SUPPLEMENTARY INFORMATION

Contents:

1. Antibacterial activity

Clinical control strains of *Enterococcus faecalis* (Gram-positive, ATCC 29212), *Escherichia coli* (Gram-negative, ATCC 25922), *Pseudomonas aeruginosa* (Gram-negative, ATCC 27853), and *Staphylococcus aureus* (Gram-positive, ATCC 25923) were obtained from Microbiologics Inc. (St. Cloud, Minnesota, USA). Bacterial cultures were initiated on cation-adjusted MH (Mueller Hinton) agar (Becton Dickinson, Franklin Lakes, NJ, USA) slants and prior to the assays, suspensions were prepared in cation-adjusted MH broth (Becton Dickinson, Franklin Lakes, NJ, USA) and incubated at 37 °C for 16–20 h at 100 rpm. Antimicrobial assays were performed by the broth microdilution method in 96-well plate format according to the CLSI guidelines[1] and according to the reported procedures.[2]

Table 1S. Antibacterial activity (expressed as % of inhibition) of the tested compounds against selected Gram-positive and Gram-negative bacterial strains at 50 μM concentration.

Compound	Inhibition (%)[a]			
	E. faecalis (ATCC 29212)	*S. aureus* (ATCC 25923)	*E. coli* (ATCC 25922)	*P. aeruginosa* (ATCC 27853)
7	17 ± 6.7	4.5 ± 8.3	9.0 ± 5.8	-24 ± 10
16	15 ± 10	-6.0 ± 26	0.20 ± 0.87	-37 ± 18
17	**25 ± 10**	-22 ± 6.2	-2.7 ± 1.0	-11 ± 10

25	-18 ± 19	-60 ± 6.4	2.9 ± 0.7	8.3 ± 5.7
26	**17 ± 10**	-6.3 ± 20	**16 ± 8.2**	3.9 ± 4.0
27	**19 ± 10**	-49 ± 1.9	6.9 ± 0.8	2.9 ± 4.7
28	9.4 ± 8.1	-18 ± 14	14 ± 8.6	-1.3 ± 4.8

[a] Inhibition of growth (mean ± SD) measured at 50 μM concentration of test compounds after 24 h incubation (n = 3). Ciprofloxacin was used as a positive control; MIC (minimum inhibitory concentration) values against *E. faecalis*, *S. aureus*, *E. coli* and *P. aeruginosa* were 3, 1.5, 0.05 and 3 μM, respectively.

2. General information - chemistry

Chemicals were obtained from Acros Organics (Geel, Belgium), Sigma-Aldrich (St. Louis, MO, USA) and Apollo Scientific (Stockport, UK), and they were used without further purification. Analytical TLC was performed on silica gel Merck 60 F_{254} plates (0.25 mm), with visualisation with UV light and spray reagents. Column chromatography was carried out on silica gel 60 (particle size 240-400 mesh). HPLC analyses were performed on a 1100 system (Agilent Technologies, Santa Clara, CA, USA) with a UV-Vis detector (G1365B), a thermostat (G1316A) and an autosampler (G1313A). A C18 column was used (Phenomenex Luna 5 μm, 4.6 × 150 mm), with a flow rate of 1.0 mL/min. The eluent consisted of trifluoroacetic acid (0.1% in water) as solvent A and acetonitrile as solvent B. Melting points were determined on a Reichert hot stage microscope, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on an AVANCE III 400 spectrometer (Bruker Corporation, Billerica, MA, USA) in DMSO-d_6 or $CDCl_3$, with TMS as the internal standard. The infrared spectra were recorded on a Fourier-transform infrared spectrometer (Thermo Nicolet Nexus 470 ESP; Thermo Fisher Scientific, Waltham, MA, USA). Mass spectra were obtained using a mass spectrometer (Q-TOF Premier; Micromass, Waters, Manchester, UK). The purity of the tested compounds was ≥95%, as established by HPLC.

3. Synthetic procedures and analytical data

Methyl 2-(4-nitrophenoxy)acetate (3). To a suspension of 4-nitrophenol (**1**, 1.50 g, 11.0 mmol) and potassium carbonate (1.52 g, 11.0 mmol) in acetonitrile (50 mL) methyl bromoacetate (**2**, 1.05 mL, 11.0 mmol) was added dropwise. The reaction mixture was stirred overnight at rt. Solvent was evaporated under reduced pressure and the solid residue was dissolved in ethyl acetate (100 mL).

The organic phase was washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Yield: 80%; white crystals (2.12 g); mp: 98-100 ºC (98-99 ºC)[3]; Rf (dichlorometane/methanol = 10/1): 0.84; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.72 (s, 3H, CH_3), 5.02 (s, 2H, CH_2), 7.12 (d, 2H, J = 9.2 Hz, Ar-H-2, 6), 8.21 (d, 2H, J = 9.2 Hz, Ar-H-3,5); IR (ATR) ν = 3402, 3313, 3116, 2956, 1756, 1722, 1610, 1592, 1498, 1436, 1330, 1198, 1173, 1110, 1000, 856, 752 cm^{-1}.

Methyl 2-(4-aminophenoxy)acetate (4). Compound **3** (2.07 g) was dissolved in tetrahydrofuran (50 mL) and Pd/C (0.414 g) was added. The reaction was stirred under H_2 atmosphere for 5 h after which the catalyst was filtered off and the solvent was removed under reduced pressure, to obtain **4** (1.73 g) as a yellow oil. Yield: 96%; yellow oil (1.73 g); mp: 215-217 ºC; Rf (dichlorometane/methanol = 10/1): 0.29; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.68 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 4.68 (s, 2H, NH_2), 6.49-6.51(m, 2H, Ar-H-2,6), 6.65 (d, 2H, J = 9.2 Hz, Ar-H-3, 5); IR (ATR) ν = 3456, 3434, 3359, 3046, 2953, 2922, 2856, 1748, 1509, 1440, 1214, 826 cm^{-1}.

General procedure A. Synthesis of compounds 5 and 14 (compound 5 is given as an example). A solution of 4,5-dibromo-pyrrole-2-carboxylic acid (245 mg, 0.911 mmol), TBTU (319 mg, 0.993 mmol) and *N*-methylmorpholine (273 µL, 2.48 mmol) in dichloromethane (20 mL) was stirred at rt for 30 min. Compound **3** (144 mg, 0.69 mmol) was added and the mixture was stirred at 50 °C overnight. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (20 mL) and the organic phase was washed with water (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. To the crude product ether (10 mL) was added, the obtained suspension was sonicated and the undissolved solid was filtered off, washed with ether and dried.

Methyl 2-(4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetate (5). Compound was prepared according to general procedure A. Yield: 46%; yellow crystals (165 mg); mp: 190-192 ºC; Rf (ethyl acetate/petroleum ether = 1/2): 0.42; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 6.92-6.94 (m, 2H, Ar-H-2,6), 7.19 (s, 1H, pyrrole-CH), 7.60 (d, 2H, J = 9.2 Hz, Ar-H-3,5), 9.77 (s, 1H, NH), 12.88 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.77 (CH_3), 64.71 (CH_2), 98.03, 105.55, 113.44, 114.55, 121.49, 127.97, 132.38, 153.67, 157.07, 169.29; IR (ATR) ν = 3388, 3300, 3204, 2955, 2852, 1757, 1730, 1650, 1553, 1525, 1509, 1417,

1389, 1223, 1177, 1078, 973, 820, 750 cm^{-1}; MS (ESI) *m/z* (%) = 428.9 ($[M-H]^-$). HRMS for $C_{14}H_{11}N_2O_4Br_2$: calculated 428.9086; found 428.9088; HPLC: t_R = 19.554 min (98.6% at 280 nm).

General procedure B. Synthesis of compounds 6, 15 and 26 (compound 6 is given as an example. Compound **5** (670 mg, 1.55 mmol) and hydrazine monohydrate (0.754 mL, 15.5 mmol) were dissolved in ethanol (10 mL) and the mixture was stirred at 80 °C overnight. The reaction mixture was cooled on an ice bath and the white precipitate was filtered off, washed with ethanol and dried to obtain **6** as white crystals (0.565 mg).

4,5-Dibromo-*N*-(4-(2-hydrazineyl-2-oxoethoxy)phenyl)-1*H*-pyrrole-2-carboxamide (6). Compound was prepared according to general procedure B. Yield: 84%; white crystals (0.565 g); mp: 257-259 ºC; Rf (dichloromethane/methanol = 20/1): 0.12; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.37 (br s, 2H, NH_2), 4.47 (s, 2H, CH_2), 6.95 (d, 2H, J = 9.2 Hz, Ar-H), 7.19 (s, 1H, pyrrol-CH), 7.59 (d, 2H, J = 9.2 Hz, Ar-H), 9.34 (s, 1H, NH), 9.77 (s, 1H, NH), 12.87 (s, 1H, pyrrol-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 66.46 (CH_2), 98.02, 105.54, 113.43, 114.70, 121.46, 12.99, 132.28, 153.93, 157.07, 166.67; IR (ATR) ν = 3436, 3303, 3119, 3072, 2950, 2861, 2687, 1649, 1605, 1512, 1419, 1391, 1224, 1075, 831 cm^{-1}; MS (ESI) *m/z* (%) = 429.0 ($[M-H]^-$). HRMS for $C_{13}H_{11}N_4O_3Br_2$: calculated 428.9198; found 428.9201; HPLC: t_R = 5.843 min (96.4% at 280 nm).

General procedure C. Synthesis of compounds 7, 16 and 27 (compound 7 is given as an example). Compound **7** (150 mg, 0.35 mmol) and 1,1-carbonyldiimidazole (85 mg, 0.52 mmol) were suspended in 1,4-dioxane (15 mL), and the reaction mixture was heated at 101°C overnight. The solvent was evaporated under reduced pressure and the solid residue was purified using column chromatography (dichloromethane/methanol = 20/1), to obtain **7** as white solid (71 mg).

4,5-Dibromo-*N*-(4-((5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-pyrrole-2-carboxamide (7). Compound was prepared according to general procedure C. Yield: 45%; white solid (71 mg); mp: 260-262 ºC; Rf (dichloromethane/methanol= 20/1): 0.17; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.04 (s, 2H, CH_2), 7.04 (d, 2H, J = 8.8 Hz, Ar-H), 7.20 (s, 1H, pyrrole-CH), 7.63 (d, 2H, J = 8.8 Hz, Ar-H), 9.80 (s, 1H, NH), 12.53 (s, 1H, NH), 12.89 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.69 (CH_2), 98.05, 105.63, 113.50, 115.12, 121.44, 127.94, 132.94, 152.92, 153.28, 154.60, 157.10; IR (ATR) ν = 3344, 3205, 1775, 1745, 1641, 1605, 1553, 1524, 1508, 1414, 1385, 1334, 1299, 1222, 1171, 1093, 939, 820, 742, 656; MS (ESI) *m/z* (%) = 455.0

([M-H]$^-$). HRMS for $C_{14}H_9N_4O_4Br_2$: calculated 454.8991; found 454.8980; HPLC: t_R: 9.517 min (98.1% at 280 nm).

General procedure D. Synthesis of compounds 8, 17, 28 (compound 28 is given as an example). To a solution of compound **25** (51 mg, 0.096 mmol) in tetrahydrofuran (6 mL) 2 M NaOH (145 µL, 0.29 mmol) and water (2 mL) were added. The reaction mixture was stirred overnight at room temperature and neutralized with 1M HCl. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL). Organic phase was washed with 1M HCl (2 × 7 mL), saturated solution of $NaHCO_3$ (2 × 30 mL), brine (7 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure, to obtain **28** as grey solid (32 mg).

2-(4-(4,5-Dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetic acid (8). Compound was prepared according to general procedure D. Reported previously.[4]

***tert*-Butyl (2,4-dihydroxyphenyl)carbamate (10).** To a solution of 2,4-dihydroxybenzenaminium chloride (**9**, 2.75 g, 17.1 mmol) and triethylamine (2.61 mL, 18.7 mmol) in glacial acetic acid (100 mL) cooled on an ice bath, a solution of di-*tert*-butyl dicarbonate (5.57 g, 25.5 mmol) in methanol (5 mL) was added dropwise. The reaction mixture was stirred overnight at rt, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). Organic phase was washed with water (2 × 30 mL), 10% citric acid (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified with flash column chromatography (dichloromethane/methanol = 20/1) to obtain **10** (2.51 g) as a dark oil. Yield, 68%; dark oil (2.51 g); Rf (dichloromethane/methanol = 20/1): 0.16; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (s, 9H, 3 × CH_3), 6.14-6.17 (m, 1H, Ar-H-5), 6.30 (d, 1H, J = 2.8 Hz, Ar-H-3), 7.14 (d, 1H, J = 8.4 Hz, Ar-H-6), 7.66 (s, 1H, NH), 9.04 (s, 1H, OH), 9,40 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.11 (3 × CH_3), 78.46, 102.71, 105.57, 117.58, 123.88, 149.74, 153.59, 154.45; IR (ATR) ν = 3307, 2979, 2934, 1680, 1609, 1523, 1452, 1368, 1284, 1246, 1152, 1112, 1054, 971, 841, 802, 732 cm^{-1}; MS (ESI) *m/z* (%) = 224.1 ([M-H]$^-$). HRMS for $C_{11}H_{14}NO_4$: calculated 224.0923; found 224.0922.

***tert*-Butyl (2-(benzyloxy)-4-hydroxyphenyl)carbamate (11).** To a suspension of compound **10** (2.50 g, 11.9 mmol) and potassium carbonate (3.29 g, 23.7 mmol) in acetonitrile (100 mL) benzyl bromide (1.41 mL, 11.9 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred

overnight at rt. Solvent was removed under reduced pressure and the solid residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with water (3 × 20 mL), saturated solution of $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified with column chromatography (dichlorometane/ethyl acetate = 20/1) to obtain **11** (1.30 g) as a white solid. Yield: 36%; white solid (1.30 g); mp: 135-136 ºC; Rf (dichloromethane/ethyl acetate = 20/1): 0.20; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9H, 3 × CH_3), 5.06 (s, 2H, CH_2), 6.28-6.31 (m, 1H, Ar-H-5), 6.30 (d, 1H, J = 2.8 Hz, Ar-H-3), 7.16 (d, 1H, J = 8.8 Hz, Ar-H-6), 7.33-7.40 (m, 3H, 3 × Ar-H), 7.47-7.49 (m, 2H, 2 × Ar-H), 7.83 (s, 1H, NH), 9.29 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.12 (3 × CH_3), 69.30 (CH_2), 78.29, 100.68, 106.43, 118.69, 125.44, 127.37, 127.69, 128.28, 137.10, 151.99, 153.68, 155.14; IR (ATR) v = 3358, 3289, 3032, 2979, 1680, 1597, 1524, 1507, 1457, 1363, 1281, 1242, 1177, 1153, 1107, 1013, 974, 832, 702, 628 cm^{-1}; MS (ESI) *m/z* (%) = 314.1 ([M-H]$^-$). HRMS for $C_{18}H_{20}NO_4$: calculated 314.1392; found 314.1401.

Methyl 2-(3-(benzyloxy)-4-((*tert*-butoxycarbonyl)amino)phenoxy)acetate (12). To a suspension of compound **11** (500 mg, 1.63 mmol) and potassium carbonate (450 mg, 3.25 mmol) in acetonitrile (20 mL) methyl bromoacetate (155 µL, 1.63 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred overnight at rt. Solvent was removed under reduced pressure and the solid residue was dissolved in ethyl acetate (20 mL). The organic phase was washed with water (3 × 10 mL), saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, and the solvent was removed under reduced pressure to obtain **12** (0.610 g) as a yellow solid. Yield: 99%; yellow solid (610 mg); Mp: 101-103 ºC; Rf (dichloromethane/methanol = 20/1): 0.79; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (s, 9H, 3 × CH_3), 3.69 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.30-6.46 (m, 1H, Ar-H-5), 6.68 (d, 1H, J = 2.4 Hz, Ar-H-3), 7.31-7.41 (m, 4H, 4 × Ar-H-), 7.50-7.51 (m, 2H, 2 × Ar-H), 7.96 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.09 (3 × CH_3), 51.75 (CH_3), 64.60 (CH_2), 69.59 (CH_2), 78.60, 100.82, 104.93, 121.10, 124.67, 127.50, 127.78, 128.32, 136.91, 151.54, 153.46, 155.06, 169.18; IR (ATR) v = 3431, 3061, 3033, 2981, 2957, 1753, 1718, 1617, 1521, 1485, 1429, 1364, 1243, 1165, 1127, 1009, 826, 773, 701 cm^{-1}; MS (ESI) *m/z* (%) = 388.2 ([M-H]$^+$). HRMS for $C_{21}H_{26}NO_6$: calculated 388.1760; found 388.1767.

2-(Benzyloxy)-4-(2-methoxy-2-oxoethoxy)benzenaminium chloride (13). Compound **12** (0.550 g, 1.45 mmol) was dissolved in diethyl ether (20 mL), $HCl_{(g)}$ was bubbled through the solution for

40 min and the reaction mixture was stirred overnight at rt. Precipitated crystals were filtered off, washed with cold diethyl ether (2 × 10 mL) and dried. Yield: 42%; white crystals (185 mg); mp: 199-200 ºC; Rf (ethyl acetate/petroleum ether = 1/1): 0.55; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.25 (s, 2H, CH_2), 6.58-6.60 (m, 1H, Ar-H-5), 6.87 (d, 1H, J = 2.4 Hz, Ar-H-3), 7.40-7.44 (m, 4H, 4 × Ar-H), 7.57-7.59 (m, 2H, 2 × Ar-H), 7.91 (s, 3H, NH_3^+); ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.84 (CH_3), 64.77 (CH_2), 69.94 (CH_2), 101.38, 105.70, 114.11, 124.49, 127.67, 127.99, 128.38, 136.16, 152.16, 158.08, 168.88; IR (ATR) v = 2846, 2623, 2588, 1744, 1633, 1506, 1448, 1304, 1234, 1200, 1165, 1067, 997, 834, 751 cm^{-1}; MS (ESI) *m/z* (%) = 288.1 ([M-H]$^+$). HRMS for $C_{16}H_{18}NO_4$: calculated 288.1236; found 288.1241.

Methyl 2-(3-(benzyloxy)-4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetate (14). Compound was prepared according to general procedure A. Yield, 60%; brown crystals (115 mg); mp: 168-169 ºC; Rf (ethyl acetate/petroleum ether = 1/1): 0.56; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.06 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 6.50-6.53 (m, 1H, Ar-H-5), 6.72 (d, 1H, J = 2.4 Hz, Ar-H-3), 7.31 (s, 1H, Ar-H-6), 7.31-7.38 (m, 4H, 4 × Ar-H), 7.47 (d, 2H, J = 8 Hz, Ar-H), 9.21 (s, 1H, NH), 12.89 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 51.79 (CH_3), 64.72 (CH_2), 69.52 (CH_2), 98.00, 101.12, 105.13.113.36.119.98, 127.04, 127.67, 128.01, 128.32, 128.49, 137.00, 152.68, 156.11, 157.63, 169.13; IR (ATR) v = 3420, 3191, 3031, 2952, 2858, 1746, 1730, 1656, 1527, 1551, 1427, 1395, 1212, 1167, 1131, 1006, 972, 825, 742 cm^{-1}; MS (ESI) *m/z* (%) = 535.0 ([M-H]$^-$). HRMS for $C_{21}H_{17}N_2O_5Br_2$: calculated 534.9504; found 534.9514; HPLC: t_R = 14.643 min (95.8% at 280 nm).

***N*-(2-(Benzyloxy)-4-(2-hydrazineyl-2-oxoethoxy)phenyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (15).** Compound was prepared according to general procedure B. Yield: 74%; white crystals (43 mg); mp: 197-199 ºC; Rf (dichloromethane/methanol = 20/1): 0.21; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.35 (s, 2H, NH_2), 4.48 (s, 2H, CH_2), 5.16 (s, 2H, CH_2), 6.54-6.57 (m, 1H, Ar-H-5), 6.78 (d, 1H, J = 2.4 Hz, Ar-H-3), 7.11 (s, 1H, Ar-H-6), 7.29-7.38 (m, 4H, 4 × Ar-H), 7.48 (d, 1H, J = 7.2 Hz, Ar-H-2',6'), 9.21 (s, 1H, NH), 9.35 (s, 1H, NH), 12.90 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 66.48 (CH_2), 69.54 (CH_2), 98.01, 101.32, 105.35, 113.35, 119.86, 126.94, 127.10, 127.71, 128.01, 128.34, 128.50, 136.94, 152.67, 156.39, 157.64, 166.55; IR (ATR) v = 3429, 3326, 3105, 3065, 3029, 2913, 2861, 2805, 2675, 1682, 1656, 1556, 1532, 1425, 1294,

1221, 1177, 1066, 1023, 838, 735 cm^{-1}; MS (ESI) *m/z* (%) = 535.0 ($[M-H]^-$). HRMS for $C_{20}H_{17}N_4O_4Br_2$: calculated 534.9617; found 534.9626; HPLC: t_R = 9.472 min (95.2% at 280 nm).

***N*-(2-(Benzyloxy)-4-((5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (16).** Compound was prepared according to general procedure C. Yield: 22%; white solid (10 mg); mp: 215-217 ºC; Rf (dichloromethane/methanol = 20/1): 0,11; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.06 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 6.65-6.68 (m, 1H, Ar-H-5), 6.83 (d, 1H, J = 2.4 Hz, Ar-H-3), 7.11 (s, 1H, pyrrole-CH), 7.31-7.48 (m, 6H, 6 × Ar-H), 9.22 (s, 1H, NH), 12.54 (s, 1H, NH), 12.90 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 60.68 (CH_2), 69.60 (CH_2), 98.03, 101.51, 105.37, 105.59, 113.39, 120.49, 126.86, 127.13, 127.72, 127.96, 128.33, 136.88, 152.63, 152.78, 154.57, 155.73, 157.58; IR (ATR) v = 3420, 3297, 3213, 2962, 2931, 2854, 1800, 1664, 1551, 1530, 1497, 1431, 1288, 1212, 1171, 1132, 1039, 936, 743 cm^{-1}; MS (ESI) *m/z* (%) = 560.9 ($[M-H]^-$); HPLC: t_R = 13.070 min (95.4% at 280 nm).

2-(3-(Benzyloxy)-4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetic acid (17). Compound was prepared according to general procedure D. Yield, 47%; grey solid (25 mg); mp: 203-204 ºC; Rf (ethyl acetate/petroleum ether/acetic acid = 1/1/0.01): 0.04; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.67 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 6.48-6.51 (m, 1H, Ar-H-5), 6.72 (s, 1H, Ar-H-3), 7.11 (s, 1H, Ar-H-6), 7.31-7.48 (m, 6H, 6 × Ar-H), 9.21 (s, 1H, NH), 12.90 (s, 1H, pyrrole-NH), 13.02 (br s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.63 (CH_2), 69.55 (CH_2), 98.01, 101.18, 104.96, 105.28, 113.34, 119.78, 126.92, 127.08, 127.68, 128.02, 128.33, 137.00, 152.72, 156.31, 157.62, 170.09 (COOH); IR (ATR) v = 3419, 3210, 3116, 2914, 1742, 1639, 1615, 1523, 1547, 1490, 1421, 1384, 1289, 1268, 1210, 1180, 1135, 1018, 826, 755, 738 cm^{-1}; MS (ESI) *m/z* (%) = 521.0 ($[M-H]^-$). HRMS for $C_{20}H_{15}N_2O_5Br_2$: calculated 520.9348; found 520.9336; HPLC: t_R = 12.390 min (95.7% at 280 nm).

***tert*-Butyl-(1-(*tert*-butyloxy)carbonyl)(2-cyano-4-nitrophenyl)carbamate (19).** To a solution of 2-amino-5-nitrobenzonitrile (18, 3.00 g, 18.4 mmol) in a mixture of dichloromethane (30 mL) and acetonitrile (30 mL) di-*tert*-butyl dicarbonate (10.0 g, 45.8 mmol) and DMAP (50.0 g, 0.41 mol) were added and the mixture was heated at 70 ºC for 24 h. The solvent was evaporated and the solid residue was dissolved in ethyl acetate (50 mL). Organic phase was washed with water (2 × 20 mL), saturated solution of $NaHCO_3$ (2 × 20 mL), 0.5 M HCl (2 × 20 mL) and brine (2 x 20 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified

by crystallization from diethyl ether (30 mL). Yield: 40%; pale yellow crystals (5.2 g); mp: 87-88 ºC; R_f (dichloromethane/petroleum ether = 8/2): 0.19; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 18H, 2 × C(CH_3)$_3$), 7.93-7.95 (d, 1H, J = 8.8 Hz, Ar-H-6), 8.57-8.60 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, Ar-H-5), 8.90 (d, J = 2.44 Hz, 1H, Ar-H-3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.30 (C(CH_3)$_3$), 84.01 (C(CH_3)$_3$), 112.93, 114.34, 128.48, 129.01, 131.29, 146.58, 146.71, 149.08; IR (ATR) ν = 3080, 2978, 2936, 2237, 1798, 1529, 1368, 1347, 1276, 1254, 1150, 1095, 845, 832, 786, 776 cm^{-1}; MS (ESI) *m/z* (%) = 362.1 ([M-H]$^-$).

***tert*-Butyl (*E*)-(2-(*N*'-hydroxycarbamimidoyl)-4-nitrophenyl)carbamate (20).** To a solution of compound 19 (4.00 g, 11.0 mmol) in absolute ethanol (50 mL), hydroxylamine hydrochloride (2.29 g, 33.0 mmol) and trietylamine (6.10 mL, 44.0 mmol) were added. The reaction mixture was heated overnight at 65 ºC. The solvent was evaporated and the solid residue was dissolved in ethyl acetate (50 mL). Organic phase was washed with water (2 × 20 mL), saturated solution of $NaHCO_3$ (2 × 20 mL), 0.5 M HCl (2 × 20 mL) and brine (2 × 20 mL), dried with Na_2SO_4 and the solvent was removed under reduced pressure. Yield: 53%; pale yellow solid (3.33 g); mp: 155-156 ºC; R_f (dichloromethane/methanol = 20/1): 0.60; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.50 (s, 9H, C(CH_3)$_3$), 6.44 (s, 2H, NH_2), 8.23-8.26 (m, 1H, Ar-H), 8,45-8.51 (m, 2H, 2 × Ar-H), 10.36 (s, 1H, OH/NH), 11.16 (s, 1H, OH/NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.82 (C($\underline{C}H_3$)$_3$), 80.96 ($\underline{C}$(CH_3)$_3$), 118.00, 118.79, 123.36, 124.88, 140.93, 143.18, 151.02, 151.80; IR (ATR) ν = 3367, 2982, 1735, 1597, 1497, 1368, 1339, 1309, 1233, 1131, 900, 827, 771, 747, 706 cm^{-1}; MS (ESI) *m/z* (%) = 297.1 ([M-H]$^+$).

***tert*-Butyl (2-(5-methyl-1,2,4-oxadiazol-3-yl)-4-nitrophenyl)carbamate (21).** Compound 20 (2.86 g, 9.65 mmol) was dissolved in glacial acetic acid (30 mL), acetic anhydride was added (1.37 mL, 14.5 mmol) and the mixture was heated overnight at 85 ºC. The solvent was evaporated and the solid residue was dissolved in ethyl acetate (40 mL). Organic phase was washed with water (2 × 20 mL), saturated solution of $NaHCO_3$ (2 × 20 mL), 0.5 M HCl (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with flash column chromatography (ethyl acetate/petroleum ether = 1/8 to 1/4). Yield: 37%; yellow solid (1.6 g); mp: 139-142 ºC; R_f (ethyl acetate/petroleum ether = 1/4): 0.50; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52 (s, 9H, C(CH_3)$_3$), 2.76 (s, 3H, CH_3), 8.42 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.8 Hz, Ar-H), 8.50 (d,1H, J = 9.2 Hz, Ar-H), 8.81 (d, 1H, J = 2.8 Hz, Ar-H-3), 9.83 (s, 1H, NH);

^{13}C NMR (100 MHz, DMSO-d_6): δ 11.98 (CH_3), 27.73 ($C(CH_3)_3$), 81.69 ($C(CH_3)_3$), 113.75, 119.23, 124.80, 127.26, 141.45, 143.30, 151.51, 165.68, 177.35; IR (ATR) ν = 3293, 3076, 2977, 1725, 1579, 1547, 1512, 1341, 1284, 1237, 1131, 1048, 1025, 871, 852, 765, 683, 640 cm^{-1}; MS (ESI) *m/z* (%) = 221.1 ([M-H]$^+$).

***tert*-Butyl (4-amino-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamate (22).** To a solution of compound 21 (1.32 g, 4.11 mmol) in a mixture of ethanol (25 mL) and ethyl acetate (25 mL) tin(II) chloride (3.89 g, 20.5 mmol) was added and the reaction mixture was heated at 70 ºC for 6 h. Saturated solution of sodium hydrogen phosphate (20 mL) was added and the mixture was heated at 70 ºC for an additional hour. Solvent was evaporated and the solid residue was dissolved in ethyl acetate (30 mL). Organic phase was washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with flash column chromatography (ethyl acetate/petroleum ether = 1/2). Yield: 82%; white solid (1.08 g); mp: 154-155 ºC; R_f (ethyl acetate/petroleum ether = 1/1): 0.42; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (s, 9H, $C(CH_3)_3$), 2.76 (s, 3H, CH_3), 5.20 (s, 2H, NH_2), 6.72 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz, Ar-H-5), 7.24 (d, 1H, J = 2.8 Hz, Ar-H-3), 7.57-7.59 (m, 1H, Ar-H-6), 8.76 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.30 (CH_3), 28.05 ($C(CH_3)_3$), 78.93 ($C(CH_3)_3$), 113.60 (2 × C, overlapping signals), 117.25, 123.45, 126.33, 144.96, 152.88, 167.26, 176.18; IR (ATR) ν = 3432, 3357, 2978, 2932, 2360, 2340, 1713, 1528, 1525, 1513, 1296, 1281, 1246, 1231, 1156, 1056, 879, 764, 662 cm^{-1}; MS (ESI) *m/z*(%) = 291.1 ([M-H]$^+$), HRMS for $C_{14}H_{19}N_4O_3$: calculated 291.1457, found 291.1452.

Methyl 3-((4-((*tert*-butoxycarbonyl)amino)-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoate (23). To a suspension of compound 22 (0.844 g, 2.91 mmol) and potassium carbonate (804 mg, 5.81 mmol) in acetonitrile (20 mL) methyl malonyl chloride (343 µL, 3.19 mmol) in acetonitrile (5 mL) was added dropwise and the reaction mixture was stirred at rt overnight. The solvent was evaporated and the solid residue was dissolved in ethyl acetate (20 mL). Organic phase was washed with water (2 × 15 mL), saturated solution of $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with flash column chromatography (ethyl acetate/petroleum ether = 1/2). Yield: 43%; white solid (550 mg); mp: 143 ºC; R_f (ethyl acetate/petroleum ether = 1/1): 0.29; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.47 (s, 9H, $C(CH_3)_3$), 2.71 (s, 3H, CH_3), 3.49 (s, 2H, CH_2),

3.67 (s, 3H, OCH_3), 7.67 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz, Ar-H-5), 8.06 (d, 1H, J = 8.8 Hz, Ar-H-6), 8.38 (d, 1H, J = 2.0 Hz, Ar-H-3), 9.26 (s, 1H, NH), 10.37 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.94 (CH_3), 27.92 ($C(CH_3)_3$), 43.36 (CH_2), 51.98 (OCH_3), 78.96 ($C(CH_3)_3$), 115.02, 119.66, 120.95, 122.61, 133.21, 134.01, 152.29, 163.98, 166.80, 168.04, 176.66; IR (ATR) ν = 3275, 3109, 2976, 2360, 2340, 1746, 1729, 1662, 1561, 1512, 1391, 1362, 1295, 1267, 1230, 1155, 1048, 1018, 766, 751 cm^{-1}; MS (ESI) *m/z* (%) = 389.1 ([M-H]$^-$), HRMS for $C_{18}H_{21}N_4O_6$: calculated 389.1461, found 389.1454.

Methyl 3-((4-amino-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoate (24). To a solution of compound 23 (50 mg, 0.13 mmol) in 1,4-dioxane (4 mL) 4 M HCl (320 µL, 1.28 mmol) in 1,4-dioxane was added and the mixture was stirred overnight at rt. The solvent was evaporated under reduced pressure, to the solid residue ether (15 mL) was added, the obtained suspension was sonicated and the undissolved solid was filtered off, washed with ether and dried. Yield: 84%; grey solid (42 mg); mp: 122-123 ºC; R_f (dichloromethane/methanol/ammonia = 20/1/0.01): 0.61; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.48 (s, 2H, CH_2), 3.57 (s, 3H, OCH_3), 5.21 (s, 2H, NH_2), 7.08 (d, 1H, J = 8.0 Hz, Ar-H-5), 7.53 (dd 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, Ar-H-6), 8.28 (d, 1H, J = 2.4 Hz, Ar-H-2), 10.34 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.85 (CH_3), 43.24 (CH_2), 51.93 (OCH_3), 110.66, 118.59, 120.04, 123.79, 130.70, 139.14, 163.60, 167.05, 168.20, 176.04; IR (ATR) ν = 3531, 3469, 3226, 3051, 2847, 2580, 1727, 1717, 1582, 1553, 1508, 1362, 1346, 1264, 1131, 833, 717 cm^{-1}; MS (ESI) *m/z* (%) = 291.1 ([M-H]$^+$), HRMS for $C_{13}H_{15}N_4O_4$: calculated 291.1093, found 291.1092.

Methyl 3-((4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoate (25). To a solution of 4,5-dibromopyrrol-2-carboxylic acid (1.30 mg, 1.01 mmol) in dichloromethane (7 mL) 2 M oxalyl chloride in dichloromethane (1.66 mL, 1.66 mmol) was added and the mixture was stirred overnight under an argon atmosphere. The solvent was evaporated, fresh dichloromethane (5 mL), pyridine (2.5 mL) and compound 23 (161 mg, 0.55 mmol) were added and the mixture was stirred at rt for 6 h. The solvent was evaporated and the solid residue was dissolved in ethyl acetate (15 mL). Organic phase was washed with water (2 × 10 mL), saturated solution of $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Yield: 38%; white solid (176 mg); mp: 225-227 ºC; R_f (ethyl acetate/petroleum ether = 2/1): 0.21; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3H,

CH_3), 3.51 (s, 2H, CH_2), 3.68 (s, 3H, OCH_3), 7.03 (s, 1H, pirol-CH), 7.72 (dd 1H, J_1 = 9.0 Hz, J_2 = 2.6 Hz, Ar-H-6), 8.16-8.19 (d, 1H, J = 8.8 Hz, Ar-H-5), 8.43 (d, 1H, J = 2.4 Hz, Ar-H-2), 10.28 (s, 1H, NH), 10.46 (s, 1H, NH), 13.07 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.96 (CH_3), 43.41 (CH_2), 52.01 (OCH_3), 98.44, 106.52, 113.29, 117.17, 119.60, 122.33, 123.60, 127.95, 132.25, 135.23, 157.02, 164.13, 166.73, 168.03, 176.83; IR (ATR) v = 3231, 3116, 2955, 2360, 1725, 1671, 1608, 1584, 1524, 1390, 1350, 1324, 1303, 1252, 1217, 1168, 808, 751, 636 cm^{-1}; MS (ESI) *m/z* (%) = 537.9 ([M-H]$^-$), HRMS for $C_{18}H_{14}N_5O_5Br_2$: calculated 537.9362, found 537.9370; HPLC: t_R: 12.046 min (95.4% at 280 nm).

4,5-Dibromo-*N*-(4-(3-hydrazineyl-3-oxopropanamido)-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-1*H*-pyrrole-2-carboxamide (26). Compound was prepared according to general procedure B. Yield 35%; brown solid (75 mg); mp: 251-253 ºC; R_f (dichloromethane/methanol = 20/1): 0.17; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3H, CH_3), 3.21 (s, 2H, CH_2), 4.31 (s, 2H, NH_2), 7.02 (s, 1H, pyrrole-CH), 7.74 (dd 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz, Ar-H), 8.16-8.18 (m, 1H, Ar-H), 8.41-8.42 (d, 1H, J = 2.8 Hz, Ar-H), 9.21 (s, 1H, NH), 10.27 (s, 1H, NH), 10.34 (s, 1H, NH), 13.06 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.96 (CH_3), 42.95 (CH_2), 98.42, 106.49, 113.27, 117.14, 119.62, 122.32, 123.56, 127.98, 132.07, 135.41, 157.02 (CO), 165.57, 165.79, 166.76, 176.73; IR (ATR) v = 3294, 3118, 2932, 2851, 2795, 2687, 1649, 1580, 1511, 1407, 1390, 1326, 1237, 762, 683 cm^{-1}; MS (ESI) *m/z* (%) = 537.9 ([M-H]$^-$), HRMS for $C_{17}H_{14}N_7O_4Br_2$: calculated 537.9474, found 537.9489; HPLC: t_R = 7.626 min (95.6% at 254 nm).

4,5-Dibromo-*N*-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetamido)phenyl)-1*H*-pyrrole-2-carboxamide (27). Compound was prepared according to general procedure C. To the solid residue obtained after the purification with column chromatography ether (7 mL) was added, the obtained suspension was sonicated and the undissolved solid was filtered off, washed with ether and dried. Yield: 45%; brown solid (31 mg); mp: 172-173 ºC; R_f (dichloromethane/methanol = 10/1): 0.36; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.74 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 7.03 (s, 1H, pyrrole-CH), 7.73 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.6 Hz, Ar-H), 8.19 (d, 1H, J = 9.2 Hz, Ar-H), 8.43 (d, 1H, J = 2.4 Hz. Ar-H), 10.29 (s, 1H, NH), 10.60 (s, 1H, NH), 12.31 (s, 1H, NH), 13.06 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.95 (CH_3), 34.73 (CH_2), 98.44, 106.57, 113.32, 117.15, 119.77, 122.41, 123.58, 127.94, 132.41, 134.99, 152.32, 154.96, 157.03, 164.10, 166.71, 176.81; IR (ATR) v = 3231, 1659, 1574, 1523,

1391, 1327, 1223, 1184, 742, 639 cm^{-1}; MS (ESI) *m/z* (%) = 563.9 ($[M-H]^-$), HRMS for $C_{18}H_{12}N_7O_5Br_2$: calculated 563.9267, found 563.9280; HPLC: t_R = 10.513 min (95.9% at 280 nm).

3-((4-(4,5-Dibromo-1*H*-pyrrole-2-carboxamido)-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoic acid (28). Compound was prepared according to general procedure D. Yield: 63%; grey solid (32 mg); mp: 243-246 ºC; R_f (dichloromethane/methanol/acetic acid = 10/1/0.01): 0.18; ^1H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3H, CH_3), 3.38 (s, 2H, CH_2), 7.03 (s, 1H, pyrrole-CH), 7.73 (dd 1H, J_1 = 9.0 Hz, J_2 = 2.6 Hz, Ar-H-5), 8.17 (d, 1H, J = 9.2 Hz, Ar-H-6), 8.43 (d, 1H, J = 2.4 Hz, Ar-H-2), 10.27 (s, 1H, NH), 10.40 (s, 1H, NH), 12.66 (s, 1H, OH), 13.06 (s, 1H, pyrrole-NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.46 (CH_3), 44.43 (CH_2), 98.94, 107.00, 113.78, 117.74, 120.07, 122.78, 124.15, 128.45 132.62, 135.90, 157.53, 165.19, 167.25, 169.68, 177.30; IR (ATR) ν = 3269, 3114, 3070, 2961, 2926, 2617, 2520, 1709, 1588, 1526, 1393, 1319, 1252, 1082, 1017, 798, 760 cm^{-1}; MS (ESI) *m/z* (%) = 518.7 ($[M-H]^-$); HPLC: t_R = 10.231 min (95.0% at 280 nm).

4. Molecular modelling

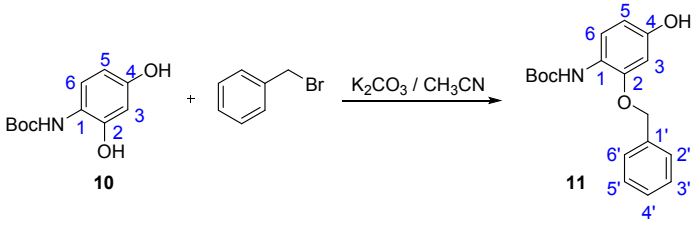
***Protein and Ligand Preparation*.** 3D compound models were built using ChemBio3D Ultra 16.0.[5] MMFF94 force field[6] was used for the optimization of geometries and partial atomic charges were added. Energy was minimized to less than 0.001 kcal/(mol Å) gradient value. The structure was refined with GAMESS interface using PM3 method, QA optimization algorithm and Gasteiger Hückel charges for all atoms for 100 steps.[5] GOLD Suite v5.4[7] was used for molecular docking calculations. GOLD graphical user interface was used for receptor preparation. To the protein hydrogen atoms were added and correct tautomers and protonation states were assigned. Except for HOH614, all water molecules and ligands were deleted from the crystal structure. Amino acid residues within 7 Å around the ligand (PDB entry: 4DUH[8]) were selected as the binding site.

***Ligand Docking*.** Compounds were docked to the defined binding site in 25 independent genetic algorithm (GA) runs by applying different GA parameters (population size = 100, selection pressure = 1.1, number of operations = 100,000, niche size = 2, number of islands = 5, mutation frequency = 95, crossover frequency = 95, migration frequency = 10) and scoring functions (GoldScore, ChemScore, CHEMPLP). The most representative results were obtained using

GoldScore as a scoring function. Ligands with RMSD value less than 1.5 Å were joined in clusters and early termination was allowed if the top 3 solutions were within 1.0 Å of the RMSD value. Proposed binding modes of the top 5 highest scored docking poses were evaluated for each ligand and the highest scored pose was used for graphical representation with PyMOL.[9]

5. Benzylation of *tert*-butyl (2,4-dihydroxyphenyl)carbamate

Benzylation of the 2-hydroxyl group of *tert*-butyl (2,4-dihydroxyphenyl)carbamate (**10**) was performed in acetonitrile using one equivalent of benzyl bromide and potassium carbonate as base (Scheme 1S). Since compound **10** contains two hydroxyl groups at carbons 2-C and 4-C, there are two possible sites of benzylation. To confirm the formation of the desired product **11**, we have performed ^{1}H-^{13}C HSQC (heteronuclear single-quantum correlation spectroscopy) and ^{1}H-^{13}C HMBC (heteronuclear multiple-bond correlation spectroscopy) 2D NMR experiments for this compound. First, the ^{1}H-^{13}C HSQC was used for full assignation of all protons and carbons in the molecule. Then ^{1}H-^{13}C HMBC spectrum was recorded to identify long-range ^{1}H-^{13}C couplings (Fig. 1S). From the ^{1}H-^{13}C HMBC spectrum of compound **11** it can be seen, that carbons at 3-C and 5-C positions couple with the OH proton with the same intensity. These signals are marked in Fig. 1S with a blue ellipse. This is only possible if the benzyl group is attached to the 2-OH group. In the case of 4-benzyloxy derivative, the coupling between the OH proton and the 5-C would not be possible because of the 5-bond distance between the two atoms. Additionally, we do not see the coupling between the OH proton and 1-C carbon that would be seen in 4-benzyloxy derivative.



Scheme 1S Benzylation of *tert*-butyl (2,4-dihydroxyphenyl)carbamate (**10**).

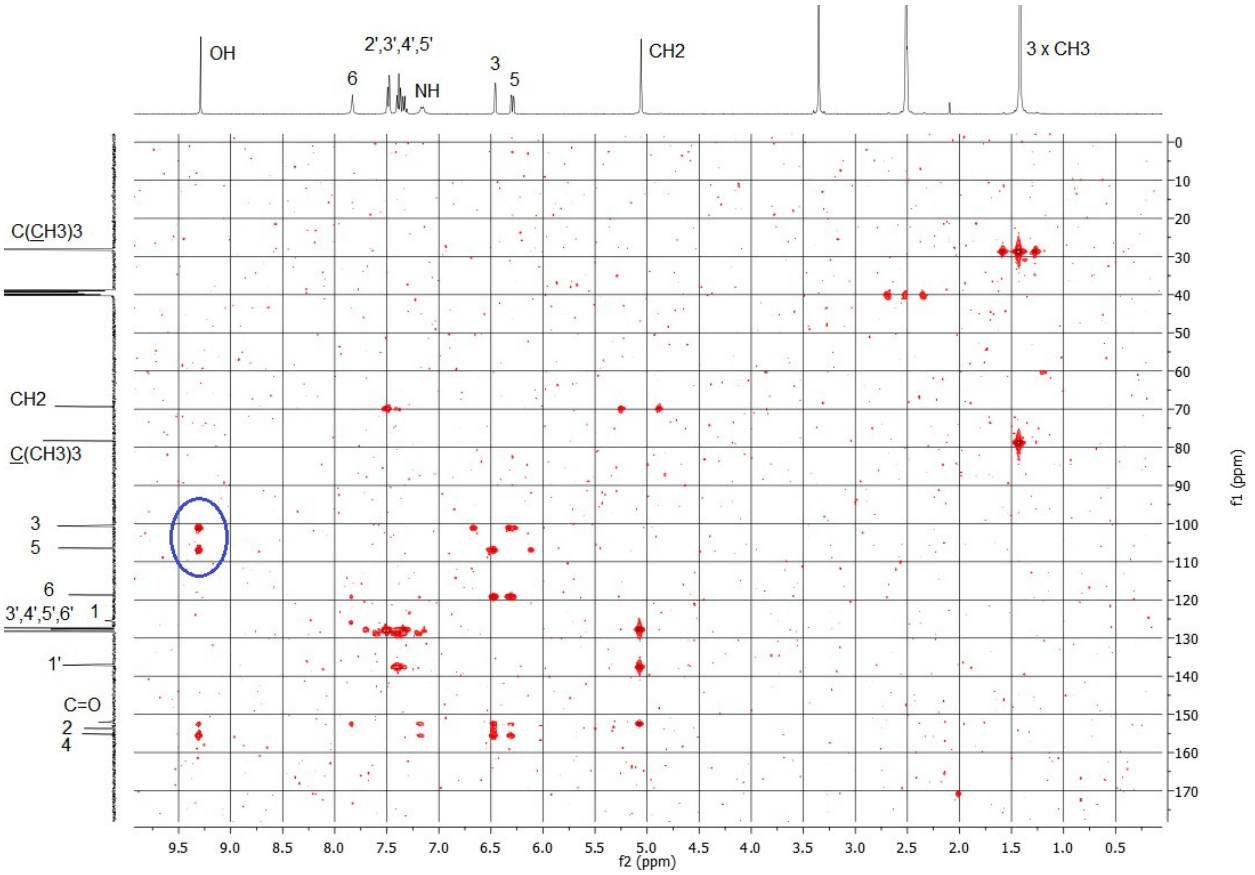
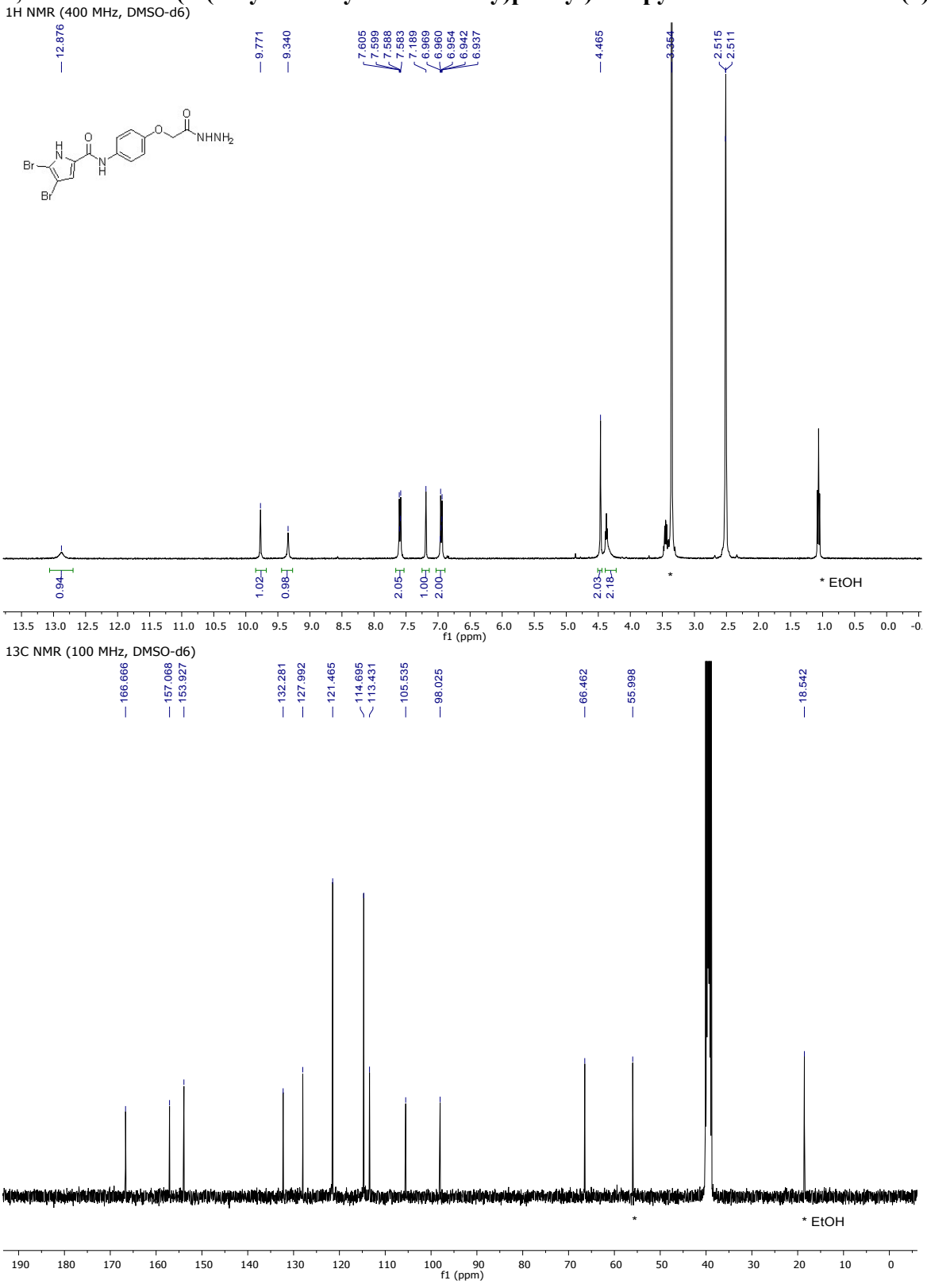


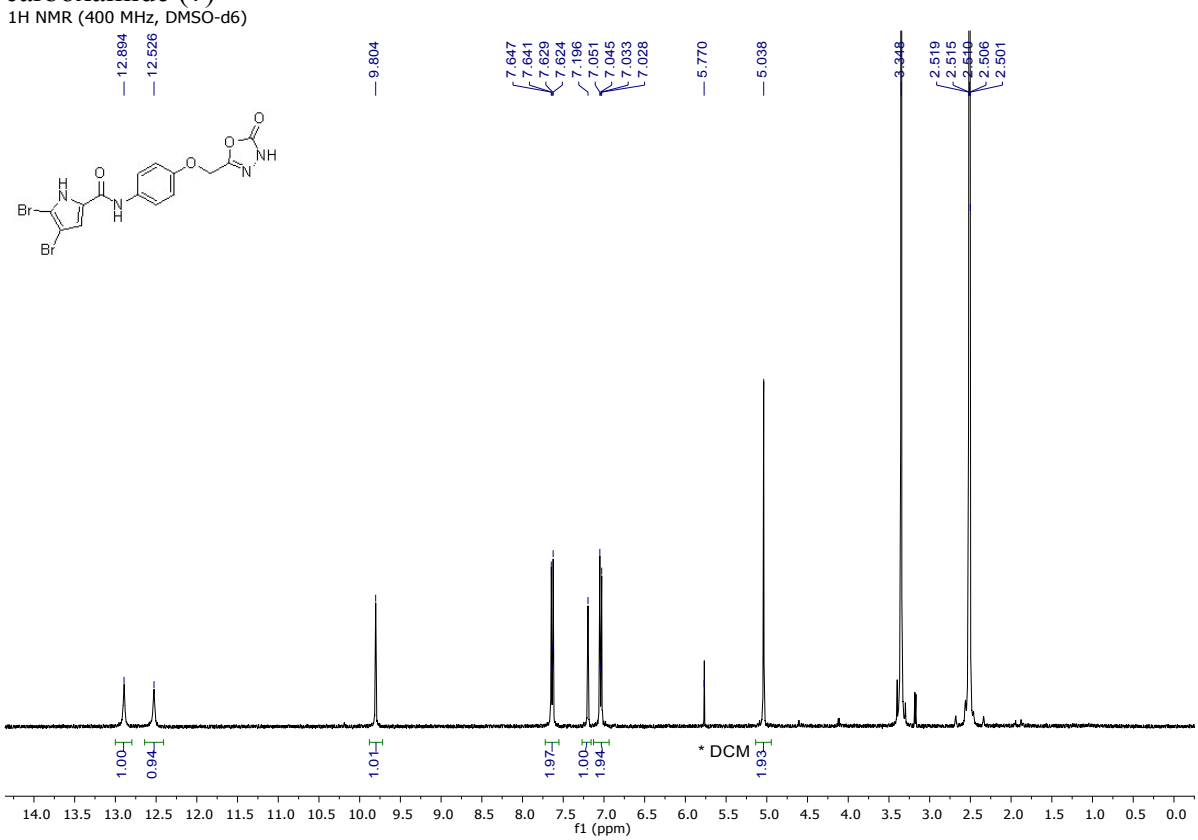
Fig. 1S ^{1}H-^{13}C HMBC spectrum of compound **11**. The coupling of the OH proton with C-2 and C-5 is marked with a blue ellipse.

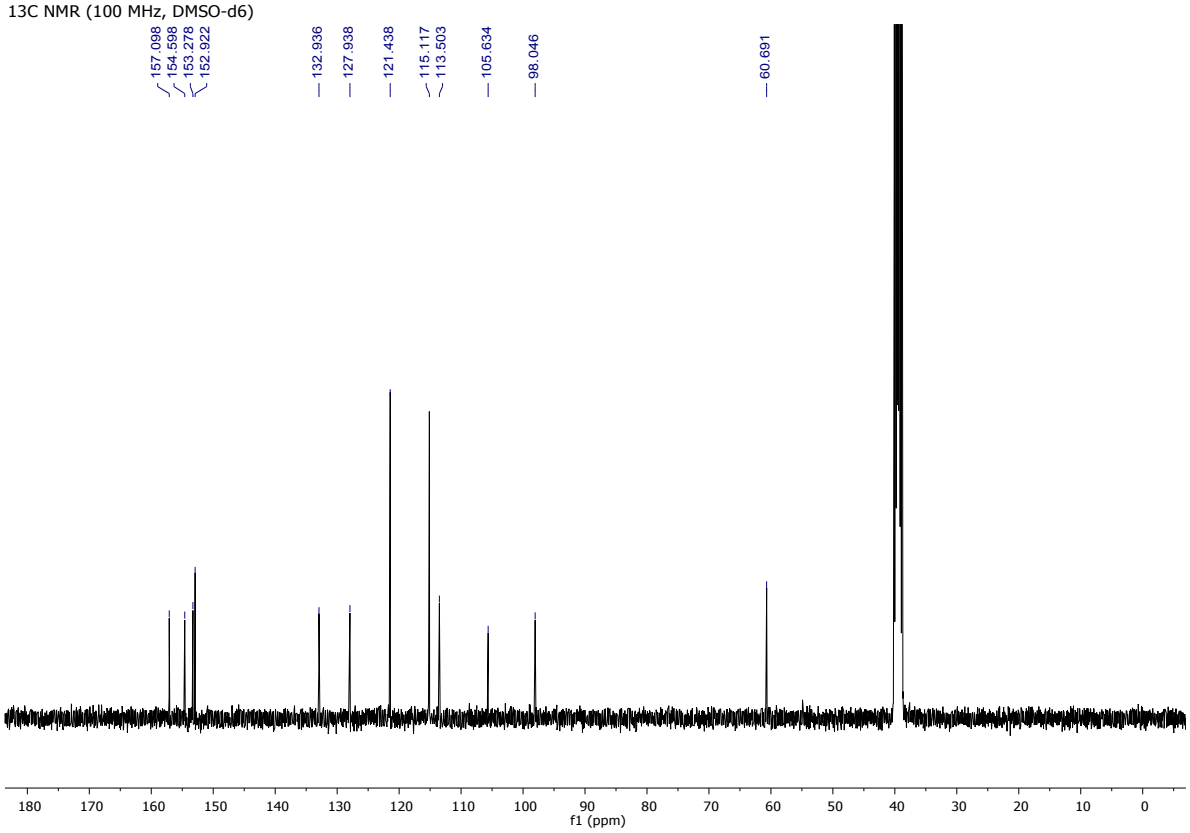
6. ^{1}H and ^{13}C NMR spectra of the final compounds

4,5-Dibromo-*N*-(4-(2-hydrazineyl-2-oxoethoxy)phenyl)-1*H*-pyrrole-2-carboxamide (6)

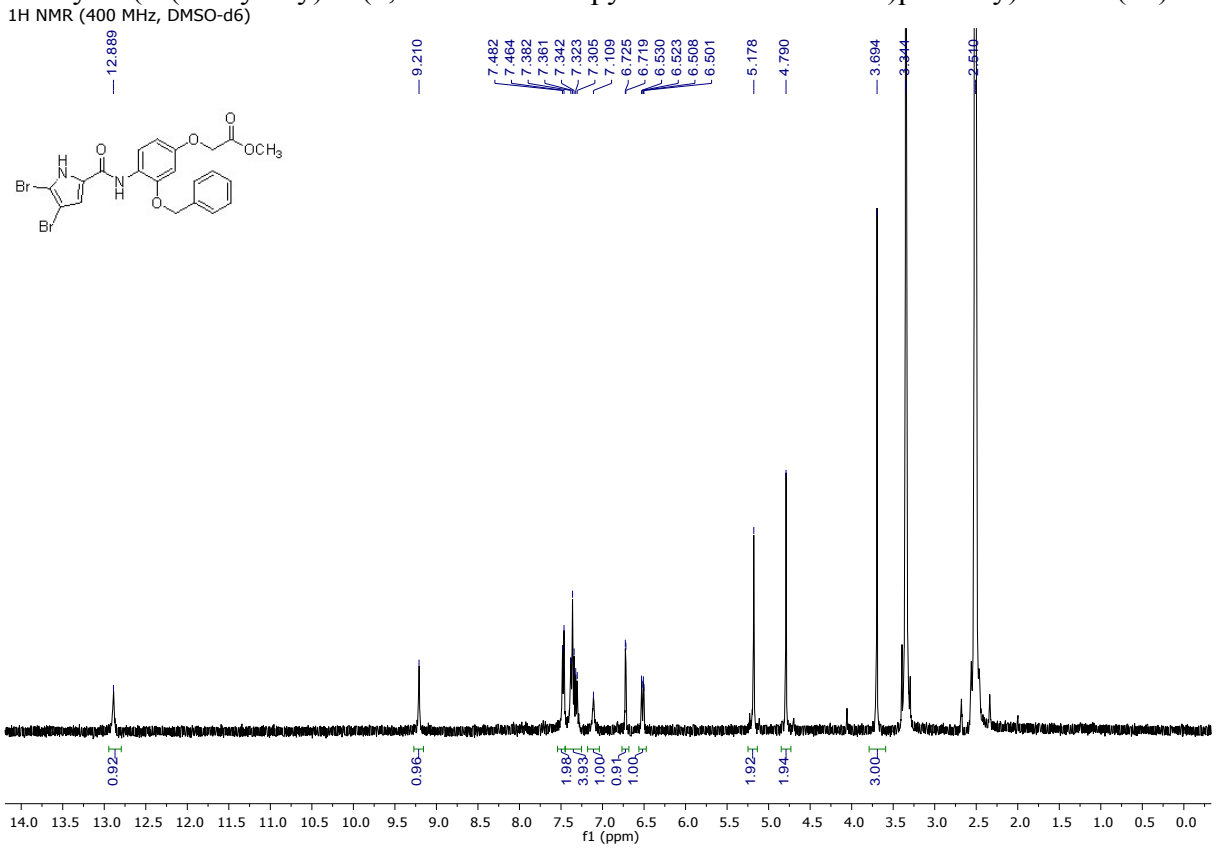


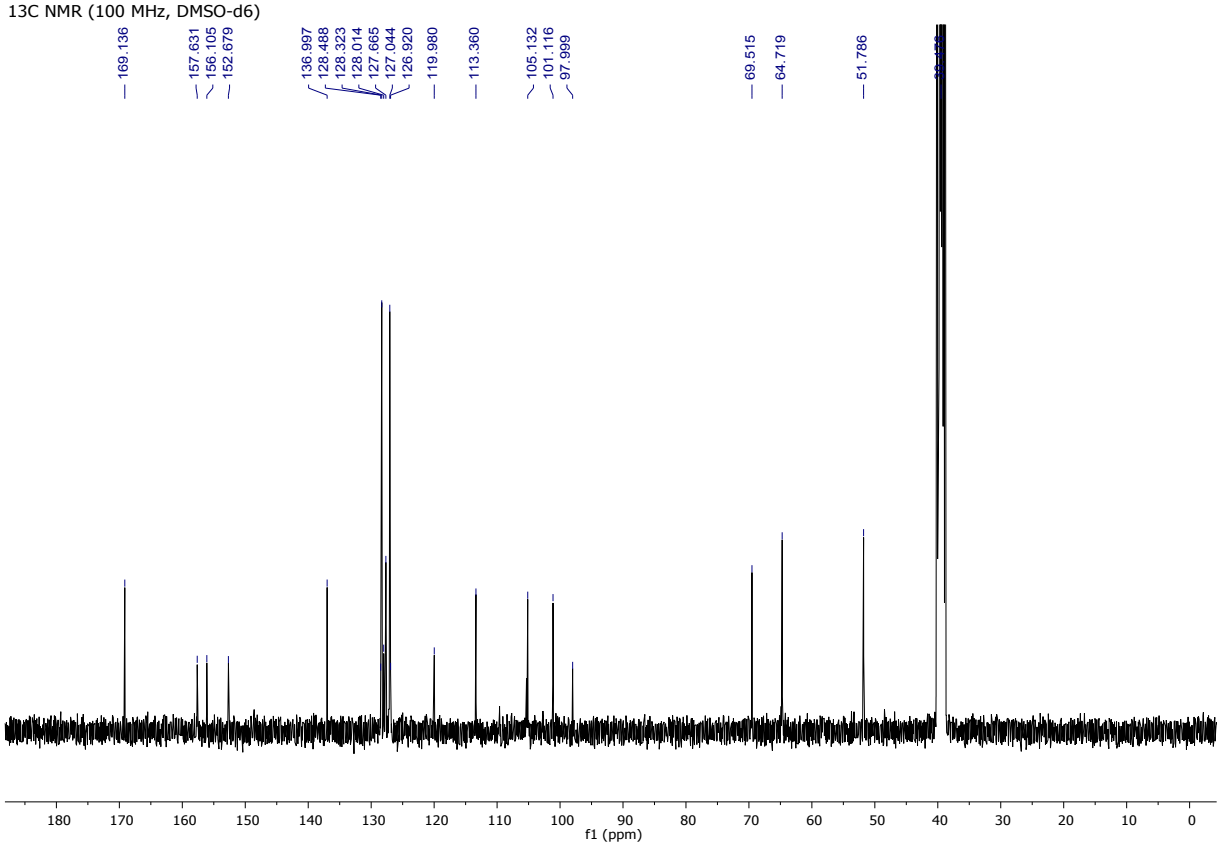
4,5-Dibromo-*N*-(4-((5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-pyrrole-2-carboxamide (**7**)



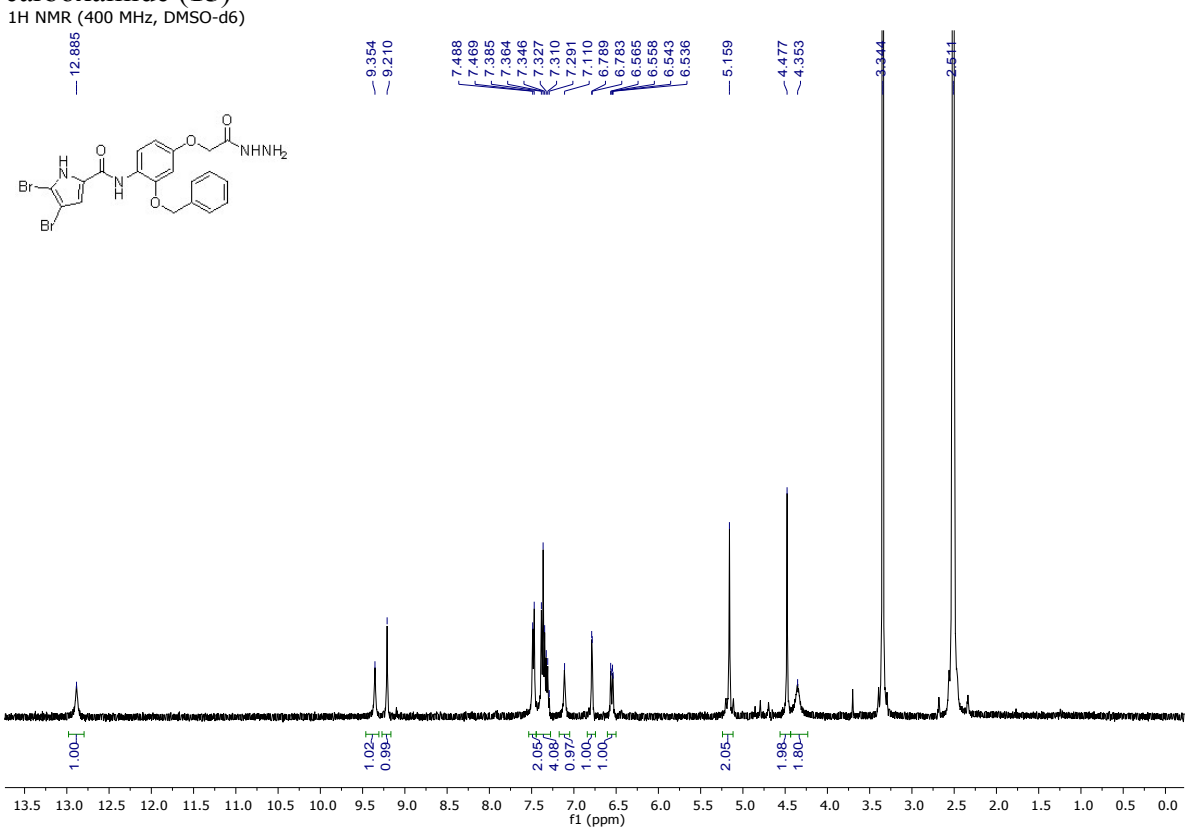


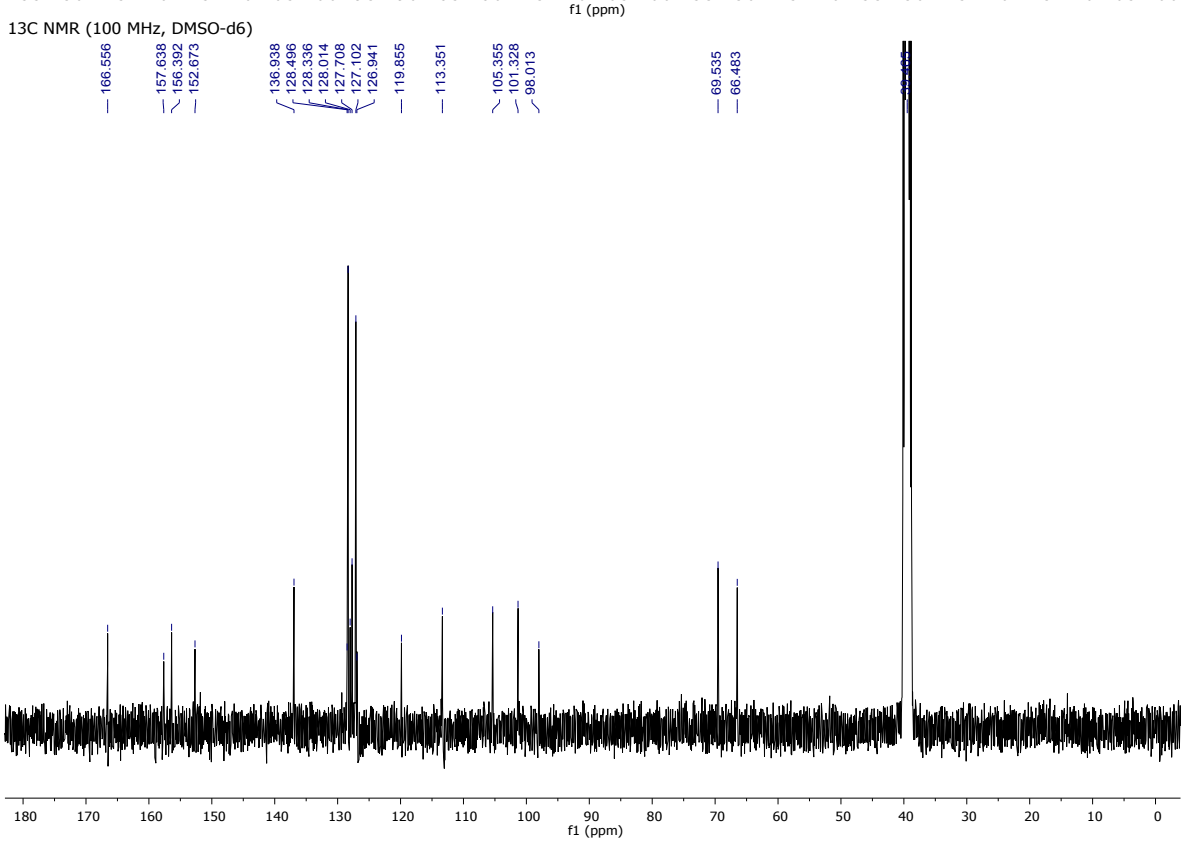
Methyl 2-(3-(benzyloxy)-4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetate (**14**)



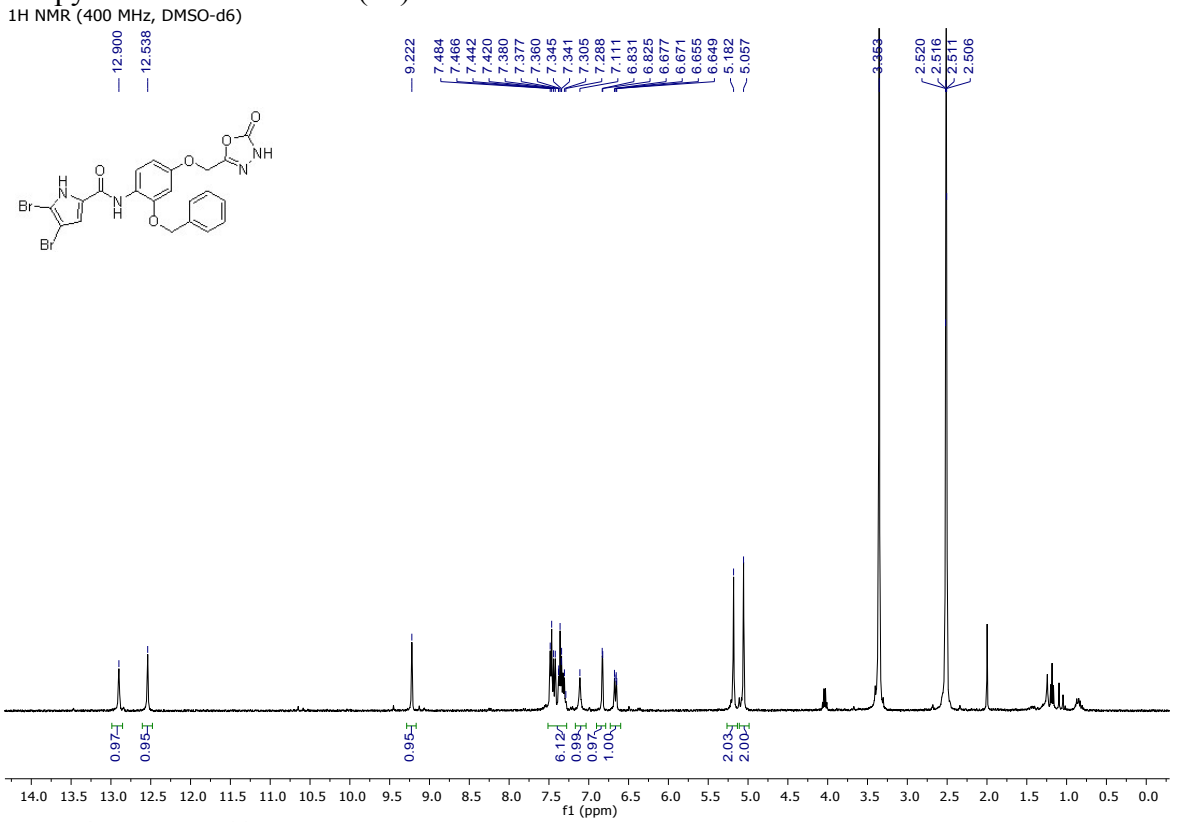


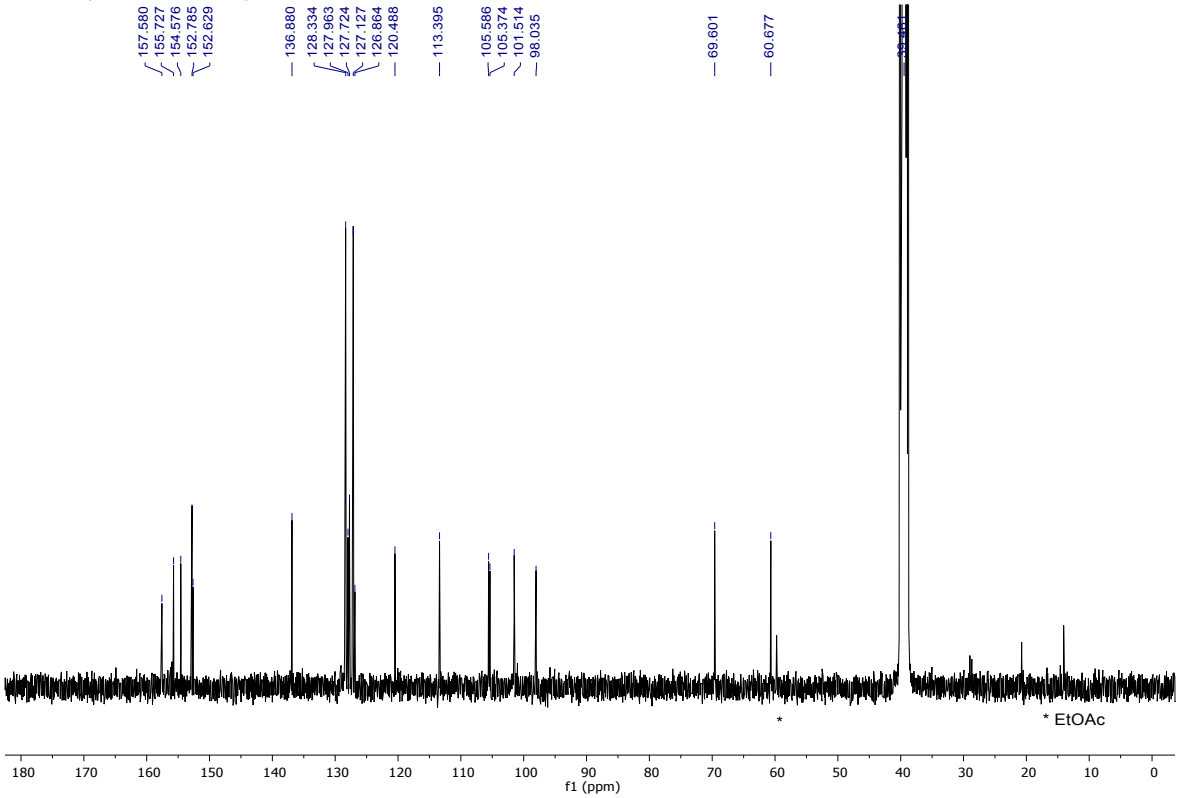
N-(2-(Benzyloxy)-4-(2-hydrazineyl-2-oxoethoxy)phenyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (**15**)





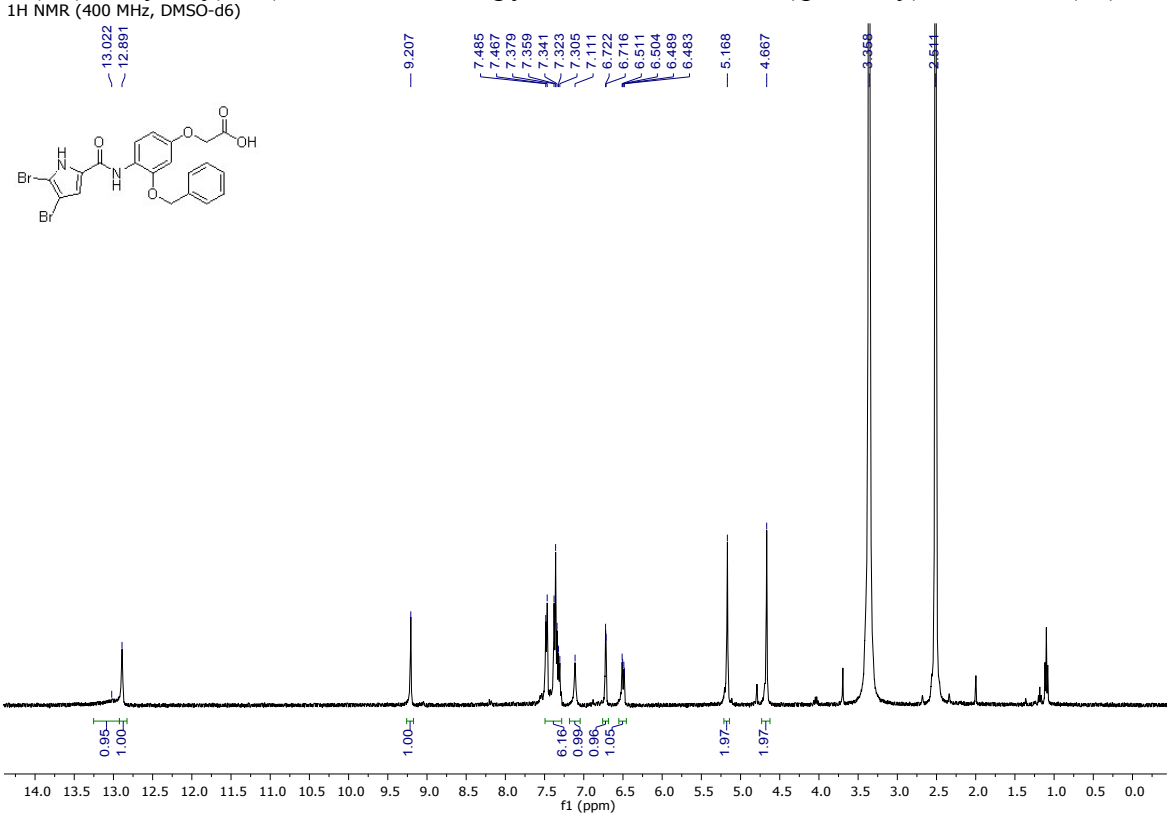
N-(2-(Benzyloxy)-4-((5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-4,5-dibromo-1*H*-pyrrole-2-carboxamide (**16**)



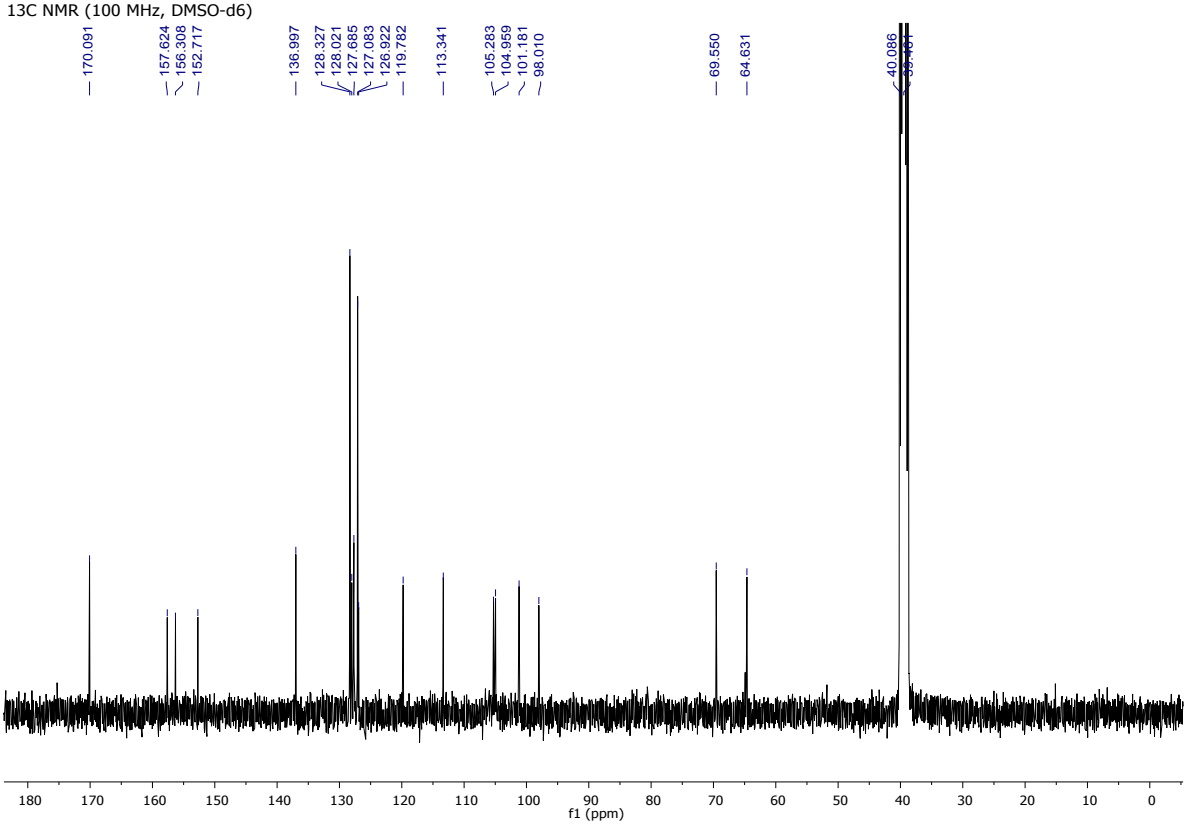


2-(3-(Benzyloxy)-4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)phenoxy)acetic acid (**17**)

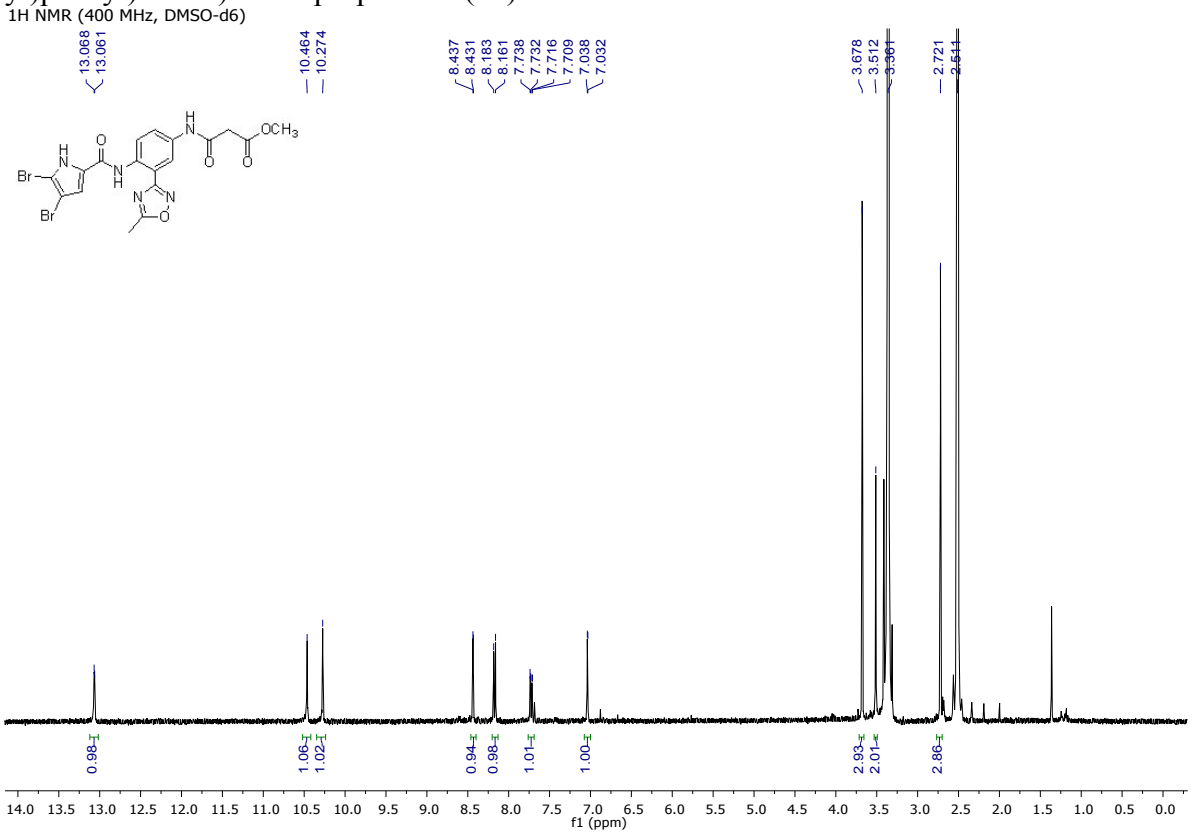
1H NMR (400 MHz, DMSO-d6)

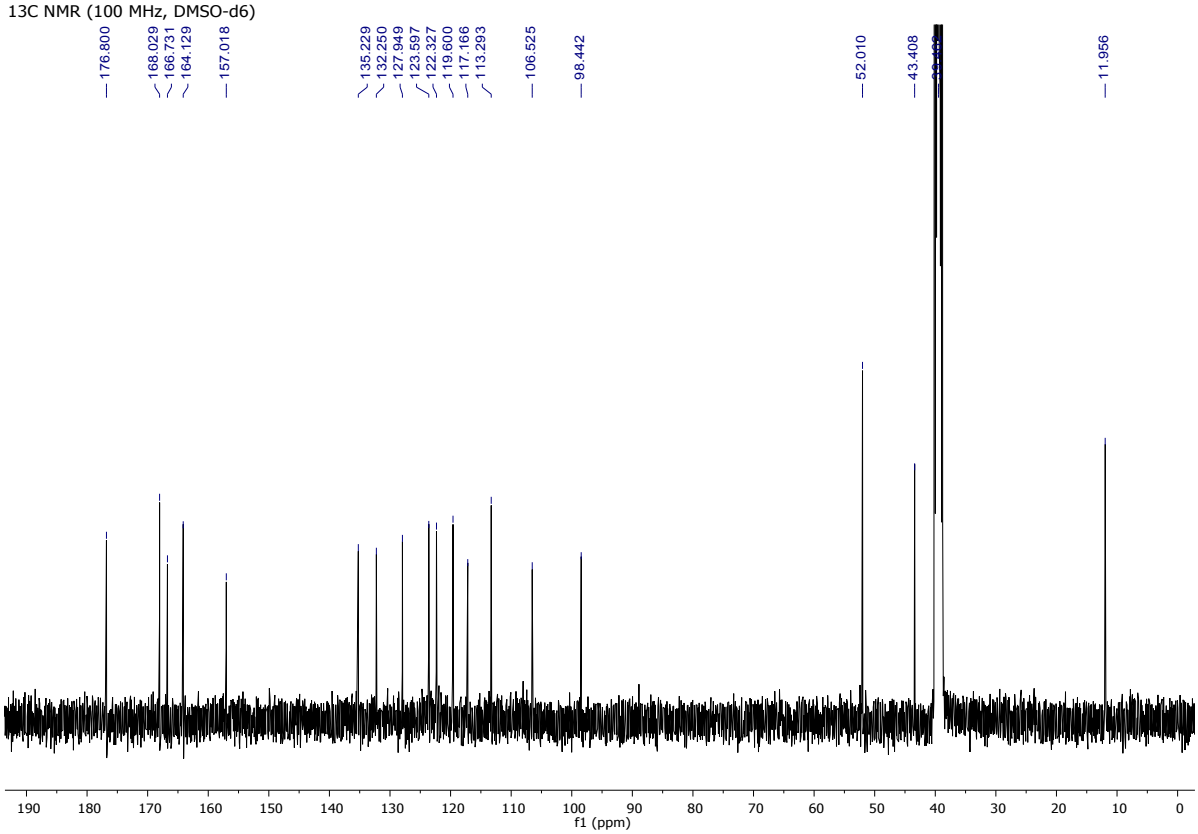


13C NMR (100 MHz, DMSO-d6)



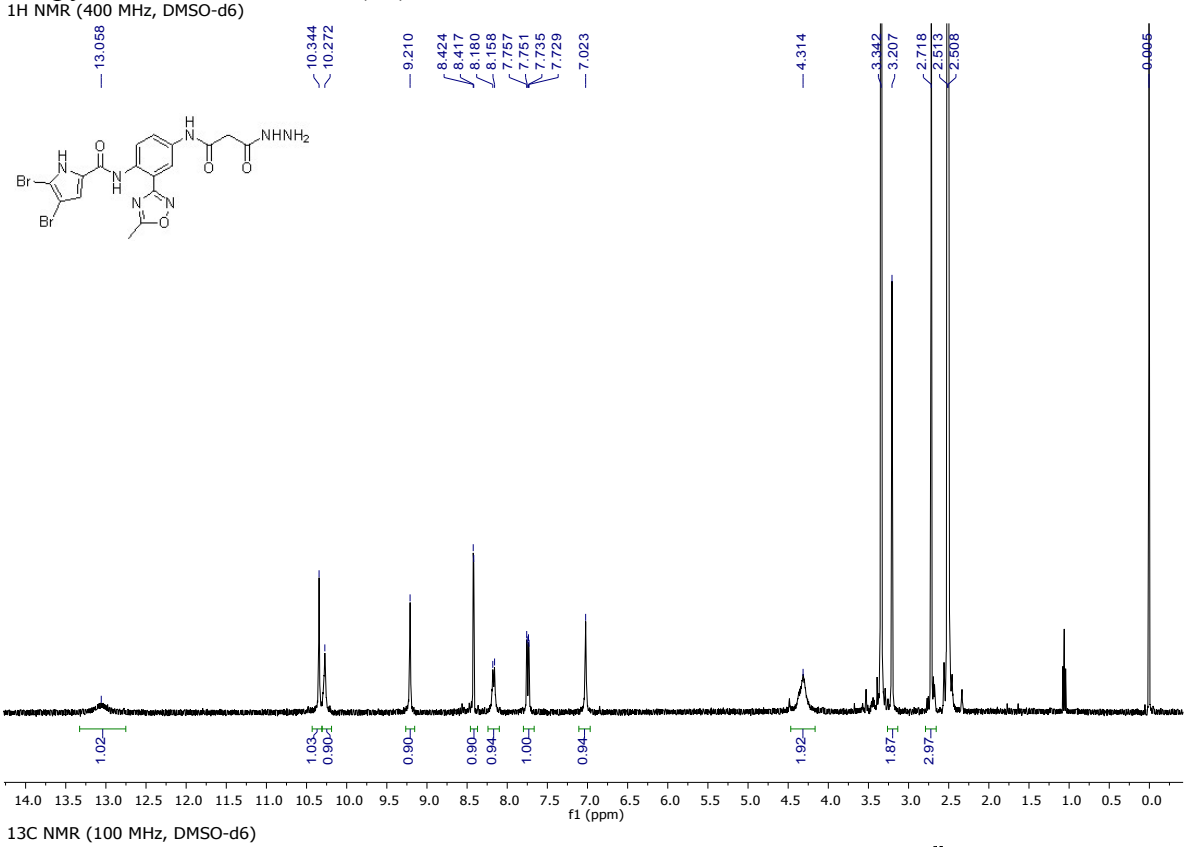
Methyl 3-((4-(4,5-dibromo-1*H*-pyrrole-2-carboxamido)-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoate (**25**)



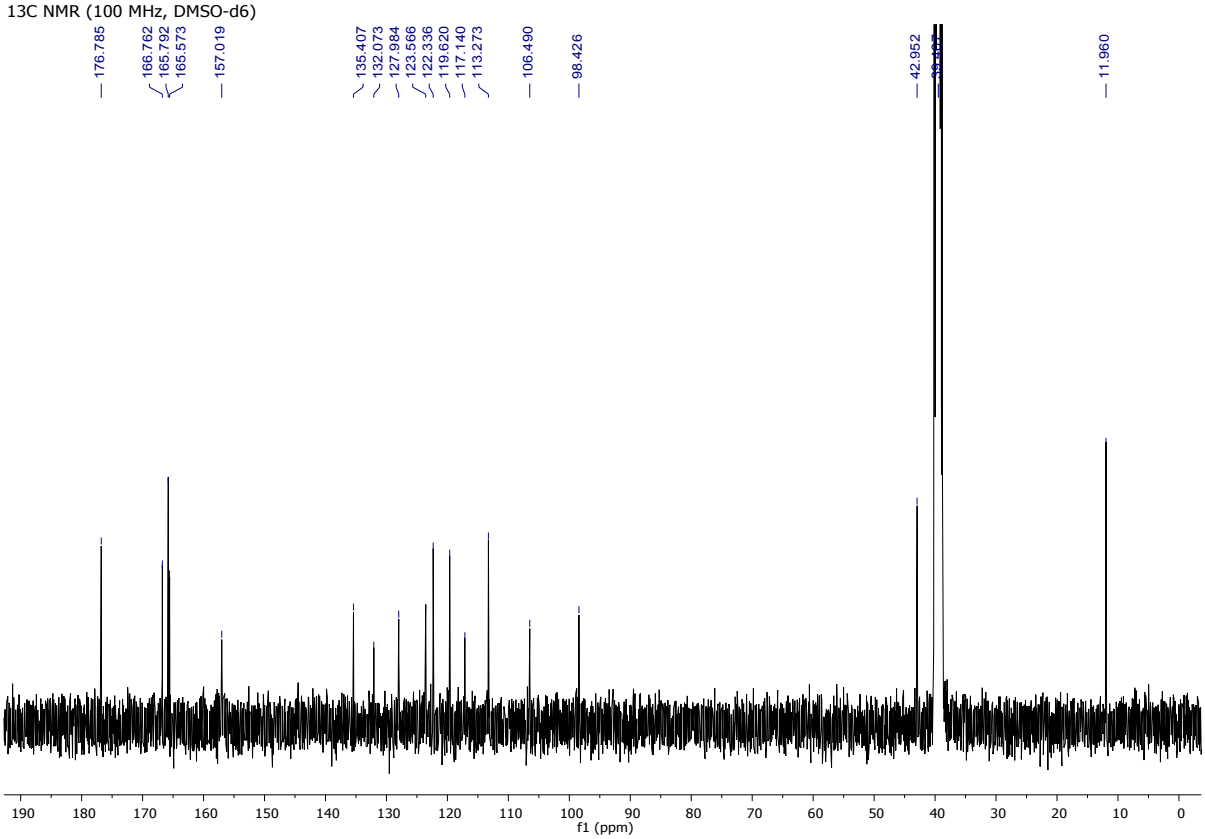


4,5-Dibromo-*N*-(4-(3-hydrazineyl-3-oxopropanamido)-2-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-1*H*-pyrrole-2-carboxamide (**26**)

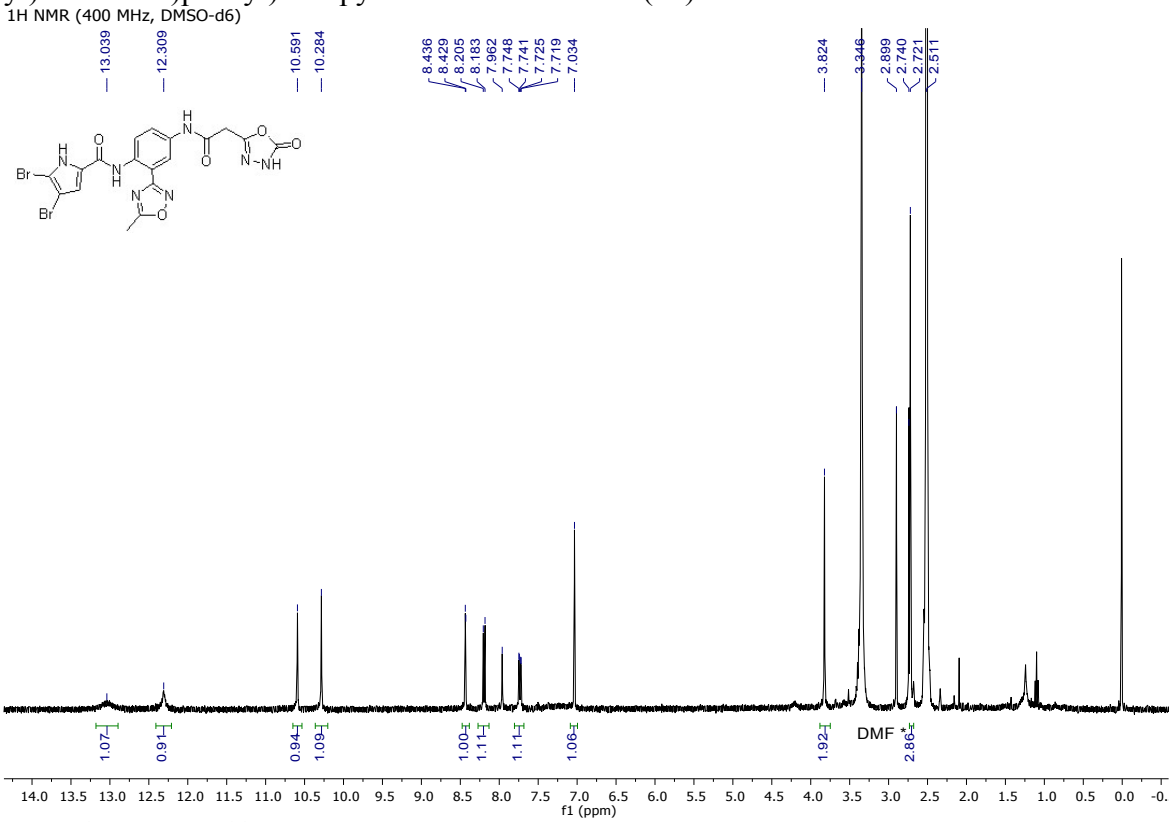
1H NMR (400 MHz, DMSO-d6)

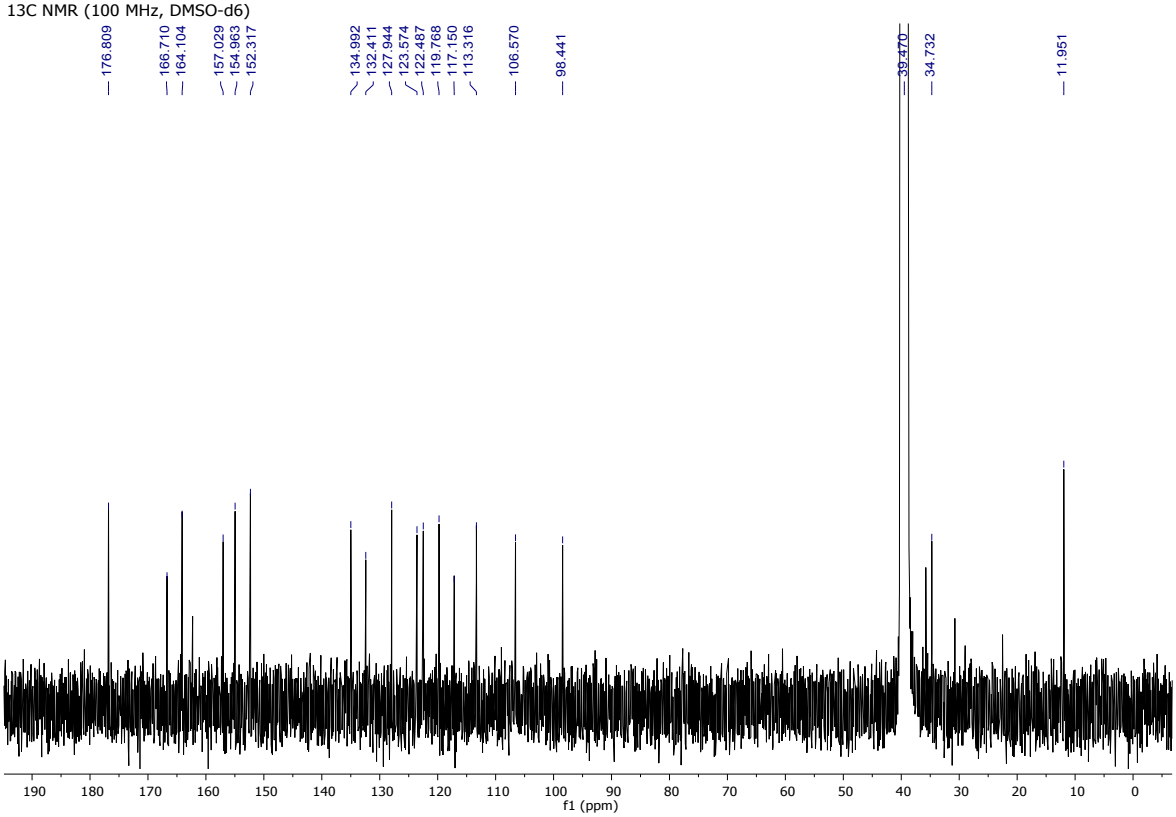


13C NMR (100 MHz, DMSO-d6)



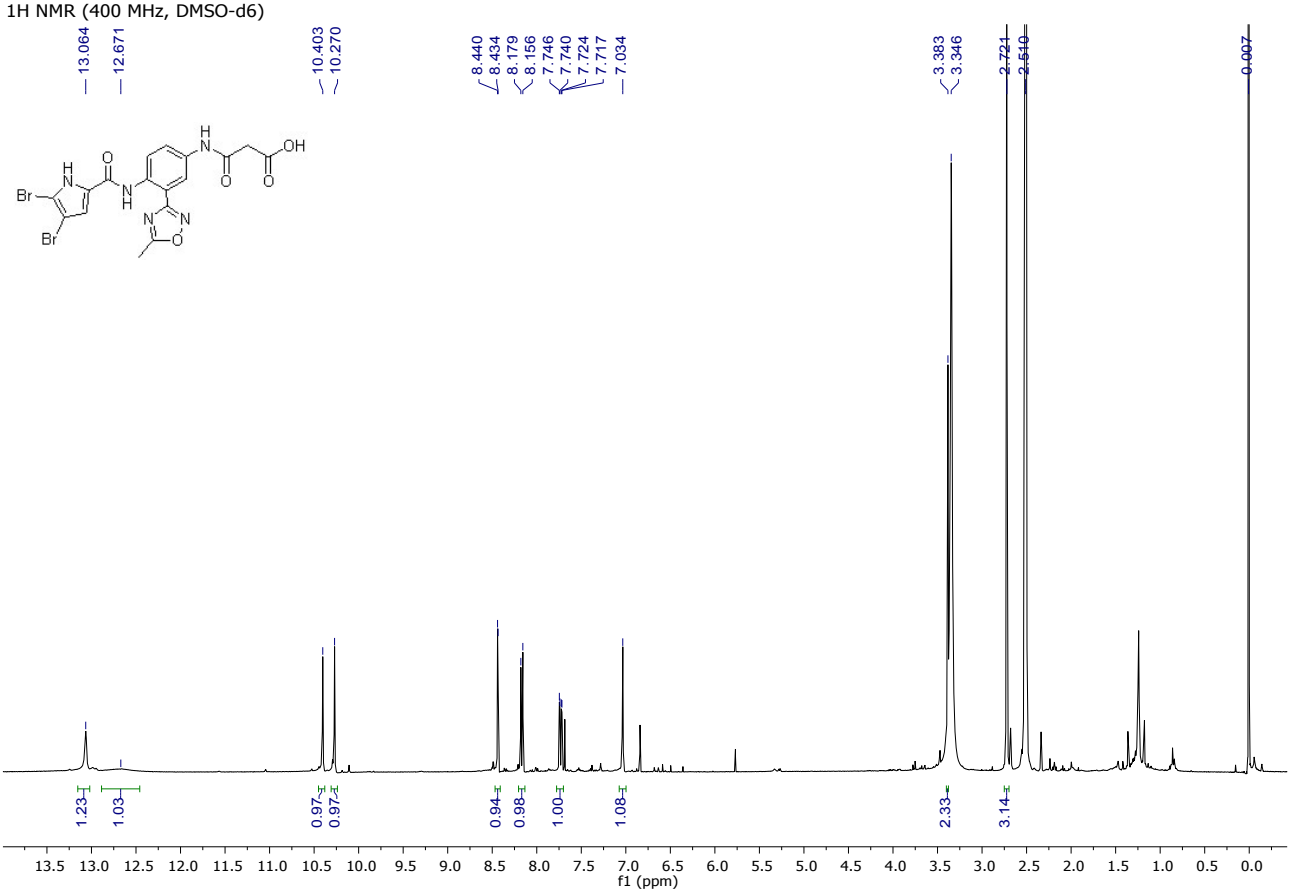
4,5-Dibromo-*N*-(2-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(2-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetamido)phenyl)-1*H*-pyrrole-2-carboxamide (**27**)



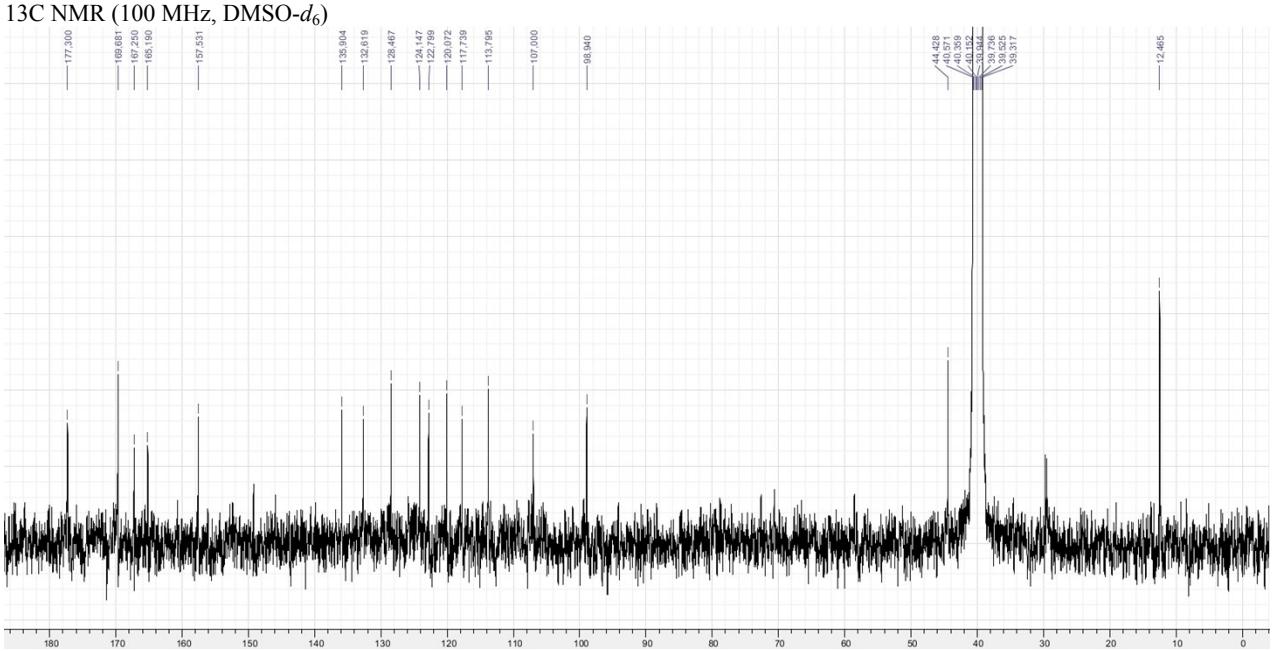


3-((4-(4,5-Dibromo-1*H*-pyrrole-2-carboxamido)-3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-3-oxopropanoic acid (**28**)

1H NMR (400 MHz, DMSO-d6)



13C NMR (100 MHz, DMSO-d_6)



REFERENCES

1 CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition. CLSI document M07-A9. Wayne, PA: Clinical Standards Institute; 2012.

2 N. Zidar, T. Tomašič, H. Macut, A. Sirc, M. Brvar, S. Montalvão, P. Tammela, J. Ilaš and D. Kikelj, *Eur. J. Med. Chem.*, 2016, **117**, 197–211.

3 M. Oguchi, K. Wada, H. Honma, A. Tanaka, T. Kaneko, S. Sakakibara, J. Ohsumi, N. Serizawa, T. Fujiwara, H. Horikoshi and T. Fujita, *J. Med. Chem.*, 2000, **43**, 3052–3066.

4 N. Zidar, H. Macut, T. Tomašič, M. Brvar, S. Montalvão, P. Tammela, T. Solmajer, L. Peterlin Mašič, J. Ilaš and D. Kikelj, *J. Med. Chem.*, 2015, **58**, 6179–6194.

5 GAMESS interface, Chem3D 16.0, ChemOffice Professional 16.0 Suite, CambridgeSoft.

6 T. A. Halgren, *J. Comput. Chem.*, 1996, **17**, 490–519.

7 G. Jones, P. Willett, R. C. Glen, A. R. Leach and R. Taylor, *J. Mol. Biol.*, 1997, **267**, 727–748.

8 M. Brvar, A. Perdih, M. Renko, G. Anderluh, D. Turk and T. Solmajer, *J. Med. Chem.*, 2012, **55**, 6413–6426.

9 PyMOL, Delano Scientific LLC, San Francisco, CA, http://pymol.sourceforge.net.