Electronic Supplementary Information for

Synthesis, Thiol-Mediated Reactive Oxygen Species Generation Profiles and Anti-Proliferative Activities of 2,3-Epoxy-1,4-Naphthoquinones

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Compounds **2**,[1] **3**,[2] **4**,[3] **5**,[4] **6**,[5] **7**,[6] **12**,[7] **13**,[7] **16**,[7] **17**,[8] **18**,[9] **19**,[7] **1a**,[10] **5a**,[10] **7a**,[10] **9a**[10] and **12a**[11] are previously reported and spectral data that we obtained was consistent with literature values.

General procedure for coupling of arylboronic acids with 2-bromo-1,4-naphthoquinone

To a mixture of THF: H_2O (9:1 v/v, 100 mL) under nitrogen atmosphere, 2-bromo-1,4-naphthoquinone (1eq.), sodium carbonate (2 eq.), arylboronic acid (1.5 eq.) and $Pd(PPh_3)_4$ (3 mol%) were added. The reaction mixture was stirred at room temperature until TLC analysis showed complete disappearance of starting material. Work up involved separation of the aqueous layer from the organic layer, washing of the aqueous layer with ethyl acetate (3 × 10 mL). The combined organic layers were dried (sodium sulphate) and filtered; removal of solvent under reduced pressure from the filtrate produced the crude product, which was purified by silica gel column chromatography (5 → 15 % ethyl acetate in petroleum ether) to obtain the desired product.

General Procedure for Epoxidation

To a stirred solution of the naphthoquinone (1 mmol) in THF (2 mL), sodium hypochlorite (1 mmol, 1.5 mL of 5 wt % solution) was added and the resulting reaction mixture was stirred at room temperature (25 °C). The reaction mixture was diluted with water (15 mL), and extracted using ethyl acetate (3 × 10 mL). The organic layers were combined and then washed with brine (10 mL), and dried (Na_2SO_4). The crude obtained by removal of sodium sulfate by filtration was then purified by silica gel column chromatography (1 → 5 % ethyl acetate in petroleum ether).

5-(4-Trifluoromethylbenzyloxy)-1,4-naphthoquinone (8). Starting from **5** (200 mg, 1.15 mmol), the naphthoquinone **8** was isolated as a bright yellow crystalline solid (366 mg, 96%): mp 136 – 138 °C; FT-IR (ν_{max}, cm^{-1}): 3075, 1658, 1614, 1583, 1451, 1386, 1305, 1250, 1170, 1106, 1058, 1026, 955; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 6.0 Hz, 1H), 7.77 (d, *J* = 5.2 Hz, 1H), 7.69 (d, *J* = 5.6 Hz, 3H), 7.44 (t, *J* = 5.8 Hz, 1H), 7.35 (d, *J* = 6.2 Hz, 1H), 6.90 (s, 2H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 184.4, 158.1, 141.0, 136.5, 135.3, 128.4, 127.9, 112.0, 119.3, 77.5, 77.2, 77.0, 67.1; HRMS (ESI): calcd. for $C_{18}H_{11}F_3O_3$ $[M+Na]^+$: 355.0558; Found: 355.0558.

5-Benzyloxy-2-methyl-1,4-naphthoquinone (11). Starting from **10** (200 mg, 1.06 mmol), the naphthoquinone **11** was isolated as a bright yellow solid (298 mg, 98%): mp 150 – 152 °C; FT-IR (ν_{max}, cm^{-1}): 3043, 2854, 2346, 1747, 1653, 1575, 1446, 1363, 1251, 1054, 965, 903, 831, 768, 729; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.55-7.62 (m, 3H),7.40 (t, *J* = 7.5 Hz, 2H), 7.28-7.33 (m, 2H), 6.72 (q, *J* = 1.5 Hz, 1H), 5.27 (s, 2H), 2.10 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 184.4, 158.4, 145.5, 138.0, 136.2, 134.6, 128.8, 128.0, 126.8, 120.6, 119.8, 119.6, 71.0, 16.0; HRMS (ESI): calcd. for $C_{18}H_{14}O_3$ $[M+Na]^+$: 301.0841; Found: 301.0844.

2-(4-Acetylphenyl)-1,4-naphthoquinone (14). Starting from 2-bromo-1,4-naphthoquinone (300 mg, 1.27 mmol), the naphthoquinone **14** was isolated as a yellow solid (159 mg, 43%): mp 170 – 172 °C; FT-IR (ν_{max}, cm^{-1}): 3068, 1744, 1657, 1591, 1548, 1402, 1357, 1302, 1258, 1171, 1109, 1018, 958; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.19 (m, 1H), 8.12-8.13 (m, 1H), 8.04 (d, *J* = 6.3 Hz, 2H), 7.80 (d, *J* = 3.4 Hz, 2H), 7.66 (d, *J* = 6.4 Hz, 2H), 7.10 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 184.9, 184.0, 147.2, 137.9, 136.0, 134.2,134.17, 129.8, 129.1, 128.4, 127.5, 127.2, 126.2, 26.9; HRMS (ESI): calcd. for $C_{18}H_{12}O_3$ $[M+Na]^+$: 299.0684; Found: 299.0684.

2-(4-Fluorophenyl)-1,4-naphthoquinone (15). Starting from 2-bromo-1,4-naphthoquinone (154 mg, 1.10 mmol), the naphthoquinone **15** was isolated as a yellow solid (142 mg, 66%): mp 142 – 144 °C; FT-IR (ν_{max}, cm^{-1}): 3068, 2961, 1742, 1685, 1593, 1507, 1301, 1259, 1160, 1102, 1009; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.18 (m, 1H), 8.10-8.12 (m, 1H), 7.76-7.78 (m, 2H), 7.55-7.59 (m, 2H), 7.16 (t, *J* = 8.6 Hz, 2H), 7.05 (s, 1H); ^{13}C NMR (100, MHz, $CDCl_3$): δ 185.1, 184.4, 165.3, 162.8, 147.1, 135.1, 134.0, 132.4, 132.1, 131.6, 131.5, 129.4, 127.2, 126.1, 115.9, 115.7; HRMS (ESI): calcd. for $C_{16}H_9FO_2$ $[M+Na]^+$: 275.0484; Found: 275.0484.

2,3-Epoxy-2,3-dihydro-5-nitro-1,4-naphthoquinone (2a). Starting from **2** (100 mg, 0.49 mmol), the epoxide **2a** was isolated as a white solid (72 mg, 67%): mp 141 – 142 °C; FT-IR (ν_{max}, cm^{-1}): 3051, 2922, 2852, 1703, 1595, 1542, 1373, 1323, 1294; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 4.15 (d, *J* = 4.1 Hz, 1H), 4.12 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 188.2, 148.7, 134.4, 132.6, 130.5, 129.2, 126.3, 55.6, 55.1; Elem. Anal. Calcd. for $C_{10}H_5NO_5 \cdot 0.05H_2O$: C, 54.81; H, 2.30; N, 6.39. Found: C, 54.69; H, 2.77; N, 6.49.

2,3-Epoxy-2,3-dihydro-6-nitro-1,4-naphthoquinone (3a). Starting from **3** (100 mg, 0.49 mmol), the epoxide **3a** was isolated as a white solid (94 mg, 88%): mp 140 – 141 °C; FT-IR (ν_{max}, cm^{-1}): 3076, 3040, 2372, 1705, 1603, 1573, 1344, 1290, 994; ^{1}H NMR (400, MHz, $CDCl_3$): δ 8.82 (d, *J* = 2.2 Hz, 1H), 8.58 (dd, *J* = 2.3, 8.3 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 4.15 (dd, *J* = 3.7, 6.4 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 189.2, 188.6, 144.9, 135.5, 129.3, 128.8, 122.7, 55.7, 55.6; HRMS (MALDI): calcd. for $C_{10}H_5NO_5$ $[M+K]^+$: 258.2487; Found: 258.2380.

2,3-Epoxy-2,3-dihydro-5-amino-1,4-naphthoquinone (4a). Starting from **4** (173 mg, 1.00 mmol), epoxide **4a** was isolated as a pale yellow solid (81 mg, 43%): mp 131 – 132 °C; FT-IR (ν_{max}, cm^{-1}): 3746, 3403, 2926, 1704, 1646, 1601, 1540, 1327, 1287, 1002, 993; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.4, 8.2 Hz, 1H), 7.28 (dd, *J* = 1.2, 7.3 Hz, 1H), 6.92 (dd, *J* = 0.9, 8.7 Hz, 1H), 6.33 (broad, 2H), 3.94 (d, *J* = 3.7 Hz, 1H), 3.90 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 191.6, 150.4, 135.3, 133.0, 123.1, 116.9, 111.4, 56.0, 55.2; HRMS (MALDI) calcd. for $C_{10}H_7NO_3$ $[M+K]^+$: 228.0063; Found: 228.0014.

2,3-Epoxy-2,3-dihydro-5-ethyloxy-1,4-naphthoquinone (6a). Starting from **6** (150 mg, 0.74 mmol), the epoxide **6a** was isolated as a grayish white solid (109 mg, 68%): mp 110 – 112 °C; FT-IR (ν_{max}, cm^{-1}): 3079, 2982, 2940, 1697, 1584, 1457, 1396, 1325, 1285, 1156, 1115, 1048, 995; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (t, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 4.16-4.22 (m, 1H), 3.96-4.14 (m, 1H), 3.96 (s, 2H), 1.47 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 190.2, 158.7, 135.1, 133.9, 120.4, 119.1, 65.3, 55.5, 55.3, 14.6; HRMS (ESI): calcd for $C_{12}H_{10}O_4$ $[M+Na]^+$: 241.0477; Found: 241.0478.

2,3-Epoxy-2,3-dihydro-5-(4trifluoromethylbenzyloxy)-1,4-naphthoquinone (8a). Starting from **8** (150 mg, 0.45 mmol), the epoxide **8a** was isolated as a white solid (129 mg, 82%): mp 144 – 146 °C; FT-IR (ν_{max}, cm^{-1}): 3080, 1698, 1585, 1450, 1395, 1317, 1284, 1261, 1173, 1109, 1064, 985; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.62-7.68 (m, 3H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 5.40 (d, *J* = 13.7 Hz, 1H), 5.34 (d, *J* = 13.7 Hz, 1H), 3.99-4.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 190.1, 157.6, 135.4, 134.5, 134.0, 132.7, 128.1, 127.9, 125.9, 125.8, 120.6, 119.9, 119.3, 66.92, 66.89, 55.6, 55.3; HRMS (ESI): calcd. for $C_{18}H_{11}F_3O_4$ $[M+Na]^+$: 371.0507; Found: 371.0506. [Note: Multiple and weak signals were seen in the aromatic region of ^{13}C NMR due to the coupling of fluorine atoms (–CF_3) with the adjacent phenyl ring carbons].

2,3-Epoxy-2-methyl-5-benzyloxy-1,4-naphthoquinone (11a). Starting from **13** (150 mg, 0.57 mmol), the epoxide **13a** was isolated as a pale yellow solid (72 mg, 45%): mp 115 – 117 °C. FT-IR (ν_{max}, cm^{-1}): 3080, 1699, 1583, 1447, 1387, 1327, 1286, 1251, 1075, 1032, 965; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.59 (m, 2H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.27-7.32 (m, 2H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 3.83 (s, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 191.1, 157.9, 135.9, 135.0, 134.4, 128.8,128.2 126.9, 121.1, 119.9, 119.4, 71.0, 61.7, 61.65, 14.6; HRMS (ESI): calcd for $C_{18}H_{14}O_4$ $[M+Na]^+$: 317.0790; Found: 317.0790.

2,3-Epoxy-2-(3-nitrophenyl)-1,4-naphthoquinone (13a). Starting from **13** (100 mg, 0.36 mmol), the epoxide **13a** was isolated as a white solid (84 mg, 81%): mp 129 – 131 °C; FT-IR (ν_{max}, cm^{-1}): 3089, 2924, 1695, 1590, 1530, 1345, 1296, 1200, 1123, 1028; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.06-8.09 (m, 1H), 7.99-8.02 (m, 1H), 7.79-7.83 (m, 3H), 7.63 (td, *J* = 2.8, 8.0 Hz, 1H), 3.96 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 189.4, 148.3, 135.1, 135.06, 133.8, 133.1, 132.1, 131.8, 129.7, 128.1, 127.2, 124.4, 122.9, 63.5, 63.0; HRMS (MALDI): calcd. for $C_{16}H_9NO_5$ $[M+K]^+$: 334.0118; Found: 334.0220.

2,3-Epoxy 2-(4-acetylphenyl)-1,4-naphthoquinone (14a). Starting from **14** (100 mg, 0.36 mmol), the epoxide **14a** was isolated as a pale yellow solid (78 mg, 74%): mp 147 – 149 °C; FT-IR (ν_{max}, cm^{-1}): 3068, 2319, 1744, 1657, 1592, 1548, 1462, 1402, 1357, 1302, 1258, 1171, 1109, 1018; ^1H NMR (500 MHz, $CDCl_3$): δ 8.08-8.10 (m, 1H), 8.02 (d, *J* = 8.4 Hz, 3H), 7.79-7.81 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 2H,), 3.94 (s, 1H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 190.4, 189.8, 137.7, 135.9, 135.0, 134.9, 132.3, 131.8, 129.1, 128.5, 128.0, 127.9, 127.5, 127.1, 64.1, 63.0, 26.9; HRMS (MALDI): calcd for $C_{18}H_{12}O_4$ $[M+H]^+$: 293.0814; Found: 293.0990.

2,3-Epoxy-2-(4-fluorophenyl)-1,4-naphthoquinone (15a). Starting from **15** (70 mg, 0.28 mmol), the epoxide **15a** was isolated as a white solid (39 mg, 52%): mp 143 – 145 °C; FT-IR (ν_{max}, cm^{-1}): 2923, 1690, 1597, 1515, 1333, 1298, 1233, 1160, 1023; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07-8.09 (m, 1H), 8.00-8.02 (m, 1H), 7.79 (dd, *J* = 3.5, 5.7 Hz, 2H), 7.44-7.48 (m, 2H), 7.13 (t, *J* = 8.7 Hz, 2H), 3.94 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ 190.8, 190.2, 134.9, 134.8, 132.4, 131.9, 129.7, 128.0, 127.0, 126.7, 115.9, 115.6, 64.1, 63.1; HRMS (MALDI): calcd for $C_{16}H_9FO_3$ $[M+Na]^+$: 291.0433; Found: 291.0443.

2,3-Epoxy-2-(4-methylphenyl)-1,4-naphthoquinone (16a). Starting from **16** (100 mg, 0.40 mmol), the epoxide **16a** was isolated as a white solid (81 mg, 78%): mp 146 – 148 °C; FT-IR (ν_{max}, cm^{-1}): 2919, 1701, 1585, 1516, 1457, 1381, 1324, 1282, 1260, 1152, 1115, 1028; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 3.2, 5.5 Hz, 1H), 7.89 (dd, *J* = 3.2, 6.0 Hz, 1H), 7.66 (dd, *J* = 3.4, 5.9 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 3.84 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 190.5, 139.4, 134.8, 134.6, 132.6, 131.9, 129.3, 128.0, 127.8, 127.6, 127.0, 64.7, 63.1, 21.4; HRMS (MALDI): calcd. for $C_{17}H_{12}O_3$ $[M+Na]^+$: 287.0684; Found: 287.0773.

2,3-Epoxy-2-(2-methoxyphenyl)-1,4-naphthoquinone (17a). Starting from **17** (110 mg, 0.42 mmol), the epoxide **17a** was isolated as a white solid (96 mg, 82%): mp 122 – 124 °C; FT-IR (ν_{max}, cm^{-1}): 2934, 2842, 1694, 1594, 1498, 1463, 1398, 1284, 1193, 1105, 1019; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06-8.08 (m, 1H), 8.02-8.04 (m, 1H), 7.75-7.77 (m, 2H), 7.37-7.43 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 189.4, 157.9, 134.7, 134.5, 132.4, 132.1, 130.9, 128.1, 128.0, 127.0, 120.7, 110.5, 63.4, 62.0, 55.7; HRMS (ESI): calcd. for $C_{17}H_{12}O_4$ ([M+Na]$^+$: 303.0663; Found: 303.0634.

2,3-Epoxy-2-(3-methoxyphenyl)-1,4-naphthoquinone (18a). Starting from **18** (100 mg, 0.34 mmol), the epoxide **18a** was isolated as a pale yellow semi-solid (89 mg, 93%): FT-IR (ν_{max}, cm^{-1}): 2926, 2844, 1697, 1594, 1460, 1279, 1234, 1179, 1114, 1045; ^1H NMR

(400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 2.6, 4.6 Hz, 1H), 7.95 (dd, *J* = 2.7, 4.4 Hz, 1H), 7.72 (dd, *J* = 2.6, 4.6 Hz, 2H), 7.29 (t, *J* = 6.4 Hz, 1H,), 6.99 (d, *J* = 6.1 Hz, 1H), 6.93 (d, *J* = 1.1 Hz, 1H), 6.90 (dd, *J* = 1.4, 6.6 Hz, 1H), 3.89 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 190.2, 159.7, 134.8, 134.7, 132.6, 132.3, 131.9, 129.7, 128.0, 127.0, 120.0, 115.3, 113.0, 64.6, 63.0, 58.4; HRMS (MALDI): calcd. for $C_{17}H_{12}O_4$ $[M+H]^+$: 281.0814; Found: 281.0966.

2,3-Epoxy-2-(4-methoxyphenyl)-1,4-naphthoquinone (19a). Starting from **19** (70 mg, 0.27 mmol), the epoxide **19a** was isolated as a white solid (60 mg, 81%): mp 126 – 128 °C; FT-IR (ν_{max}, cm^{-1}): 2988, 2924, 2826, 1696, 1601, 1515, 1463, 1392, 1301, 1246, 1180, 1111, 1034; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 3.0, 6.0 Hz, 1H), 8.00 (dd, *J* = 3.3, 6.4 Hz, 1H), 7.77 (dd, *J* = 3.4, 5.5 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.95 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 190.7, 160.4, 134.8, 134.6, 132.6, 131.9, 129.2, 128.0, 126.9, 122.7, 114.1, 64.6, 63.1, 55.5; HRMS (ESI): calcd. for $C_{17}H_{12}O_4$ $[M+Na]^+$: 303.0633; Found: 303.0632. Additional evidence for structure of **19a** was obtained by X-ray crystallography analysis (Figure S1).

Figure S1. Ortep diagrams for **5a** (left) and **19a** (right).

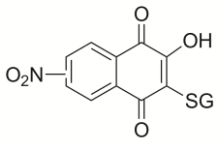
Nucleophile-mediated decomposition of epoxides

Reaction of epoxides with nucleophiles

To a solution of the naphthoquinone epoxide (10 mM) in CH_3CN: H_2O (1:1, v/v, 10 μL), 10 eq. of nucleophile (10 mM, 100 μL) in pH 7.4 phosphate buffer (25 mM) was added. This solution was diluted to 1 mL by adding 890 μL CH_3CN: H_2O (1:1, v/v). The reaction mixture was maintained at RT before the measurement of amount of epoxide remaining by using high performance liquid chromatography (HPLC).

Reaction of epoxides with GSH

To a solution of 10 mM naphthoquinone epoxide in DMSO (10 μL), 1 eq. of GSH (10 mM, 10 μL) in water, and pH 7.4 phosphate buffer (180 μL, 25 mM) were added and the solution was diluted to 1ml by adding 800 μL CH_3CN: H_2O (1:1, v/v). The reaction mixture was kept at RT for 30 min before the measurement of amount of epoxide remaining by using high performance liquid chromatography (HPLC). Below are representative curves that we obtained for the decomposition of **1a**, **3a**, **9a** and **12a** in the presence of GSH (Figures S2-S5). Mass spectrometric analysis of the products of reaction of **1a** and **3a** with GSH provided evidence for the formation of **1c** and **3c** respectively.



3c

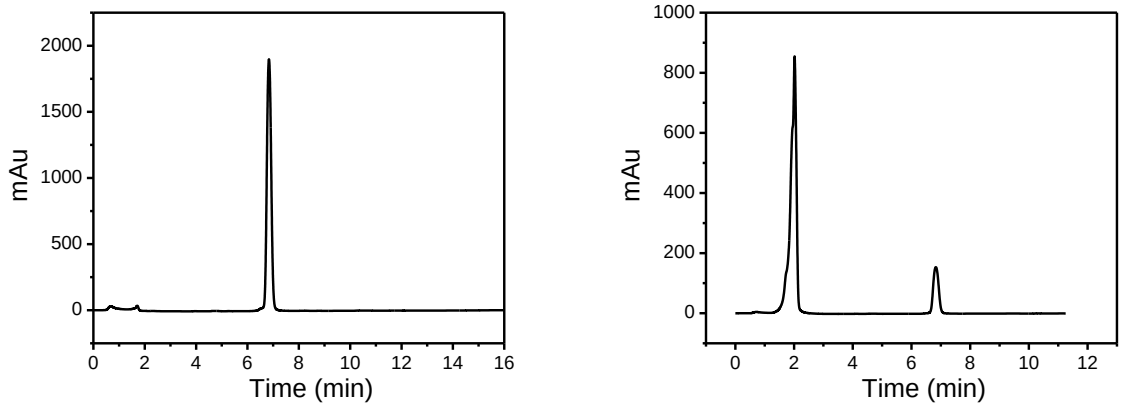


Figure S2. Decomposition of **1a** (left) in the presence of GSH after 5 min (right).

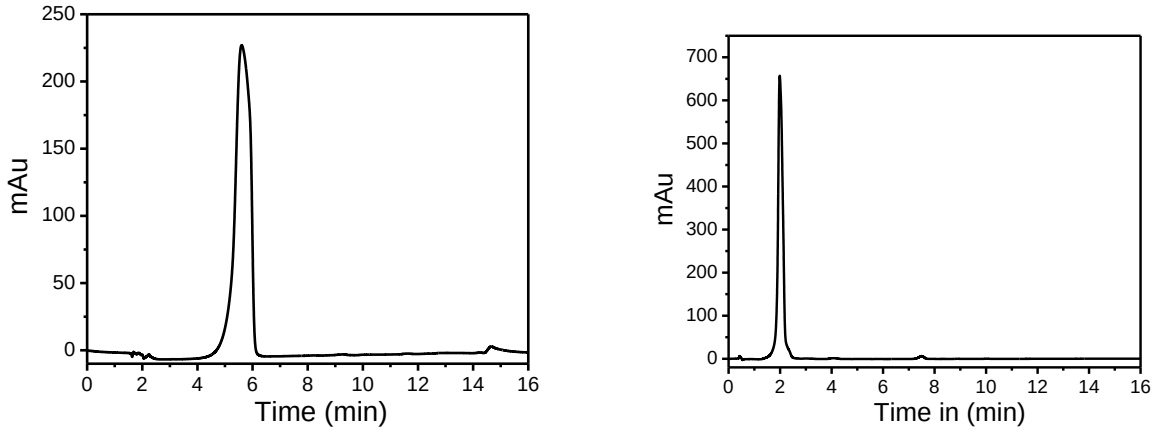


Figure S3. Decomposition of **3a** (left) in the presence of GSH after 5 min (right).

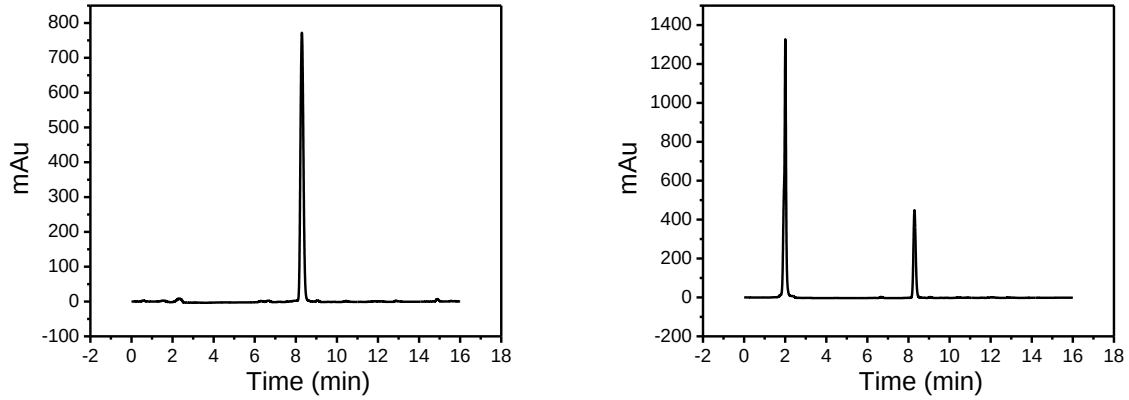


Figure S4. Decomposition of **9a** (left) in the presence of GSH after 5 min (right).

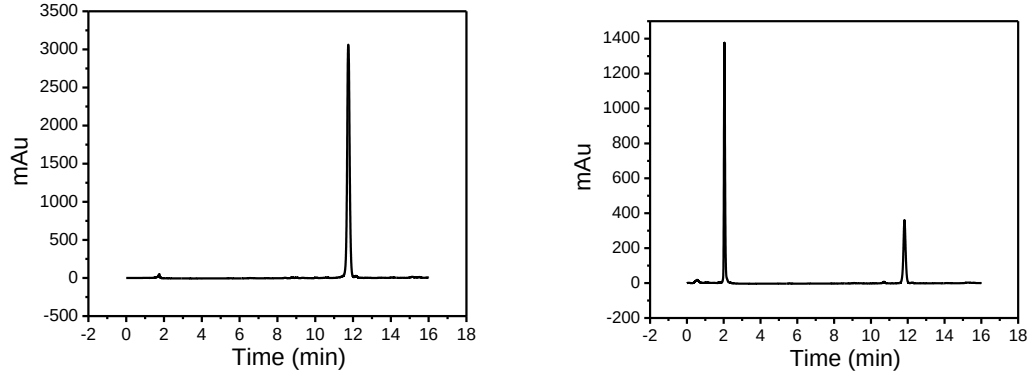


Figure S5. Decomposition of **12a** (left) in the presence of GSH after 5 min (right).

Peroxide Estimation

Xylenol orange (1.25 mM) stock solution was prepared by dissolving 9.5 mg (12.5 μmol) in 10 mL of de-ionised water. This solution was diluted 10-fold using de-ionised water to get 125 μM stock solution. A 1 M solution of sorbitol (1.82 g, 1 mol in 10 mL dI water) was also prepared and diluted to produce 100 mM stock solution. A 250 mM ferrous ammonium sulphate (FAS) solution was prepared by dissolving 980.3 mg of FAS in 10 mL of 2.5 M sulphuric acid. This solution was further diluted 10-fold by using 2.5 M sulphuric acid for the final stock solution of FAS (25 mM). Xylenol orange and sorbitol stock solutions were mixed together in a ratio of 1:1 (v/v) and to this 100:1 (v/v) FAS stock solution was added to obtain the final FOX stock solution, which is used for the hydrogen peroxide estimation. A calibration curve was generated with hydrogen peroxide (Figure S6).

Estimation of hydrogen peroxide generated during the reaction of epoxides with GSH: To a solution of 10 mM epoxide in DMSO (5 μL) 5 eq. of GSH (10 mM, 25 μL) in water and 70 μL pH 7.4 phosphate buffer (25 mM) were added and the reaction mixture was exposed to 1 mL of oxygen gas and kept at RT for 30 min and 900 μL of FOX solution. The final solution was kept at RT for 25 min and the absorption at 586 nm was measured using a spectrophotometer.

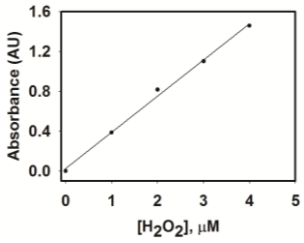


Figure S6. Calibration curve for peroxide.

In vitro anti-proliferative activity

THP1 (acute monocytic leukemia cell line) and HEK293T cell lines were obtained from National Centre for Cell Science (Pune, India). THP-1 cells were cultured as suspension in RPMI-1640 medium (HiMedia, India) supplemented with 2 mM glutamine (Himedia, India), antibiotics (100 U/mL penicillin A and 100 U/mL streptomycin; Himedia, India) and 10% heat-inactivated fetal bovine serum (HiMedia, India). HEK293T were cultured as monolayers in DMEM medium (HiMedia, India) supplemented with 2 mM glutamine (Himedia, India), antibiotics (100 U/mL penicillin A and 100 U/mL streptomycin; Himedia, India) and 10% heat-inactivated fetal bovine serum (HiMedia, India). Both the cells were cultured in 75 cm^2 flasks with loosened caps and incubated in 5% CO_2 humidified air at 37°C. The toxicity of compounds was determined by means of a reported 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide inner salt (XTT) assay. Fresh stock solutions of each compound were prepared in DMSO at a concentration of 100 mM. Dilution in 50:50 RPMI:DMSO mixtures produced stock solutions of compounds ranging from 10^{-8}M to 10^{-4}M. Cells were diluted to a final density of 1 x 10^5 cells/mL. 50 μL of the cell suspension were sowed into the wells of a 96-well culture plate (Axygen, USA) and treated with varying concentrations of compounds in triplicates. After incubation with compounds at 37 °C (in 5% CO_2 humidified atmosphere) 50 μL of freshly prepared XTT reagent with XTT-labeling reagent and electron-coupling reagent in a ratio of 50:1, was added to each well of the 96-well plate. The plates were incubated for about 72 h at 37 °C, 5% CO_2 in humidified atmosphere and read out after incubation. Quantification of cell cytotoxicity was performed in an ELISA plate reader (Bio-Rad, Munchen, Germany) at 450 nm with a reference wavelength of 655 nm.

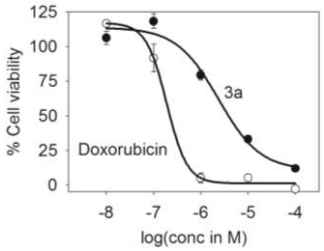
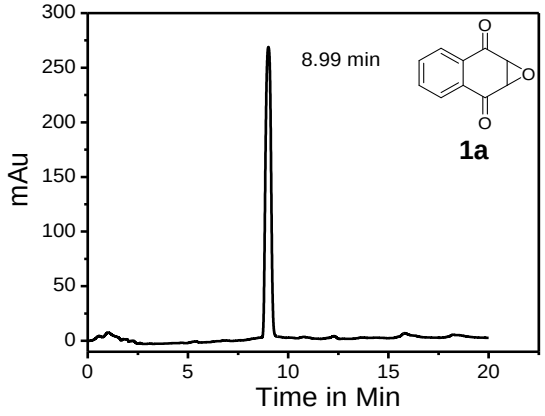
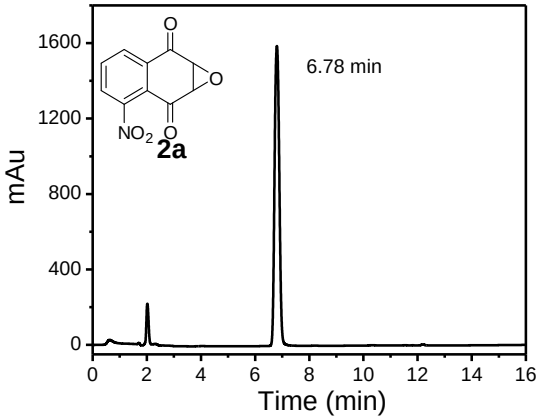
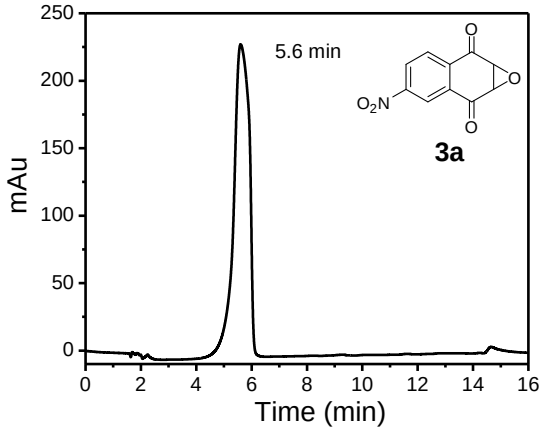


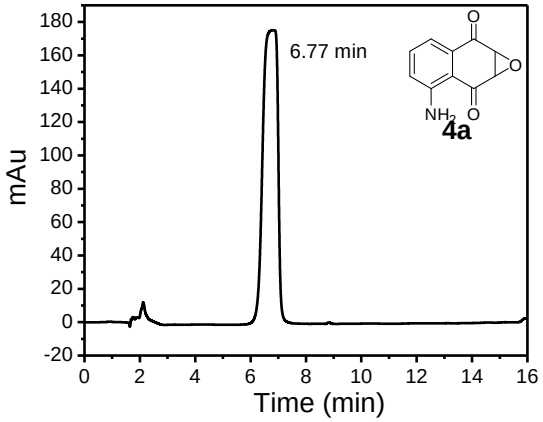
Figure S7. Cell viability measurements carried out for **3a** in comparison with Doxorubicin under similar assay conditions. Curve fitting program of SigmaPlot or Origin was used to calculate IC_{50} values. The R^2 value for curve fitting to a sigmoidal dose-response curve was 0.98 (**3a**) and 0.99 (Doxorubicin)

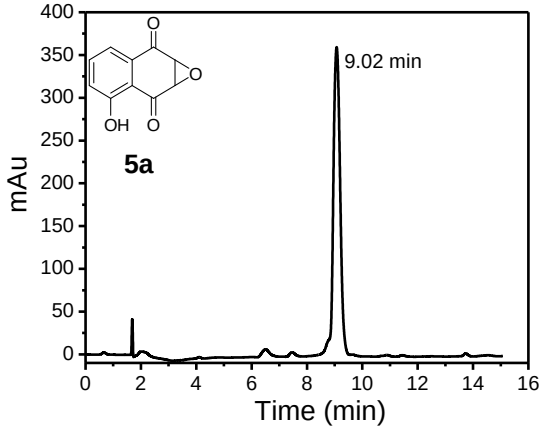
HPLC Traces:

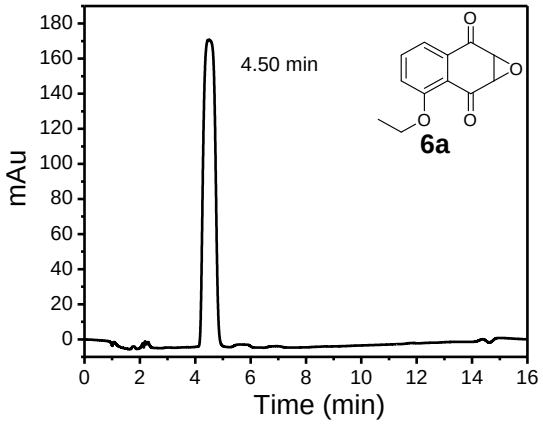


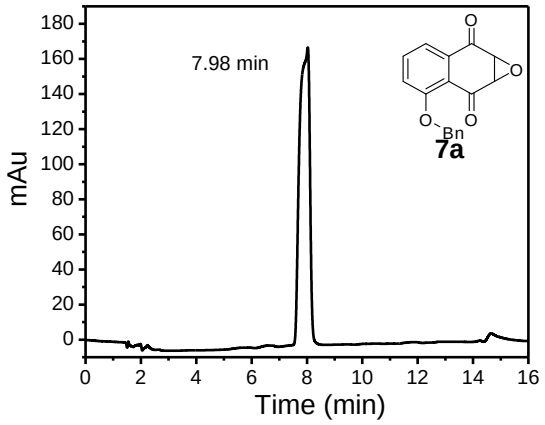


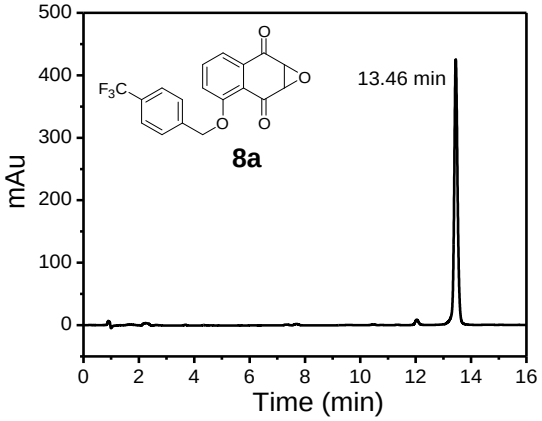


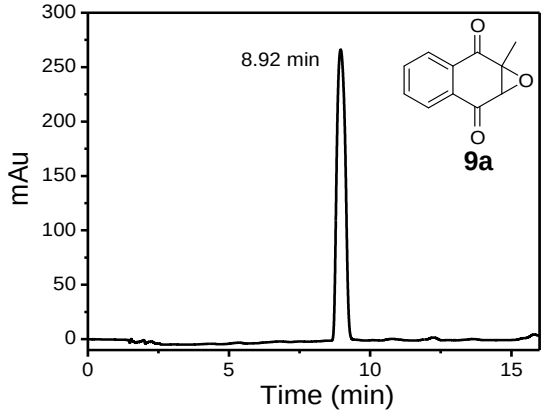


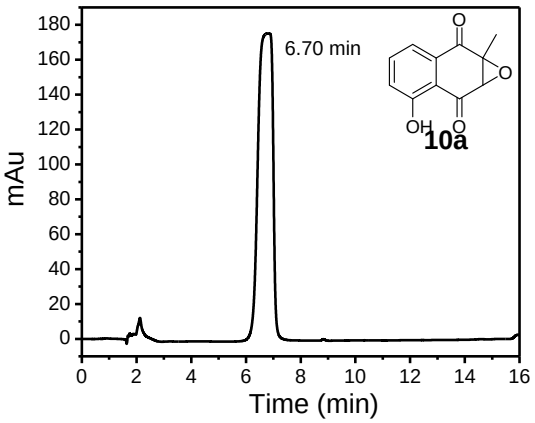





7.98 min
7a
mAu
Time (min)


13.46 min
8a
mAu
Time (min)


8.92 min
9a
mAu
Time (min)


6.70 min
10a
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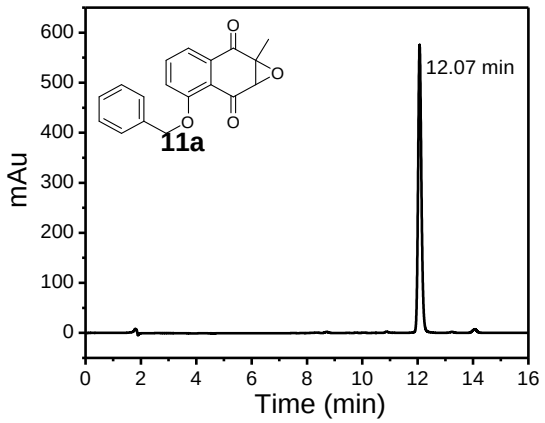
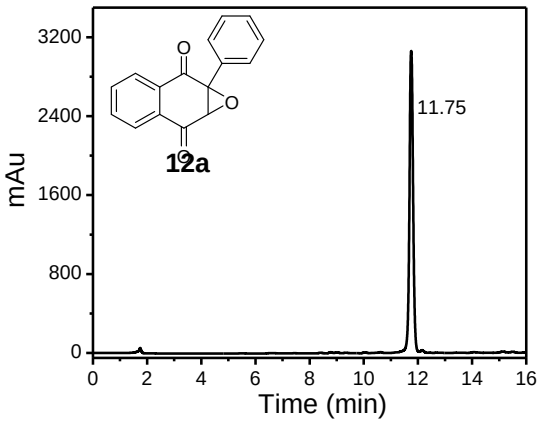
Time (min)


12.07 min
11a
mAu
Time (min)


11.75
12a
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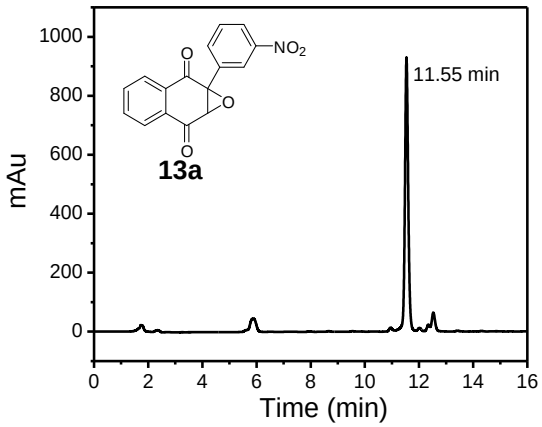
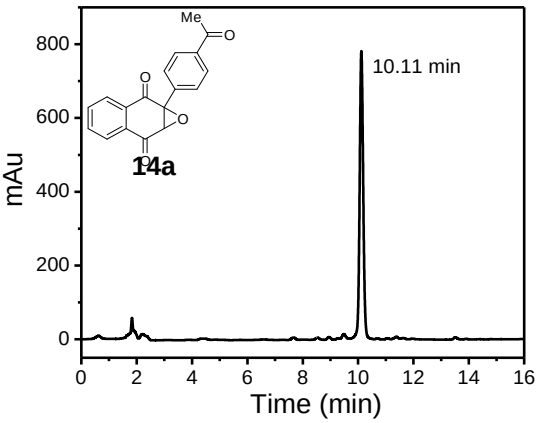
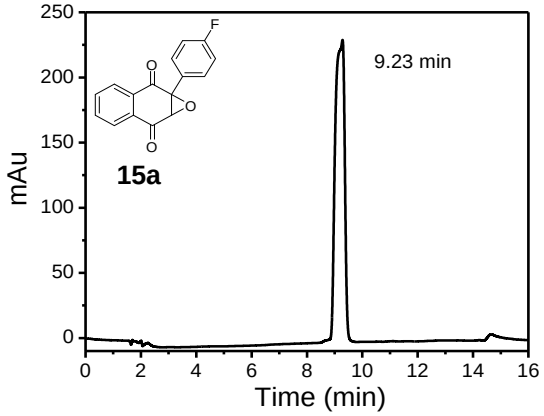
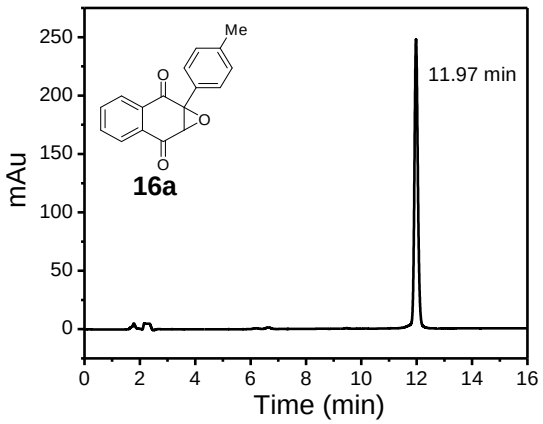
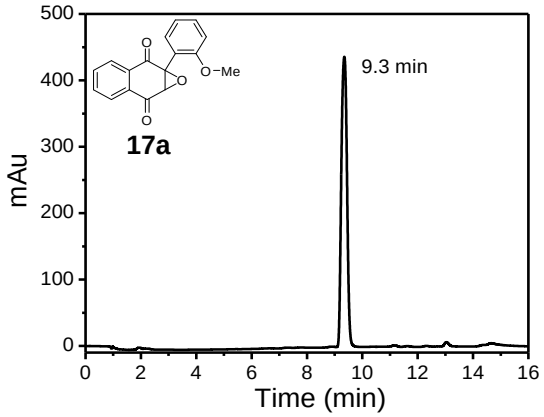
Time (min)

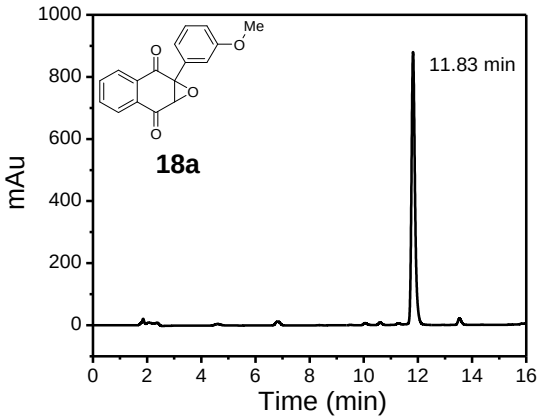

11.55 min
13a
mAu
Time (min)

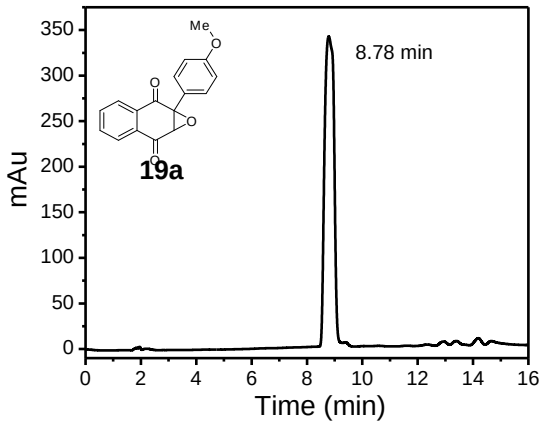

10.11 min
14a
mAu
Time (min)











References

1. N. Maugel and B. B. Snider, *Org. Lett.*, 2009, **11**, 4926-4929.
2. D. W. Cameron, G. I. Feutrill and A. F. Patti, *Aust. J. Chem.*, 1980, **33**, 1805-1816.
3. J. M. Herbert, P. D. Woodgate and W. A. Denny, *Heterocycles* 1987, **26**, 1043-1050.
4. R. L. Betts, S. T. Murphy and C. R. Johnson, *Tetrahedron Asymm.*, 2004, **15**, 2853-2860.
5. M. Yoshizawa, Y. Takeyama, T. Okano and M. Fujita, *J. Am. Chem. Soc.*, 2003, **125**, 3243-3247.
6. J. A. Valderrama, O. Espinoza, M. F. Gonza´lez, R. A. Tapia, J. A. Rodríguez, C. Theodulozb and G. Schmeda-Hirschmann, *Tetrahedron*, 2006, **62**, 2631–2638.
7. M. T. Molina, C. Navarro, A. Moreno and A. G. Csaky, *Org. Lett.*, 2009, **11**, 4938-4941.
8. O. M. Demchuk and K. M. Pietrusiewicz, *Synlett*, 2009, **7**, 1149-1153.
9. A. J. Shand and R. H. Thomson, *Tetrahedron*, 1963, **19**, 1919-1937.
10. J. A. G. Valderrama, M. Florencia; Torres, Cristián, *Heterocycles*, 2003, **60**, 2343-2348.
11. S. Colona, N. Gaggero, A. Manfredil, M. Spadoni, L. Casella, G. Carrea and P. Pasta, *Tetrahedron*, 1988, **44**, 5169-5178.