Structure-Activity Relationship for the Oxadiazole Class of Antibacterials

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Supporting Information

Contents

General Experimental Procedures for Intermediates

Key Intermediates. The allyl-protected phenols of **8**,[1] **11**,[2] **12**,[3] and **19**,[4] are known compounds and were synthesized using previously described procedures.[5] Compounds **49**, **13**, and **14** were synthesized using previously described procedures.[6,7]

General procedure for syntheses of benzoyl chlorides. We followed a general literature method for this purpose.[6]

General procedure for syntheses of heteroaryl acyl chlorides. The given carboxylic acid (1.0 equiv.) was dissolved in thionyl chloride (25.0 equiv.), and the mixture was heated to reflux for 2.5 h. The excess thionyl chloride was removed *in vacuo*, and the resulting solid was used without further purification.

General procedure for syntheses of diphenyl ethers, Method A (nucleophilic aromatic substitution). A 4-fluorobenzonitrile derivative (1.0 equiv.), a phenol derivative (1.0 equiv.), and K_2CO_3 (2.0 equiv.) were dissolved in either DMSO or DMF, and the mixture was stirred at 100 °C for 16 h. The mixture was cooled to room temperature and was diluted with water (2× volume of DMSO or DMF used), then it was washed with ethyl acetate (3×). The combined ethyl acetate layer was washed with water (3×), then with brine, and dried (anhydrous Na_2SO_4). The suspension was filtered, and the filtrate was concentrated *in vacuo* to dryness. The resulting residue was purified by column chromatography on silica gel.

General procedure for syntheses of diphenyl ethers, Method B (Ullmann coupling). We followed a general literature method for this purpose.[6]

General procedure for syntheses of *N*'-hydroxybenzimidamides. We followed a general literature method for this purpose.[6]

Experimental Procedures for Final Compounds

4-(3-(4-(4-(Trifluoromethoxy)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)phenol (62a).
4-(Benzyloxy)benzoyl chloride (169 mg, 0.68 mmol) was dissolved in pyridine (15 mL) followed by the addition of (Z)-*N*'-hydroxy-4-(4-(trifluoromethoxy)phenoxy)benzimidamide (202 mg, 0.65 mmol). The resulting mixture was stirred under reflux for 23 h. The solvent was removed *in vacuo* and the crude product was purified by silica-gel chromatography (EtOAc/hexane, 1:5) to afford white needle-like crystals (benzyl group protected precursor, 192 mg, 56%).
A portion of the crystals (82 mg, 0.16 mmol) was dissolved in anhydrous DCM (2 mL). The resulting mixture was stirred at -78 °C for 20 min before 1 M BBr_3 in DCM (0.64 mL, 0.32 mmol) was added dropwise. The reaction was quenched with water (13 mL) after 20 min. The mixture was warmed up to room temperature and was washed with DCM (10 mL, 2×). The combined organic layer was evaporated to dryness *in vacuo*. The residue was purified by silica-gel chromatography (EtOAc/hexane, 1:3) to afford **62a** as a white solid (68 mg, > 99%)

Compounds **63a**, **67a**, **68a**, **70a**, **71a**, **73a**, **74a**, **75a**, **76a**, **77a**, **93a**, **94a**, **78a**, **79a**, **80a**, **81a**, **82a**, **83a**, **85a**, **88a**, **89a**, **90a**, **91a**, **95a**, **97a**, **98a**, **99a**, **100a**, **101a**, **103a**, **104a**, **105a**, **107a**, **108a**, **111a**, **112a**, **113a**, **115a**, **117a**, **118a**, **119a**, **120a** and **121a** were synthesized according to the procedure for **62a**; the overall yields ranged from 23% to 74%.

5-(4-Chloro-1H-pyrazol-3-yl)-3-(4-(3,4-dichlorophenoxy)phenyl)-1,2,4-oxadiazole (60b).
4-Chloro-1H-pyrazole-3-carboxylic acid (108 mg, 0.74 mmol) was dissolved in $SOCl_2$ (1.5 mL, 14.78 mmol), and the solution was stirred under reflux for 1 h. The excess $SOCl_2$ was removed *in vacuo*, and the residue was taken up in pyridine (15 mL), followed by the addition of (Z)-4-(3,4-

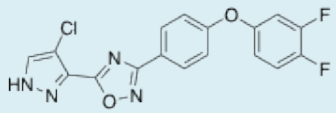
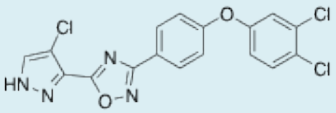
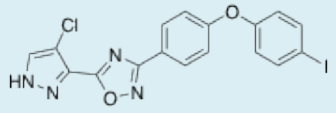
dichlorophenoxy)-*N*'-hydroxybenzimidamide (191 mg, 0.64 mmol). The resulting mixture was stirred under reflux overnight. The solvent was removed *in vacuo* and the residue was purified by silica-gel chromatography (EtOAc/hexane, 1:5) to afford **60b** as a yellow powder (141 mg, 54%).

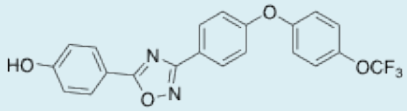
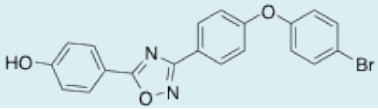
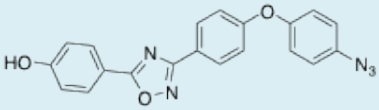
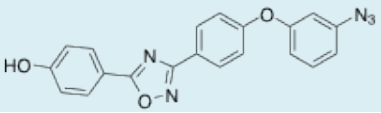
Compounds **59b**, **61b**, **69b**, **78b**, **85b**, **86b**, **87b**, **92b**, **96b**, **106b**, **109b**, **114b**, **116b**, **120b** and **121b** were synthesized according to the procedure for **60b**; the overall yields ranged from 16% to 66%.

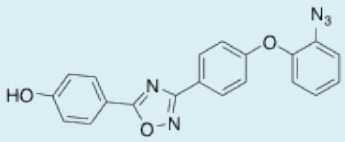
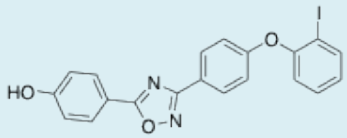
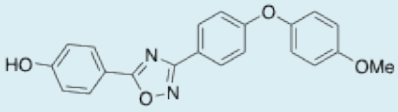
3-(4-(4-Fluorophenoxy)phenyl)-5-(1H-indol-5-yl)-1,2,4-oxadiazole (72c).
A solution of (Z)-4-(4-fluorophenoxy)-*N*'-hydroxybenzimidamide (1.00 g, 4.07 mmol) in anhydrous THF (15 mL) was stirred under an atmosphere of argon. Sodium hydride (60% in mineral oil, 0.244 g, 6.10 mmol) was then added to the flask carefully. The mixture was stirred for 1 h at room temperature, and then a solution of methyl 1H-indole-5-carboxylate (0.783 g, 4.48 mmol) in anhydrous THF (20 mL) was added and the mixture was refluxed for 4 h. Once the solution had cooled to room temperature, water (40 mL) was added, and the resulting mixture was washed with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then filtered, and the filtrate was evaporated to leave a yellow residue. This was purified using column chromatography on silica gel (dichloromethane/hexanes, 5:1) to give **72c** as a white solid (498 mg, 33%).
Compound **78c** was synthesized according to the procedure for **72c** to afford **78c** as a white solid (626 mg, 40%).

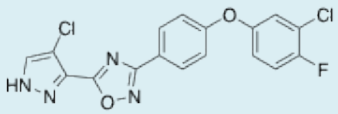
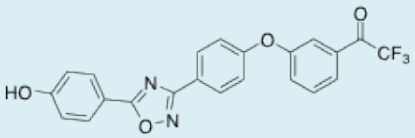
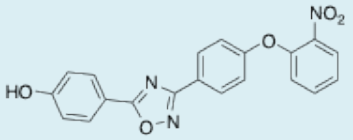
Deprotection of the Boc group. Compounds **108b** and **117b** were synthesized from their Boc-protected precursors. Hydrochloric acid (4 M in dioxane) was added to the solution of precursor in DCM. The mixture was stirred at room temperature for 30 min, then the solvent was removed *in vacuo* to give the final product.
Acylation using acetic anhydride. Compounds **102a** and **110a** were synthesized from **101a** and **108a**, respectively, by following a literature method.[8]
Nitro reduction using $SnCl_2 \cdot H_2O$. Aniline **84a** was synthesized from **71a** by following a literature method.[8]
Introduction of azides (64a, 65a, 66a). Azides **64a** and **65a** were synthesized from the corresponding aryl iodides by following a literature method.[5] We synthesized azide **66a** from the corresponding aniline by following a literature method.[9]

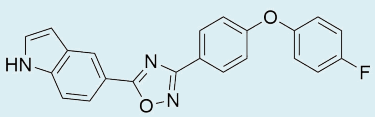
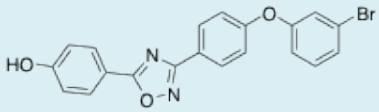
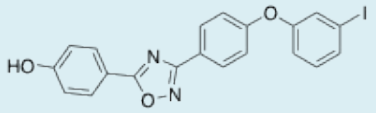
Table S1. Spectral Data of Final Compounds

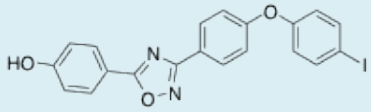
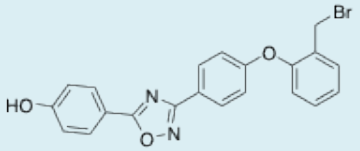
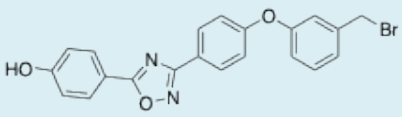
Compound Number	Structure and data
59b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.00–7.02 (m, 1H, ArH), 7.21 (d, 2H, J = 8.6 Hz, ArH), 7.35–7.39 (m, 1H, ArH), 7.49–7.54 (m, 1H, ArH), 8.08 (d, 2H, J = 8.1 Hz, ArH), 8.36 (s, 1H, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 110.3, 110.5, 116.9 (dd, 1C, J_{CF} = 3.5, 6.5 Hz), 118.8, 118.9, 119.0, 121.6, 122.3, 129.8, 130.8, 147.0 (dd, 1C, J_{CF} = 12.6, 242.1 Hz), 150.3 (dd, 1C, J_{CF} = 14.0, 247.5 Hz), 152.1 (dd, 1C, J_{CF} = 2.9, 8.8 Hz), 160.0, 167.9.
^{19}F NMR	(376 MHz, DMSO-d_6) δ -143.6 (d, 1F, J = 22.7 Hz), -134.8 (d, 1F, J = 23.0 Hz)
HRMS (ESI)	calcd for $C_{17}H_{10}ClF_2N_4O_2$, 375.0455, found 375.0461 $[MH]^+$
60b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.15–7.17 (m, 1H, ArH), 7.27 (d, 2H, J = 8.5 Hz, ArH), 7.49 (d, 1H, J = 2.0 Hz, ArH), 7.70 (d, 1H, J = 9.0 Hz, ArH), 8.12 (d, 2H, J = 9.0 Hz, ArH), 8.38 (s, 1H, ArH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 110.1, 119.1, 119.7, 121.5, 121.6, 126.4, 129.4, 130.2, 131.7, 132.2, 133.4, 155.1, 158.7, 167.3, 169.4.
HRMS (ESI)	calcd for $C_{17}H_{10}Cl_3N_4O_2$, 406.9864, found 406.9876 $[MH]^+$
61b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 6.97 (d, 2H, J = 8.5 Hz, ArH), 7.21 (d, 2H, J = 8.5 Hz, ArH), 7.77 (d, 2H, J = 8.5 Hz, ArH), 8.09 (d, 2H, J = 8.5 Hz, ArH), 8.37 (s, 1H, ArH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 88.2, 110.0, 118.7, 121.0, 121.9, 129.3, 129.5, 130.2, 133.4, 138.9, 155.5, 159.1, 167.4.
HRMS (ESI)	calcd for $C_{17}H_{11}ClIN_4O_2$, 464.9615, found 464.9633 $[MH]^+$

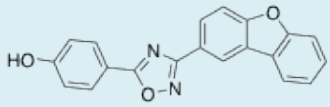
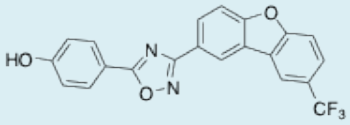
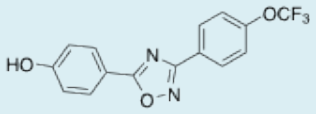
62a	
^{1}H NMR	(600 MHz, CD_3OD) δ 6.97 (d, 2H, *J* = 9.0 Hz, ArH), 7.15 (d, 2H, *J* = 8.8 Hz, ArH), 7.17 (d, 2H, *J* = 9.1 Hz, ArH), 7.34 (d, 2H, *J* = 9.1 Hz, ArH), 8.06 (d, 2H, *J* = 9.0 Hz, ArH), 8.13 (d, 2H, *J* = 8.8 Hz, ArH).
^{13}C NMR	(150 MHz, CD_3OD) δ 116.5, 117.3, 119.8, 122.0, 122.1 (q, 1C, J_{CF} = 255.3 Hz), 123.7, 124.2, 130.5, 131.4, 146.6, 156.6, 161.2, 163.6, 169.4, 177.5
HRMS (ESI)	calcd for $C_{21}H_{14}F_3N_2O_4$ 415.0900, found 415.0899 $[MH]^+$
63a	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 7.00 (d, 2H, *J* = 8.9 Hz, ArH), 7.11 (d, 2H, *J* = 8.9 Hz, ArH), 7.19 (d, 2H, *J* = 8.9 Hz, ArH), 7.63 (d, 2H, *J* = 8.9 Hz, ArH), 8.02 (d, 2H, *J* = 8.9 Hz, ArH), 8.08 (d, 2H, *J* = 8.9 Hz, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 114.1, 116.2, 116.3, 118.7, 121.5, 121.8, 129.3, 130.2, 133.1, 155.0, 159.2, 162.1, 167.5, 175.5.
HRMS (ESI)	calcd for $C_{20}H_{14}BrN_2O_3$ 409.0182, found 409.0155 $[MH]^+$
64a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.00 (d, 2H, *J* = 9.0 Hz, ArH), 7.16 (d, 2H, *J* = 9.0 Hz, ArH), 7.20–7.22 (m, 4H, ArH), 8.03 (d, 2H, *J* = 9.0 Hz, ArH), 8.07 (d, 2H, *J* = 9.0 Hz, ArH), 10.55 (s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 114.1, 116.3, 118.1, 120.9, 121.1, 121.5, 129.2, 130.1, 135.4, 152.5, 159.8, 162.1, 167.5, 175.4.
HRMS (ESI)	calcd for $C_{20}H_{14}N_5O_3$ 372.1091, found 372.1082 $[MH]^+$
65a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 5.36 (s, 1H, OH), 6.74 (t, 1H, *J* = 2.3 Hz, ArH), 6.83–6.86 (m, 2H, ArH), 6.99 (d, 2H, *J* = 8.8 Hz, ArH), 7.12 (d, 2H, *J* = 9.0 Hz, ArH), 7.35 (t, 1H, *J* = 8.1 Hz, ArH), 8.11–8.16 (m, 4H, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 110.6, 114.7, 116.0, 116.4, 116.9, 119.1, 122.3, 129.5, 130.6, 131.1, 142.0, 157.8, 159.6, 160.1, 168.4, 175.8.
HRMS (ESI)	calcd for $C_{20}H_{14}N_5O_3$ 372.1091, found 372.1093 $[MH]^+$

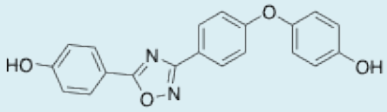
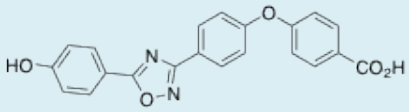
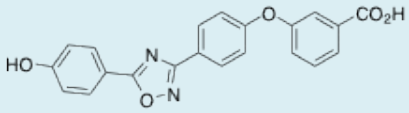
66a	
^{1}H NMR	(500 MHz, acetone-d_6) δ 7.09 (d, 2H, J = 8.9 Hz, ArH), 7.11 (d, 2H, J = 9.0 Hz, ArH), 7.20 (ddd, 1H, J = 8.0, 1.4, 0.4 Hz, ArH), 7.27–7.36 (m, 3H, ArH), 8.10 (d, 2H, J = 8.9 Hz, ArH), 8.14 (d, 2H, J = 9.0 Hz, ArH), 9.37 (s, 1H, OH).
^{13}C NMR	(125 MHz, acetone-d_6) δ 113.3, 117.1, 117.9, 122.3, 122.8, 123.5, 127.2, 127.3, 130.1, 131.1, 133.2, 147.6, 161.2, 162.7, 168.9, 176.7.
HRMS (ESI)	calcd for $C_{20}H_{14}N_5O_3$ 372.1091, found 372.1106 $[MH]^+$
67a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 6.76 (s, 1H, OH), 6.95 (ddd, 1H, J = 8.0, 7.4, 1.6 Hz, ArH), 8.98 (d, 2H, J = 8.8 Hz, ArH), 7.03 (dd, 1H, J = 8.0, 1.6 Hz, ArH), 7.04 (d, 2H, J = 9.0 Hz, ArH), 7.35 (ddd, 1H, J = 8.1, 7.4, 1.6 Hz, ArH), 7.89 (dd, 1H, J = 8.1, 1.6 Hz, ArH), 8.09 (d, 2H, J = 8.8 Hz, ArH), 8.12 (d, 2H, J = 9.0 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 89.8, 116.4, 116.8, 118.1, 121.0, 121.8, 126.5, 129.6, 130.1, 130.6, 140.3, 155.6, 159.8, 160.2, 168.4, 175.8.
HRMS (ESI)	calcd for $C_{20}H_{14}IN_2O_3$ 457.0044, found 457.0020 $[MH]^+$
68a	
^{1}H NMR	(600 MHz, $CDCl_3$) δ 5.44 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 6.93 (d, 2H, J = 9.0 Hz, ArH), 6.98 (d, 2H, J = 8.8 Hz, ArH), 7.03 (d, 2H, J = 8.8 Hz, ArH), 7.05 (d, 2H, J = 9.0 Hz, ArH), 8.09 (d, 2H, J = 8.8 Hz, ArH), 8.12 (d, 2H, J = 8.8 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 56.2, 116.3, 116.6, 117.2, 118.3, 122.3, 122.7, 130.3, 131.3, 150.4, 158.3, 162.9, 163.6, 169.5, 177.4.
HRMS (ESI)	calcd for $C_{21}H_{16}N_2NaO_4$ 383.1002, found 383.1022 $[MNa]^+$

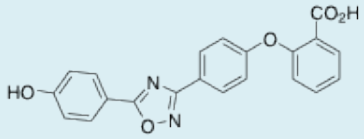
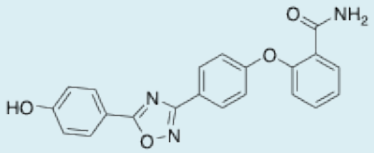
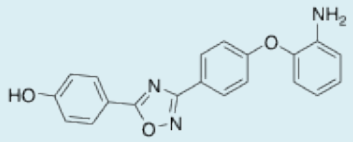
69b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.18–7.22 (m, 3H, ArH), 7.48–7.53 (m, 2H, ArH), 8.09 (d, 2H, J = 7.0 Hz, ArH), 8.38 (s, 1H, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 110.6, 118.5 (d, 1C, J_{CF} = 22.7 Hz), 118.9, 120.9 (d, 1C, J_{CF} = 7.6 Hz), 121.1, 121.6, 122.5, 129.8, 130.7, 133.9, 152.3 (d, 1C, J_{CF} = 2.7 Hz), 154.7 (d, 1C, J_{CF} = 243.1 Hz), 160.0, 167.9, 169.9.
^{19}F NMR	(376 MHz, DMSO-d_6) δ -121.68 (s, 1F).
HRMS (ESI)	calcd for $C_{17}H_{10}Cl_2FN_4O_2$, 390.0159, found 390.0148 $[MH]^+$
70a	
^{1}H NMR	(400 MHz, $CDCl_3$) δ 6.02 (s, 1H, OH), 6.99 (d, 2H, J = 8.9 Hz, ArH), 7.14 (d, 2H, J = 9.1 Hz, ArH), 7.42 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 7.57 (t, 1H, J = 8.0 Hz, ArH), 7.77 (s, 1H, ArH), 7.87 (dd, 1H, J = 8.0, 1.2 Hz, ArH), 8.12 (d, 2H, J = 8.9 Hz, ArH), 8.18 (d, 2H, J = 9.1 Hz, ArH).
^{13}C NMR	(100 MHz, $CDCl_3$) δ 116.3, 117.1, 119.3, 120.4, 123.0, 125.7, 126.5, 129.8, 130.6, 131.0, 131.8, 158.9, 160.0, 160.5, 168.3, 175.9.
HRMS (ESI)	calcd for $C_{22}H_{14}F_3N_2O_4$ 427.0900, found 427.0883 $[MH]^+$
71a	
^{1}H NMR	(500 MHz, CD_3OD) δ 6.96 (d, 2H, J = 8.8 Hz, ArH), 7.13 (d, 2H, J = 8.9 Hz, ArH), 7.24 (dd, 1H, J = 8.4, 1.2 Hz, ArH), 7.39 (ddd, 1H, J = 8.4, 7.6, 1.2 Hz, ArH), 7.68 (ddd, 1H, J = 8.2, 7.6, 1.7 Hz, ArH), 8.02 (dd, 1H, J = 8.2, 1.7 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 8.11 (d, 2H, J = 8.9 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 116.5, 117.3, 119.4, 123.7, 124.2, 126.2, 127.0, 130.6, 131.4, 135.9, 143.8, 150.2, 160.7, 163.7, 169.4, 177.5.
HRMS (ESI)	calcd for $C_{20}H_{14}N_3O_5$ 376.0928, found 376.0932 $[MH]^+$

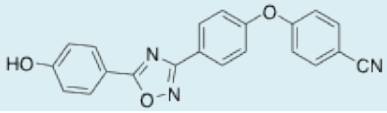
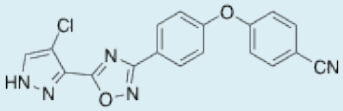
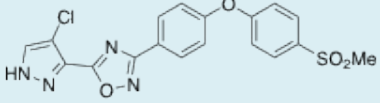
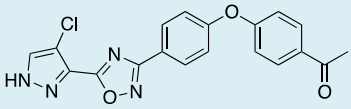
72c	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 6.66–6.71 (m, 1H, ArH), 7.16 (d, J = 8.8 Hz, 2H, ArH), 7.19–7.26 (m, 2H, ArH), 7.31 (t, J = 8.8 Hz, 2H, ArH), 7.55 (t, J = 2.7 Hz, 1H, ArH), 7.63 (d, J = 8.6 Hz, 1H, ArH), 7.91 (dd, J = 8.6, 1.6 Hz, 1H, ArH), 8.11 (d, J = 8.9 Hz, 2H, ArH), 8.44–8.50 (m, 1H, ArH), 11.64 (s, 1H, NH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 102.7, 112.5, 114.2, 116.9 (d, 2C, J_{CF} = 23.5 Hz), 117.8, 120.6, 121.2, 121.3, 121.8 (d, 2C, J_{CF} = 8.6 Hz), 127.8 (2C), 129.2, 138.4, 151.4 (d, 1C, J_{CF} = 1.7 Hz), 158.8 (d, 1C, J_{CF} = 240.6 Hz), 160.0, 167.6, 176.9.
^{19}F NMR	(376 MHz, DMSO-d_6) δ -118.5 (s, 1F)
HRMS (ESI)	calcd for $C_{22}H_{15}FN_3O_2$ 372.1148, found 372.1166 $[MH]^+$
73a	
^{1}H NMR	(400 MHz, $CDCl_3$) δ 6.99 (d, 2H, J = 8.9 Hz, ArH), 6.99–7.02 (m, 1H, ArH), 7.11 (d, 2H, J = 8.7 Hz, ArH), 7.22–7.24 (m, 2H, ArH), 7.28 (dt, 1H, J = 8.2, 1.5 Hz, ArH), 8.11 (d, 2H, J = 8.9 Hz, ArH), 8.14 (d, 2H, J = 8.7 Hz, ArH).
^{13}C NMR	(150 MHz, $CDCl_3$) δ 116.4, 116.6, 118.3, 119.1, 122.4, 122.8, 123.2, 127.3, 129.6, 130.6, 131.2, 157.3, 159.4, 160.4, 168.3, 175.9
HRMS (ESI)	calcd for $C_{20}H_{13}BrN_2NaO_3$ 431.0002, found 431.0005 $[MNa]^+$
74a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 6.99 (d, 2H, J = 8.8 Hz, ArH), 7.15 (dd, 1H, J = 8.1, 2.3 Hz, ArH), 7.19 (d, 2H, J = 8.9 Hz, ArH), 7.24 (t, 1H, J = 8.1 Hz, ArH), 7.48 (dd, 1H, J = 2.3, 1.6 Hz, ArH), 7.58 (dd, 1H, J = 8.1, 1.6 Hz, ArH), 8.02 (d, 2H, J = 8.8 Hz, ArH), 8.08 (d, 2H, J = 8.9 Hz, ArH), 10.57 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 95.3, 114.1, 116.3, 118.9, 119.0, 121.7, 127.9, 129.2, 130.1, 132.1, 133.1, 136.4, 158.9, 162.1, 167.5, 175.5.
HRMS (ESI)	calcd for $C_{20}H_{13}IN_2NaO_3$ 478.9863, found 478.9873 $[MNa]^+$

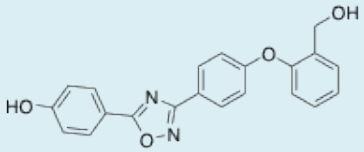
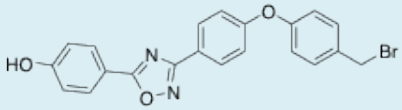
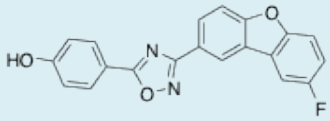
75a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 6.96 (d, 2H, J = 8.5 Hz, ArH), 6.99 (d, 2H, J = 8.6 Hz, ArH), 7.18 (d, 2H, J = 8.7 Hz, ArH), 7.77 (d, 2H, J = 8.7 Hz, ArH), 8.02 (d, 2H, J = 8.5 Hz, ArH), 8.07 (d, 2H, J = 8.6 Hz, ArH), 10.57 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 88.3, 114.1, 116.3, 118.7, 121.5, 122.0, 129.2, 130.1, 138.9, 155.6, 159.1, 162.1, 167.5, 175.5.
HRMS (ESI)	calcd for $C_{20}H_{14}IN_2O_3$ 457.0044, found 457.0029 $[MH]^+$
76a	
^{1}H NMR	(600 MHz, $CDCl_3$) δ 4.58 (s, 2H, CH_2Br), 5.94 (s, 1H, OH), 6.95 (d, 1H, J = 8.4 Hz, ArH), 6.99 (d, 2H, J = 8.5 Hz, ArH), 7.12 (d, 2H, J = 8.8 Hz, ArH), 7.17 (t, 1H, J = 7.4 Hz, ArH), 7.31 (td, 1H, J = 8.5, 1.3 Hz, ArH), 7.49 (dd, 1H, J = 7.4, 1.3 Hz, ArH), 8.11 (d, 2H, J = 8.8 Hz, ArH), 8.14 (d, 2H, J = 8.5 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 28.0, 116.3, 117.1, 118.7, 120.0, 122.2, 124.8, 129.6, 129.7, 130.5, 130.6, 131.7, 149.7, 154.5, 160.0, 168.5, 175.7.
HRMS (ESI)	calcd for $C_{21}H_{16}BrN_2O_3$ 423.0339, found 423.0337 $[MH]^+$
77a	
^{1}H NMR	(500 MHz, CD_3OD) δ 4.57 (s, 2H, CH_2Br), 6.97 (d, 2H, J = 8.9 Hz, ArH), 7.03 (ddd, 1H, J = 7.9, 2.2, 1.2 Hz, ArH), 7.13 (d, 2H, J = 8.9 Hz, ArH), 7.16 (t, 1H, J = 2.2 Hz, ArH), 7.26 (dt, 1H, J = 7.9, 1.2 Hz, ArH), 7.40 (t, 1H, J = 7.9 Hz, ArH), 8.06 (d, 2H, J = 8.9 Hz, ArH), 8.12 (d, 2H, J = 8.9 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 79.6, 116.5, 117.3, 119.7, 120.7, 121.4, 123.4, 126.1, 130.5, 131.4, 131.6, 142.2, 157.9, 161.5, 163.6, 169.5, 177.5.
HRMS (ESI)	calcd for $C_{21}H_{16}BrN_2O_3$ 423.0339, found 423.0316 $[MH]^+$

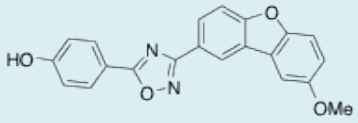
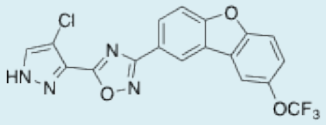
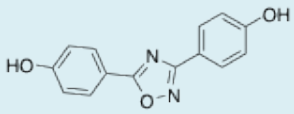
93a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.00 (d, 2H, J = 8.2 Hz, ArH), 7.41 (t, 1H, J = 7.4 Hz, ArH), 7.54 (d, 1H, J = 7.4 Hz, ArH), 7.69 (d, 1H, J = 7.8 Hz, ArH), 7.81 (d, 1H, J = 8.5 Hz, ArH), 8.02 (d, 2H, J = 8.2 Hz, ArH), 8.16 (d, 1H, J = 8.5 Hz, ArH), 8.26 (d, 1H, J = 7.8 Hz, ArH), 8.77 (s, 1H, ArH), 10.56 (br s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 111.8, 112.4, 114.2, 116.3, 120.2, 121.6, 121.7, 123.0, 123.5, 124.3, 126.5, 128.2, 130.1, 156.0, 162.0, 168.0, 175.5.
HRMS (ESI)	calcd for $C_{20}H_{13}N_2O_3$ 329.0926, found 329.0908 $[MH]^+$
94a	
^{1}H NMR	(600 MHz, $CDCl_3$) δ 7.03 (d, 2H, J = 8.5 Hz, ArH), 7.94 (d, 1H, J = 9.0 Hz, ArH), 7.98–8.00 (m, 2H, ArH), 8.08 (d, 2H, J = 8.5 Hz, ArH), 8.31 (d, 1H, J = 9.0 Hz, ArH), 8.94 (s, 1H, ArH), 9.10 (s, 1H, ArH), 10.60 (s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 112.9 (d, 1C, J_{CF} = 0.4 Hz), 114.2, 116.4, 120.1 (d, 1C, J_{CF} = 3.9 Hz), 121.4, 122.3, 123.6, 123.8, 124.6 (q, 1C, J_{CF} = 31.7 Hz), 124.6 (q, J_{CF} = 272.1 Hz), 125.3 (d, J_{CF} = 3.4 Hz), 127.7, 130.2, 157.7 (d, J_{CF} = 1.2 Hz), 157.7, 162.1, 168.0, 175.6.
^{19}F NMR	(282 MHz, acetone-d_6) δ -61.7 (s, 3F).
HRMS (ESI)	calcd for $C_{21}H_{10}F_3N_2O_3$ 395.0649, found 395.0656 $[M-H]^-$
78a	
^{1}H NMR	(600 MHz, CD_3OD) δ 6.89 (d, 2H, J = 9.0 Hz, ArH), 7.38 (d, 2H, J = 8.5 Hz, ArH), 7.91 (d, 2H, J = 9.0 Hz, ArH), 8.06 (d, 2H, J = 8.5 Hz, ArH).
^{13}C NMR	(100 MHz, CD_3OD) δ 116.4, 116.5, 121.6, 121.8 (q, 1C, J_{CF} = 256.4 Hz), 130.3, 131.9, 133.0, 152.2, 158.6, 163.7, 166.5.
^{19}F NMR	(282 MHz, CD_3OD) δ -60.8 (s, 3F).
HRMS (ESI)	calcd for $C_{15}H_{10}F_3N_2O_3$ 323.0638, found 323.0635 $[MH]^+$

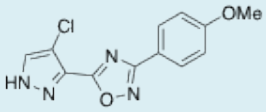
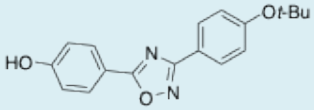
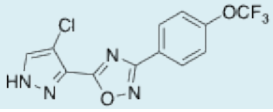
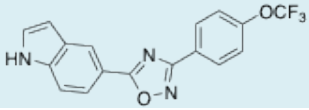
79a	
^{1}H NMR	(600 MHz, acetone-d_6) δ 6.93 (d, 2H, J = 9.1 Hz, ArH), 7.01 (d, 2H, J = 9.1 Hz, ArH), 7.06 (d, 2H, J = 8.8 Hz, ArH), 7.08 (d, 2H, J = 8.8 Hz, ArH), 8.08 (d, 2H, J = 8.8 Hz, ArH), 8.09 (d, 2H, J = 8.8 Hz, ArH), 8.83 (br s, 2H, OH).
^{13}C NMR	(150 MHz, acetone-d_6) δ 116.6, 117.1, 117.3, 117.9, 121.9, 122.6, 129.9, 131.0, 148.9, 155.4, 162.6, 162.7, 169.0, 176.6.
HRMS (ESI)	calcd for $C_{20}H_{14}N_2NaO_4$ 369.0846, found 369.0835 $[MH]^+$
80a	
^{1}H NMR	(500 MHz, acetone-d_6) δ 7.08 (d, 2H, J = 8.8 Hz, ArH), 7.18 (d, 2H, J = 8.0 Hz, ArH), 7.27 (d, 2H, J = 8.2 Hz, ArH), 8.09–8.11 (m, 4H, ArH), 8.20 (d, 2H, J = 8.2 Hz, ArH).
^{13}C NMR	(125 MHz, acetone-d_6) δ 116.5, 117.1, 119.3, 120.7, 124.1, 127.0, 130.3, 131.1, 133.0, 142.5, 159.6, 161.6, 162.8, 168.9, 176.8.
HRMS (ESI)	calcd for $C_{21}H_{15}N_2O_5$ 375.0975, found 375.0956 $[MH]^+$
81a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 6.99 (d, 2H, J = 8.8 Hz, ArH), 7.23 (d, 2H, J = 8.9 Hz, ArH), 7.42 (ddd, 1H, J = 7.9, 2.4, 1.2 Hz, ArH), 7.55 (dd, 1H, J = 2.4, 1.2 Hz, ArH), 7.59 (t, 1H, J = 7.9 Hz, ArH), 7.79 (dt, 1H, J = 7.9, 1.2 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 8.11 (d, 2H, J = 8.9 Hz, ArH), 10.57 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 114.2, 116.5, 119.1, 119.5, 121.7, 123.6, 125.2, 129.4, 130.3, 130.7, 137.0, 155.9, 159.2, 162.2, 167.1, 167.6, 175.6.
HRMS (ESI)	calcd for $C_{21}H_{15}N_2O_5$ 375.0975, 375.0965 found $[MH]^+$

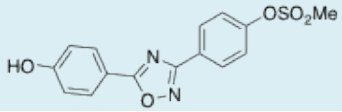
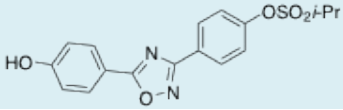
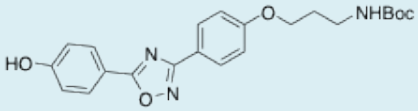
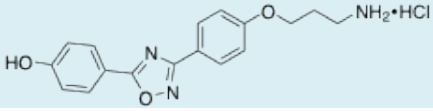
82a	
^{1}H NMR	(500 MHz, acetone-d_6) δ 7.08 (d, 2H, J = 9.0 Hz, ArH), 7.09 (d, 2H, J = 9.0 Hz, ArH), 7.22 (dd, 1H, J = 7.8, 1.0 Hz, ArH), 7.40 (td, 1H, J = 7.8, 1.0 Hz, ArH), 7.69 (td, 1H, J = 7.8, 1.7 Hz, ArH), 8.03 (dd, 1H, J = 7.8, 1.7 Hz, ArH), 8.09 (d, 2H, J = 9.0 Hz, ArH), 8.11 (d, 2H, J = 9.0 Hz, ArH).
^{13}C NMR	(125 MHz, acetone-d_6) δ 96.9, 116.5, 117.1, 118.4, 122.3, 123.3, 125.8, 129.9, 131.0, 133.1, 135.0, 155.7, 161.8, 162.7, 166.4, 169.0, 176.6.
HRMS (ESI)	calcd for $C_{21}H_{13}N_2O_5$ 373.0830, 373.0814 found $[M-H]^-$
83a	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 7.00 (d, 2H, J = 8.8 Hz, ArH), 7.09 (dd, 1H, J = 7.7, 1.0 Hz, ArH), 7.15 (d, 2H, J = 8.8 Hz, ArH), 7.31 (td, 1H, J = 7.7, 1.0 Hz, ArH), 7.52 (td, 1H, J = 7.7, 1.8 Hz, ArH), 7.52 (br s, 1H, NH), 7.68 (br s, 1H, NH), 7.72 (dd, 2H, J = 7.7, 1.8 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 8.06 (d, 2H, J = 8.8 Hz, ArH), 10.56 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 114.1, 116.3, 118.3, 120.6, 121.1, 124.6, 128.8, 129.0, 130.1, 130.2, 132.0, 152.4, 159.6, 162.1, 166.7, 167.5, 175.4.
HRMS (ESI)	calcd for $C_{21}H_{16}N_3O_4$ 374.1135, found 374.1123 $[MH]^+$
84a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 4.99 (br s, 2H, NH_2), 6.60 (td, 1H, J = 7.8, 1.5 Hz, ArH), 6.85 (dd, 1H, J = 7.8, 1.6 Hz, ArH), 6.91 (dd, 1H, J = 7.8, 1.5 Hz, ArH), 6.97–6.98 (m, 1H, ArH), 6.99 (d, 2H, J = 8.9 Hz, ArH), 7.05 (d, 2H, J = 8.9 Hz, ArH), 8.02 (d, 2H, J = 8.9 Hz, ArH), 8.03 (d, 2H, J = 8.9 Hz, ArH), 10.55 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 114.2, 116.1, 116.3, 116.5, 116.7, 120.1, 121.3, 125.9, 128.9, 130.1, 140.3, 140.9, 160.3, 162.0, 167.6, 175.3.
HRMS (ESI)	calcd for $C_{20}H_{16}N_3O_3$ 346.1186, found 346.1199 $[MH]^+$

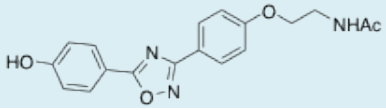
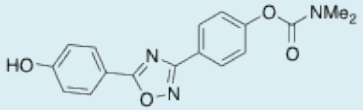
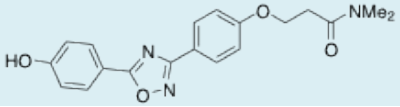
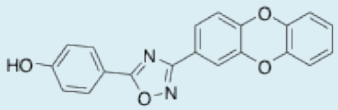
85a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 5.41 (br s, 1H, OH), 6.98–7.00 (m, 2H, ArH), 7.09–7.11 (m, 2H, ArH), 7.17–7.19 (m, 2H, ArH), 7.65–7.67 (m, 2H, ArH), 8.12–8.14 (m, 2H, ArH), 8.20–8.22 (m, 2H, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 106.9, 116.3, 117.2, 118.8, 118.9, 120.4, 124.0, 129.8, 130.6, 134.5, 157.6, 159.8, 160.9, 168.2, 175.8.
HRMS (ESI)	calcd for $C_{21}H_{14}N_3O_3$, 356.1030, found 356.1023 $[MH]^+$
85b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.24 (d, 2H, J = 8.5 Hz, ArH), 7.33 (d, 2H, J = 8.5 Hz, ArH), 7.89 (d, 2H, J = 8.5 Hz, ArH), 8.14 (d, 2H, J = 8.5 Hz, ArH), 8.37 (s. 1H, ArH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 106.8, 110.8, 119.2, 119.8, 120.0, 123.0, 130.2, 130.9, 134.1, 135.4, 158.2, 160.6, 168.0, 170.2.
HRMS (ESI)	calcd for $C_{18}H_{11}ClN_5O_2$, 364.0596, found 364.0614 $[MH]^+$
86b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 3.23 (s, 3H, CH_3), 7.31 (d, 2H, J = 8.5 Hz, ArH), 7.36 (d, 2H, J = 8.5 Hz, ArH), 7.97 (d, 2H, J = 8.5 Hz, ArH), 8.16 (d, 2H, J = 8.5 Hz, ArH), 8.39 (s, 1H, ArH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 43.7, 110.1, 118.7, 120.3, 122.3, 129.5, 129.7, 130.3, 133.4, 135.7, 157.8, 160.2, 167.4, 169.5.
HRMS (ESI)	calcd for $C_{18}H_{13}ClN_4NaO_4S$, 439.0238, found 439.0245 $[MNa]^+$
87b	
^{1}H NMR	(500MHz, DMSO-d_6) δ 2.57 (s, 3H, CH_3), 7.20 (d, 2H, J = 8.5 Hz, ArH), 7.30 (d, 2H, J = 8.5 Hz, ArH), 8.03 (d, 2H, J = 8.5 Hz, ArH), 8.14 (d, 2H, J = 8.0 Hz, ArH), 8.37 (s, 1H, ArH).
^{13}C NMR	(125MHz, DMSO-d_6) δ 27.3, 110.8, 119.0, 120.5, 122.5, 130.1, 130.9, 131.5, 133.2, 134.1, 158.9, 160.6, 168.0, 170.1, 197.2.
HRMS (ESI)	calcd for $C_{19}H_{14}ClN_4O_3$, 381.0749, found 381.0748 $[MH]^+$

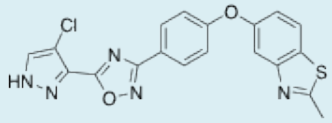
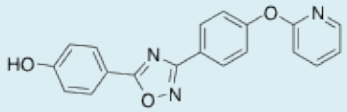
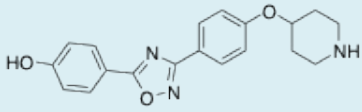
88a	
^{1}H NMR	(500 MHz, acetone-d_6) δ 4.24 (t, 1H, J = 5.5 Hz, OH), 4.69 (d, 2H, J = 5.5 Hz, CH_2), 7.03 (d, 1H, J = 7.6 Hz, ArH), 7.07–7.09 (m, 4H, ArH), 7.28 (t, 1H, J = 7.6 Hz, ArH), 7.35 (t, 1H, J = 7.6 Hz, ArH), 7.68 (d, 1H, J = 7.6 Hz, ArH), 8.08–8.12 (m, 4H, ArH), 9.37 (s, 1H, OH).
^{13}C NMR	(125 MHz, acetone-d_6) δ 59.5, 116.5, 117.1, 118.3, 120.9, 122.4, 125.8, 129.3, 129.6, 130.0, 131.0, 135.3, 153.3, 161.4, 162.7, 169.0, 176.6.
HRMS (ESI)	calcd for $C_{21}H_{17}N_2O_4$ 361.1183, found 361.1170 $[MH]^+$
89a	
^{1}H NMR	(300 MHz, $CDCl_3$) δ 4.52 (s, 2H, CH_2), 6.99 (d, 2H, J = 8.9 Hz, ArH), 7.04 (d, 2H, J = 8.9 Hz, ArH), 7.12 (d, 2H, J = 8.9 Hz, ArH), 7.41 (d, 2H, J = 8.9 Hz, ArH), 8.13 (d, 2H, J = 8.9 Hz, ArH), 8.14 (d, 2H, J = 8.9 Hz, ArH).
^{13}C NMR	(125 MHz, acetone-d_6) δ 34.0, 116.4, 117.1, 119.7, 120.5, 123.3, 130.1, 131.0, 132.1, 135.2, 157.3, 160.6, 162.7, 168.9, 176.7.
HRMS (ESI)	calcd for $C_{21}H_{16}BrN_2O_3$ 423.0339, found 423.0317 $[MH]^+$
90a	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 7.01–7.03 (m, 2H, ArH), 7.41–7.45 (m, 1H, ArH), 7.78–7.91 (m, 2H, ArH), 8.04–8.07 (m, 2H, ArH), 8.23–8.27 (m, 2H, ArH), 8.88 (d, 1H J = 12.4 Hz, ArH), 10.59 (s, 1H, OH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 108.2 (d, 1C, J_{CF} = 26.0 Hz), 112.8, 113.1 (d, 1C, J_{CF} = 9.4 Hz), 114.2, 115.6 (d, 1C, J_{CF} = 26.1 Hz), 116.4, 121.0, 121.7, 124.2 (d, 1C, J_{CF} = 2.3 Hz), 124.3 (d, 1C, J_{CF} = 5.1 Hz), 127.2, 130.2, 152.2, 158.0, 158.7 (d, 1C, J_{CF} = 237.7 Hz), 162.1, 168.0, 175.6.
HRMS (ESI)	calcd for $C_{20}H_{12}FN_2O_3$, 347.0826, found 347.0803 $[MH]^+$

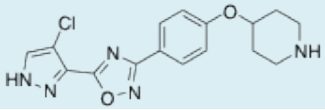
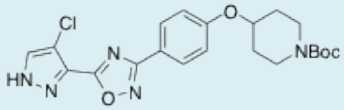
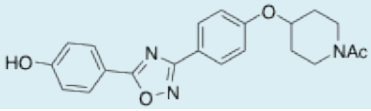
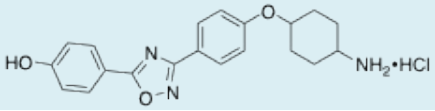
91a	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 3.87 (s, 3H, CH_3), 7.01 (d, 2H, J = 8.8 Hz, ArH), 7.10–7.13 (m, 1H, ArH), 7.62 (d, 1H, J = 8.8 Hz, ArH), 7.80 (d, 1H, J = 8.8 Hz, ArH), 7.91 (d, 1H, J = 2.4 Hz, ArH), 8.04 (d, 2H, J = 8.8 Hz, ArH), 8.14–8.17 (m, 1H, ArH), 8.82 (d, 1H, J = 1.6 Hz, ArH), 10.58 (s, 1H, OH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 55.8, 104.6, 112.3, 112.4, 114.2, 116.3, 116.4, 120.4, 121.3, 123.6, 124.7, 126.4, 130.1, 150.6, 156.0, 157.7, 162.0, 168.1, 175.5.
HRMS (ESI)	calcd for $C_{21}H_{15}N_2O_4$, 359.1026, found 359.1030 $[MH]^+$
92b	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 7.56–7.59 (m, 1H, ArH), 7.88 (d, 1H, J = 8.8 Hz, ArH), 7.95 (d, 1H, J = 8.8 Hz, ArH), 8.27–8.29 (m, 1H, ArH), 8.39 (s, 1H, ArH), 8.54 (s, 1H, ArH), 9.02 (d, 1H, J = 1.2 Hz, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 110.2, 112.9, 113.2, 115.3, 120.3 (q, 1C, J_{CF} = 256.0 Hz), 121.4, 121.5, 121.7, 124.0, 124.3, 127.6, 130.3, 133.5, 144.4, 144.4, 154.2, 158.1, 167.9.
HRMS (ESI)	calcd for $C_{18}H_9ClF_3N_4O_3$, 421.0310, found 421.0307 $[MH]^+$
95a	
^{1}H NMR	(500 MHz, CD_3OD) δ 6.91 (d, 2H, J = 8.9 Hz, ArH), 6.97 (d, 2H, J = 8.9 Hz, ArH), 7.95 (d, 2H, J = 8.9 Hz, ArH), 8.04 (d, 2H, J = 8.9 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 116.7, 116.9, 117.2, 119.4, 130.2, 131.3, 161.8, 163.6, 170.0, 177.2.
HRMS (ESI)	calcd for $C_{14}H_{11}N_2O_3$ 255.0764, found 255.0756 $[MH]^+$

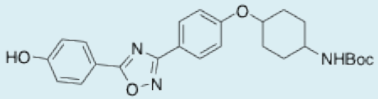
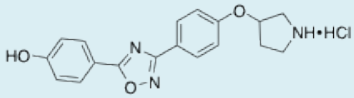
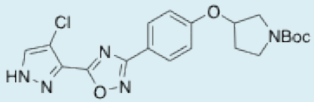
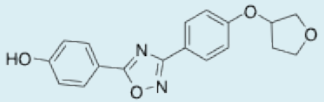
96b	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 3.85 (s, 3H, CH_3), 7.15 (d, 2H, J = 8.6 Hz, ArH), 8.02 (d, 2H, J = 8.6 Hz, ArH), 8.36 (s, 1H, ArH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 56.0, 110.7, 115.3, 118.9, 129.5, 130.8, 134.2, 162.5, 168.3, 169.8.
HRMS(ESI)	calcd for $C_{12}H_{10}ClN_4O_2$ 277.0487, found 277.0499 $[MH]^+$
97a	
^{1}H NMR	(600 MHz, $CDCl_3$) δ 1.41 (s, 9H, $C(CH_3)_3$), 5.64 (br s, 1H, OH), 6.98 (d, 2H, J = 8.5 Hz, ArH), 7.11 (d, 2H, J = 8.5 Hz, ArH), 8.06 (d, 2H, J = 8.5 Hz, ArH), 8.12 (d, 2H, J = 8.5 Hz, ArH).
^{13}C NMR	(150 MHz, $CDCl_3$) δ 29.1, 79.6, 116.3, 117.4, 121.9, 124.1, 128.7, 130.6, 158.5, 159.7, 168.8, 175.6.
HRMS (ESI)	calcd for $C_{18}H_{18}N_2NaO_3$ 333.1210, found 333.1202 $[MNa]^+$
78b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.60 (d, 2H, J = 8.5 Hz), 8.21 (d, 2H, J = 8.5 Hz), 8.37 (s, 1H).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 110.7, 120.4 (q, 1C, J_{CF} = 257.4 Hz), 122.1, 125.6, 129.9, 130.8, 133.8, 151.0, 167.4, 170.1.
^{19}F NMR	(376 MHz, DMSO) δ -56.75 (s, 3F).
HRMS (ESI)	calcd for $C_{12}H_7ClF_3N_4O_2$, 331.0204, found 331.0218 $[MH]^+$
78c	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 6.70 (ddd, 1H, J = 3.1, 2.3, 0.8 Hz, ArH), 7.31 (dd, 1H, J = 3.1, 2.3 Hz, ArH), 7.35 (d, 2H, J = 8.9 Hz, ArH), 7.51 (d, 1H, J = 8.6 Hz, ArH), 8.04 (dd, 1H, J = 8.6, 1.6 Hz, ArH), 8.24 (d, 2H, J = 8.9 Hz, ArH), 8.55 (dd, 1H, J = 1.6, 0.8 Hz, ArH), 8.61 (br s, 1H, NH).
^{13}C NMR	(100 MHz, $CDCl_3$) δ 104.2, 111.9, 116.1, 120.6 (q, 1C, J_{CF} = 258.2 Hz) 121.2, 122.1, 122.4, 126.15, 126.24, 128.2, 129.4, 138.4, 151.3, 168.0, 177.6.
HRMS (ESI)	calcd for $C_{17}H_{11}F_3N_3O_2$ 346.0798, found 346.0823 $[MH]^+$

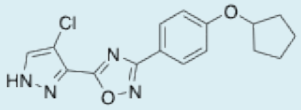
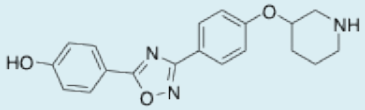
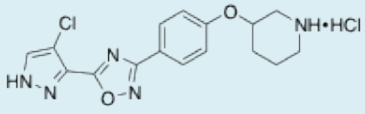
98a	
^{1}H NMR	(500 MHz, CD_3OD) δ 3.29 (s, 3H, CH_3), 4.87 (s, 1H, OH), 6.96 (d, 2H, *J* = 8.8 Hz, ArH), 7.48 (d, 2H, *J* = 8.7 Hz, ArH), 8.03 (d, 2H, *J* = 8.8 Hz, ArH), 8.18 (d, 2H, *J* = 8.7 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 38.0, 116.4, 117.3, 124.1, 127.6, 130.3, 131.4, 153.1, 163.7, 169.1, 177.8.
HRMS (ESI)	calcd for $C_{15}H_{13}N_2O_5S$ 333.0540, found 333.0549 $[MH]^+$
99a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.60 (d, 6H, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 3.55 (sept, 1H, *J* = 6.8 Hz, CH(C*H*$_3)_2$), 6.92 (d, 2H, *J* = 8.2 Hz, ArH), 7.39 (d, 2H, *J* = 8.4 Hz, ArH), 8.05 (d, 2H, *J* = 8.2 Hz, ArH), 8.16 (d, 2H, *J* = 8.4 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 16.8, 53.1, 116.1, 116.5, 122.4, 125.9, 129.2, 130.3, 150.8, 159.9, 167.7, 175.8.
HRMS (ESI)	calcd for $C_{17}H_{17}N_2O_5S$ 361.0853, found 361.0877 $[MH]^+$
100a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.46 (s, 9H, $C(CH_3)_3$), 2.00 (pent, 2H, *J* = 6.1 Hz, CH_2), 3.36 (q, 2H, *J* = 6.1 Hz, CH_2N), 4.04 (t, 2H, *J* = 6.1 Hz, CH_2O), 4.84 (br s, 1H, NH), 6.93 (d, 2H, *J* = 8.8 Hz, ArH), 6.97 (d, 2H, *J* = 8.6 Hz, ArH), 8.03 (d, 2H, *J* = 8.8 Hz, ArH), 8.05 (d, 2H, *J* = 8.6 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 28.6, 29.8, 38.2, 65.9, 80.1, 114.8, 116.3, 116.8, 119.9, 129.3, 130.5, 156.7, 160.4, 161.2, 168.6, 175.6.
HRMS (ESI)	calcd for $C_{22}H_{26}N_3O_5$ 412.1867, found 412.1851 $[MH]^+$
101a	
^{1}H NMR	(500 MHz, CD_3OD) δ 2.19 (s, 2H, CH_2), 3.18 (s, 2H, CH_2N), 4.18 (s, 2H, CH_2O), 6.95 (d, 2H, *J* = 8.4 Hz, ArH), 7.07 (d, 2H, *J* = 7.8 Hz, ArH), 7.99–8.05 (m, 4H, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 28.5, 38.8, 66.6, 116.0, 116.5, 117.2, 121.1, 130.1, 131.3, 162.4, 163.5, 169.6, 177.2.
HRMS (ESI)	calcd for $C_{17}H_{18}N_3O_3$ 312.1343, found 312.1350 $[MH]^+$

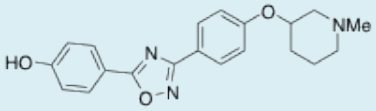
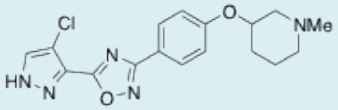
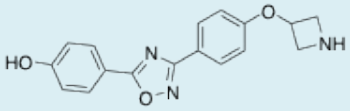
102a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 1.83 (s, 3H, CH_3), 3.44 (q, 2H, J = 5.6 Hz, CH_2N), 4.07 (t, 2H, J = 5.6 Hz, CH_2O), 6.99 (d, 2H, J = 9.0 Hz, ArH), 7.14 (d, 2H, J = 9.0 Hz, ArH), 8.00 (d, 2H, J = 9.0 Hz, ArH), 8.02 (d, 2H, J = 9.0 Hz, ArH), 8.14 (br s, 1H, NH), 10.54 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 22.5, 38.2, 66.6, 114.2, 115.1, 116.3, 118.8, 128.7, 130.1, 160.8, 162.0, 167.7, 169.5, 175.2.
HRMS (ESI)	calcd for $C_{18}H_{18}N_3O_4$ 340.1292, found 340.1286 $[MH]^+$
103a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 2.94 (s, 3H, CH_3N), 3.07 (s, 3H, CH_3N), 7.00 (d, 2H, J = 8.8 Hz, ArH), 7.35 (d, 2H, J = 8.8 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 8.08 (d, 2H, J = 8.8 Hz, ArH), 10.58 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 36.2, 36.4, 114.1, 116.3, 122.7, 123.2, 128.2, 130.1, 153.5, 153.7, 162.1, 167.5, 175.5.
HRMS (ESI)	calcd for $C_{17}H_{16}N_3O_4$ 326.1135, found 326.1149 $[MH]^+$
104a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 2.83 (t, 2H, J = 5.0 Hz, CH_2), 2.84 (s, 3H, CH_3N), 3.01 (s, 3H, CH_3N), 4.28 (t, 2H, J = 5.0 Hz, CH_2N), 6.99 (d, 2H, J = 8.8 Hz, ArH), 7.12 (d, 2H, J = 8.8 Hz, ArH), 8.00 (d, 2H, J = 8.8 Hz, ArH), 8.02 (d, 2H, J = 8.8 Hz, ArH), 10.55 (s, 1H, OH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 32.1, 34.8, 36.7, 64.3, 114.2, 115.0, 116.3, 118.6, 128.8, 130.1, 160.9, 162.0, 167.7, 169.4, 175.2.
HRMS (ESI)	calcd for $C_{19}H_{20}N_3O_4$ 354.1448, found 354.1450 $[MH]^+$
105a	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 6.99 (d, 2H, J = 8.1 Hz, ArH, 7.00–7.05 (m, 5H, ArH), 7.17 (d, 1H, J = 9.1 Hz, ArH), 7.54 (s, 1H, ArH), 7.67 (d, 1H, J = 8.7 Hz, ArH), 8.01 (d, 2H, J = 8.1 Hz, ArH), 10.58 (s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 114.0, 114.7, 116.3, 117.23, 117.24, 117.3, 122.5, 123.5, 124.7, 124.8, 130.1, 140.9 (2C), 141.8, 143.8, 162.1, 166.9, 175.5.
HRMS (ESI)	calcd for $C_{20}H_{12}N_2NaO_4$ 367.0689, found 367.0661 $[MH]^+$

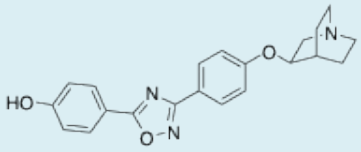
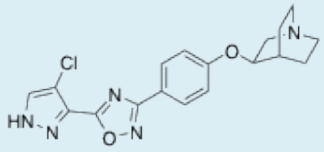
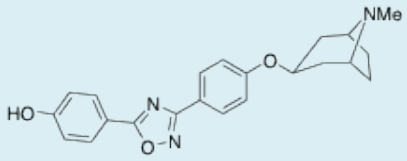
106b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 2.81 (s, 3H, CH_3), 7.20–7.25 (m, 3H, ArH), 7.66 (d, 1H, J = 2.5 Hz, ArH), 8.08–8.12 (m, 3H, ArH), 8.37 (s, 1H, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 20.5, 113.4, 118.3, 118.9, 121.4, 123.9, 129.9, 130.9, 131.9, 154.7, 154.9, 160.8, 168.2, 169.9.
HRMS (ESI)	calcd for $C_{19}H_{13}ClN_5O_2S$, 410.0473, found 410.0497 $[MH]^+$
107a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 7.00 (d, 2H, J = 8.2 Hz, ArH), 7.15 (d, 1H, J = 6.7 Hz, ArH), 7.20 (t, 1H, J = 6.7 Hz, ArH), 7.33 (d, 2H, J = 8.2 Hz, ArH), 7.92 (t, 1H, J = 6.7 Hz, ArH), 8.04 (d, 2H, J = 8.2 Hz, ArH), 8.11 (d, 2H, J = 8.2 Hz, ArH), 8.21 (d, 1H, J = 6.7 Hz, ArH), 10.58 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 112.2, 114.1, 116.3, 119.7, 121.5, 122.4, 128.7, 130.2, 140.5, 147.6, 156.6, 162.1, 162.4, 167.6, 175.5.
HRMS (ESI)	calcd for $C_{19}H_{14}N_3O_3$ 332.1030, found 332.1031 $[MH]^+$
108a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 1.90 (br s, 2H, CH_2), 2.15 (br s, 2H, CH_2), 3.09 (br s, 2H, CH_2N), 3.23 (br s, 2H, CH_2N), 4.79 (br s, 1H, CHOAr), 7.02 (d, 2H, J = 8.2 Hz, ArH), 7.19 (d, 2H, J = 8.2 Hz, ArH), 7.99 (d, 2H, J = 8.2 Hz, ArH), 8.00 (d, 2H, J = 8.2 Hz, ArH), 9.20 (br s, 1H, NH), 10.69 (s, 1H, OH).
^{13}C NMR	(125 MHz, DMSO-d_6) δ 27.0, 40.4, 69.2, 114.1, 116.2, 116.3, 119.0, 128.8, 130.0, 159.1, 162.1, 167.6, 175.3.
HRMS (FAB+)	calcd for $C_{19}H_{20}N_3O_3$ 338.1505, found 338.1498 $[MH]^+$

108b	
^{1}H NMR	(500 MHz, CD_3OD) δ 1.99–2.04 (m, 2H, CH_2), 2.12–2.17 (m, 2H, CH_2), 3.16–3.24 (m, 3H, NCH_2 + ArOCH), 3.34–3.39 (m, 2H, NCH_2), 7.10 (d, 2H, J = 8.8 Hz, ArH), 7.94 (s, 1H, ArH), 8.05 (d, 2H, J = 8.8 Hz, ArH).
^{13}CNMR	(100 MHz, CD_3OD) 27.2, 40.7, 68.6, 111.7, 115.6, 116.1, 118.6, 119.9, 129.2, 129.3, 159.6, 168.3
HRMS (ESI)	calcd for $C_{16}H_{17}ClN_5O_2$, 346.1065, found 346.1088 $[MH]^+$
109b	
^{1}H NMR	(500MHz, $CDCl_3$) δ 1.78–1.82 (m, 2H, CH_2), 1.95–1.99 (m, 2H, CH_2), 3.37–3.42 (m, 2H, NCH_2), 3.69–3.74 (m, 2H, NCH_2), 4.59 (br s, 1H, ArOCH), 7.03 (d, 2H, J = 8.5 Hz, ArH), 7.95 (s, 1H, ArH), 8.11 (d, 2H, J = 8.5 Hz, ArH).
^{13}C NMR	(100 MHz, $CDCl_3$) δ 28.6, 30.6, 40.8, 72.5, 79.9, 112.9, 116.3, 119.2, 129.6, 129.7, 131.9, 155.1, 160.1, 168.6.
HRMS (ESI)	calcd for $C_{21}H_{24}ClN_5NaO_4$ 468.1409, found 468.1400 $[MNa]^+$
110a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.84 (m, 4H, 2 × CH_2), 2.13 (s, 3H, CH_3), 3.65 (br s, 2H, CH_2N), 4.21 (br s, 2H, CH_2N), 4.62 (br s, 1H, ArOCH), 6.89 (d, 2H, J = 8.6 Hz, ArH), 6.94 (d, 2H, J = 8.0 Hz, ArH), 7.96–7.99 (m, 4H, ArH).
^{13}C NMR	(150 MHz, acetone-d_6) δ 21.5, 32.0, 43.9, 73.3, 116.6, 117.07, 117.14, 120.6, 129.9, 131.0, 160.9, 162.6, 162.7, 169.2, 176.5.
HRMS (ESI)	calcd for $C_{21}H_{22}N_3O_4$ 380.1605, found 380.1599 $[MH]^+$
111a	
^{1}H NMR	(500 MHz, CD_3OD) δ 1.55–1.67 (m, 4H, 2 × CH_2), 2.14 (m, 2H, CH_2), 2.27 (m, 2H, CH_2), 3.21 (br s, 1H, CHN), 4.44 (br s, 1H, CHOAr), 6.96 (d, 2H, J = 8.6 Hz, ArH), 7.07 (d, 2H, J = 8.4 Hz, ArH), 8.01–8.04 (m, 4H, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 29.6, 30.7, 50.6, 75.2, 116.5, 117.1, 117.2, 120.8, 130.2, 131.3, 161.5, 163.6, 169.7, 177.3.
HRMS (ESI)	calcd for $C_{20}H_{22}N_3O_3$ 352.1656, found 352.1655 $[MH]^+$

112a	
^{1}H NMR	(500 MHz, $CDCl_3$) δ 1.20–1.29 (m, 2H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$) 1.50–1.57 (m, 2H, CH_2), 1.99–2.05 (m, 2H, CH_2), 2.09–2.12 (m, 2H, CH_2), 3.46 (br s, 1H, CHN), 4.20–4.25 (m, 1H, ArOCH), 6.86–6.95 (m, 4H, ArH), 7.97–8.00 (m, 4H, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 25.6, 30.1, 30.7, 48.8, 75.0, 79.6, 115.6, 116.0, 116.1, 119.4, 129.2, 130.3, 132.8, 160.1, 161.5, 168.4, 175.8.
HRMS (ESI)	calcd for $C_{25}H_{30}N_3O_5$ 452.2180, found 452.2202 $[MH]^+$
113a	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 2.38 (dt, 2H, J = 7.8, 3.3 Hz, CH_2), 3.49–3.52 (m, 2H, CH_2N), 3.58–3.60 (m, 2H, CH_2N), 5.31–5.33 (m, 1H, ArOCH), 6.97 (d, 2H, J = 8.9 Hz, ArH), 7.15 (d, 2H, J = 8.9 Hz, ArH), 8.05 (d, 2H, J = 8.9 Hz, ArH), 8.10 (d, 2H, J = 8.9 Hz, ArH).
^{13}C NMR	(125 MHz, CD_3OD) δ 31.8, 45.4, 52.2, 77.1, 116.5, 117.2, 117.3, 122.0, 130.4, 131.4, 160.3, 163.7, 169.6, 177.5.
HRMS (ESI)	calcd for $C_{18}H_{18}N_3O_3$ 324.1343, found 324.1343 $[MH]^+$
114b	
^{1}H NMR	(400 MHz, $CDCl_3$) δ 1.48 (s, 9H, $C(CH_3)_3$), 2.13–2.21 (m, 2H, CH_2), 3.49–3.70 (m, 4H, 2 × CH_2), 4.95 (br s, 1H, ArOCH), 6.93 (d, 2H, J = 8.8 Hz, ArH), 7.91 (s, 1H, ArH), 8.02 (d, 2H, J = 8.8 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 28.7, 31.2, 44.2, 51.8, 76.3, 80.0, 112.5, 115.9, 119.4, 129.6, 131.1, 134.2, 154.9, 159.9, 168.5, 168.9.
HRMS (ESI)	calcd for $C_{20}H_{22}ClN_5NaO_4$, 454.1253, found 454.1266 $[MNa]^+$
115a	
^{1}H NMR	(400 MHz, CD_3OD) δ 2.10–2.16 (m, 1H, OCH_aH_bC*), 2.25–2.34 (m, 1H OCH_aH_bC*), 3.86–4.02 (m, 4H, 2 × CH_2), 5.09–5.12 (m, 1H, ArOCH), 6.96 (d, 2H, J = 8.4 Hz), 7.04 (d, 2H, J = 8.8 Hz), 8.04 (m, 4H).
^{13}C NMR	(100 MHz, CD_3OD) δ 32.6, 66.9, 72.7, 77.7, 115.2, 115.5, 115.9, 119.7, 128.9, 130.0, 160.1, 162.2, 168.3, 176.0.
HRMS (ESI)	calcd for $C_{18}H_{17}N_2O_4$, 325.1183, found 325.1205 $[MH]^+$

116b	
^{1}H NMR	(500 MHz, DMSO-d_6) δ 1.60 (br s, 2H), 1.72–1.74 (m, 4H, 2 × CH_2), 1.95–1.98 (m, 2H, CH_2), 4.91 (br s, 1H, ArOCH), 7.09 (d, 2H, J = 8.8 Hz, ArH), 7.99 (d, 2H, J = 8.8 Hz, ArH), 8.36 (s, 1H, ArH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 24.3, 32.9, 79.8, 110.7, 116.6, 118.5, 122.4, 129.5, 130.8, 134.2, 161.0, 168.4.
HRMS (ESI)	calcd for $C_{16}H_{16}ClN_4O_2$, 331.0956, found 331.0967 $[MH]^+$
117a	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 1.66–1.70 (m, 1H, CH), 1.86–1.94 (m, 3H, CH + CH_2), 3.07–3.11 (m, 2H, CH_2N), 3.28 (dd, 1H, J = 13.0, 4.6 Hz, CH_aH$_b$N), 3.35 (dd, 1H, J = 13.0, 2.4 Hz, CH$_a$$H_b$N), 4.83–4.85 (m, 1H, CHOAr), 7.00 (d, 2H, J = 8.9 Hz, ArH), 7.22 (d, 2H, J = 8.9 Hz, ArH), 8.02 (d, 2H, J = 8.9 Hz, ArH), 8.04 (d, 2H, J = 8.9 Hz, ArH), 8.57 (br s, 1H, NH), 10.56 (br s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 18.2, 25.9, 43.0, 45.6, 68.5, 114.2, 116.3, 116.5, 119.4, 128.9, 130.1, 158.8, 162.0, 167.6, 175.3.
HRMS (ESI)	calcd for $C_{19}H_{20}N_3O_3$ 338.1499, found 338.1510 $[MH]^+$
117b	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 1.70–1.73 (m, 1H, CH), 1.86–1.96 (m, 3H, CH + CH_2), 3.05–3.10 (m, 2H, CH_2N), 3.22–3.24 (m, 1H, CH_aH$_b$N), 3.33–3.37 (m, 1H, CH$_a$$H_b$), 4.88 (pent, 1H, J = 2.8 Hz, CHOR), 7.25 (d, 2H, J = 9.0 Hz, ArH), 8.05 (d, 2H, J = 9.0 Hz, ArH), 8.37 (s, 1H, ArH), 8.60 (br s, 1H, NH_aH$_b$), 9.24 (br s, 1H, NH$_a$$H_b$).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 18.3, 26.1, 42.7, 45.3, 68.5, 110.1, 116.5, 118.9, 129.0, 130.2, 133.4, 158.9, 167.5, 169.2.
HRMS (ESI)	calcd for $C_{16}H_{17}ClN_5O_2$ 346.1065, found 346.1069 $[MH]^+$

118a	
^{1}H NMR	(400 MHz, $CDCl_3$) δ 1.64–1.77 (m, 2H, CH_2), 1.95–2.05 (m, 2H, CH_2), 2.35–2.41 (m, 1H, CHN), 2.38 (s, 3H, CH_3N), 2.43–2.59 (m, 1H, CHN), 2.67–2.71 (m, 1H, CHN), 2.96–3.03 (m, 1H, CHN), 4.52 (pent, 1H, J = 3.9 Hz, CHOR), 6.83 (d, 2H, J = 9.0 Hz, ArH), 6.91 (d, 2H, J = 9.0 Hz, ArH), 8.00 (d, 2H, J = 9.0 Hz, ArH), 8.03 (d, 2H, J = 9.0 Hz, ArH).
^{13}C NMR	(100 MHz, $CDCl_3$) δ 22.4, 29.4, 35.8, 46.2, 55.5, 72.0, 116.0, 116.5, 120.2, 129.3, 130.5, 159.8, 161.2, 162.4, 168.5, 175.7.
HRMS (ESI)	calcd for $C_{20}H_{22}N_3O_3$ 352.1656, found 352.1677 $[MH]^+$
118b	
^{1}H NMR	(400 MHz, $CDCl_3$) δ 1.60–1.72 (m, 2H, CH_2), 1.93–2.04 (m, 2H, CH_2), 2.34–2.40 (m, 1H, CHN), 2.39 (s, 3H, CH_3N), 2.43–2.51 (m, 1H, CHN), 2.66–2.69 (m, 1H, CHN), 2.95–3.04 (m, 1H, CHN), 4.59 (pent, 1H, J = 3.9 Hz, CHOR), 7.04 (d, 2H, J = 9.1 Hz, ArH), 7.83 (s, 1H, ArH), 8.07 (d, 2H, J = 9.1 Hz, ArH).
^{13}C NMR	(125 MHz, $CDCl_3$) δ 22.6, 29.1, 46.3, 55.5, 59.3, 72.3, 112.8, 114.2, 116.1, 119.2, 129.6, 132.7, 160.3, 168.6, 168.7.
HRMS (ESI)	calcd for $C_{17}H_{19}ClN_5O_2$ 360.1222, found 360.1199 $[MH]^+$
119a	
^{1}H NMR	(400 MHz, DMSO-d_6) δ 4.06 (dd, 2H, J = 12.2, 4.8 Hz, CH_aH$_b$N), 4.50 (dd, 2H, J = 12.2, 6.6 Hz, CH$_a$$H_b$N), 5.19 (tt, 1H, J = 6.6, 4.8 Hz, CHOR), 7.00 (d, 2H, J = 9.1 Hz, ArH), 7.07 (d, 2H, J = 9.1 Hz, ArH), 8.02 (d, 2H, J = 9.1 Hz, ArH), 8.03 (d, 2H, J = 9.1 Hz, ArH), 9.05 (br s, 1H, NH), 10.61 (s, 1H, OH).
^{13}C NMR	(100 MHz, DMSO-d_6) δ 52.4, 67.6, 114.1, 115.5, 116.3, 120.0, 129.0, 130.0, 158.1, 162.0, 167.5, 175.4.
HRMS (ESI)	calcd for $C_{17}H_{16}N_3O_3$ 310.1186, found 310.1196 $[MH]^+$

120a	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 1.73–1.78 (m, 1H, CH), 1.86–1.91 (m, 1H, CH), 1.93–1.98 (m, 1H, CH), 2.04–2.1 (m, 1H, CH), 2.41–2.44 (m, 1H, CH), 3.15–3.20 (m, 1H, CHN), 3.22–3.33 (m, 4H, 2 × CH_2N), 3.81 (dd, 1H, J = 13.6, 8.1 Hz, CHN), 4.93–4.96 (m, 1H, CHOAr), 7.00 (d, 2H, J = 8.8 Hz, ArH), 7.18 (d, 2H, J = 8.8 Hz, ArH), 8.02 (d, 2H, J = 8.8 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 10.56 (s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 16.4, 20.0, 23.7, 45.2, 45.8, 52.5, 69.9, 114.2, 116.1, 116.3, 119.4, 128.9, 130.1, 158.9, 162.0, 167.6, 175.3.
HRMS (ESI)	calcd for $C_{21}H_{22}N_3O_3$ 364.1656, found 364.1637 $[MH]^+$
120b	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 1.57–1.64 (m, 1H, CH), 1.74–1.80 (m, 1H, CH), 1.82–1.88 (m, 1H, CH), 1.95–2.01 (m, 1H, CH), 2.28–2.32 (m, 1H, CH), 2.94–3.13 (m, 5H, CHN), 3.58–3.63 (m, 1H, CHN), 4.79–4.82 (m, 1H, CHOAr), 7.17 (d, 2H, J = 8.8 Hz, ArH), 8.03 (d, 2H, J = 8.8 Hz, ArH), 8.35 (s, 1H, ArH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 16.9, 20.7, 24.0, 45.1, 45.7, 52.7, 70.5, 110.2, 116.2, 118.8, 129.0, 130.8, 139.3, 159.2, 167.6, 169.1.
HRMS (ESI)	calcd for $C_{18}H_{19}ClN_5O_2$ 372.1222, found 372.1230 $[MH]^+$
121a	
^{1}H NMR	(600 MHz, DMSO-d_6) δ 2.16–2.18 (m, 2H, CH_2), 2.22–2.26 (m, 4H, 2 × CH_2), 2.38–2.40 (m, 2H, CH_2), 3.88–3.91 (m, 2H, 2 × CHN), 4.82–4.85 (m, 1H, CHOAr), 7.00 (d, 2H, J = 9.0 Hz, ArH), 7.17 (d, 2H, J = 9.0 Hz, ArH), 8.016 (d, 2H, J = 9.0 Hz, ArH), 8.02 (d, 2H, J = 9.0 Hz, ArH), 10.56 (s, 1H, OH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 23.8, 33.5, 53.6, 61.5, 67.0, 114.2, 116.1, 116.3, 119.1, 129.0, 130.1, 158.8, 162.0, 167.7, 175.3.
HRMS (ESI)	calcd for $C_{22}H_{24}N_3O_3$ 378.1812, found 378.1824 $[MH]^+$

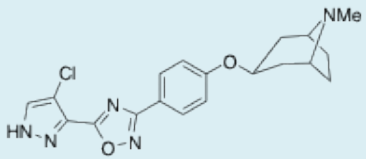
121b	
^{1}H NMR	(600 MHz, CD_3OD) δ 2.19–2.22 (m, 2H, CH_2), 2.23–2.26 (m, 2H, CH_2), 2.36–2.42 (m, 4H, 2 × CH_2), 2.66 (s, 3H, CH_3), 3.64–3.69 (m, 2H, 2 × CHN), 4.77–4.80 (m, 1H, CHOR), 7.08 (d, 2H, *J* = 8.8 Hz, ArH), 7.47 (br s, 1H, NH), 8.00 (s, 1H, ArH), 8.80 (d, 2H, 8.12, ArH).
^{13}C NMR	(150 MHz, DMSO-d_6) δ 25.0, 33.9, 59.8, 62.1, 68.6, 110.1, 116.1, 118.2, 129.0, 130.9, 132.9, 159.5, 167.6, 169.1.
HRMS (ESI)	calcd for $C_{19}H_{21}ClN_5O_2$ 386.1378, found 386.1397 $[MH]^+$

Table S2. Minimal-Inhibitory Concentrations (MICs)

Compound	*E. faecium* NCTC 7171 MIC (μg/mL)	*S. aureus* ATCC 29213 MIC (μg/mL)
59b	8	0.5
60b	128	1
61b	128	1
62a	1	2
63a	1	2
64a	0.5	2
65a	1	2
66a	1	2
67a	2	2
68a	1	2
69b	128	2
70a	2	4
71a	2	4
72c	1	1−2
73a	1	4
74a	2	4
75a	0.5	4
76a	16	4
77a	4	4
93a	>128	>128
94a	>128	>128

Compound	*E. faecium* NCTC 7171 MIC (μg/mL)	*S. aureus* ATCC 29213 MIC (μg/mL)
78a	16	1
78b	>128	>128
78c	64	>128
79a	32	32
80a	>128	64
81a	128	64
82a	>128	>128
83a	>128	>128
84a	128	>128
85a	>128	>128
85b	128	128
86b	128	128
87b	>128	>128
88a	>128	>128
89a	16	>128
90a	8	>128
91a	1	>128
92b	>128	>128
95a	32	>128
96a	16	32
96b	>128	>128
97a	>128	>128
98a	>128	>128
99a	>128	>128
100a	–	>128
101a	16	16
102a	128	>128
103a	>128	>128
104a	128	>128
105a	>128	>128
106b	>128	>128
107a	>128	>128

Compound	*E. faecium* NCTC 7171 MIC (μg/mL)	*S. aureus* ATCC 29213 MIC (μg/mL)
108a	16	16
108b	64	>128
109b	>128	>128
110a	>128	>128
111a	>128	>128
112a	–	>128
113a	16	16
114b	>128	>128
115a	>128	>128
116b	>128	>128
117a	64	64
117b	128	>128
118a	64	64
118b	128	128
119a	64	64
120a	32	64
120b	128	128
121a	32	32
121b	64	64

Plasma protein binding. Plasma protein binding experiments were performed with a rapid equilibrium dialysis (RED) device (Pierce Biotechnology, Thermo Scientific, Waltham, MA) and human plasma (BioreclamationIVT, Chestertown, MD). Thawed human plasma was centrifuged at 1,000 *g* for 10 min; the supernatant was removed, aliquoted, and stored at -20 ºC until analysis. Working solutions of each compound were prepared at a concentration of 5 mM in DMSO. An aliquot (0.5 μL) of each compound was added to 500 μL of thawed human plasma. A 200-μL aliquot of the plasma-compound mixture (200 μL) was loaded into the sample chamber of the RED device inserts, and 350 μL of phosphate buffered saline (pH 7.4) was loaded into the buffer chamber. Samples were dialyzed at 37 ºC with orbital shaking at 300 rpm for 2 h. Subsequently, sample and buffer chamber contents were removed. Buffer chamber contents were typically concentrated 10-fold using a heated, centrifugal concentrator (GeneVac, miVac Duo Concentrator, Ipswich, UK) and subsequently diluted with internal standard and analyzed using ultra performance liquid chromatography (UPLC) with multiple-reaction monitoring (MRM). A 50-μL aliquots from the sample chamber was quenched with 150 μL internal standard solution (1 μg/mL) and was centrifuged (22,000 *g* for 15 min) with subsequent analysis of the protein-free supernatant using UPLC-MRM. The percent bound was determined following the equations from the RED device manufacturer:

% Free = (Concentration buffer chamber/Concentration plasma chamber) x 100
% Bound = 100 - %Free

Mass spectrometry and bioanalytical method. Samples were analyzed on an UPLC system (Waters Corp., Milford, MA) coupled with a triple quadrupole mass spectrometer (TQD, Waters, Milford, MA) operating in MRM mode. Standard curves of each compound were prepared in 50 μL of mouse plasma, which were subsequently quenched with 150 μL of internal standard in acetonitrile. Samples were centrifuged at 22,000 *g* for 15 min, and the supernatants were analyzed using UPLC-MRM. Acquisition parameters were as follows: Supelco Ascentis C18 column (3 μm particle size, 10 cm × 2.1 mm; Sigma-Aldrich, St. Louis, MO), electrospray ionization positive mode (ESI+), flow rate 0.5 mL/min, capillary voltage 4 kV, cone voltage 30 V, and collision voltage 25 V. The solvent program was as follows: 95% A-5% B for 0.25 min, 0.75-min linear gradient to 5% A-95% B, hold for 4 min, where A = 0.1% formic acid/water and B = 0.1% formic acid/acetonitrile. The methods were linear between 0-20 μM (R^2 values 0.98–0.99). MRM transitions for each compound are listed in the table below. Waters MassLynx software was used to calculate peak areas of the compound relative to those of the internal standard. A standard curve of the ratios plotted against standard concentration was generated, from which compound concentrations were determined using regression parameters.

Table S3. MRM Transitions for Quantification of Oxadiazoles

Compound	Precursor *m/z*	Product *m/z*
internal standard	401.1	122.8
59b	374.9	129.1
60b	408.0	129.1
61b	465.0	129.1
62a	415.0	121.1
69b	392.0	129.1
72c	371.9	144.3

XTT assay. The XTT cytotoxicity assay was carried out in triplicates using HepG2 cells (ATCC HB-8065), by a reported method.[1] The IC_{50} values were calculated with GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA).
Hemolysis. Hemolysis was performed using human blood by a reported method.[10]
MIC determination with ESKAPE panel of organisms. *E. faecium* NCTC (ATCC 19734), S. aureus ATCC 29213, *K. pneumonia* ATCC 700603, *A. baumannii* ATCC 17961, *P. aeruginosa* ATCC 17853, *E. aerogenes* ATCC 35029) and *E. coli* ATCC 25922) were purchased from the American Type Culture Collection (Manassas, VA). We followed a general literature method for determination of the MIC values.[1]
MIC determination in a broader panel of Gram-positive bacteria. *S. aureus* ATCC 29213, *S. aureus* ATCC 27660, *S. epidermis* ATCC 35547, *S. hemolyticus* ATCC 29970, *B. cereus* ATCC 13061, *B. licheniformis* ATCC 12759, *E. faecalis* ATCC 29212, and *E. faecium* NCTC7171 were

purchased from the American Type Culture Collection (Manassas, VA). *S. aureus* strains NRS70, NRS100, NRS119, NRS120, VRS1, and VRS2 were obtained from the Network on Antimicrobial Resistance in Staphylococcus aureus (Chantilly, VA). *E. faecalis* strains 201 and 99, and *E. faecium* strains 119-39A and 106 were collected from Wayne State University School of Medicine. Vancomycin was purchased from Sigma-Aldrich (St. Louis, MO) and linezolid was obtained from AmplaChem Inc, (Carmel, IN). The MICs of the oxadiazoles compared to vancomycin and linezolid, against an extended panel of Gram-positive organisms were determined using the broth microdilution technique according to the Clinical Laboratory Standards Institute (CLSI) guidelines. Cation adjusted Mueller-Hinton II broth (CAMHB-II, Becton Dickinson and Co, Sparks, MD) was used and the experiment was conducted in triplicates.

Animals. Female ICR mice (6–8 weeks old, ~20-g body weight, Envigo RMS, Inc. Indianapolis, IN) were used for the PK and mouse peritonitis studies. Animals were given Teklad 2918 Irradiated Rodent Diet (Envigo RMS, Inc. Indianapolis, IN) and water *ad libitum*. Mice were housed in polycarbonate shoebox cages with $^1/_4$ inch corncob (The Andersons Inc., Maumee, OH) and Alpha-dri (Sheperd Specialty Papers, Inc., Richland, MI) bedding at 72 ± 2 °F with a 12-h light/12-h dark cycle. All animal procedures were approved by the University of Notre Dame Institutional Animal Care and Use Committee.

Dose formulations. Compound **72c** was dissolved in 10% DMSO/25% Tween-80/65% water at a concentration of 5 mg/mL. The solution was sterilized with an Acrodisc syringe filter (Pall Life Sciences, Ann Arbor, MI) containing a 0.2 μm, 13 mm diameter PTFE membrane.

Full PK study. Mice (n = 3 per time point) were administered 100 μL (equivalent to 20 mg/kg) orally (po) of compound **72c** by gavage or intravenously (iv) by tail-vein injection. Terminal blood was collected by cardiac puncture with sodium heparin at the following time points: 0.5, 1, 2, 3, 4, 6, 9, 24, 36 h for po administration and 2, 5, 10, 20, 40 min and 1, 2, 3, 4, 8, 24 h for iv administration. Whole blood was centrifuged at 1000 *g* for 10 min to obtain plasma. Plasma samples were analyzed the day of collection by UPLC-MRM. The remaining plasma was stored at -80 ºC.

Pharmacokinetic parameters. Phoenix WinNonlin 6.3 (Certara LP, St Louis, MO) non-compartmental analysis with uniform weighing was used to calculate the area-under-the-curve (AUC), clearance (CL), volume of distribution (V_d), and terminal half-lives. Half-lives were estimated from the linear portion of the initial or terminal phase of the concentration–time data by linear regression, where the slope of the line was the rate constant k and $t_{1/2} = \ln 2/k$.

Mouse peritonitis study. Compound **72c** was evaluated in a mouse peritonitis model of infection, a simple and widely used model for evaluation of efficacy of drugs with the end points being death or survival. *S. aureus* ATCC 27660 was cultured in brain heart infusion agar overnight and colonies were used to inoculate brain heart infusion broth to an optical density of 0.5 at 540 nm. The inoculum was stored on ice and just prior to infection it was warmed to room temperature and mixed in 1:1 ratio with a sterile suspension of 10% mucin (Sigma-Aldrich Chemical Co., St Louis, MO, USA) in saline to obtain a final bacterial concentration of 5×10^7 CFU/mL and 5% mucin. The mice were divided into 3 groups (n = 6 mice per group) and each mouse was injected ip with 0.5 mL of the final bacterial suspension. The mice were treated with **72c** (20 mg/kg), vancomycin (5 mg/kg) or vehicle, at 30 min and 7.5 h after infection given intravenously by tail-vein injection. The animals were monitored for 2 days. Survival was 3 of 6 mice with **72c**, 6 of 6 with vancomycin, and 0 of 6 with vehicle.

Mouse neutropenic thigh infection study. Mice (n = 8 per group) were rendered neutropenic by intraperitoneal administration of cyclophosphamide (200 mg/kg) at 4 days and 1 day prior to

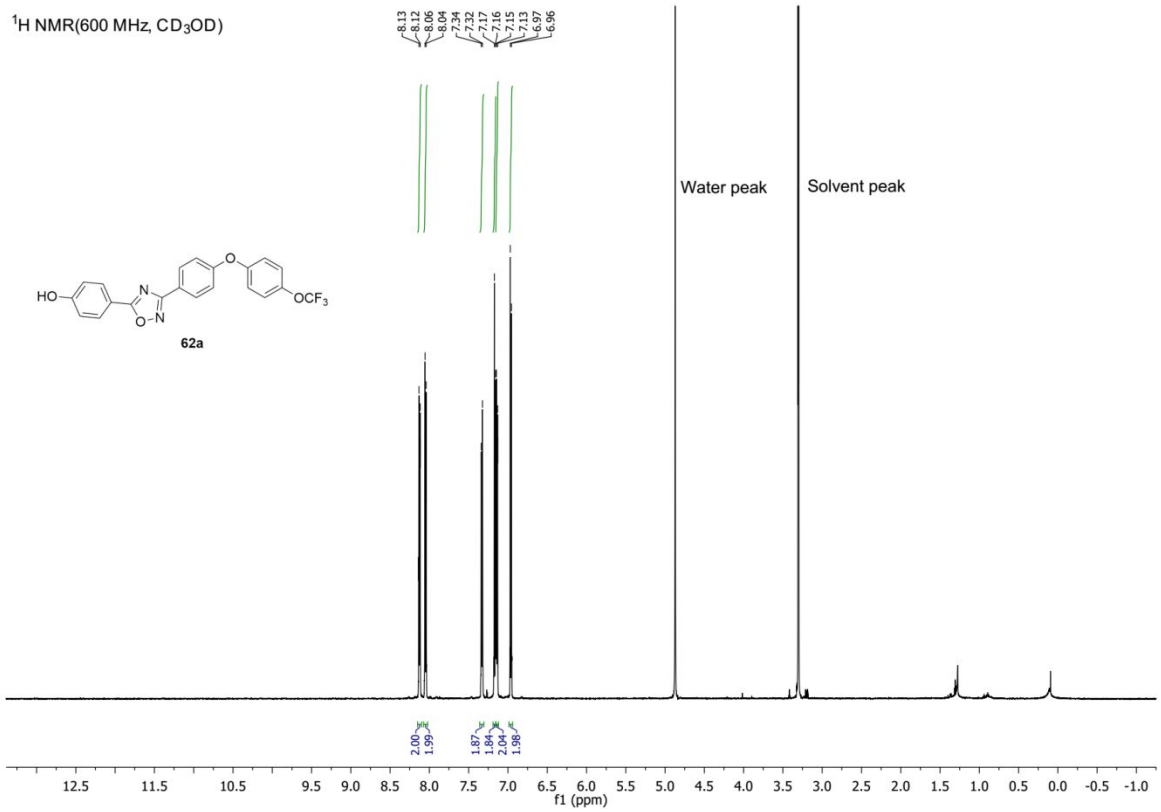
infection. MRSA strains NRS70 (linezolid-sensitive) and NRS119 (linezolid-resistant) were injected (10^5 cfu) into the right thighs. A single oral dose at 40 mg/kg of compounds **72c**, **8**, linezolid, or vehicle (10% DMSO/25% Tween-20/65% water) was given by oral gavage 1 h after infection. The infected thighs were harvested at 48 h after infection, homogenized, and plated for colony counts. The uninfected thighs were also harvested, homogenized, and analyzed for drug levels by UPLC with MRM detection. Terminal blood was also collected by cardiac puncture, centrifuged to obtain plasma, and the plasma was analyzed for drug concentrations by UPLC with MRM detection. Drug concentrations are shown in Table S4.

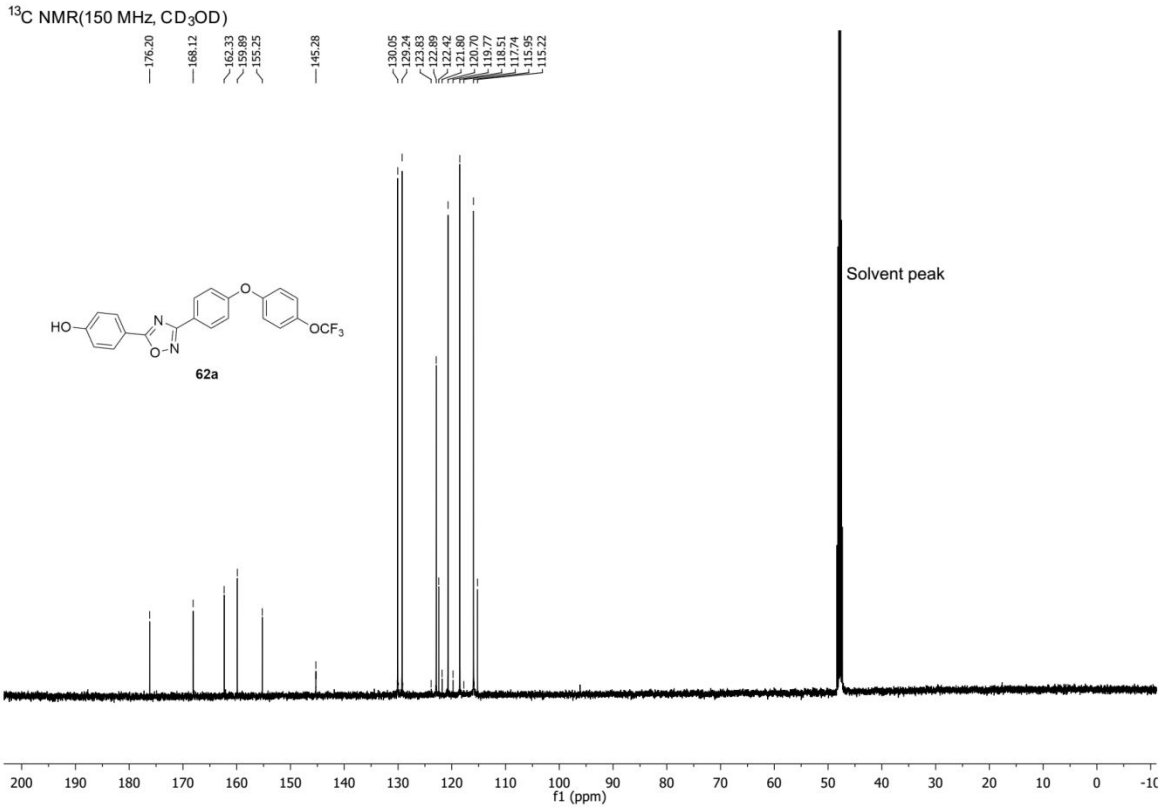
Table S4. Drug Concentrations in Neutropenic Thigh Infected Mice (n = 8 mice per group)

Treatment	NRS70		NRS119	
	Plasma (μg/mL)	Thigh (μg/g tissue)	Plasma (μg/mL)	Thigh (μg/g tissue)
Compound **8**	0.91 ± 0.46	7.6 ± 2.3	0.61 ± 0.29	6.0 ± 1.2
Compound **72c**	0.63 ± 0.18	5.8 ± 1.4	0.41 ± 0.14	6.4 ± 1.3
Linezolid	NQ[a]	NQ[a]	NQ[a]	NQ[a]

[a]NQ = non quantifiable

Figure S1. NMR Spectra for Representative Compounds 62a, 60b and 72c





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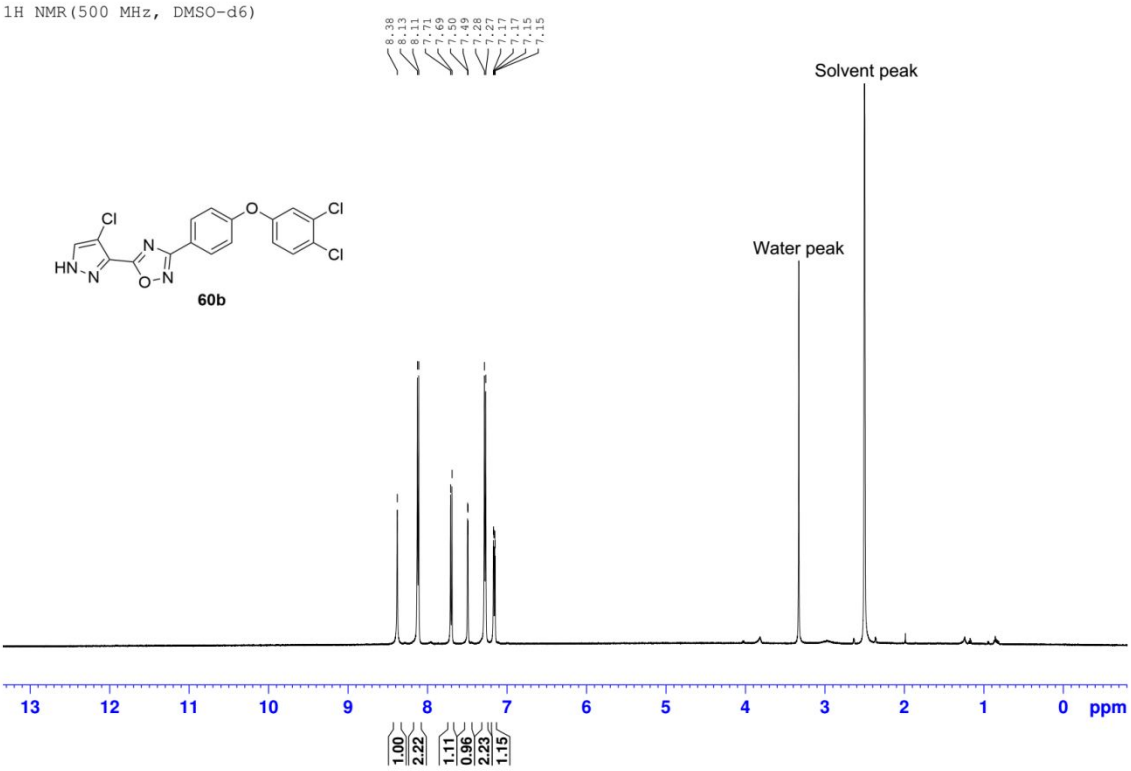
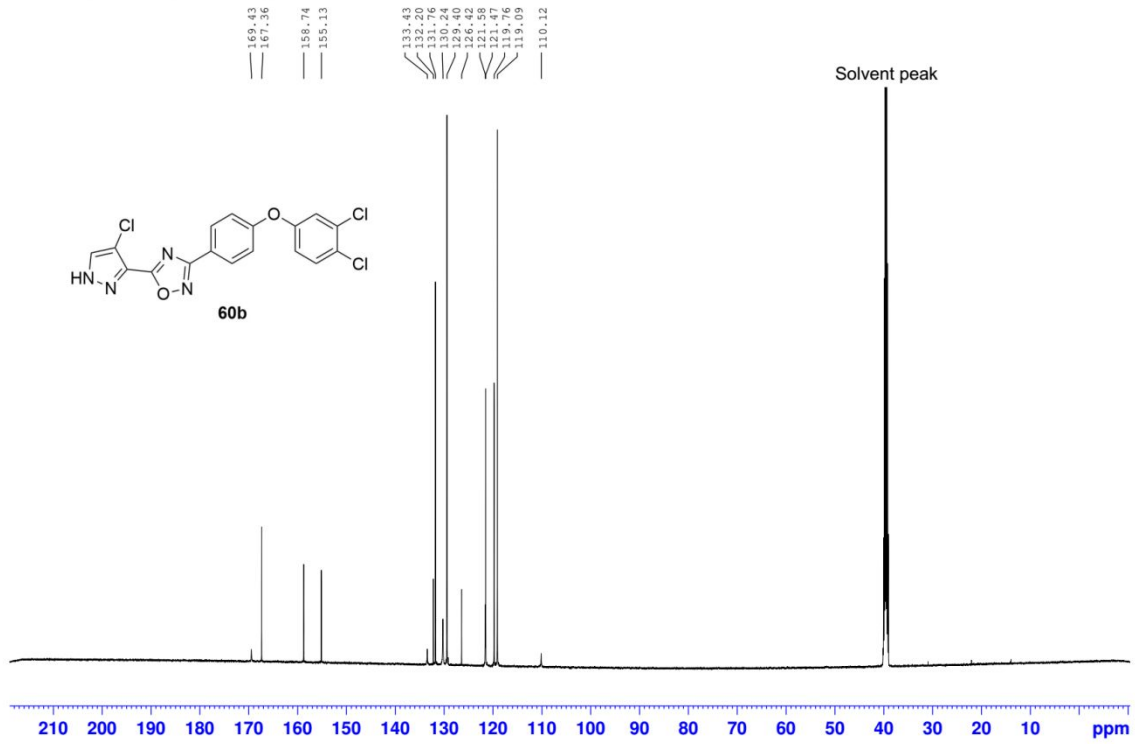
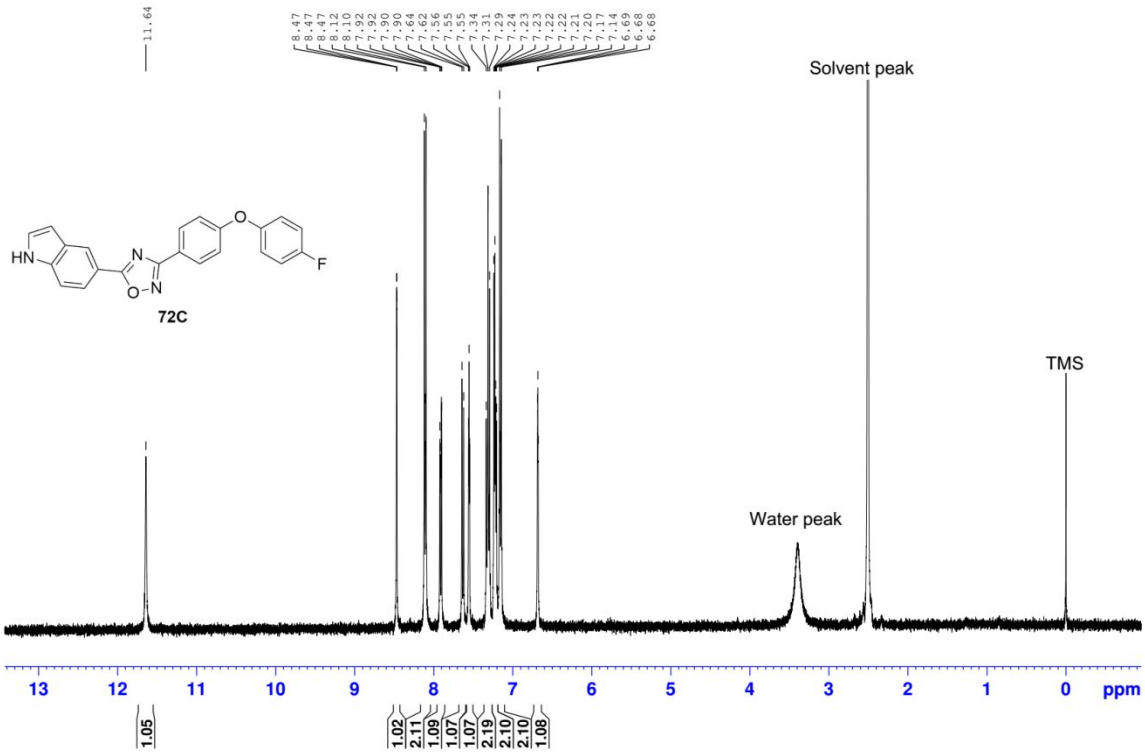


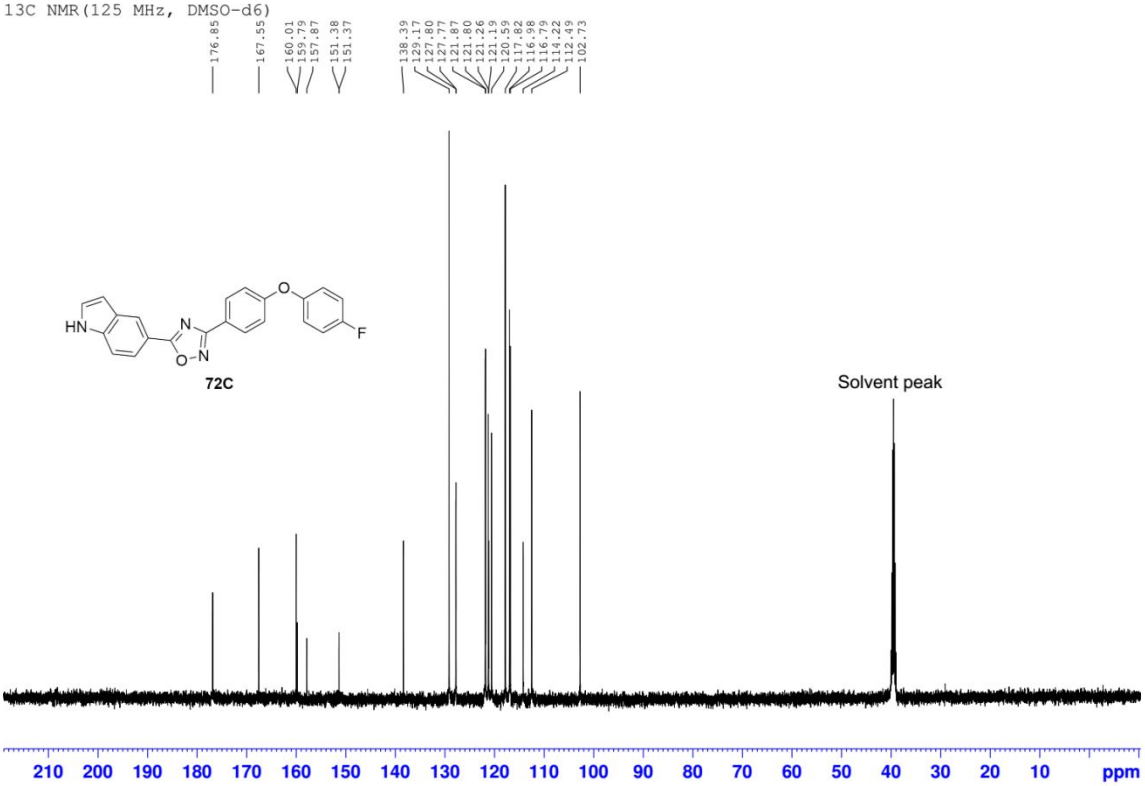
13C NMR(125 MHz, DMSO-d6)

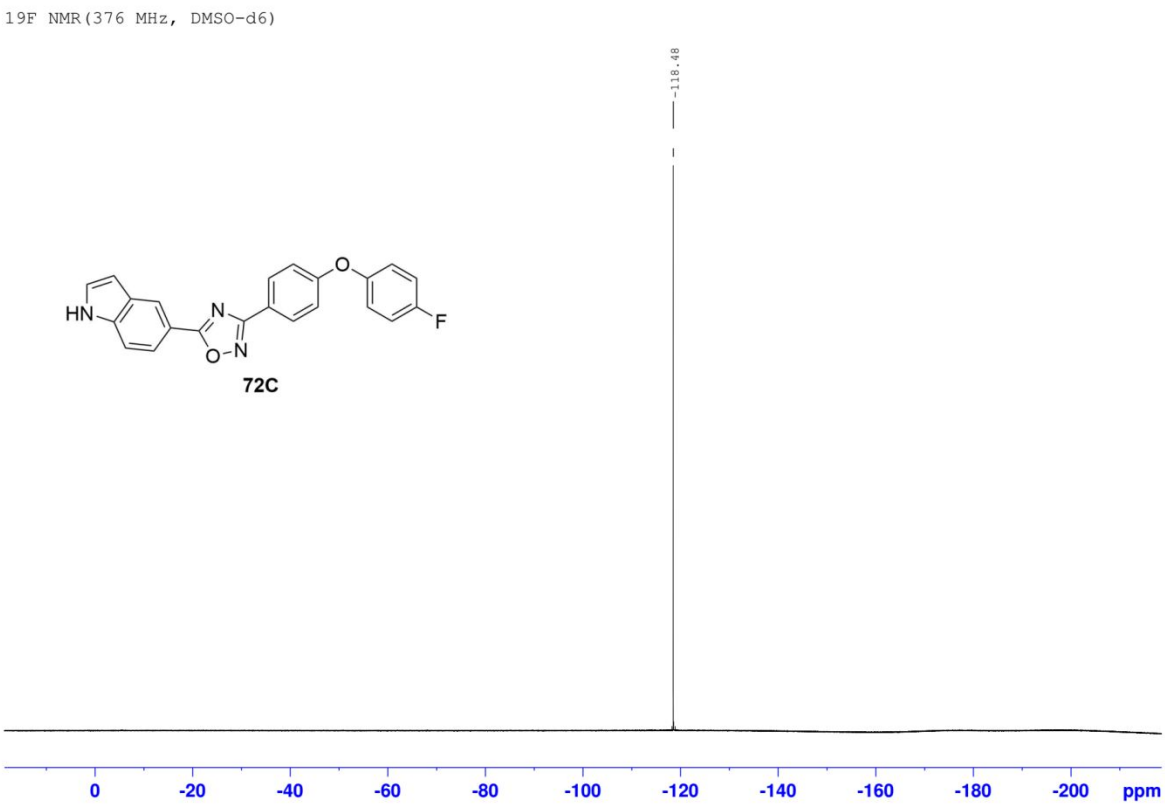


1H NMR(400 MHz, DMSO-d6)



13C NMR(125 MHz, DMSO-d6)





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