), 130.8 (2C), 127.8, 127.3, 122.9, 121.9, 119.2, 119.1, 115.8, 110.5, 109.5, 48.1, 35.1, 32.8, 29.0, 24.4, 21.5; IR (film) ν_{max} 2919, 1696, 1578, 1478, 1396, 1331, 1161, 738 cm^{-1}; HRESI-TOF *m/z* 447.1849 ($C_{25}H_{26}N_4O_2S$ + H^+ requires 447.1849).



2,5-Bis(methylthio)-1,3,4-oxadiazole (S17). COS gas was bubbled through a solution of hydrazine monohydrate (11 mL, 0.23 mol) and Et_3N (70 mL, 0.50 mol) in EtOH (30 mL) at 0 °C. The flow of gas was stopped when no additional precipitate was produced. The total gas consumed was about 37 g (about 0.5 mol). MeI (30 mL, 0.50 mol) was added to the reaction mixture slowly at 0 °C. The stirring was continued for 1 h before the removal of COS gas with a stream of N_2. H_2O (400 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (1 L × 3) and EtOAc (500 mL). The combined organic layer was concentrated under reduced pressure to give a white solid (~ 40 g). A suspension of the above product (360 mg, ~ 2 mmol) was treated with CBr_4 (996 mg, 3.0 mmol) and PPh_3 (786 mg, 3.0 mmol). After the reaction mixture became clear, Et_3N (0.60 mL, 4.0 mmol) was added and the solution was stirred for 1 h before being quenched by the addition of H_2O (10 mL). The organic layer was washed with saturated aqueous NaCl and dried over Na_2SO_4. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **S17** (235 mg, 1.45 mmol, 72%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 14.9; IR (film) ν_{max} 1514, 1467, 1320, 1126, 973 cm^{-1}; HRESI-TOF *m/z* 162.9996 ($C_4H_6N_2OS_2$ + H^+ requires 162.9994).

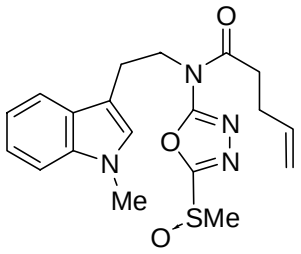


2-(Methylsulfinyl)-5-(methylthio)-1,3,4-oxadiazole (S18). A solution of **S17** (480 mg, 3.0 mmol) in CH_2Cl_2 (30 mL) was treated with *m*-CPBA (~ 70%, 820 mg, 3.3 mmol) at 0 °C. After completion of the reaction as judged by TLC, the mixture was filtered and the filtrate was washed with saturated aqueous Na_2SO_3, H_2O, and saturated aqueous NaCl and dried over Na_2SO_4. Flash chromatography (SiO_2, 33–50% EtOAc–hexanes gradient elution) provided **S18** (350 mg, 2.0 mmol, 66%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 2.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 167.1, 39.3, 14.6; IR (film) ν_{max} 1802, 1461, 1420, 1302, 1249, 1120, 1067, 967 cm^{-1}; HRESI-TOF *m/z* 178.9950 ($C_4H_6N_2O_2S_2$ + H^+ requires 178.9943).

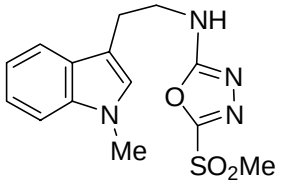


2-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]amino-5-(methylsulfinyl)-1,3,4-oxadiazole (S19). A solution of **S18** (350 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) was treated with *m*-CPBA (~ 70%, 500 mg, 2.0 mmol) at 0 °C. After 30 min, additional *m*-CPBA (250 mg, 1.0 mmol) was added while the reaction mixture was kept at 0 °C. After the completion of the reaction as judged by TLC, the mixture was filtered. The filtrate was treated with methyl

sulfide (0.3 mL, 4.0 mmol) for 30 min to reduce the excess *m*-CPBA. A solution of N^1-methyl tryptamine (510 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) was added followed by Et_3N (1 mL, 7.1 mmol). The reaction mixture was stirred for 2 h before being concentrated. Flash chromatography (SiO_2, 17% acetone–CH_2Cl_2) provided **S19** (350 mg, 1.2 mmol, 66%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.23–7.20 (m, 1H), 7.08 (td, *J* = 1.2, 8.0 Hz, 1H), 6.87 (s, 1H), 5.90 (t, *J* = 6.0 Hz, 1H), 3.70 (s, 3H), 3.67 (q, *J* = 6.4 Hz, 2H), 3.06 (t, *J* = 6.4 Hz, 2H), 2.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 159.4, 137.4, 127.7, 127.5, 122.1, 119.3, 118.9, 110.4, 109.7, 44.0, 38.7, 32.9, 25.2; IR (film) ν_{max} 3248, 3048, 2919, 1625, 1472, 1372, 1319, 1055, 955, 744 cm^{-1}; HRESI-TOF *m/z* 305.1065 ($C_{14}H_{16}N_4O_2S$ + H^+ requires 305.1067).

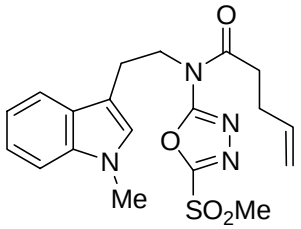


***N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-*N*-[5-(methylsulfinyl)-1,3,4-oxadiazol-2-yl]pent-4-enamide (37a).** DMAP (24 mg, 0.20 mmol) was added to a solution of 4-pentenoic acid (0.10 mL, 1.0 mmol), EDCI (192 mg, 1.0 mmol) and **S19** (60 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **37a** (45 mg, 0.12 mmol, 58%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 1H), 7.19–7.15 (m, 1H), 7.08 (td, *J* = 1.2, 7.6 Hz, 1H), 6.82 (s, 1H), 5.84–5.74 (m, 1H), 5.07–4.97 (m, 2H), 4.20 (td, *J* = 2.4, 6.8 Hz, 2H), 3.68 (s, 3H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.90 (s, 3H), 2.84 (dt, *J* = 1.6, 7.2 Hz, 2H), 2.41 (q, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 163.5, 163.1, 137.2, 136.6, 127.9, 127.6, 122.0, 119.4, 119.0, 116.1, 110.0, 109.5, 48.2, 38.9, 35.6, 32.8, 28.9, 24.5; IR (film) ν_{max} 2908, 1708, 1567, 1478, 1384, 1331, 1172, 1072, 738 cm^{-1}; HRESI-TOF *m/z* 409.1303 ($C_{19}H_{22}N_4O_3S$ + Na^+ requires 409.1305).

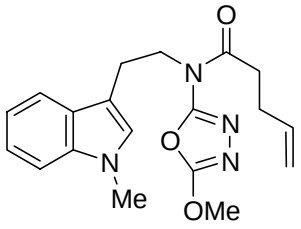


2-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]amino-5-(methylsulfonyl)-1,3,4-oxadiazole (S20). A solution of **S19** (680 mg, 2.2 mmol) in MeOH (10 mL) at 0 °C was treated with Na_2WO_4 dihydrate (74 mg, 2.2 mmol) followed by 30% aqueous H_2O_2 (2.2 mL, 20 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was diluted with CH_2Cl_2 (10 mL) and a solution of Na_2SO_3 was added.

The biphasic mixture was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with saturated aqueous NaCl, and dried over Na_2SO_4. Flash chromatography (SiO_2, 33% EtOAc–hexanes) provided **S20** (620 mg, 1.9 mmol, 88%) as a light brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dt, *J* = 0.8, 8.4 Hz, 1H), 7.29 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.24–7.20 (m, 1H), 7.10 (dt, *J* = 1.2, 6.8 Hz, 1H), 6.90 (s, 1H), 5.44 (br m, 1H), 3.73 (s, 3H), 3.71 (q, *J* = 6.4 Hz, 2H), 3.26 (s, 3H), 3.08 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 156.0, 137.4, 127.60, 127.55, 122.2, 119.4, 118.8, 110.0, 109.7, 44.0, 43.0, 33.0, 25.2; IR (film) ν_{max} 3366, 2919, 1631, 1472, 1343, 1138, 967, 744 cm^{-1}; HRESI-TOF *m/z* 321.1012 ($C_{14}H_{16}N_4O_3S$ + H^+ requires 321.1016).

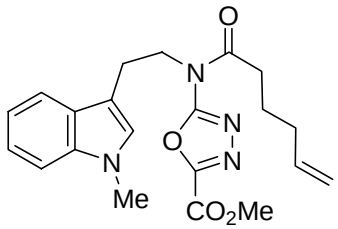


***N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-*N*-[5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl]pent-4-enamide (38a).** DMAP (24 mg, 0.20 mmol) was added to a solution of 4-pentenoic acid (0.10 mL, 1.0 mmol), EDCI (192 mg, 1.0 mmol) and **S20** (64 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **38a** (52 mg, 0.13 mmol, 61%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.21–7.18 (m, 1H), 7.15–7.13 (m, 1H), 7.08–7.04 (m, 1H), 6.79 (s, 1H), 5.81–5.71 (m, 1H), 5.01 (dd, *J* = 1.6, 17.2 Hz, 1H), 4.96 (dd, *J* = 1.6, 14.4 Hz, 1H), 4.17 (t, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 3.08–3.04 (m, 5H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.40–2.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 162.3, 158.9, 137.1, 136.5, 127.9, 127.6, 122.0, 119.4, 118.9, 116.2, 109.9, 109.6, 48.4, 42.7, 35.8, 32.8, 28.8, 24.4; IR (film) ν_{max} 2919, 1708, 1566, 1472, 1396, 1343, 1149, 973, 750, 656 cm^{-1}; HRESI-TOF 425.1267 ($C_{19}H_{22}N_4O_4S$ + Na^+ requires 425.1254).

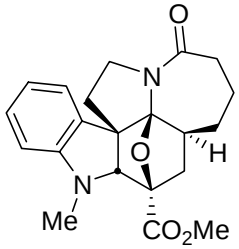


***N*-(5-Methoxy-1,3,4-oxadiazol-2-yl)-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamide (39a).** A solution of **38a** (39 mg, 0.097 mmol) in MeOH (2 mL) was treated with one drop of Et_3N at room temperature. The reaction mixture was stirred at room temperature for 30 min before being concentrated under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) gave **39a** (32 mg, 0.090 mmol, 91%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.21–7.15 (m, 1H), 7.09 (td, *J* = 1.2, 6.8 Hz, 1H), 6.85 (s, 1H), 5.82–5.62 (m, 1H), 5.01

(dd, *J* = 1.6, 17.2 Hz, 1H), 4.96 (dd, *J* = 1.6, 14.4 Hz, 1H), 4.11 (s, 3H), 4.00–3.97 (m, 2H), 3.70 (s, 3H), 3.07–3.03 (m, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.38 (q, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 164.4, 156.0, 137.2, 136.9, 127.8, 127.4, 121.9, 119.2, 119.1, 115.9, 110.5, 109.4, 59.2, 48.2, 34.3, 32.8, 29.0, 24.3; IR (film) ν_{max} 2931, 1696, 1637, 1467, 1326, 1243, 738 cm^{-1}; HRESI-TOF *m/z* 355.1763 ($C_{19}H_{22}N_4O_3$ + H^+ requires 355.1765).

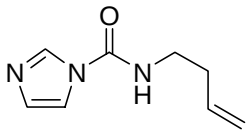


Methyl 5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]hex-5-enamido}-1,3,4-oxadiazole-2-carboxylate (40a). DMAP (0.25 g, 2.08 mmol) was added to a solution of 5-hexenoic acid (0.24 g, 2.08 mmol), **S3** (0.25 g, 0.83 mmol), and EDCI (0.40 g, 2.08 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The mixture was gradually warmed to 25 °C and stirred for 16 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **40a** (0.26 g, 0.65 mmol, 78%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 6.9 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 6.00–5.86 (m, 1H), 5.18 (dd, *J* = 1.8, 17.1, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 2H), 4.15 (s, 3H), 3.85 (s, 3H), 3.26 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.25 (dt, *J* = 7.1, 7.1 Hz, 2H), 1.94 (tt, *J* = 7.3, 7.5, Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 161.9, 153.9, 153.1, 137.6, 136.8, 127.4, 127.3, 121.5, 118.9, 118.7, 115.3, 109.7, 109.1, 53.5, 47.6, 35.4, 32.8, 32.4, 24.1, 23.8; IR (film) ν_{max} 2952, 1749, 1703, 1565, 1441 cm^{-1}; HRESI-TOF *m/z* 397.1876 ($C_{21}H_{24}N_4O_4$ + H^+ requires 397.1870).

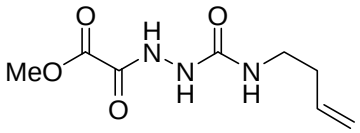


Compound 40b. A solution of **40a** (22 mg, 0.057 mmol) in 11 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (50 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **40b** (9 mg, 0.024 mmol, 43%) as a yellow oil: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.11 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.8, 1H), 6.61 (t, *J* = 7.4 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 4.24 (ddd, *J*

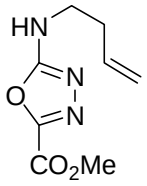
= 2.0, 10.3, 12.4 Hz, 1H), 3.90 (ddd, *J* = 7.5, 11.9, 11.9 Hz, 1H), 3.73 (d, *J* = 1.6 Hz, 1H), 3.36 (s, 3H), 2.73 (dd, *J* = 7.2, 15.2 Hz, 1H), 2.63 (s, 3H), 2.42 (ddd, *J* = 2.1, 11.1, 15.3 Hz, 1H), 2.28 (dd, *J* = 8.2, 12.7 Hz, 1H), 1.89 (ddd, *J* = 9.7, 12.2, 12.2 Hz, 1H), 1.69–1.55 (m, 2H), 1.24–1.11 (m, 4H), 1.02 (br t, *J* = 11.1 Hz, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 173.8, 171.1, 153.0, 129.8, 129.5, 123.7, 118.1, 106.8, 105.0, 86.7, 80.6, 69.9, 51.8, 51.5, 40.0, 39.6, 36.6, 36.3, 35.5, 33.8, 20.7; IR (film) ν_{max} 2949, 1736, 1650, 1606, 1493, 1449 cm^{-1}.



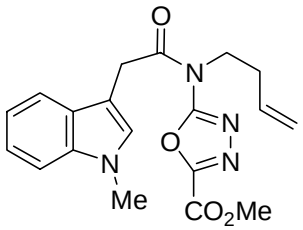
***N*-(But-3-enyl)-1*H*-imidazole-1-carboxamide** (**S21**). 4-Amino-1-butene hydrochloride[S8] (5.10 g, 35.0 mmol) was suspended in anhydrous CH_2Cl_2 (500 mL) under Ar. Carbonyldiimidazole (8.50 g, 53.0 mmol) was added in one portion followed by Et_3N (4.90 mL, 35.0 mmol). The reaction mixture was stirred for 16 h at 23 °C before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 5% MeOH–$CHCl_3$) provided **S21** (5.30 g, 32.1 mmol, 91%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.90 (s, 1H), 7.41 (s, 1H), 7.03 (s, 1H), 5.76 (m, 1H), 5.10 (m, 2H), 3.46 (dt, *J* = 5.7, 7.0 Hz, 2H), 2.37 (dt, *J* = 6.7, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.3, 136.3, 135.1, 130.3, 118.2, 116.7, 40.4, 33.9; IR (film) ν_{max} 3448, 1729, 1528, 1510, 1477, 1099, 909 cm^{-1}; MALDIFTMS (DHB) *m/z* 166.0975 ($C_8H_{11}N_3O$ + H^+ requires 166.0975).



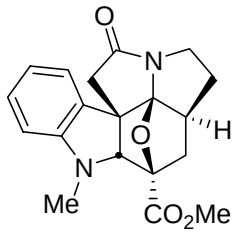
Methyl 2-(2-(But-3-enylcarbamoyl)hydrazinyl)-2-oxoacetate (S22). A solution of **S21** (5.30 g, 32.0 mmol) in THF (300 mL) and AcOH (3.6 mL, 64.0 mmol) under Ar was treated with methyl oxalylhydrazide[S1] (2.70 g, 32.0 mmol) and the reaction mixture was warmed at 40 °C for 16 h. The solvent was removed under reduced pressure and flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% $CHCl_3$) provided **S22** (3.50 g, 16.3 mmol, 46%; typically 46–64%) as a white solid: mp 110–112 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.45 (s, 1H), 7.99 (s, 1H), 6.50 (s, 1H), 5.81–5.75 (m, 1H), 5.03–4.99 (m, 2H), 3.79 (s, 3H), 3.05 (dt, *J* = 6.3, 7.0 Hz, 2H), 2.13 (dt, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1, 158.1, 157.6, 137.0, 117.1, 53.7, 39.6, 35.0; IR (film) ν_{max} 3374, 1728, 1707, 1528, 1482, 917 cm^{-1}; FABHRMS (NBA/NaI) *m/z* 216.0986 ($C_8H_{13}N_3O_4$ + H^+ requires 216.0984).



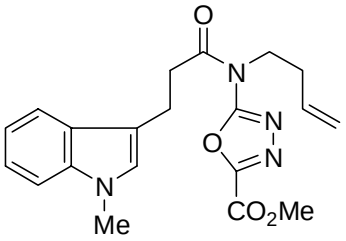
Methyl 5-(But-3-en-1-yl)amino-1,3,4-oxadiazole-2-carboxylate (S23). TsCl (3.10 g, 16 mmol) was added to a solution of **S21** (3.50 g, 16.0 mmol) in anhydrous CH_2Cl_2 (160 mL) immediately followed by Et_3N (5.6 mL, 41.0 mmol). The reaction mixture was allowed to stir at 25 °C for 16 h before being concentrated in vacuo to 30 mL. The crude solution was diluted with EtOAc (150 mL) and the organic layer was washed with 1 N aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Chromatography (SiO_2, 5% MeOH–CH_2Cl_2) provided **S23** (2.80 g, 14.2 mmol, 89%) as a white solid: mp 92–93 °C (EtOAc–hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.26 (s, 1H), 5.83–5.70 (m, 1H), 5.17–5.07 (m, 2H), 3.97 (s, 3H), 3.51 (dd, *J* = 5.2, 6.2 Hz, 2H), 2.41 (dt, *J* = 6.7, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 155.0, 151.0, 134.3, 118.4, 53.5, 42.6, 33.8; IR (film) ν_{max} 1738, 1633, 1551, 1445, 1358, 1282, 1205, 1167, 1052 cm^{-1}; MALDIFTMS (DHB) *m/z* 198.0873 ($C_8H_{11}N_3O_3$ + H^+ requires 198.0872).



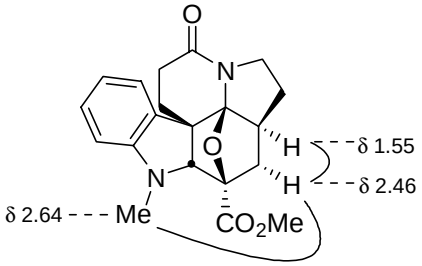
Methyl 5-[*N*-(But-3-enyl)-2-(1-methyl-1*H*-indol-3-yl)acetamido]-1,3,4-oxadiazole-2-carboxylate (41a). Trimethylacetyl chloride (0.34 mL, 2.79 mmol) was added to a solution of 1-methyl-3-indoleacetic acid (0.53 g, 2.79 mmol) and Et_3N (0.39 mL, 2.79 mmol) in THF (13 mL) at 0 °C. After 30 min, the solution was cooled to −78 °C. In a separate flask, BuLi (2.5 M in hexanes, 1.01 mL, 2.54 mmol) was added dropwise to a solution of **S23** (0.50 g, 2.54 mmol) in THF (13 mL) at −78 °C and the mixture was stirred for 10 min. The resulting solution was transferred via cannula to the stirring solution of the mixed anhydride. The reaction mixture was maintained at −78 °C for 1 h and then quenched by pouring onto saturated aqueous $NaHCO_3$. The aqueous solution was extracted three times with CH_2Cl_2. The combined organic layers were dried, concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **41a** (0.24 g, 0.574 mmol, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 5.74–5.66 (m, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 4.34 (s, 2H), 4.05 (s, 3H), 4.01 (t, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 2.38 (dt, *J* = 7.1, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 162.0, 154.2, 153.6, 136.8, 133.7, 128.0, 127.4, 121.9, 119.3, 118.9, 117.8, 109.2, 105.7, 53.7, 46.7, 33.3, 32.6, 32.5; IR (film) ν_{max} 2954, 1748, 1705, 1565, 1441 cm^{-1}; HRESI-TOF *m/z* 369.1560 ($C_{19}H_{20}N_4O_4$ + H^+ requires 369.1557).



Compound 41b. A solution of **41a** (36 mg, 0.096 mmol) in 19 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 16 h. The cooled reaction mixture was loaded directly onto deactivated SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (50 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **41b** (21 mg, 0.061 mmol, 63%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (t, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.0 Hz, 1H), 6.24 (d, *J* = 8.0 Hz, 1H), 4.04 (s, 1H), 3.36 (s, 3H), 3.29 (d, *J* = 15.7 Hz, 1H), 3.25 (dd, *J* = 8.7, 11.1 Hz, 1H), 3.04 (ddd, *J* = 6.1, 10.9, 10.9 Hz, 1H), 2.63 (s, 3H), 2.59 (d, *J* = 15.6 Hz, 1H), 2.08 (dd, *J* = 7.6, 12.9 Hz, 1H), 1.81–1.71 (m, 1H), 1.64 (dd, *J* = 2.2, 13.0 Hz, 1H), 1.41–1.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 171.0, 152.0, 129.6, 129.0, 122.7, 118.2, 116.1, 107.0, 88.0, 80.8, 57.9, 51.7, 50.2, 45.3, 36.2, 35.3, 34.7, 33.7; IR (film) ν_{max} 2951, 1718, 1606, 1495, 1438 cm^{-1}; HRESI-TOF *m/z* 341.1495 ($C_{19}H_{20}N_2O_4$ + H^+ requires 341.1496).



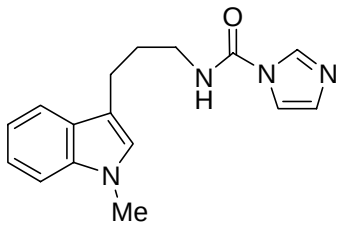
Methyl 5-{(But-3-en-1-yl)-[3-(1-methyl-1*H*-indol-3-yl)propionyl]amino}-1,3,4-oxadiazole-2-carboxylate (42a). A solution of 3-(1-methyl-1*H*-indol-3-yl)propionic acid (93 mg, 0.46 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated with EDCI (88 mg, 0.46 mmol) followed by DMAP (5.6 mg, 0.05 mmol). Oxadiazole **S23** was added (30 mg, 0.15 mmol) and the reaction mixture was allowed to stir at 23 °C for 9 h. The reaction was concentrated in vacuo to 1 mL and diluted with 30 mL of EtOAc and 10 mL of 1 N aqueous HCl. The organic layer was separated and washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. PTLC (SiO_2, 50% EtOAc–hexanes) provided **42a** (47 mg, 0.12 mmol, 82%) as a white solid: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.56 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.22 (dd, *J* = 7.0, 7.9 Hz, 1H), 7.10 (dd, *J* = 7.0, 7.9 Hz, 1H), 6.90 (s, 1H), 5.74–5.66 (m, 1H), 5.05–4.98 (m, 2H), 4.05 (s, 3H), 4.01 (t, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 3.24 (dd, *J* = 7.0, 7.9 Hz, 2H), 3.77 (t, *J* = 7.0 Hz, 2H), 2.39 (dt, *J* = 6.6, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.3, 162.0, 154.3, 153.6, 137.0, 133.8, 127.4, 126.8, 121.7, 118.9, 118.8, 118.0, 112.8, 109.3, 53.8, 46.4, 37.0, 32.8, 32.7, 20.9; IR (film) ν_{max} 2944, 1749, 1703, 1564, 1441, 1149 cm^{-1}; MALDIFTMS (DHB) *m/z* 383.1725 ($C_{20}H_{22}N_4O_4$ + H^+ requires 383.1714).



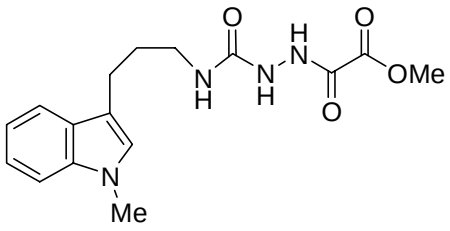
Solid curved lines represent nOe's observed in 1D ^{1}H–^{1}H GOESY (C_6D_6, 600 MHz)

Compound 42b. A solution of **42a** (10 mg, 0.026 mmol) in 2.6 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 165 °C for 2 h. The solution was concentrated under a stream of N_2 and the crude material was purified by PTLC (SiO_2, 40% EtOAc–CH_2Cl_2) providing **42b** (6.6 mg, 0.019 mmol, 72%) as a yellow solid: ^{1}H NMR (C_6D_6, 600 MHz) δ 7.09 (ddd, *J* = 1.3, 7.5, 7.9 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.56 (dd, *J* = 7.5, 7.9 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 3.69 (t, *J* = 10.1 Hz, 1H), 3.64 (d, *J* = 0.9 Hz, 1H), 3.52 (dt, *J* = 7.9, 10.5 Hz, 1H), 3.35 (s, 3H), 2.70–2.65 (m, 1H), 2.64 (s, 3H), 2.46 (ddd, *J* = 1.3, 7.0, 11.8 Hz, 1H), 2.22 (dd, *J* = 7.9, 11.8 Hz, 1H), 2.16 (dt, *J* =

7.5, 13.2 Hz, 1H), 1.69–1.63 (m, 1H), 1.55 (ddd, *J* = 1.8, 7.0, 11.8 Hz, 1H), 1.50 (dd, *J* = 1.8, 13.2 Hz, 1H), 1.36–1.28 (m, 1H), 1.27–1.21 (m, 1H); ^{13}C NMR (C_6D_6, 150 MHz) δ 171.6, 169.1, 163.9, 153.7, 129.9, 124.2, 118.4, 107.5, 105.6, 87.4, 81.2, 54.4, 52.1, 48.5, 43.3, 35.8, 34.5, 32.3, 30.4, 29.0; IR (film) ν_{max} 2952, 1735, 1666, 1603, 1493, 1441, 1124, 1071 cm^{-1}; MALDIFTMS (DHB) *m/z* 355.1651 ($C_{20}H_{22}N_2O_4$ + H^+ requires 355.1651).

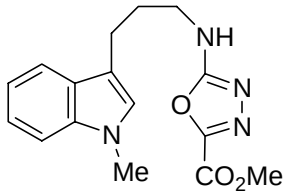


***N*-[3-(1-Methyl-1*H*-indol-3-yl)propyl]-1*H*-imidazole-1-carboxamide (S24).** 3-(1-Methyl-1*H*-indol-3-yl)propyl-1-amine (1.42 g, 7.54 mmol) in CH_2Cl_2 (38 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (1.83 g, 11.31 mmol) in THF (8 mL) under Ar cooled to 0 ºC. The reaction mixture was allowed to stir and equilibrate to 23 ºC overnight before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 2% MeOH–8% acetone–90% $CHCl_3$) provided **S24** (1.32 g, 4.67 mmol, 62%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.15 (br s, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 3.69 (s, 3H), 3.48 (dt, *J* = 6.5, 6.5 Hz, 2H), 2.86 (t, *J* = 7.0 Hz, 2H), 2.11–2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.5, 137.0, 135.5, 128.4, 127.4, 126.4, 121.6, 118.7 (2C), 116.5, 113.5, 109.3, 41.0, 32.4, 29.3, 22.6; IR (film) ν_{max} 3052, 2937, 1721, 1544, 1483, 1375 cm^{-1}; HRESI-TOF *m/z* 283.1564 ($C_{16}H_{18}N_4O$ + H^+ requires 283.1553).

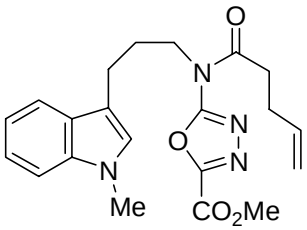


Methyl 2-{2-[3-(1-Methyl-1*H*-indol-3-yl)propylcarbamoyl]hydrazinyl}-2-oxoacetate (S25). Methyl oxalylhydrazide[S1] (0.22 g, 1.86 mmol) was added to a solution of **S24** (0.50 g, 1.77 mmol) and AcOH (0.11 mL, 1.86 mmol) in THF (12 mL) under Ar and the reaction mixture was warmed at 40 ºC for 16 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2% MeOH–8% acetone–90% $CHCl_3$) provided **S25** (0.46 g, 1.38 mmol, 78%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.80 (s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.24 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 1.91–1.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

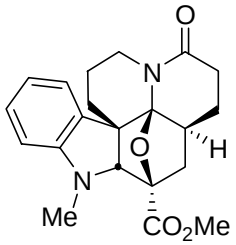
159.2, 157.3, 154.7, 136.9, 127.6, 126.3, 121.4, 118.8, 118.5, 113.7, 109.1, 53.6, 40.0, 32.4, 30.1, 22.1; IR (film) ν_{max} 3335, 2930, 1706, 1654, 1560 cm^{-1}; HRESI-TOF *m/z* 333.1555 ($C_{16}H_{20}N_4O_4 + H^+$ requires 333.1557).



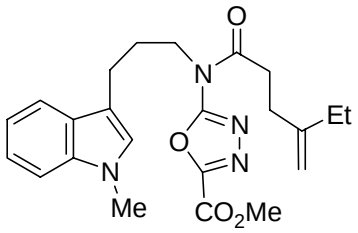
Methyl 5-[3-(1-Methyl-1*H*-indol-3-yl)propylamino]-1,3,4-oxadiazole-2-carboxylate (S26). Et_3N (0.45 mL, 3.22 mmol) was added to a stirring solution of **S25** (0.43 g, 1.29 mmol) and TsCl (0.25 g, 1.29 mmol) in CH_2Cl_2 (13 mL) under Ar at 23 °C. The reaction mixture was stirred for 18 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 15% EtOAc–CH_2Cl_2) provided **S26** (0.34 g, 1.09 mmol, 84%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.91 (s, 1H), 3.98 (s, 3H), 3.74 (s, 3H), 3.51 (br t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.09 (tt, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 154.7, 151.0, 137.0, 127.5, 126.4, 121.4, 118.7, 118.6, 113.1, 109.1, 53.2, 43.0, 32.5, 29.6, 21.9; IR (film) ν_{max} 2938, 1742, 1626, 1540, 1473 cm^{-1}; HRESI-TOF *m/z* 315.1448 ($C_{16}H_{18}N_4O_3 + H^+$ requires 315.1452).



Methyl 5-{*N*-[3-(1-Methyl-1*H*-indol-3-yl)propyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxylate (43a). DMAP (0.25 g, 2.07 mmol) was added to a solution of 4-pentenoic acid (0.21 g, 2.07 mmol), **S26** (0.26 g, 0.83 mmol), and EDCI (0.40 g, 2.07 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 15 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **43a** (0.18 g, 0.44 mmol, 54%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 5.96–5.87 (m, 1H), 5.15 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.15 (t, *J* = 7.4 Hz, 2H), 4.12 (s, 3H), 3.82 (s, 3H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.51 (dd, *J* = 7.0, 14.0 Hz, 2H), 2.18 (tt, *J* = 7.3, 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 162.0, 154.2, 153.5, 136.9, 136.4, 127.5, 126.0, 121.5, 118.7, 118.6, 115.8, 113.2, 109.1, 53.7, 46.9, 35.5, 32.5, 28.7, 28.1, 22.0; IR (film) ν_{max} 2953, 1748, 1706, 1565, 1441 cm^{-1}; HRESI-TOF *m/z* 397.1870 ($C_{21}H_{24}N_4O_4 + H^+$ requires 397.1870).

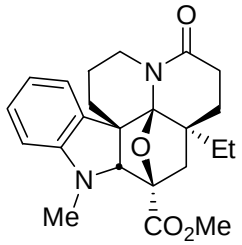


Compound 43b. A solution of **43a** (105 mg, 0.27 mmol) in 53 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (50 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **43b** (87 mg, 0.24 mmol, 89%) as a white solid. Recrystallization from EtOAc–hexanes provided colorless crystals: mp 150–153 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.4 Hz, 1H), 6.26 (d, *J* = 7.4 Hz, 1H), 4.80 (td, *J* = 4.1, 12.8 Hz, 1H), 3.65 (d, *J* = 1.4 Hz, 1H), 3.38 (s, 3H), 3.07 (ddd, *J* = 3.7, 10.2, 13.4 Hz, 2H), 2.66 (s, 3H), 2.26–2.18 (m, 2H), 1.77 (dd, *J* = 4.9, 14.0 Hz, 1H), 1.69 (dd, *J* = 4.6, 14.3 Hz, 1H), 1.63 (dd, *J* = 4.7, 13.1 Hz, 1H), 1.59–1.37 (m, 3H), 1.29 (dt, *J* = 3.9, 12.8 Hz, 1H), 1.21 (ddd, *J* = 1.5, 4.3, 11.9 Hz, 1H), 0.77 (dddd, *J* = 2.5, 4.7, 4.7, 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 169.6, 153.1, 130.7, 129.2, 123.6, 118.1, 106.8, 98.3, 85.5, 82.6, 57.0, 51.8, 39.4, 38.6, 37.7, 35.5, 34.0, 32.4, 25.5, 20.9; IR (film) ν_{max} 2950, 1735, 1663, 1604, 1492 cm^{-1}; HRESI-TOF *m/z* 369.1803 ($C_{21}H_{24}N_2O_4$ + H^+ requires 369.1809). The structure and stereochemistry of **43b** were unambiguously established by X-ray (CCDC 297502) conducted with white crystals obtained from EtOAc–hexanes.

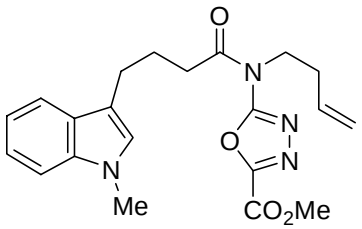


Methyl 5-{*N*-[3-(1-Methyl-1*H*-indol-3-yl)propyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (44a). DMAP (0.24 g, 2.00 mmol) was added to a solution of 4-ethyl-4-pentenoic acid[S6] (0.26 g, 2.00 mmol), **S26** (0.25 g, 0.80 mmol), and EDCI (0.38 g, 2.00 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **44a** (0.24 g, 0.574 mmol, 72%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.88 (s, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 4.09–4.03 (m, 2H), 4.04 (s, 3H), 3.74 (s, 3H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.15–2.00 (m, 4H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 162.0, 154.1, 153.5,

149.4, 136.9, 127.5, 126.0, 121.4, 118.7, 118.6, 113.2, 109.1, 108.3, 53.6, 46.9, 34.7, 32.5, 30.8, 28.9, 28.1, 22.0, 12.2; IR (film) ν_{max} 2961, 1748, 1706, 1564, 1441, 1409 cm^{-1}; HRESI-TOF *m/z* 425.2187 ($C_{23}H_{28}N_4O_4 + H^+$ requires 425.2183).

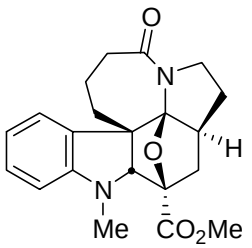


Compound 44b. A solution of **44a** (25 mg, 0.059 mmol) in 120 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (50 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 40% EtOAc–hexanes) providing **44b** (3.5 mg, 0.0088 mmol, 15%) as a colorless oil: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.07 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.57 (t, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 7.9 Hz, 1H), 5.04 (br d, *J* = 12.8 Hz, 1H), 3.62 (s, 1H), 3.38 (s, 3H), 3.02 (dt, *J* = 3.1, 12.3 Hz, 1H), 2.66 (s, 3H), 2.28 (d, *J* = 11.6 Hz, 1H), 2.28–2.25 (m, 1H), 2.13 (dt, *J* = 5.0, 14.7 Hz, 1H), 2.04 (dt, *J* = 3.7, 13.1 Hz, 1H), 1.79 (dt, *J* = 3.1, 13.1 Hz, 1H), 1.67 (br t, *J* = 12.0 Hz, 1H), 1.58 (br d, *J* = 12.8 Hz, 1H), 1.48 (d, *J* = 11.7 Hz, 1H), 1.28–1.22 (m, 1H), 1.13 (br dd, *J* = 4.2, 13.9 Hz, 1H), 0.92 (dq, *J* = 7.4, 15.1 Hz, 1H), 0.50 (dq, *J* = 7.3, 15.1 Hz, 1H), 0.28 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 171.0, 153.7, 131.2, 129.1, 125.0, 118.1, 107.6, 100.6, 84.6, 83.6, 56.5, 51.8, 47.5, 42.0, 40.3, 40.2, 34.6, 29.7, 28.4, 24.0, 20.6, 10.1; IR (film) ν_{max} 2956, 1736, 1666, 1445, 1370, 1275 cm^{-1}; HRESI-TOF *m/z* 397.2126 ($C_{23}H_{28}N_2O_4 + H^+$ requires 397.2127).

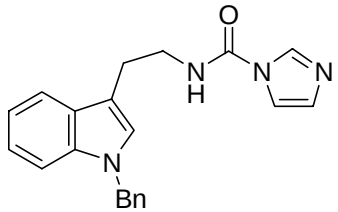


Methyl 5-(*N*-(But-3-enyl)-4-(1-methyl-1*H*-indol-3-yl)butanamido)-1,3,4-oxadiazole-2-carboxylate (45a). DMAP (0.33 g, 2.74 mmol) was added to a solution of 4-(1-methyl-1*H*-indol-3-yl)butanoic acid (0.59 g, 2.74 mmol), **S23** (0.22 g, 1.10 mmol), and EDCI (0.52 g, 2.74 mmol) in CH_2Cl_2 (11 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 25% EtOAc–hexanes) providing **45a** (0.34 g, 0.85 mmol, 78%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 5.73 (dddd, *J* = 7.0, 7.0, 10.1, 17.1 Hz, 1H), 5.05

(d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 4.05 (s, 1H), 4.02 (t, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.39 (dt, *J* = 7.1, 7.1 Hz, 2H), 2.10 (tt, *J* = 7.3, 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 162.0, 154.2, 153.5, 137.0, 133.7, 127.7, 126.4, 121.4, 118.9, 118.6, 117.9, 113.8, 109.1, 53.7, 46.2, 35.8, 32.6, 32.5, 25.5, 24.2; IR (film) ν_{max} 2951, 1748, 1706, 1560, 1441 cm^{-1}; HRESI-TOF *m/z* 397.1871 ($C_{21}H_{24}N_4O_4$ + H^+ requires 397.1870).

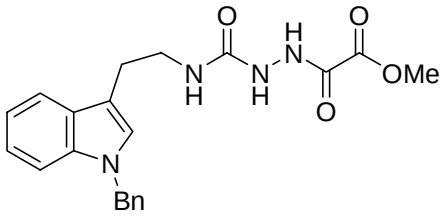


Compound 45b. A solution of **45a** (87 mg, 0.22 mmol) in 88 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (50 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 40% EtOAc–hexanes) providing **45b** (21 mg, 0.057 mmol, 26%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 6.62 (t, *J* = 7.4 Hz, 1H), 6.24 (d, *J* = 7.9 Hz, 1H), 4.25 (dd, *J* = 8.4, 11.6 Hz, 1H), 3.65 (s, 1H), 3.36 (s, 3H), 3.23 (ddd, *J* = 6.2, 12.0, 12.0 Hz, 1H), 2.76–2.74 (m, 1H), 2.64 (s, 3H), 2.16 (dd, *J* = 8.4, 11.4 Hz, 1H), 2.06 (dddd, *J* = 4.5, 7.8, 7.8, 11.9 Hz, 1H), 1.71–1.64 (m, 2H), 1.52–1.46 (m, 1H), 1.40 (dd, *J* = 4.1, 11.6 Hz, 1H), 1.29–1.12 (m, 3H), 1.04 (dt, *J* = 7.0, 13.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 171.2, 152.9, 130.4, 129.2, 123.6, 118.1, 106.9, 103.9, 87.5, 82.8, 58.6, 52.5, 51.8, 47.9, 41.4, 38.5, 35.8, 34.0, 28.7, 18.4; IR (film) ν_{max} 2953, 1735, 1648, 1605, 1491 cm^{-1}; HRESI-TOF *m/z* 369.1812 ($C_{21}H_{24}N_2O_4$ + H^+ requires 369.1814).

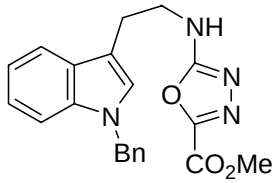


***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-1*H*-imidazole-1-carboxamide (S27).** N^1-Benzyl tryptamine (5.57 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (4.86 g, 30.0 mmol) in THF (200 mL) under Ar cooled to 0 °C. The reaction mixture was allowed to stir overnight at room temperature before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 3% MeOH–$CHCl_3$) provided **S27** (5.20 g, 15.1 mmol, 76%) as a pale yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (br s, 1H), 7.55 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.26–7.22 (m, 2H), 7.15 (td, *J* = 1.2, 6.8 Hz, 1H), 7.08–7.04 (m, 3H), 6.94 (s, 1H), 6.87 (s, 1H), 5.21 (s,

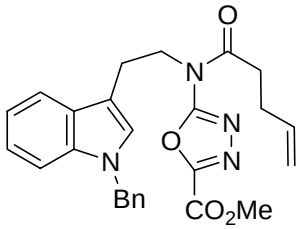
2H), 3.68 (q, J = 4.8 Hz, 2H), 3.06 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 137.6, 137.0, 135.9, 129.9, 129.0 (2C), 128.2, 128.0, 127.1 (2C), 126.5, 122.3, 119.6, 119.0, 116.5, 111.9, 110.2, 50.1, 41.6, 25.3; IR (film) ν_{max} 3440, 1644, 1465 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 367.1536 ($C_{21}H_{20}N_4O$ + Na^+ requires 367.1529).



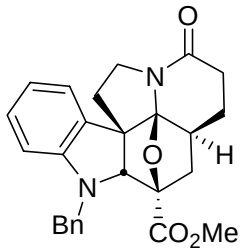
Methyl 2-{2-[2-(1-Benzyl-1*H*-indol-3-yl)ethylcarbamoyl]hydrazinyl}-2-oxoacetate (S28). Methyl oxalylhydrazide[S1] (1.33 g, 11.3 mmol) was added to a solution of **S27** (3.70 g, 11.3 mmol) and AcOH (0.76 mL, 11.0 mmol) in THF (90 mL) under Ar. The reaction mixture was warmed at 50 °C for 16 h. The mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% CH_2Cl_2) provided **S28** (3.20 g, 8.1 mmol, 82%) as a white foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.21–7.16 (m, 3H), 7.10 (dt, J = 1.2, 6.8 Hz, 1H), 7.05–7.01 (m, 2H), 6.89 (s, 1H), 5.97 (br s, 1H), 5.15 (s, 2H), 3.71 (s, 3H), 3.41 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5, 157.5, 155.2, 137.9, 136.8, 128.9 (2C), 128.2, 127.7, 127.0 (2C), 126.7, 122.0, 119.3, 119.1, 112.1, 110.0, 53.8, 50.0, 40.9, 25.8; IR (film) ν_{max} 3406, 1650, 1241 cm^{-1}; MALDIFTMS (DHB) *m*/*z* 417.1526 ($C_{21}H_{22}N_4O_4$ + Na^+ requires 417.1533).



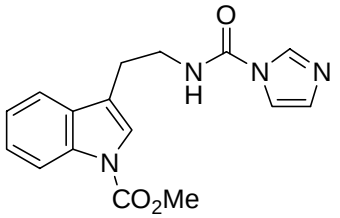
Methyl 5-[2-(1-Benzyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate (S29). Et_3N (2.9 mL, 22.0 mmol) was added to a stirring solution of **S28** (3.2 g, 8.37 mmol) and TsCl (1.59 g, 8.33 mmol) in CH_2Cl_2 (70 mL) under Ar at room temperature. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided **S29** (2.10 g, 5.59 mmol, 69%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, J = 7.6 Hz, 1H), 7.39–7.34 (m, 4H), 7.27 (t, J = 7.0 Hz, 1H), 7.22–7.18 (m, 3H), 7.08 (s, 1H), 5.97 (br s, 1H), 5.35 (s, 2H), 4.05 (s, 3H), 3.86 (s, 2H), 3.22 (t, J = 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 155.2, 151.2, 137.8, 137.3, 129.2 (2C), 128.2, 128.1, 127.24, 127.22, 127.0, 122.6, 119.9, 119.2, 111.2, 110.3, 53.7, 50.4, 44.1, 25.6; IR (film) ν_{max} 3451, 1639, 1359 cm^{-1}; MALDIFTMS (DHB) *m/z* 377.1610 ($C_{21}H_{20}N_4O_3$ + H^+ requires 377.1608).



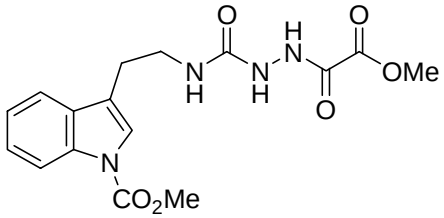
Methyl 5-{*N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxylate (46a). DMAP (488 mg, 4.0 mmol) was added to a mixture of **S29** (286 mg, 0.76 mmol), 4-pentenoic acid (300 mg, 3.0 mmol) and EDCI (760 mg, 4.0 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, extracted with EtOAc (4 × 10 mL), and dried over Na_2SO_4. Flash chromatography (SiO_2, 5–30% EtOAc–hexanes gradient elution) provided **46a** (150 mg, 0.33 mmol, 49%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.61 (m, 1H), 7.22–7.12 (m, 4H), 7.10–6.99 (m, 4H), 6.83 (s, 1H), 5.78–5.68 (m, 1H), 5.13 (s, 2H), 4.98 (dq, *J* = 1.6, 17.2 Hz, 1H), 4.91 (dq, *J* = 1.6, 14.0 Hz, 1H), 4.18–4.14 (m, 2H), 3.90 (s, 3H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.36–2.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 162.2, 154.3, 153.5, 137.6, 136.9, 136.7, 129.0 (2C), 127.9, 127.9, 127.1 (2C), 127.0, 122.1, 119.6, 119.2, 116.1, 110.8, 110.0, 53.9, 50.1, 47.9, 35.9, 28.9, 24.5; IR (film) ν_{max} 3064, 2916, 1748, 1705, 1562, 1440, 1403, 1154 cm^{-1}; MALDIFTMS (DHB) *m/z* 458.2034 ($C_{26}H_{26}N_4O_4$ + H^+ requires 458.2027).



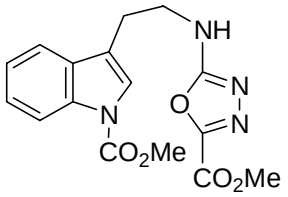
Compound 46b. A solution of **46a** (69 mg, 0.16 mmol) in in anhydrous, degassed 1,2-dichlorobenzene (30 mL) was warmed under Ar at 180 °C for 3 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes and subsequent elution with 50% EtOAc–hexanes gave **46b** (54 mg, 0.13 mmol, 83%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.22 (m, 3H), 7.17–7.11 (m, 3H), 6.77 (dd, *J* = 1.2, 7.2 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.21 (d, *J* = 1.2 Hz, 1H), 4.10–4.03 (m, 1H), 3.82 (dt, *J* = 2.8, 10.0 Hz, 1H), 3.74 (s, 3H), 2.55–2.44 (m, 2H), 2.35–2.21 (m, 3H), 1.88–1.83 (m, 1H), 1.70–1.60 (m, 2H), 1.50 (dt, *J* = 1.0, 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.1, 170.7, 152.6, 138.1, 129.6, 128.9 (2C), 128.7, 127.7 (2C), 127.5, 123.1, 118.7, 108.1, 105.6, 87.2, 79.1, 64.9, 52.8, 51.7, 47.0, 35.9, 34.7, 33.7, 31.8, 26.3; IR (film) ν_{max} 1740, 1668, 1596, 1449, 1443, 1392, 1346, 1269, 1115 cm^{-1}; MALDIFTMS (DHB) *m/z* 431.1968 ($C_{26}H_{26}N_2O_4$ + H^+ requires 431.1965).



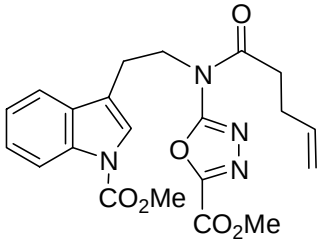
Methyl 3-[2-(1*H*-Imidazole-1-carboxamido)ethyl]-1*H*-indole-1-carboxylate (S30). 1-Methoxycarbonyltryptamine (0.28 g, 1.27 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (0.31 g, 1.90 mmol) in THF (1.5 mL) under Ar cooled to 0 °C. The reaction mixture was allowed to stir and equilibrate to 23 °C overnight before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 2% MeOH–8% acetone–90% $CHCl_3$) provided **S30** (0.22 g, 0.70 mmol, 55%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.68 (t, *J* = 5.5 Hz, 1H), 8.22 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 3.97 (s, 3H), 3.56 (dd, *J* = 7.0, 12.8 Hz, 2H), 2.97 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 150.8, 148.8, 135.8, 134.8, 130.1, 129.5, 124.5, 122.8, 122.7, 119.1, 118.3, 116.5, 114.6, 53.9, 39.9, 24.3; IR (KBr) ν_{max} 3223, 1737, 1720, 1616, 1538 cm^{-1}; HRESI-TOF *m/z* 313.1292 ($C_{16}H_{16}N_4O_3$ + H^+ requires 313.1295).



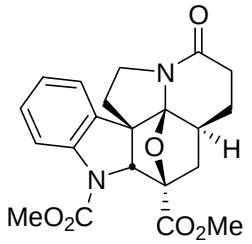
Methyl 3-{2-[2-(2-Methoxy-2-oxoacetyl)hydrazinecarboxamido]ethyl}-1*H*-indole-1-carboxylate (S31). Methyl oxalylhydrazide[S1] (0.34 g, 2.89 mmol) was added to a solution of **S30** (0.86 g, 2.76 mmol) and AcOH (0.17 mL, 2.89 mmol) in THF (18 mL) under Ar and the reaction mixture was warmed at 40 ºC for 24 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2% MeOH–18% acetone–80% $CHCl_3$) provided **S31** (0.72 g, 1.98 mmol, 72%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.40 (br s, 1H), 8.08 (br s, 1H), 7.94 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 5.85 (br t, *J* = 5.5 Hz, 1H), 3.96 (s, 3H), 3.81 (s, 3H), 3.48 (q, *J* = 6.5 Hz, 2H), 2.85 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7, 159.1, 156.8, 151.5, 138.1, 130.3, 124.7, 122.9, 122.8, 118.9, 118.4, 115.2, 53.8, 53.7, 39.7, 25.4; IR (film) ν_{max} 3390, 1702, 1637, 1457 cm^{-1}; HRESI-TOF *m/z* 363.1288 ($C_{16}H_{18}N_4O_6$ + H^+ requires 363.1299).



Methyl 5-{2-[1-(Methoxycarbonyl)-1*H*-indol-3-yl]ethylamino}-1,3,4-oxadiazole-2-carboxylate (S32). Et_3N (0.26 mL, 1.85 mmol) was added to a stirring solution of **S31** (0.25 g, 0.74 mmol) and TsCl (0.14 g, 0.74 mmol) in CH_2Cl_2 (7 mL) under Ar at 23 °C. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexane) provided **S32** (0.21 g, 0.62 mmol, 84%) as white crystals: mp 164–165 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (br d, *J* = 5.1 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 5.99 (br s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.78 (q, *J* = 6.4 Hz, 2H), 3.08 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8, 155.2, 151.7, 151.4, 138.0, 130.4, 125.4, 123.6, 123.5, 119.2, 117.9, 115.8, 54.2, 53.7, 43.3, 25.4; IR (film) ν_{max} 3334, 2955, 1738, 1625, 1456, 1382 cm^{-1}; HRESI-TOF *m/z* 345.1181 ($C_{16}H_{16}N_4O_5$ + H^+ requires 345.1193).

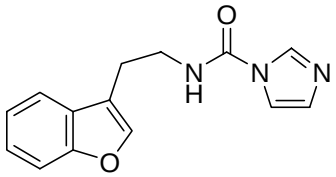


Methyl 5-(*N*-{2-[1-(Methoxycarbonyl)-1*H*-indol-3-yl]ethyl}pent-4-enamido)-1,3,4-oxadiazole-2-carboxylate (47a). DMAP (90 mg, 0.74 mmol) was added to a solution of 4-pentenoic acid (74 mg, 0.74 mmol), **S32** (101 mg, 0.29 mmol), and EDCI (141 mg, 0.74 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30–50% EtOAc–hexanes gradient elution) providing **47a** (111 mg, 0.66 mmol, 89%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br d, *J* = 4.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 5.87–5.78 (m, 1H), 5.07 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 4.24 (t, *J* = 7.7 Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.07 (t, *J* = 7.7 Hz, 2H), 2.45 (dt, *J* = 7.0, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 162.3, 154.5, 153.9, 151.7, 136.8, 135.9, 130.4, 125.3, 123.8, 123.5, 119.5, 117.5, 116.4, 115.6, 54.2 (2C), 47.3, 36.1, 29.1, 24.4; IR (film) ν_{max} 2956, 1743, 1565, 1456, 1382 cm^{-1}; HRESI-TOF *m/z* 427.1598 ($C_{21}H_{22}N_4O_6$ + H^+ requires 427.1612).



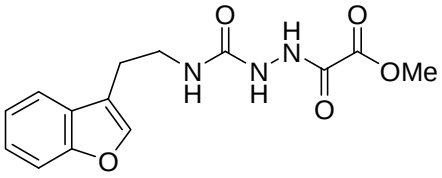
Compound 47b. A solution of **47a** (15 mg, 0.035 mmol) in 7 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 3 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (50 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 75% EtOAc–hexanes) providing **47b** (10 mg, 0.026 mmol, 74%) as a white solid.

Alternatively, a solution of **47a** (18 mg, 0.042 mmol) in 9 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (50 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 75% EtOAc–hexanes) providing **47b** (13 mg, 0.034 mmol, 81%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz, 325K) δ 7.76 (br s, 1H), 7.24 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.97 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.81 (dd, *J* = 0.8, 7.6 Hz, 1H), 4.84 (br s, 1H), 4.08 (dt, *J* = 9.2, 12.0 Hz, 1H), 3.86 (dt, *J* = 2.4, 10.4 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.52 (dt, *J* = 9.6, 12.8 Hz, 1H), 2.41 (ddd, *J* = 1.6, 4.2, 18.4 Hz, 1H), 2.29 (ddd, *J* = 2.4, 8.8, 13.4 Hz, 1H), 2.12 (dt, *J* = 6.4, 13.2 Hz, 1H), 2.00 (dd, *J* = 8.0, 13.6 Hz, 1H), 1.76 (dq, *J* = 5.2, 13.6 Hz, 1H), 1.67–1.57 (m, 2H), 1.40–1.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 170.3, 169.2, 129.5, 124.6, 124.0, 122.9, 115.4, 115.1, 106.2, 86.1, 74.9, 67.9, 52.8, 52.7, 47.0, 34.6, 34.4, 31.5, 30.9, 25.9; IR (film) ν_{max} 2954, 1746, 1725, 1672, 1485 cm^{-1}; MALDIFTMS (DHB) *m/z* 399.1555 ($C_{21}H_{22}N_2O_6$ + H^+ requires 399.1556).

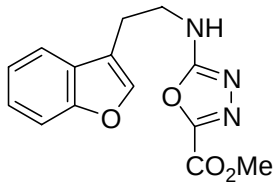


***N*-[2-(Benzofuran-3-yl)ethyl]-1*H*-imidazole-1-carboxamide (S33).** 2-(Benzofuran-3-yl)ethylamine (0.42 g, 2.61 mmol) in CH_2Cl_2 (13 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (0.64 g, 3.92 mmol) in THF (3 mL) under Ar cooled to 0 ºC. The reaction mixture was allowed to stir and equilibrate to 23 ºC overnight before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 2% MeOH–8% acetone–90% $CHCl_3$) provided **S33** (0.67 g, 1.64 mmol, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (t, *J* = 5.5 Hz, 1H), 7.99 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 6.6 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.18

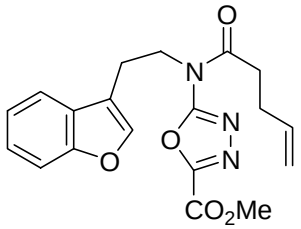
(t, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 3.67 (dd, *J* = 6.6, 12.7 Hz, 2H), 2.99 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 148.9, 141.5, 135.6, 128.7, 127.4, 124.1, 122.2, 119.0, 116.7, 116.4, 111.2, 40.2, 23.3; IR (film) ν_{max} 3221, 1722, 1548, 1453, 1288 cm^{-1}; HRESI-TOF *m/z* 256.1082 ($C_{14}H_{13}N_3O_2$ + H^+ requires 256.1086).



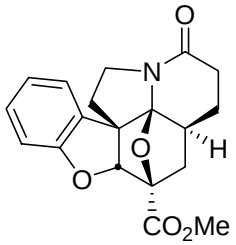
Methyl 2-{2-[2-(Benzofuran-3-yl)ethylcarbamoyl]hydrazinyl}-2-oxoacetate (S34). Methyl oxalylhydrazide[S1] (0.24 g, 2.03 mmol) was added to a solution of **S33** (0.49 g, 1.93 mmol) and AcOH (0.12 mL, 2.03 mmol) in THF (13 mL) under Ar and the reaction mixture was warmed at 40 ºC for 24 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2% MeOH–18% acetone–80% $CHCl_3$) provided **S34** (0.42 g, 1.39 mmol, 72%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.80 (br s, 1H), 8.23 (s, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.10 (br s, 1H), 3.74 (s, 3H), 3.42 (br t, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 158.2, 156.3, 155.6, 142.5, 128.3, 124.7, 122.9, 119.9, 117.6, 111.8, 54.1, 39.9, 24.4; IR (film) ν_{max} 3344, 1755, 1721, 1667, 1558, 1453 cm^{-1}; HRESI-TOF *m/z* 306.1087 ($C_{14}H_{15}N_3O_5$ + H^+ requires 306.1084).



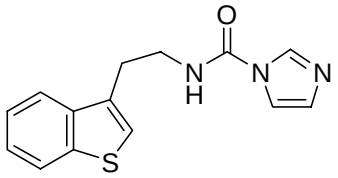
Methyl 5-[2-(Benzofuran-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate (S35). Et_3N (0.49 mL, 3.52 mmol) was added to a stirring solution of **S34** (0.43 g, 1.41 mmol) and TsCl (0.27 g, 1.41 mmol) in CH_2Cl_2 (14 mL) under Ar at 23 °C. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) provided **S35** (0.34 g, 1.18 mmol, 84%) as white crystals: mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, *J* = 7.1 Hz, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.95 (br s, 1H), 3.96 (s, 3H), 3.79 (br t, *J* = 6.7 Hz, 2H), 3.09 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1, 155.3, 154.6, 150.6, 142.2, 127.4, 124.5, 122.6, 119.3, 116.2, 111.6, 53.3, 42.8, 23.7; IR (film) ν_{max} 3247, 1737, 1630, 1450 cm^{-1}; HRESI-TOF *m/z* 288.0981 ($C_{14}H_{13}N_3O_4$ + H^+ requires 288.0979).



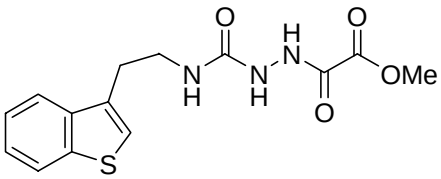
Methyl 5-{*N*-[2-(Benzofuran-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxylate (48a). DMAP (0.43 g, 3.48 mmol) was added to a solution of 4-pentenoic acid (0.35 g, 3.48 mmol), **S35** (0.40 g, 1.39 mmol), and EDCI (0.67 g, 3.48 mmol) in CH_2Cl_2 (14 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 13 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **48a** (0.31 g, 0.83 mmol, 60%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J* = 7.2 Hz, 1H), 7.55 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 5.94–5.86 (m, 1H), 5.16 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.34 (t, *J* = 7.7 Hz, 2H), 4.11 (s, 3H), 3.15 (t, *J* = 7.6 Hz, 2H), 3.03 (t, *J* = 7.3 Hz, 2H), 2.52 (dt, *J* = 7.1, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 161.8, 155.3, 154.1, 153.5, 142.2, 136.3, 127.4, 124.4, 122.6, 119.5, 115.9, 115.8, 111.5, 53.7, 46.6, 35.6, 28.6, 22.6; IR (film) ν_{max} 1748, 1705, 1565, 1441, 1409 cm^{-1}; HRESI-TOF *m/z* 370.1386 ($C_{19}H_{19}N_3O_5$ + H^+ requires 370.1397).



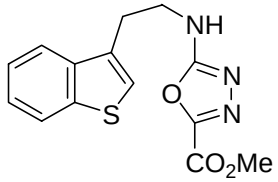
Compound 48b. A solution of **48a** (30 mg, 0.081 mmol) in 81 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **48b** (17.6 mg, 0.052 mmol, 63%) as colorless oil: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.13 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 4.13 (dt, *J* = 9.0, 11.8 Hz, 1H), 3.82 (dt, *J* = 2.3, 10.0 Hz, 1H), 2.40–2.35 (m, 2H), 2.08 (dt, *J* = 9.7, 13.4 Hz, 1H), 1.95 (ddd, *J* =6.2, 13.2, 18.9 Hz, 1H), 1.81 (ddd, *J* = 2.5, 8.8, 13.2 Hz, 1H), 1.72 (ddt, *J* = 5.2, 13.0, 13.0 Hz, 1H), 1.54 (br d, *J* = 14.4 Hz, 1H), 1.22–1.16 (m, 1H), 1.05 (dt, *J* = 5.9, 12.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 169.0, 161.4, 142.3, 129.9, 123.4, 122.0, 110.4, 106.4, 93.4, 85.7, 64.7, 52.0, 47.0, 34.8, 33.5, 32.0, 31.8, 25.2; IR (film) ν_{max} 2952, 1740, 1672, 1477, 1452 cm^{-1}.



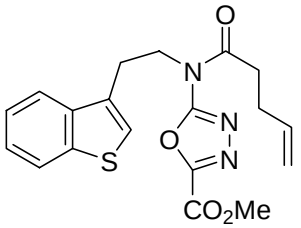
***N*-[2-(Benzothiophen-3-yl)ethyl]-1*H*-imidazole-1-carboxamide (S36).** 2-(Benzothiophen-3-yl)ethylamine (0.60 g, 3.39 mmol) in CH_2Cl_2 (17 mL) was added dropwise to a stirring solution of 1,1-carbonyldiimidazole (0.82 g, 5.08 mmol) in THF (4 mL) under Ar cooled to 0 ºC. The reaction mixture was allowed to stir and equilibrate to 23 ºC overnight before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 2% MeOH–8% acetone–90% $CHCl_3$) provided **S36** (0.49 g, 1.80 mmol, 53%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (br s, 1H), 8.06 (s, 1H), 7.79 (dd, *J* = 3.8, 6.1 Hz, 1H), 7.71 (dd, *J* = 2.6, 6.4 Hz, 1H), 7.42 (s, 1H), 7.31 (t, *J* = 5.4 Hz, 1H), 7.29 (t, *J* = 5.4 Hz, 1H), 7.12 (s, 1H), 6.80 (s, 1H), 3.69 (dt, *J* = 6.7, 6.7 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 140.1, 138.4, 135.6, 132.7, 128.6, 124.1, 123.8, 122.6, 122.4, 121.1, 116.5, 40.2, 28.1; IR (film) ν_{max} 3219, 1718, 1549, 1480, 1290 cm^{-1}; HRESI-TOF *m/z* 272.0847 ($C_{14}H_{13}N_3OS$ + H^+ requires 272.0858).



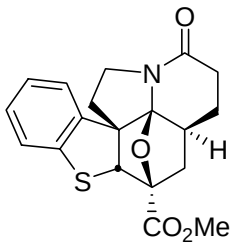
Methyl 2-{2-[2-(Benzothiophen-3-yl)ethylcarbamoyl]hydrazinyl}-2-oxoacetate (S37). Methyl oxalylhydrazide[S1] (0.15 g, 1.23 mmol) was added to a solution of **S36** (0.32 g, 1.17 mmol) and AcOH (71 μL, 1.23 mmol) in THF (8 mL) under Ar and the reaction mixture was warmed at 40 ºC for 24 h. The reaction mixture was concentrated under reduced pressure and flash chromatography (SiO_2, 2% MeOH–18% acetone–80% $CHCl_3$) provided **S37** (0.24 g, 0.75 mmol, 64%) as a white amorphous solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.32–7.26 (m, 2H), 7.10 (s, 1H), 3.75 (s, 3H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.96 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.1, 157.3, 155.1, 140.3, 138.6, 133.1, 124.2, 124.0, 122.8, 122.6, 121.5, 53.7, 39.6, 28.8; IR (film) ν_{max} 3333, 1719, 1664, 1560 cm^{-1}; HRESI-TOF *m/z* 322.0859 ($C_{14}H_{15}N_3O_4S$ + H^+ requires 322.0861).



Methyl 5-[2-(Benzothiophen-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate (S38). Et_3N (0.26 mL, 1.88 mmol) was added to a stirring solution of semicarbazide **S39** (0.24 g, 0.75 mmol) and TsCl (0.14 g, 0.75 mmol) in CH_2Cl_2 (8 mL) under Ar at 23 °C. The reaction mixture was stirred for 16 h before the solvent was removed under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexane) provided **S38** (0.16 g, 0.55 mmol, 73%) as white crystals: mp 149–152 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 6.81 (br s, 1H), 3.95 (s, 3H), 3.80 (br t, *J* = 6.7 Hz, 2H), 3.23 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1, 154.6, 150.6, 140.4, 138.4, 132.2, 124.1, 123.2, 122.9, 122.8, 121.4, 53.3, 42.8, 28.4; IR (film) ν_{max} 3248, 1742, 1626, 1547, 1439 cm^{-1}; HRESI-TOF *m/z* 304.0750 ($C_{14}H_{13}N_3O_3S$ + H^+ requires 304.0750).

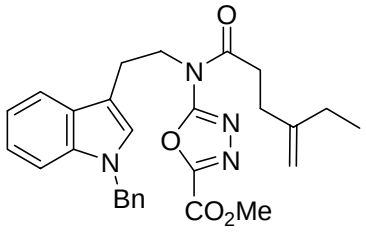


Methyl 5-{*N*-[2-(Benzothiophen-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxylate (49a). DMAP (0.26 g, 2.12 mmol) was added to a solution of 4-pentenoic acid (0.21 g, 2.12 mmol), **S38** (0.26 g, 0.85 mmol), and EDCI (0.41 g, 2.12 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 15 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **49a** (0.24 g, 0.63 mmol, 74%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 5.88–5.80 (m, 1H), 5.08 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.28 (t, *J* = 7.7 Hz, 2H), 4.03 (s, 3H), 3.24 (br t, *J* = 7.7 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.45 (dt, *J* = 6.8, 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 161.8, 154.0, 153.4, 140.4, 138.4, 136.3, 131.8, 124.4, 124.3, 123.7, 122.9, 121.6, 115.9, 53.7, 46.8, 35.7, 28.6, 27.4; IR (film) ν_{max} 1748, 1706, 1565, 1440, 1410 cm^{-1}; HRESI-TOF *m/z* 386.1172 ($C_{19}H_{19}N_3O_4S$ + H^+ requires 386.1169).

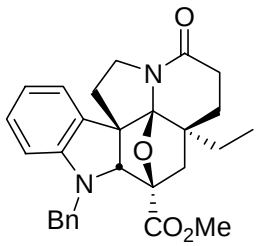


Compound 49b. A solution of **49a** (40 mg, 0.10 mmol) in 21 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 16 h. The cooled reaction

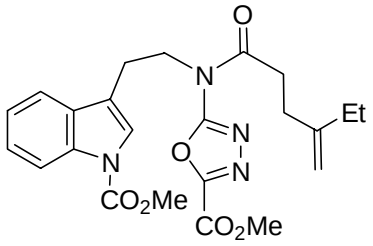
mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **49b** (23 mg, 0.065 mmol, 62%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88–6.85 (m, 2H), 6.73 (ddd, *J* = 3.2, 5.2, 7.8 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 4.25 (d, *J* = 1.7 Hz, 1H), 4.01 (dt, *J* = 9.0, 12.2 Hz, 1H), 3.63 (ddd, *J* = 2.4, 10.1, 12.6 Hz, 1H), 3.30 (s, 3H), 2.64 (dd, *J* = 8.0, 12.9 Hz, 1H), 2.20 (br dd, *J* = 3.7, 18.0 Hz, 1H), 1.92 (ddd, *J* = 9.1, 10.3, 13.3 Hz, 1H), 1.80–1.72 (m, 2H), 1.55 (ddt, *J* = 5.1, 12.9, 12.9 Hz, 1H), 1.33 (td, *J* = 2.3, 13.0 Hz, 1H), 1.04 (dddd, *J* = 3.0, 4.8, 7.9, 12.7 Hz, 1H), 0.87 (br td, *J* = 5.3, 6.6 Hz, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 169.6, 169.3, 142.5, 140.0, 129.1, 125.5, 123.7, 122.4, 106.5, 86.9, 70.7, 63.1, 52.0, 46.8, 37.3, 35.1, 33.9, 31.9, 26.1; IR (film) ν_{max} 2951, 1738, 1670, 1442, 1388 cm^{-1}; HRESI-TOF *m/z* 358.1110 ($C_{19}H_{19}NO_4S$ + H^+ requires 358.1107).



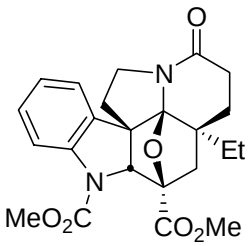
Methyl 5-{*N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (50a). DMAP (366 mg, 3.0 mmol) was added to a mixture of **S29** (364 mg, 1.0 mmol), 4-ethyl-4-pentenoic acid (384 mg, 3.0 mmol) and EDCI (570 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, extracted with EtOAc (4 × 20 mL), and dried over Na_2SO_4. Flash chromatography (SiO_2, 5–25% EtOAc–hexanes gradient elution) provided **50a** (340 mg, 0.70 mmol, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74–7.11 (m, 1H), 7.31–7.21 (m, 4H), 7.17–7.12 (m, 2H), 7.10–7.08 (m, 2H), 6.92 (s, 1H), 5.22 (s, 2H), 4.77 (d, *J* = 1.6 Hz, 1H), 4.71 (d, *J* = 1.2 Hz, 1H), 4.27–4.24 (m, 2H), 3.98 (s, 3H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.98–2.95 (m, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 2.07–2.02 (m, 2H), 1.04 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 162.2, 154.3, 153.5, 149.7, 137.6, 136.9, 129.0 (2C), 128.0, 127.9, 127.1 (2C), 127.0, 122.1, 119.6, 119.2, 110.9, 110.0, 108.6, 53.9, 50.1, 47.9, 35.1, 31.1, 29.2, 24.5, 12.6; IR (film) ν_{max} 3073, 1749, 1707, 1566, 1439, 1409, 1155 cm^{-1}; MALDIFTMS (DHB) *m/z* 487.2350 ($C_{28}H_{30}N_4O_4$ + H^+ requires 487.2340).



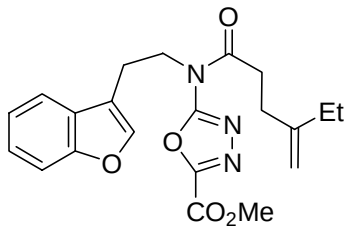
Compound 50b. A solution of **50a** (60 mg, 0.13 mmol) in anhydrous, degassed 1,2-dichlorobenzene (30 mL) was warmed under Ar at 180 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with hexanes and subsequent elution with 50% EtOAc–hexanes gave **50b** (43 mg, 0.094 mmol, 76%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.23 (m, 3H), 7.20 (d, *J* = 6.8 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 4.27 (s, 1H), 4.00–3.93 (m, 1H), 3.77 (s, 3H), 2.44–2.28 (m, 3H), 2.25–2.16 (m, 2H), 1.80–1.73 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 1H), 0.96–0.89 (m, 1H), 0.63 (t, *J* = 7.2 Hz, 3H), 0.45–0.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 170.6, 153.0, 138.1, 129.7, 128.9, 128.8 (2C), 127.8 (2C), 127.5, 124.0, 118.6, 108.3, 106.8, 86.1, 80.0, 65.2, 52.8, 51.8, 47.1, 44.0, 39.3, 37.7, 29.4, 28.1, 22.9, 10.0; IR (film) ν_{max} 2952, 1740, 1668, 1601, 1489, 1443, 1387, 1346, 1269, 1218, 1156, 1120, 1069 cm^{-1}; MALDIFTMS (DHB) *m/z* 459.2272 ($C_{28}H_{30}N_2O_4$ + H^+ requires 459.2278).



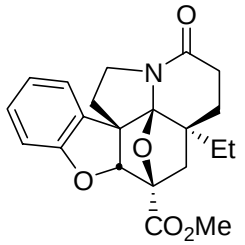
Methyl 5-{*N*-[2-(1-(Methoxycarbonyl)-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (51a). DMAP (244 mg, 2.0 mmol) was added to a mixture of **S32** (172 mg, 0.50 mmol), 4-ethyl-4-pentenoic acid (0.15 mL, 1.5 mmol) and EDCI (380 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was concentrated and the residue was subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) to provide **51a** (170 mg, 0.37 mmol, 76%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, *J* = 6.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.42 (s, 1H), 7.28 (m, 3H), 4.74 (s, 1H), 4.67 (s, 1H), 4.23–4.19 (m, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.04 (t, *J* = 8.0 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.01 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 162.1, 154.3, 153.7, 149.6, 135.7, 130.1, 125.1, 123.6, 123.3, 123.1, 119.3, 117.3, 115.4, 108.6, 54.0 (2C), 47.1, 35.1, 31.0, 29.2, 24.2, 12.5; IR (film) ν_{max} 3426, 2954, 2913, 1738, 1641, 1564, 1451, 1379, 1257, 1154 cm^{-1}; MALDIFTMS (DHB) *m/z* 455.1927 ($C_{23}H_{26}N_4O_6$ + H^+ requires 455.1925).



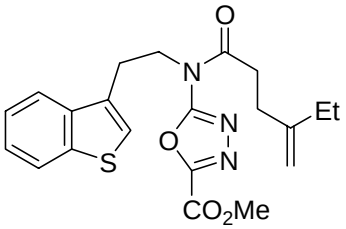
Compound 51b. A solution of **51a** (20 mg, 0.044 mmol) in 18 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (50 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 40% EtOAc–hexanes) providing **51b** (9.8 mg, 0.023 mmol, 52%) as a colorless oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 8.27 (br s, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.1 Hz, 1H), 4.68 (br s, 1H), 3.94–3.78 (m, 2H), 3.41 (br s, 3H), 3.36 (s, 3H), 2.25–1.93 (m, 4H), 1.75 (d, *J* = 13.3 Hz, 1H), 1.61 (ddd, *J* = 2.4, 7.1, 12.7 Hz, 1H), 1.38–1.11 (m, 2H), 0.61 (ddd, *J* = 7.4, 14.7, 14.7 Hz, 1H), 0.17 (t, *J* = 7.4 Hz, 3H), –0.07 (ddd, *J* = 7.1, 14.3, 14.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 169.1, 152.3, 143.7, 131.5, 129.5, 124.2, 123.6, 115.4, 108.1, 85.4, 75.7, 63.6, 52.2, 52.1, 47.3, 43.8, 37.0, 36.4, 29.4, 28.2, 22.9, 9.5; IR (film) ν_{max} 2954, 1746, 1725, 1671, 1485, 1443 cm^{-1}; HRESI-TOF *m/z* 427.1865 ($C_{23}H_{26}N_2O_6$ + H^+ requires 427.1869).



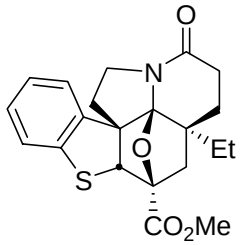
Methyl 5-{*N*-[2-(Benzofuran-3-yl)ethyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (52a). DMAP (0.36 g, 2.91 mmol) was added to a solution of 4-ethyl-4-pentenoic acid[S6] (0.37 g, 2.91 mmol), **S35** (0.33 g, 1.16 mmol), and EDCI (0.56 g, 2.91 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 15 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **52a** (0.31 g, 0.79 mmol, 68%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, *J* = 7.1 Hz, 1H), 7.47 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 4.26 (br t, *J* = 7.7 Hz, 2H), 4.03 (s, 3H), 3.07 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.04 (dd, *J* = 7.3, 14.8 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 162.3, 155.7, 154.5, 153.9, 149.8, 142.7, 127.9, 124.9, 123.1, 120.0, 116.4, 112.0, 108.9, 54.2, 47.1, 35.3, 31.3, 29.4, 23.1, 12.7; IR (film) ν_{max} 2964, 1749, 1707, 1566, 1450, 1409 cm^{-1}; HRESI-TOF *m/z* 398.1717 ($C_{21}H_{23}N_3O_5$ + H^+ requires 398.1710).



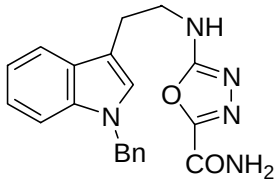
Compound 52b. A solution of **52a** (10 mg, 0.025 mmol) in 50 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **52b** (5.3 mg, 0.014 mmol, 57%) as colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90 (t, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.02 (s, 1H), 3.85–3.73 (m, 2H), 3.36 (s, 3H), 2.20–1.98 (m, 4H), 1.71 (d, *J* = 12.9 Hz, 1H), 1.58 (dd, *J* = 7.5, 13.2 Hz, 1H), 1.31–1.20 (m, 2H), 0.63 (dq, *J* = 7.2, 14.3 Hz, 1H), 0.55 (dd, *J* = 7.9, 15.5 Hz, 1H), 0.22 (t, *J* = 7.5 Hz, 3H), 0.06 (dq, *J* = 7.1, 14.2 Hz, 1H); IR (film) ν_{max} 2954, 1733, 1669, 1653, 1559, 1457 cm^{-1}; HRESI-TOF *m/z* 370.1654 ($C_{21}H_{23}NO_5$ + H^+ requires 370.1654).



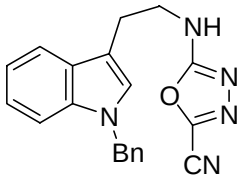
Methyl 5-(*N*-(2-(benzo[*b*]thiophen-3-yl)ethyl)-4-methylenehexanamido)-1,3,4-oxadiazole-2-carboxylate (53a). DMAP (0.17 g, 1.35 mmol) was added to a solution of 4-ethyl-4-pentenoic acid[S6] (0.17 g, 1.35 mmol), **S38** (0.17 g, 0.54 mmol), and EDCI (0.26 g, 1.35 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 18 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 20% EtOAc–CH_2Cl_2) providing **53a** (0.15 g, 0.35 mmol, 65%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.20 (s, 1H), 4.77 (s, 1H), 4.71 (s, 1H), 4.28 (t, *J* = 7.7 Hz, 2H), 4.03 (s, 3H), 3.24 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H), 2.42 (t, *J* = 7.7 Hz, 2H), 2.05 (q, *J* = 7.4 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 161.8, 154.0, 153.5, 149.3, 140.4, 138.4, 131.8, 124.4, 124.3, 123.7, 122.9, 121.6, 108.4, 53.7, 46.8, 34.9, 30.8, 29.0, 27.4, 12.3; IR (film) ν_{max} 2962, 1750, 1700, 1559, 1437, 1152 cm^{-1}; HRESI-TOF *m/z* 414.1481 ($C_{21}H_{23}N_3O_4S$ + H^+ requires 414.1482).



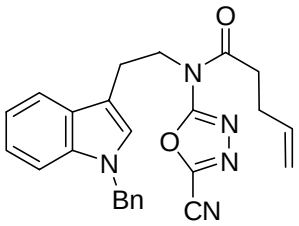
Compound 53b. A solution of **53a** (92 mg, 0.22 mmol) in 45 mL of anhydrous, degassed 1,3,5-triisopropylbenzene was warmed under Ar at 230 °C for 24 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,3,5-triisopropylbenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled EtOAc (25 mL). The EtOAc was concentrated and the residue was purified by column chromatography (SiO_2, 45% EtOAc–hexanes) providing **53b** (58 mg, 0.15 mmol, 68%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.83 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.39 (s, 1H), 3.90–3.79 (m, 2H), 3.32 (s, 3H), 2.63 (d, *J* = 12.8 Hz, 1H), 2.17 (dd, *J* = 4.5, 17.0 Hz, 1H), 1.96–2.13 (m, 3H), 1.65–1.70 (m, 2H), 1.22 (dd, *J* = 4.5, 12.6 Hz, 1H), 0.66 (dq, *J* = 7.3, 14.5 Hz, 1H), 0.24 (t, *J* = 7.3 Hz, 3H), 0.14 (dq, *J* = 6.8, 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 169.1, 142.5, 139.6, 129.2, 128.6, 125.0, 122.5, 107.7, 85.6, 71.2, 63.9, 52.0, 46.8, 44.1, 40.4, 39.4, 29.5, 28.1, 23.4, 9.7; IR (film) ν_{max} 2954, 1757, 1739, 1670, 1394 cm^{-1}; HRESI-TOF *m/z* 386.1409 ($C_{21}H_{23}NO_4S$ + H^+ requires 386.1420).



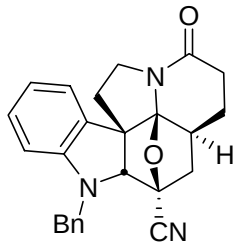
5-[2-(1-Benzyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxamide (S39). Ammonia was passed through a suspension of **S29** (300 mg, 0.82 mmol) in MeOH (10 mL) at 0 °C. A white precipitate was formed after 2 min. After bubbling NH_3 for 30 min, the white precipitate was collected by filtration, washed with MeOH and dried under reduced pressure to give **S39** (300 mg, quant.) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.15–8.13 (m, 2H), 7.79 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.26–7.22 (m, 2H), 7.19–7.15 (m, 1H), 7.13–7.11 (m, 2H), 7.04 (td, *J* = 1.2, 6.8 Hz, 1H), 6.96 (dt, *J* = 1.2, 7.6 Hz, 1H), 5.31 (s, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.0, 155.7, 153.5, 139.0, 136.7, 129.1 (2C), 128.4, 127.9, 127.6 (2C), 127.5, 121.9, 119.3, 111.8, 110.8, 49.6, 43.9, 25.2; IR (film) ν_{max} 3500, 1639 cm^{-1}; MALDIFTMS (DHB) *m/z* 362.1617 ($C_{20}H_{19}N_5O_2$ + H^+ requires 362.1611).



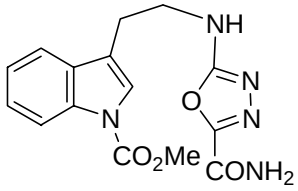
5-[2-(1-Benzyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carbonitrile (S40). Trifluoroacetic anhydride (216 μL, 1.5 mmol) was added dropwise to a solution of **S39** (250 mg, 0.69 mmol) in anhydrous 1,4-dioxane (3 mL) and pyridine (224 μL, 2.76 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. MeOH (10 mL) was added and the mixture was warmed at reflux for 0.5 h. The solvents were removed under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) gave **S40** (216 mg, 0.63 mmol, 90%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.22–7.16 (m, 4H), 7.12 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.04 (dt, *J* = 1.0, 7.2 Hz, 1H), 7.03–6.99 (m, 2H), 6.91 (s, 1H), 5.90 (br s, 1H), 5.18 (s, 2H), 3.65 (q, *J* = 6.4 Hz, 2H), 3.03 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 137.1, 129.0 (2C), 128.0, 127.8, 127.1 (2C), 126.8, 122.5, 119.8, 118.9, 110.8, 110.2, 107.1, 50.2, 44.1, 25.4; IR (film) ν_{max} 3339, 3204, 2324, 1672, 1616 cm^{-1}; MALDIFTMS (DHB) *m/z* 344.1507 ($C_{20}H_{17}N_5O$ + H^+ requires 344.1506).



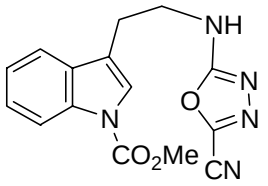
***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-*N*-(5-cyano-1,3,4-oxadiazol-2-yl)pent-4-enamide (54a).** DMAP (106 mg, 0.87 mmol) was added to a solution of 4-pentenoic acid (0.1 mL, 1.0 mmol), EDCI (162 mg, 0.85 mmol) and **S40** (100 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to room temperature. After being stirred for 5 h, the reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 20–30% EtOAc–hexanes gradient elution) gave **54a** as a white solid (108 mg, 0.25 mmol, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.23–7.00 (m, 9H), 6.81 (s, 1H), 5.77–5.67 (m, 1H), 5.15 (s, 2H), 5.00–4.95 (m, 2H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.34 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.6, 162.3, 138.5, 137.4, 136.8, 136.4, 129.0 (2C), 128.0, 127.7, 127.1 (2C), 127.0, 122.5, 119.8, 118.9, 116.3, 110.5, 110.1, 105.8, 50.1, 48.1, 36.0, 28.8, 24.4; IR (film) ν_{max} 2916, 2333, 1711, 1562, 1456, 1398, 1176 cm^{-1}; MALDIFTMS (DHB) *m/z* 426.1924 ($C_{25}H_{23}N_5O_2$ + H^+ requires 426.1924).



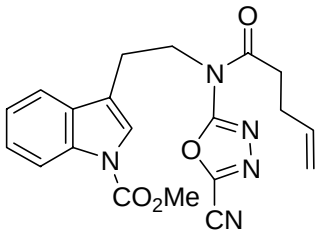
Compound 54b. A solution of **54a** (85 mg, 0.20 mmol) in 40 mL of anhydrous, degassed 1,2-dichlorobenzene was placed in a capped, silated tube under Ar and warmed at 180 °C for 3 h. The cooled reaction mixture was loaded onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was evaporated and the residue was purified by flash chromatography (SiO_2, 33% EtOAc–hexanes) to yield **54b** (46 mg, 0.12 mmol, 58%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.35 (m, 1H), 7.29–7.11 (m, 5H), 6.73–6.66 (m, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.50 (d, *J* = 16.0 Hz, 1H), 4.37 (d, *J* = 16.0 Hz, 1H), 4.25 (s, 1H), 4.02 (dt, *J* = 11.2, 12.4 Hz, 1H), 3.76 (dt, *J* = 4.0, 8.8 Hz, 1H), 2.46–2.41 (m, 2H), 2.28–2.24 (m, 2H), 2.20–2.15 (m, 1H), 1.77 (dd, *J* = 4.2, 13.2 Hz, 1H), 1.68–1.62 (m, 1H), 1.56–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 151.9, 137.1, 130.7, 130.0, 129.1 (2C), 128.1 (2C), 127.9, 123.3, 119.3, 117.9, 108.2, 106.8, 81.4 75.5, 64.5, 52.6, 47.0, 35.9, 35.2, 34.4, 31.7, 26.2; IR (film) ν_{max} 2921, 2349, 1668, 1642, 1601, 1555, 1484, 1443, 1387 cm^{-1}; MALDIFTMS (DHB) *m/z* 398.1866 ($C_{25}H_{23}N_3O_2$ + H^+ requires 398.1863).



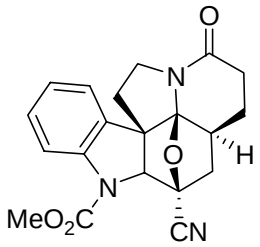
Methyl 3-[2-(5-Carbamoyl-1,3,4-oxadiazol-2-ylamino)ethyl]-1*H*-indole-1-carboxylate (S41). Ammonia was passed through a suspension of **S32** (540 mg, 1.57 mmol) in MeOH (25 mL) at 0 °C. The reaction became clear in 5 min and then a white precipitate was formed after 20 min. After bubbling NH_3 for an additional 10 min, the white precipitate was collected by filtration, washed with MeOH and dried to give **S41** (510 mg, quant.): ^{1}H NMR (DMSO-d_6–CD_3OD, 400 MHz) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 (s, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.52 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6–CD_3OD, 100 MHz) δ 164.8, 155.6, 153.4, 151.4, 135.6, 130.7, 124.9, 123.4, 123.1, 119.6, 118.7, 115.2, 54.1, 42.6, 24.5; IR (film) ν_{max} 3340, 1736, 1690, 1643, 1443, 1367, 1243, 1208, 1090 cm^{-1}; MALDIFTMS (DHB) *m/z* 330.1205 ($C_{15}H_{15}N_5O_4$ + H^+ requires 330.1197).



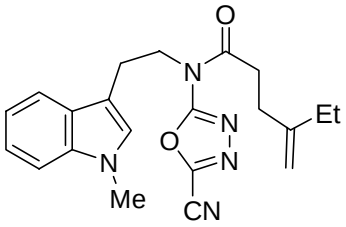
Methyl 3-[2-(5-Cyano-1,3,4-oxadiazol-2-ylamino)ethyl]-1*H*-indole-1-carboxylate (S42). Trifluoroacetic anhydride (0.5 mL, 3.6 mmol) was added dropwise to a solution of **S41** (510 mg, 1.57 mmol) in anhydrous 1,4-dioxane (6 mL) and pyridine (0.5 mL, 6.3 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. MeOH (10 mL) was added and the mixture was warmed at reflux for 0.5 h. The solvents were evaporated under reduced pressure. Flash chromatography (SiO_2, 33% EtOAc–hexanes) gave **S42** (440 mg, 1.4 mmol, 90%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.41 (s, 1H), 7.31 (dt, *J* = 1.2, 8.4 Hz, 1H), 7.24–7.21(m, 1H), 6.52 (br s, 1H), 3.94 (s, 3H), 3.72 (q, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 135.9, 135.7, 130.1, 125.3, 123.4, 123.3, 118.9, 117.4, 115.5, 107.0, 54.1, 43.2, 25.1; IR (film) ν_{max} 3305, 2249, 1734, 1632, 1456, 1383, 1259, 1093 cm^{-1}; MALDIFTMS (DHB) *m/z* 312.1092 ($C_{15}H_{13}N_5O_3$ + H^+ requires 312.1092).



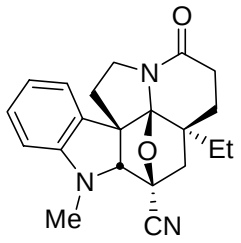
Methyl 3-{2-[*N*-(5-Cyano-1,3,4-oxadiazol-2-yl)pent-4-enamido]ethyl}-1*H*-indole-1-carboxylate (55a). DMAP (50 mg, 0.41 mmol) was added to a solution of 4-pentenoic acid (0.1 mL, 1 mmol), EDCI (120 mg, 0.64 mmol) and **S42** (70 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under vacumn. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **55a** (65 mg, 0.17 mmol, 72%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, *J* = 8.8 Hz, 1H), 7.58 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.40 (s, 1H), 7.34 (td, *J* = 1.2, 7.6 Hz, 1H), 7.25 (td, *J* = 1.2, 7.2 Hz, 1H), 5.81–5.74 (m, 1H), 5.06 (dt, *J* = 1.6, 13.2, 1H), 4.99 (dt, *J* = 1.2, 10.4 Hz, 2H), 4.23–4.19 (m, 2H), 4.00 (s, 3H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.42 (q, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.4, 162.1, 138.7, 136.3, 129.9, 125.3, 123.7, 123.4, 119.0, 116.9, 116.4, 115.6, 105.9, 54.1, 47.2, 36.1, 28.7, 24.1; IR (film) ν_{max} 2247, 1734, 1565, 1456, 1382, 1260 cm^{-1}; MALDIFTMS (DHB) *m/z* 416.1328 ($C_{20}H_{19}N_5O_4$ + Na^+ requires 416.1329).



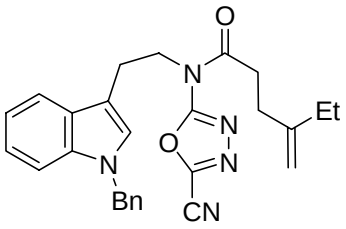
Compound 55b. A solution of **55a** (9.2 mg, 0.023 mmol) in 5 mL of anhydrous, degassed 1,2-dichlorobenzene was placed in a capped, silated tube under Ar and warmed at 180 °C for 3 h. The cooled reaction mixture was loaded onto SiO_2 equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was evaporated and the residue was purified by flash chromatography (SiO_2, 40% EtOAc–hexanes) to yield **55b** (3.9 mg, 42%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz, 325K) δ 7.87 (br s, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 4.84 (br s, 1H), 4.08–4.05 (m, 1H), 3.86–3.83 (m, 4H), 2.50–2.45 (m, 2H), 2.36–2.33 (m, 1H), 2.23–2.18 (m, 2H), 1.83 (dt, *J* = 6.4, 13.2 Hz, 1H), 1.63 (m, 2H), 1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 152.5, 142.7, 130.1, 124.5, 122.8, 117.4, 115.6, 106.2, 75.7, 75.1, 62.9, 53.0, 47.0, 36.8, 35.1, 34.6, 34.2, 31.6, 26.1; IR (film) ν_{max} 2944, 2260, 1728, 1672, 1605, 1487, 1441, 1385, 1292, 1261, 1169, 1051, 918, 754, 733 cm^{-1}.



***N*-(5-Cyano-1,3,4-oxadiazol-2-yl)-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-4-methylenehexanamide (56a).** DMAP (137 mg, 1.12 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (144 mg, 1.12 mmol), EDCI (215 mg, 1.12 mmol) and **S9** (120 mg, 0.45 mmol) in CH_2Cl_2 (4.5 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 3 h, the mixture was treated with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 6–20% EtOAc–hexanes gradient elution) provided **56a** (122 mg, 0.32 mmol, 72%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 4.24 (t, *J* = 7.4 Hz, 2H), 3.73 (s, 3H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.7 Hz, 2H), 2.42 (t, *J* = 7.7 Hz, 2H), 2.05 (q, *J* = 7.5 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6, 162.0, 149.2, 138.1, 136.8, 127.5, 127.1, 122.0, 119.2, 118.4, 109.5, 109.4, 108.4, 105.6, 48.0, 34.8, 32.5, 30.7, 28.9, 24.2, 12.2; IR (film) ν_{max} 2253, 1714, 1647, 1563, 1167, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 400.1746 ($C_{21}H_{23}N_5O_2$ + Na^+ requires 400.1744).

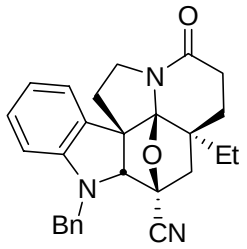


Compound 56b. A solution of **56a** (4.6 mg, 0.012 mmol) in 5.0 mL of anhydrous, degassed 1,3,5-trisopropylbenzene (TIPB) was warmed under Ar at 230 °C for 12 h. The cooled reaction mixture was loaded directly onto SiO_2 equilibrated in hexanes. The TIPB was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was concentrated and the residue was purified by PTLC (SiO_2, 40% EtOAc–hexanes) to yield **56b** (1.1 mg, 0.0032 mmol, 26%) as a white solid: ^{1}H NMR (C_6D_6, 600 MHz) δ 6.98 (t, *J* = 7.7 Hz, 1H), 6.51 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 7.0 Hz, 1H), 6.05 (d, *J* = 7.9 Hz, 1H), 3.82–3.77 (m, 2H), 3.75 (s, 1H), 2.35 (s, 3H), 2.15 (dd, *J* = 5.3, 18.4 Hz, 1H), 1.98–1.84 (m, 2H), 1.89 (d, *J* = 12.3 Hz, 1H), 1.79 (ddd, *J* = 13.6, 13.6, 5.3 Hz, 1H), 1.56 (ddd, *J* = 12.7, 7.0, 2.0 Hz, 1H), 1.40 (d, *J* = 12.3 Hz, 1H), 1.08 (dd, *J* = 13.6, 5.7 Hz, 1H), 0.61 (m, 1H), 0.14 (t, *J* = 6.6 Hz, 3H), 0.19–0.13 (m, 1H); IR (film) 2184, 1716, 1663, 1589, 1463, 1356, 1143 cm^{-1}; MALDIFTMS (DHB) *m/z* 350.1867 ($C_{21}H_{23}N_3O_2$ + H^+ requires 350.1863).

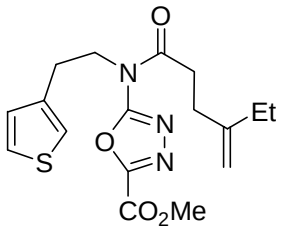


***N*-[2-(1-Benzyl-1*H*-indol-3-yl)ethyl]-*N*-(5-cyano-1,3,4-oxadiazol-2-yl)-4-methylenehexanamide (57a).** DMAP (150 mg, 1.23 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (0.12 mL, 1.2 mmol), EDCI (230 mg, 1.20 mmol) and **S40** (140 mg, 0.41 mmol) in CH_2Cl_2 (3 mL) under Ar at 0 °C. The reaction mixture was allowed to warm to room temperature. After being stirred for 5 h, the reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **57a** (92 mg, 0.20 mmol, 53%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.59 (m, 1H), 7.31–7.23 (m, 5H), 7.18 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.13 (dt, *J* = 1.2, 7.2 Hz, 1H), 6.87 (s, 1H), 5.21 (s, 2H), 4.75–4.74 (m, 1H), 4.66–4.65 (m, 1H), 4.25–4.22 (m, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.91–2.88 (m, 2H), 2.36 (t, *J* = 8.0 Hz, 2H), 2.01 (q, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 162.3, 149.5, 138.5, 137.4, 136.8, 129.0 (2C), 128.0, 127.6, 127.1 (2C), 127.0, 122.5, 119.8, 118.9, 110.5, 110.1, 108.7, 105.8, 50.1, 48.2, 35.2, 31.0, 29.2, 24.5, 12.5; IR (film) ν_{max} 2958, 2333, 1710, 1694,

1568, 1467, 1403, 1170 cm^{-1}; MALDIFTMS (DHB) *m/z* 476.2068 ($C_{27}H_{27}N_5O_2$ + Na^+ requires 476.2057).

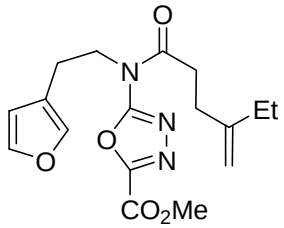


Compound 57b. A solution of **57a** (29 mg, 0.064 mmol) in 32 mL of anhydrous, degassed 1,3,5-trisopropylbenzene (TIPB) was placed in a capped, silated tube under Ar and warmed at 180 °C for 7 d (other times examined = 15–80 h). The cooled reaction mixture was loaded onto SiO_2 equilibrated in hexanes. The TIPB was eluted with distilled hexanes and the column was flushed with EtOAc. The EtOAc was evaporated and the residue was purified by PTLC (SiO_2, 40% EtOAc–hexanes) to yield **57b** (6 mg, 0.014 mmol, 15%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.19 (m, 5H), 7.15–7.11 (m, 1H), 6.82 (dd, *J* = 0.8, 7.2 Hz, 1H), 6.67–6.61 (m, 2H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 16.0 Hz, 1H), 4.29 (s, 1H), 3.96–3.83 (m, 2H), 2.28–2.04 (m, 6H), 1.79 (d, *J* = 12.4 Hz, 1H), 1.72–1.65 (m, 1H), 0.88–0.80 (m, 1H), 0.54 (t, *J* = 7.2 Hz, 3H), 0.32–0.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 150.9, 134.7, 130.0, 129.1 (2C), 128.3 (2C), 128.1, 124.1, 119.2, 117.8, 108.4, 106.5, 82.3, 74.6, 64.5, 58.4, 47.1, 43.9, 40.8, 40.0, 37.2, 29.3, 28.1, 22.8, 9.9; IR (film) ν_{max} 2911, 2348, 1668, 1642, 1601, 1484, 1448, 1392 cm^{-1}; MALDIFTMS (DHB) *m/z* 426.2175 ($C_{27}H_{27}N_3O_2$ + H^+ requires 426.2176).

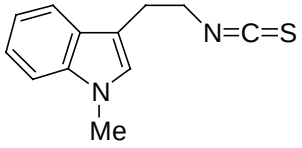


Methyl 5-{-*N*-[2-(Thiophen-3-yl)ethyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (58, X = S). DMAP (0.29 g, 2.37 mmol) was added to a solution of 4-ethyl-4-pentenoic acid[S6] (0.30 g, 2.37 mmol), methyl 5-[2-(thiophen-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate (0.24 g, 0.95 mmol), and EDCI (0.45 g, 2.37 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 18 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 20% EtOAc–hexanes) providing **58** (X = S) (0.29 g, 0.81 mmol, 85%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.21 (m, 1H), 7.00 (br s, 1H), 6.94 (d, *J* = 4.9 Hz, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 4.20 (t, *J* = 6.5 Hz, 2H), 4.04 (s, 3H), 3.00 (t, *J* = 7.4 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 161.8, 154.0, 153.5, 149.2, 137.4, 128.0, 125.8, 122.0, 108.3, 53.6, 47.5, 34.6, 30.7, 28.8, 28.7, 12.1;

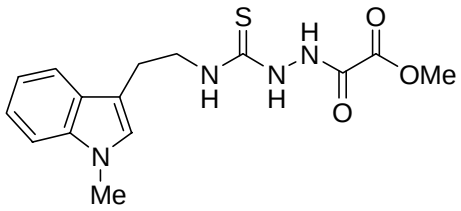
IR (film) ν_{max} 2964, 1749, 1708, 1647, 1567, 1442, 1409 cm^{-1}; HRESI-TOF *m/z* 364.1316 ($C_{17}H_{21}N_3O_4S + H^+$ requires 364.1325).



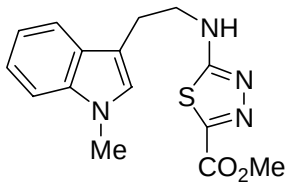
Methyl 5-{*N*-[2-(Furan-3-yl)ethyl]-4-methylenehexanamido}-1,3,4-oxadiazole-2-carboxylate (58, X = O). DMAP (0.17 g, 1.38 mmol) was added to a solution of 4-ethyl-4-pentenoic acid[S6] (0.18 g, 1.38 mmol), methyl 5-[2-(furan-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxylate (0.13 g, 0.55 mmol), and EDCI (0.27 g, 1.38 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The reaction mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 30% EtOAc–hexanes) providing **58** (X = O) (0.11 g, 0.31 mmol, 56%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1H), 7.24 (s, 1H), 6.29 (s, 1H), 4.76 (s, 1H), 4.69 (s, 1H), 4.15 (t, *J* = 7.4 Hz, 2H), 4.05 (s, 3H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.04 (q, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 161.9, 154.2, 153.6, 149.3, 143.2, 140.0, 120.3, 110.8, 108.4, 53.8, 47.3, 34.7, 30.8, 29.0, 23.7, 12.3; IR (film) ν_{max} 2962, 1749, 1706, 1566, 1441, 1408 cm^{-1}; HRESI-TOF *m/z* 348.1559 ($C_{17}H_{21}N_3O_5 + H^+$ requires 348.1554).



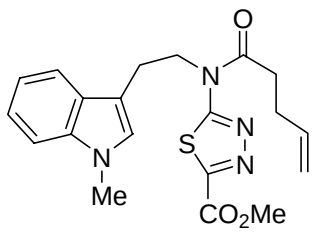
3-(2-Isothiocyanatoethyl)-1-methylindole (S43).[S12] A solution of CS_2 (0.7 mL, 11.6 mmol) in pyridine (0.3 mL) under Ar at –10 °C was treated with Et_3N (190 μL, 1.38 mmol). A solution of N^1-methyl tryptamine (241 mg, 1.38 mmol) in pyridine (0.7 mL) was added dropwise to the reaction over 30 min and the mixture was stirred at –10 °C for 1 h. A solution of DCC (285 mg, 1.38 mmol) in pyridine (0.7 mL) was added dropwise over 5 min and stirring was continued at –10 °C for 1 h, then warmed to 25 °C for 1 h. The reaction mixture was concentrated to dryness in vacuo, dissolved in Et_2O, and the precipitated thiourea was removed by filtration. The filtrate was concentrated and chromatography (SiO_2, 25% EtOAc–CH_2Cl_2) gave **S43** (154 mg, 0.71 mmol, 51%) as a white solid: mp 34–35 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.37 (ddd, *J* = 0.9, 8.2, 8.2 Hz, 1H), 7.27 (ddd, *J* = 1.2, 7.9, 7.9 Hz, 1H), 7.02 (s, 1H), 3.81 (s, 3H), 3.79 (t, *J* = 6.7 Hz, 2H), 3.21 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 130.3, 127.7, 127.2, 121.8, 119.1, 118.4, 109.6, 109.5, 45.8, 32.7, 26.4; IR (film) ν_{max} 2919, 2179, 2097, 1472, 1373, 1337, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 217.0794 ($C_{12}H_{12}N_2S + H^+$ requires 217.0794).



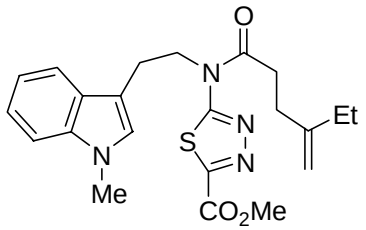
1-Methoxalyl-4-[(1-methyl-1*H*-indol-3-yl)ethyl]thiosemicarbazide (S44). A solution of **S43** (155 mg, 0.72 mmol) in MeOH (5 mL) under Ar at 25 ºC was treated with methyl oxalylhydrazide[S1] (85 mg, 0.72 mmol). The reaction mixture was warmed at 60 °C for 42 h before the solvent was removed in vacuo. Chromatography (SiO_2, 0.6% MeOH–6% acetone–$CHCl_3$) afforded **S44** (87 mg, 0.26 mmol, 36%) as a light yellow solid: mp 145–147 °C (EtOAc–hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.34 (br s, 1H), 9.58 (br s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.90 (s, 1H), 3.90 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.08 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 158.5, 151.4 (br), 137.2, 127.9, 127.2, 121.9, 119.1, 118.9, 111.1, 109.5, 54.0, 45.6, 32.8, 24.6; IR (film) ν_{max} 3302, 3052, 2934, 1759, 1714, 1552, 1472, 1161 cm^{-1}; MALDIFTMS (DHB) *m/z* 357.0988 ($C_{15}H_{18}N_4O_3S$ + Na^+ requires 357.0992).



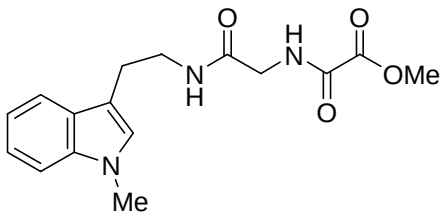
Methyl 5-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]amino-1,3,4-thiadiazole-2-carboxylate (S45). Substrate **S44** (90.2 mg, 0.27 mmol) was dissolved in conc. H_2SO_4 (0.8 mL)[S9] at 0 ºC, then warmed to 25 °C for 2 h. The reaction mixture was slowly pipetted into 50 g ice water, and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc–CH_2Cl_2) afforded **S45** (43.3 mg, 0.14 mmol, 51%) as a white solid: mp 146–148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.94 (s, 1H), 6.69 (br s, 1H), 3.97 (s, 3H), 3.75 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.16 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (10% CD_3OD–$CDCl_3$, 100 MHz) δ 159.6, 137.1, 127.5, 127.3, 127.2, 121.9, 119.1, 118.5, 110.3, 109.5, 53.3, 47.8, 32.6, 24.5; IR (film) ν_{max} 3272, 1739, 1713, 1544, 1446, 1318, 1277, 1097 cm^{-1}; MALDIFTMS (DHB) *m/z* 339.0883 ($C_{15}H_{16}N_4O_2S$ + Na^+ requires 339.0886).



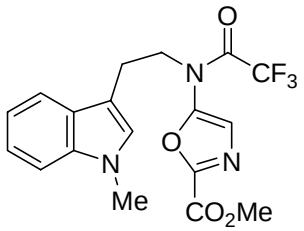
Methyl 5-{Pent-4-enoyl-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-thiadiazole-2-carboxylate (59a). A stirring solution of thiadiazole **S45** (48 mg, 0.15 mmol) and EDCI (115 mg, 0.60 mmol) in CH_2Cl_2 (2 mL) under Ar at 25 °C was treated with 4-pentenoic acid (31 μL, 0.30 mmol) and DMAP (37 mg, 0.30 mmol). The mixture was stirred at 25 °C for 16 h before the reaction was concentrated. Chromatography (SiO_2, 5% EtOAc–CH_2Cl_2) afforded **59a** (59 mg, 0.15 mmol, 99%) as a white solid: mp 119–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (ddd, *J* = 0.9, 7.5, 7.5 Hz, 1H), 7.14 (ddd, *J* = 0.9, 7.2, 7.2 Hz, 1H), 6.82 (s, 1H), 5.58 (m, 1H), 4.93 (d, *J* = 12.3 Hz, 1H), 4.89 (d, *J* = 17.5 Hz, 1H), 4.53 (t, *J* = 7.0 Hz, 2H), 4.04 (s, 3H), 3.73 (s, 3H), 3.28 (t, *J* = 7.4 Hz, 2H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.24 (q, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 162.4, 160.4, 156.0, 137.2, 136.2, 127.7, 127.4, 122.2, 119.6, 118.8, 116.1, 110.2, 109.6, 53.4, 49.0, 33.0, 32.8, 28.3, 23.9; IR (film) ν_{max} 2954, 2923, 2851, 1744, 1718, 1677, 1456, 1421, 1272 cm^{-1}; MALDIFTMS (DHB) *m/z* 421.1301 ($C_{20}H_{22}N_4O_3S$ + Na^+ requires 421.1305).



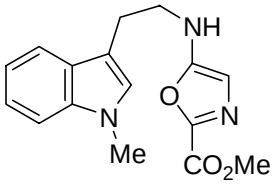
Methyl 5-{(4-Ethylpent-4-enoyl)-[2-(1-methyl-1*H*-indol-3-yl)ethyl]amino}-1,3,4-thiadiazole-2-carboxylate (60a). A stirring solution of **S45** (87 mg, 0.28 mmol), 4-ethyl-4-pentenoic acid[S6] (35 mg, 0.28 mmol), and EDCI (105 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) was treated with DMAP (34 mg, 0.28 mmol). The mixture was stirred at 25 °C for 16 h before the reaction was concentrated. Chromatography (SiO_2, 2% MeOH–$CHCl_3$) afforded **60a** (87 mg, 0.20 mmol, 75%) as a white solid: mp 109–111 °C (EtOAc–hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.82 (s, 1H), 4.68 (s, 1H), 4.56 (t, *J* = 7.0 Hz, 2H), 4.45 (s, 1H), 4.05 (s, 3H), 3.73 (s, 3H), 3.31 (t, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.21 (t, *J* = 8.2 Hz, 2H), 1.84 (q, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 162.4, 160.4, 156.0, 149.3, 137.2, 127.7, 127.4, 122.2, 119.6, 118.8, 110.2, 109.6, 108.4, 53.5, 49.1, 32.8, 32.3, 30.5, 29.0, 23.9, 12.4; IR (film) ν_{max} 2962, 1746, 1721, 1673, 1455, 1422, 1269 cm^{-1}; MALDIFTMS (DHB) *m/z* 427.1799 ($C_{22}H_{26}N_4O_3S$ + H^+ requires 427.1798).



Methyl 2-{2-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-2-oxoethylamino}-2-oxoacetate (S46). DMAP (390 mg, 3.2 mmol) was added to a solution of 2-(2-methoxy-2-oxoacetamido)acetic acid (1.18 g, 7.3 mmol), EDCI (4.0 g, 20 mmol) and N^1-methyl tryptamine (1180 mg, 6.8 mmol) in CH_2Cl_2 (14 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, extracted with EtOAc and dried over Na_2SO_4. Flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% CH_2Cl_2) gave **S46** (1.43 g, 4.5 mmol, 65%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (t, *J* = 4.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.18 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.06 (dt, *J* = 0.8, 8.0 Hz, 1H), 6.84 (s, 1H), 6.27 (t, *J* = 4.2 Hz, 1H), 3.85 (s, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.53 (q, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4, 160.4, 156.8, 137.3, 127.8, 127.2, 122.0, 119.2, 118.9, 111.2, 109.6, 53.9, 43.2, 40.4, 32.8, 25.2; IR (film) ν_{max} 3342, 3060, 2931, 1749, 1696, 1660, 1537, 1472, 1437, 1373, 1319, 1220, 1014, 744 cm^{-1}; HRESI-TOF *m/z* 318.1458 ($C_{16}H_{19}N_3O_4 + H^+$ requires 318.1448).

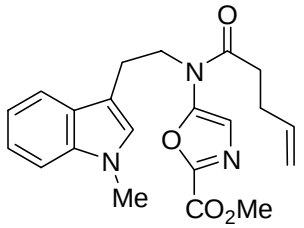


Methyl 5-{2,2,2-Trifluoro-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]acetamido}oxazole-2-carboxylate (S47). Trifluroacetic anhydride (0.7 mL, 5.0 mmol) was added dropwise to a solution of **S46** (500 mg, 1.58 mmol) in anhydrous 1,4-dioxane (10 mL) and pyridine (0.7 mL, 8.8 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 25–33% EtOAc–hexane gradient elution) gave **S47** (256 mg, 0.65 mmol, 41%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 6.8 Hz, 1H), 6.84 (s, 1H), 6.68 (s, 1H), 4.02–3.98 (m, 5H), 3.72 (s, 3H), 3.13–3.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 150.5, 146.0, 137.2, 127.7, 127.2, 125.0, 122.2, 119.4, 118.7, 117.1, 114.3, 109.7, 109.6, 53.7, 51.7, 32.9, 23.4; IR (film) ν_{max} 3072, 1684, 1542, 1490, 1190, 745 cm^{-1}; HRESI-TOF 396.1174 *m/z* ($C_{18}H_{16}F_3N_3O_4 + H^+$ requires 396.1166).

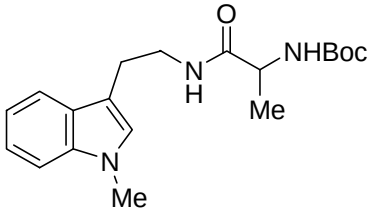


Methyl 5-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]oxazole-2-carboxylate (S48). A solution of **S47** (150 mg, 0.38 mmol) in 2 mL of MeOH was warmed at reflux for 8 h. The MeOH was evaporated under reduced pressure. Flash chromatography (SiO_2, 33%

EtOAc–hexanes) gave **S48** (92 mg, 0.31 mmol, 82%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.29 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.24–7.19 (m, 1H), 7.10 (dt, *J* = 0.8, 8.0 Hz, 1H), 6.87 (s, 1H), 6.11 (s, 1H), 4.49 (t, *J* = 5.6 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.43 (q, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 156.2, 142.9, 137.4, 127.6, 127.4, 122.2, 119.4, 118.8, 110.4, 109.7, 102.8, 52.8, 44.3, 32.9, 25.1; IR (film) ν_{max} 3342, 2931, 1676, 1613, 1531, 1466, 1373, 1266, 738 cm^{-1}; HRESI-TOF *m/z* 300.1357 ($C_{16}H_{17}N_3O_3$ + H^+ requires 300.1343).

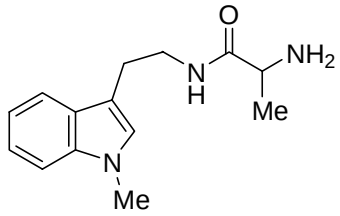


Methyl 5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}oxazole-2-carboxylate (61a). DMAP (95 mg, 0.78 mmol) was added to a solution of 4-pentenoic acid (0.1 mL, 1.0 mmol), EDCI (150 mg, 0.78 mmol) and **S48** (60 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **61a** (42 mg, 0.11 mmol, 54%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (br s, 1H), 7.26–7.23 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.06 (br, 1H), 6.82 (s, 1H), 6.60 (br s, 1H), 5.71 (br s, 1H), 5.00–4.93 (m, 2H), 3.97 (s, 3H), 3.92 (br s, 2H), 3.70 (s, 3H), 3.06–3.03 (m, 2H), 2.40–2.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 155.8, 150.3, 137.1, 136.8, 136.6, 127.9, 127.1, 122.9, 122.0, 119.2, 118.9, 115.9, 110.7, 109.5, 53.5, 49.9, 33.7, 32.8, 29.0, 24.2; IR (film) ν_{max} 2955, 1719, 1654, 1607, 1467, 1349, 1267, 1184, 726 cm^{-1}; HRESI-TOF *m/z* 382.1767 ($C_{21}H_{23}N_3O_4$ + H^+ requires 382.1761).

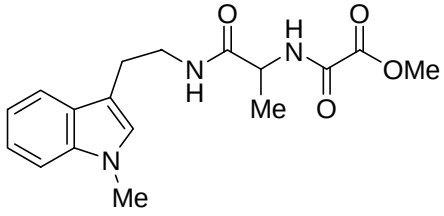


***tert*-Butyl 1-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-1-oxopropan-2-yl-carbamate (S49).** DMAP (350 mg, 2.95 mmol) was added to a solution of *N*-Boc alanine (1.96 g, 10.0 mmol), EDCI (5.75 g, 30.0 mmol) and *N*^{1}-methyl tryptamine (1.74 g, 10.0 mmol) in CH_2Cl_2 (100 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 3 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 50–75% EtOAc–hexanes gradient elution) gave **S49** (2.62 g, 7.6 mmol, 76%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 1.2, 6.8 Hz, 1H), 7.11–7.07 (m, 1H), 6.86 (s, 1H), 6.16 (br s, 1H), 5.00 (br s, 1H), 4.06 (br s, 1H), 3.72 (s, 3H), 3.54 (q, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 1.38 (s,

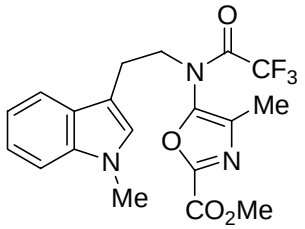
9H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 155.6, 137.3, 127.9, 127.1, 122.0, 119.1, 119.0, 111.5, 109.5, 50.4, 40.1, 32.9, 28.5, 25.4, 18.9; IR (film) ν_{max} 3307, 2966, 2919, 1698, 1531, 1372, 1326, 1249, 1161, 1061, 750 cm^{-1}; HRESI-TOF *m/z* 368.1945 ($C_{19}H_{27}N_3O_3$ + Na^+ requires 368.1945).



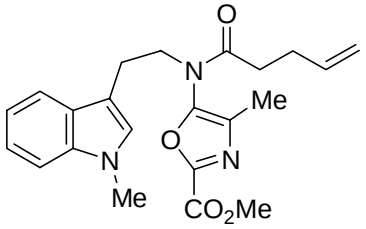
2-Amino-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]propanamide (S50). S49 (2.62 g, 7.1 mmol) was dissolved in 4 M HCl in EtOAc at 0 °C. The ice bath was removed after the reaction mixture was stirred for 30 min. The solvent was removed under a stream of N_2. The residue was dried under reduced pressure to give **S50** (1.86 g, quant.) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 1.2, 6.8 Hz, 1H), 7.11–7.07 (m, 1H), 6.86 (s, 1H), 3.72 (s, 3H), 3.57–3.52 (m, 2H), 3.43 (q, *J* = 6.8 Hz, 1H), 2.94 (t, *J* = 6.8 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.6, 137.3, 128.1, 126.9, 121.9, 119.1, 119.0, 111.9, 109.4, 51.0, 40.0, 32.8, 25.5, 21.9; IR (film) ν_{max} 3426, 1644, 1532, 1326, 1261, 1132, 750 cm^{-1}; MALDIFTMS (DHB) *m/z* 246.1602 ($C_{14}H_{19}N_3O$ + H^+ requires 246.1601).



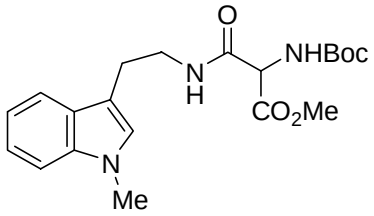
Methyl 2-{1-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-1-oxopropan-2-ylamino}-2-oxoacetate (S51). Methyl oxalyl chloride (0.80 mL, 8.7 mmol) was added dropwise to a solution of **S50** (1.86 g, 7.6 mmol) in CH_2Cl_2 (10 mL) and Et_3N (2 mL, 15.2 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature before being washed with saturated aqueous $NaHCO_3$, extracted with EtOAc and dried over Na_2SO_4. Flash chromatography (SiO_2, 2.5% MeOH–22.5% acetone–75% CH_2Cl_2) gave **S51** (1.68 g, 5.1 mmol, 73%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.54 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.28 (dt, *J* = 0.8, 8.4 Hz, 1H), 7.24–7.19 (m, 1H), 7.12–7.07 (m, 1H), 6.85 (s, 1H), 5.81 (br s, 1H), 4.35–4.30 (m, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.60–3.56 (m, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 160.5, 156.1, 137.3, 127.9, 127.1, 122.0, 119.2, 118.9, 111.3, 109.6, 53.8, 49.6, 40.3, 32.8, 25.2, 18.6; IR (film) ν_{max} 3377, 1748, 1660, 1531, 1465, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 332.1600 ($C_{17}H_{21}N_3O_4$ + H^+ requires 332.1605).



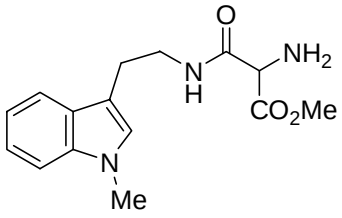
Methyl 4-Methyl-5-{2,2,2-trifluoro-*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]acetamido}oxazole-2-carboxylate (S52). Trifluoroacetic anhydride (2.6 mL, 18.5 mmol) was added dropwise to a solution of **S51** (1.68 g, 5.5 mmol) in anhydrous 1,4-dioxane (20 mL) and pyridine (2.6 mL, 32.9 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **S52** (1.92 g, 4.7 mmol, 85%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.27–7.17 (m, 1H), 7.20 (dt, *J* = 0.8, 6.8 Hz, 1H), 7.07 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.85 (s, 1H), 4.00–3.96 (m, 5H), 3.70 (s, 3H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 149.6, 141.6, 137.3, 135.1, 127.6, 127.1, 122.1, 119.4, 118.7, 117.1, 114.2, 109.6, 53.7, 51.5, 32.8, 23.7, 11.2; IR (film) ν_{max} 1672, 1519, 1472, 1390, 1202, 1138, 738 cm^{-1}; MALDIFTMS (DHB) *m/z* 410.1317 ($C_{19}H_{18}F_3N_3O_4$ + H^+ requires 410.1322).



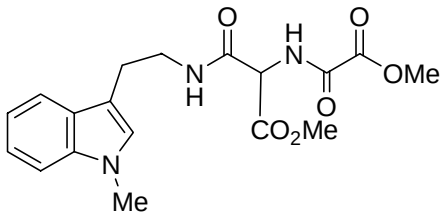
Methyl 4-Methyl-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}oxazole-2-carboxylate (62a). A refluxing solution of **S52** (205 mg, 0.50 mmol) in 2 mL of MeOH was treated with 1 drop of Et_3N. After TLC showed the disappearance of starting material, the solvents was quickly removed under reduced pressure. The crude amine was dissolved in 3 mL CH_2Cl_2 and 4-pentenoic acid (0.1 mL, 1.0 mmol), EDCI (192 mg, 1.0 mmol) and DMAP (122 mg, 1.0 mmol) were added under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **62a** as an oil (35 mg, 0.18 mmol, 17%, 2 steps, unoptimized): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.21–7.17 (m, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 5.73–5.63 (m, 1H), 4.96–4.84 (m, 2H), 3.94 (s, 3H), 3.87 (t, *J* = 8.0 Hz, 2H), 3.66 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 2.30 (q, *J* = 6.4 Hz, 2H), 2.10 (t, *J* = 7.6 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 155.9, 145.8, 141.4, 137.2, 136.8, 132.7, 127.7, 126.9, 121.9, 119.1, 119.0, 116.0, 110.7, 109.4, 53.6, 49.0, 33.4, 32.8, 28.9, 24.4, 11.3; IR (film) ν_{max} 2942, 1755, 1660, 1555, 1455, 1408, 1343, 1249, 1131, 1102, 750 cm^{-1}; MALDIFTMS (DHB) *m/z* 396.1913 ($C_{22}H_{25}N_3O_4$ + H^+ requires 196.1918).



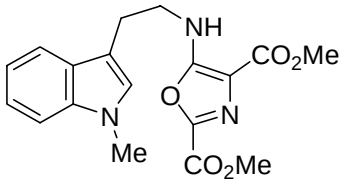
Methyl 2-(*tert*-Butoxycarbonylamino)-3-[2-(1-methyl-1*H*-indol-3-yl)ethylamino]-3-oxopropanoate (S53). DMAP (1.55 g, 12.7 mmol) was added to a solution of 2-(*tert*-butoxycarbonylamino)-3-methoxy-3-oxopropanoic acid (1.50 g, 6.8 mmol), EDCI (2.44 g, 12.7 mmol) and N^1-methyl tryptamine (740 mg, 4.25 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, extracted with EtOAc and dried over Na_2SO_4. Flash chromatography (SiO_2, 50–75% EtOAc–hexanes gradient elution) gave **S53** (1.12 g, 2.88 mmol, 70%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.09 (dt, *J* = 0.8, 7.2 Hz, 1H), 6.85 (s, 1H), 6.37 (br s, 1H), 5.75 (d, *J* = 5.6 Hz, 1H), 4.74 (d, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.56 (q, *J* = 6.8 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 164.8, 155.4, 137.3, 127.8, 127.1, 122.6, 119.2, 118.9, 111.0, 109.5, 80.8, 58.1, 53.2, 40.6, 32.9, 28.4, 25.1; IR (film) ν_{max} 3392, 1724, 1502, 1367, 1249, 1161, 738 cm^{-1}; HRESI-TOF *m/z* 412.1849 ($C_{20}H_{27}N_3O_5$ + Na^+ requires 412.1843).



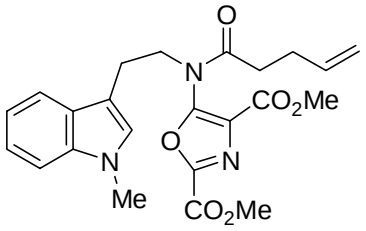
Methyl 2-Amino-3-[2-(1-methyl-1*H*-indol-3-yl)ethylamino]-3-oxopropanoate (S54). **S53** (502 mg, 1.29 mmol) was dissolved in 4 M HCl in EtOAc at 0 °C. The ice bath was removed after the reaction mixture was stirred for 30 min. The solvent was removed under a stream of N_2 and the residue was further dried under reduced pressure to give **S54** as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.23–7.08 (m, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.81 (s, 1H), 5.34 (br s, 1H), 3.90 (br s, 2H), 3.54 (s, 3H), 3.52 (s, 3H), 3.44–3.41 (m, 2H), 2.90–2.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 162.4, 137.1, 127.9, 127.5, 121.6, 119.0, 118.9, 111.1, 109.3, 56.2, 54.2, 41.1, 32.6, 24.7; IR (film) ν_{max} 3401, 1655, 1543, 748 cm^{-1}; HRESI-TOF *m/z* 290.1513 ($C_{15}H_{19}N_3O_3$ + H^+ requires 290.1499).



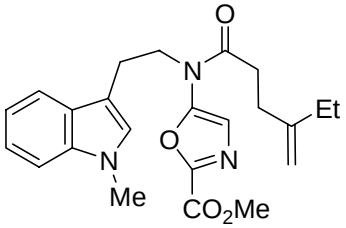
Methyl 2-(2-Methoxy-2-oxoacetamido)-3-[2-(1-methyl-1*H*-indol-3-yl)ethylamino]-3-oxopropanoate (S55). Methyl oxalyl chloride (0.40 mL, 4.3 mmol) was added dropwise to a solution of the crude amine **S54** in CH_2Cl_2 (10 mL) and Et_3N (1.0 mL, 7.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h before being concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **S55** (160 mg, 0.43 mmol, 33%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, *J* = 6.8 Hz, 1H), 7.55–7.53 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.23–7.19 (m, 1H), 7.09 (dt, *J* = 0.8, 6.8 Hz, 1H), 6.86 (s, 1H), 6.42 (br m, 1H), 4.93 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.64 (s, 3H), 3.58 (q, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 163.0, 159.9, 156.3, 137.3, 127.7, 127.2, 122.1, 119.3, 118.8, 110.8, 109.6, 56.9, 54.0, 53.6, 40.9, 32.9, 25.0; IR (film) ν_{max} 3366, 2919, 1749, 1684, 1531, 1466, 1361, 1273, 744 cm^{-1}; HRESI-TOF 376.1508 ($C_{18}H_{21}N_3O_6$ + H^+ requires 376.1503).



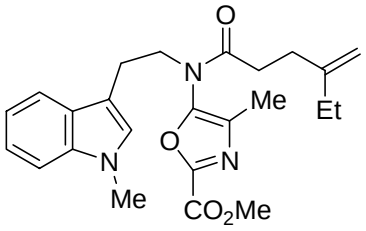
Dimethyl 5-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]oxazole-2,4-dicarboxylate (S56). Trifluoroacetic anhydride (0.10 mL, 0.71 mmol) was added dropwise to a solution of **S55** (92 mg, 0.245 mmol) in anhydrous 1,4-dioxane (2.0 mL) and pyridine (0.1 mL, 1.27 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) gave the trifluoroacetamide of **S56**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.19–7.16 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.82 (s, 3H), 3.65 (s, 3H), 3.08 (t, *J* = 7.2 Hz, 2H). A solution of this product in 2 mL MeOH was warmed at reflux for 8 h before the MeOH was evaporated under reduced pressure. Flash chromatography (SiO_2, 60% EtOAc–hexanes) gave **S56** (48 mg, 0.13 mmol, 55%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.24–7.20 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.54 (m, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.76–3.74 (m, 5H), 3.08 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 161.2, 155.9, 140.4, 137.4, 127.6, 127.3, 122.1, 119.3, 118.8, 110.3, 109.6, 105.6, 53.0, 51.6, 43.9, 32.9, 26.0; IR (film) ν_{max} 3448, 2990, 1684, 1631, 1472, 1407, 1202, 1138, 726 cm^{-1}; HRESI-TOF *m/z* 358.1404 ($C_{18}H_{19}N_3O_5$ + H^+ requires 358.1395).



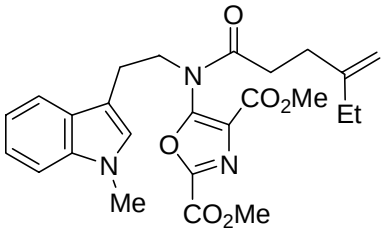
Dimethyl 5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}oxazole-2,4-dicarboxylate (63a). DMAP (18 mg, 0.15 mmol) was added to a solution of 4-pentenoic acid (0.07 mL, 0.7 mmol), EDCI (86 mg, 0.45 mmol) and **S56** (52 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 10 h before being concentrated. Flash chromatography (SiO_2, 30% EtOAc–hexanes) gave **63a** (50 mg, 0.11 mmol, 78%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 5.70–5.60 (m, 1H), 4.93–4.84 (m, 2H), 4.06 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 3.62 (s, 3H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.31–2.26 (m, 2H), 2.20–2.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 160.1, 155.2, 153.4, 147.9, 137.1, 136.7, 127.30, 127.27, 125.1, 121.9, 119.1, 118.9, 115.9, 110.4, 53.7, 52.7, 49.3, 33.8, 32.7, 29.0, 24.8; IR (film) ν_{max} 2943, 1749, 1655, 1555, 1437, 1355, 1255, 1138, 1073, 726 cm^{-1}; HRESI-TOF *m/z* 440.1818 ($C_{23}H_{25}N_3O_6$ + H^+ requires 440.1813).



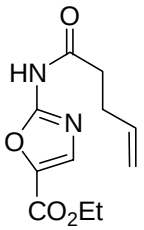
Methyl 5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}oxazole-2-carboxylate (64a). DMAP (95 mg, 0.78 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (0.1 mL, 1.0 mmol), EDCI (150 mg, 0.78 mmol) and **S48** (60 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **64a** (45 mg, 0.11 mmol, 54%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, *J* = 6.4 Hz, 1H), 7.26–7.22 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08–7.06 (m, 1H), 6.82 (s, 1H), 6.60 (br s, 1H), 4.67 (br s, 1H), 4.55 (br s, 1H), 3.97 (s, 3H), 3.93–3.90 (m, 2H), 3.70 (s, 3H), 3.04 (br s, 2H), 2.29 (br s, 4H), 1.92 (br s, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 155.8, 150.4, 149.8, 137.1, 127.9, 127.1, 122.9, 122.0, 119.2, 118.9, 110.7, 109.5, 108.4, 53.5, 49.9, 32.8 (2C), 31.2, 29.1, 24.2, 12.4; IR (film) ν_{max} 2943, 1743, 1689, 1643, 1607, 1519, 1469, 1372, 1272, 1202, 1149, 744 cm^{-1}; HRESI-TOF *m/z* 410.2079 ($C_{23}H_{27}N_3O_4$ + H^+ requires 410.2074).



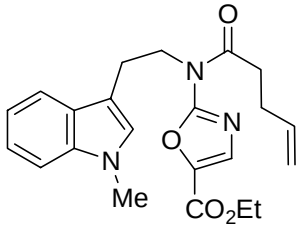
Methyl 4-Methyl-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}oxazole-2-carboxylate (65a). A refluxing solution of **S52** (205 mg, 0.50 mmol) in 2 mL of MeOH was treated with 1 drop of Et_3N. After TLC showed the disappearance of starting material, the solvents was quickly evaporated under reduced pressure. The crude amine was dissolved in 3 mL of CH_2Cl_2 and 4-ethyl-4-pentenoic acid (0.1 mL, 1.0 mmol), EDCI (192 mg, 1.0 mmol) and DMAP (122 mg, 1.0 mmol) were added under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduce pressure. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **65a** (32 mg, 0.075 mmol, 15%, 2 steps, unoptimized) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.25–7.21 (m, 1H), 7.17 (td, *J* = 1.2, 8.0 Hz, 1H), 7.06–7.02 (m, 1H), 6.82 (s, 1H), 4.67 (s, 1H), 4.55 (s, 1H), 3.97 (s, 3H), 3.93–3.89 (m, 2H), 3.69 (s, 3H), 2.99 (t, *J* = 8.0 Hz, 2H), 2.32 (t, *J* = 8.0 Hz, 2H), 2.20–2.17 (m, 2H), 2.02 (s, 3H), 1.93 (q, *J* = 7.6 Hz, 2H), 0.96 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 155.9, 149.9, 148.9, 145.9, 137.2, 132.7, 127.7, 127.0, 121.9, 119.1, 119.0, 110.7, 109.4, 108.3, 53.6, 49.1, 32.8, 32.6, 31.1, 29.1, 24.5, 12.4, 11.3; IR (film) ν_{max} 2943, 1743, 1678, 1631, 1531, 1449, 1378, 1331, 1208, 1170, 738 cm^{-1}; HRESI-TOF *m/z* 424.2238 ($C_{24}H_{29}N_3O_4$ + H^+ requires 424.2231).



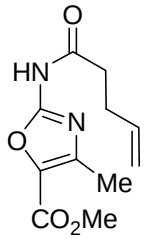
Dimethyl 5-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}oxazole-2,4-dicarboxylate (66a). DMAP (18 mg, 0.15 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (0.07 mL, 0.7 mmol), EDCI (86 mg, 0.45 mmol) and **S56** (52 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 10 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 30% EtOAc–hexanes) gave **66a** (48 mg, 0.10 mmol, 71%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10 (td, *J* = 0.8, 8.0 Hz, 1H), 6.99–6.95 (m, 1H), 6.72 (s, 1H), 4.62 (s, 1H), 4.49 (s, 1H), 4.06 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 3.62 (s, 3H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.28–2.20 (m, 4H), 1.86 (q, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 158.9, 154.0, 152.2, 148.5, 146.6, 135.9, 126.1, 123.8, 120.6, 117.9, 117.7, 109.3, 108.2, 107.1, 52.5, 51.5, 48.1, 31.8, 31.5, 29.9, 27.8, 23.6, 11.2; IR (film) ν_{max} 2955, 1749, 1690, 1608, 1549, 1437, 1331, 1214, 1149, 1067, 756 cm^{-1}; HRESI-TOF *m/z* 468.2133 ($C_{25}H_{29}N_3O_6$ + H^+ requires 468.2123).



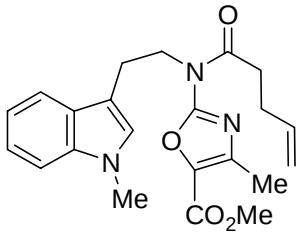
Ethyl 2-(Pent-4-enamido)oxazole-5-carboxylate (S57). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-pentenoic acid (0.20 mL, 1.6 mmol), EDCI (600 mg, 3.0 mmol) and ethyl 2-aminooxazole-5-carboxylate (150 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) gave **S57** (125 mg, 0.53 mmol, 52%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (br s, 1H), 7.53 (d, *J* = 11.6 Hz, 1H), 5.65–5.55 (m, 1H), 4.89–4.80 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.30–2.21 (m, 4H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 164.3, 151.9, 136.1, 134.8, 116.5, 105.6, 62.6, 36.4, 28.5, 14.4; IR (film) ν_{max} 3213, 2955, 1713, 1613, 1549, 1443, 1390, 1349, 1284, 1196, 1138, 1096, 920, 732 cm^{-1}; MALDIFTMS (DHB) *m/z* 239.1027 ($C_{11}H_{14}N_2O_4$ + H^+ requires 239.1026).



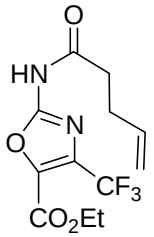
Ethyl 2-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}oxazole-5-carboxylate (67a). A solution of **S57** (45 mg, 0.18 mmol) in 2 mL of 4:1 DMF–THF was treated with Cs_2CO_3 (116 mg, 0.36 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (90 mg, 0.36 mmol) was added in one portion. The reaction mixture was stirred for 15 h before being quenched with the addition of H_2O and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **67a** (12 mg, 0.030 mmol, 17%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (dd, *J* = 2.0, 11.6 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.51–7.42 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.07 (s, 1H), 5.85–5.75 (m, 1H), 5.16–5.09 (m, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 3.48 (s, 3H), 3.29 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.55–1.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 163.1, 152.1, 137.3, 136.2, 133.2, 127.7, 127.3, 122.2, 119.6, 118.7, 116.2, 110.4, 109.7, 106.7, 62.1, 46.1, 35.8, 29.9, 28.4, 25.2, 14.5; IR (film) ν_{max} 2943, 1713, 1684, 1613, 1560, 1484, 1378, 1331, 1243, 1190, 926, 756 cm^{-1}; MALDIFTMS (DHB) *m/z* 396.1921 ($C_{22}H_{25}N_3O_4$ + H^+ requires 396.1918).



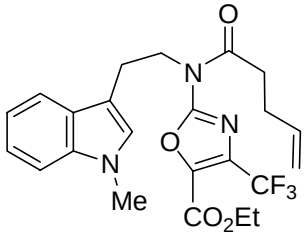
Methyl 4-Methyl-2-(pent-4-enamido)oxazole-5-carboxylate (S58). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-pentenoic acid (0.80 mL, 8.0 mmol), EDCI (1.92 g, 10 mmol) and methyl 2-amino-4-methyloxazole-5-carboxylate (780 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 24 h before being concentrated. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **S58** (925 mg, 3.9 mmol, 78%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.70 (br s, 1H), 5.84–5.75 (m, 1H), 5.03 (dd, *J* = 1.6, 17.2 Hz, 1H), 4.95 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 2.70 (br s, 2H), 2.44–2.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 154.3, 146.9, 136.6, 133.5, 116.1, 52.0, 35.9, 28.7, 13.4; IR (film) ν_{max} 3213, 2966, 1719, 1602, 1549, 1437, 1390, 1349, 1296, 1196, 1132, 1102, 743 cm^{-1}; MALDIFTMS (DHB) *m/z* 239.1029 ($C_{11}H_{14}N_2O_4$ + H^+ requires 239.1026).



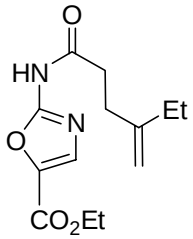
Methyl 4-Methyl-2-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}oxazole-5-carboxylate (68a). A solution of **S58** (786 mg, 3.0 mmol) in 40 mL of 1:1 DMF–THF was treated with Cs_2CO_3 (1.93 g, 6.0 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (952 mg, 4.0 mmol) was added in one portion. The reaction mixture was stirred for 15 h before being quenched with the addition of H_2O, and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **68a** (210 mg, 0.53 mmol, 18%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.25–7.17 (m, 2H), 7.12–7.08 (m, 1H), 6.86 (s, 1H), 5.88–5.78 (m, 1H), 5.04 (dq, *J* = 1.6, 17.2 Hz, 1H), 4.98 (dq, *J* = 1.6, 11.6 Hz, 1H), 4.19–4.15 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.08–3.04 (m, 2H), 2.88 (t, *J* = 11.6 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5, 158.9, 156.7, 147.2, 137.22, 137.17, 134.5, 127.9, 127.4, 121.8, 119.4, 119.1, 115.7, 110.8, 109.3, 52.0, 47.5, 36.0, 32.8, 29.2, 24.5, 13.7; IR (film) ν_{max} 2955, 1713, 1678, 1614, 1555, 1490, 1367, 1326, 1231, 1190, 732 cm^{-1}; MALDIFTMS (DHB) *m/z* 396.1909 ($C_{22}H_{25}N_3O_4$ + H^+ requires 396.1918).



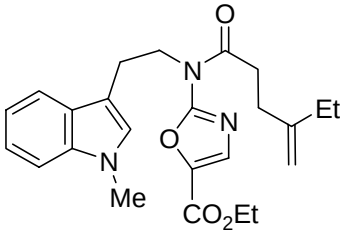
Ethyl 2-(Pent-4-enamido)-4-(trifluoromethyl)oxazole-5-carboxylate (S59). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-pentenoic acid (0.60 mL, 6.0 mmol), EDCI (1.45 g, 6.0 mmol) and ethyl 2-amino-4-(trifluoromethyl)oxazole-5-carboxylate (672 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **S59** (832 mg, 2.7 mmol, 90%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.50 (br s, 1H), 5.85–5.75 (m, 1H), 5.01 (dq, *J* = 1.6, 17.2 Hz, 1H), 4.95 (dd, *J* = 1.2, 9.6 Hz, 1H), 4.32–4.26 (m, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.42 (q, *J* = 6.8 Hz, 2H), 1.27 (td, *J* = 3.2, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 155.9, 154.1, 136.4, 135.8, 120.9, 118.2, 116.0, 62.6, 35.9, 28.5, 13.9; IR (film) ν_{max} 3237, 2966, 1737, 1602, 1548, 1455, 1396, 1319, 1190, 1143, 1037, 761 cm^{-1}; MALDIFTMS (DHB) *m/z* 307.0905 ($C_{12}H_{13}F_3N_2O_4$ + H^+ requires 307.0900).



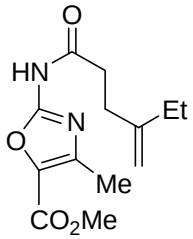
Ethyl 2-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}-4-(trifluoromethyl)oxazole-5-carboxylate (69a). A solution of **S59** (306 mg, 1.0 mmol) in 10 mL of 1:1 DMF–THF was treated with Cs_2CO_3 (415 mg, 1.3 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (300 mg, 1.3 mmol) was added in one portion. The reaction mixture was stirred for 15 h before being quenched with the addition of H_2O and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 17% EtOAc–hexanes) provided **69a** as a colorless oil (56 mg, 0.12 mmol, 12%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.23–7.14 (m, 2H), 7.08 (dt, *J* = 1.2, 6.8 Hz, 1H), 6.83 (s, 1H), 5.85 (m, 1H), 5.06 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.00 (dq, *J* = 1.6, 10.4 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.23 (dt, *J* = 6.0, 7.2 Hz, 2H), 3.68 (s, 3H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.44–2.40 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 156.8, 155.6, 137.1, 136.9, 135.7, 127.7, 127.6, 121.9, 119.2, 119.1, 115.9, 110.3, 109.41, 109.37, 62.5, 47.7, 36.0, 32.7, 29.1, 24.5, 14.2; IR (film) ν_{max} 2978, 1737, 1696, 1614, 1561, 1419, 1302, 1167, 1090, 1026, 926, 743 cm^{-1}; MALDIFTMS (DHB) *m/z* 464.1792 ($C_{23}H_{24}F_3N_3O_4$ + H^+ requires 464.1792).



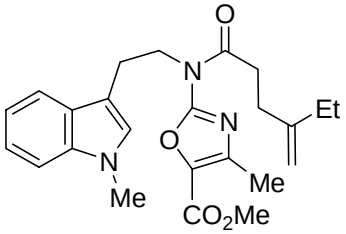
Ethyl 2-(4-Methylenehexanamido)oxazole-5-carboxylate (S60). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (0.2 mL, 1.6 mmol), EDCI (600 mg, 3.0 mmol) and ethyl 2-aminooxazole-5-carboxylate (156 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **S60** (133 mg, 0.50 mmol, 50%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (br s, 1H), 7.53 (d, *J* = 11.6 Hz, 1H), 4.58 (s, 1H), 4.51 (s, 1H), 4.15 (q, *J* = 6.8 Hz, 2H), 2.36–2.32 (m, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.83 (t, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 164.3, 151.7, 149.2, 134.9, 109.0, 105.6, 62.5, 35.8, 30.8, 29.1, 14.4, 12.4; IR (film) ν_{max} 3237, 2955, 1708, 1625, 1472, 1372, 1331, 1232, 1196, 1149, 1102, 897, 756 cm^{-1}; MALDIFTMS (DHB) *m/z* 267.1342 ($C_{13}H_{18}N_2O_4$ + H^+ requires 267.1339).



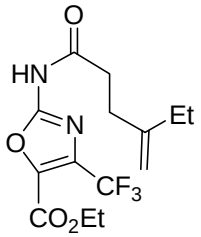
Ethyl 2-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}oxazole-5-carboxylate (70a). A solution of **S60** (54 mg, 0.18 mmol) in 2 mL of 4:1 DMF–THF was treated with Cs_2CO_3 (116 mg, 0.36 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (89 mg, 0.36 mmol) was added in one portion. The reaction mixture was stirred for 15 h before being quenched with the addition of H_2O, and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **70a** (15 mg, 0.035 mmol, 20%) as a colorless oil:^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, *J* = 11.2 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.25–7.05 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.81 (s, 1H), 4.62 (s, 1H), 4.41 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 3.04 (t, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.13 (t, *J* = 7.6 Hz, 2H), 1.78 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 163.1, 152.2, 149.4, 137.3, 133.2, 127.7, 127.3, 122.3, 119.6, 118.7, 110.5, 109.7, 108.5, 106.7, 62.1, 46.2, 35.2, 32.9, 30.6, 29.1, 25.2, 14.5, 12.4; IR (film) ν_{max} 2943, 1702, 1625, 1554, 1437, 1402, 1326, 1190, 1137, 744 cm^{-1}; MALDIFTMS (DHB) *m/z* 424.2232 ($C_{24}H_{29}N_3O_4$ + H^+ requires 424.2231).



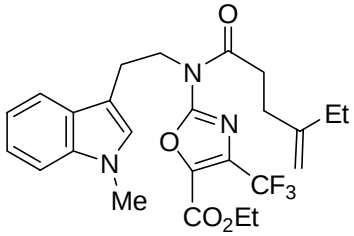
Methyl 4-Methyl-2-(4-methylenehexanamido)oxazole-5-carboxylate (S61). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (1.6 mL, 16 mmol), EDCI (4.6 g, 24 mmol) and methyl 2-amino-4-methyloxazole-5-carboxylate (1.25 g, 8.0 mmol) in CH_2Cl_2 (40 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 24 h before being concentrated under reduced pressure. Flash chromatography (SiO_2, 50% EtOAc–hexanes) gave **S61** (1.02 g, 3.8 mmol, 48%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.30 (br s, 1H), 4.75 (s, 1H), 4.71 (s, 1H), 3.84 (s, 3H), 2.78 (br s, 2H), 2.43–2.39 (m, 5H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.00 (dt, *J* = 0.8, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 154.3, 149.6, 147.0, 133.6, 108.7, 52.0, 35.1, 30.8, 29.2, 13.5, 12.5; IR (film) ν_{max} 3460, 2955, 1713, 1625, 1596, 1555, 1437, 1390, 1343, 1196, 1132, 1096 cm^{-1}; MALDIFTMS (DHB) *m/z* 267.1342 ($C_{13}H_{18}N_2O_4$ + H^+ requires 267.1339).



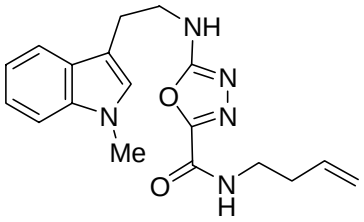
Methyl 4-Methyl-2-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}oxazole-5-carboxylate (71a). A solution of **S61** (780 mg, 3.0 mmol) in 30 mL of 1:2 DMF–THF was treated with Cs_2CO_3 (1.93 g, 6.0 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (952 mg, 4.0 mmol) was added in one portion. The reaction mixture was stirred for an additional 15 h before being quenched with the addition of H_2O, and extracted with EtOAc. The combined organic layer was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 25% EtOAc–hexanes) provided **71a** (225 mg, 0.53 mmol, 18%) as a colorless oil:^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.24–7.16 (m, 2H), 7.09 (td, *J* = 1.2, 8.0 Hz, 1H), 6.86 (s, 1H), 4.74–4.73 (m, 1H), 4.69 (br s, 1H), 4.19–4.15 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.05 (dt, *J* = 6.0, 8.0 Hz, 2H), 2.94–2.90 (m, 2H), 2.42–2.36 (m, 5H), 2.03 (q, *J* = 7.6 Hz, 2H), 1.02 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 158.9, 156.7, 150.2, 147.2, 137.2, 134.5, 127.9, 127.4, 121.8, 119.4, 119.1, 110.8, 109.3, 108.3, 52.0, 47.5, 35.2, 32.8, 31.4, 29.2, 24.5, 13.6, 12.6; IR (film) ν_{max} 2943, 1719, 1684, 1619, 1561, 1437, 1402, 1337, 1190, 1143, 750 cm^{-1}; MALDIFTMS (DHB) *m/z* 424.2242 ($C_{24}H_{29}N_3O_4$ + H^+ requires 424.2231).



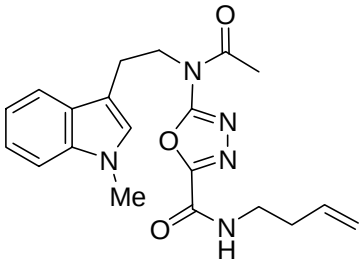
Ethyl 2-(4-Methylenehexanamido)-4-(trifluoromethyl)oxazole-5-carboxylate (S62). DMAP (122 mg, 1.0 mmol) was added to a solution of 4-ethyl-4-pentenoic acid (0.60 mL, 6.0 mmol), EDCI (1.15 g, 6.0 mmol) and ethyl 2-amino-4-(trifluoromethyl)oxazole-5-carboxylate (672 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 5 h before being concentrated. Flash chromatography (SiO_2, 20% EtOAc–hexanes) gave **S62** (845 mg, 2.5 mmol, 84%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.00 (br s, 1H), 4.73 (s, 1H), 4.67 (s, 1H), 4.35–4.30 (m, 2H), 2.76 (br s, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.01 (q, *J* = 7.6 Hz, 2H), 1.32–1.29 (m, 3H), 1.01–0.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 155.9, 154.1, 149.4, 135.6, 120.9, 118.2, 108.6, 62.7, 35.1, 30.6, 29.1, 14.0, 12.4; IR (film) ν_{max} 3472, 3237, 2978, 1719, 1602, 1548, 1390, 1319, 1149, 1032, 761 cm^{-1}; MALDIFTMS (DHB) *m/z* 335.1221 ($C_{14}H_{17}F_3N_2O_4$ + H^+ requires 335.1213).



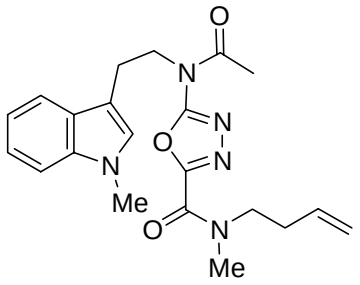
Ethyl 2-{*N*-[2-(1-Methyl-1*H*-indol-3-yl)ethyl]-4-methylenehexanamido}-4-(trifluoromethyl)oxazole-5-carboxylate (72a). A solution of **S62** (334 mg, 1.0 mmol) in 10 mL of 1:1 DMF–THF was treated with Cs_2CO_3 (420 mg, 1.3 mmol). The mixture was stirred at room temperature for 1 h before 3-(2-bromoethyl)-1-methyl-1*H*-indole (300 mg, 1.3 mmol) was added in one portion. The reaction mixture was stirred for 15 h before being quenched with the addition of H_2O and extracted with EtOAc. The combined organic layer was washed with the addition of H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (SiO_2, 17% EtOAc–hexanes) provided **72a** (52 mg, 0.11 mmol, 11%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.23–7.14 (m, 2H), 7.05 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.82 (s, 1H), 4.74 (d, *J* = 0.8 Hz, 1H), 4.68 (s, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.23 (t, *J* = 7.4 Hz, 2H), 3.68 (s, 3H), 3.08 (t, *J* = 7.4 Hz, 2H), 2.96–2.92 (m, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5, 156.8, 155.5, 149.9, 137.1, 136.1, 127.7, 127.6, 121.8, 119.2, 110.3, 109.4, 108.4, 62.4, 47.7, 35.3, 32.7, 31.2, 29.2, 24.5, 14.2, 12.5; IR (film) ν_{max} 2955, 1737, 1701, 1619, 1572, 1472, 1402, 1308, 1149, 1025, 744 cm^{-1}; MALDIFTMS (DHB) *m/z* 492.2105 ($C_{25}H_{28}F_3N_3O_4$ + H^+ requires 492.2105).



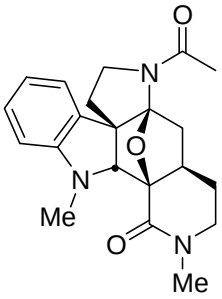
***N*-(But-3-enyl)-5-[2-(1-methyl-1*H*-indol-3-yl)ethylamino]-1,3,4-oxadiazole-2-carboxamide (S63).** 3-Butenylamine hydrochloride (0.44 g, 4.17 mmol) was added to a solution of **S3** (0.25 g, 0.83 mmol), triethylamine (0.42 g, 4.17 mmol), and DMAP (10 mg, 0.083 mmol) in 1,2-dichloroethane (4 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The mixture was filtered, concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 60% EtOAc–hexanes) providing **S63** (0.19 g, 0.55 mmol, 66%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.03 (br s, 1H), 6.89 (s, 1H), 5.75 (dddd, *J* = 6.8, 6.8, 10.1, 17.0 Hz, 1H), 5.56 (br s, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 10.1 Hz, 1H), 3.74 (s, 3H), 3.74–3.71 (m, 2H), 3.44 (dt, *J* = 6.5, 6.5 Hz, 2H), 3.07 (t, *J* = 6.6 Hz, 2H), 2.31 (dt, *J* = 6.7, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.4, 153.7, 153.1, 137.2, 134.4, 127.4, 127.2, 121.9, 119.1, 118.6, 117.8, 110.2, 109.4, 43.5, 38.6, 33.4, 32.6, 25.0; IR (film) ν_{max} 3267, 1675, 1635, 1568, 1472 cm^{-1}; HRESI-TOF *m/z* 340.1771 ($C_{18}H_{21}N_5O_2$ + H^+ requires 340.1768).



***N*-(But-3-enyl)-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]acetamido}-1,3,4-oxadiazole-2-carboxamide (S64).** DMAP (0.27 g, 2.21 mmol) was added to a solution of acetic acid (0.13 g, 2.21 mmol), **S63** (0.30 g, 0.88 mmol), and EDCI (0.42 g, 2.21 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 60% EtOAc–hexanes) providing **S64** (0.33 g, 0.87 mmol, 98%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.01 (br s, 1H), 6.98 (s, 1H), 5.89 (dddd, *J* = 6.9, 6.9, 10.2, 17.1 Hz, 1H), 5.26 (d, *J* = 17.0 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.30 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 3.61 (dt, *J* = 6.6, 6.6 Hz, 2H), 3.19 (t, *J* = 7.7 Hz, 2H), 2.56 (s, 3H), 2.47 (dt, *J* = 6.6, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3, 162.1, 155.7, 152.6, 136.9, 134.3, 127.4, 127.3, 121.6, 119.1, 118.9, 118.0, 110.0, 109.1, 47.8, 38.7, 33.4, 32.6, 24.5, 24.1; IR (film) ν_{max} 3313, 2937, 1699, 1568, 1519 cm^{-1}; HRESI-TOF *m/z* 382.1878 ($C_{20}H_{23}N_5O_3$ + H^+ requires 382.1874).

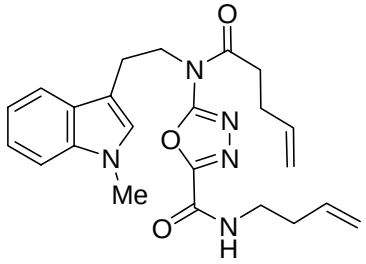


***N*-(But-3-enyl)-*N*-methyl-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]acetamido}-1,3,4-oxadiazole-2-carboxamide (73a).** NaH (33 mg, 0.82 mmol) was added to a solution of **S64** (329 mg, 0.75 mmol) in DMF (7.5 mL) at 0 °C. After 30 min, iodomethane (56 μL, 0.89 mmol) was added. The reaction mixture was gradually warmed to 25 °C and stirred for 14 h. The mixture was diluted with Et_2O (20 mL) and the organic layer was washed with H_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 50% EtOAc–hexanes) providing **73a** (273 mg, 0.60 mmol, 80%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz, 1:1 mixture of rotamers) δ 7.81 (d, *J* = 7.8 Hz, 0.5H), 7.80 (d, *J* = 7.9 Hz, 0.5H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 0.5H), 7.20 (t, *J* = 7.4 Hz, 0.5H), 7.00 (s, 1H), 5.95–5.81 (m, 1H), 5.24 (d, *J* = 17.0 Hz, 0.5H), 5.21 (d, *J* = 17.0 Hz, 0.5H), 5.18 (d, *J* = 11.0 Hz, 0.5H), 5.16 (d, *J* = 10.6 Hz, 0.5H), 4.31 (t, *J* = 7.5 Hz, 2H), 3.99 (t, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.70 (t, *J* = 7.3 Hz, 1H), 3.49 (s, 1.5H), 3.21 (s, 1.5H), 3.19 (t, *J* = 7.5 Hz, 2H), 2.60 (s, 1.5H), 2.59 (s, 1.5H), 2.54–2.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4 (2), 161.2, 155.8, 155.7, 153.9, 153.7, 136.9, 134.4, 133.9, 127.6, 127.5, 127.3 (2), 121.6, 119.0, 117.9, 117.5, 110.1, 109.1, 50.1, 48.6, 47.7, 37.0, 34.7, 33.0, 32.6, 31.3, 24.7, 24.6, 24.0; IR (film) ν_{max} 2934, 1703, 1656, 1573, 1475 cm^{-1}; HRESI-TOF *m/z* 396.2029 ($C_{21}H_{25}N_5O_3$ + H^+ requires 396.2030).

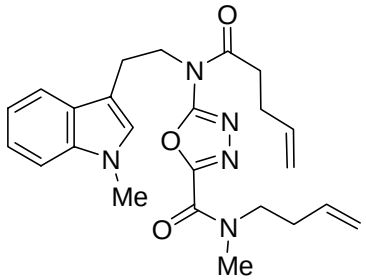


Compound 73b. A solution of **73a** (26 mg, 0.057 mmol) in 11 mL of anhydrous, degassed 1,2-dichlorobenzene was warmed under Ar at 180 °C for 144 h. The cooled reaction mixture was loaded directly onto SiO_2 (1.5 × 10 cm) equilibrated in hexanes. The 1,2-dichlorobenzene was eluted with distilled hexanes (100 mL) and the column was flushed with distilled 5% MeOH–EtOAc (25 mL). The solvent was concentrated and the residue was purified by column chromatography (SiO_2, 5% MeOH–EtOAc) providing unreacted starting material **73a** (10 mg, 0.023 mmol, 41%) and **73b** (13 mg, 0.031 mmol,

55%) as a colorless oil: ^{1}H NMR (CD_3CN, 500 MHz) δ 7.14 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 4.35 (s, 1H), 4.13–3.83 (m, 3H), 3.31 (dd, *J* = 11.6, 11.6 Hz, 1H), 3.21 (ddd, *J* = 3.5, 3.5, 12.5 Hz, 1H), 2.93 (s, 3H), 2.72 (s, 3H), 2.71–2.61 (m, 1H), 2.29–2.10 (m, 2H), 2.09 (br s, 3H), 1.82–1.73 (m, 1H), 1.63–1.55 (m, 1H), 1.42–1.39 (m, 1H); ^{13}C NMR (CD_3CN, 150 MHz) δ 172.0, 166.8, 153.0, 130.7, 129.9, 124.2, 117.5, 106.3, 80.4, 67.2, 60.9, 52.4, 49.8, 37.0, 35.1, 34.3, 32.6, 29.0, 24.6, 21.1, 14.4; IR (film) ν_{max} 2930, 1651, 1605, 1495, 1397 cm^{-1}; HRESI-TOF *m/z* 368.1979 ($C_{21}H_{25}N_3O_3$ + H^+ requires 368.1969).

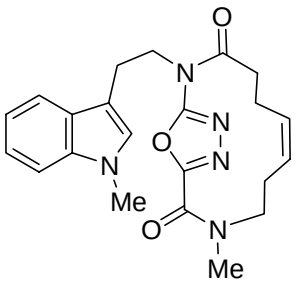


***N*-(But-3-enyl)-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxamide (S65).** DMAP (0.27 g, 2.21 mmol) was added to a solution of 4-pentenoic acid (0.22 g, 2.21 mmol), **S63** (0.30 g, 0.88 mmol), and EDCI (0.42 g, 2.21 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was gradually warmed to 25 °C and stirred for 16 h. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 50% EtOAc–hexanes) providing **S65** (0.34 g, 0.80 mmol, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.97 (br s, 1H), 6.91 (s, 1H), 5.88–5.79 (m, 2H), 5.22–5.17 (m, 2H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.24 (t, *J* = 7.6 Hz, 2H), 3.74 (s, 3H), 3.54 (dt, *J* = 6.6, 6.6 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.45 (dt, *J* = 7.0, 7.0 Hz, 2H), 2.41 (dt, *J* = 6.7, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 162.0, 155.8, 152.6, 136.9, 136.5, 134.3, 127.4, 127.3, 121.6, 119.1, 118.9, 118.0, 115.8, 110.0, 109.1, 48.0, 38.7, 35.4, 33.3, 32.5, 28.7, 24.2; IR (film) ν_{max} 3313, 2931, 1696, 1566, 1517 cm^{-1}; HRESI-TOF *m/z* 422.2192 ($C_{23}H_{27}N_5O_3$ + H^+ requires 422.2187).

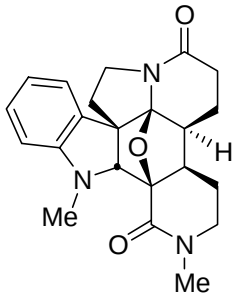


***N*-(But-3-enyl)-*N*-methyl-5-{*N*-[2-(1-methyl-1*H*-indol-3-yl)ethyl]pent-4-enamido}-1,3,4-oxadiazole-2-carboxamide (S66).** NaH (27 mg, 0.68 mmol) was added to a solution of **S65** (297 mg, 0.62 mmol) in DMF (6 mL) at 0 °C. After 30 min, iodomethane (46 μL, 0.74 mmol) was added. The reaction mixture was gradually warmed to 25 °C and

stirred for 14 h. The mixture was diluted with Et_2O (20 mL) and the organic layer was washed with H_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 40% EtOAc–hexanes) providing **S66** (251 mg, 0.51 mmol, 82%) as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 500 MHz, 1:1 mixture of rotamers) δ 7.80 (d, *J* = 7.5 Hz, 0.5H), 7.79 (d, *J* = 7.5 Hz, 0.5H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.22–7.18 (m, 1H), 6.99 (s, 0.5H), 6.98 (s, 0.5H), 5.96–5.80 (m, 2H), 5.25–5.08 (m, 4H), 4.31 (t, *J* = 7.3 Hz, 2H), 3.99 (t, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.70 (t, *J* = 7.2 Hz, 1H), 3.48 (s, 1.5H), 3.21 (s, 1.5H), 3.22–3.19 (m, 2H), 3.00–2.97 (m, 2H), 2.53–2.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.6 (2), 161.1, 155.8, 155.7, 153.9, 153.7, 136.9, 136.5, 134.4, 133.9, 127.5 (2), 127.3 (2), 121.6, 119.0, 117.9, 117.5, 115.7, 110.1, 109.0, 50.1, 48.6, 47.9, 37.0, 35.5, 35.4, 34.6, 32.9, 32.5, 31.3, 28.7, 24.1; IR (film) ν_{max} 2932, 1703, 1656, 1569, 1417, 1178 cm^{-1}; HRESI-TOF *m/z* 436.2351 ($C_{24}H_{29}N_5O_3 + H^+$ requires 436.2343).



(*Z*)-10-Methyl-2-[2-(1-methyl-1*H*-indol-3-yl)ethyl]-15-oxa-2,10,13,14-tetraazabicyclo[10.2.1]pentadeca-1(14),6,12-triene-3,11-dione (74a). The second generation Grubbs catalyst (17 mg, 0.020 mmol) was added to a solution of **S66** (99 mg, 0.20 mmol) in degassed CH_2Cl_2 (100 mL). The resulting solution was warmed to 40 °C for 16 h and then cooled to 25 °C. The mixture was concentrated under reduced pressure, and subjected to flash chromatography (SiO_2, 60% EtOAc–hexanes) providing the metathesis product as a mixture of olefin isomers (0.079 g, 0.17 mmol, 84%). Further purification of this mixture by flash chromatography (SiO_2, 60% EtOAc–hexanes) provided the (*Z*)-isomer **74a** (32 mg, 0.069 mmol, 34%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.78 (s, 1H), 5.71 (dd, *J* = 8.4, 8.4 Hz, 1H), 5.42 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 3.72 (s, 3H), 3.15 (t, *J* = 7.2 Hz, 2H), 3.09 (s, 3H), 2.92–2.89 (m, 2H), 2.43 (dd, *J* = 8.3, 8.3 Hz, 2H), 2.26 (dd, 8.5, 8.5 Hz, 2H), 2.13–2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.5, 161.0, 157.4, 154.5, 136.6, 131.9, 128.4, 127.1, 125.9, 121.5, 119.0, 118.8, 109.8, 109.3, 51.3, 51.1, 37.5, 33.5, 32.6, 26.9, 24.8, 23.5; IR (film) ν_{max} 2934, 1696, 1655, 1560, 1472 cm^{-1}; HRESI-TOF *m/z* 408.2032 ($C_{22}H_{25}N_5O_3 + H^+$ requires 408.2036).



Compound 74b. A solution of **74a** (5.5 mg, 0.12 mmol) in 2.5 mL of anhydrous, degassed benzene was warmed under Ar at 80 °C for 40 h. The cooled reaction mixture was concentrated under reduced pressure and subjected to PTLC (SiO_2, 5% MeOH–EtOAc) providing **74b** (3.6 mg, 0.0082 mmol, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.16 (t, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 4.53 (s, 1H), 4.12 (ddd, *J* = 9.0, 9.0, 12.0 Hz, 1H), 3.83 (ddd, *J* = 2.5, 10.5, 12.6 Hz, 1H), 3.35 (ddd, *J* = 3.0, 3.0, 12.0 Hz, 1H), 3.30 (ddd, *J* = 4.1, 4.1, 7.8 Hz, 1H), 2.57 (ddd, *J* = 10.0, 10.0, 13.3 Hz, 1H), 2.52 (ddd, *J* = 1.8, 4.9, 17.8 Hz, 1H), 2.46 (ddd, *J* = 5.1, 8.2, 13.1 Hz, 1H), 2.32 (ddd, *J* = 2.6, 9.0, 13.2 Hz, 1H), 2.19 (ddd, *J* = 5.6, 13.1, 18.5 Hz, 1H), 1.98–1.91 (m, 1H), 1.82–1.75 (m, 2H), 1.69–1.67 (m, 1H), 1.57–1.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.2, 166.5, 152.0, 129.2, 129.1, 123.0, 117.6, 106.0, 105.9, 85.0, 81.3, 64.5, 49.4, 46.7, 38.7, 36.8, 36.0, 35.3, 33.3, 31.5, 22.1, 20.1; IR (film) ν_{max} 2935, 1650, 1606, 1494, 1431, 1383 cm^{-1}; HRESI-TOF *m/z* 380.1968 ($C_{22}H_{25}N_3O_3 + H^+$ requires 380.1969).

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