SAR and identification of 2-(quinolin-4-yloxy)acetamides as *Mycobacterium tuberculosis* cytochrome bc_1 inhibitors

Narisa Phummarin,[a] Helena I. Boshoff,[b] Patricia S. Tsang,[b] James Dalton,[c] Siouxsie Wiles,[c,d] Clifton E. Barry 3rd,[b] Brent R. Copp*[,a]

[a] *School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*
[b] *Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland, USA*
[c] *Bioluminescent Superbugs Lab, Department of Molecular Medicine and Pathology, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*
[d] *Te Pūnaha Matatini, c/o University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*

Electronic supplementary information

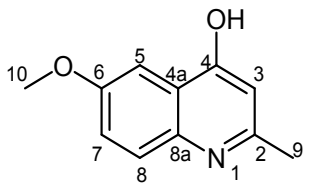
Table of Contents

1. Experimental Section, Chemistry

All materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (GF 254) using UV light. Silica gel 60-120 mesh was used for column chromatography. The reaction percentage yield was calculated based on the amount of substance (mole) of the purified product and the limiting reactant. Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra

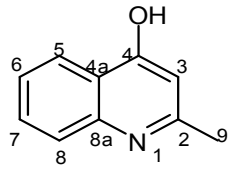
were recorded using a Perkin-Elmer spectrum One Fourier-Transform IR spectrometer as a dry film. NMR spectra were recorded on Bruker Avance DRX spectrometers operating at 300 or 400 MHz for ^{1}H nuclei and 75 or 100 MHz for ^{13}C nuclei. Proto-deutero solvent signals or TMS were used as internal references (DMSO-d_6: δ_H 2.50, δ_C 39.5; $CDCl_3$: δ_H TMS, δ_C 77.16; CD_3OD: δ_H 3.31, δ_C 49.00). NMR assignments were made utilizing data acquired with standard 2D NMR pulse sequences. HRESIMS data were acquired on a Bruker micrOTOF Q II mass spectrometer.

General procedure for the preparation of 4-hydroxyquinolines 10a-f. The appropriate aniline (1.0 equiv.) was dissolved in ethyl acetoacetate (1.0 equiv.) followed by addition of polyphosphoric acid (2-3 mL). The solution was heated at reflux (130 ^{o}C) for 2 h, cooled to room temperature, poured into ice and the resultant precipitate filtered and dried.

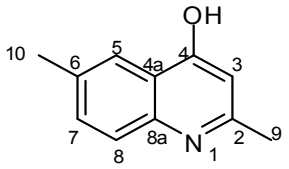


6-Methoxy-2-methylquinolin-4-ol (**10a**). The reaction was carried out according to the general procedure using *p*-anisidine (1.99 g, 16.16 mmol), ethyl acetoacetate (2.10 mL, 16.16 mmol) and polyphosphoric acid (3.00 mL) to give **10a** as a pale grey solid (2.37g, 77%). R_f (10% MeOH/ CH_2Cl_2) 0.77; m.p. > 230 ^{o}C; IR (ATR) ν_{max} 2366, 1851, 1600, 1501, 1227, 970, 846 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD+NaOH) δ 7.62 (1H, d, J = 2.8 Hz, H-5), 7.57 (1H, d, J = 9.2 Hz, H-8), 7.10 (1H, dd, J = 9.2, 2.8 Hz, H-7), 6.34 (1H, s, H-3), 3.88 (3H, s, H_3-10), 2.40 (3H, s, H_3-9); ^{13}C NMR (100 MHz, CD_3OD+NaOH) δ 173.9 (C-4), 158.6 (C-2), 156.5 (C-6), 146.1 (C-8a), 128.3 (C-8), 126.9 (C-4a), 121.2 (C-7), 108.6 (C-3), 103.3 (C-5),

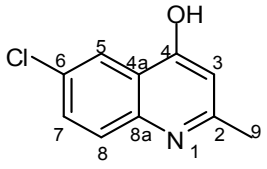
55.8 (C-10), 24.3 (C-9); (+)-HRESIMS $[M+Na]^+$ *m/z* 212.0682 (calcd for $C_{11}H_{11}NNaO_2$, 212.0682).



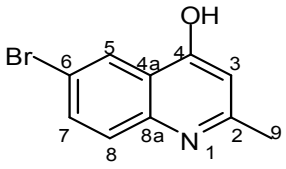
2-Methylquinolin-4-ol (**10b**). The reaction was carried out according to the general procedure using aniline (0.85 g, 9.14 mmol), ethyl acetoacetate (1.16 mL, 9.14 mmol) and polyphosphoric acid (2 mL) to give **10b** as a white solid (0.636 g, 44%). m.p. > 200 ^oC; IR (ATR) v_{max} 3061, 1640, 1597, 1498, 1470, 1355 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.52 (1H, br s, OH), 8.03 (1H, dd, *J* = 8.0, 1.6 Hz, H-5), 7.60 (1H, ddd, *J* = 8.0, 8.0, 0.8 Hz, H-7), 7.49 (1H, dd, *J* = 8.0, 0.8 Hz , H-8), 7.27 (1H, ddd, *J* = 8.0, 8.0, 0.8 Hz, H-6), 5.91 (1H, s, H-3), 2.33 (3H, s, H_3-9); (+)-HRESIMS $[M+H]^+$ *m/z* 160.0757 (calcd for $C_{10}H_{10}NO$, 160.0757).



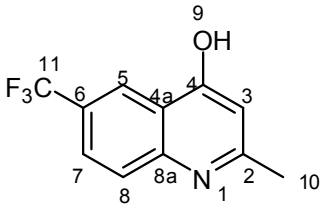
2,6-Dimethylquinolin-4-ol (**10c**). The reaction was carried out according to the general procedure using 4-methylaniline (0.979 g, 9.14 mmol), ethyl acetoacetate (1.16 mL, 9.14 mmol) and polyphosphoric acid (2 mL) to give **10c** as a pale yellow solid (0.549 g, 35%). m.p. > 200 ^oC; IR (ATR) v_{max} 2985, 1634, 1593, 1544, 1423, 1461 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.57 (1H, br s, OH), 7.82 (1H, br s, H-5), 7.43 (1H, dd, *J* = 8.8, 2.2 Hz, H-7), 7.39 (1H, d, *J* = 8.4 Hz, H-8), 5.85 (1H, s, H-3), 2.38 (3H, s), 2.32 (3H, s); (+)-HRESIMS $[M+Na]^+$ *m/z* 196.0738 (calcd for $C_{11}H_{11}NNaO$, 196.0733).



6-Chloro-2-methylquinolin-4-ol (**10d**). The reaction was carried out according to the general procedure using 4-chloroaniline (1.170 g, 9.17 mmol), ethyl acetoacetate (1.190 g, 9.14 mmol) and polyphosphoric acid (2 mL) to give **10d** as a white solid (0.700 g, 40%). m.p. > 200 ^{o}C; IR (ATR) v_{max} 3242, 3060, 1637, 1597, 1508, 1466, 1350, 680 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (1H, br s, OH), 7.98 (1H, d, J = 2.4 Hz, H-5), 7.68 (1H, dd, J = 8.8, 2.4 Hz, H-7), 7.57 (1H, d, J = 8.8 Hz, H-8), 6.05 (1H, s, H-3), 2.38 (3H, s, H_3-9); (+)-HRESIMS $[M+H]^+$ *m/z* 194.0366 (calcd for $C_{10}H_9{}^{35}ClNO$, 194.0367).

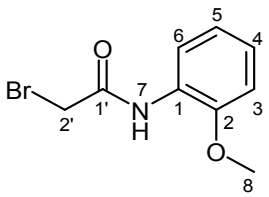


6-Bromo-2-methylquinolin-4-ol (**10e**). The reaction was carried out according to the general procedure using 4-bromoaniline (1.303 g, 7.6 mmol), ethyl acetoacetate (0.985 g, 7.57 mmol) and polyphosphoric acid (2 mL) to give **10e** as a white solid (0.737 g, 41%). m.p. > 200 ^{o}C; IR (ATR) v_{max} 3060, 1636, 1596, 1506, 1466, 1350, 680 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (1H, br s, OH), 8.10 (1H, d, J = 2.4 Hz, H-5), 7.75 (1H, dd, J = 8.4, 2.4 Hz, H-7), 7.46 (1H, d, J = 8.8 Hz, H-8), 5.96 (1H, s, H-3), 2.34 (3H, s, H_3-9); (+)-HRESIMS $[M+H]^+$ *m/z* 237.9859 (calcd for $C_{10}H_9{}^{79}BrNO$, 237.9862).



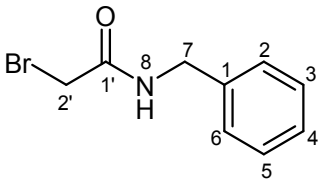
2-Methyl-6-(trifluoromethyl)quinolin-4-ol (**10f**). The reaction was carried out according to the general procedure using 4-(trifluoromethyl)aniline (1.15 mL, 9.14 mmol), ethyl acetoacetate (1.16 mL, 9.14 mmol) and polyphosphoric acid (2 mL) to give **10f** as a light brown solid (0.510 g, 25%). m.p. > 200 ^{o}C; IR (ATR) ν_{max} 3238, 3096, 1648, 1600, 1496, 1409, 1371 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (1H, br s, OH), 8.30 (1H, br s, H-5), 7.90 (1H, dd, *J* = 8.8, 2.0 Hz, H-7), 7.68 (1H, d, *J* = 8.8 Hz, H-8), 6.03 (1H, s, H-3), 2.37 (3H, s, H_3-10); (+)-HRESIMS $[M+H]^+$ *m/z* 228.0633 (calcd for $C_{11}H_9F_3NO$, 228.0631).

General procedure for the preparation of α-bromoacetamides 11a-x. To a solution of amine (2.0 equiv.) in CH_2Cl_2 (50.0 mL) under N_2 at –77 ^{o}C was added bromoacetylbromide (0.44 mL, 1.0 equiv.) while stirring. The mixture was then stirred for 2 h whilst being allowed to warm to room temperature. The crude reaction product was washed with aqueous HCl (10%, 3 x 20 mL), satd sodium bicarbonate (3 x 20 mL), and H_2O (3 x 20 mL), before drying the organic layer ($MgSO_4$), filtered and concentrated in vacuo to give the target α-bromoacetamide.

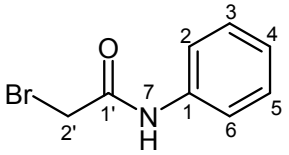


2-Bromo-*N*-(2-methoxyphenyl)acetamide (**11a**). The reaction was carried out according to the general procedure using 2-methoxyaniline (1.14 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to give **11a** as brown solids (1.12 g, 92%). R_f (EtOAc) 0.91; m.p. 64-66 ^{o}C; IR (ATR) ν_{max} 3281, 1661, 1492, 1252, 1067, 750, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (1H, br s, NH-7), 8.31 (1H, dd, *J* = 8.0, 1.6 Hz, H-6), 7.09 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz, H-4), 6.97 (1H, ddd, *J* = 7.8, 7.8, 1.3 Hz, H-5), 6.90 (1H, dd, *J* = 8.4, 1.2 Hz, H-3), 4.02 (2H, s, H_2-2'), 3.91 (3H, s, H_3-8); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 163.3 (C-1'), 148.4 (C-2), 127.0 (C-1), 124.7 (C-4), 121.2 (C-5), 119.7 (C-6), 110.2 (C-3), 56.0 (C-8), 29.8 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 265.9789 (calcd for $C_9H_{10}{}^{79}BrNNaO_2$, 265.9787).

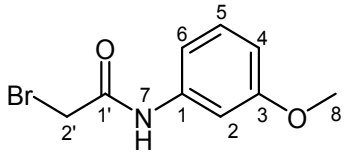


N-Benzyl-2-bromoacetamide (**11b**). The reaction was carried out according to the general procedure using benzylamine (1.09 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11b** as beige solids (1.06 g, 93%). R_f (EtOAc) 0.87; m.p. 108.5 °C; IR (ATR) ν_{max} 3265, 3077, 1633, 1513, 1156, 1021, 743, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m, H-2, H-3, H-4, H-5, H-6), 6.76 (1H, br s, NH-8), 4.48 (2H, d, *J* = 5.6 Hz, H_2-7), 3.93 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C-1'), 137.4 (C-1), 129.0 (C-3, C-5), 127.9 (C-4), 127.9 (C-2, C-6), 44.3 (C-7), 29.2 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 249.9841 (calcd for $C_9H_{10}{}^{79}BrNNaO$, 249.9838). ^1H and ^{13}C NMR data agreed with literature values.[1]

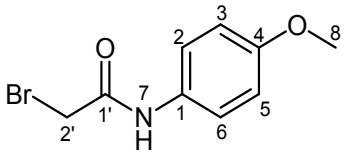


2-Bromo-*N*-phenylacetamide (**11c**). The reaction was carried out according to the general procedure using aniline (0.91 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11c** as light brown solids (0.66 g, 62%). R_f (EtOAc) 0.89; m.p. 134-135.5 °C; IR (ATR) ν_{max} 3298, 1655, 1608, 1596, 1553, 1445, 758, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, br s, NH-7), 7.53 (2H, dd, *J* = 8.6, 1.0 Hz, H-2, H-6), 7.36 (2H, t, *J* = 8.0 Hz, H-3, H-5), 7.17 (1H, t, *J* = 8.0 Hz, H-4), 4.02 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5

(C-1'), 137.0 (C-1), 129.3 (C-3, C-5), 125.4 (C-4), 120.2 (C-2, C-6), 29.6 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 235.9688 (calcd for $C_8H_8{}^{79}BrNNaO$, 235.9681). All characterization data agreed with those reported in the literature.[2]

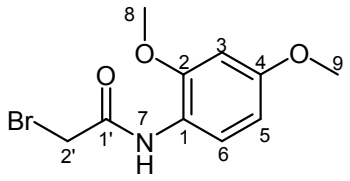


2-Bromo-*N*-(3-methoxyphenyl)acetamide (**11d**). The reaction was carried out according to the general procedure using *m*-anisidine (1.12 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11d** as beige solids (0.99 g, 81%). R_f (EtOAc) 0.93; m.p. 97-98 °C; IR (ATR) ν_{max} 3277, 2955, 1670, 1612, 1493, 1200, 852, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, br s, NH-7), 7.26 (1H, s, H-2), 7.24 (1H, t, *J* = 8.1 Hz, H-5), 7.01 (1H, dd, *J* = 8.0, 1.8 Hz, H-4) , 6.72 (1H, dd, *J* = 8.7, 2.4 Hz, H-6) 4.01 (2H, s, H_2-2'), 3.81 (3H, s, H_3-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 160.4 (C-3), 138.2 (C-1), 130.0 (C-5), 112.3 (C-4), 111.1 (C-6), 105.9 (C-2), 55.5 (C-8), 29.6 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 265.9784 (calcd for $C_9H_{10}{}^{79}BrNNaO_2$, 265.9787). All characterization data agreed with those reported in the literature.[2]

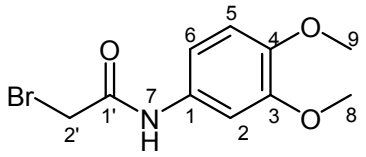


2-Bromo-*N*-(4-methoxyphenyl)acetamide (**11e**). The reaction was carried out according to the general procedure using 4-anisidine (1.23 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11e** as brown crystals (1.01 g, 83%). R_f (EtOAc) 0.90; m.p. 127.5-128.0 °C; IR (ATR) ν_{max} 3286, 1655, 1509, 1238, 1027, 827, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, br s, NH-7), 7.42 (2H, d, *J* = 9.0 Hz, H-2, H-6), 6.89 (2H, d, *J* = 9.0 Hz,

H-3, H-5), 4.01 (2H, s, H_2-2'), 3.80 (3H, s, H_3-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 157.2 (C-4), 130.1 (C-1), 122.2 (C-2, C-6), 114.4 (C-3, C-5), 55.6 (C-8), 29.6 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 265.9790 (calcd for $C_9H_{10}{}^{79}BrNNaO_2$, 265.9787). All characterization data agreed with those reported in the literature.[2]

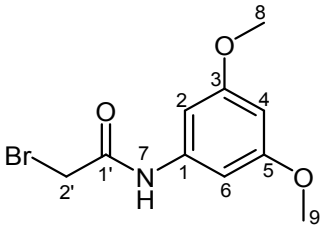


2-Bromo-*N*-(2,4-dimethoxyphenyl)acetamide (**11f**). The reaction was carried out according to the general procedure using 2,4-dimethoxyaniline (1.53 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11f** as dark grey solids (1.26 g, 92%). R_f (EtOAc) 0.89; m.p. 108-109 ^oC; IR (ATR) ν_{max} 3245, 2938, 1660, 1542, 1210, 1159, 837, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, br s, NH-7), 8.18 (1H, dd, *J* = 8.0, 0.8 Hz, H-6), 6.49-6.47 (2H, m, H-3, H-5), 4.01 (2H, s, H_2-2'), 3.88 (3H, s, H_3-8), 3.80 (3H, s, H_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (C-1'), 157.2 (C-4), 149.9 (C-2), 120.7 (C-1), 120.69 (C-6), 103.9 (C-5), 98.8 (C-3), 56.0 (C-8), 55.7 (C-9), 29.9 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 295.9897 (calcd for $C_{10}H_{12}{}^{79}BrNNaO_3$, 295.9893). ^{1}H NMR data agreed with literature values.[3]

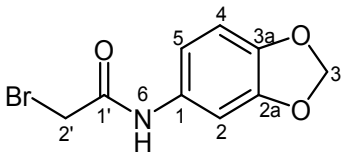


2-Bromo-*N*-(3,4-dimethoxyphenyl)acetamide (**11g**). The reaction was carried out according to the general procedure using 3,4-dimethoxyaniline (1.53 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11g** as grey solids (1.25 g, 91%). R_f

(EtOAc) 0.76; m.p. 152-154 °C; IR (ATR) v_{max} 3259, 2969, 1659, 1514, 1216, 11130, 845, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, br s, NH-7), 7.27 (1H, s, H-2), 6.94 (1H, dd, *J* = 8.4, 2.4 Hz, H-6), 6.83 (1H, d, *J* = 8.8 Hz, H-5), 4.01 (2H, s, H_2-2'), 3.89 (3H, s, H_3-8), 3.87 (3H, s, H_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (C-1'), 149.3 (C-3), 146.7 (C-4), 130.6 (C-1), 112.5 (C-6), 111.4 (C-5), 105.1 (C-2), 56.3 (C-8), 56.1 (C-9), 29.7 (C-2'); (+)-HRESIMS $[M+H]^+$ *m/z* 274.0065 (calcd for $C_{10}H_{13}{}^{79}BrNO_3$, 274.0073).

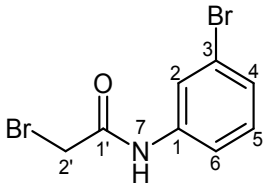


2-Bromo-*N*-(3,5-dimethoxyphenyl)acetamide (**11h**). The reaction was carried out according to the general procedure using 3,5-dimethoxyaniline (1.53 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11h** as pale yellow solids (0.94 g, 68% yield). R_f (EtOAc) 0.89; m.p. 101-103 °C; IR (ATR) v_{max} 3268, 2938, 1671, 1555, 1201, 1151, 822, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, br s, NH-7), 6.75 (2H, d, *J* = 2.4 Hz, H-2, H-6), 6.29 (1H, s, H-4), 4.00 (2H, s, H_2-2'), 3.79 (6H, s, H_3-8, H_3-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 161.3 (C-3, C-5), 138.8 (C-1), 98.4 (C-2, C-6), 97.6 (C-4), 55.6 (C-8, C-9), 29.7 (C-2'); (+)-HRESIMS $[M+Na]^+$ m/z 295.9883 (calcd for $C_{10}H_{12}{}^{79}BrNNaO_3$, 295.9893). All characterization data agreed with those reported in the literature.[2]

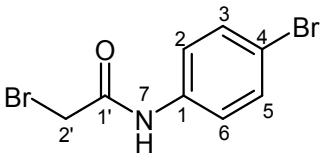


N-(Benzo[*d*][1,3]dioxol-5-yl)-2-bromoacetamide (**11i**). The reaction was carried out according to the general procedure using 3,4-(methylenedioxy)aniline (1.37 g, 10.0 mmol)

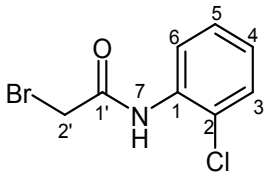
and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11i** as dark brown solids (1.10 g, 86%). R_f (EtOAc) 0.91; m.p. 153-155 ^oC; IR (ATR) v_{max} 3276, 2907, 1662, 1499, 1215, 1039, 813, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, br s, NH-6), 7.21 (1H, d, *J* = 2.4 Hz, H-4), 6.83 (1H, dd, *J* = 8.6, 2.2 Hz, H-5), 6.76 (1H, d, *J* = 8.0 Hz, H-2), 5.97 (2H, s, H_2-3), 4.00 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (C-1'), 148.1 (C-3a), 145.2 (C-2a), 131.2 (C-1), 113.7 (C-5), 108.3 (C-2), 103.0 (C-3), 101.6 (C-4), 29.6 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 279.9587 (calcd for $C_9H_8{}^{79}BrNNaO_3$, 279.9580).



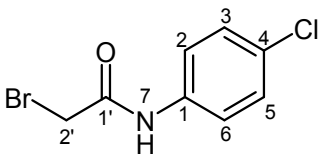
2-Bromo-*N*-(3-bromophenyl)acetamide (**11j**). The reaction was carried out according to the general procedure using 3-bromoaniline (1.09 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11j** as brown solids (0.93 g, 63%). R_f (EtOAc) 0.94; m.p. 102-104 ^oC; IR (ATR) v_{max} 3250, 3108, 1649, 1590, 1540, 1421, 875, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, br s, NH-7), 7.79 (1H, t, *J* = 1.8 Hz, H-2), 7.45 (1H, d, *J* = 8.0 Hz, H-4), 7.30 (1H, d, *J* = 8.0 Hz, H-6), 7.22 (1H, t, *J* = 8.0 Hz, H-5), 4.02 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C-1'), 138.3 (C-1), 130.5 (C-5), 128.4 (C-6), 123.1 (C-2), 122.9 (C-3), 118.6 (C-4), 29.5 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 313.8776 (calcd for $C_8H_7{}^{79}Br_2NNaO$, 313.8787). All characterization data agreed with those reported in the literature.[2]



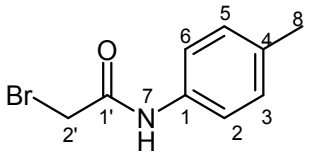
2-Bromo-*N*-(4-bromophenyl)acetamide (**11k**). The reaction was carried out according to the general procedure using 4-bromoaniline (1.72 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11k** as brown solids (0.99 g, 68%). R_f (EtOAc) 0.93; m.p. 165-168 ^oC; IR (ATR) v_{max} 3257, 3085, 1647, 1610, 1486, 1397, 815, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, br s, NH-7), 7.48 (2H, dd, *J* = 6.8, 2.4 Hz, H-3, H-5), 7.44 (2H, dd, *J* = 6.8, 2.4 Hz, H-2, H-6), 4.02 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 136.1 (C-1), 132.3 (C-3, C-5), 121.7 (C-2, C-6), 118.1 (C-4), 29.5 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 313.8788 (calcd for $C_8H_7{}^{79}Br_2NNaO$, 313.8787).



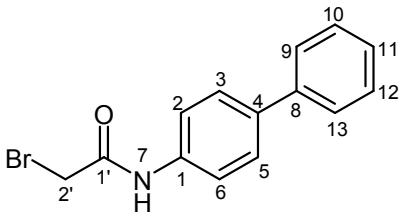
2-Bromo-*N*-(2-chlorophenyl)acetamide (**11l**). The reaction was carried out according to the general procedure using 2-chloroaniline (1.05 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11l** as light brown solids (1.24 g, 100%). R_f (EtOAc) 0.94; m.p. 87-89 ^oC; IR (ATR) v_{max} 3276, 1663, 1534, 1441, 1312, 1058, 754, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (1H, br s, NH-7), 8.34 (1H, dd, *J* = 8.4, 1.2 Hz, H-6), 7.40 (1H, dd, 8.0 , 1.2 Hz, H-3), 7.30 (1H, ddd, *J* = 8.0, 8.0, 1.6 Hz, H-5), 7.10 (1H, ddd, *J* = 8.0, 8.0, 1.6 Hz, H-4), 4.07 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 134.0 (C-1), 129.3 (C-3), 127.9 (C-5), 125.6 (C-4), 123.6 (C-2), 121.4 (C-6), 29.7 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 269.9299 (calcd for $C_8H_7{}^{79}Br^{35}ClNNaO$, 269.9292). ^1H and ^{13}C NMR data agreed with literature values.[4]



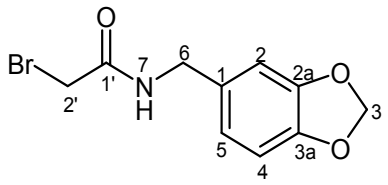
2-Bromo-*N*-(4-chlorophenyl)acetamide (**11m**). The reaction was carried out according to the general procedure using 4-chloroaniline (1.28 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11m** as yellow solids (0.76 g, 61%). R_f (EtOAc) 0.89; m.p. 157-158.5 ^oC; IR (ATR) v_{max} 3258, 2975, 1649, 1548, 1488, 1090, 817, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, br s ,NH-7), 7.49 (2H, d, *J* = 8.8 Hz, H-2, H-6), 7.32 (2H, d, *J* = 8.8 Hz, H-3, H-5), 4.02 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 135.6 (C-4), 130.5 (C-1), 129.3 (C-3, C-5), 121.4 (C-2, C-6), 29.5 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 269.9294 (calcd for $C_8H_7{}^{79}Br^{35}ClNNaO$, 269.9292).



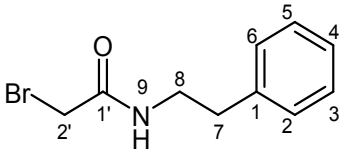
2-Bromo-*N*-(*p*-tolyl)acetamide (**11n**). The reaction was carried out according to the general procedure using 4-methylaniline (1.07 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11n** as yellow solids (1.06 g, 93%). R_f (EtOAc) 0.89; m.p. 164-166 ^oC; IR (ATR) v_{max} 3262, 2917, 1650, 1610, 1510, 1406, 814, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, br s, NH-7), 7.40 (2H, dd, *J* = 6.8, 1.8 Hz, H-2, H-6), 7.15 (2H, d, *J* = 8.0 Hz, H-3, H-5), 4.01 (2H, s, H_2-2'), 2.33 (3H, s, H_3-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (C-1'), 135.1 (C-4), 134.5 (C-1), 129.8 (C-3, C-5), 120.3 (C-2, C-6), 29.7 (C-2'), 21.1 (C-8); (+)-HRESIMS $[M+H]^+$ *m/z* 228.0010 (calcd for $C_9H_{11}{}^{79}BrNO$, 228.0019). ^1H and ^{13}C NMR data agreed with literature values.[1]



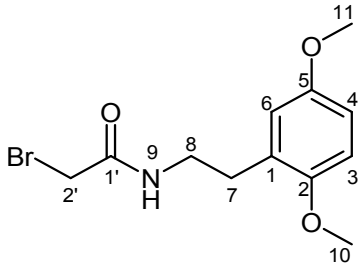
N-([1,1'-Biphenyl]-4-yl)-2-bromoacetamide (**11o**). The reaction was carried out according to the general procedure using 4-aminobiphenyl (1.69 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11o** as beige solids (0.39 g, 27%). R_f (CH_2Cl_2) 0.83; m.p. 91-93 ^oC ; IR (ATR) ν_{max} 3287, 1656, 1598, 1534, 1487, 1204, 832, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, br s, NH-7), 7.63-7.56 (6H, m, H-2, H-3, H-5, H-6, H-10, H-12), 7.44 (2H, td, *J* = 6.8, 1.6 Hz, H-9, H-13), 7.34 (1H, tt, *J* = 6.8, 1.6 Hz, H-11), 4.05 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (C-1'), 140.4 (C-8), 138.3 (C-4), 136.3 (C-1), 129.0 (C-9, C-13), 127.9 (C-11), 127.5 (C-3, C-5), 127.1 (C-10, C-12), 120.5 (C-2, C-6), 29.6 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 311.9998 (calcd for $C_{14}H_{12}{}^{79}BrNNaO$, 311.9994).



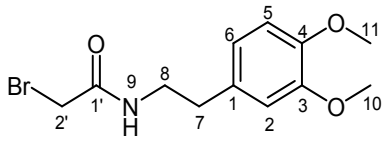
N-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2-bromoacetamide (**11p**). The reaction was carried out according to the general procedure using piperonylamine (1.25 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11p** as beige solids (0.90 g, 66%). R_f (EtOAc) 0.81; m.p. 108-110 ^oC; IR (ATR) ν_{max} 3290, 2899, 1644, 1490, 1245, 1031, 820, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, d, *J* = 1.2 Hz, H-4), 6.77 (1H, s, H-2), 6.76 (1H, d, *J* = 1.6 Hz, H-5), 6.74 (1H, d, *J* = 1.6 Hz, NH-7), 5.96 (2H, s, H_2-3), 4.37 (2H, d, *J* = 5.6 Hz, H_2-6), 3.91 (2H, s, H_2-2'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-1'), 148.2 (C-3a), 147.4 (C-2a), 131.2 (C-1), 121.3 (C-5), 108.6 (C-2), 108.5 (C-4), 101.3 (C-3), 44.2 (C-6), 29.3 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 293.9741 (calcd for $C_{10}H_{10}{}^{79}BrNNaO_3$, 293.9736).



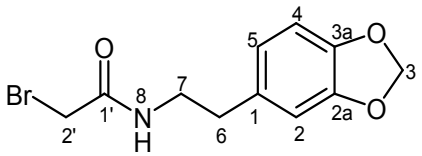
2-Bromo-*N*-phenethylacetamide (**11q**). The reaction was carried out according to the general procedure using phenethylamine (1.26 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11q** as orange/brown solids (1.04 g, 86%). R_f (EtOAc) 0.83; m.p. 67-70 ^oC; IR (ATR) v_{max} 3240, 2935, 1650, 1569, 1454, 1197, 747, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, t, *J* = 7.3 Hz, H-3, H-5), 7.27-7.20 (3H, m, H-2, H-4, H-6), 6.50 (1H, br s, NH-9), 3.85 (2H, s, H_2-2'), 3.55 (2H, q, *J* = 7.2 Hz, H_2-8), 2.85 (2H, t, *J* = 7.0 Hz, H_2-7); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-1'), 138.5 (C-1), 128.9 (C-3, C-5), 128.8 (C-2, C-6), 126.9 (C-4), 41.5 (C-8), 35.6 (C-7), 29.4 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 263.9992 (calcd for $C_{10}H_{12}{}^{79}BrNNaO$, 263.9994). ^1H and ^{13}C NMR data agreed with literature values.[1]



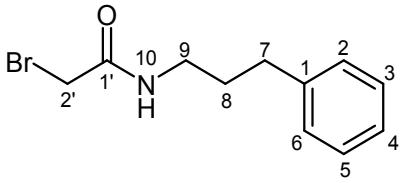
2-Bromo-*N*-(2,5-dimethoxyphenethyl) acetamide (**11r**). The reaction was carried out according to the general procedure using 2-(2,5-dimethoxyphenyl)ethan-1-amine (1.82 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11r** as an orange solid (1.30 g, 86%). R_f (EtOAc) 0.86; m.p. 82.5-85 ^oC; IR (ATR) v_{max} 3252, 3092, 1644, 1500, 1221, 1042, 803, 701, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, br s, NH-9), 6.80 (1H, d, *J* = 9.0 Hz, H-3), 6.76 (1H, d, *J* = 3.0 Hz, H-6), 6.73 (1H, t, *J* = 2.6 Hz, H-4), 3.83 (2H, s, H_2-2'), 3.82 (3H, s, H_3-10), 3.76 (3H, s, H_3-11), 3.51 (2H, dt, *J* = 6.2, 6.2 Hz, H_2-8), 2.85 (2H, t, *J* = 6.6 Hz, H_2-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C-1'), 153.8 (C-5), 151.7 (C-2), 128.3 (C-1), 116.9 (C-6), 112.4 (C-4), 111.4 (C-3), 56.1 (C-10), 55.9 (C-11), 41.2 (C-8), 29.9 (C-7), 29.4 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 324.0218 (calcd for $C_{12}H_{16}{}^{79}BrNNaO_3$, 324.0206).



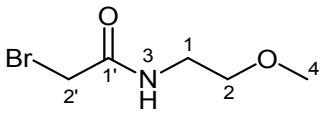
2-Bromo-*N*-(3,4-dimethoxyphenethyl) acetamide (**11s**). The reaction was carried out according to the general procedure using 2-(3,4-dimethoxyphenyl)ethan-1-amine (1.69 mL, 10.0 mmol) and bromo acetylbromide (0.44 mL, 5.0 mmol) to afford **11s** as light brown crystals (1.32 g, 88%). R_f (EtOAc) 0.70; m.p. 112-113 ^oC; IR (ATR) v_{max} 3226, 1631, 1513, 1237, 1136, 1020, 806, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 8.0 Hz, H-2), 6.76 (1H, s, H-5), 6.72 (1H, d, *J* = 2.0 Hz, H-6), 6.51 (1H, br s, NH-9), 3.88-3.86 (8H, m, H_3-10, H_3-11, H_2-2'), 3.53 (2H, dd, *J* = 12.9, 6.8 Hz, H_2-8), 2.79 (2H, t, *J* = 6.8 Hz, H_2-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-1'), 149.2 (C-3), 148.0 (C-4), 131.0 (C-1), 120.8 (C-5), 112.1 (C-6), 111.6 (C-2), 56.1 (C-11), 56.0 (C-10), 41.6 (C-8), 35.1 (C-7), 29.4 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 324.0218 (calcd for $C_{12}H_{16}{}^{79}BrNNaO_3$, 324.0206).



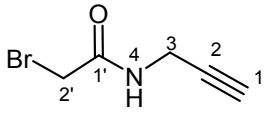
N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-bromoacetamide (**11t**). The reaction was carried out according to the general procedure using homopiperonylamine (1.35 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11t** as pale orange solids (1.30 g, 91%). R_f (EtOAc) 0.79; m.p. 76-78 ^oC; IR (ATR) v_{max} 3283, 2892, 1647, 1490, 1242, 1038, 804, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, d, *J* = 7.9 Hz, H-4), 6.69 (1H, d, *J* = 1.6 Hz, H-2), 6.65 (1H, dd, *J* = 7.8, 1.6 Hz, H-5), 6.49 (1H, br s, NH-8), 5.94 (2H, s, H_2-3), 3.85 (2H, s, H_2-2'), 3.50 (2H, q, *J* = 6.7 Hz, H_2-7), 2.76 (2H, t, *J* = 6.9 Hz, H_2-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-1'), 148.1 (C-3a), 146.5 (C-2a), 132.2 (C-1), 121.8 (C-5), 109.2 (C-2), 108.6 (C-4), 101.1 (C-3), 41.6 (C-7), 35.3 (C-6), 29.4 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 307.9896 (calcd for $C_{11}H_{12}{}^{79}BrNNaO_3$, 307.9893).



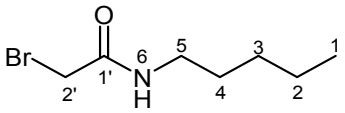
2-Bromo-*N*-(3-phenylpropyl)acetamide (**11u**). The reaction was carried out according to the general procedure using 3-phenyl-1-propylamine (1.35 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11u** as orange solids (1.13 g, 88%). R_f (EtOAc) 0.87; m.p. 37-39 ^oC; IR (ATR) v_{max} 3281, 2942, 1648, 1558, 1451, 1422, 745, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, dt, *J* = 5.2, 1.5 Hz, H-3, H-5), 7.20 (3H, dt, *J* = 7.4, 1.6 Hz, H-2, H-4, H-6), 6.48 (1H, br s, NH-10), 3.85 (2H, s, H_2-2'), 3.32 (2H, dt, *J* = 6.7, 6.7 Hz, H_2-9), 2.67 (2H, t, *J* = 7.6 Hz, H_2-8), 1.93-1.85 (2H, m, H_2-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-1'), 141.2 (C-1), 128.7 (C-3, C-5), 128.5 (C-2, C-6), 126.3 (C-4), 40.0 (C-9), 33.3 (C-8), 30.9 (C-7), 29.4 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 278.0158 (calcd for $C_{11}H_{14}{}^{79}BrNNaO$, 278.0151). ^1H and ^{13}C NMR data agreed with literature values.[1]



2-Bromo-*N*-(2-methoxyethyl)acetamide (**11v**)**.** The reaction was carried out according to the general procedure using 2-methoxyethylamine (0.87 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11v** as a white solid (0.49 g, 50%). R_f (EtOAc) 0.70; m.p. 30-33 ^oC; IR (ATR) v_{max} 3278, 1652, 1509, 1123, 1021, 828, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (1H, br s, NH-3), 3.89 (2H, s, H_2-2'), 3.49 (2H, br s, H_2-2), 3.48 (2H, br s, H_2-1), 3.38 (3H, s, H_3-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (C-1'), 70.9 (C-2), 59.0 (C-4), 40.1 (C-1), 29.2 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 217.9795 (calcd for $C_5H_{10}{}^{79}BrNNaO_2$, 217.9787). Characterization data agrees with those reported in the literature.[5]



2-Bromo-*N*-(prop-2-yn-1-yl) acetamide (**11w**). The reaction was carried out according to the general procedure using propargylamine (0.64 mL, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11w** as orange/brown solids (0.45 g, 51%). R_f (EtOAc) 0.17; m.p. 64-65 ^{o}C; IR (ATR) v_{max} 3286, 1634, 1536, 1405, 1212, 690, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, br s, NH-4), 4.09 (2H, dd, *J* = 5.4, 2.5 Hz, H_2-3), 3.90 (2H, s, H_2-2'), 2.28 (1H, t, *J* = 2.5 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-1'), 78.7 (C-2), 72.4 (C-1), 30.1 (C-3), 28.8 (C-2'); (+)-HRESIMS $[M+Na]^+$ *m/z* 197.9524 (calcd for $C_5H_6{}^{79}BrNNaO$, 197.9525). Characterization data agrees with those reported in the literature.[6]

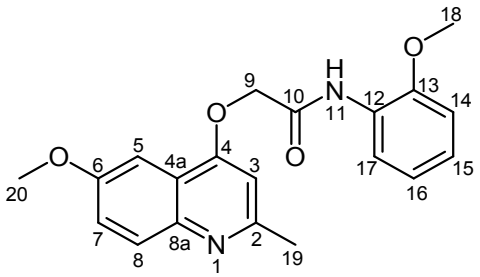


2-Bromo-*N*-pentylacetamide (**11x**). The reaction was carried out according to the general procedure using amylamine (1.16 g, 10.0 mmol) and bromoacetylbromide (0.44 mL, 5.0 mmol) to afford **11x** as dark orange oil (0.91 g, 87%). R_f (EtOAc) 0.77; m.p. 25 °C; IR (ATR) v_{max} 3287, 2931, 2860, 1649, 1552, 1437, 1378, 1210 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, br s, NH-6), 3.89 (2H, s, H_2-2'), 3.29 (2H, dt, *J* = 5.0, 5.0 Hz, H_2-5), 1.55 (2H, p, *J* = 7.2 Hz, H_2-4), 1.34-1.31 (4H, m, H_2-3, H_2-2), 0.91 (3H, t, *J* = 6.8 Hz, H_3-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-1'), 40.4 (C-5), 29.5 (C-4), 29.1 (C-2', C-3), 22.4 (C-2), 14.1 (C-1); (+)-HRESIMS $[M+Na]^+$ *m/z* 230.0147 (calcd for $C_7H_{14}{}^{79}BrNNaO$, 230.0151).

General procedure for the synthesis of quinoloxyacetamide analogues 5, 9, 12a-aa: Quinolin-4-ol (1.0 equiv.) and potassium carbonate (5.0 equiv.) were suspended in acetone

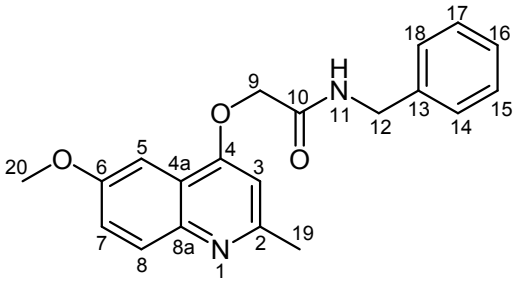
(8.0 mL) and heated to reflux at 100 °C for 0.5 h. The appropriate α-bromoacetamide (2.0 equiv.), dissolved in acetone (2.0 mL), was then added to the mixture and heating continued for 5 h. After this time, the mixture was dried in vacuo, the crude product dissolved in CH_2Cl_2 (50.0 mL) and washed with H_2O (3 x 30.0 mL). The organic solvent was dried ($MgSO_4$), and subjected to purification by silica gel column chromatography (EtOAc).

An alternative method was also used, whereby reaction of quinolin-4-ol (1.0 equiv.), bromide (1.05 equiv.) and K_2CO_3 (2.5 equiv.) were stirred at room temperature for 20 h in DMF. Pouring into H_2O (100 mL) afforded the product as a precipitate that was filtered, and washed with cold methanol.

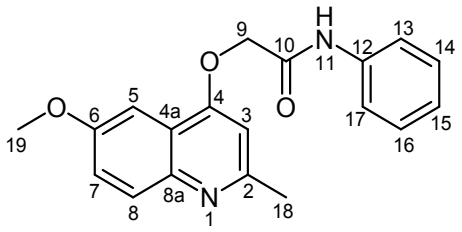


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(2-methoxyphenyl)acetamide (**5**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (78.0 mg, 0.32 mmol) in acetone afforded **5** as off-white solids (50 mg, 89%). R_f (EtOAc) 0.60; m.p. 165-166 ^oC; IR (ATR) v_{max} 3397, 1686, 1545, 1211, 1113, 1029, 729, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (1H, br s, NH-11), 8.43 (1H, dd, *J* = 8.0, 1.6 Hz, H-17), 7.94 (1H, d, *J* = 9.2 Hz, H-8), 7.56 (1H, d, *J* = 2.8 Hz, H-5), 7.40 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.10 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz, H-15), 7.01 (1H, ddd, *J* = 7.6, 7.6, 1.5 Hz, H-16), 6.89 (1H, dd, *J* = 8.0, 1.6 Hz, H-14), 6.66 (1H, s, H-3), 4.84 (2H, s, H_2-9), 3.98 (3H, s, H_3-20), 3.80 (3H, s, H_3-18), 2.68 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (C-10), 158.9 (C-4), 157.7 (C-2), 157.3 (C-6), 148.3 (C-13), 145.0 (C-8a), 130.2 (C-8), 126.8 (C-12),

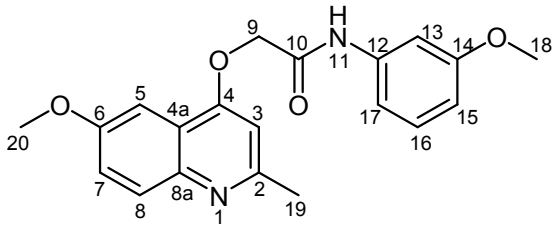
124.7 (C-15), 121.4 (C-7, C-16), 120.1 (C-4a), 120.0 (C-17), 110.4 (C-14), 102.1 (C-3), 100.8 (C-5), 67.4 (C-9), 55.9 (C-20), 55.8 (C-18), 25.8 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 375.1317 (calcd for $C_{20}H_{20}N_2NaO_4$, 375.1315).



N-Benzyl-2((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**9**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(prop-2-yn-1-yl)acetamide (**11b**) (36.0 mg, 0.32 mmol) in acetone afforded **9** as white solids (19 mg, 35%). R_f (EtOAc) 0.44; m.p. 189-191 ^oC; IR (ATR) v_{max} 3000, 2938, 1660, 1223, 1101, 1026, 828, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 9.2 Hz, H-8), 7.34-7.24 (7H, m, H-5, H-7, H-14, H-15, H-16, H-17, H-18), 6.73 (1H, br s, NH-11), 6.58 (1H, s, H-3), 4.78 (2H, s, H_2-9), 4.56 (2H, d, *J* = 5.6 Hz, H_2-12), 3.80 (3H, s, H_3-20), 2.65 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C-11), 159.1 (C-4), 157.5 (C-2), 157.2 (C-6), 145.0 (C-8a), 137.6 (C-14), 130.1 (C-8), 129.0 (C-15, C-17), 128.0 (C-14, C-18), 127.8 (C-16), 122.3 (C-7), 119.9 (C-4a), 102.2 (C-3), 99.4 (C-5), 67.6 (C-9), 55.5 (C-20), 43.4 (C-12), 25.7 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 359.1377 (calcd for $C_{20}H_{20}N_2NaO_3$, 359.1366).

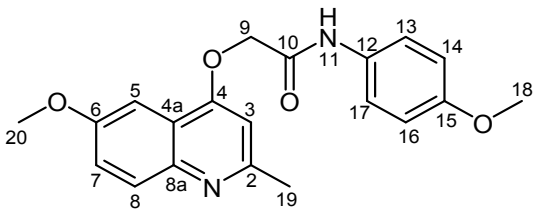


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-phenylacetamide (**12a**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-phenylacetamide (**11c**) (48.0 mg, 0.32 mmol) in acetone afforded **12a** as white solids (11 mg, 31%). R_f (EtOAc) 0.34; m.p. 223-225 ^oC; IR (ATR) v_{max} 2938, 1670, 1599, 1492, 1222, 1101, 827, 758 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 10.26 (1H, br s, NH-11), 7.78 (1H, d, *J* = 9.2 Hz, H-8), 7.64 (2H, d, *J* = 8.8 Hz, H-13, H-17), 7.52 (1H, d, *J* = 2.8 Hz, H-5), 7.36 (1H, d, *J* = 2.8 Hz, H-7), 7.34-7.32 (2H, m, H-14, H-16), 7.09 (1H, t, *J* = 3.4 Hz, H-15), 6.86 (1H, s, H-3), 5.01 (2H, s, H_2-9), 3.90 (3H, s, H_3-19), 2.55 (3H, s, H_3-18); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.7 (C-10), 159.5 (C-4), 156.9 (C-2), 156.3 (C-6), 144.2 (C-8a), 138.4 (C-12), 129.5 (C-8), 128.8 (C-14, C-16), 123.8 (C-15), 121.6 (C-7), 119.7 (C-4a), 119.7 (C-13), 119.6 (C-17), 102.2 (C-3), 100.1 (C-5), 67.1 (C-9), 55.4 (C-19), 25.1 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 323.1392 (calcd for $C_{19}H_{19}N_2O_3$, 323.1390).

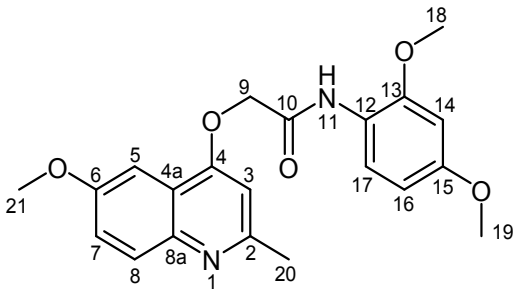


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(3-methoxyphenyl) acetamide (**12b**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3-methoxyphenyl)acetamide (**11d**) (78.0 mg, 0.32 mmol) in acetone afforded **12b** as white solids (10 mg, 18%). R_f (EtOAc) 0.34; m.p. 169-171 ^oC; IR (ATR) v_{max} 3241, 2940, 1681, 1488, 1152, 1101, 833, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, br s, NH-11), 7.92 (1H, d, *J* = 9.2 Hz, H-8), 7.41 (1H, d, *J* = 2.8 Hz, H-5), 7.38 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.33 (1H, t, *J* = 2.2 Hz, H-13), 7.25 (1H, t, *J* = 8.2 Hz, H-16), 7.00 (1H, dd, *J* = 7.8, 1.8 Hz, H-17), 6.72 (1H, dd, *J* =

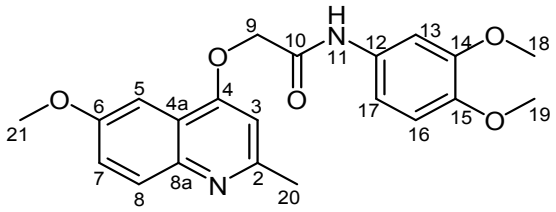
8.6, 2.6 Hz, H-15), 6.64 (1H, s, H-3), 4.84 (2H, s, H_2-9), 3.97 (3H, s, H_3-20), 3.81 (3H, s, H_3-18), 2.67 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-10), 160.5 (C-14), 159.0 (C-4), 157.6 (C-2), 157.4 (C-6), 145.1 (C-8a), 137.9 (C-12), 130.3 (C-8), 130.1 (C-16), 122.3 (C-7), 119.9 (C-4a), 112.3 (C-17), 111.0 (C-15), 106.1 (C-16), 102.4 (C-3), 99.5 (C-5), 67.8 (C-9), 55.7 (C-20), 55.5 (C-18), 25.8 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 375.1309 (calcd for $C_{20}H_{20}N_2NaO_4$, 375.1315).



2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(4 methoxyphenyl) acetamide (**12c**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(4-methoxyphenyl)acetamide (**11e**) (78.0 mg, 0.32 mmol) in acetone afforded **12c** as white solids (19 mg, 34%). R_f (EtOAc) 0.47; m.p. 203-207.5 ^{o}C; IR (ATR) ν_{max} 3337, 2931, 1661, 1598, 1514, 1222, 1098, 829 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, br s, NH-11), 7.90 (1H, d, *J* = 9.2 Hz, H-8), 7.45 (2H, d, *J* = 8.9 Hz, H-13, H-17), 7.40-7.34 (2H, m, H-5, H-7), 6.88 (2H, d, *J* = 8.9 Hz, H-14, H-16), 6.62-6.60 (1H, m, H-3), 4.82 (2H, s, H_2-9), 3.95 (3H, s, H_3-23), 3.79 (3H, s, H_3-18), 2.65 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-10), 159.0 (C-4), 157.6 (C-15), 157.3 (C-2), 157.2 (C-6), 145.0 (C-8a), 130.2 (C-12), 129.7 (C-8), 122.2 (C-13, C-17, C-7), 119.9 (C-4a), 114.5 (C-14, C-16), 102.3 (C-3), 99.7 (C-5), 67.8 (C-9), 55.7 (C-18), 55.6 (C-20), 25.7 (C-19); (+)-HRESIMS $[M+Na]^+$ *m/z* 375.1302 (calcd for $C_{20}H_{20}N_2NaO_4$, 375.1315).

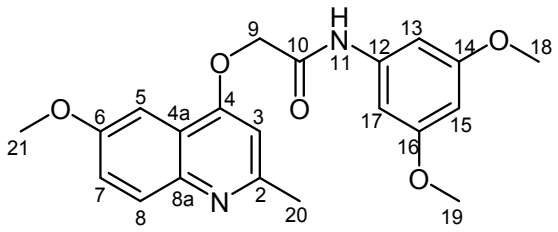


N-(2,4-Dimethoxyphenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12d**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(2,4-dimethoxyphenyl)acetamide (**11f**) (88.0 mg, 0.32 mmol) in acetone afforded **12d** as pale purple solids (10 mg, 16%). R_f (EtOAc) 0.17; m.p. 191-193 ^oC; IR (ATR) ν_{max} 3401, 2944, 1676, 1542, 1509, 1209, 1027, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (1H, br s, NH-11), 8.30 (1H, d, *J* = 8.8 Hz, H-17), 7.93 (1H, d, *J* = 9.2 Hz, H-8), 7.54 (1H, d, *J* = 2.8 Hz, H-5), 7.39 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 6.65 (1H, s, H-3), 6.52-6.48 (2H, m, H-14, H-16), 4.83 (2H, s, H_2-9), 3.97 (3H, s, H_3-21), 3.80 (3H, s, H_3-18), 3.77 (3H, s, H_3-19), 2.67 (3H, s, H_3-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C-10), 158.9 (C-4), 157.7 (C-2), 157.3 (C-6), 157.1 (C-13), 149.6 (C-15), 145.0 (C-8a), 130.2 (C-8), 121.4 (C-7), 120.8 (C-17), 120.3 (C-12), 120.1 (C-4a), 104.1 (C-16), 102.2 (C-3), 100.8 (C-5), 99.0 (C-14), 67.4 (C-9), 56.0 (C-21), 55.8 (C-18), 55.7 (C-19), 25.8 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 383.1595 (calcd for $C_{21}H_{23}N_2O_5$, 383.1601).

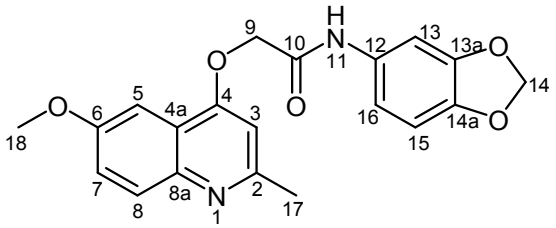


N-(3,4-Dimethoxyphenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12e**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol),

potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3,4-dimethoxyphenyl)acetamide (**11g**) (88.0 mg, 0.32 mmol) in acetone afforded **12e** as off-white solids (16 mg, 26%). R_f (EtOAc) 0.20; m.p. 208-210 ^oC; IR (ATR) ν_{max} 3260, 2937, 1666, 1516, 1480, 1222, 1111, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, br s, NH-11), 7.91 (1H, d, *J* = 8.8 Hz, H-8), 7.40 (1H, d, *J* = 2.8 Hz, H-5), 7.38 (1H, s, H-13), 7.36 (1H, dd, *J* = 5.0, 3.0 Hz, H-7), 6.92 (1H, dd, *J* = 8.8, 2.4 Hz, H-17), 6.82 (1H, d, *J* = 8.4 Hz, H-16), 6.62 (1H, s, H-3), 4.82 (2H, s, H_2-9), 3.95 (3H, s, H_3-21), 3.88 (3H, s, H_3-18), 3.86 (3H, s, H_3-19), 2.66 (3H, s, H_3-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-10), 159.1 (C-4), 157.6 (C-2), 157.3 (C-6), 149.3 (C-14), 146.6 (C-15), 145.0 (C-8a), 130.3 (C-12), 130.1 (C-8), 122.2 (C-7), 119.9 (C-4a), 112.3 (C-17), 111.5 (C-16), 105.2 (C-13), 102.3 (C-3), 99.7 (C-5), 67.9 (C-9), 56.2 (C-18), 56.1 (C-19), 55.7 (C-21), 25.6 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 383.1588 (calcd for $C_{21}H_{23}N_2O_5$, 383.1601).

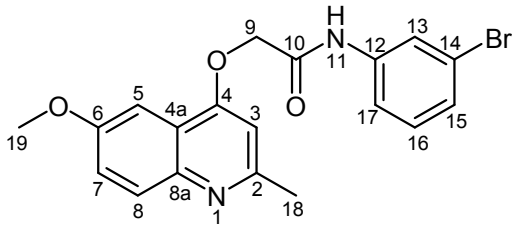


N-(3,5-Dimethoxyphenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12f**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3,5-dimethoxyphenyl)acetamide (**11h**) (88.0 mg, 0.32 mmol) in acetone afforded **12f** as white solids (18 mg, 29%). R_f (EtOAc) 0.32; m.p. 178-179 ^oC; IR (ATR) v_{max} 3420, 2943, 1690, 1600, 1421, 1153, 831, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, br s, NH-11), 7.91 (1H, d, *J* = 8.8 Hz, H-8), 7.39-7.36 (2H, m, H-5, H-7), 6.79 (2H, d, *J* = 2.0 Hz, H-13, H-17), 6.62 (1H, s, H-3), 6.28 (1H, t, *J* = 2.0 Hz, H-15), 4.81 (2H, s, H_2-9), 3.96 (3H, s, H_3-21), 3.78 (6H, s, H_3-18 and H_3-19), 2.66 (3H, s, H_3-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (C-10), 161.4 (C-14, C-16), 158.9 (C-4), 157.6 (C-2), 157.4 (C-6), 145.1 (C-8a), 138.5 (C-12), 130.3 (C-8), 122.3 (C-7), 119.9 (C-4a), 102.3 (C-3), 99.5 (C-5), 98.5 (C-13, C-17), 97.4 (C-15), 67.8 (C-9), 55.7 (C-21), 55.6 (C-18 and C-19), 25.7 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 383.1588 (calcd for $C_{21}H_{23}N_2O_5$, 383.1601).

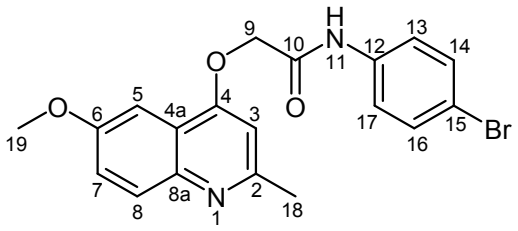


N-(Benzo[*d*][1,3]dioxol-5-yl)-2-((6-methoxy-2-methylquinolin-4yl)oxy) acetamide (**12g**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and *N*-(benzo[*d*][1,3]dioxol-5-yl)-2-bromoacetamide (**11i**) (83.0 mg, 0.32 mmol) in acetone afforded **12g** as off-white solids (12 mg, 20%). R_f (EtOAc) 0.31; m.p. 212-214 ^oC; IR (ATR) v_{max} 3243, 2922, 1677, 1479, 1221, 1100, 1032, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, br s, NH-11), 7.91 (1H, dd, *J* = 8.4, 0.8 Hz, H-8), 7.39-7.36 (2H, m, H-5, H-7), 7.27-7.26 (1H, m, H-15), 6.82 (1H, dd, *J* =

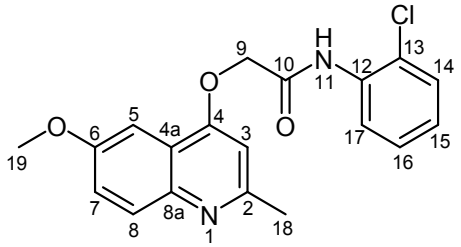
8.2, 2.2, H-16), 6.76 (1H, d, *J* = 8.4 Hz, H-13)), 6.62 (1H, s, H-3) 5.97 (2H, s, H_2-14), 4.82 (2H, s, H_2-9), 3.96 (3H, s, H_3-18), 2.66 (3H, s, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-10), 159.0 (C-4), 157.6 (C-2), 157.4 (C-6), 148.2 (C-14a), 145.1 (C-8a and C-13a), 130.9 (C-12), 130.2 (C-8), 122.2 (C-7), 119.9 (C-4a), 113.6 (C-16), 108.3 (C-13), 103.1 (C-14), 102.3 (C-15), 101.6 (C-3), 99.6 (C-5), 67.8 (C-9), 55.7 (C-18), 25.7 (C-17); (+)-HRESIMS $[M+H]^+$ *m/z* 367.1288 (calcd for $C_{20}H_{19}N_2O_5$, 367.1288).



N-(3-Bromophenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12h**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3-bromophenyl)acetamide (**11j**) (87.0 mg, 0.32 mmol) in acetone afforded **12h** as white solids (20 mg, 31%). R_f (EtOAc) 0.60; m.p. 205-208 ^{o}C; IR (ATR) ν_{max} 3071, 2917, 1689, 1587, 1419, 1021, 830, 779 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (1H, br s, NH-11), 7.99 (1H, s, H-13), 7.79 (1H, d, *J* = 9.2 Hz, H-8), 7.56 (1H, dt, *J* = 6.8, 2.0 Hz, H-15), 7.51 (1H, d, *J* = 2.8 Hz, H-5), 7.36 (1H, dd, *J* = 8.8, 2.8 Hz, H-7), 7.33-7.27 (2H, m, H-16, H-17), 6.88 (1H, s, H-3), 5.04 (2H, s, H_2-9), 3.90 (3H, s, H_3-19), 2.55 (3H, s, H_3-18); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1 (C-10), 159.6 (C-4), 156.9 (C-2), 156.4 (C-6), 143.9 (C-8a), 140.0 (C-14), 130.9 (C-16), 129.3 (C-8), 126.4 (C-17), 122.0 (C-13), 121.8 (C-7), 121.6 (C-12), 119.8 (C-4a), 118.4 (C-15), 102.3 (C-3), 100.2 (C-5), 67.0 (C-9), 55.4 (C-19), 24.9 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 401.0489 (calcd for $C_{19}H_{18}{}^{79}BrN_2O_3$, 401.0495).

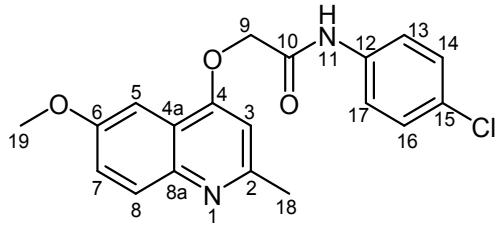


N-(4-Bromophenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12i**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(4-bromophenyl)acetamide (**11k**) (87.0 mg, 0.32 mmol) in acetone afforded **12i** as off-white solids (13 mg, 20%). R_f (EtOAc) 0.41; m.p. 217-219 ^oC; IR (ATR) ν_{max} 3419, 2915, 1709, 1599, 1500, 1098, 823, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, br s, NH-11), 7.91 (1H, d, *J* = 10.0 Hz, H-8), 7.47 (4H, s, H-13, H-14, H-16, H-17), 7.39 (1H, d, *J* = 3.2 Hz, H-5), 7.37 (1H, dd, *J* = 5.8, 2.6 Hz, H-7), 6.60 (1H, s, H-3), 4.83 (2H, s, H_2-9), 3.96 (3H, s, H_3-19), 2.65 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C-10), 158.9 (C-4), 157.6 (C-2), 157.4 (C-6), 145.1 (C-8a), 135.8 (C-12), 132.4 (C-15), 130.3 (C-8), 122.2 (C-7), 121.8 (C-13, C-17), 119.9 (C-4a), 118.0 (C-14, C-16), 102.3 (C-3), 99.7 (C-5), 67.8 (C-9), 55.7 (C-19), 25.7 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 401.0500 (calcd for $C_{19}H_{18}{}^{79}BrN_2O_3$, 401.0495).

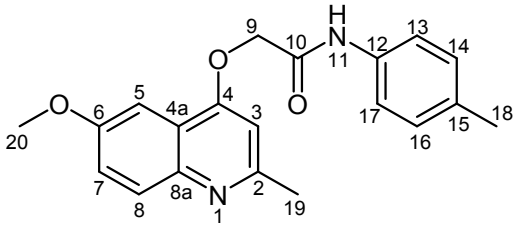


N-(2-Chlorophenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy)acetamide (**12j**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(2-chlorophenyl)acetamide (**11l**) (59.0 mg, 0.32 mmol) in acetone afforded **12j** as off-white solids (15 mg, 26%). R_f (EtOAc) 0.57; m.p. 198-201 ^oC; IR (ATR) ν_{max} 3390, 2927, 1697, 1596, 1444, 1098, 826, 752 cm^{-1}; ^1H

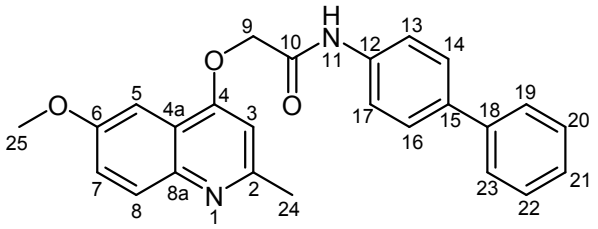
NMR (400 MHz, DMSO-d_6) δ 9.83 (1H, br s, NH-11), 7.87-7.84 (2H, m, H-8, H-17), 7.57 (1H, d, *J* = 2.8 Hz, H-5), 7.55 (1H, dd, *J* = 8.2, 2.6, Hz, H-14), 7.43 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.38 (1H, td, *J* = 7.8, 1.2 Hz, H-16), 7.25 (1H, *J* = 7.8, 1.6 Hz, H-15), 7.04 (1H, s, H-3), 5.12 (2H, s, H_2-9), 3.91 (3H, s, H_3-19), 2.61 (3H, s, H_3-18); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.0 (C-10), 159.5 (C-4), 156.9 (C-2), 156.6 (C-6), 143.3 (C-8a), 134.0 (C-12), 129.6 (C-14), 128.9 (C-8), 127.8 (C-16), 126.8 (C-15, C-13), 125.7 (C-17), 122.1 (C-7), 119.7 (C-4a), 102.7 (C-3), 100.1 (C-5), 67.2 (C-9), 55.5 (C-19), 24.7 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 357.0996 (calcd for $C_{19}H_{18}{}^{35}ClN_2O_3$, 357.1000).



N-(4-Chlorophenyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy)acetamide (**12k**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(4-chlorophenyl)acetamide (**11m**) (59.0 mg, 0.32 mmol) in acetone afforded **12k** as white solids (13 mg, 23%). R_f (EtOAc) 0.40; m.p. 221-224 ^{o}C; IR (ATR) ν_{max} 2946, 1698, 1596, 1482, 1222, 1093, 841, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, br s, NH-11), 7.91 (1H, d, *J* = 10.0 Hz, H-8), 7.52 (2H, dd, *J* = 6.8, 2.0 Hz, H-13, H-17), 7.39-7.36 (2H, m, H-5, H-7), 7.32 (2H, dd, *J* = 6.8, 2.0 Hz, H-14, H-16), 6.61 (1H, s, H-3), 4.83 (2H, s, H_2-9), 3.96 (3H, s, H_3-19), 2.66 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C-10), 158.9 (C-4), 157.6 (C-2), 157.4 (C-6), 145.1 (C-8a), 135.3 (C-15), 130.4 (C-12), 130.3 (C-8), 129.4 (C-14, C-16), 122.2 (C-7), 121.5 (C-13, C-17), 119.9 (C-4a), 102.3 (C-3), 99.6 (C-5), 67.8 (C-9), 55.8 (C-19), 25.7 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 357.0995 (calcd for $C_{19}H_{18}{}^{35}ClN_2O_3$, 357.1000).

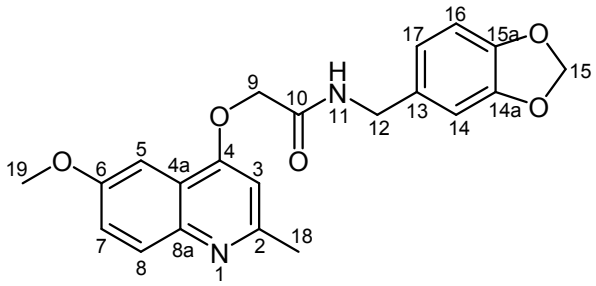


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(*p*-tolyl)acetamide (**12l**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(*p*-tolyl)acetamide (**11n**) (73.0 mg, 0.32 mmol) in acetone afforded **12l** as white solids (12 mg, 22%). R_f (EtOAc) 0.39; m.p. 200-202 ^oC; IR (ATR) v_{max} 3408, 2916, 1690, 1595, 1218, 1100, 826, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, br s, NH-11), 7.91 (1H, d, *J* = 9.2 Hz, H-8), 7.43 (2H, d, *J* = 8.4 Hz, H-13, H-17), 7.40 (1H, d, *J* = 2.8 Hz, H-5), 7.37 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.15 (2H, d, *J* = 8.4 Hz, H-14, H-16), 6.62 (1H, s, H-3), 4.82 (2H, s, H_2-9), 3.96 (3H, s, H_3-20), 2.65 (3H, s, H_3-19), 2.33 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (C-10), 159.0 (C-4), 157.6 (C-2), 157.3 (C-6), 145.1 (C-8a), 135.1 (C-15), 134.2 (C-12), 130.2 (C-8), 129.8 (C-14, C-16), 122.2 (C-7), 120.3 (C-13, C-17), 119.9 (C-4a), 102.3 (C-3), 99.6 (C-5), 67.8 (C-9), 55.7 (C-20), 25.7 (C-19), 21.0 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 337.1536 (calcd for $C_{20}H_{21}N_2O_3$, 337.1547).



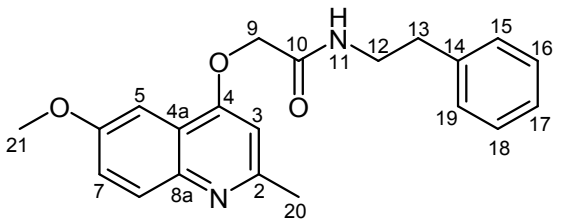
N-([1,1'-Biphenyl]-4-yl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12m**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and *N*-([1,1'-biphenyl]-4-yl)-2-bromoacetamide (**11o**) (93.0 mg, 0.32 mmol) in acetone afforded **12m** as off-white solids (20 mg, 31%). R_f (EtOAc) 0.67; m.p. 225-228 ^oC; IR (ATR) v_{max} 3328, 1667, 1594, 1528, 1481, 1228, 1105,

829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, br s, NH-11), 7.92 (1H, d, *J* = 9.2 Hz, H-8), 7.64 (2H, d, *J* = 8.4 Hz, H-13, H-17), 7.58 (4H, m, H-14, H-16, H-20, H-22), 7.45-7.41 (3H, m, H-5, H-19, H-23), 7.38 (1H, dd, *J* = 9.0, 3.0 Hz, H-7), 7.34 (1H, t, *J* = 7.4 Hz, H-21), 6.63 (1H, s, H-3), 4.85 (2H, s, H_2-9), 3.97 (3H, s, H_3-25), 2.66 (3H, s, H_3-24); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C-10), 159.0 (C-4), 157.6 (C-2), 157.4 (C-6), 145.1 (C-8a), 140.4 (C-18), 138.3 (C-15), 136.0 (C-12), 130.3 (C-8), 129.0 (C-19, C-23), 128.0 (C-21), 127.5 (C-14, C-16), 127.0 (C-20, C-22), 122.3 (C-7), 120.6 (C-13, C-17), 119.9 (C-4a), 102.3 (C-3), 99.6 (C-5), 67.8 (C-9), 55.7 (C-25), 25.7 (C-24); (+)-HRESIMS $[M+H]^+$ *m/z* 399.1691 (calcd for $C_{25}H_{23}N_2O_3$, 399.1703).

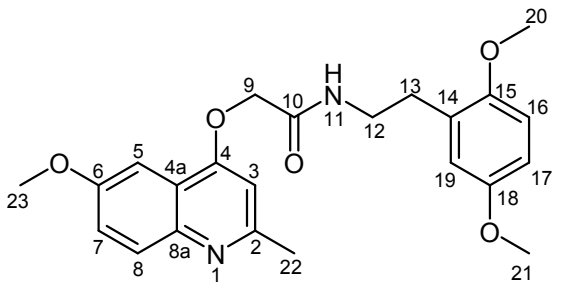


N-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy)acetamide (**12n**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and *N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-2-bromoacetamide (**11p**) (87.0 mg, 0.32 mmol) in acetone afforded **12n** as white solids (15 mg, 25%). R_f (EtOAc) 0.23; m.p. 171-172.5 °C; IR (ATR) v_{max} 3277, 2928, 1650, 1499, 1225, 1097, 1034, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 9.2 Hz, H-8), 7.32 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.26 (1H, d, *J* = 2.8 Hz, H-5), 6.75 (1H, d, *J* = 1.2 Hz, H-16), 6.72 (1H, s, H-14), 6.72 (1H, d, *J* = 1.2 Hz, H-17), 6.69 (1H, br s, NH-11), 6.57 (1H, s, H-3), 5.94 (2H, s, H_2-15), 4.76 (2H, s, H_2-9), 4.45 (2H, d, *J* = 6.0 Hz, H-12), 3.84 (3H, s, H_3-19), 2.65 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (C-10), 159.1 (C-4), 157.5 (C-2), 157.2 (C-6), 148.2 (C-14a), 147.4 (C-15a), 145.0 (C-8a), 131.4 (C-13), 130.1 (C-8), 122.3

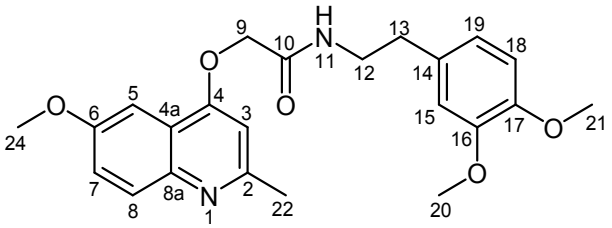
(C-7), 121.2 (C-14), 119.9 (C-4a), 108.5 (C-17), 108.3 (C-16), 102.2 (C-3), 101.3 (C-15), 99.5 (C-5), 67.6 (C-9), 55.5 (C-19), 43.2 (C-12), 25.7 (C-18); (+)-HRESIMS $[M+H]^+$ *m/z* 381.1439 (calcd for $C_{21}H_{21}N_2O_5$, 381.1445).



2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-phenethylacetamide (**12o**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-phenethylacetamide (**11q**) (77.0 mg, 0.32 mmol) in acetone afforded **12o** as white solids (18 mg, 32%). R_f (EtOAc) 0.22; m.p. 136-139.5 ^oC; IR (ATR) ν_{max} 3289, 2927, 1651, 1482, 1229, 1101, 832, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 9.2 Hz, H-8), 7.35 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.21 (1H, d, *J* = 2.8 Hz, H-5), 7.13-7.12 (3H, m, H-15, H-17, H-19), 7.04-7.01 (2H, m, H-16, H-18), 6.53 (1H, s, H-3), 6.40 (1H, br s, NH-11), 4.71 (2H, s, H_2-9), 3.85 (3H, s, H_3-21), 3.63 (2H, dt, *J* = 6.4, 6.4 Hz, H_2-12), 2.80 (2H, t, *J* = 6.8 Hz, H_2-13), 2.64 (3H, s, H_3-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C-10), 159.0 (C-4), 157.5 (C-2), 157.2 (C-6), 145.0 (C-8a), 138.2 (C-14), 130.1 (C-8), 128.8 (C-16, C-18), 128.6 (C-15, C-19), 126.8 (C-17), 122.0 (C-7), 119.9 (C-4a), 101.9 (C-3), 99.9 (C-5), 67.4 (C-9), 55.7 (C-21), 40.2 (C-12), 35.6 (C-13), 25.7 (C-20); (+)-HRESIMS $[M+Na]^+$ *m/z* 351.1713 (calcd for $C_{21}H_{22}N_2NaO_3$, 351.1703).

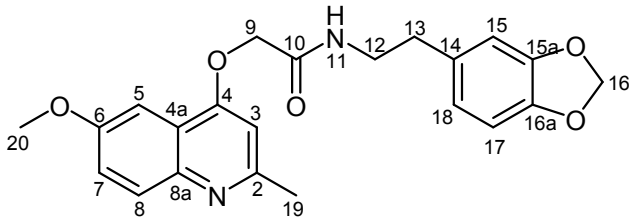


N-(2,5-Dimethoxyphenethyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12p**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(2,5-dimethoxyphenethyl) acetamide (**11r**) (96.0 mg, 0.32 mmol) in acetone afforded **12p** as white solids (14 mg, 21%). R_f (EtOAc) 0.57; m.p. 143-144 ^oC; IR (ATR) v_{max} 3311, 2939, 2833, 1653, 1499, 1221, 1103, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 9.2 Hz, H-8), 7.36 (1H, dd, *J* = 9.2, 2.8 Hz, H-7), 7.32 (1H, d, *J* = 2.8 Hz, H-5), 6.68 (1H, br s, NH-11), 6.64-6.61 (2H, m, H-16, H-19), 6.51 (1H, dd, *J* = 7.4, 2.2 Hz, H-17), 6.46 (1H, s, H-3), 4.69 (2H, s, H_2-9), 3.91 (3H, s, H_3-23), 3.67 (3H, s, H_3-21), 3.60 (2H, dt, *J* = 6.2, 6.2 Hz, H_2-12), 3.45 (3H, s, H_3-20), 2.81 (2H, t, *J* = 6.6 Hz, H_2-13), 2.60 (3H, s, H_3-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C-10), 159.4 (C-4), 157.6 (C-2), 157.2 (C-6), 153.8 (C-18), 151.6 (C-15), 145.0 (C-8a), 130.1 (C-8), 128.2 (C-14), 122.1 (C-7), 120.1 (C-4a), 116.6 (C-19), 112.2 (C-17), 111.8 (C-16), 102.1 (C-3), 99.9 (C-5), 67.9 (C-9), 56.0 (C-20), 55.7 (C-21), 55.7 (C-23), 40.2 (C-12), 29.7 (C-13), 25.7 (C-22); (+)-HRESIMS $[M+H]^+$ *m/z* 411.1926 (calcd for $C_{23}H_{27}N_2O_5$, 411.1914).



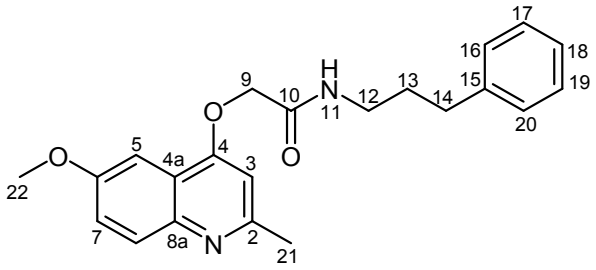
N-(3,4-Dimethoxyphenethyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy) acetamide (**12q**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3,4-dimethoxyphenethyl) acetamide (**11s**) (96.0 mg, 0.32 mmol) in acetone afforded **12q** as off-white solids (20 mg, 30%). R_f (5% MeOH in CH_2Cl_2) 0.52; m.p. 175-176 ^oC; IR (ATR) v_{max} 3286, 2921, 1658, 1504, 1229, 1024, 832, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H,

d, *J* = 8.8 Hz, H-8), 7.36 (1H, dd, *J* = 9.6, 3.0 Hz, H-7), 7.24 (1H, d, *J* = 2.8 Hz, H-5), 6.64 (1H, d, *J* = 2.0 Hz, H-15), 6.56 (1H, s, H-3), 6.49 (1H, d, *J* = 8.0 Hz, H-18), 6.41 (1H, dd, *J* = 8.0, 2.0 Hz, H-19), 6.39 (1H, br s, NH-11), 4.73 (2H, s, H_2-9), 3.87 (3H, s, H_3-23), 3.78 (6H, s, H_3-20 and H_3-21), 3.61 (2H, dt, *J* = 6.8, 6.8 Hz, H_2-12), 2.74 (2H, t, *J* = 6.8 Hz, H_2-13), 2.65 (3H, s, H_3-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C-10), 159.1 (C-4), 157.5 (C-2), 157.2 (C-6), 149.3 (C-16), 147.9 (C-17), 145.0 (C-8a), 130.6 (C-14), 130.1 (C-8), 122.0 (C-7), 120.6 (C-4a), 119.9 (C-19), 111.6 (C-15), 111.2 (C-18), 102.0 (C-3), 99.9 (C-5), 67.5 (C-10), 55.9 (C-20 and C-21), 55.7 (C-23), 40.3 (C-12), 35.2 (C-13), 25.7 (C-22); (+)-HRESIMS $[M+H]^+$ *m/z* 411.1923 (calcd for $C_{23}H_{27}N_2O_5$, 411.1914).

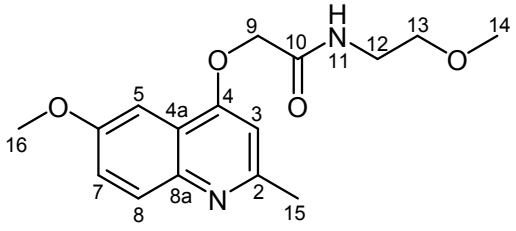


N-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-2-((6-methoxy-2-methylquinolin-4-yl)oxy)acetamide (**12r**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and *N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-2-bromoacetamide (**11t**) (92.0 mg, 0.32 mmol) in acetone afforded **12r** as white solids (16 mg, 25%). R_f (EtOAc) 0.57; m.p. 78-79 °C; IR (ATR) ν_{max} 3278, 2914, 1656, 1601, 1500, 1223, 1031, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 9.2 Hz, H-8), 7.35 (1H, dd, *J* = 9.4, 3.0 Hz, H-7), 7.23 (1H, d, *J* = 2.8 Hz, H-5), 6.56 (1H, d, *J* = 1.6 Hz, H-17), 6.53 (1H, s, H-3), 6.50 (1H, d, *J* = 8.0 Hz, H-15), 6.42 (1H, dd, *J* = 8.0, 1.6 Hz, H-18), 6.39 (1H, br s, NH-11), 5.87 (2H, s, H_2-16), 4.71 (2H, s, H_2-9), 3.89 (3H, s, H_3-20), 3.58 (2H, q, *J* = 6.8 Hz, H_2-12), 2.71 (2H, t, *J* = 6.8 Hz, H_2-13), 2.65 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C-10), 159.0 (C-4), 157.5 (C-2), 157.2 (C-6), 148.0 (C-15a), 146.4 (C-16a), 145.0 (C-8a), 131.8 (C-14), 130.1 (C-8), 121.9 (C-7), 121.5 (C-18), 119.9 (C-4a), 108.8 (C-17), 108.4 (C-15), 101.9 (C-3), 101.1 (C-2), 99.9 (C-5), 67.4 (C-9), 55.7 (C-20),

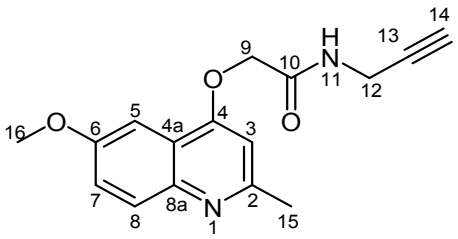
40.3 (C-12), 35.2 (C-13), 25.7 (C-19); (+)-HRESIMS $[M+H]^+$ *m/z* 395.1602 (calcd for $C_{22}H_{23}N_2O_5$, 395.1601).



2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(3-phenylpropyl)acetamide (**12s**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(3-phenylpropyl)acetamide (**11u**) (82.0 mg, 0.32 mmol) in acetone afforded **12s** as pale yellow solids (25 mg, 43%). R_f (EtOAc) 0.25; m.p. 124-126 ^oC; IR (ATR) ν_{max} 3342, 2937, 1654, 1543, 1453, 1228, 1098, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, dd, *J* = 8.0, 2.0 Hz, H-8), 7.37-7.35 (2H, m, H-5, H-7), 7.23 (2H, t, *J* = 7.6 Hz, H-17, H-19), 7.14 (1H, t, *J* = 7.6 Hz, H-18), 7.09 (2H, d, *J* = 6.8 Hz, H-16, H-20), 6.57 (1H, s, H-3), 6.41 (1H, br s, NH-11), 4.71 (2H, s, H_2-9), 3.92 (3H, s, H_3-22), 3.39 (2H, dt, *J* = 6.8, 6.8 Hz, H_2-12), 2.64 (3H, s, H_3-21), 2.62 (2H, t, *J* = 7.6 Hz, H_2-13), 1.91-1.83 (2H, m, H_2-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4 (C-10), 159.2 (C-4), 157.6 (C-2), 157.2 (C-6), 145.0 (C-8a), 141.0 (C-15), 130.2 (C-8), 128.6 (C-17, C-19), 128.3 (C-16, C-20), 126.3 (C-18), 122.0 (C-7), 119.9 (C-4a), 102.1 (C-3), 99.8 (C-5), 67.6 (C-9), 55.7 (C-22), 38.9 (C-12), 33.2 (C-13), 31.1 (C-14), 25.7 (C-21); (+)-HRESIMS $[M+H]^+$ *m/z* 365.1858 (calcd for $C_{22}H_{25}N_2O_3$, 365.1860).

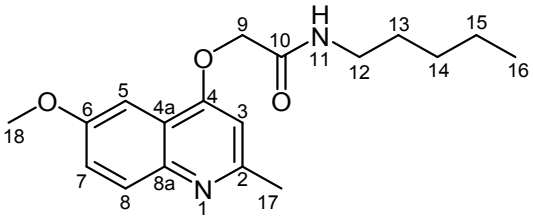


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(2-methoxyethyl) acetamide (**12t**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(2-methoxyethyl)acetamide (**11v**) (63.0 mg, 0.32 mmol) in acetone afforded **12t** as off-white solids (15 mg, 31%). R_f (3% MeOH in CH_2Cl_2) 0.11; m.p. 146.5-148 ^oC; IR (ATR) ν_{max} 3257, 2892, 1653, 1602, 1483, 1232, 1096, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, d, J = 9.2 Hz, H-8), 7.38-7.33 (2H, m, H-5, H-7), 6.92 (1H, br s, NH-11), 6.59 (1H, s, H-3), 4.73 (2H, s, H_2-9), 3.95 (3H, s, H_3-16), 3.58 (2H, dt, J = 5.0, 5.0 Hz, H_2-12), 3.49 (2H, t, J = 5.0 Hz, H_2-13), 3.30 (3H, s, H_3-14), 2.66 (3H, s, H_3-15); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (C-10), 159.1 (C-4), 157.5 (C-2), 157.2 (C-6), 145.0 (C-8a), 130.1 (C-8), 122.3 (C-7), 119.9 (C-4a), 102.1 (C-3), 99.5 (C-5), 71.0 (C-13), 67.4 (C-9), 58.9 (C-14), 55.6 (C-16), 38.9 (C-12), 25.7 (C-15); (+)-HRESIMS $[M+Na]^+$ *m/z* 327.1317 (calcd for $C_{16}H_{20}N_2NaO_4$, 327.1315).

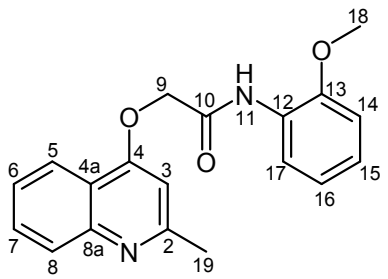


2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-(prop-2-yn-1-yl)acetamide (**12u**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-(prop-2-yn-1-yl) acetamide (**11w**) (56.0 mg, 0.32 mmol) in acetone afforded **12u** as white solids (16 mg, 35%). R_f (EtOAc) 0.59; m.p. 220.5-222 ^oC; IR (ATR) ν_{max} 3255, 3154, 2214, 2111, 1675, 1598, 1547, 833 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 8.70 (1H, t, J = 5.6 Hz, NH-11), 7.77 (1H, d, J = 9.2 Hz, H-8), 7.54 (1H, d, J = 2.8 Hz, H-5), 7.35 (1H, dd, J = 9.2, 2.8 Hz, H-7), 6.79 (1H, s, H-3), 4.81 (2H, s, H_2-9), 3.97 (2H, dd, J = 5.6, 2.8 Hz, H_2-12), 3.90 (3H, s, H_3-16), 3.14 (1H, t, J = 2.4 Hz, H-14), 2.54 (3H, s, H_3-15); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.8 (C-10),

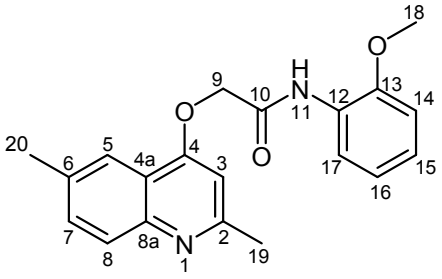
159.2 (C-4), 156.9 (C-2), 156.2 (C-6), 144.2 (C-8a), 129.5 (C-8), 121.4 (C-7), 119.7 (C-4a), 102.3 (C-3), 100.6 (C-5), 81.0 (C-13), 72.9 (C-14), 66.9 (C-9), 55.5 (C-16), 27.9 (C-12), 25.1 (C-15). (+)-HRESIMS $[M+Na]^+$ *m/z* 307.1049 (calcd for $C_{16}H_{16}N_2NaO_3$, 307.1053).



2-((6-Methoxy-2-methylquinolin-4-yl)oxy)-*N*-pentylacetamide (**12v**). The reaction was carried out according to the general procedure using **10a** (30.0 mg, 0.16 mmol), potassium carbonate (110.0 mg, 0.80 mmol) and 2-bromo-*N*-pentylacetamide (**11x**) (46.0 mg, 0.32 mmol) in acetone afforded **12v** as off-white solids (8 mg, 16%). R_f (EtOAc) 0.31; m.p. 156-158 ^oC; IR (ATR) ν_{max} 3302, 2933, 1654, 1542, 1438, 1231, 1182, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 10.0 Hz, H-8), 7.31-7.35 (2H, m, H-5, H-7), 6.59 (1H, s, H-3), 6.48 (1H, br s, NH-11), 4.75 (2H, s, H_2-9), 3.94 (3H, s, H_3-18), 3.37 (2H, dt, *J* = 2.8, 2.8 Hz, H_2-12), 2.67 (3H, s, H_3-17), 1.53 (2H, p, *J* = 3.2 Hz, H_2-13), 1.30-1.27 (4H, m, H_2-14, H_2-15), 0.87 (3H, t, *J* = 6.8 Hz, H_3-16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1 (C-10), 159.5 (C-4), 157.4 (C-2 and C-6), 144.3 (C-8a), 129.7 (C-8), 122.4 (C-7), 120.0 (C-4a), 102.2 (C-3), 99.8 (C-5), 67.7 (C-9), 55.7 (C-18), 39.3 (C-12), 29.3 (C-14), 29.1 (C-13), 25.4 (C-17), 22.4 (C-15), 14.0 (C-16); (+)-HRESIMS $[M+H]^+$ *m/z* 317.1854 (calcd for $C_{18}H_{25}N_2O_3$, 317.1860).

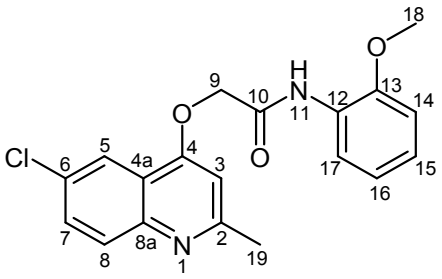


N-(2-Methoxyphenyl)-2-((2-methylquinolin-4-yl)oxy)acetamide (**12w**). The reaction was carried out according to the general procedure using 2-methylquinolin-4-ol (**10b**) (81.0 mg, 0.51 mmol), potassium carbonate (215 mg, 1.56 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (122 mg, 0.50 mmol) in DMF afforded **12w** as an off-white solid (119 mg, 74%). R_f (EtOAc) 0.68; m.p. 163-164 ^oC; IR (ATR) ν_{max} 3399, 1686, 1600, 1543, 1117, 1029 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.42 (1H, br s, NH-11), 8.22 (1H, d, J = 8.4 Hz, H-5), 8.11 (1H, d, J = 7.8 Hz, H-17), 7.89 (1H, d, J = 8.4 Hz, H-6), 7.74 (1H, dd, J = 7.8, 7.8 Hz, H-7), 7.59 (1H, dd, J = 7.8, 7.8 Hz, H-8), 7.11 (2H, m, H-14 and H-15), 6.98 (1H, s, H-3), 6.96 (1H, ddd, J = 7.9, 6.5, 1.9 Hz, H-16), 5.03 (2H, s, H_2-9), 3.89 (3H, s, H_3-18), 2.61 (3H, s, H_3-19); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3 (C-10), 159.8 (C-2), 159.5 (C-4), 148.9 (C-13), 148.4 (C-8a), 129.8 (C-7), 128.1 (C-6), 126.5 (C-12), 125.1 (C-8), 124.7 (C-15), 121.1 (C-5), 120.5 (C-17 and C-16), 119.0 (C-4a), 111.2 (C-14), 102.4 (C-3), 67.1 (C-9), 55.9 (C-18), 25.4 (C-19); (+)-HRESIMS $[M+H]^+$ *m/z* 323.1391 (calcd for $C_{19}H_{19}N_2O_3$, 323.1390).



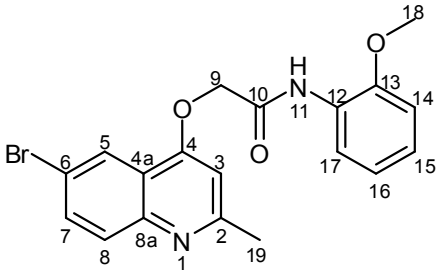
2-((2,6-Dimethylquinolin-4-yl)oxy)-*N*-(2-methoxyphenyl)acetamide (**12x**). The reaction was carried out according to the general procedure using 2,6-dimethylquinolin-4-ol (**10c**) (88.0 mg, 0.51 mmol), potassium carbonate (215 mg, 1.56 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (122 mg, 0.50 mmol) in DMF afforded **12x** as a pale yellow solid (82 mg, 49%). R_f (5% MeOH in CH_2Cl_2) 0.42; m.p. 172-173.5 ^oC; IR (ATR) ν_{max} 3403, 1693, 1600, 1536, 1338, 1184, 1111 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.37 (1H, br s,

NH-11), 8.12 (1H, d, *J* = 8.1 Hz, H-17), 7.97 (1H, br s, H-5), 7.78 (1H, d, *J* = 8.8 Hz, H-8), 7.56 (1H, dd, *J* = 8.6, 1.9 Hz, H-7), 7.12 (2H, m, H-14, H-15), 6.96 (1H, ddd, *J* = 8.1, 6.9, 2.1 Hz, H-16), 6.93 (1H, s, H-3), 5.00 (2H, s, H_2-9), 3.89 (3H, s, H_3-18), 2.58 (3H, s, H_3-19), 2.53 (3H, s, H_3-20); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3 (C-10), 159.0 (C-4), 158.7 (C-2), 148.9 (C-13), 146.9 (C-8a), 134.3 (C-6), 131.8 (C-7), 127.9 (C-8), 126.5 (C-12), 124.7 (C-15), 120.5 (C-16 and C-17), 119.9 (C-5), 118.8 (C-4a), 111.2 (C-14), 102.3 (C-3), 67.0 (C-9), 55.9 (C-18), 25.2 (C-19), 21.3 (C-20); (+)-HRESIMS $[M+H]^+$ *m/z* 337.1544 (calcd for $C_{20}H_{21}N_2O_3$, 337.1547).

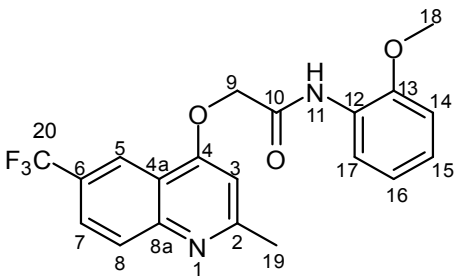


2-((6-Chloro-2-methylquinolin-4-yl)oxy)-*N*-(2-methoxyphenyl)acetamide (**12y**). The reaction was carried out according to the general procedure using 6-chloro-2-methylquinolin-4-ol (**10d**) (99.0 mg, 0.51 mmol), potassium carbonate (215 mg, 1.56 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (122 mg, 0.50 mmol) in DMF afforded **12y** as an off-white solid (61 mg, 34%). R_f (EtOAc) 0.81; m.p. 204-205 ^{o}C; IR (ATR) ν_{max} 3401, 1691, 1600, 1543, 1118, 1026, 740 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (1H, br s, NH-11), 8.20 (1H, d, *J* = 2.4 Hz, H-5), 8.09 (1H, d, *J* = 7.9 Hz, H-17), 7.91 (1H, d, *J* = 9.1 Hz, H-8), 7.75 (1H, dd, *J* = 8.9, 2.4 Hz, H-7), 7.12 (2H, m, H-14 and H-15), 7.06 (1H, s, H-3), 6.96 (1H, ddd, *J* = 7.9, 6.5, 1.9 Hz, H-16), 5.02 (2H, s, H_2-9), 3.92 (3H, s, H_3-18), 2.61 (3H, s, H_3-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C-10), 160.7 (C-2), 158.7 (C-4), 149.1 (C-13), 146.8 (C-8a), 130.3 (C-7 and C-8), 129.6 (C-6), 126.4 (C-12), 124.8 (C-15), 120.8 (C-17), 120.5 (C-

16), 120.2 (C-4a), 119.8 (C-5), 111.2 (C-14), 103.3 (C-3), 67.2 (C-9), 55.9 (C-18), 25.3 (C-19); (+)-HRESIMS $[M+H]^+$ *m/z* 357.1002 (calcd for $C_{19}H_{18}{}^{35}ClN_2O_3$, 357.1000).



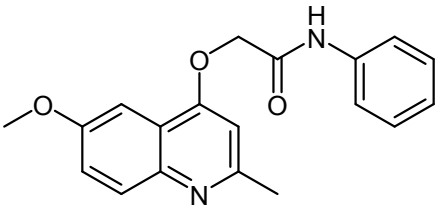
2-((6-Bromo-2-methylquinolin-4-yl)oxy)-*N*-(2-methoxyphenyl)acetamide (**12z**). The reaction was carried out according to the general procedure using reaction of 6-bromo-2-methylquinolin-4-ol (**10e**) (121.0 mg, 0.51 mmol), potassium carbonate (215 mg, 1.56 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (122 mg, 0.50 mmol) in DMF afforded **12z** as an off-white solid (184 mg, 92%). R_f (EtOAc) 0.77; m.p. 202-203 ^oC; IR (ATR) ν_{max} 3403, 1688, 1595, 1542, 1118, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.39 (1H, br s, NH-11), 8.35 (1H, br s, H-5), 8.08 (1H, d, J = 7.7 Hz, H-17), 7.85 (2H, m, H-7 and H-8), 7.12 (2H, m, H-14, H-15), 7.06 (1H, s, H-3), 6.98 (1H, dd, J = 7.0, 7.0 Hz, H-16), 5.02 (2H, s, H_2-9), 3.93 (3H, s, H_3-18), 2.60 (3H, s, H_3-19); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1 (C-10), 160.8 (C-2), 158.6 (C-4), 149.1 (C-13), 147.0 (C-8a), 132.9 (C-7), 130.4 (C-8), 126.4 (C-12), 124.8 (C-15), 123.4 (C-5), 120.8 (C-6), 120.5 (C-17), 120.3 (C-16), 118.0 (C-4a), 111.2 (C-14), 103.3 (C-3), 67.3 (C-9), 56.0 (C-18), 25.4 (C-19); (+)-HRESIMS $[M+H]^+$ *m/z* 401.0488 (calcd for $C_{19}H_{18}{}^{79}BrN_2O_3$, 401.0495).

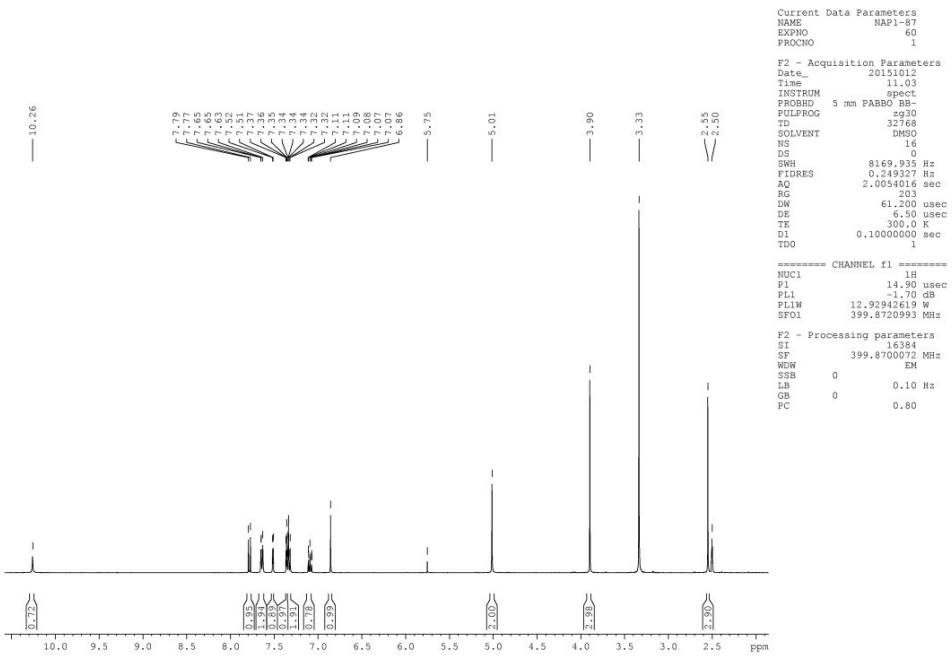


N-(2-Methoxyphenyl)-2-((2-methyl-6-(trifluoromethyl)quinolin-4-yl)oxy)acetamide (**12aa**). The reaction was carried out according to the general procedure using 2-methyl-6-(trifluoromethyl)quinolin-4-ol (**10f**) (116.0 mg, 0.51 mmol), potassium carbonate (215 mg, 1.56 mmol) and 2-bromo-*N*-(2-methoxyphenyl)acetamide (**11a**) (122 mg, 0.50 mmol) in DMF afforded **12aa** as a pale yellow solid (115 mg, 59%). R_f (EtOAc) 0.84; m.p. 196-197 ^oC (decomp.); IR (ATR) ν_{max} 3407, 1691, 1600, 1540, 1308, 1109 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.43 (1H, br s, NH-11), 8.53 (1H, br s, H-5), 8.12-7.97 (3H, m, H-7 and H-8 and H-17), 7.16-7.07 (3H, m, H-3 and H-14 and H-15), 6.95 (1H, dd, J = 7.0, 7.0 Hz, H-16), 5.10 (2H, s, H_2-9), 3.85 (3H, s, H_3-18), 2.66 (3H, s, H_3-19); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1 (C-10), 163.1 (C-2), 160.2 (C-4), 149.7 (C-8a), 149.5 (C-13), 129.7 (C-8), 126.4 (C-12), 125.3 (C-7), 125.1 (C-6), 124.9 (C-15), 124.5 (C-20), 121.2 (C-17), 120.5 (C-16), 119.5 (C-5), 118.3 (C-4a), 111.3 (C-14), 103.7 (C-3), 67.4 (C-9), 55.7 (C-18), 25.6 (C-19); (+)-HRESIMS $[M+H]^+$ *m/z* 391.1261 (calcd for $C_{20}H_{18}F_3N_2O_3$, 391.1264).

2. NMR spectra.

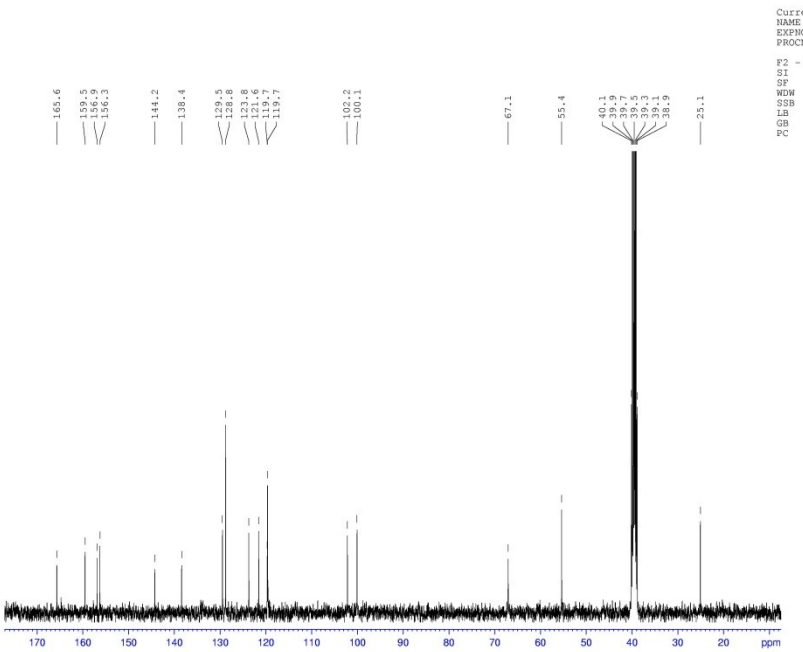
^{1}H NMR spectrum of **12a** (DMSO-d_6, 400 MHz)





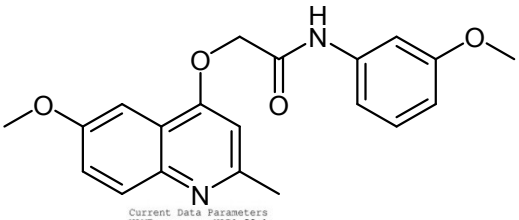

```
Current Data Parameters
NAME                  NAP1-87
EXPNO                      60
PROCNO                      1

F2 - Acquisition Parameters
Date_               20151012
Time                   11.03
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT                DMSO
NS                        16
DS                         0
SWH                 8169.935 Hz
FIDRES              0.249327 Hz
AQ                  2.0054016 sec
RG                       203
DW                    61.200 usec
DE                     6.50 usec
TE                    300.0 K
D1                 0.10000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     14.90 usec
PL1                    -1.70 dB
PL1W            12.92942619 W
SFO1            399.8720993 MHz

F2 - Processing parameters
SI                        16384
SF                 399.8700072 MHz
WDW                        EM
SSB          0
LB                     0.10 Hz
GB           0
PC                     0.80
```

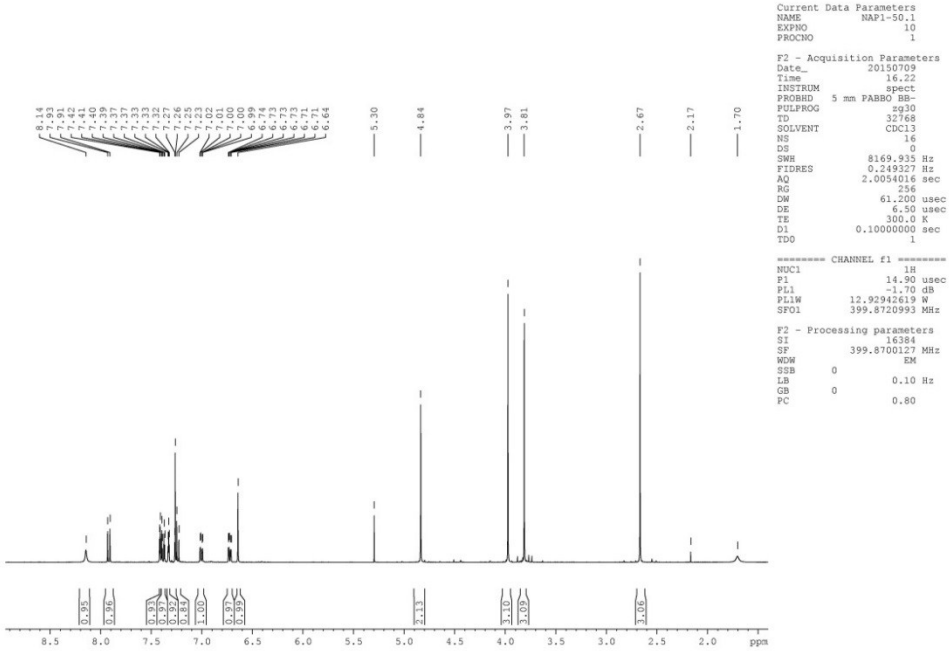
^{13}C NMR spectrum of **12a** (DMSO-d_6, 100 MHz)




```
Current Data Parameters
NAME                  NAP1-87
EXPNO                      61
PROCNO                      1

F2 - Processing parameters
SI                        32768
SF                 100.5474408 MHz
WDW                        EM
SSB          0
LB                     2.00 Hz
GB           0
PC                     0.80
```

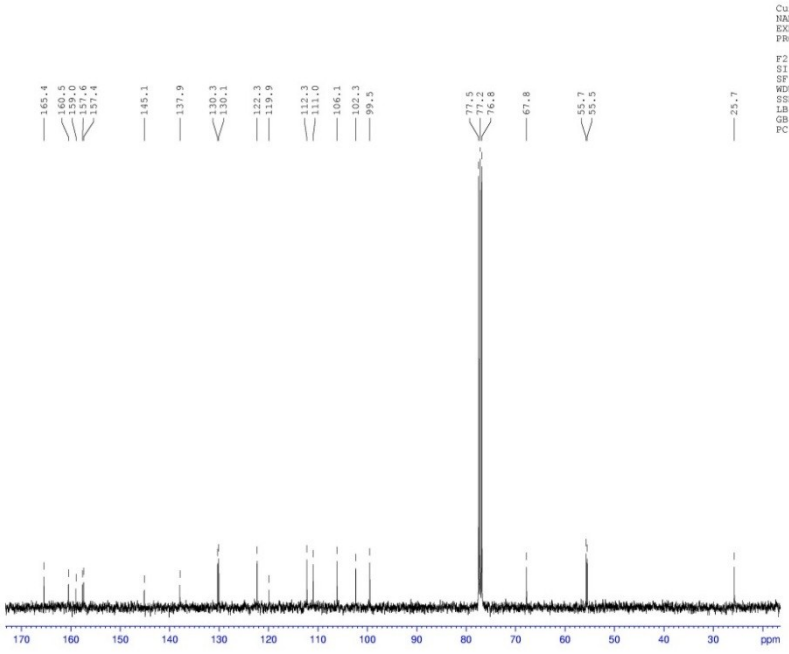
^{1}H NMR spectrum of **12b** ($CDCl_3$, 400 MHz)





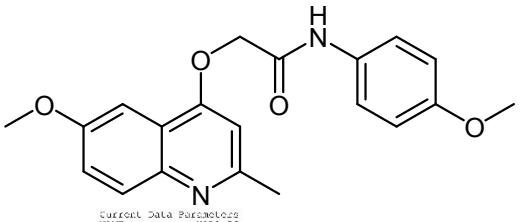

```
Current Data Parameters
NAME                  NAP1-50.1
EXPNO                        10
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20150709
Time                      16.22
INSTRUM                   spect
PROBHD     5 mm PABBO BB-
PULPROG                   zg30
TD                       32768
SOLVENT                  CDCl3
NS                           16
DS                            0
SWH                    8169.935 Hz
FIDRES                 0.249327 Hz
AQ                     2.0054016 sec
RG                          256
DW                       61.200 usec
DE                        6.50 usec
TE                       300.0 K
D1                     0.10000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                         1H
P1                        14.90 usec
PL1                       -1.70 dB
PL1W                12.92942619 W
SFO1                399.8720993 MHz

F2 - Processing parameters
SI                        16384
SF                  399.8700127 MHz
WDW                          EM
SSB                   0
LB                         0.10 Hz
GB                    0
PC                         0.80
```

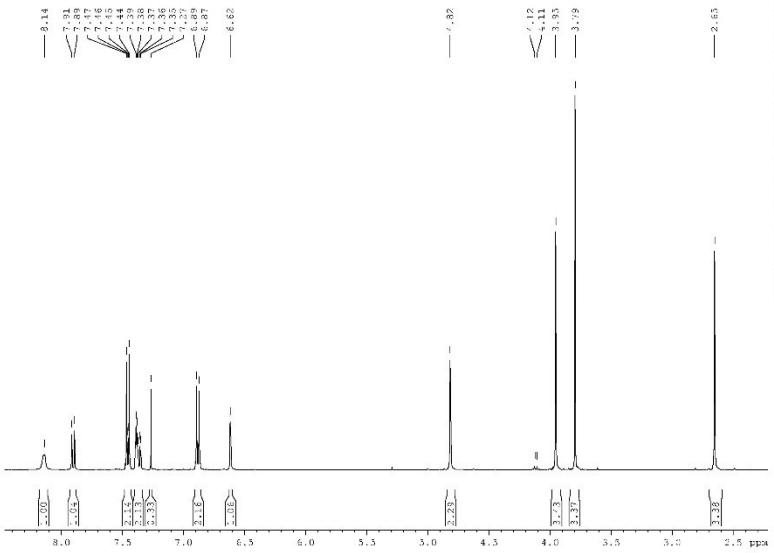
^{13}C NMR spectrum of **12b** ($CDCl_3$, 100 MHz)



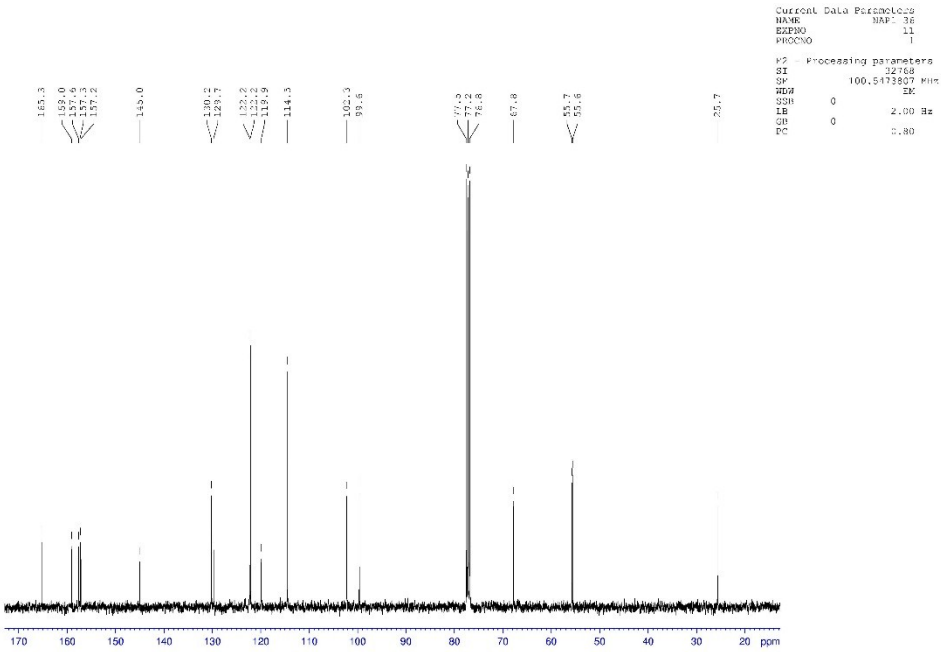

```
Current Data Parameters
NAME                  NAP1-50.1
EXPNO                        11
PROCNO                        1

F2 - Processing parameters
SI                        32768
SF                  100.5473787 MHz
WDW                          EM
SSB                   0
LB                         2.00 Hz
GB                    0
PC                         0.80
```

^{1}H NMR spectrum of **12c** ($CDCl_3$, 400 MHz)

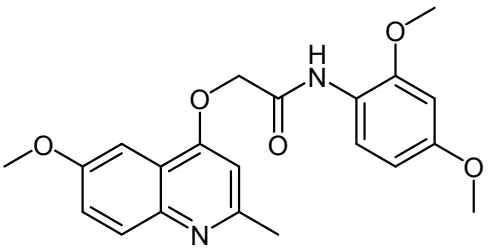


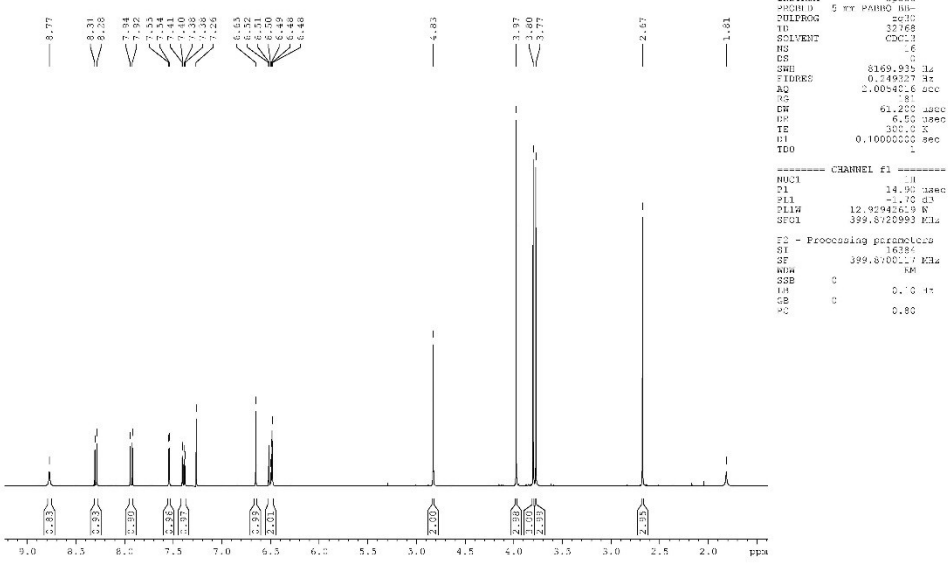


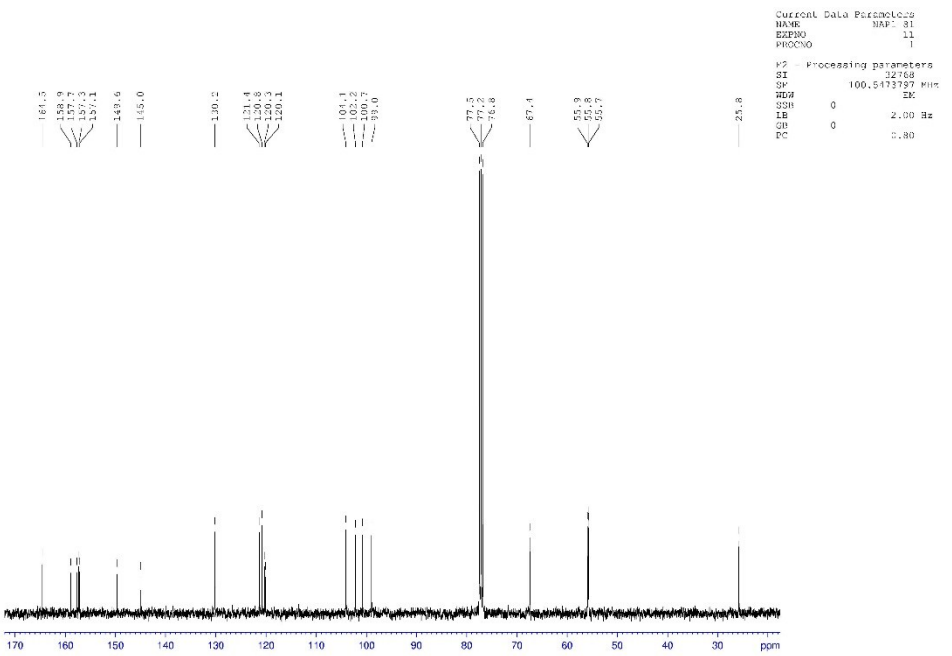
^{13}C NMR spectrum of **12c** ($CDCl_3$, 100 MHz)



^{1}H NMR spectrum of **12d** ($CDCl_3$, 400 MHz)

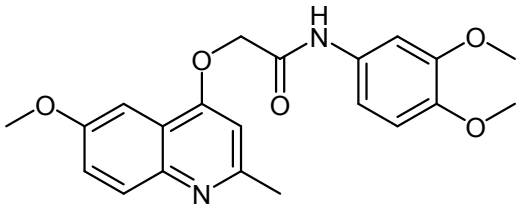


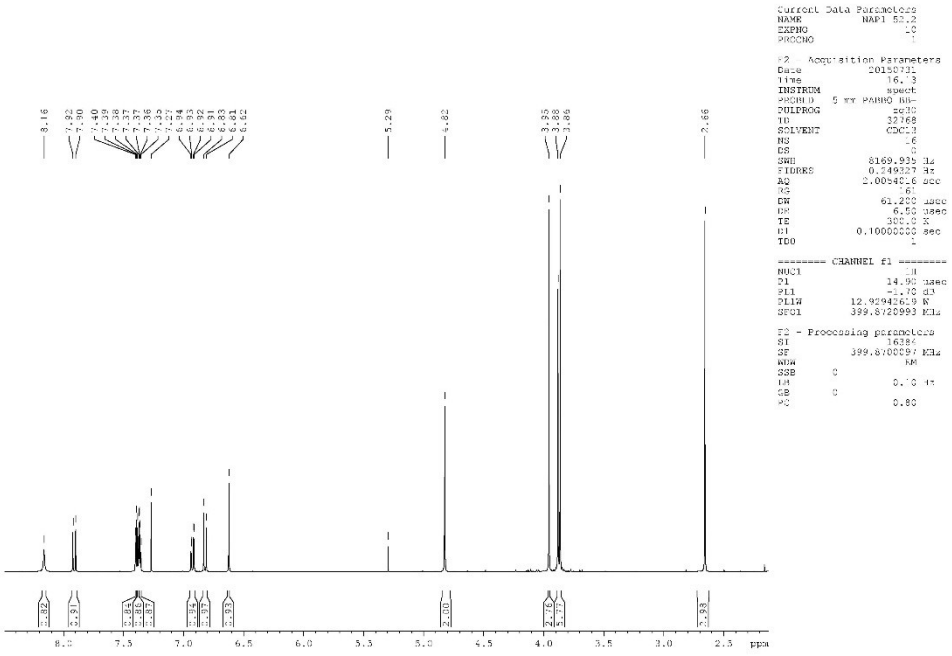




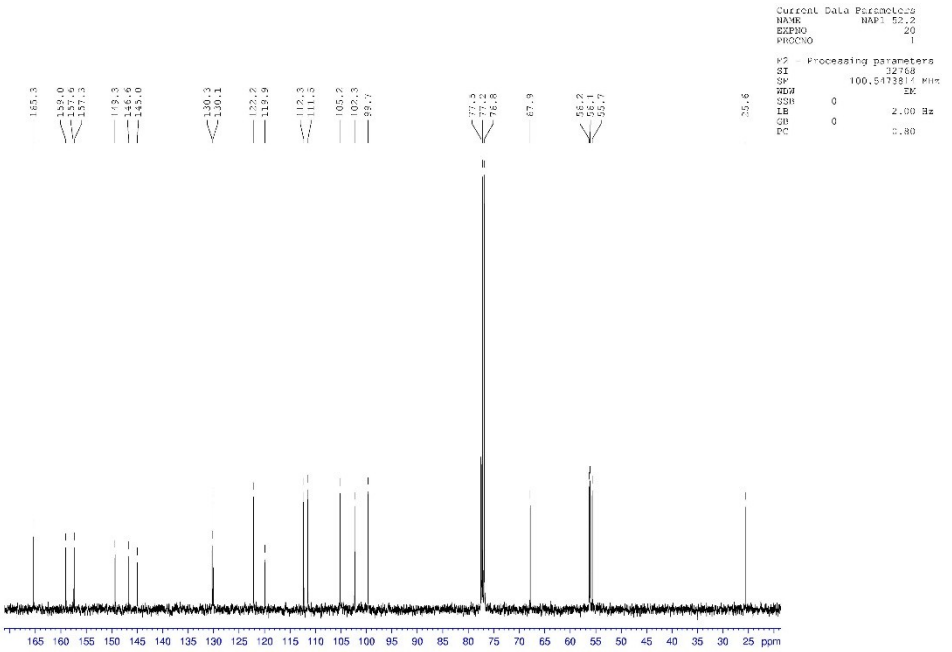
^{13}C NMR spectrum of **12d** ($CDCl_3$, 100 MHz)

^{1}H NMR spectrum of **12e** ($CDCl_3$, 400 MHz)

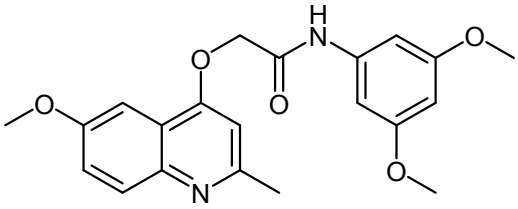


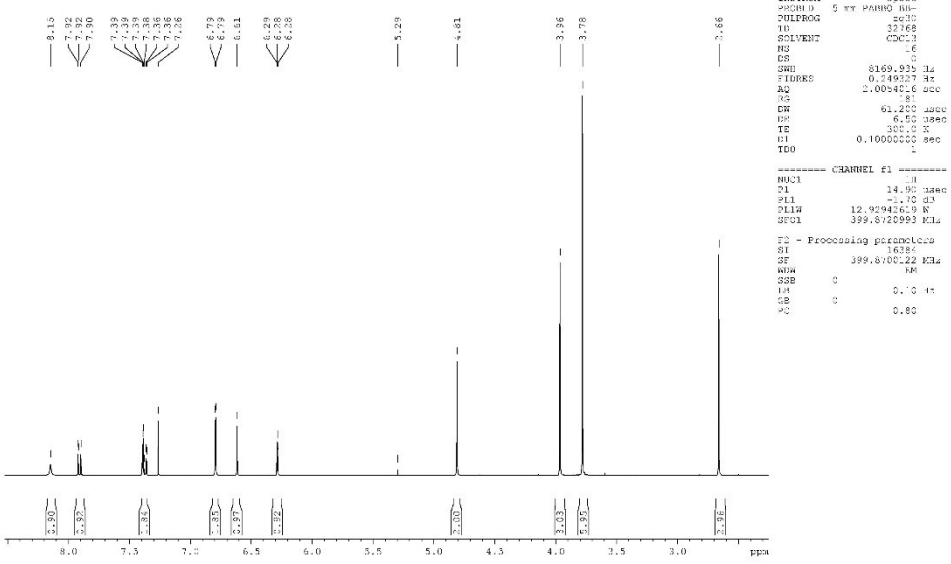


^{13}C NMR spectrum of **12e** ($CDCl_3$, 100 MHz)

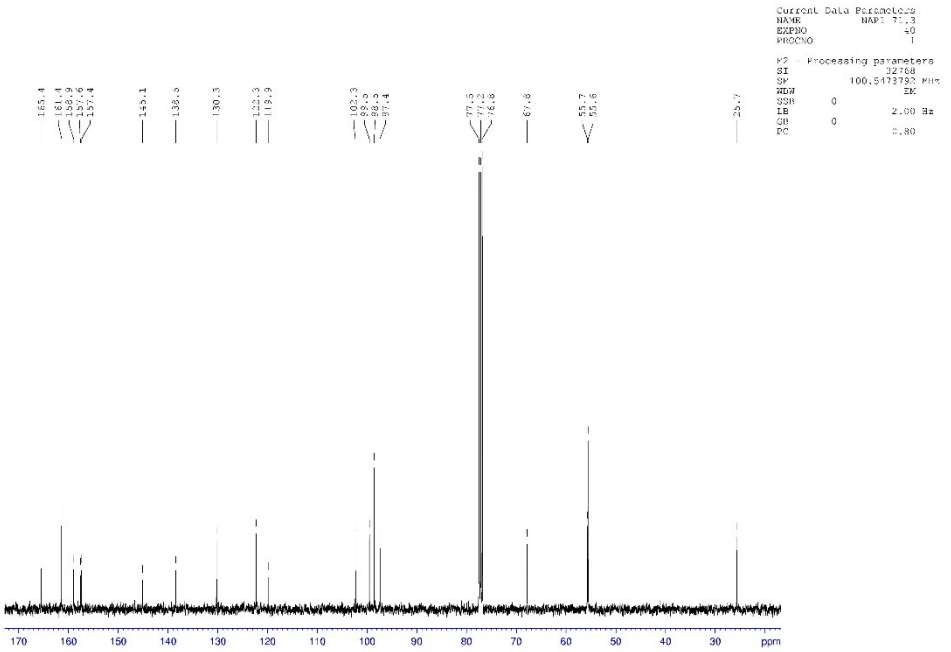


^{1}H NMR spectrum of **12f** ($CDCl_3$, 400 MHz)

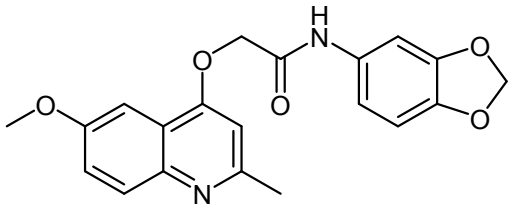


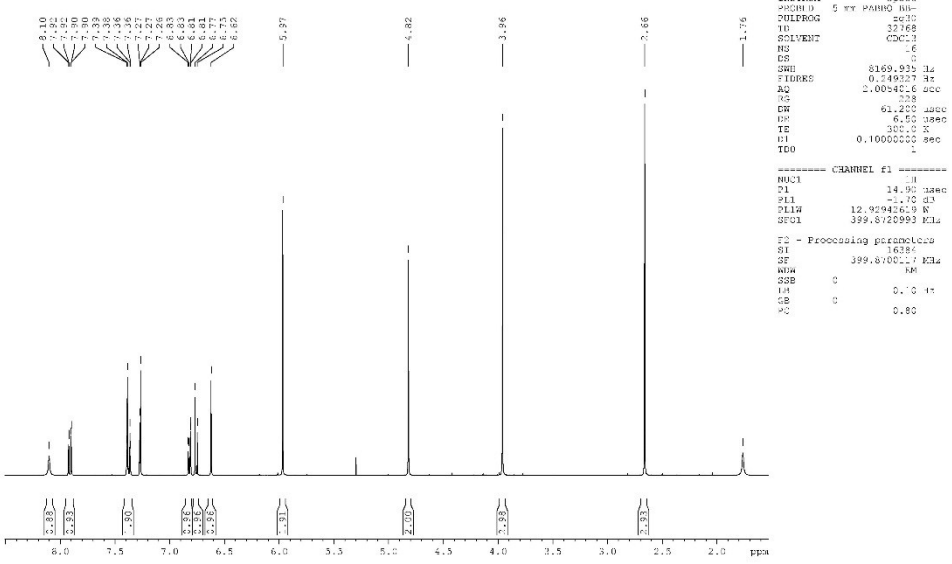


^{13}C NMR spectrum of **12f** ($CDCl_3$, 100 MHz)

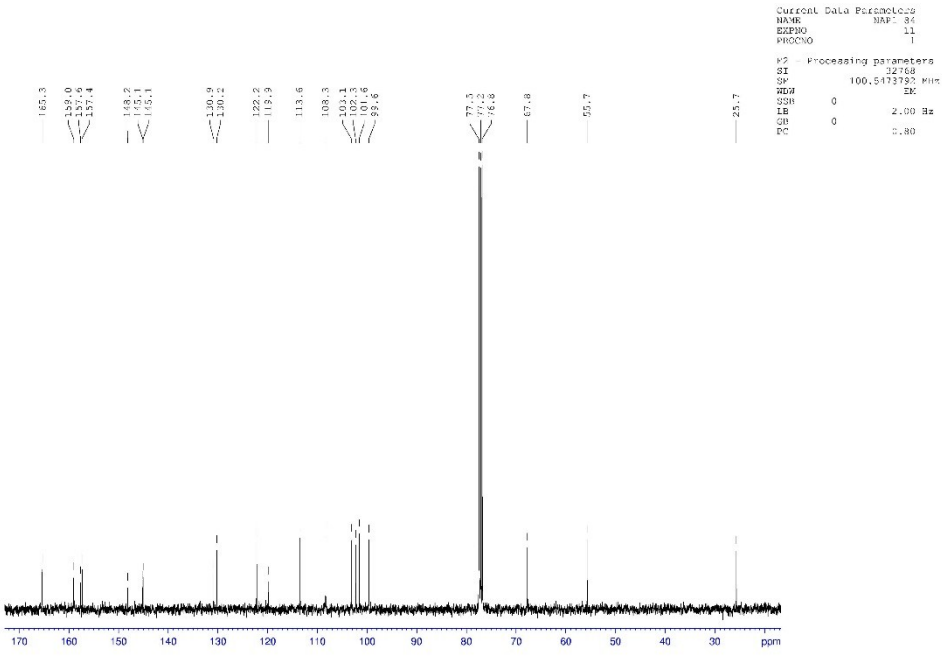


^{1}H NMR spectrum of **12g** ($CDCl_3$, 400 MHz)

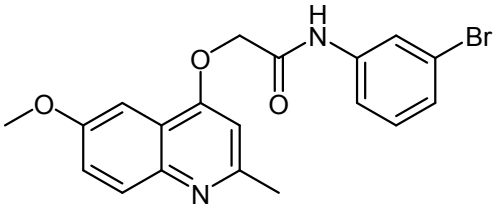


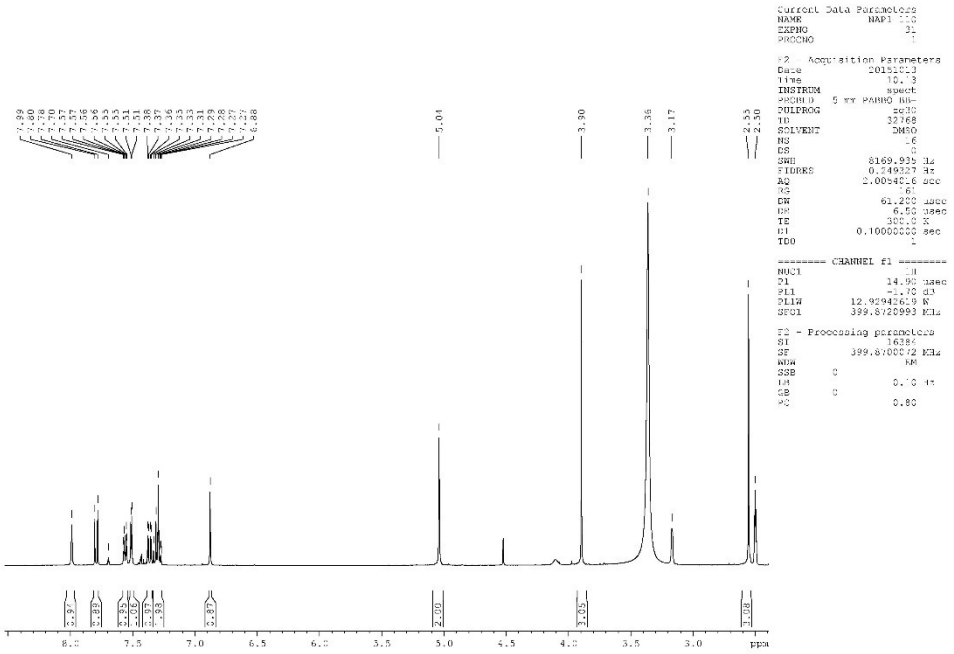


^{13}C NMR spectrum of **12g** ($CDCl_3$, 100 MHz)

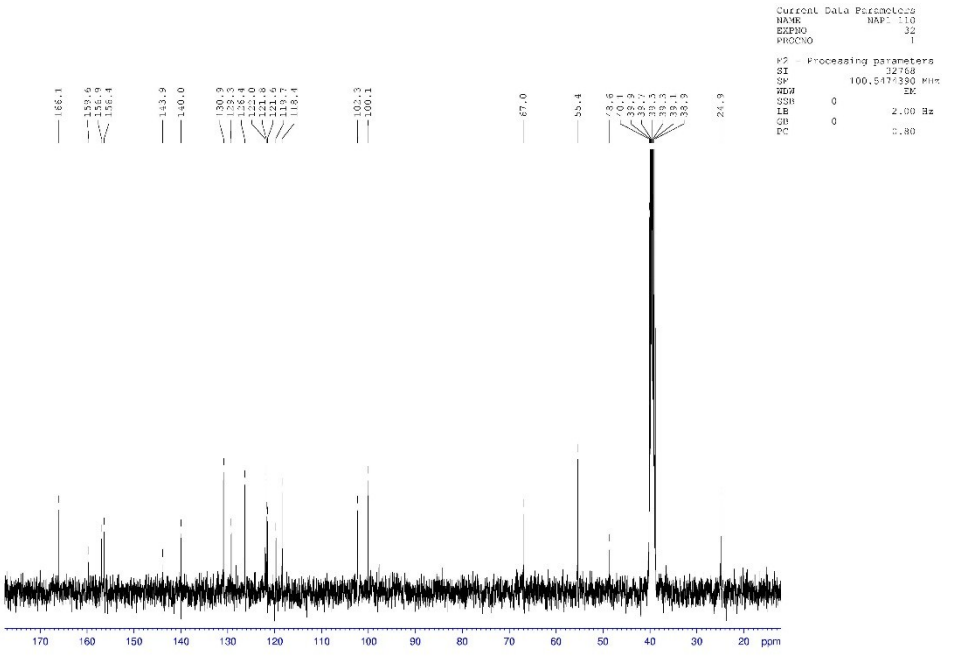


^{1}H NMR spectrum of **12h** (DMSO-d_6, 400 MHz)

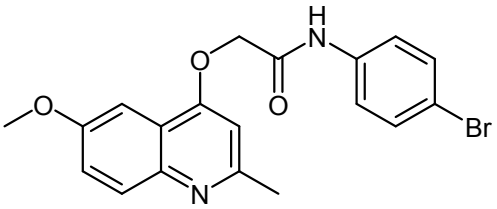


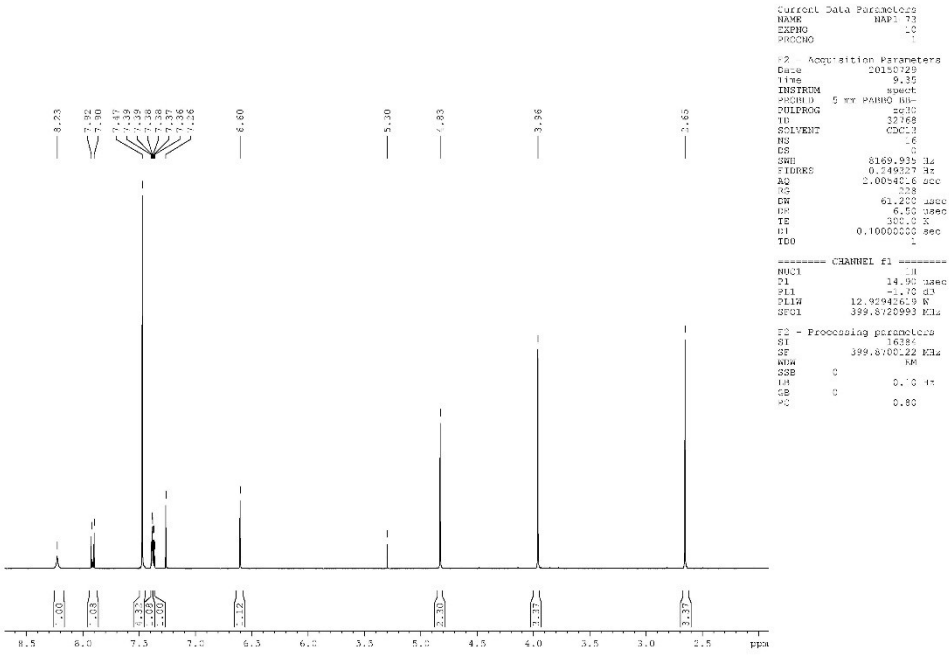


^{13}C NMR spectrum of **12h** (DMSO-d_6, 100 MHz)

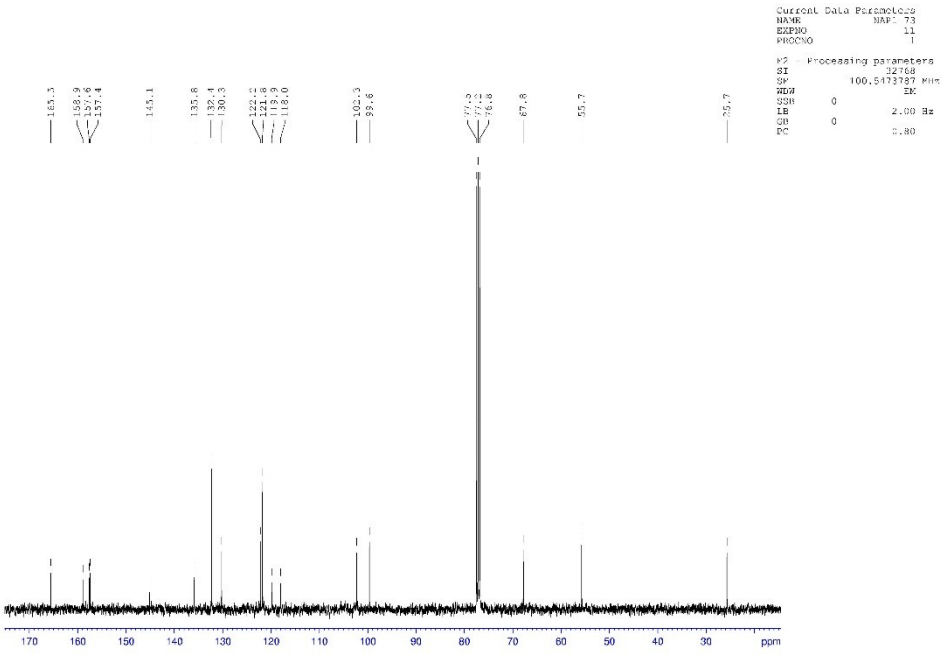


^{1}H NMR spectrum of **12i** ($CDCl_3$, 400 MHz)

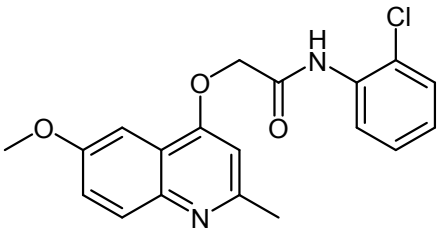


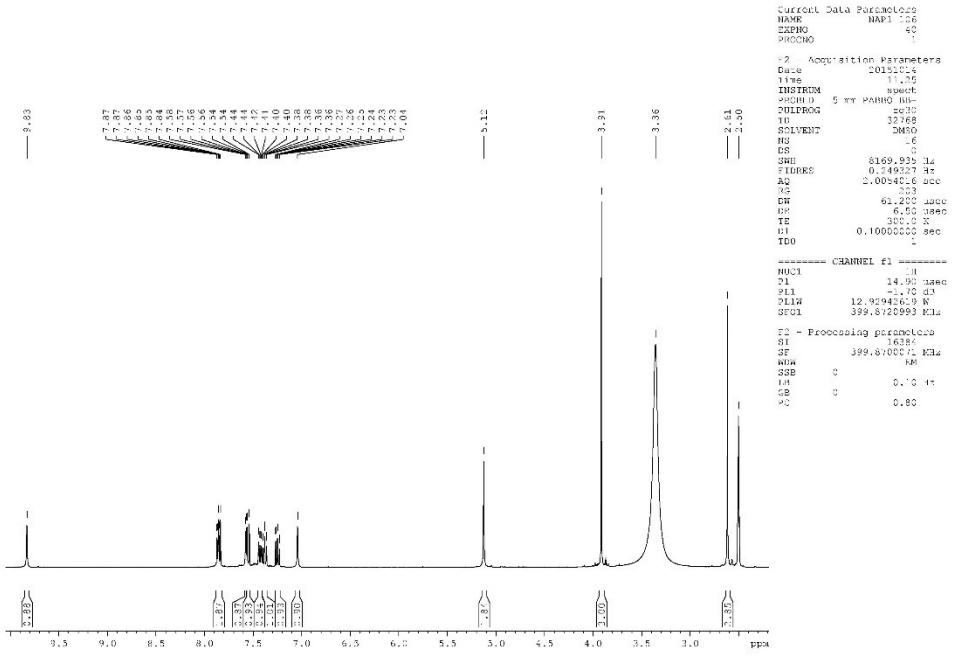


^{13}C NMR spectrum of **12i** ($CDCl_3$, 100 MHz)

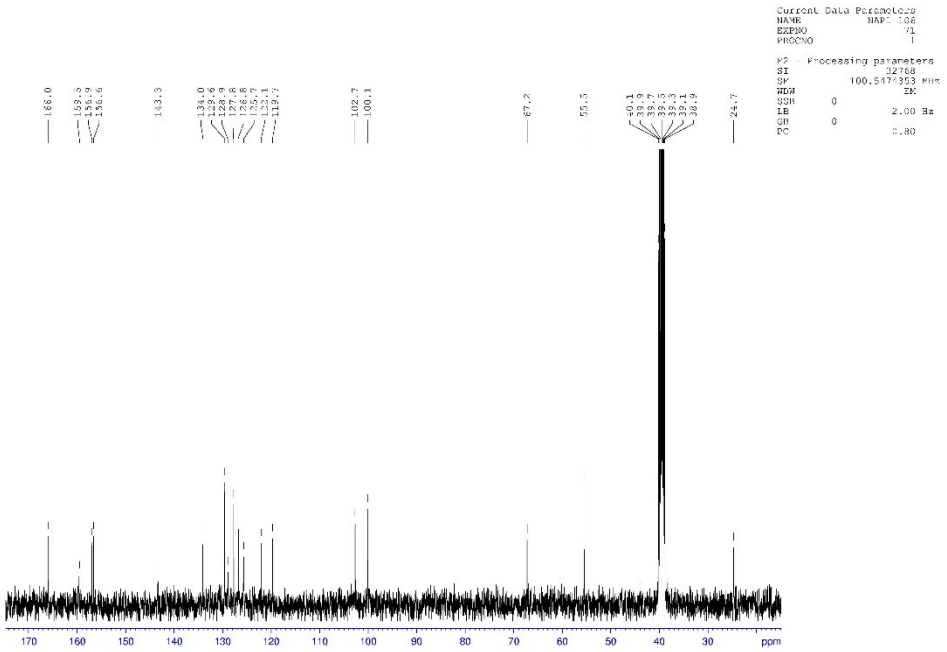


^{1}H NMR spectrum of **12j** (DMSO-d_6, 400 MHz)

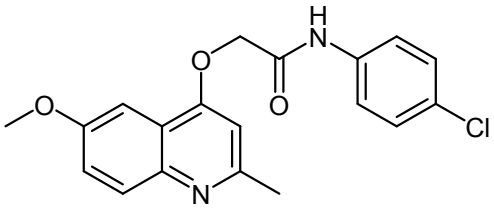


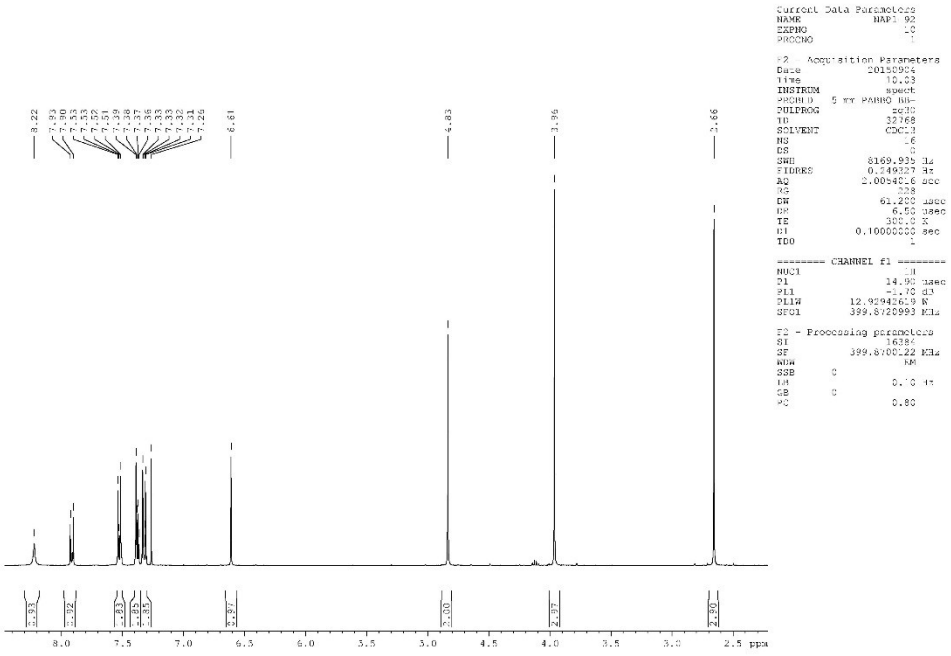


^{13}C NMR spectrum of **12j** (DMSO-d_6, 100 MHz)

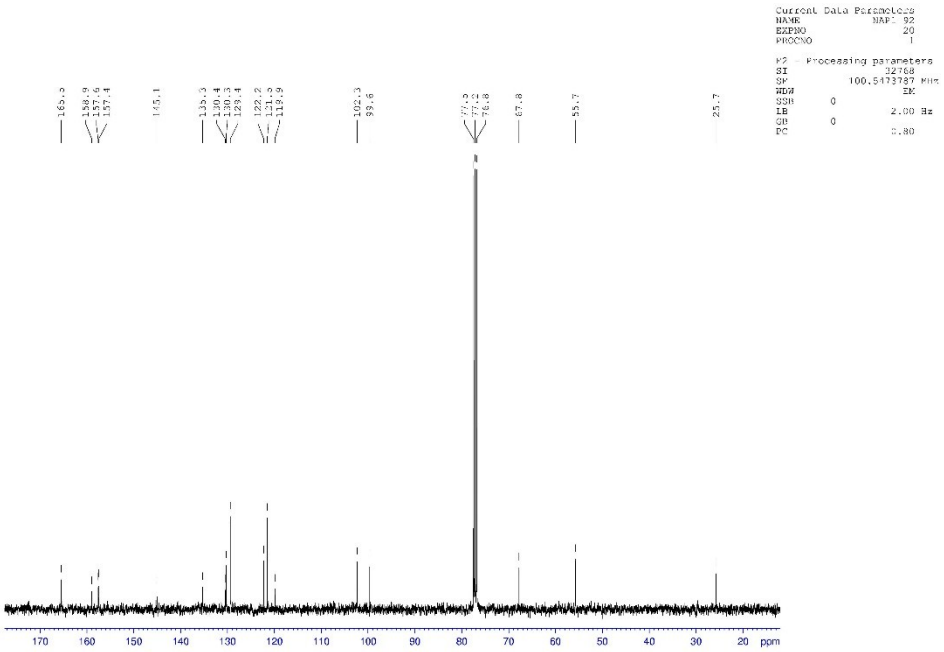


^{1}H NMR spectrum of **12k** ($CDCl_3$, 400 MHz)

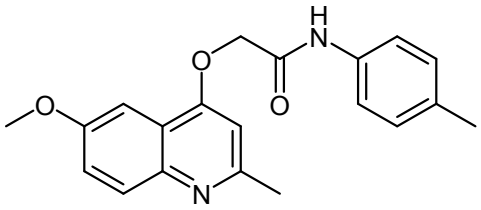


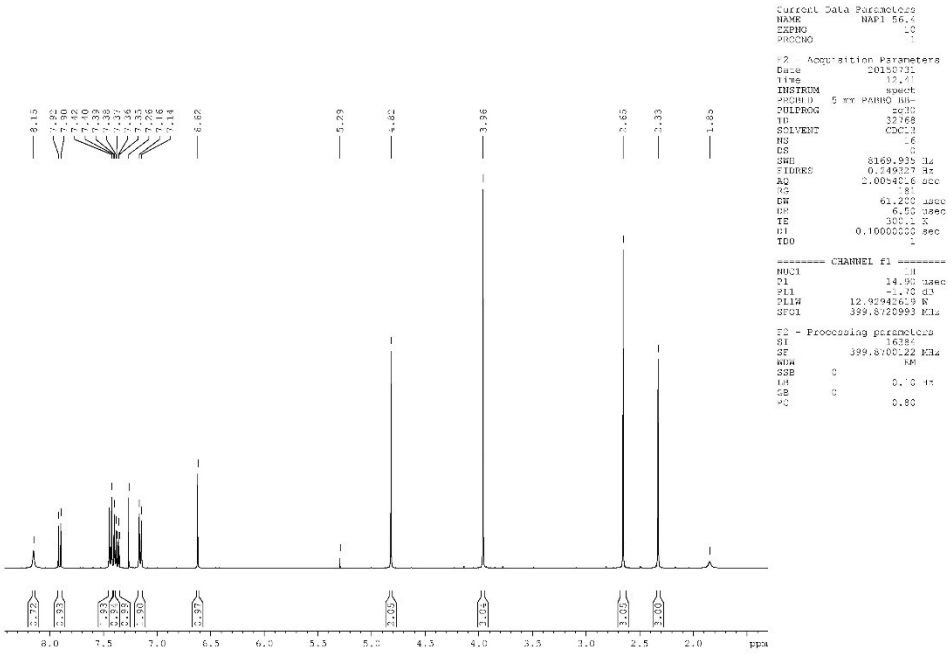


^{13}C NMR spectrum of **12k** ($CDCl_3$, 100 MHz)

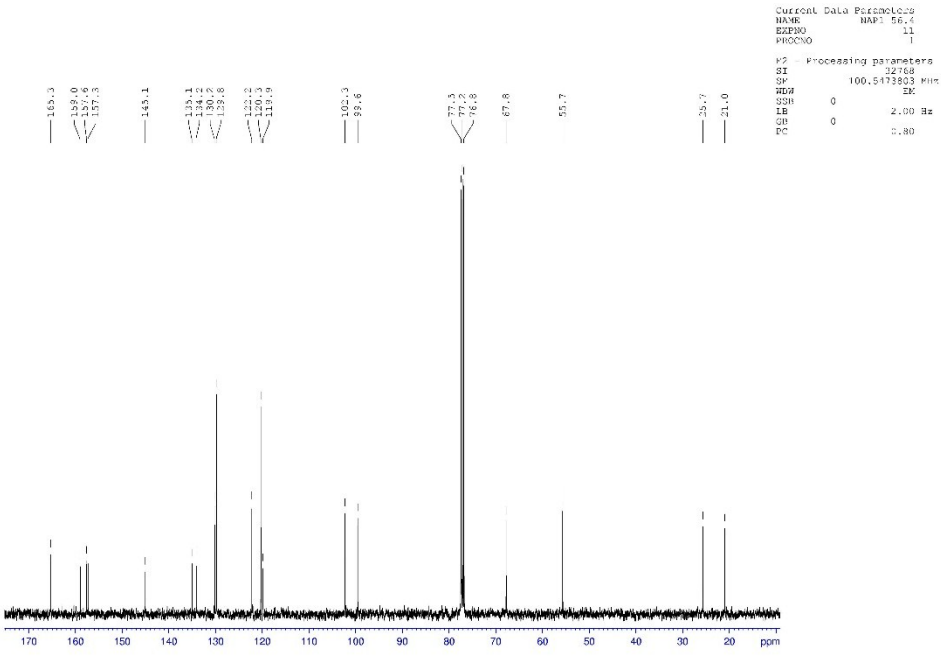


^{1}H NMR spectrum of **12l** ($CDCl_3$, 400 MHz)

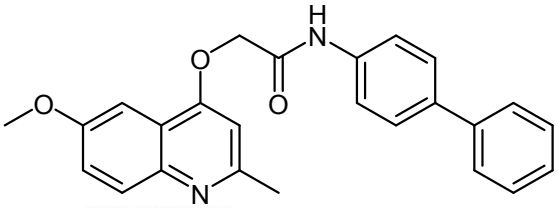


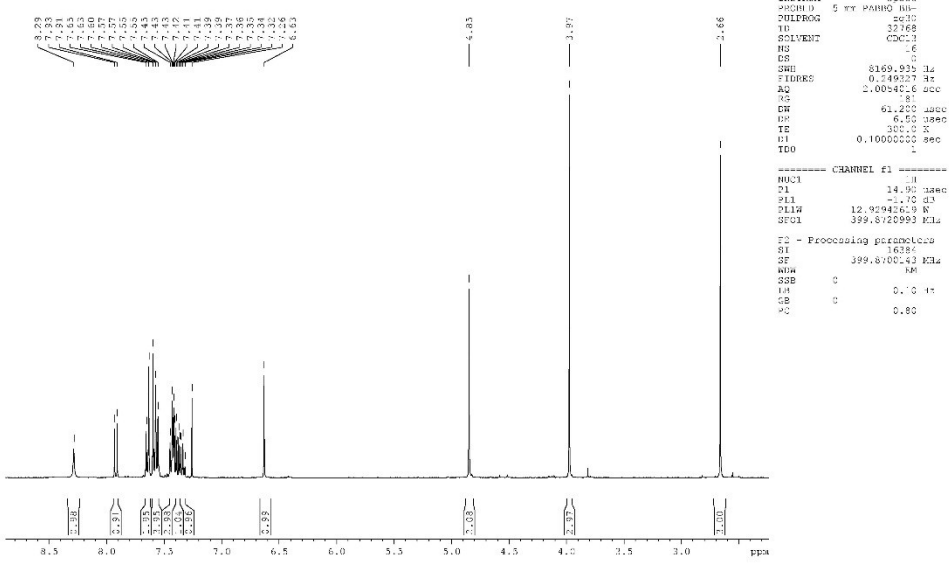


^{13}C NMR spectrum of **12l** ($CDCl_3$, 100 MHz)

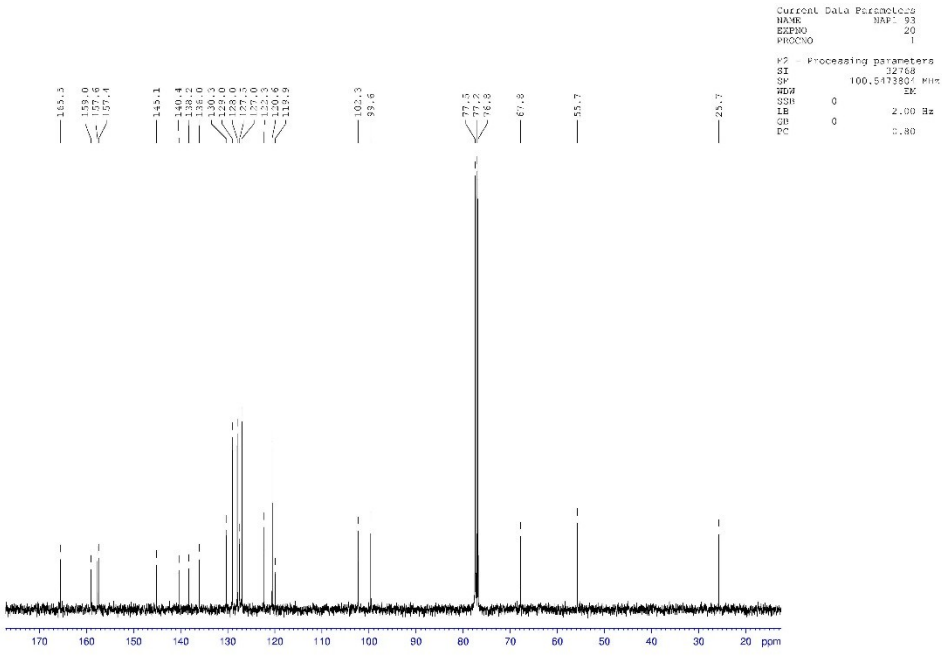


^{1}H NMR spectrum of **12m** ($CDCl_3$, 400 MHz)

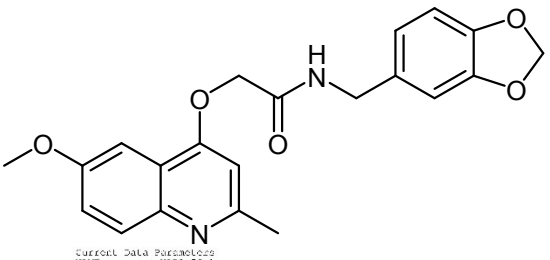


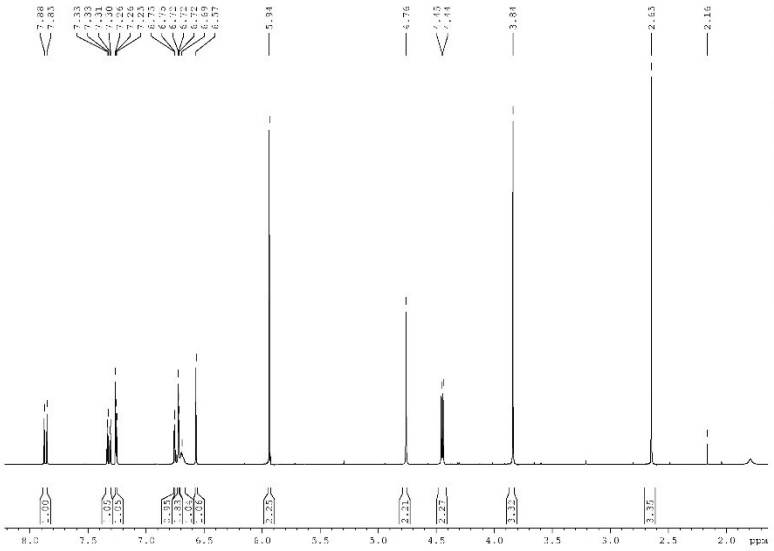


^{13}C NMR spectrum of **12m** ($CDCl_3$, 100 MHz)

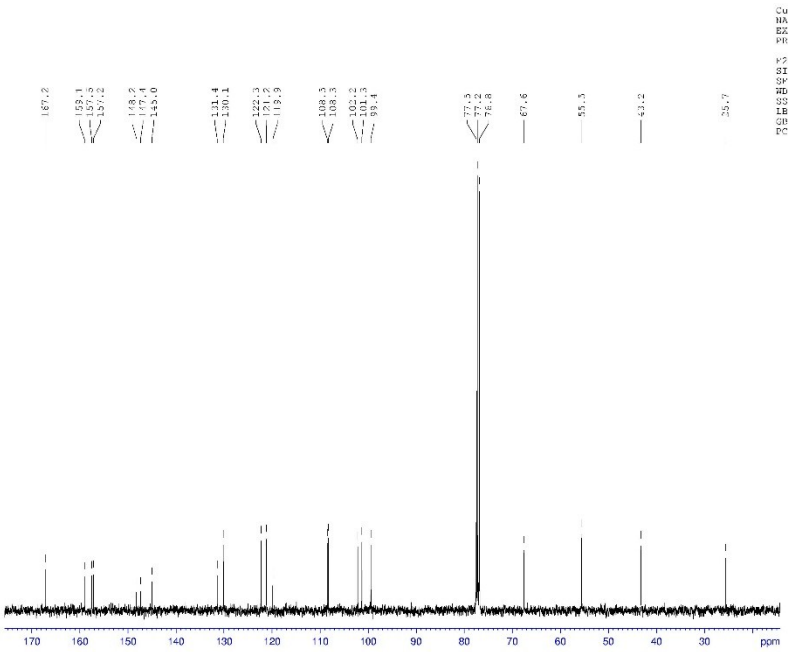


^{1}H NMR spectrum of **12n** ($CDCl_3$, 400 MHz)

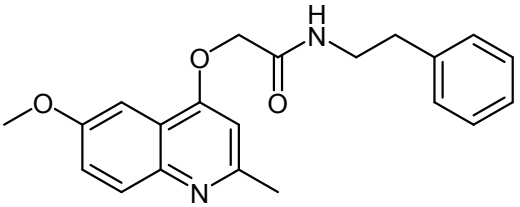


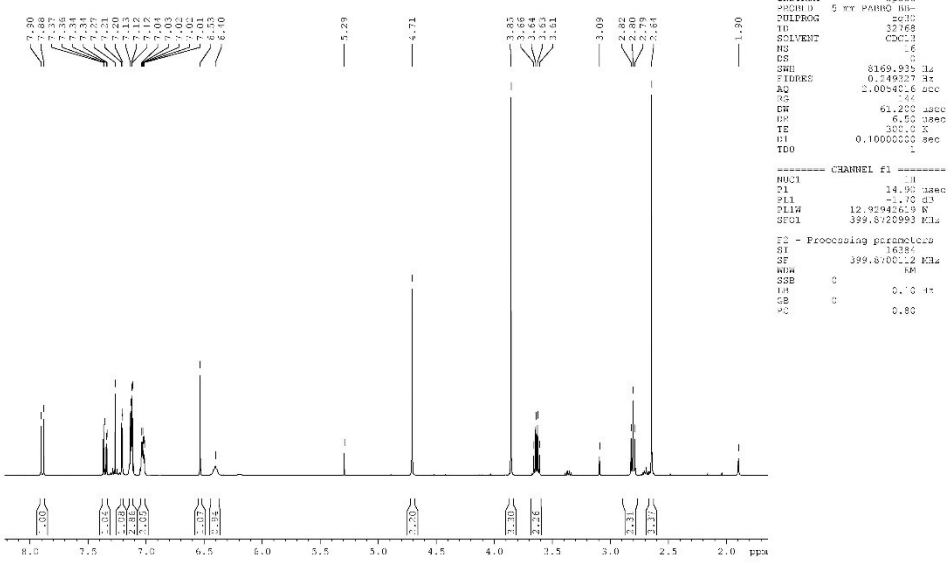


^{13}C NMR spectrum of **12n** ($CDCl_3$, 100 MHz)

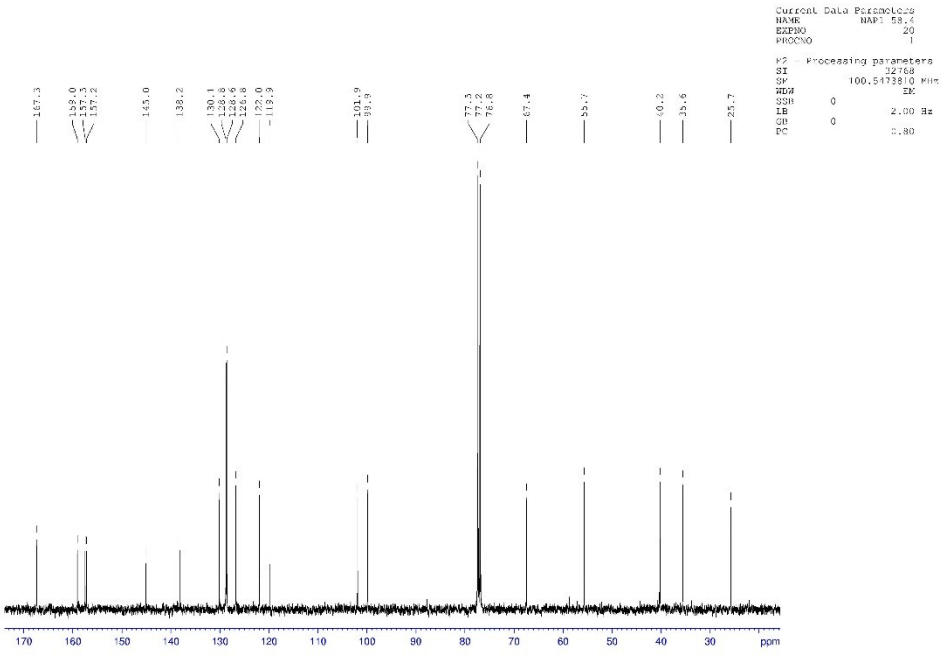


^{1}H NMR spectrum of **12o** ($CDCl_3$, 400 MHz)

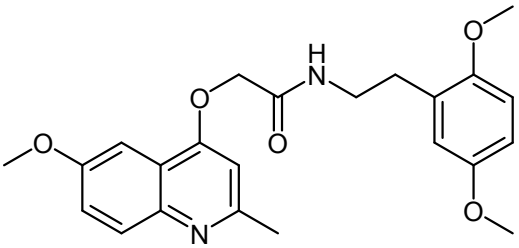


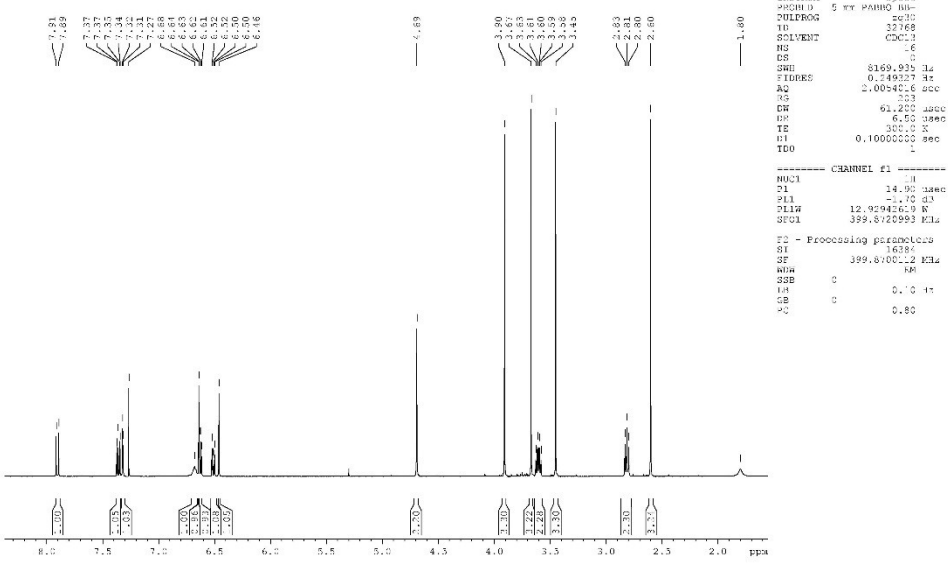


^{13}C NMR spectrum of **12o** ($CDCl_3$, 100 MHz)

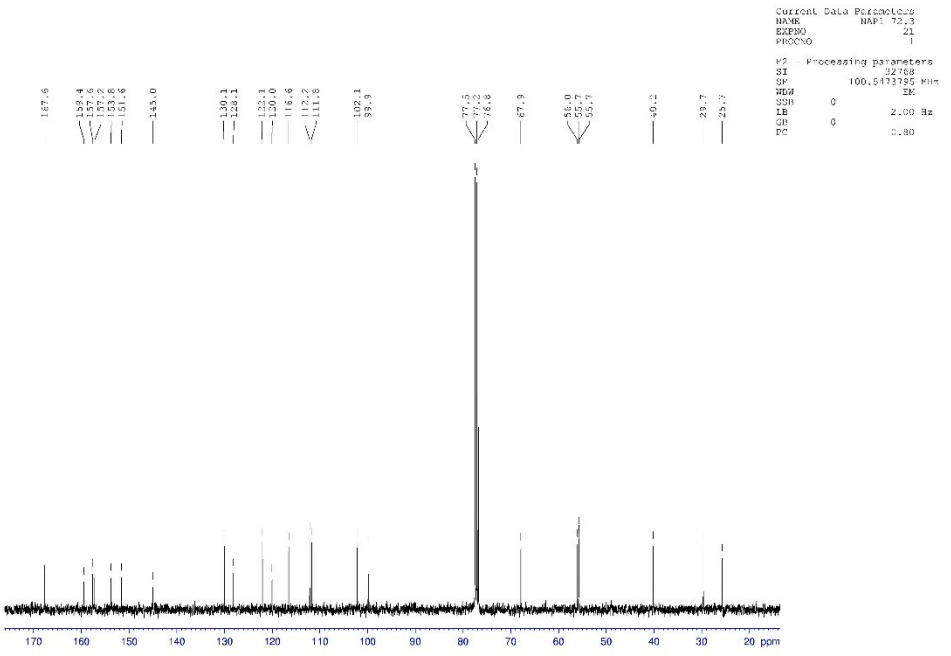


^{1}H NMR spectrum of **12p** ($CDCl_3$, 400 MHz)

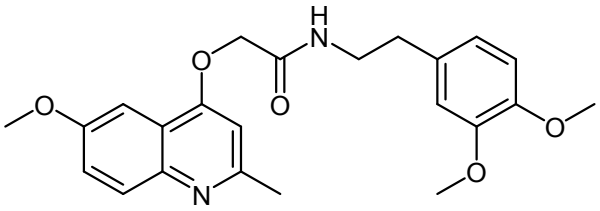


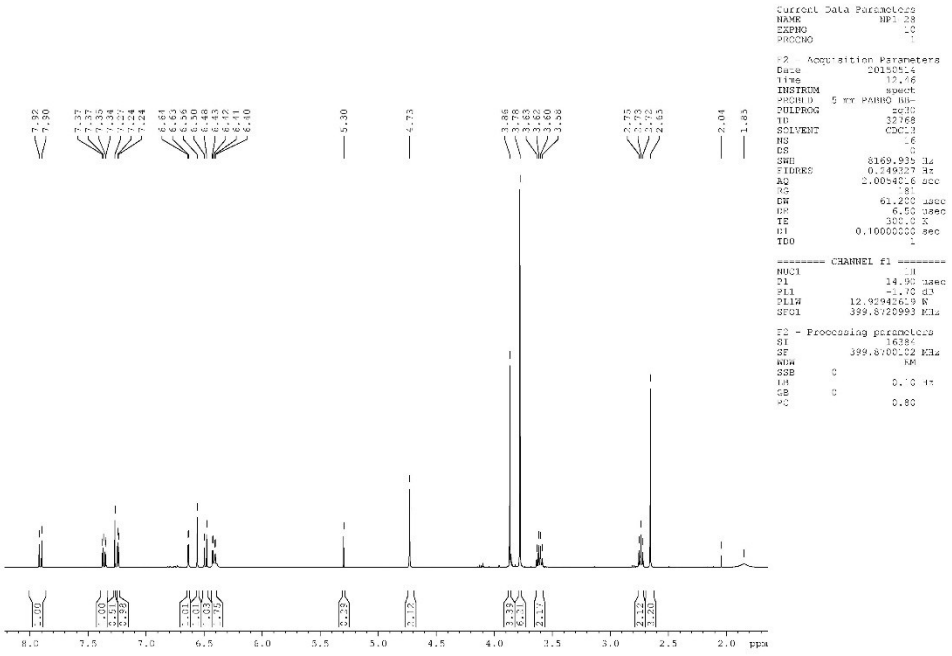


^{13}C NMR spectrum of **12p** ($CDCl_3$, 100 MHz)

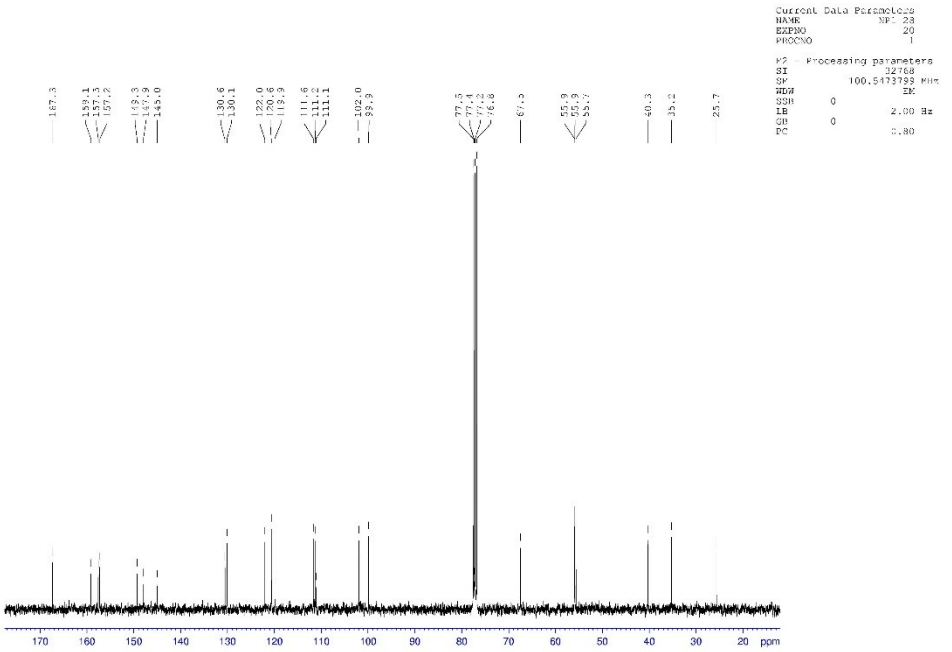


^{1}H NMR spectrum of **12q** ($CDCl_3$, 400 MHz)

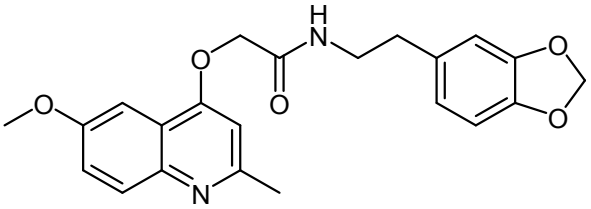


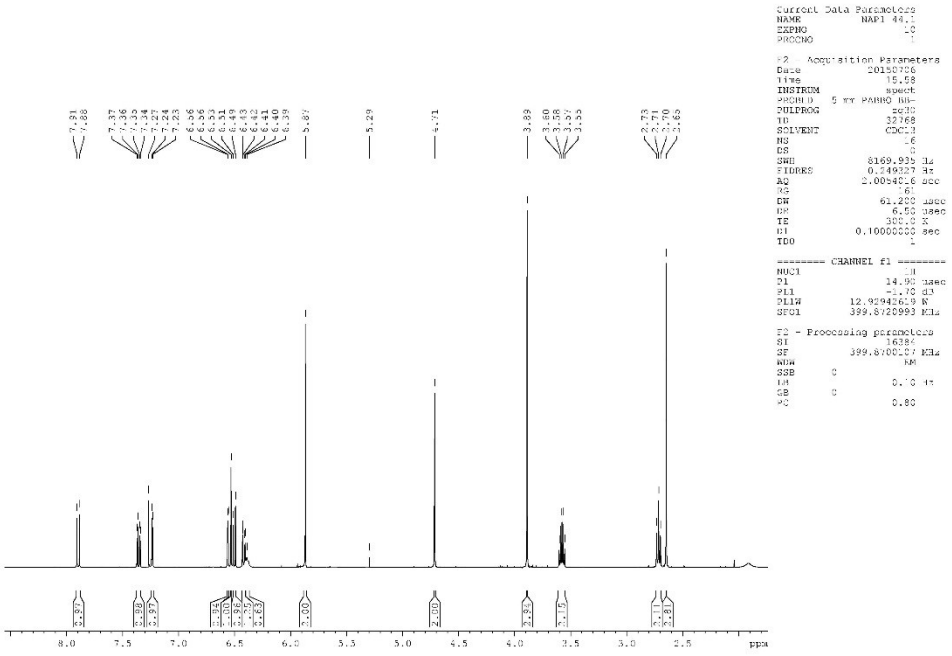


^{13}C NMR spectrum of **12q** ($CDCl_3$, 100 MHz)

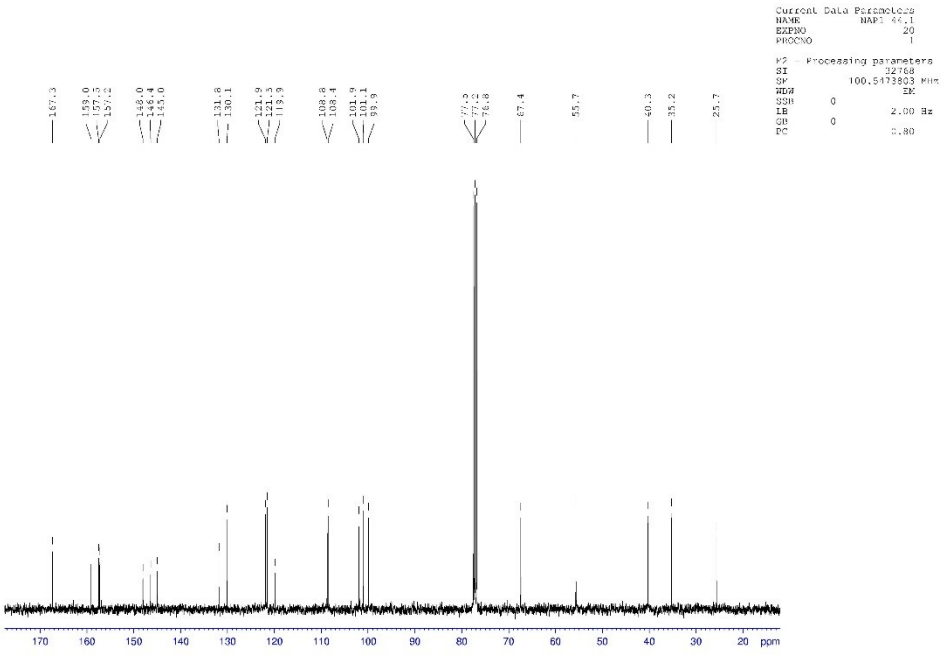


^{1}H NMR spectrum of **12r** ($CDCl_3$, 400 MHz)

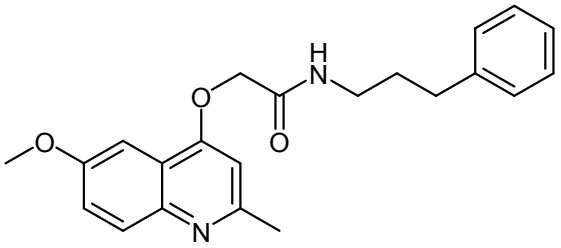


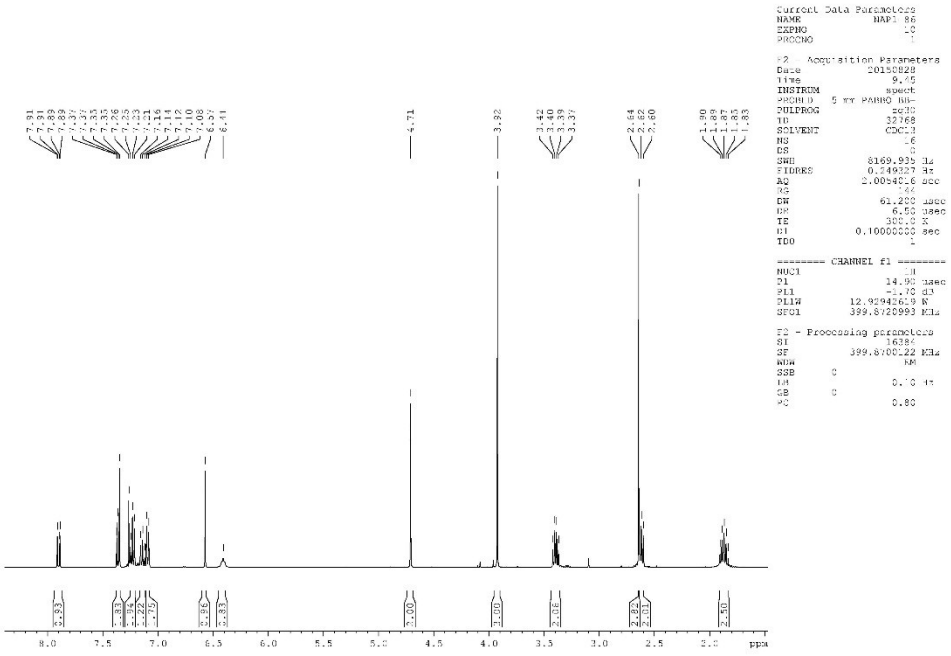


^{13}C NMR spectrum of **12r** ($CDCl_3$, 100 MHz)

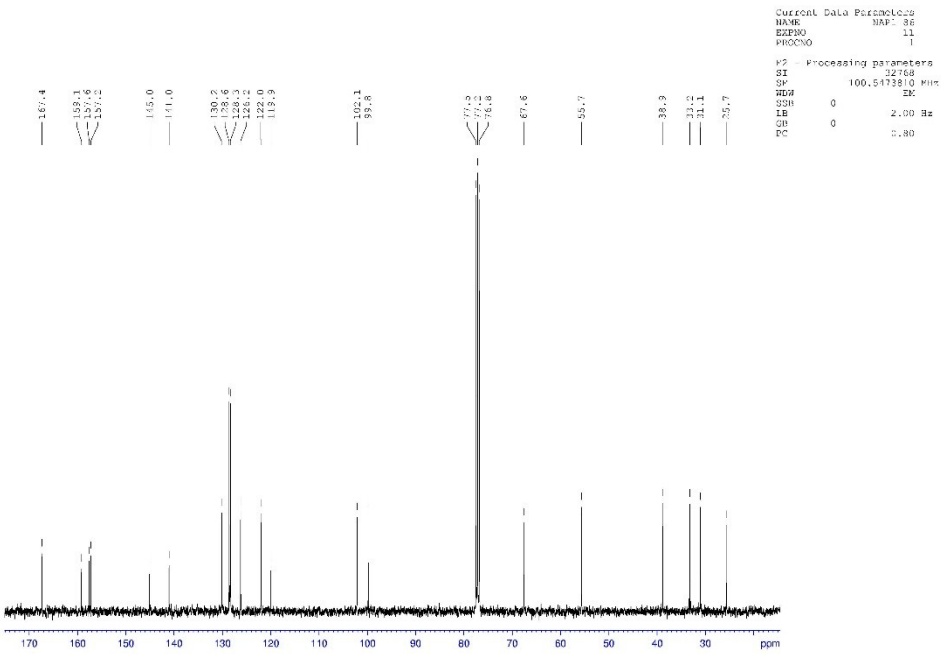


^{1}H NMR spectrum of **12s** ($CDCl_3$, 400 MHz)

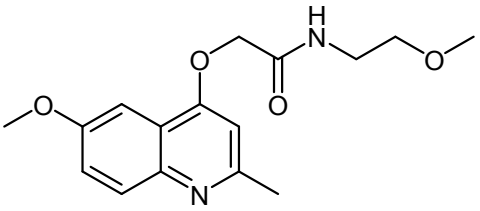


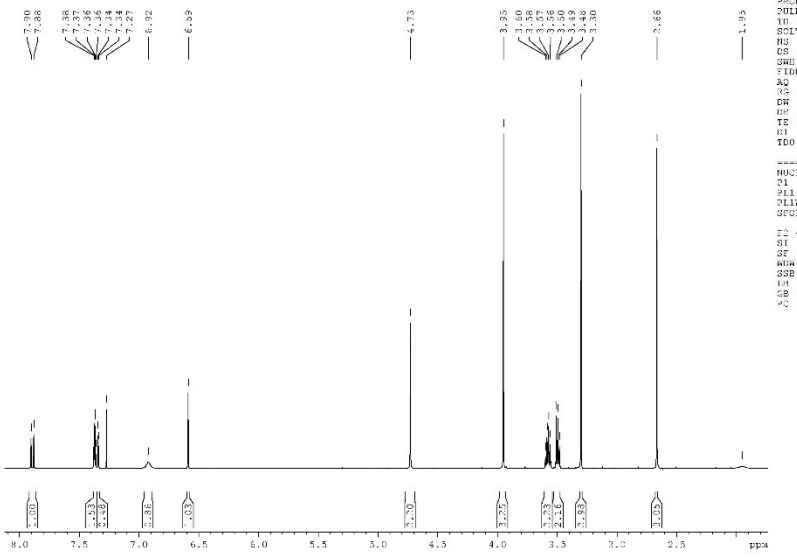


^{13}C NMR spectrum of **12s** ($CDCl_3$, 100 MHz)

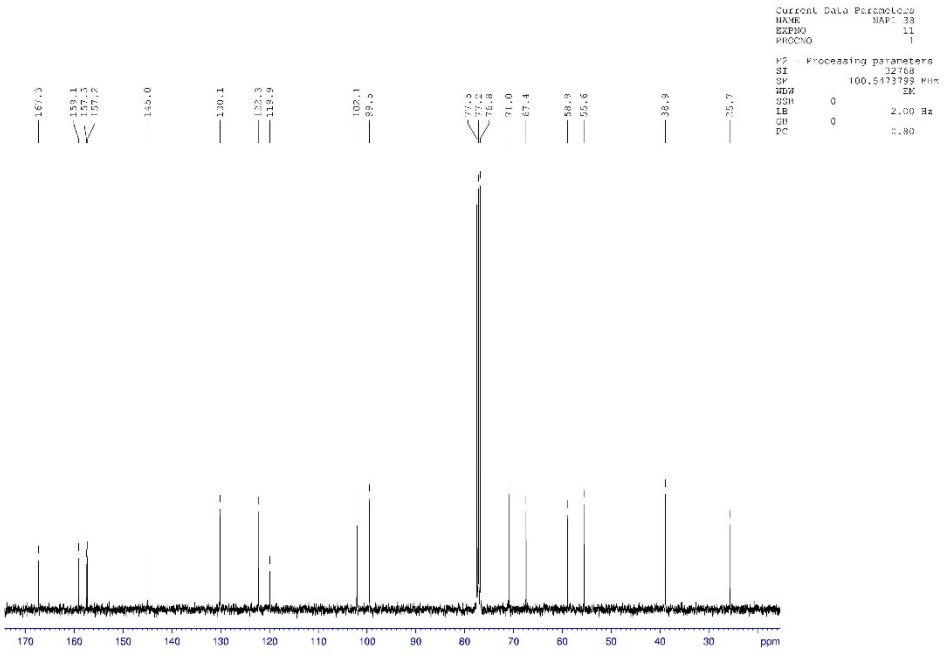


^{1}H NMR spectrum of **12t** ($CDCl_3$, 400 MHz)

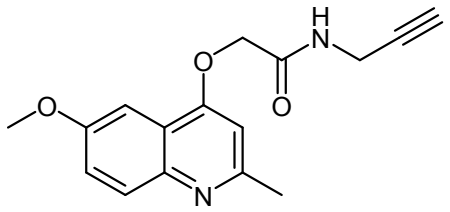


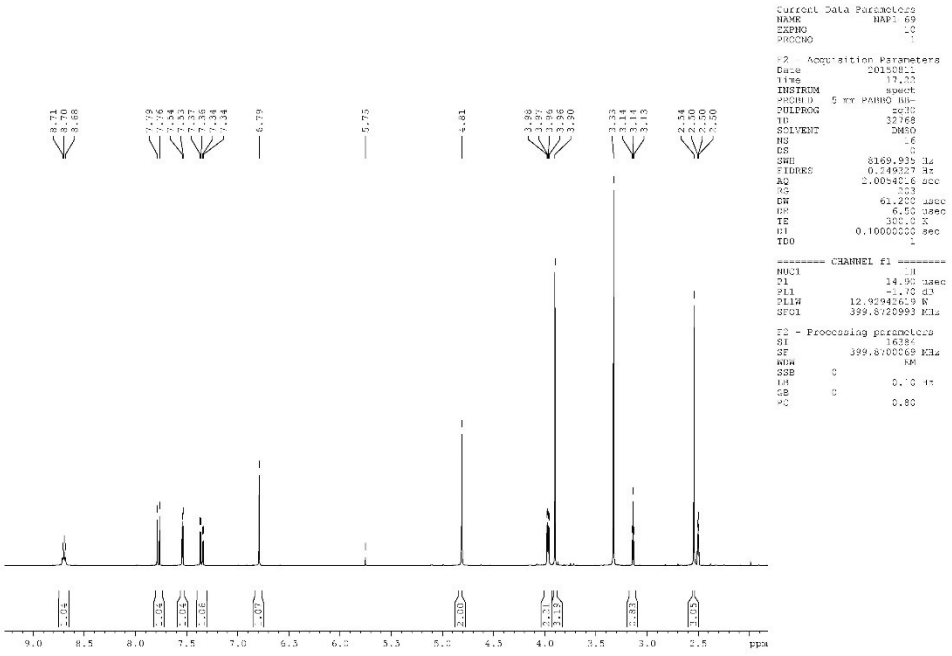


^{13}C NMR spectrum of **12t** ($CDCl_3$, 100 MHz)

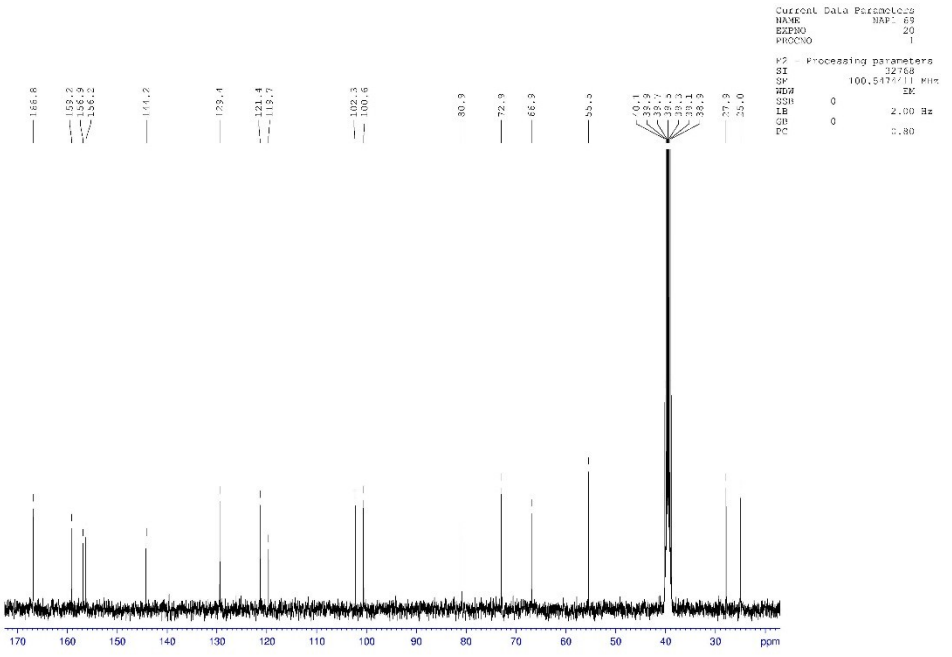


^{1}H NMR spectrum of **12u** (DMSO-d_6, 400 MHz)

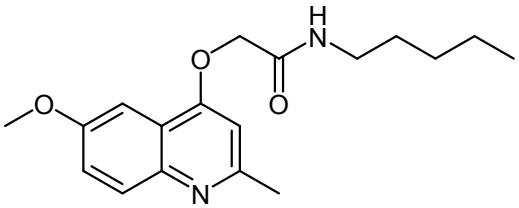


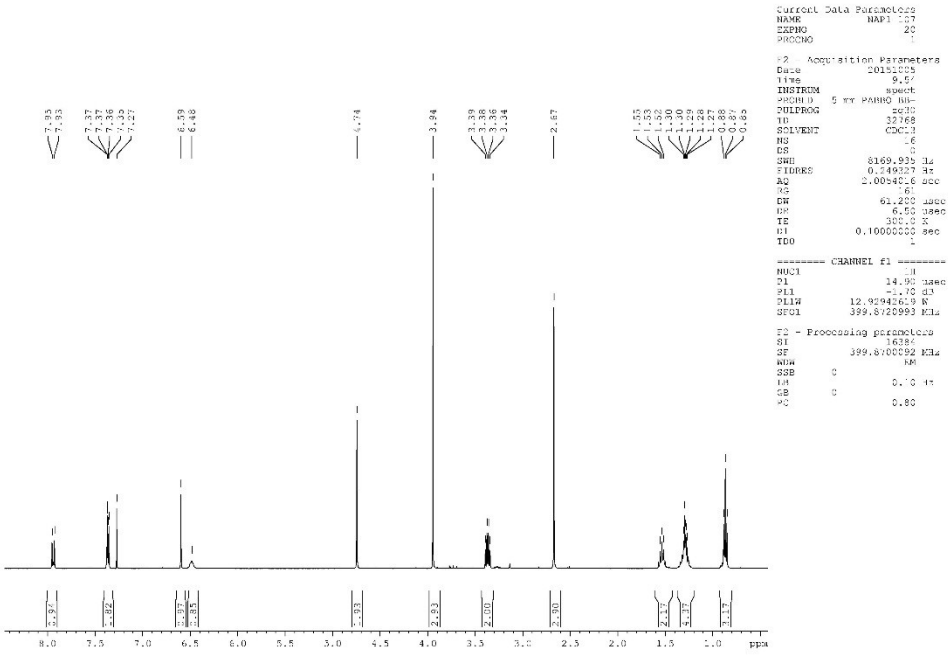


^{13}C NMR spectrum of **12u** (DMSO-d_6, 100 MHz)

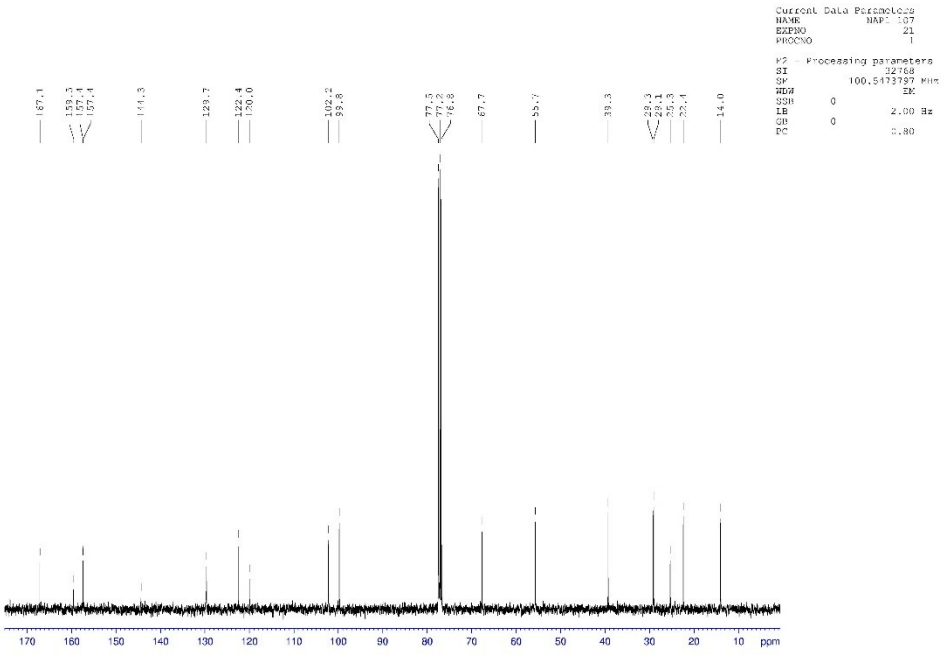


^{1}H NMR spectrum of **12v** ($CDCl_3$, 400 MHz)

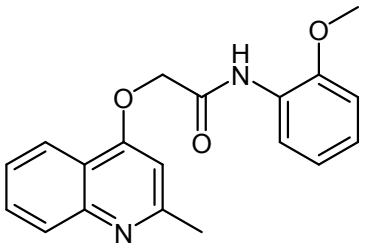


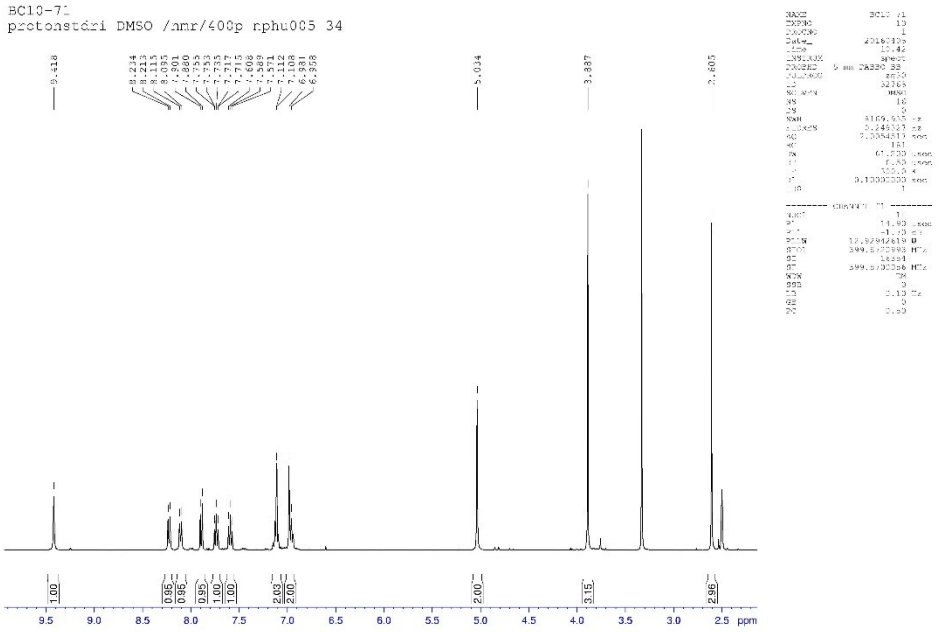


^{13}C NMR spectrum of **12v** ($CDCl_3$, 100 MHz)

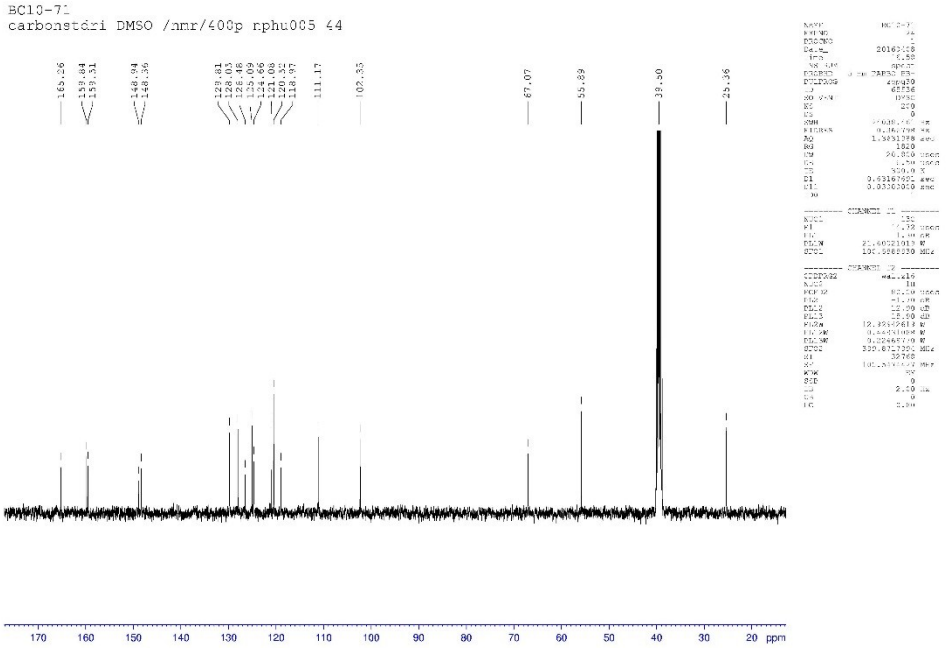


^{1}H NMR spectrum of **12w** (DMSO-d_6, 400 MHz)

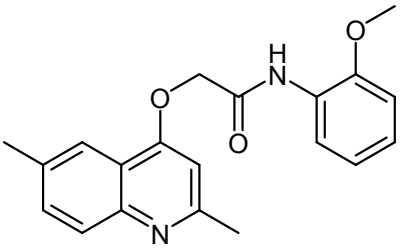


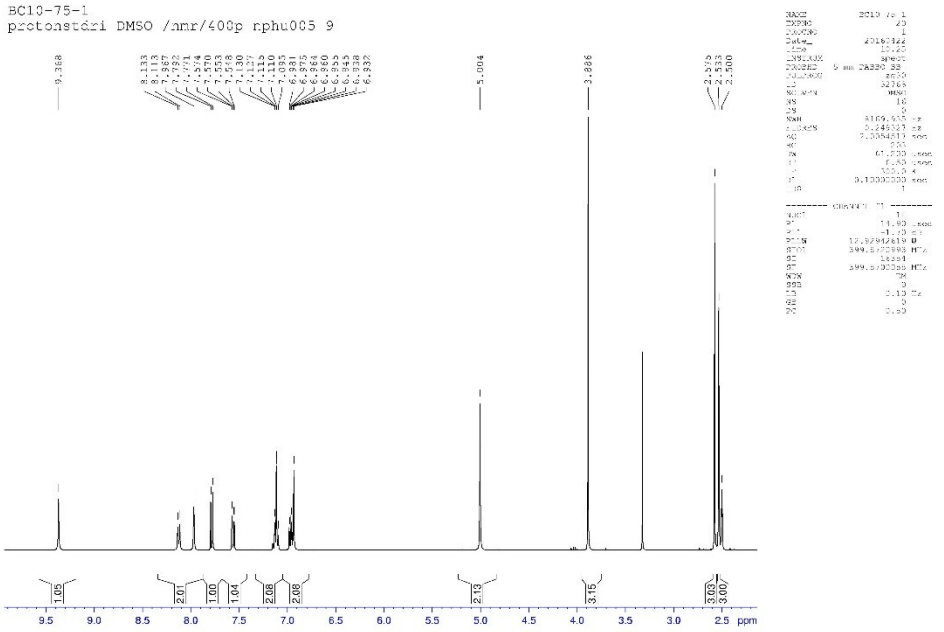


^{13}C NMR spectrum of **12w** (DMSO-d_6, 100 MHz)

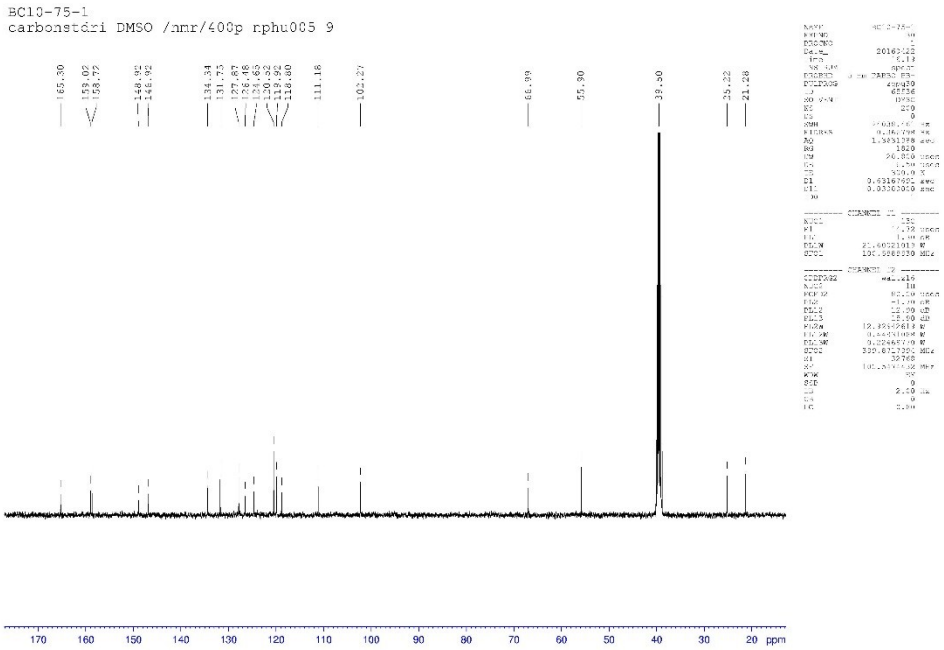


^{1}H NMR spectrum of **12x** (DMSO-d_6, 400 MHz)

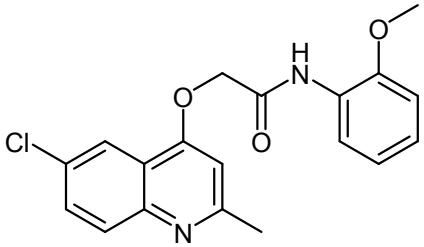


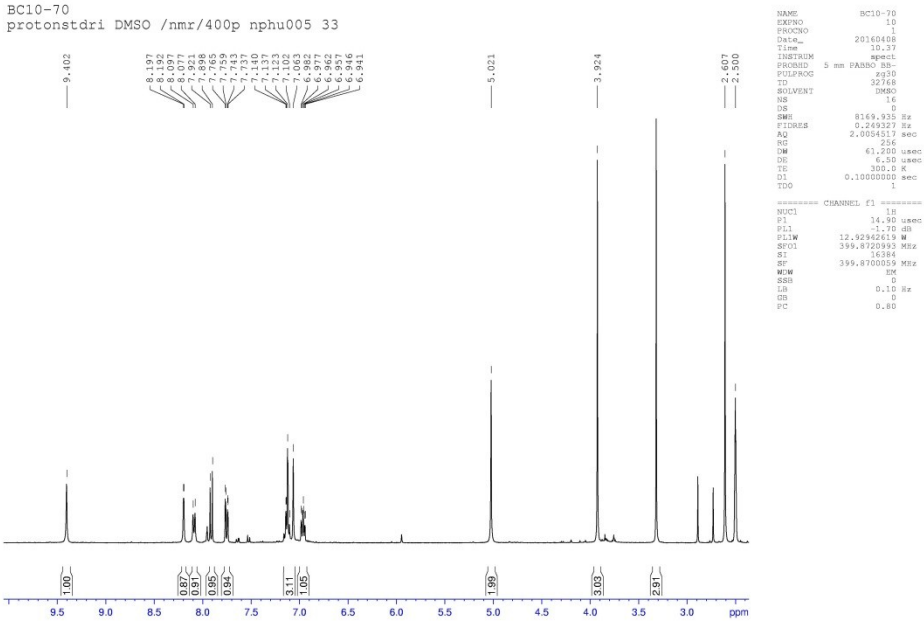


^{13}C NMR spectrum of **12x** (DMSO-d_6, 100 MHz)

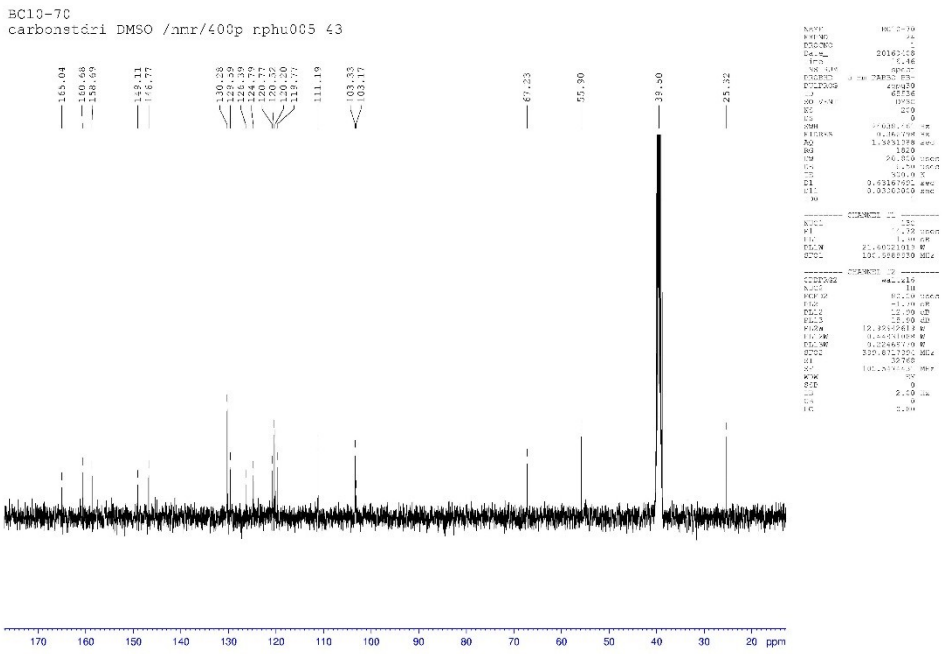


^{1}H NMR spectrum of **12y** (DMSO-d_6, 400 MHz)

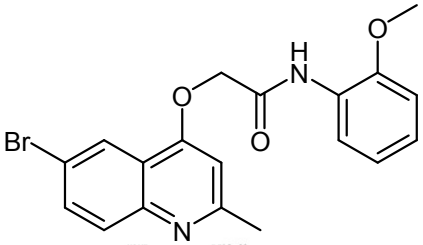


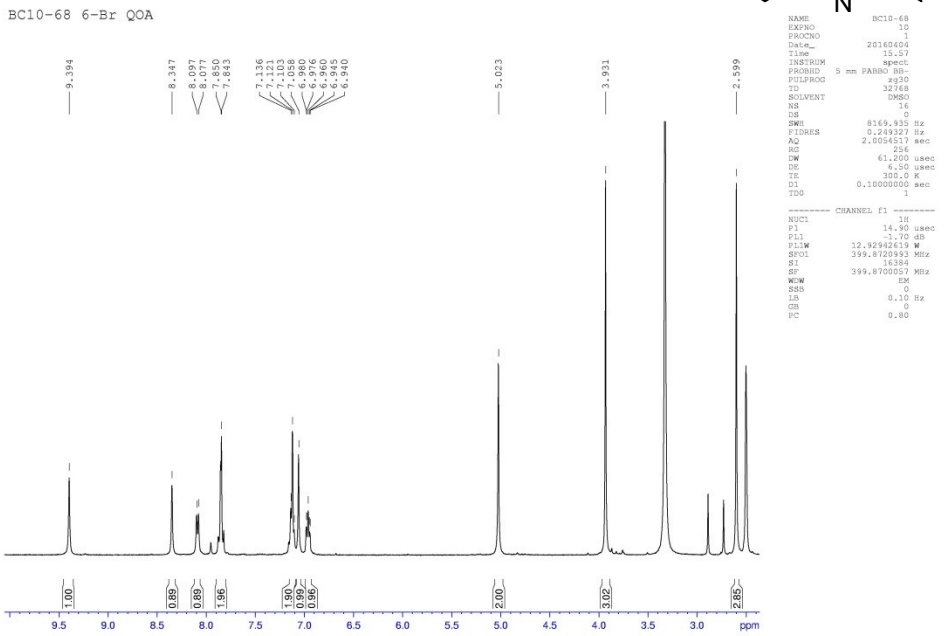


^{13}C NMR spectrum of **12y** (DMSO-d_6, 100 MHz)

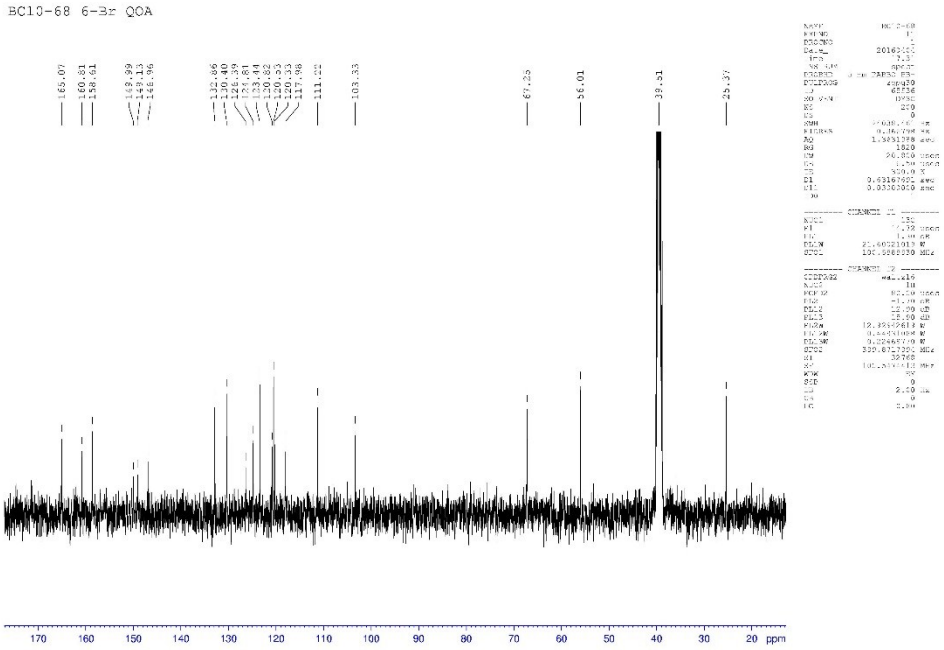


^{1}H NMR spectrum of **12z** (DMSO-d_6, 400 MHz)

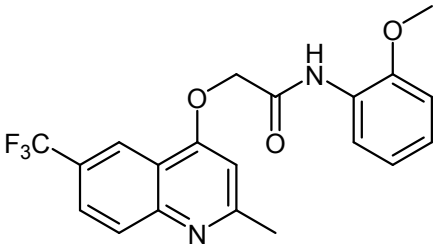


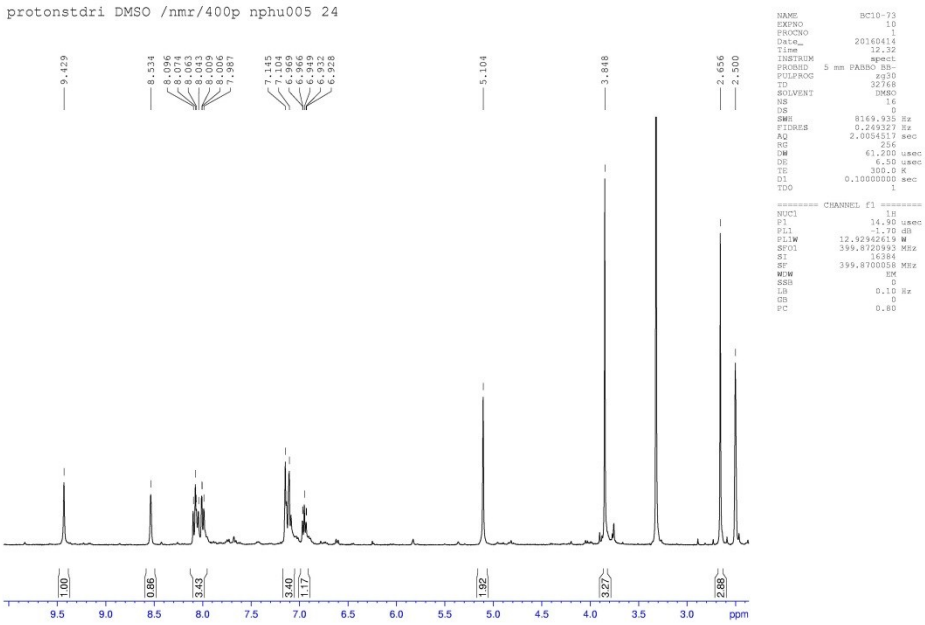


^{13}C NMR spectrum of **12z** (DMSO-d_6, 100 MHz)

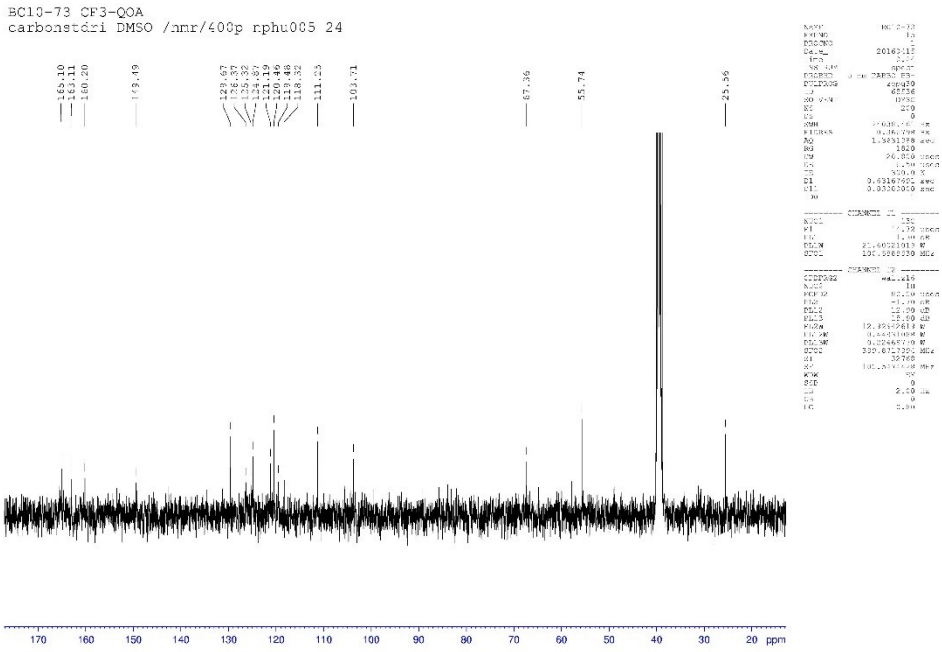


^{1}H NMR spectrum of **12aa** (DMSO-d_6, 400 MHz)





^{13}C NMR spectrum of **12aa** (DMSO-d_6, 100 MHz)



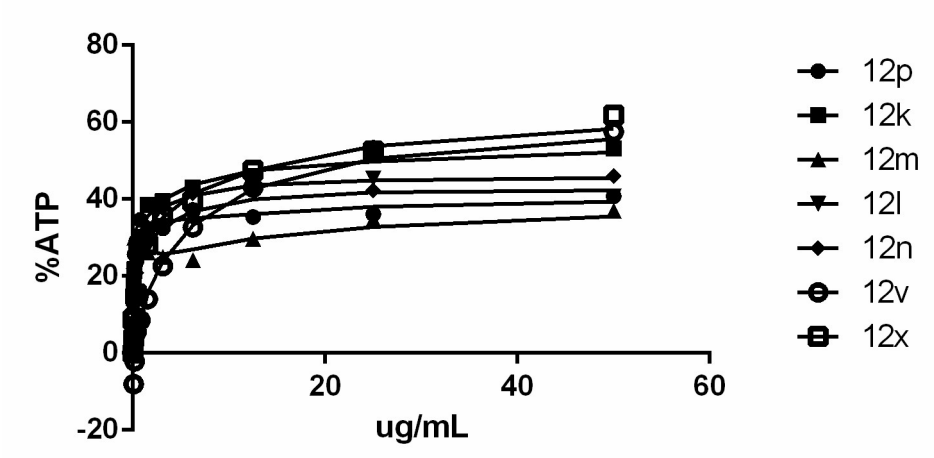
3. Experimental section, Biology.

Protocols used for the determination of Mycobacterium tuberculosis MIC under different growth conditions and media[7] and cytotoxicity towards HepG2 cells during growth on galactose and glucose[8] have been previously reported.

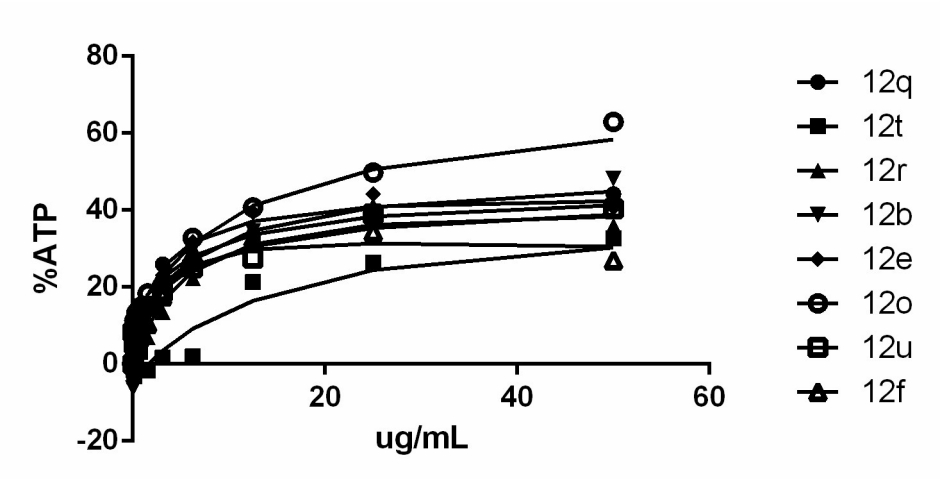
(a) Measurement of ATP levels in anaerobic cells

M. tuberculosis H37Rv was adapted to hypoxia in Dubos medium using the Wayne model wherein cells adapt to a self-generated gradient of oxygen depletion by growth of cells in sealed tubes with a head-space ratio of 0.5. At three weeks when cultures have reached stage 2 (NRP2) of non-replicating persistence, tubes were opened in the anaerobic chamber and 100uL cells (anaerobically) added to sterile white 96w plates (Corning) containing a 12-point 2-fold serial dilution of each compound in a final volume of 2uL DMSO per well. Plates were incubated for 24h at 37C in the anaerobic chamber after which plates were removed and ATP levels measured using the BacTiter-Glo microbial cell viability reagent (Promega) as recommended by the manufacturer. Drugs including isoniazid, rifampicin and metronidazole were used as control and were found not to reduce ATP levels in 24 hours. The ATP levels were calculated relative to DMSO treated cells (100% ATP) and a cell-free Dubos medium control (0% ATP).

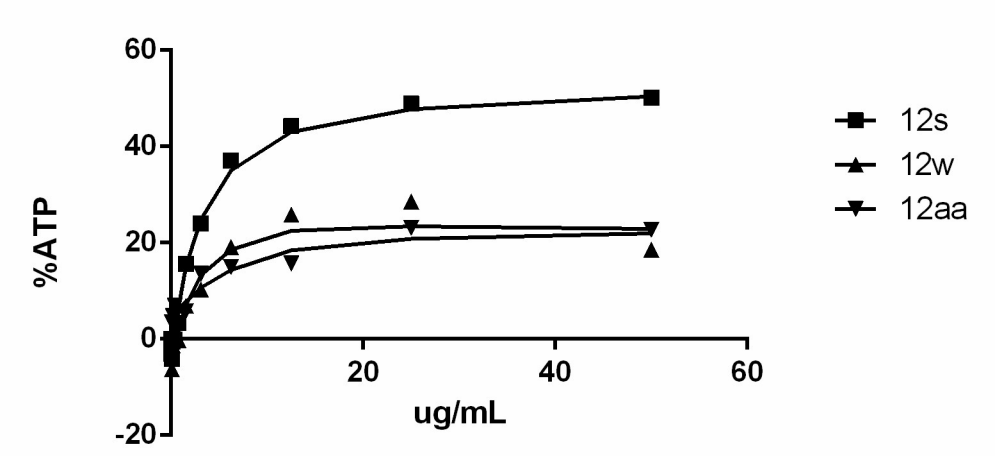
4. ATP depletion assay plots.



ESI Fig. 1 ATP depletion (%) under anaerobic conditions for test compounds **12k**, **12l**, **12m**, **12n**, **12p**, **12v** and **12x**.



ESI Fig. 2 ATP depletion (%) under anaerobic conditions for test compounds **12b**, **12e**, **12f**, **12o**, **12q**, **12r**, **12t** and **12u**.



ESI Fig. 3 ATP depletion (%) under anaerobic conditions for test compounds **12s**, **12w**, and **12aa**.

References.

1. H. Xie, D. Ng, S. N. Savinov, B. Dey, P. D. Kwong, R. Wyatt, A. B. Smith III and W. A. Hendrickson, *J. Med. Chem.* 2007, **50**, 4898–4908.

2. J. M. Hung, H. J. Arabshahi, E. Leung, J. Reynisson and D. Barker, *Eur. J. Med. Chem.* 2014, **86**, 420–437.

3. Y.-Y. Cheung, R. Zamorano, A. L. Blobaum, C. D. Weaver, P. J. Conn, C. W. Lindsley, C. M. Niswender and C. R. Hopkins, *ACS Comb. Sci.* 2011, **13**, 159–165.

4. Z. Sun, J. Khan, M. Makowska-Grzyska, M. Zhang, J. H. Cho, C. Suebsuwong, P. Vo, D. R. Gollapalli, Y. Kim, A. Joachimiak, L. Hedstrom and G. D. Cuny, *J. Med. Chem.* 2014, **57**, 10544–10550.

5. S. Morrissey, B. Pegot, D. Coleman, M. T. Garcia, D. Ferguson, B. Quilty and N. Gathergood, *Green Chem*. 2009, **11**, 475–483.

6. A. Sousa-Herves, E. Fernandez-Megia and R Riguera, *Chem. Commun.* 2008, 3136–3138.

7. G. C. Moraski, P. A. Miller, M. A. Bailey, J. Ollinger, T. Parish, H. I. Boshoff, S. Cho, J. R. Anderson, S. Mulugeta, S. G. Franzblau and M. J. Miller, *ACS Infect. Dis.*, 2015, **1**, 85–90.

8. L. D. Marroquin, J. Hynes, J. A. Dykens, J. D. Jamieson and Y. Will, *Toxicol. Sci.,* 2007, **97**, 539–547.