Organocatalytic enantioselective Michael addition of a kojic acid derivative to nitro olefins

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Supporting Information

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1. General experimental information

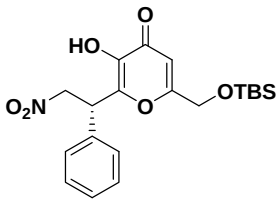
All starting materials were of the highest commercially available grade and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates. Flash chromatography (FC) was performed using silica gel HG/T2354-92. ^{1}H and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). ESI HRMS spectra were recorded on BioTOF Q. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AD and OJ columns were purchased from Daicel Chemical Industries (Hong Kong, China). Chiralpak OD column (Sino-chiral® OD) was purchased from Funsea Technology Inc. (Beijing, China). Optical rotations were measured on a Perkin-Elmer 341 Polarimeter at λ = 589 nm (c g/100 mL). All enantiomeric ratios have been controlled by coinjections of the pure sample with the racemic substrates.

Kojic acid derivative **2**[1] and bifunctional thiourea catalysts **1a-1j**[2] were prepared according to the procedures previously reported.

2. General procedure for the Michael addition of kojic acid derivative 2 to nitro olefins 3a-3o by catalyst 1j.

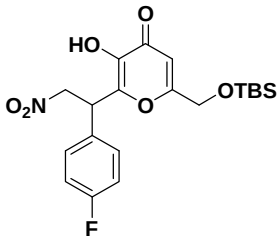
In an ordinary vial equipped with a magnetic stirring bar, to the mixture of kojic acid derivative **2** (0.15 mmol) and **1j** (0.01 mmol) in 3.0 mL of methanol was added nitro olefin **3** (0.1 mmol). The reaction mixture was stirred at -10 ℃ for 4d and was directly loaded onto silica gel and purified by flashchromatography to give the desired product.

3. Characterization data and HPLC conditions of compounds 4a-o, 4o' and 7.



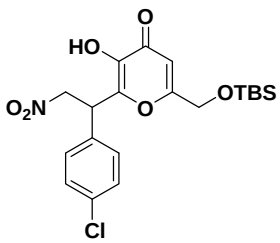
(*R*)-6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(2-nitro-1-phenylethyl)-4H-pyran-4-one (4a):

Brown solid; m.p. 159-160 °C; Yield: 95%; 91%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH/MeOH = 400 : 90 : 10, 1 mL · min^{-1}, λ = 254 nm, tr (major) = 6.95 min, tr (minor) = 10.31 min]; [α]$_D^{20}$= +66.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.30 (m, 5H), 6.60 (brs, 1H), 6.50 (s, 1H), 5.20 (dd, J_1 = 13.1 Hz, J_2 = 9.2 Hz, 1H), 5.09-5.03 (m, 1H), 4.90 (dd, J_1 = 13.2 Hz, J_2 = 6.4 Hz, 1H), 4.48 (s, 2H), 0.92 (s, 9H), 0.11 (S, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 167.6, 145.7, 141.9, 135.3, 129.3, 128.5, 127.7, 108.4, 75.32, 61.4, 43.3, 29.7, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{28}NO_6Si$ $(M+H)^+$: 406.1680; Found: 406.1687.



6-((tert-butyldimethylsilyloxy)methyl)-2-(1-(4-fluorophenyl)-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4b)

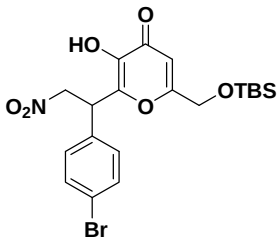
Brown solid; m.p. 154-155 °C; Yield: 85%; 92%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH/MeOH = 400 : 90 : 10, 1 mL · min^{-1}, λ = 254 nm, tr (major) = 7.28 min, tr (minor) = 10.21 min]; [α]$_D^{20}$= +52.7 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 2H), 7.07-7.02 (m, 2H), 6.75 (brs, 1H), 6.50 (s, 1H), 5.15 (dd, J_1 = 12.5 Hz, J_2 = 8.6 Hz, 1H), 5.07-5.02 (m, 1H), 4.89 (dd, J_1 = 13.0 Hz, J_2 = 6.7 Hz, 1H), 4.47 (s, 2H), 0.92 (s, 9H), 0.11 (S, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 167.6, 164.3, 161.0, 145.3, 141.8, 131.2, 131.2, 129.6, 129.5, 116.5, 116.2, 108.5, 75.4, 61.4, 42.8, 29.7, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{26}FNO_6SiNa$ $(M+Na)^+$: 446.1406; Found: 446.1372.



6-((tert-butyldimethylsilyloxy)methyl)-2-(1-(4-chlorophenyl)-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4c)

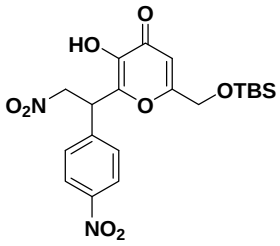
Brown solid; m.p. 74-75 °C; Yield: 86%; 93%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH/ MeOH = 400 : 90 : 10, 1 mL · min^{-1}, λ = 254 nm, tr (major) = 7.28 min, tr (minor) = 10.21 min]; [α]$_D^{20}$= +66.7 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.30 (m, 4H), 6.75 (brs, 1H), 6.50 (s, 1H), 5.15 (dd, J_1 = 12.7 Hz, J_2 = 8.3 Hz, 1H), 5.06-5.01 (m, 1H), 4.89 (dd, J_1 =

12.9 Hz, J_2 = 6.8 Hz, 1H), 4.47 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 167.7, 145.1, 141.9, 134.7, 133.8, 129.6, 129.2, 108.5, 75.2, 61.4, 42.8, 29.7, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{27}ClNO_6Si$ $(M+H)^+$: 440.1291; Found: 440.1289.



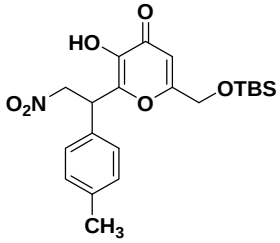
2-(1-(4-bromophenyl)-2-nitroethyl)-6-((tert-butyldimethylsilyloxy) methyl)-3-hydroxy-4H-pyran-4-one (4d)

Brown solid; m.p. 137-138 °C; Yield: 83%; 94%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/ EtOH/MeOH = 400 : 90 : 10, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 9.87 min, tr (minor) = 11.74 min]; $[\alpha]_D^{20}$= +107.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.90 (brs, 1H), 6.50 (s, 1H), 5.15 (dd, J_1 = 12.6 Hz, J_2 = 8.4 Hz, 1H), 5.06-5.02 (m, 1H), 4.90 (dd, J_1 = 12.7 Hz, J_2 = 6.6 Hz, 1H), 4.47 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.86, 167.64, 145.28, 141.97, 134.30, 132.47, 129.43, 122.71, 122.71, 108.58, 75.01, 61.33, 42.75, 29.65, 25.63, -5.52. HRMS (ESI) Calcd. for $C_{20}H_{27}BrNO_6Si$ $(M+H)^+$: 484.0786; Found: 484.0799.



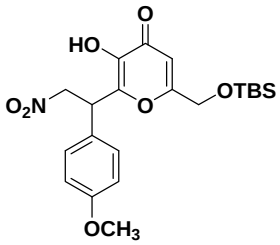
6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(2-nitro-1-(4-nitrophenyl)ethyl)-4H-pyran-4-one (4e)

Brown solid; m.p. 77-78 °C; Yield: 84%; 90%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/ EtOH/MeOH = 400 : 90 : 10, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 21.29 min, tr (minor) = 29.40 min]; $[\alpha]_D^{20}$= +107.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 6.70 (brs, 1H), 6.52 (s, 1H), 5.23-5.15 (m, 2H), 5.03-4.94 (m, 1H), 4.48 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 167.9, 148.0, 144.0, 142.4, 142.2, 128.9, 124.5, 108.7, 74.7, 61.4, 43.0, 29.7, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{27}N_2O_8Si$ $(M+H)^+$: 451.1531; Found: 451.1530.



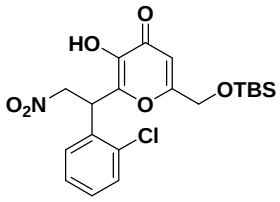
6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(2-nitro-1-p-tolylethyl)-4H-pyran-4-one (4f)

Brown solid; m.p. 123-124 °C; Yield: 77%; 87%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH/MeOH = 400 : 90 : 10, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 5.65 min, tr (minor) = 6.71 min]; $[\alpha]_D^{20}$= +107.6 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.91 (brs, 1H), 6.50 (s, 1H), 5.17 (dd, J_1 = 12.7 Hz, J_2 = 9.1 Hz, 1H), 5.07-5.02 (m, 1H), 4.88 (dd, J_1 = 12.9 Hz, J_2 = 6.4 Hz, 1H), 4.48 (s, 2H), 2.32 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 167.5, 146.1, 141.9, 138.4, 132.3, 130.0, 127.6, 108.4, 75.4, 61.4, 42.9, 25.6, 21.0, -5.5. HRMS (ESI) Calcd. for $C_{21}H_{30}NO_6Si$ $(M+H)^+$: 420.1837; Found: 420.1839.



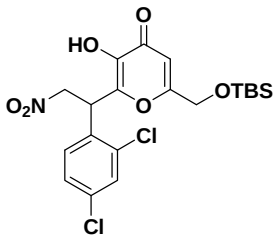
6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(1-(4-methoxyphenyl)-2-nitroethyl)-4H-pyran-4-one (4g)

Brown solid; m.p. 142-143 °C; Yield: 80%; 88%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH/MeOH = 400 : 90 : 10, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 8.64 min, tr (minor) = 11.30 min]; $[\alpha]_D^{20}$= +112.9 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (brs, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 1H), 5.14 (dd, J_1 = 12.8 Hz, J_2 = 8.8 Hz, 1H), 5.04-4.99 (m, 1H), 4.86 (dd, J_1 = 12.9 Hz, J_2 = 6.6 Hz, 1H), 4.48 (s, 2H), 3.78 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.5, 159.6, 146.1, 141.7, 128.9, 127.2, 114.7, 108.4, 75.6, 61.4, 55.3, 42.6, 29.7, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{21}H_{30}NO_7Si$ $(M+H)^+$: 436.1786; Found:436.1783.



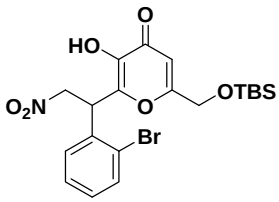
6-((tert-butyldimethylsilyloxy)methyl)-2-(1-(2-chlorophenyl)-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4h)

Brown solid; m.p. 71-72 °C; Yield: 99%; 81%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH = 80:20, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 6.53 min, tr (minor) = 10.14 min]; $[\alpha]_D^{20}$= +69.9 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 1H), 7.32-7.25 (m, 3H), 6.70 (brs, 1H), 6.53 (s, 1H), 5.56 (dd, J_1 = 10.0 Hz, J_2 = 5.7 Hz, 1H), 5.20 (dd, J_1 = 14.2 Hz, J_2 = 10.1 Hz, 1H), 4.84 (dd, J_1 = 14.2 Hz, J_2 = 5.8 Hz, 1H), 4.53-4.41 (m, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 167.9, 144.7, 142.7, 132.8, 130.4, 129.8, 129.0, 127.7, 108.4, 73.7, 61.4, 40.7, 29.7, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{27}ClNO_6Si$ $(M+H)^+$: 440.1291; Found: .440.1282.



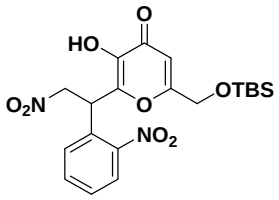
6-((tert-butyldimethylsilyloxy)methyl)-2-(1-(2,4-dichlorophenyl)-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4i)

Brown solid; m.p. 51-52 ^{o}C; Yield: 92%; 83%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH = 80:20, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 6.66 min, tr (minor) = 9.50 min]; $[\alpha]_D^{20}$= +53.8 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.28-7.22 (m, 2H), 6.80 (brs, 1H), 6.53 (s, 1H), 5.50 (dd, J_1 = 9.6 Hz, J_2 = 6.2 Hz, 1H), 5.21-5.13 (m, 1H), 4.83 (dd, J_1 = 14.1 Hz, J_2 = 6.2 Hz, 1H), 4.52-4.40 (m, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 167.9, 144.3, 142.7, 135.2, 134.6, 131.4, 130.2, 129.8, 128.0, 108.6, 73.5, 61.3, 40.2, 29.7, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{26}Cl_2NO_6Si$ $(M+H)^+$: 474.0901; Found: 473.0909.



2-(1-(2-bromophenyl)-2-nitroethyl)-6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-4H-pyran-4-one (4j)

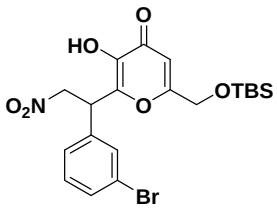
Brown solid; m.p. 59-60 ^{o}C; Yield: 87%; 84%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH = 80:20, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 6.72 min, tr (minor) = 10.72 min]; $[\alpha]_D^{20}$= +99.7 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.8 Hz, 1H), 7.30-7.26 (m, 2H), 7.20-7.17 (m, 1H), 6.80 (brs, 1H), 6.54 (s, 1H), 5.55 (dd, J_1 = 10.1 Hz, J_2 = 5.7 Hz, 1H), 5.22-5.14 (m, 1H), 4.83 (dd, J_1 = 14.2 Hz, J_2 = 5.6 Hz, 1H), 4.53-4.41 (m, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.8, 144.9, 142.7, 134.5, 133.8, 130.0, 129.0, 128.3, 124.2, 108.5, 73.8, 61.3, 43.3, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{26}BrNO_6SiNa$ $(M+Na)^+$: 506.0605; Found: 506.0601.



6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(2-nitro-1-(2-nitrophenyl)ethyl)-4H-pyran-4-one (4k)

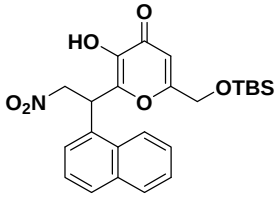
Brown solid; m.p. 64-65 ^{o}C; Yield: 80%; 86%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH = 80:20, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 10.96 min, tr (minor) = 14.48 min]; $[\alpha]_D^{20}$= +120.7 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.9 Hz, 1H), 7.79-7.59 (m, 1H), 7.54-7.49 (m, 2H),

6.75 (brs, 1H), 6.52 (s, 1H), 5.64 (dd, J_1 = 9.7 Hz, J_2 = 5.6 Hz, 1H), 5.35-5.26 (m, 1H), 5.03 (dd, J_1 = 14.5 Hz, J_2 = 5.6 Hz, 1H), 4.53-4.34 (m, 2H), 0.93 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 168.0, 149.2, 144.6, 142.6, 137.0, 133.8, 130.1, 129.6, 125.5, 108.5, 73.9, 61.4, 39.6, 29.7, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{27}N_2O_8Si$ $(M+H)^+$: 451.1531; Found: 451.1530.



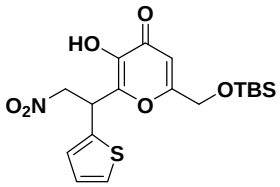
2-(1-(3-bromophenyl)-2-nitroethyl)-6-((tert-butyldimethylsilyloxy) methyl)-3-hydroxy-4H-pyran-4-one (4l)

Brown solid; m.p. 152-153 °C; Yield: 89%; 87%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/EtOH = 80:20, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 11.09 min, tr (minor) = 13.57 min]; [α]$_D^{20}$= + 7.5 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.48-7.47 (m, 1H), 7.31-7.20 (m, 2H), 6.75 (brs, 1H), 6.51 (s, 1H), 5.16 (dd, J_1 = 12.9 Hz, J_2 = 8.5 Hz, 1H), 5.07-5.02 (m, 1H), 4.90 (dd, J_1 = 13.0 Hz, J_2 = 6.6 Hz, 1H), 4.48 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.6, 145.2, 142.2, 137.4, 131.7, 130.8, 126.4, 123.2, 108.7, 75.0, 61.3, 42.8, 29.6, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{20}H_{27}BrNO_6Si$ $(M+H)^+$: 484.0786; Found: 484.0794.



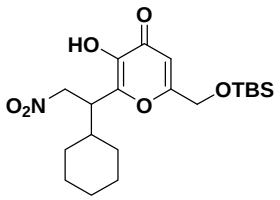
6-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-2-(1-(naphthalen-1-yl)-2-nitroethyl)-4H-pyran-4-one (4m)

Brown solid; m.p. 55-56 °C; Yield: 86%; 91%ee as determined by HPLC [Daicel Chirapak OD-H, *n*-hexane/*i*-propanol = 85:15, 1 mL·min^{-1}, λ = 220 nm, tr (major) = 14.25 min, tr (minor) = 29.07 min]; [α]$_D^{20}$= +49.1 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.4 Hz, 1H), 7.91-7.83 (m, 2H), 7.63-7.52 (m, 2H), 7.45-7.43 (m, 2H), 6.90 (brs, 1H), 6.51 (s, 1H), 6.00-5.95 (m, 1H), 5.32 (dd, J_1 = 13.6 Hz, J_2 = 9.8 Hz, 1H), 4.99 (dd, J_1 = 13.6 Hz, J_2 = 6.7 Hz, 1H), 4.44 (s, 2H), 0.91 (s, 9H), 0.08 (s, 6H)). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.8, 145.4, 142.3, 134.1, 131.0, 130.9, 129.2, 129.2, 127.4, 126.3, 125.3, 125.0, 122.3, 108.5, 75.0, 61.4, 38.6, 25.7, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{24}H_{30}NO_6Si$ $(M+H)^+$: 456.1837; Found: 456.1847.



6-((tert-butyldimethylsilyloxy)methyl)-2-(1-(thiophen-2-yl)-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4n)

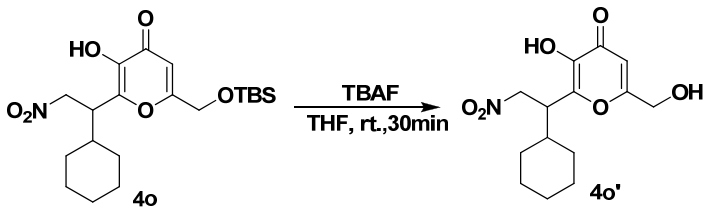
Brown solid; m.p. 128-129 ^{o}C; Yield: 58%; 97%ee as determined by HPLC [Daicel Chirapak OJ-H, *n*-hexane/*i*-propanol = 85:15, 1 mL·min^{-1}, λ = 254 nm, tr (major) = 9.77 min, tr (minor) = 13.60 min]; [α]$_D^{20}$= +80 (*c* =0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 5.8 Hz, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.99-6.96 (m, 1H), 6.52 (s, 1H), 5.43-5.38 (m, 1H), 5.12 (dd, J_1 = 13.4 Hz, J_2 = 8.8 Hz, 1H), 4.90 (dd, J_1 = 13.5 Hz, J_2 = 6.8 Hz, 1H), 4.50 (s, 2H), 0.93 (s, 9H), 0.12 (s, 6H) (The enolic OH of the product is not observed). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 167.8, 145.4, 142.3, 134.1, 131.0, 130.9, 129.2, 129.2, 127.4, 126.3, 125.3, 125.0, 122.3, 108.5, 75.0, 61.4, 38.6, 25.7, 25.6, -5.5. HRMS (ESI) Calcd. for $C_{24}H_{30}NO_6Si$ $(M+H)^+$: 412.1245; Found: 412.1257.



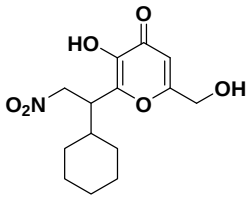
6-((tert-butyldimethylsilyloxy)methyl)-2-(1-cyclohexyl-2-nitroethyl)-3-hydroxy-4H-pyran-4-one (4o)

Brown solid; m.p. 136-137 ^{o}C; Yield: 68%; [α]$_D^{20}$= -130.5 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (brs, 1H), 6.50 (s, 1H), 4.84 (dd, J_1 = 12.9 Hz, J_2 = 10.0 Hz, 1H), 4.68 (dd, J_1 = 13.0 Hz, J_2 = 4.9 Hz, 1H), 4.46 (s, 2H), 3.66-3.64 (m, 1H), 1.79-1.57 (m, 6H), 1.27-1.05 (m, 5H), 0.91 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 167.4, 146.7, 143.0, 108.4, 74.2, 61.4, 43.6, 38.8, 30.8, 30.3, 25.9, 25.9, 25.7, -5.5. HRMS (ESI) Calcd. for $C_{24}H_{30}NO_6Si$ $(M+H)^+$: 412.2150; Found: 412.2151.

Procedure for deprotection of 4o[3]:



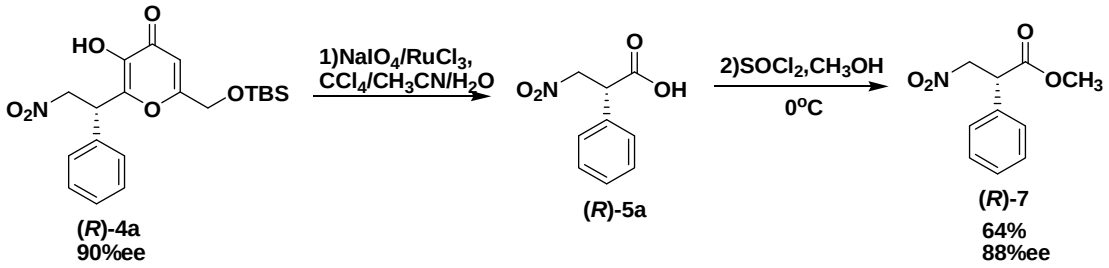
To a solution of **4o** (33.5 mg, 0.08 mmol) in 5 mL of THF was added TBAF (51.4 mg, 0.16 mol) at rt. The reaction mixture was stirred at rt for 30 min and was directly loaded onto silica gel and purified by flashchromatography to give **4o'** in 95%.



2-(1-cyclohexyl-2-nitroethyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran -4-one (4o')

Brown oil; Yield: 95%; 90%ee as determined by HPLC [Daicel Chirapak AD-H, *n*-hexane/*i*-propanol/diethylamine= 90:10:0.1, 1 mL·min^{-1}, λ = 254 nm, tr (minor) = 41.53 min, tr (major) = 44.31 min]; [α]$_D^{20}$= -145 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$/MeOD): δ = 6.44 (s, 1H), 4.92-4.82 (m, 2H), 4.41 (s, 2H), 3.75-3.30 (m, 1H), 1.81-1.62 (m, 6H), 1.29-1.01 (m, 5H) (The two OHs of the product are not observed). ^{13}C NMR (75 MHz, $CDCl_3$/MeOD): δ = 173.8, 167.2, 147.3, 143.2, 108.7, 74.3, 61.1, 52.3, 43.7, 38.9, 31.9, 30.8, 30.4, 25.9, 25.9. HRMS (ESI) Calcd. for $C_{24}H_{30}NO_6Si$ $(M+H)^+$: 298.1285; Found: 298.1296.

4. Procedure for the Oxidative Fragmentation[4] and Determination of the Absolute Configuration of 4a.



To a solution of **4a** (0.11 g, 0.27 mmol, 90%ee) in a mixture of CH_3CN (2 mL) and CCl_4 (2 mL), H_2O (5 mL) and $NaIO_4$ (0.866 g, 4.05 mmol) was added successively. After being stirred at room temperature for 10 min., $RuCl_3{\cdot}3H_2O$ (3.5 mg, 0.014 mmol) was added. The mixture was stirred at room temperature for further 2h, during which a beige suspension had been formed. The mixture was extracted with AcOEt (3 × 8 mL). The combined organic phase was treated with Et_2O (10 mL) which caused a color change from yellow to greenish black and dried over $MgSO_4$. The resulting solution was concentrated in vacuo and the residue was dissolved in 5 mL of AcOEt, and treated with DMSO (54.6 mg, 0.7 mmol) for 16h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography [petroleum ether/ethyl acetate (3/1) and petroleum ether/ethyl acetate (1/1)] to yield the carboxylic acid **5a** as a white solid (39.2 mg, 74%). To a solution of the acid (39.2 mg, 0.2 mmol) in CH_3OH (1 mL) was added a solution of $SOCl_2$ (47.8 mg, 0.4 mmol) in 5 mL of CH_3OH at 0 ℃ and the resulting mixture was stirred at 0 ℃ for 6h. Removal of the solvent and purification of the residue by column chromatography [petroleum ether/ethyl acetate (7/1)] gave compound **7** as a yellow oil (36.5 mg, 87%). The ee value was determined by chiral HPLC on Daicel Chiracel OD-H column (*n*-hexane/*i*-propanol = 90:10, 1.0 mL/min, 235 nm, $t_{R,\,major}$ = 10.6 min, $t_{R,\,minor}$ = 21.8 min), 88%ee; Rf 0.7 (3:1 petroleum ether: ethyl acetate); $[\alpha]^{20}_D$ = +150.1° (c = 2.8, $CHCl_3$, 88%ee), lit[4b]: $[\alpha]^{26}_D$ = -150.6 (*c* = 2.8, $CHCl_3$, 95:5 *er*) or $[\alpha]^{26}_D$ = -134.9 (*c* = 2.8, $CHCl_3$, 91:9 *er*) for product with (*S*) stereochemistry, lit[5]: $[\alpha]^{26}_D$ = -126.2° (*c* = 2.8, $CHCl_3$, 94:6 *er*) for product with (*S*) stereochemistry. ^{1}H NMR (300

MHz, $CDCl_3$): δ = 7.40-7.34 (m, 3H), 7.28-7.25 (m, 2H), 5.11 (dd, J_1 = 14.6 Hz, J_2 = 9.9 Hz, 1H), 4.55 (dd, J_1 = 14.6 Hz, J_2 = 5.2 Hz, 1H), 4.44 (dd, J_1 = 9.9 Hz, J_2 = 5.2 Hz, 1H), 3.73 (s, 3H).

References

1. (*a*) Y. Ma, W. Luo, P. J. Quinn, Z. D. Liu and R. C. Hider, *J. Med. Chem.* 2004, **47**, 6349 ; (*b*) J. Farard, C. Logé, B. Pfeiffer, B. Lesur and M. Duflos, *Tetrahedron Lett.* 2009, **50**, 5729.

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3. E. J. Corey and A. Wenkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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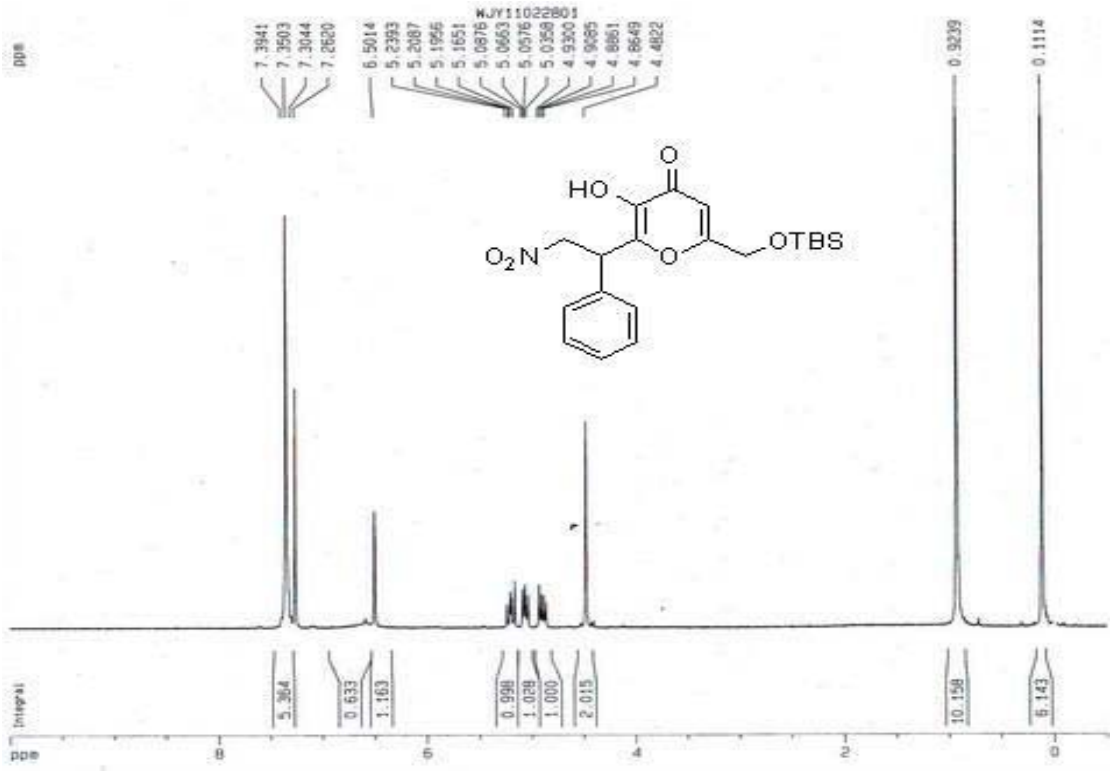
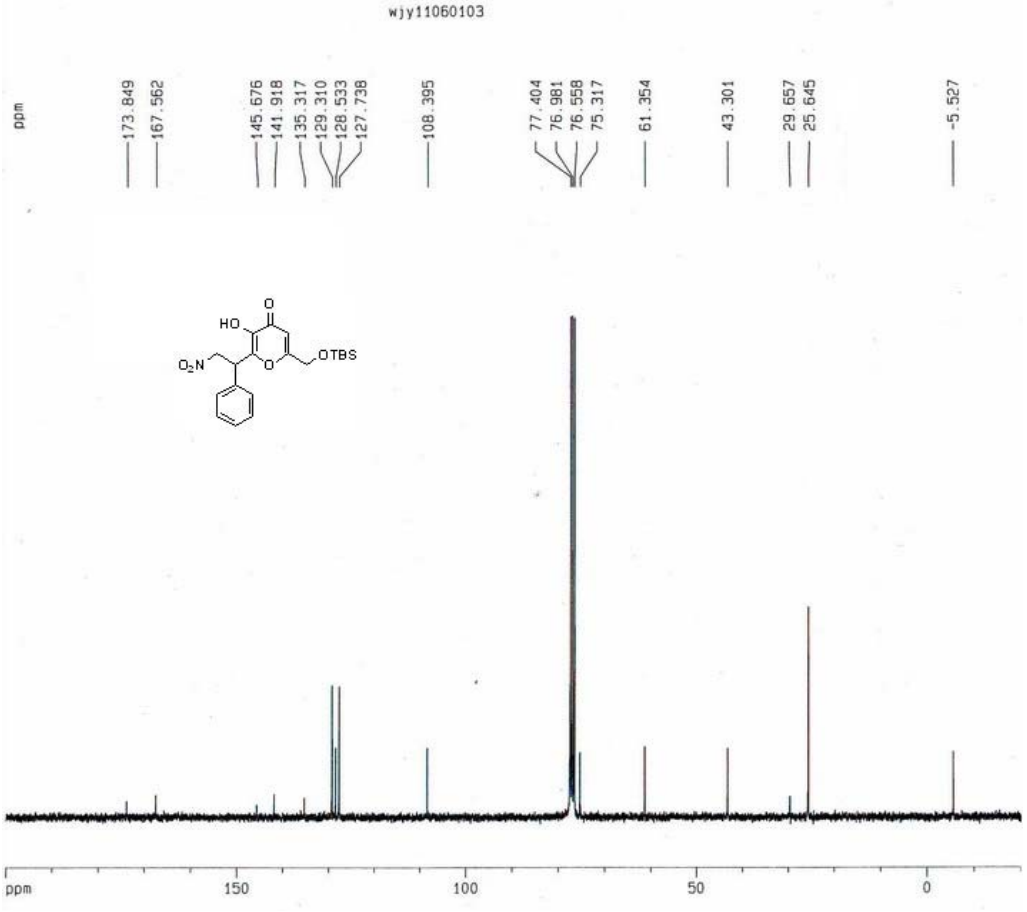
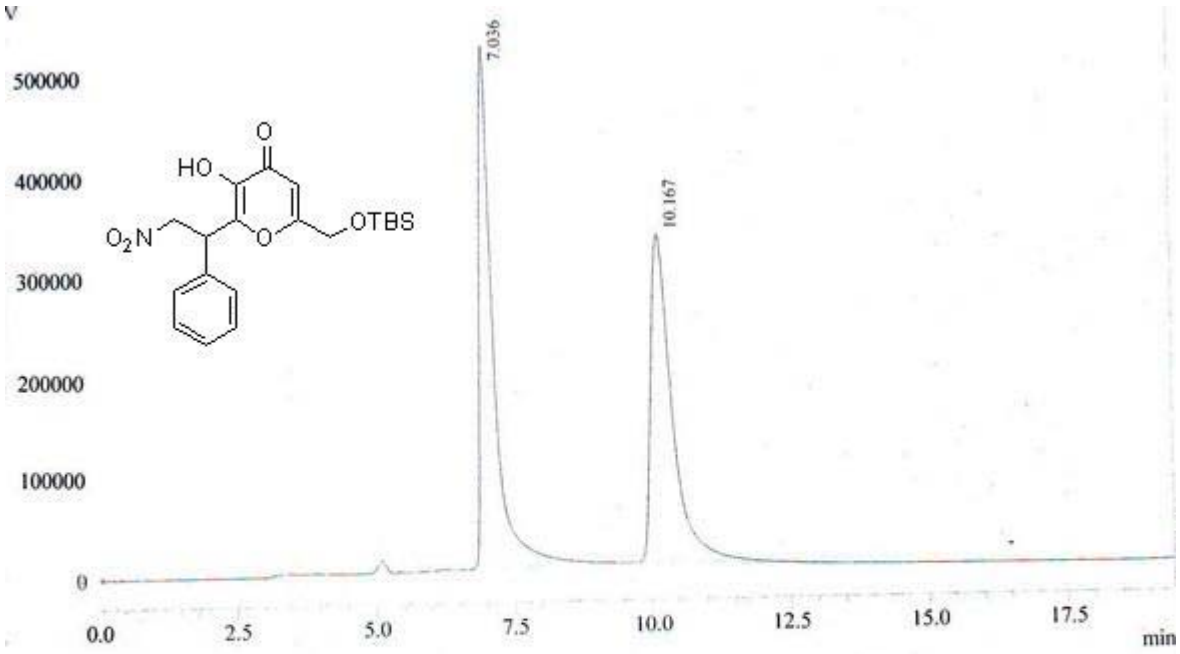
5. The copies of ^{1}H, ^{13}C NMR, and HPLC spectra for compounds 4a-o, 4o' and 7.

^{1}H NMR, ^{13}C NMR and HPLC of **4a**







1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.036	9022957	520093	50.333	61.390
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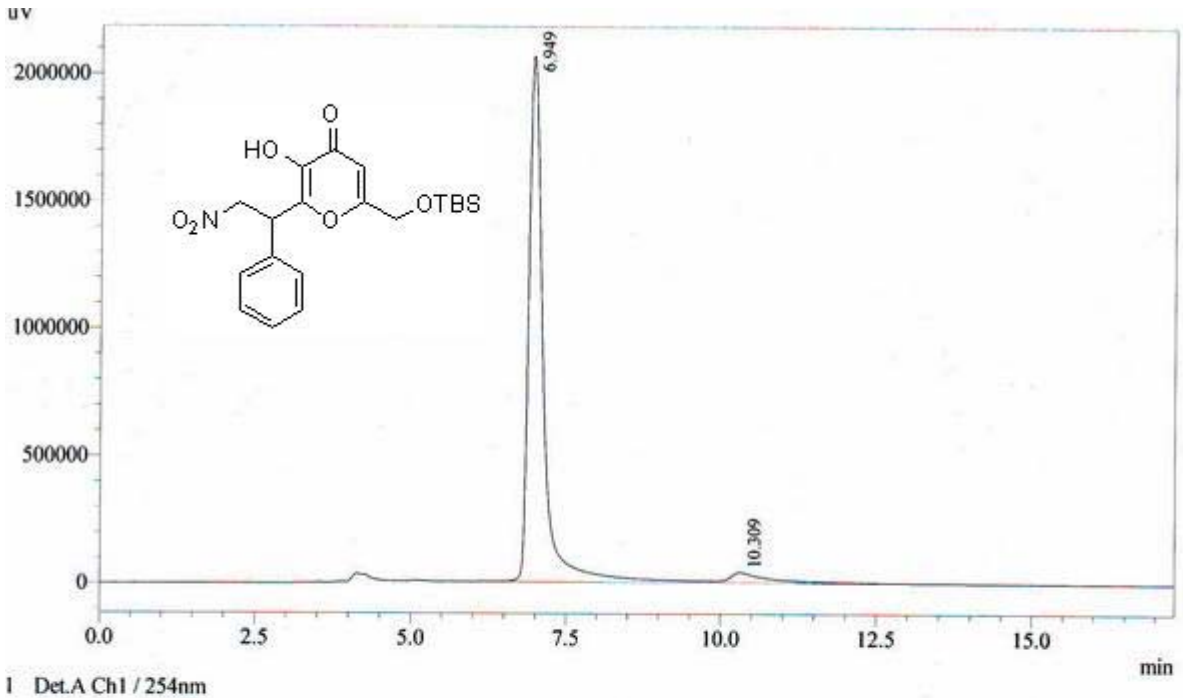
Total		17926592	847191	100.000	100.000

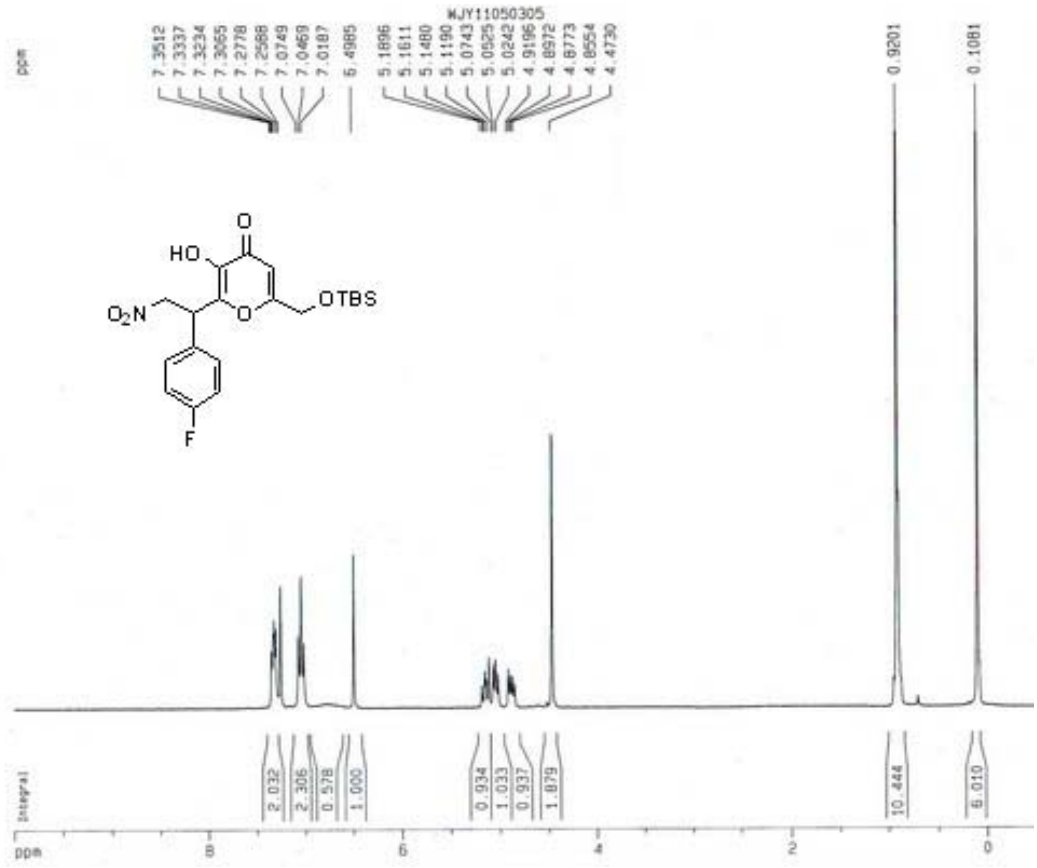


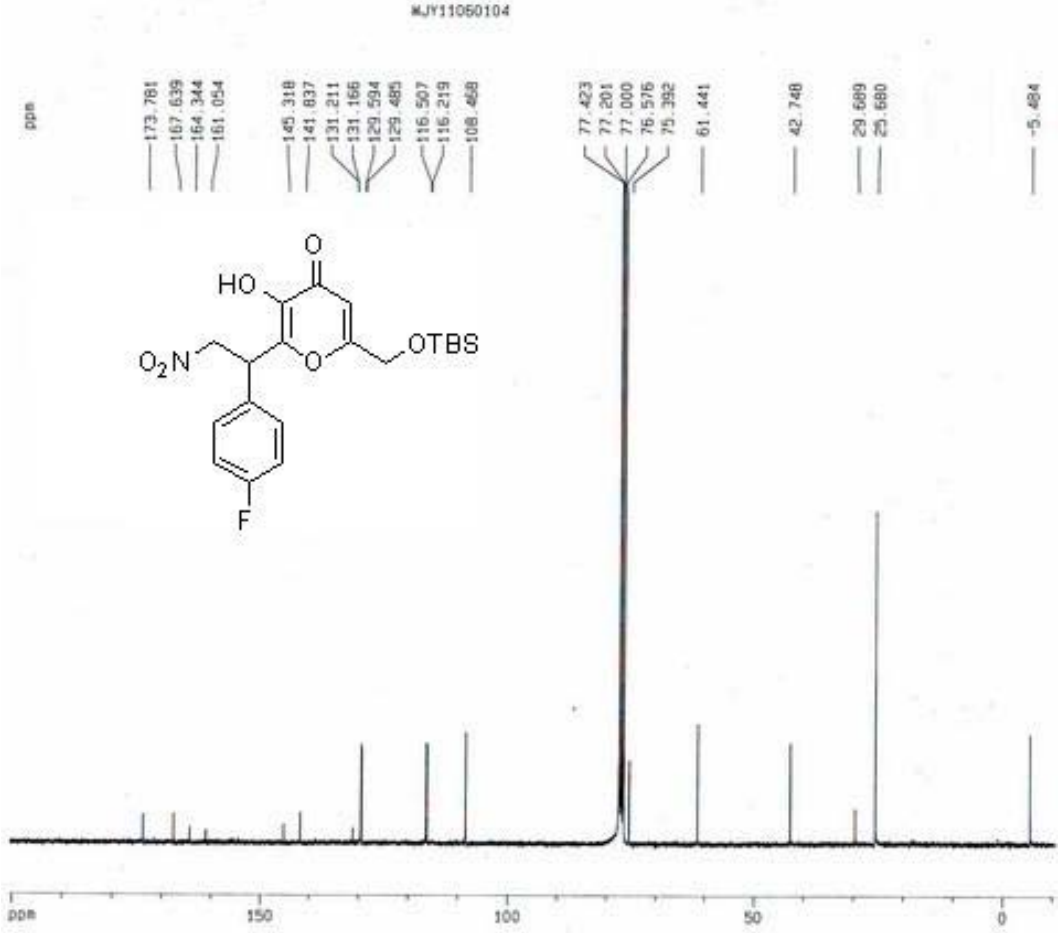
1 Det.A Ch1 / 254nm

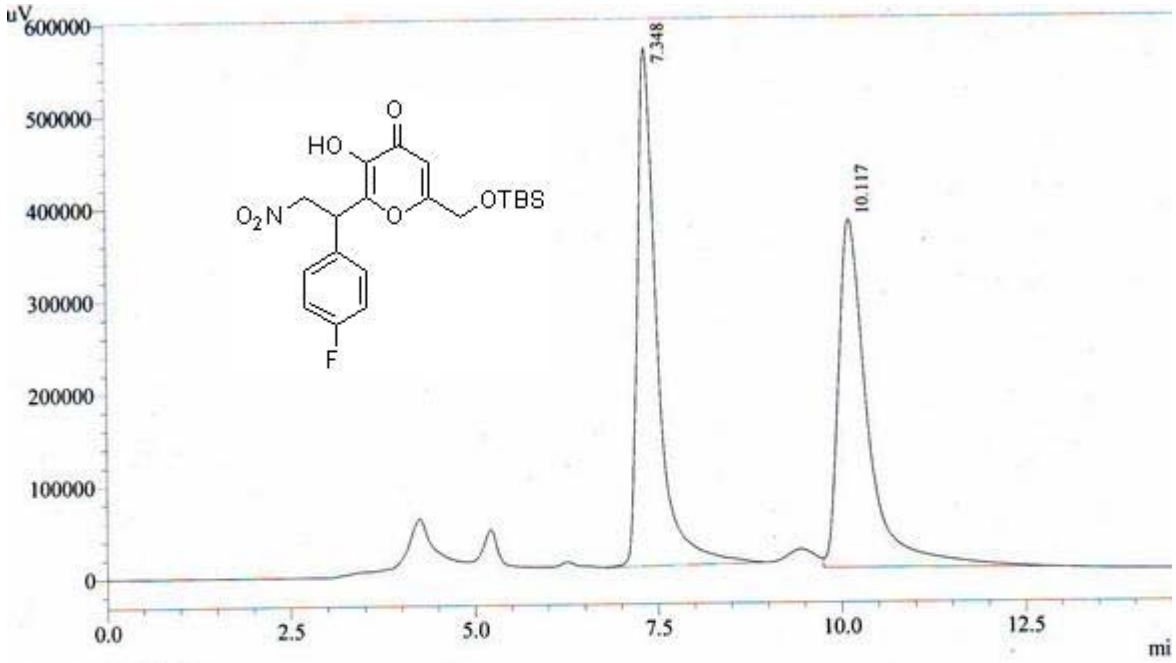
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.949	34106703	2062922	95.211	98.091
2	10.309	1715393	40148	4.789	1.909
Total		35822096	2103070	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4b**



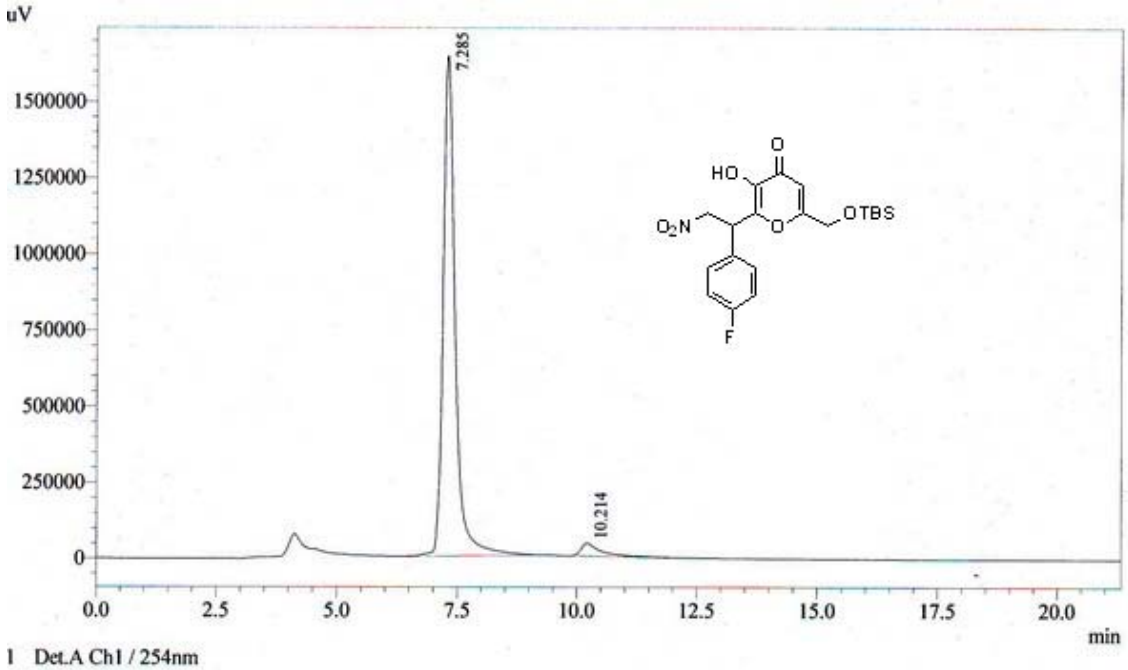




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.348	10453259	560278	50.262	59.812
2	10.117	10344151	376448	49.738	40.188
Total		20797410	936727	100.000	100.000

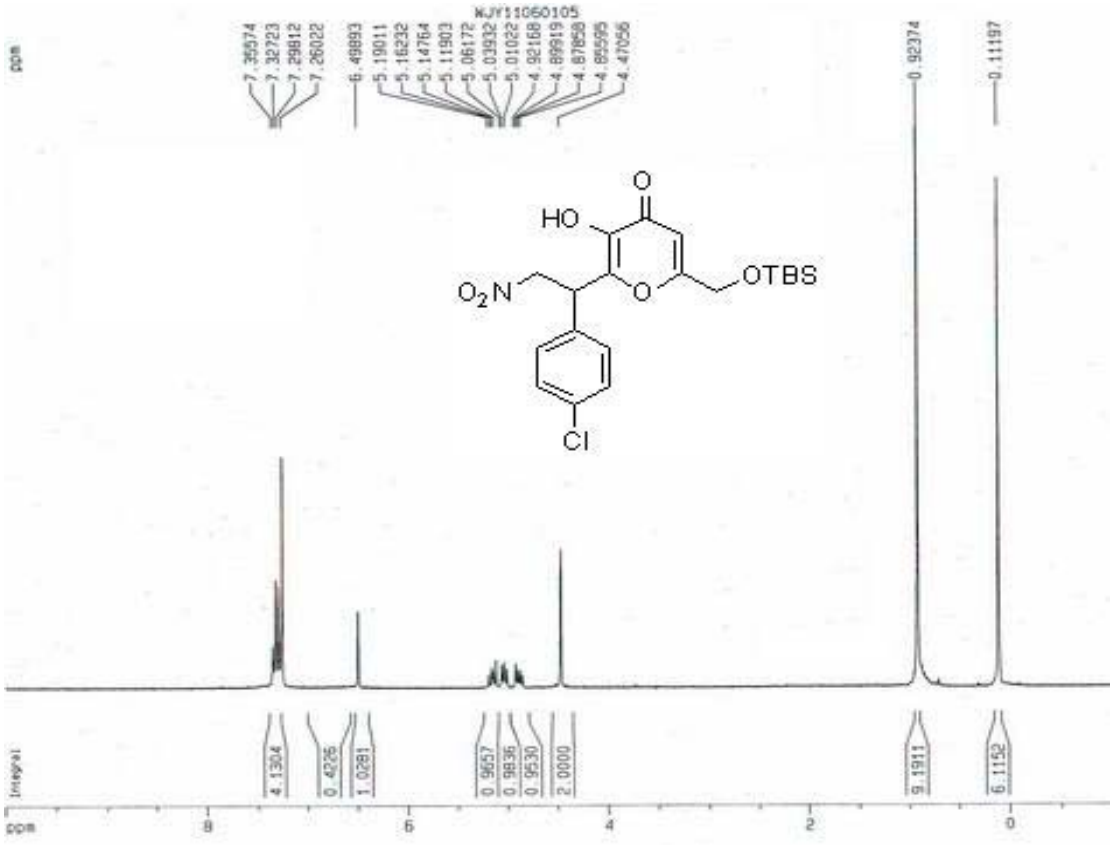


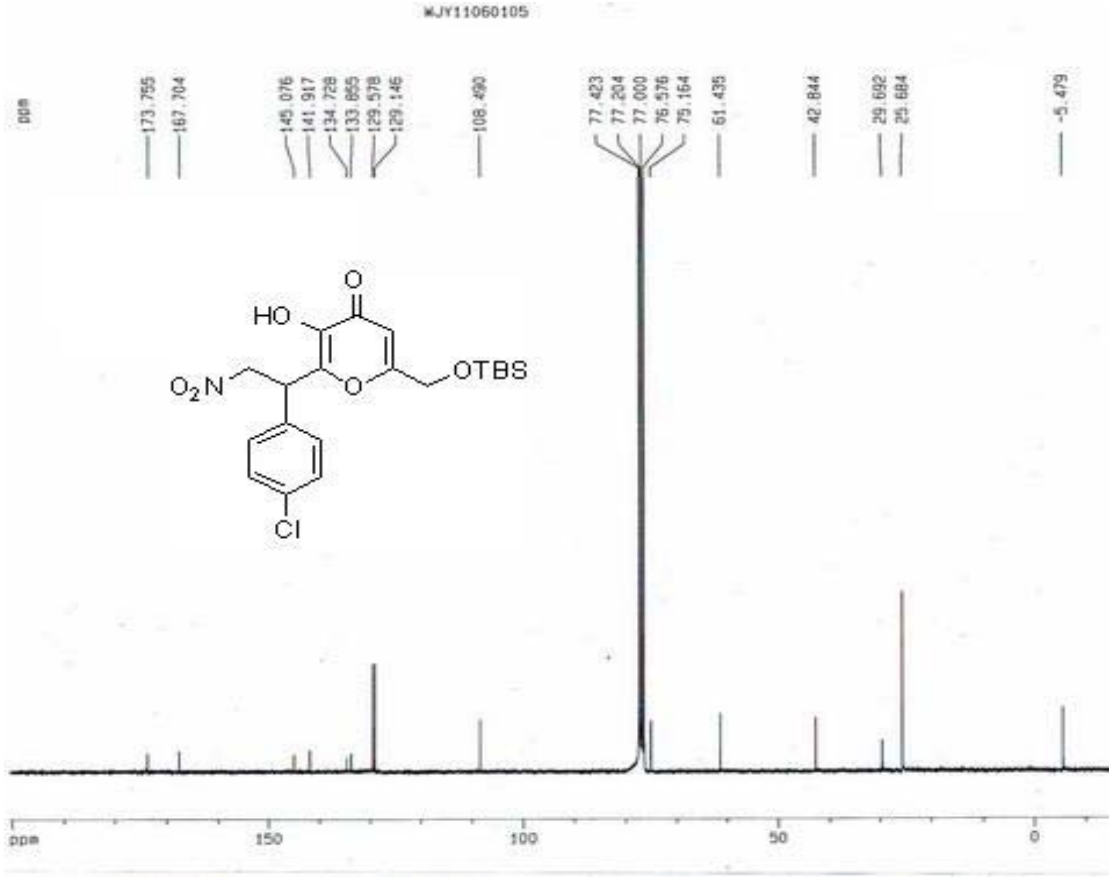
1 Det.A Ch1 / 254nm

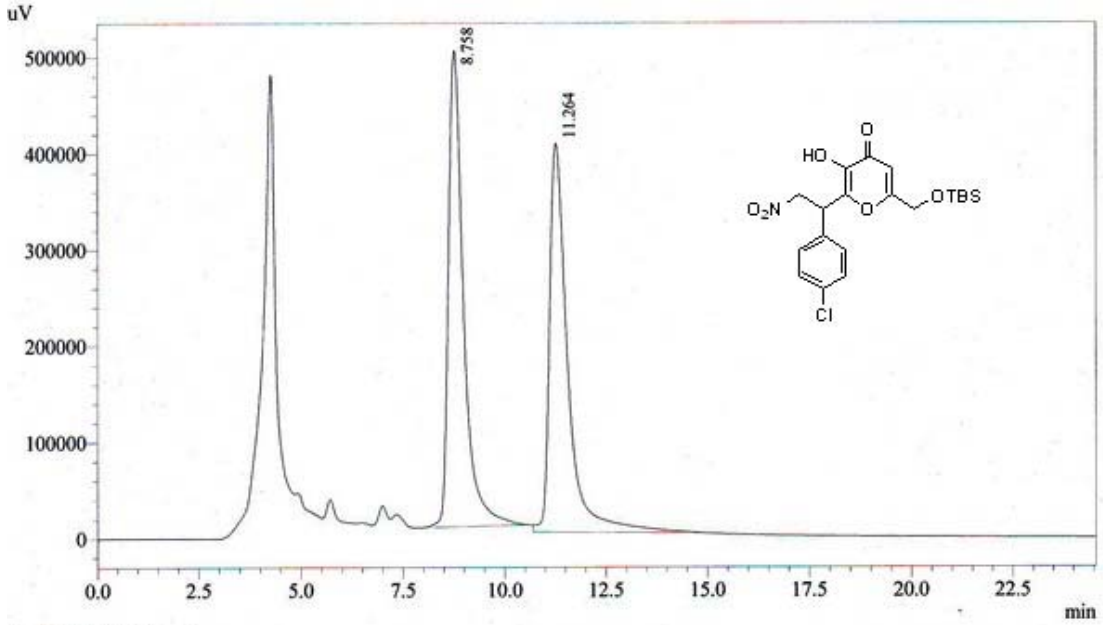
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.285	28689339	1642604	95.933	97.540
2	10.214	1216361	41428	4.067	2.460
Total		29905700	1684032	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4c**



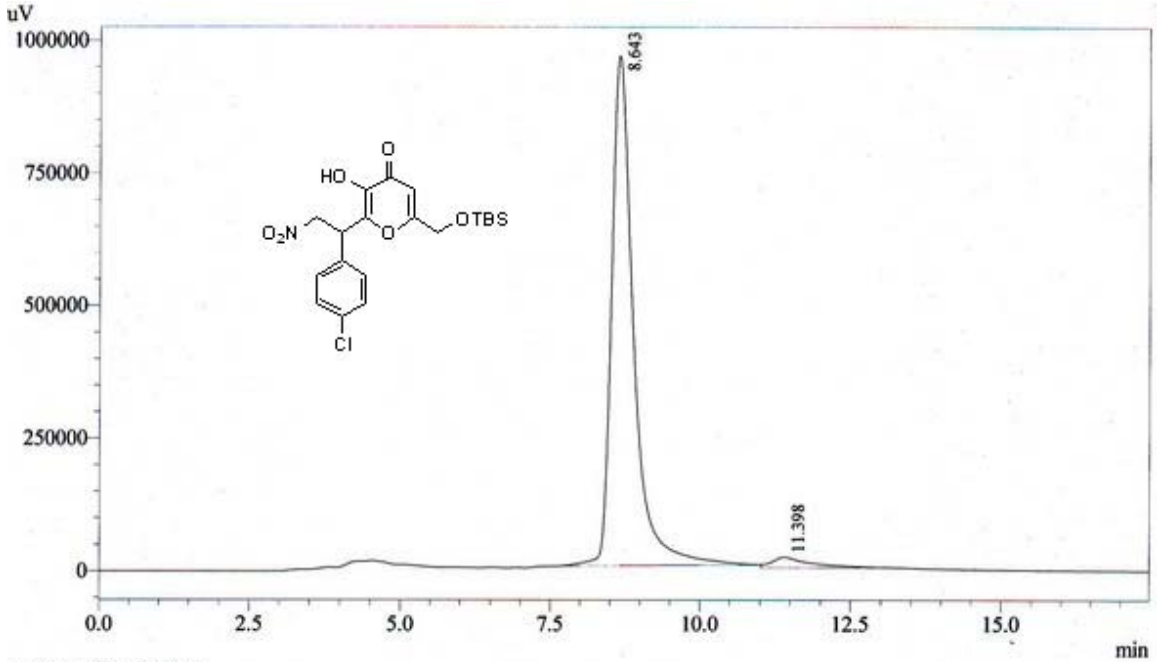




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.758	12792623	494722	50.348	55.028
2	11.264	12615607	404308	49.652	44.972
Total		25408229	899030	100.000	100.000

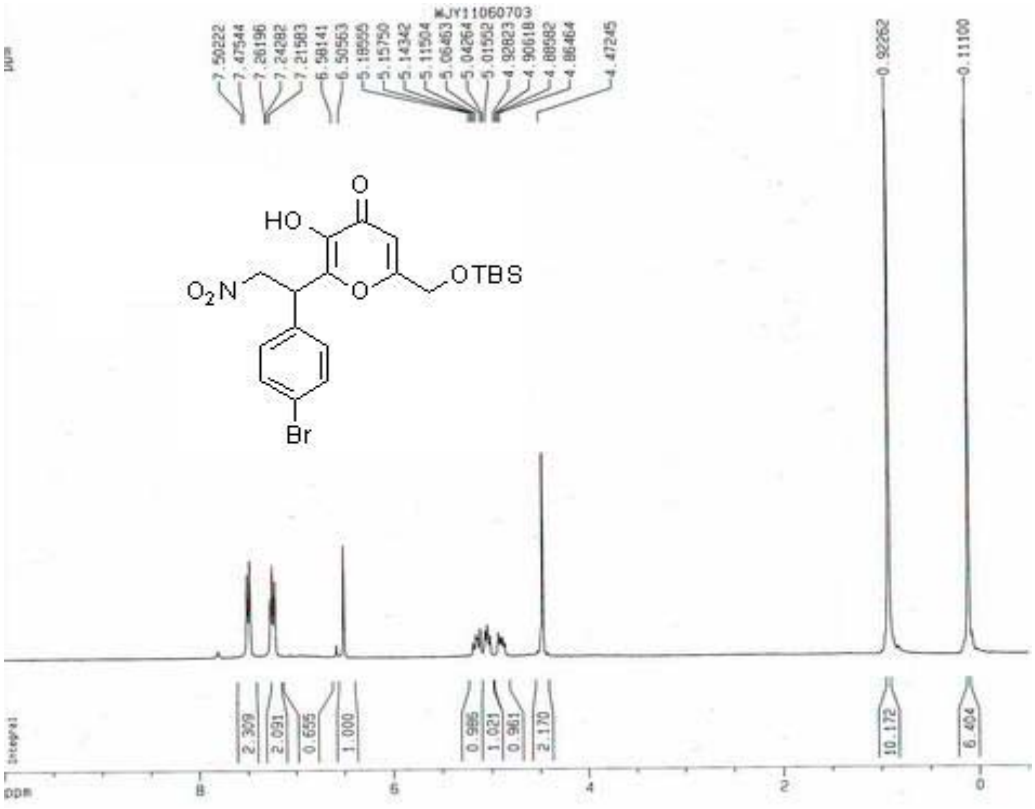


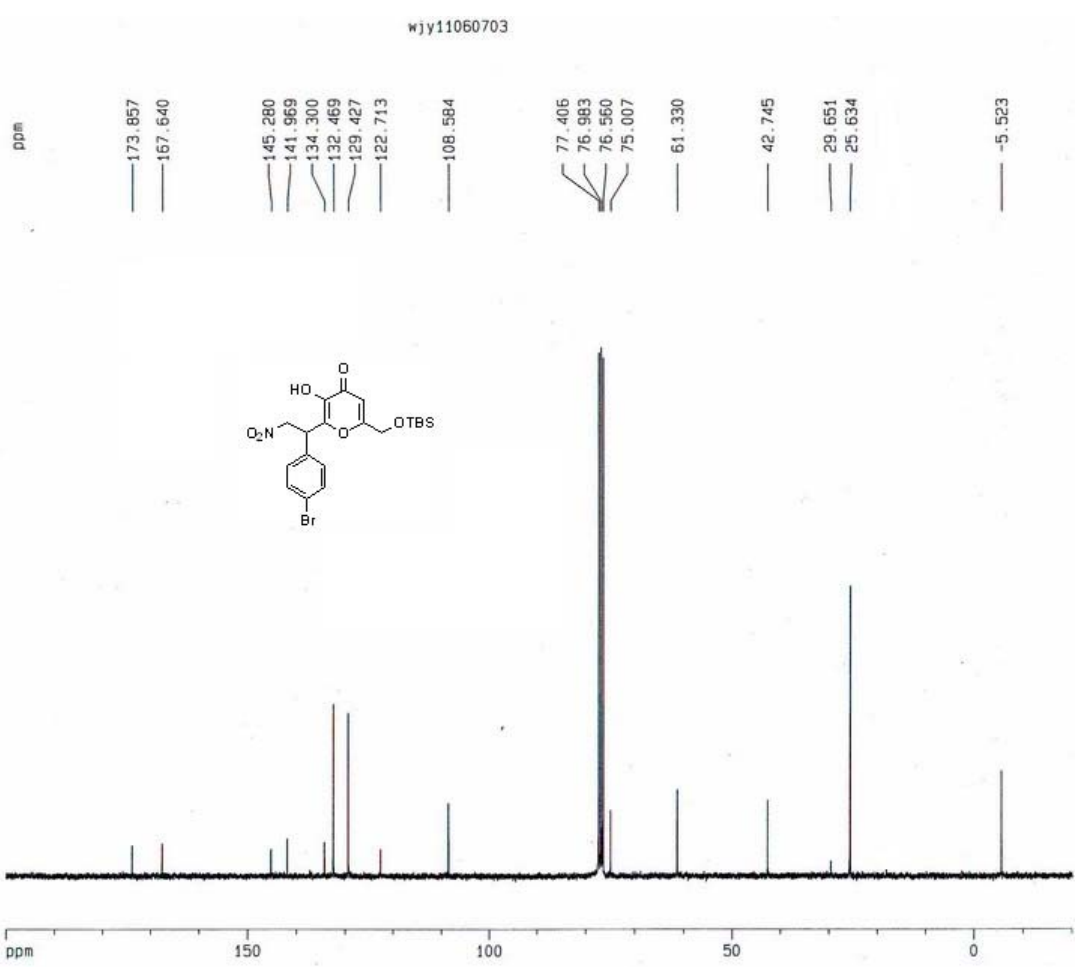
1 Det.A Ch1 / 254nm

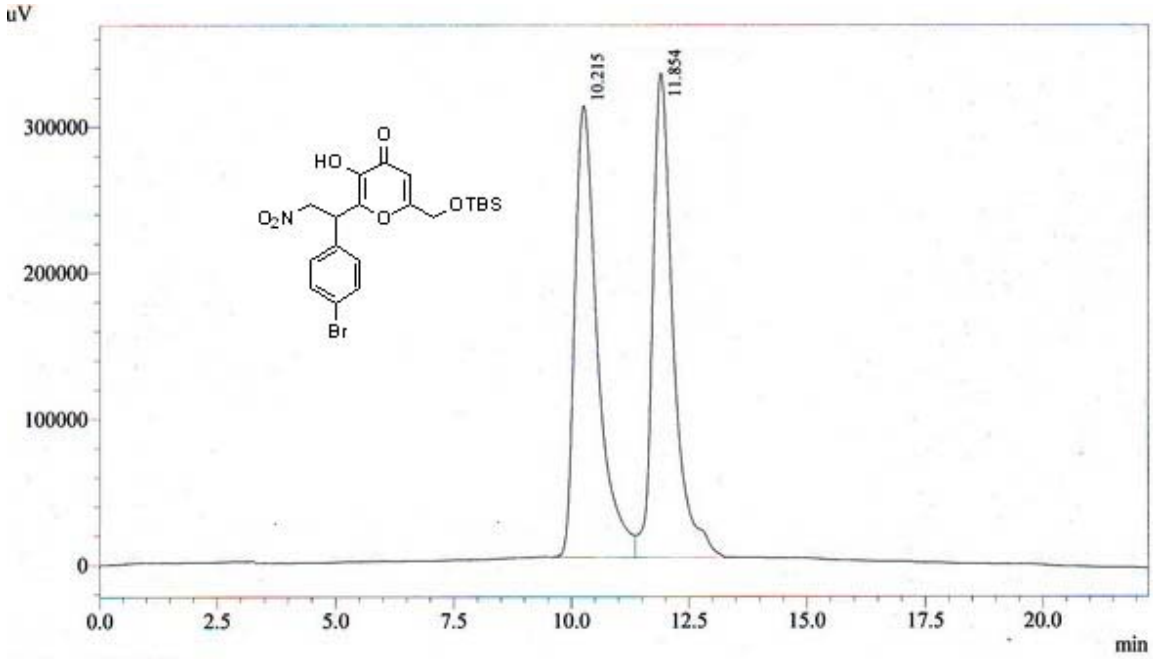
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.643	24518676	960305	96.628	98.018
2	11.398	855587	19420	3.372	1.982
Total		25374263	979725	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4d**



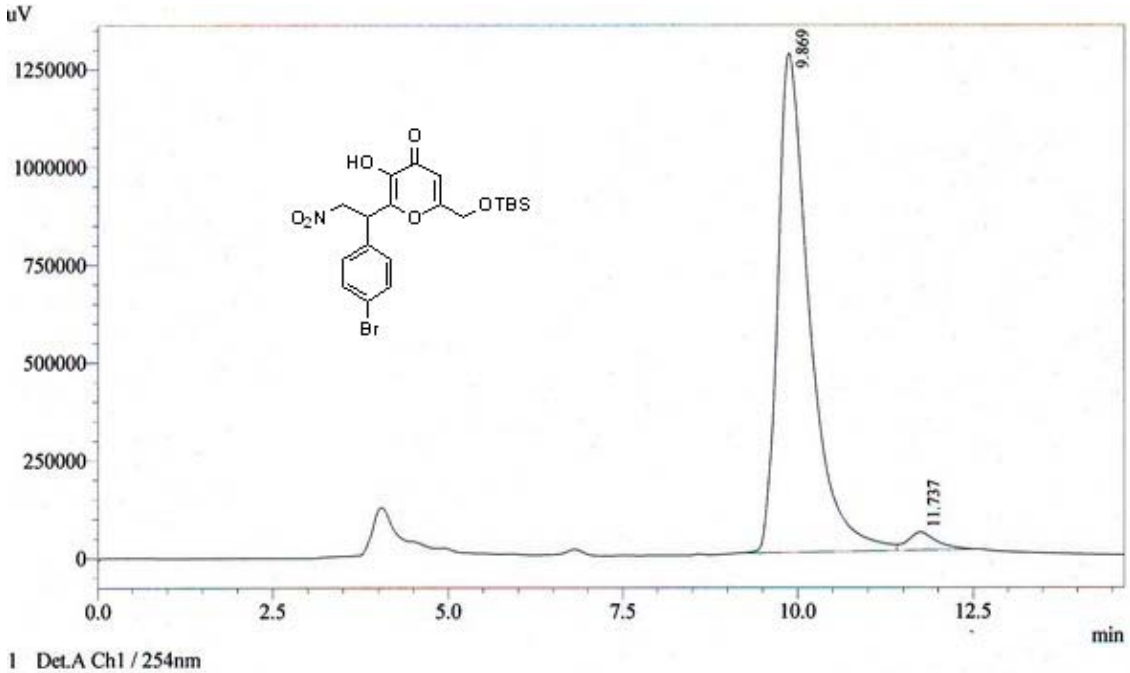




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.215	10445326	308915	50.642	48.212
2	11.854	10180440	331822	49.358	51.788
Total		20625766	640738	100.000	100.000

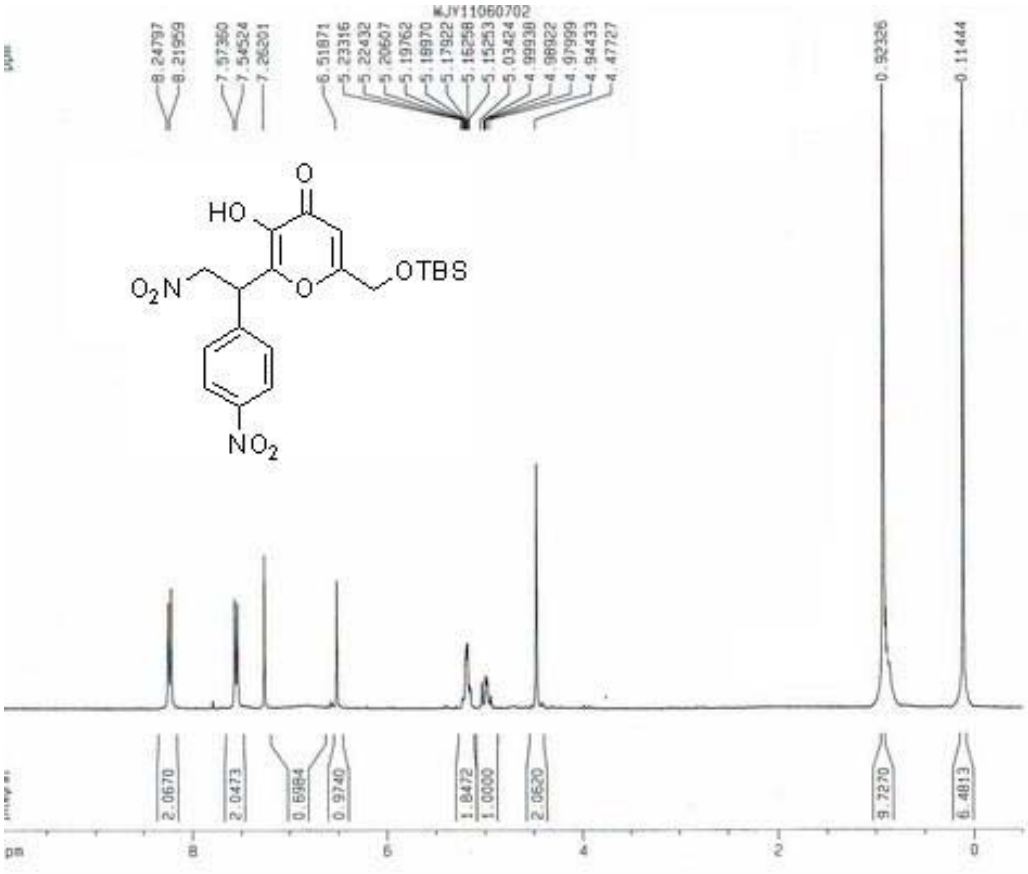


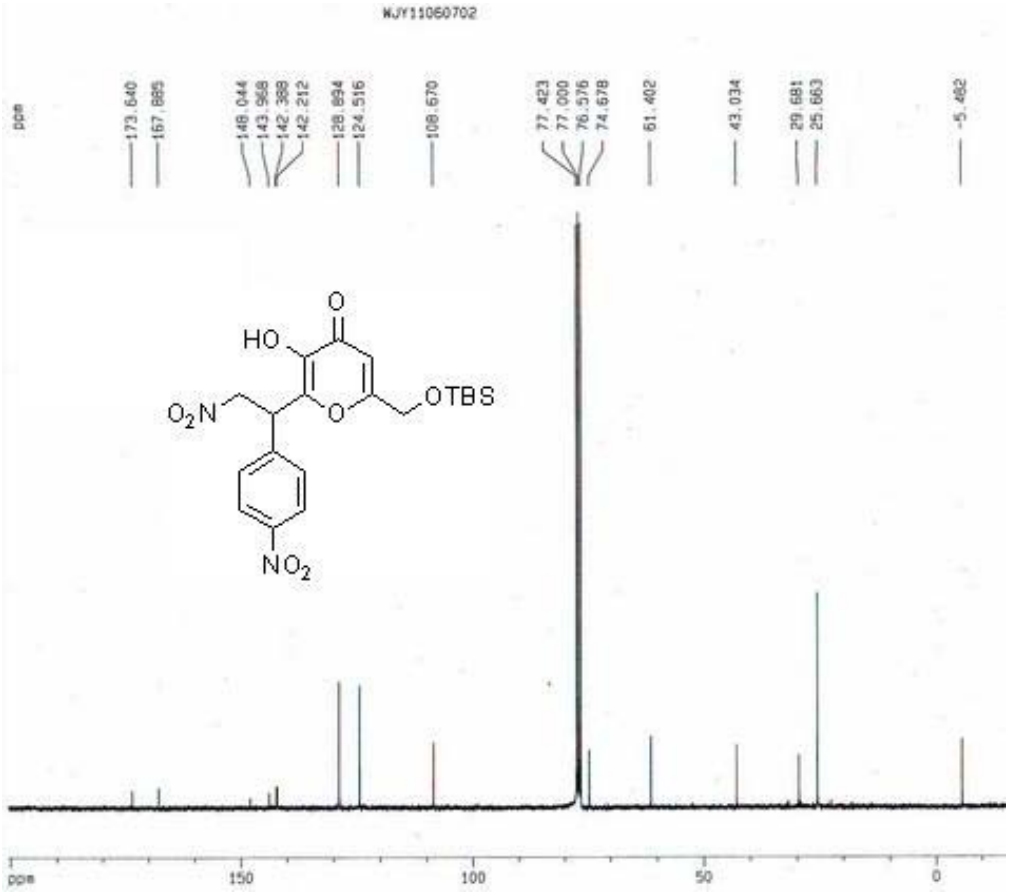
1 Det.A Ch1 / 254nm

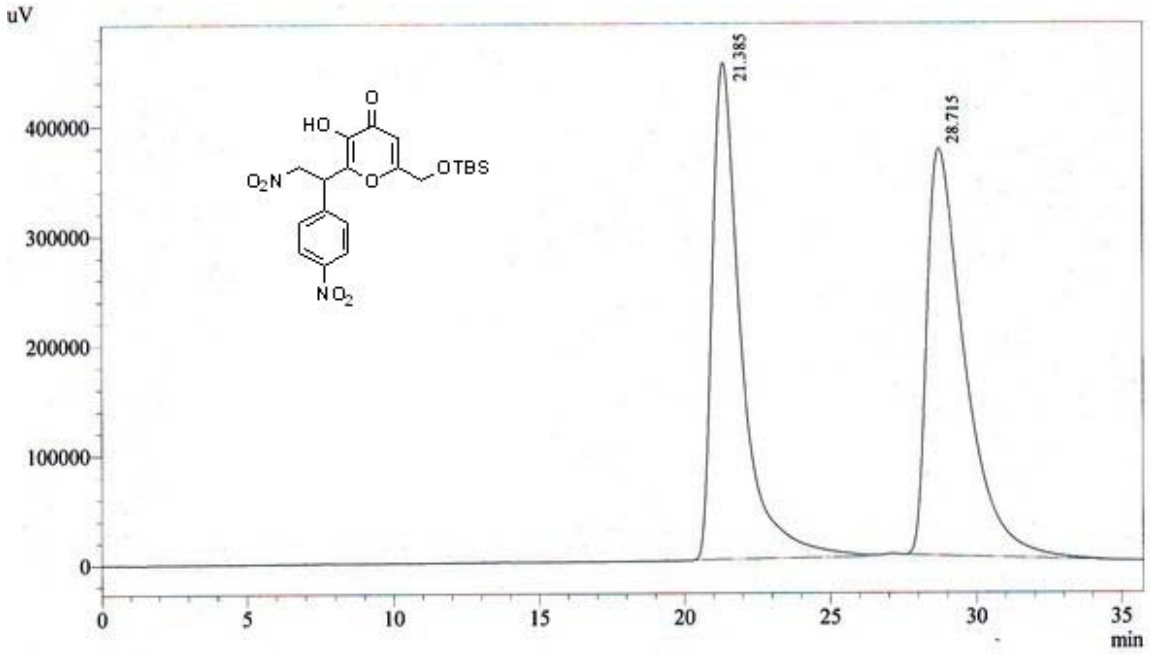
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.869	40423323	1276254	96.801	96.527
2	11.737	1335719	45920	3.199	3.473
Total		41759042	1322174	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4e**







1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.385	35552635	444782	51.424	54.509
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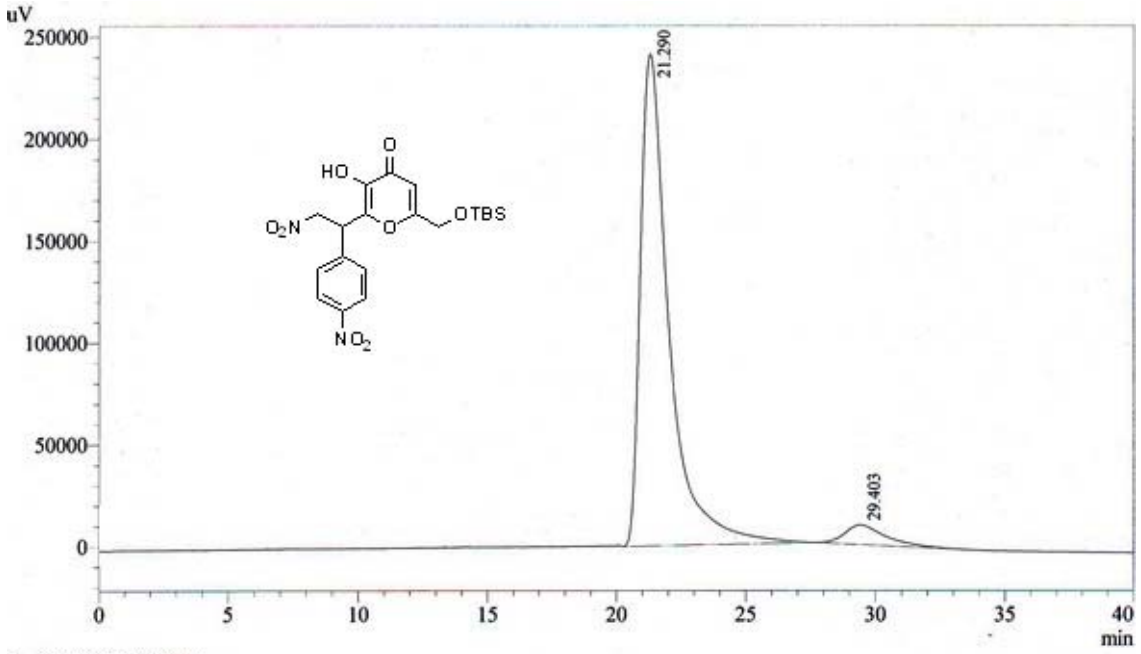
Total		69136773	815983	100.000	100.000



1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	29.403	1036547	9593	5.260	3.827
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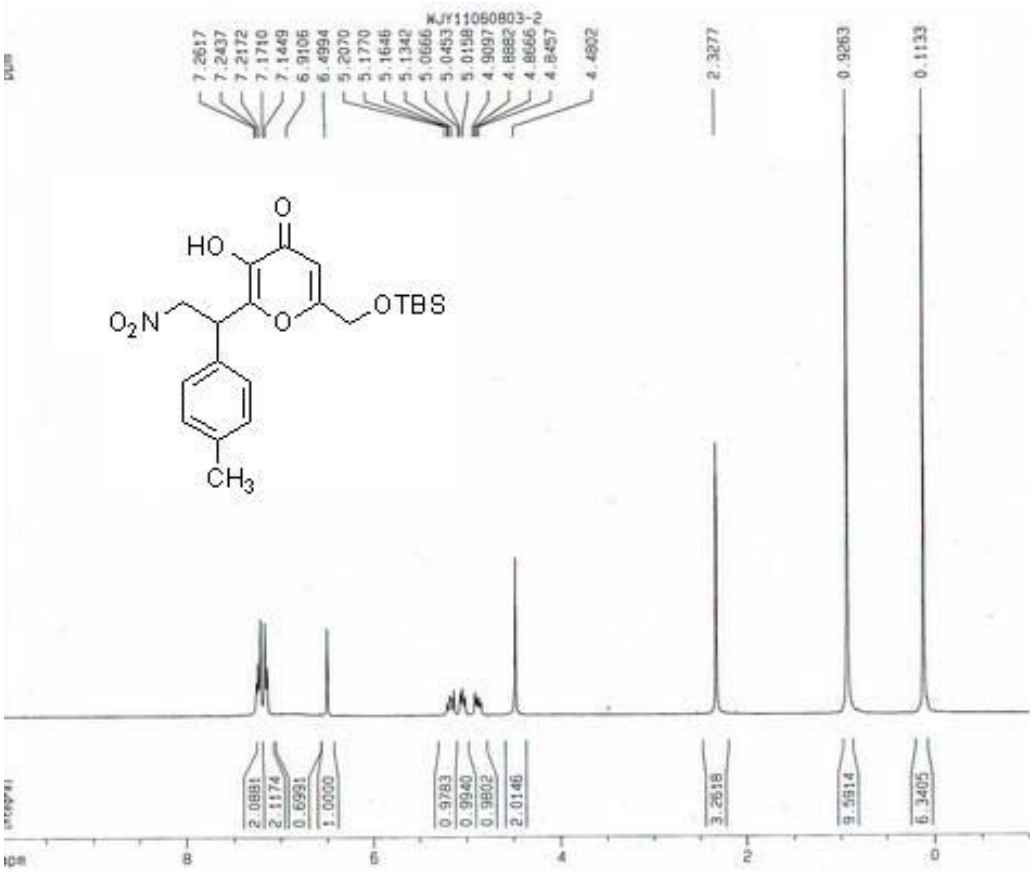
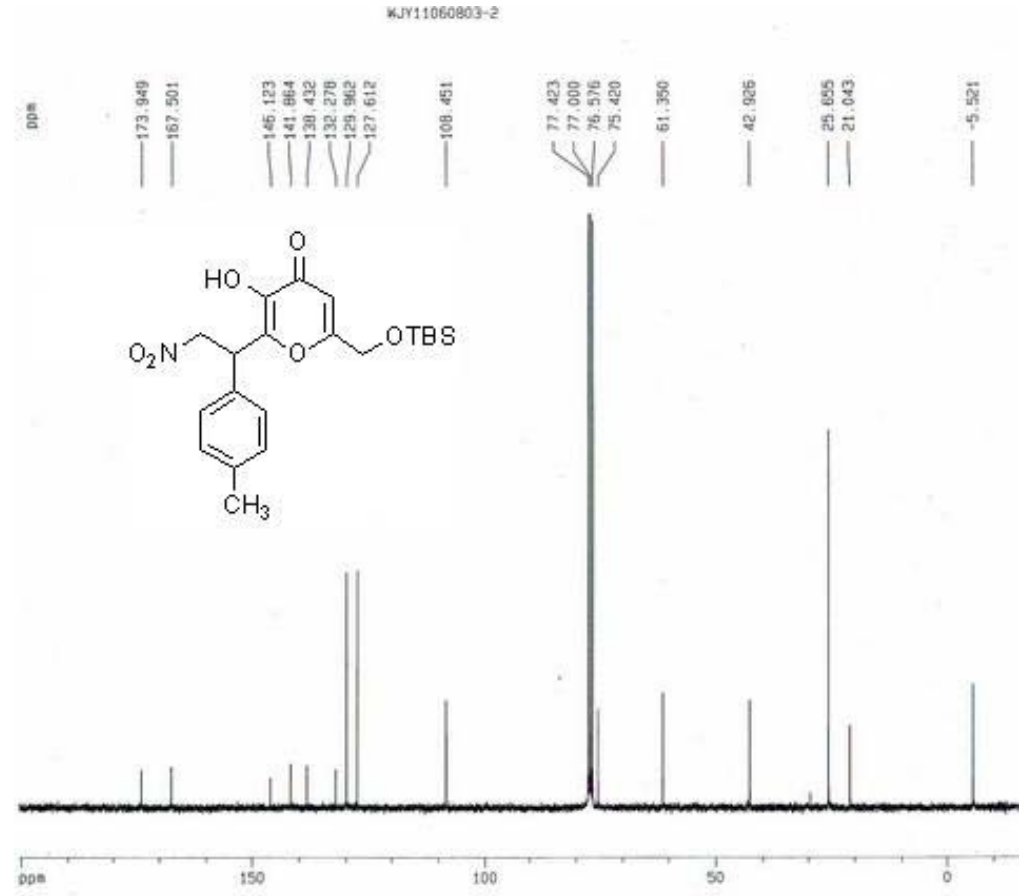
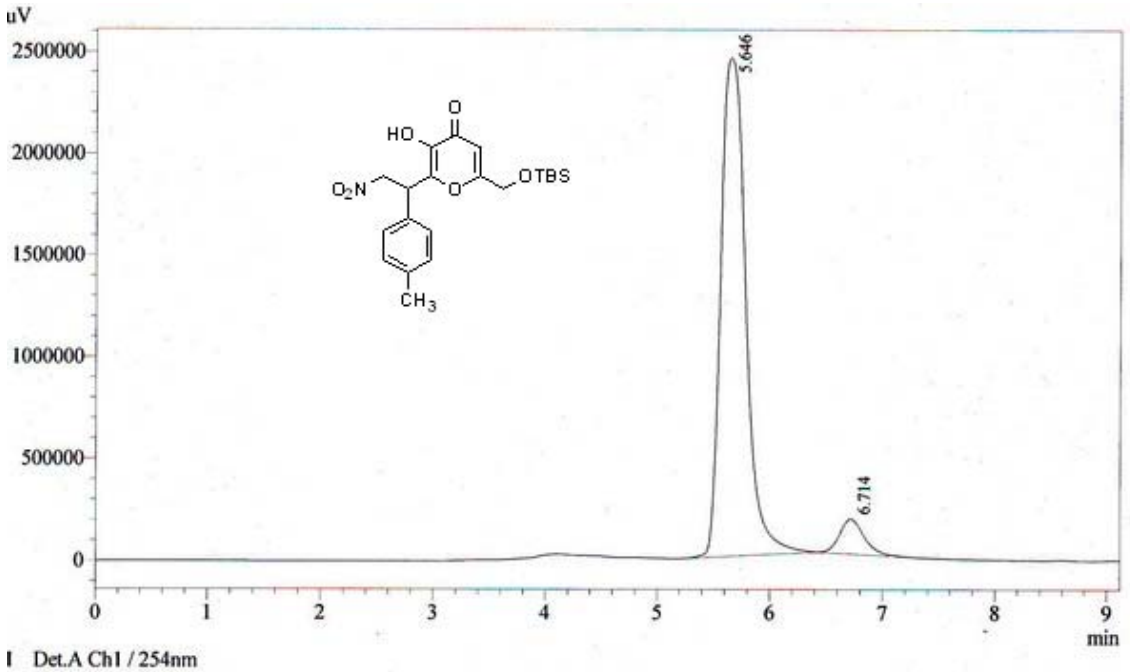
^{1}H NMR, ^{13}C NMR and HPLC of **4f**



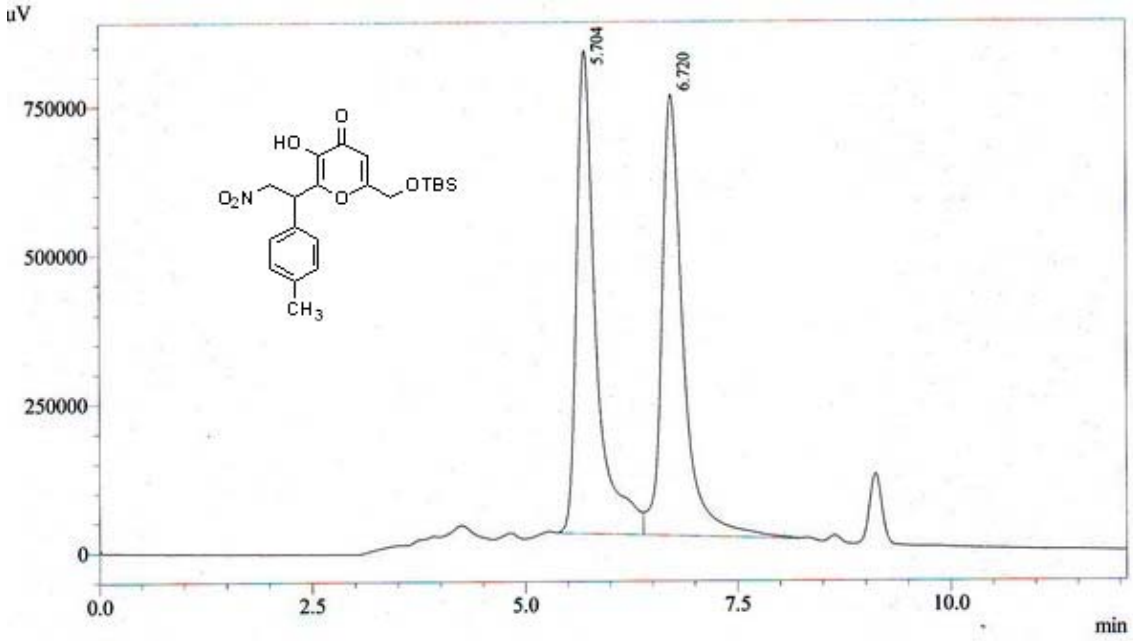




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.646	37712992	2448406	93.551	93.478
2	6.714	2599623	170833	6.449	6.522
Total		40312615	2619239	100.000	100.000

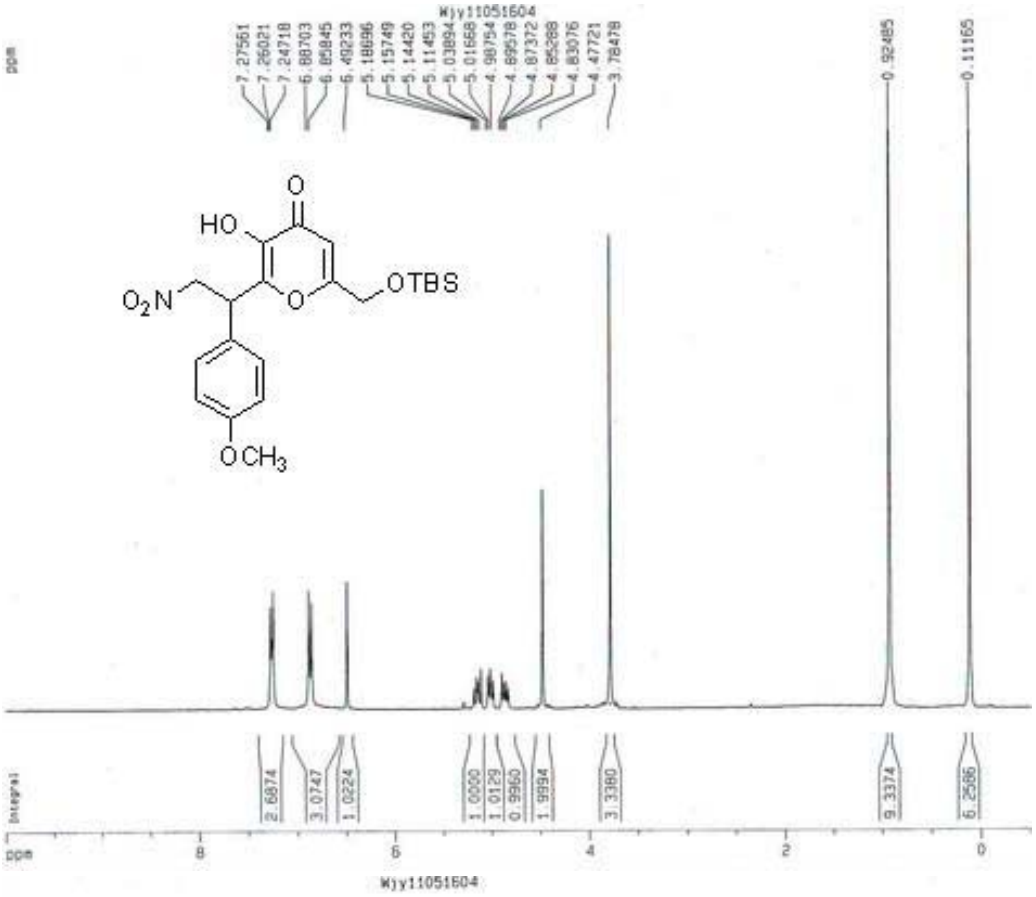


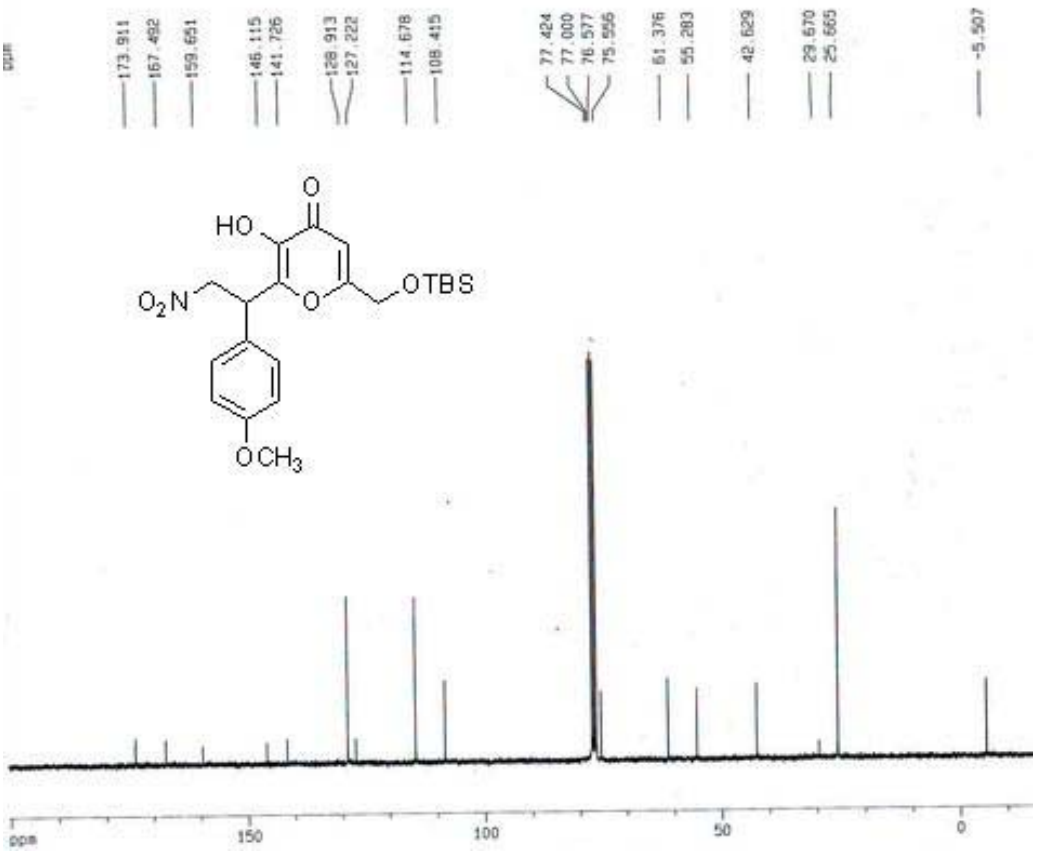
1 Det.A Ch1 / 254nm

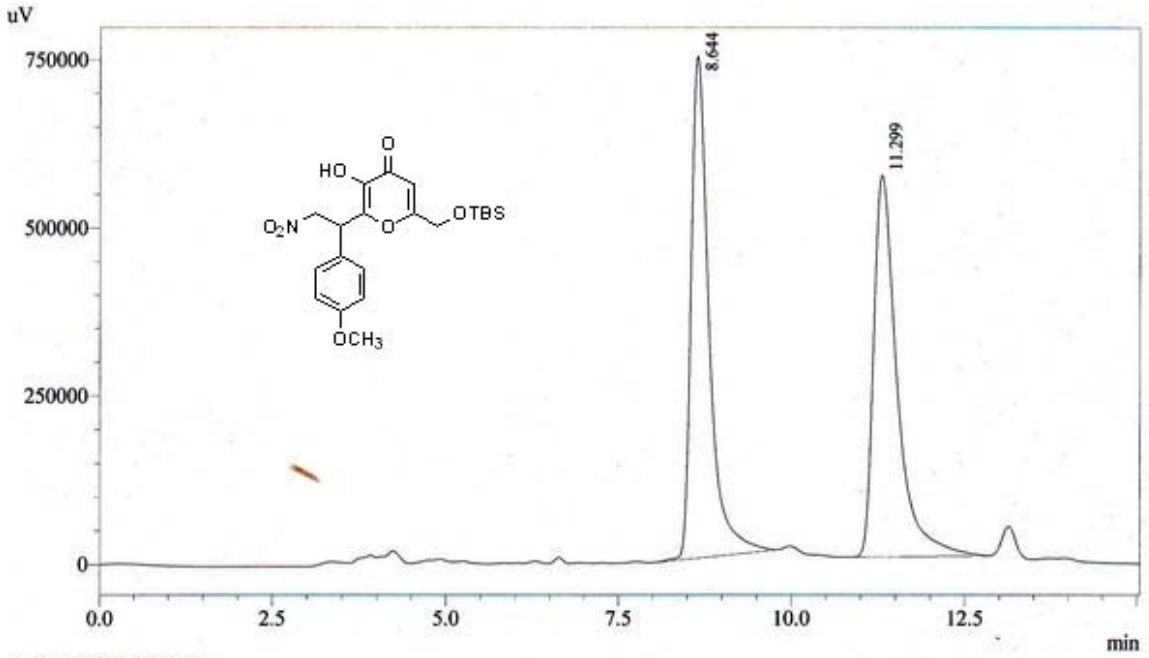
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.704	12956464	812734	49.678	52.278
2	6.720	13124497	741908	50.322	47.722
Total		26080960	1554642	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4g**



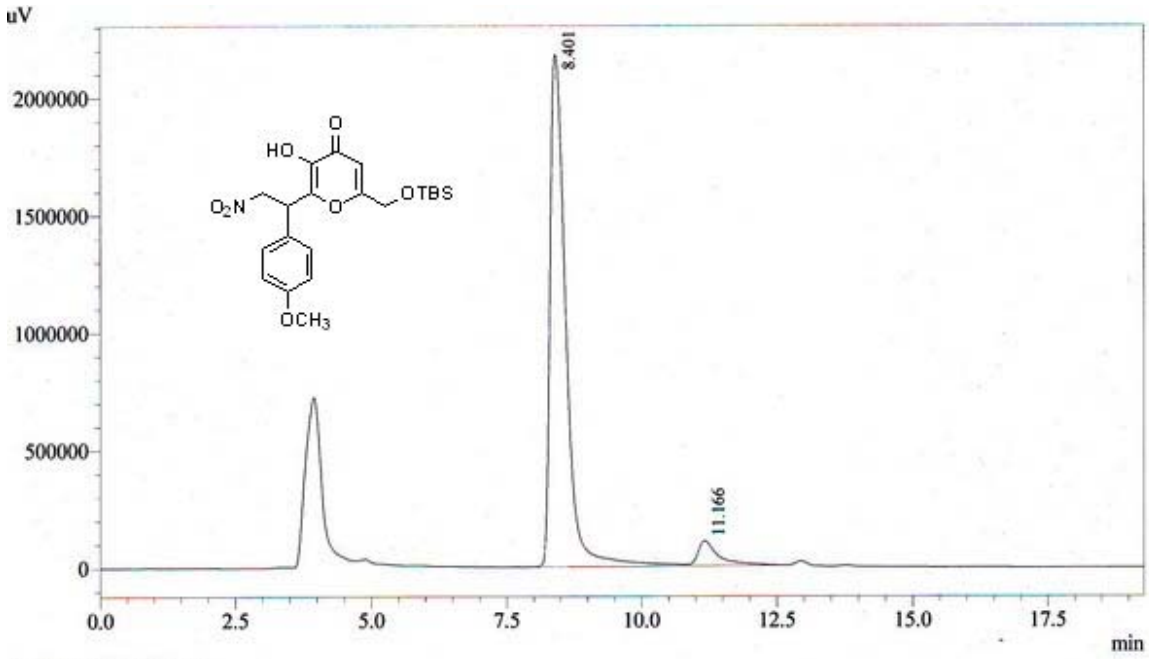




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.644	13484528	746719	50.326	56.816
2	11.299	13309747	567547	49.674	43.184
Total		26794275	1314265	100.000	100.000

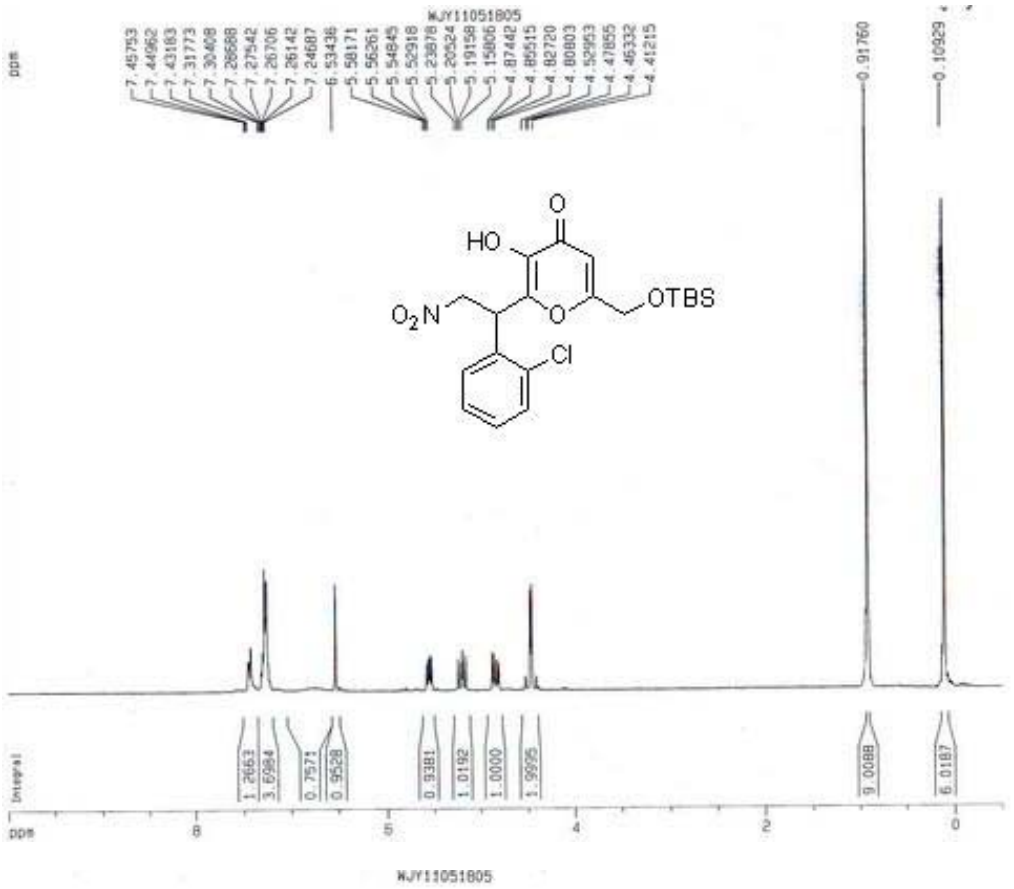


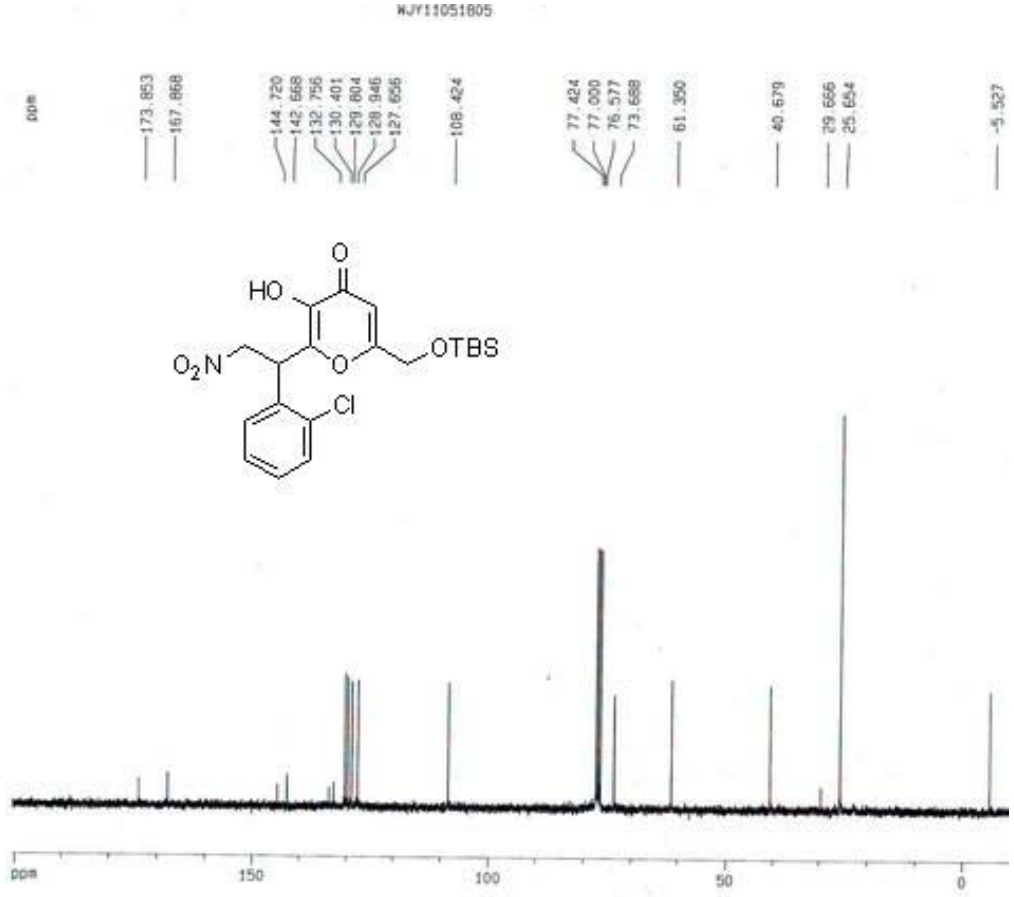
1 Det.A Ch1 / 254nm

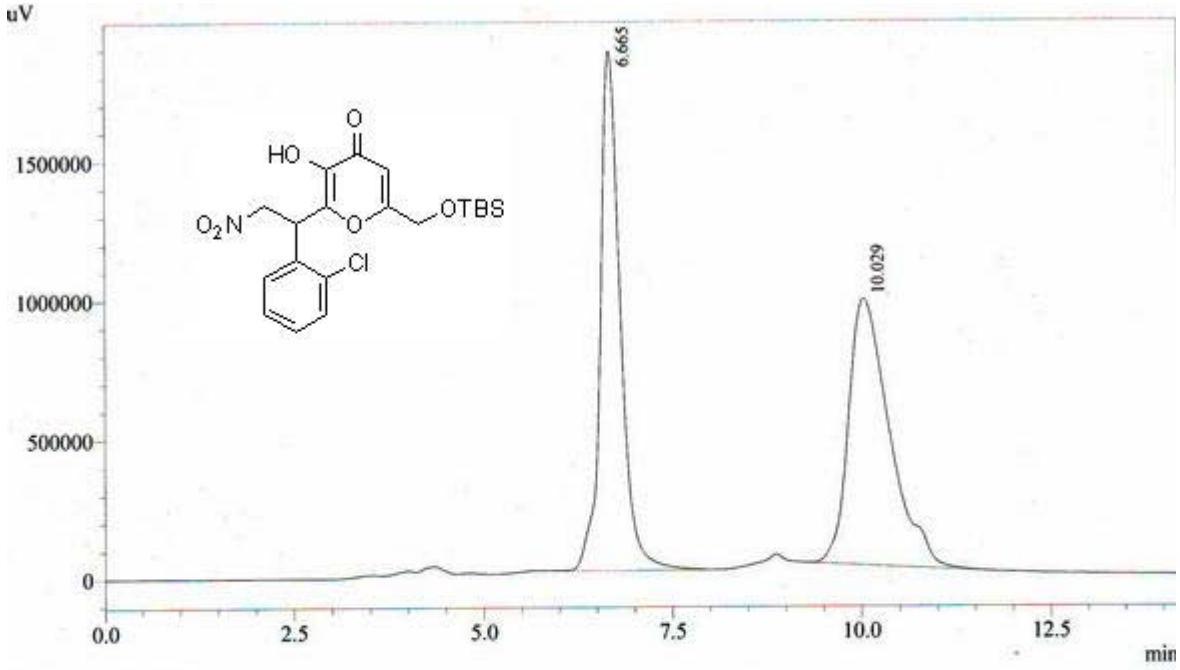
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.401	44285908	2178919	93.977	95.347
2	11.166	2838350	106344	6.023	4.653
Total		47124258	2285263	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4h**



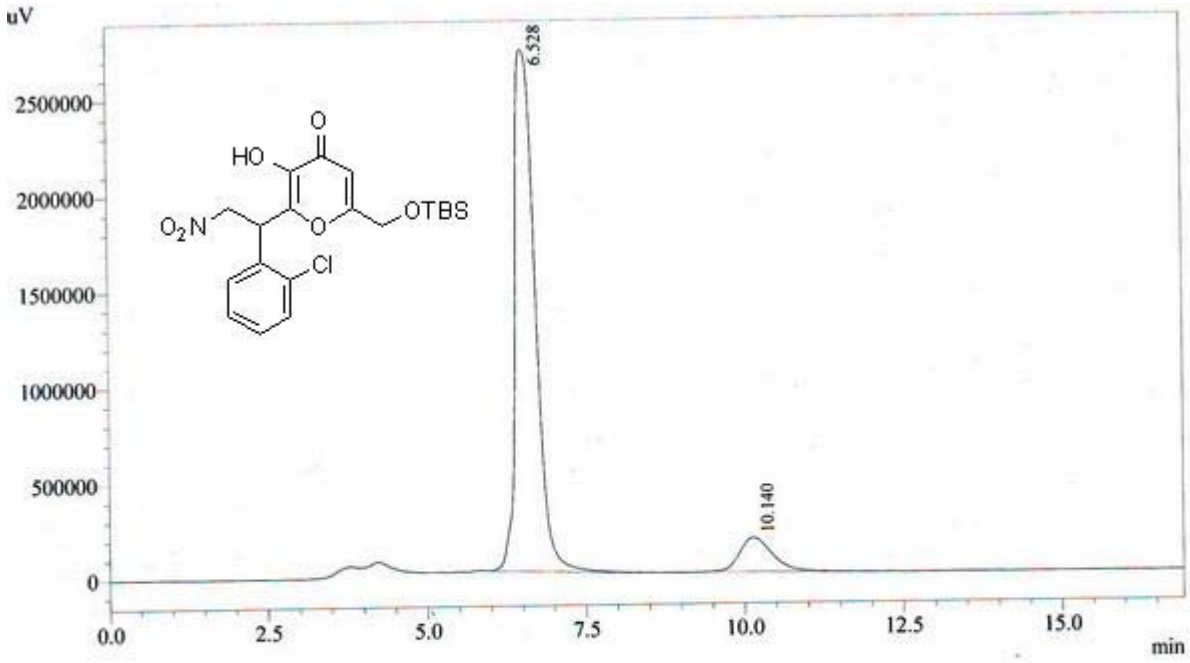




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.665	34554548	1866074	49.044	66.121
2	10.029	35901177	956155	50.956	33.879
Total		70455725	2822229	100.000	100.000

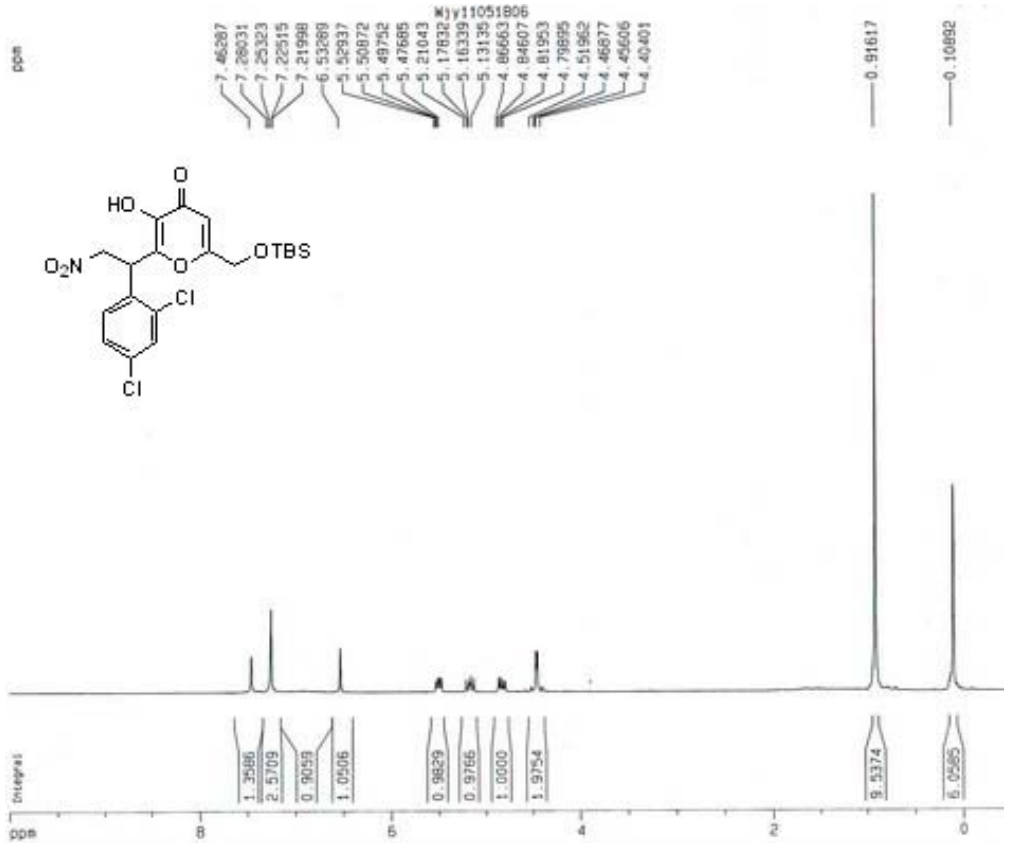


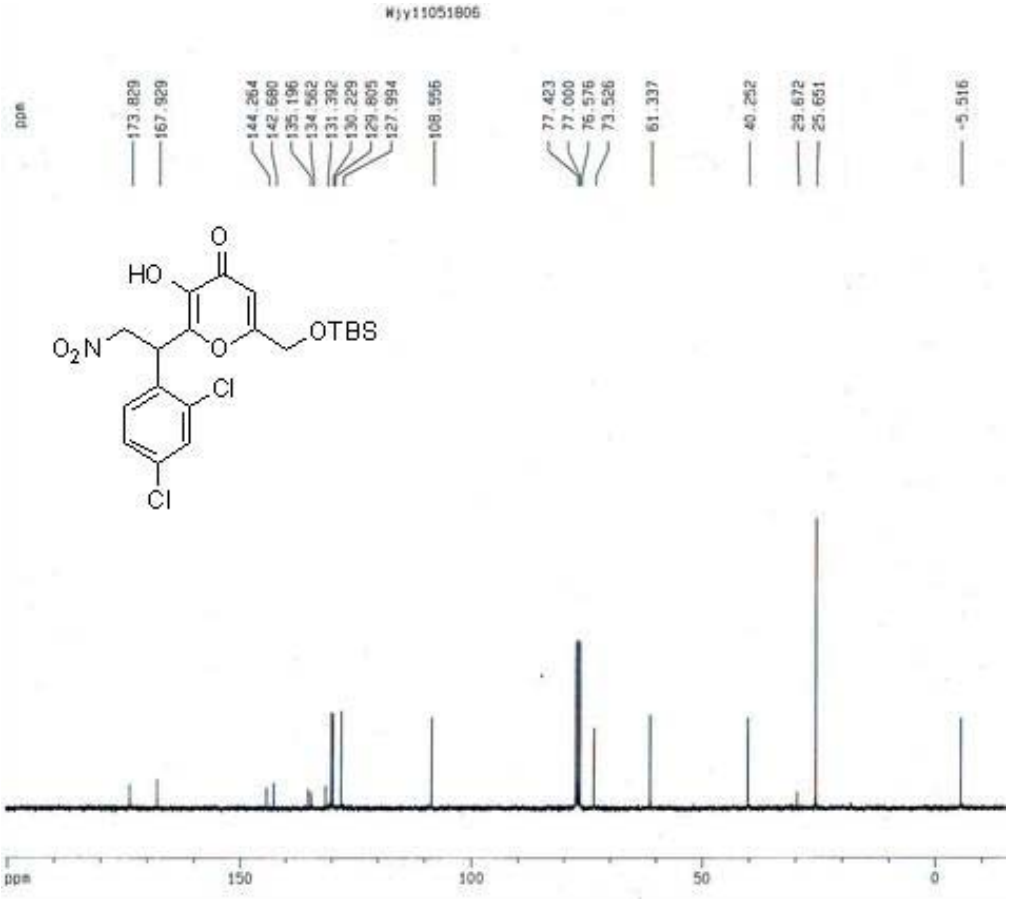
1 Det.A Ch1 / 254nm

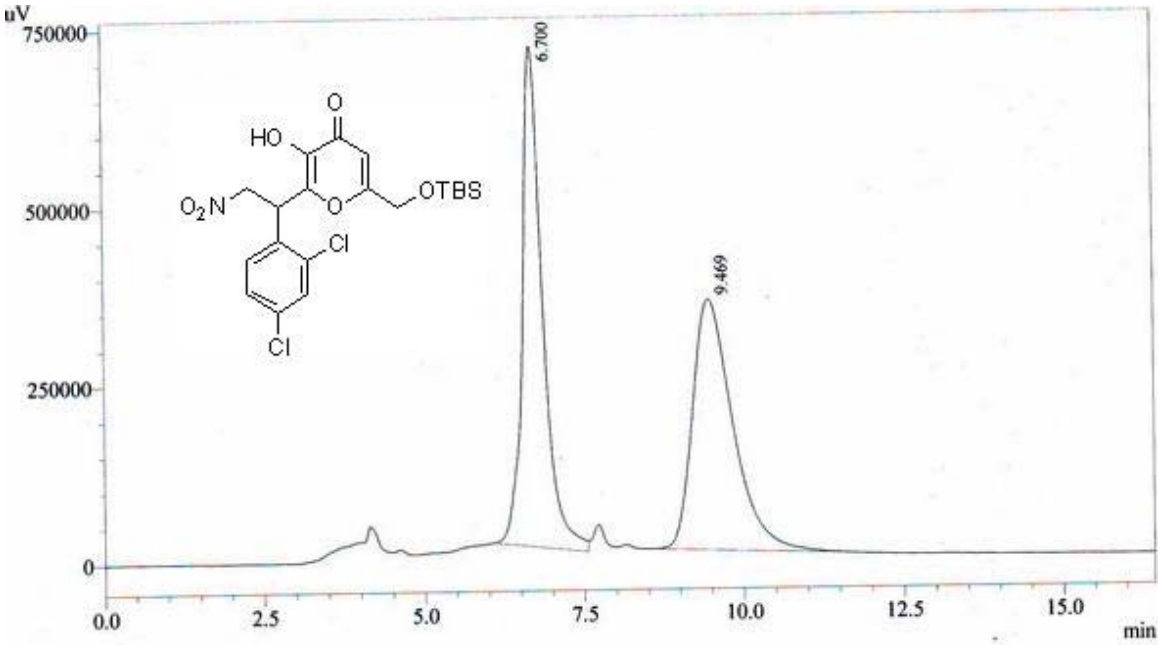
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.528	60591094	2718000	90.442	93.857
2	10.140	6403322	177880	9.558	6.143
Total		66994416	2895880	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4i**



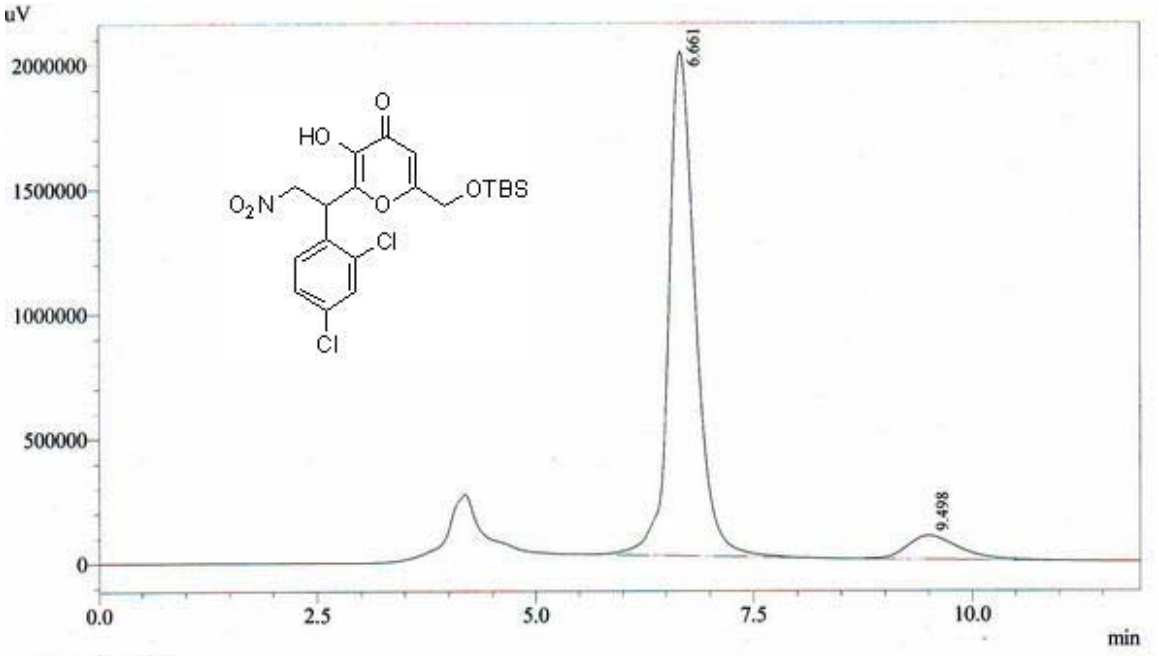




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.700	15580914	702004	50.328	66.626
2	9.469	15377574	351641	49.672	33.374
Total		30958488	1053645	100.000	100.000

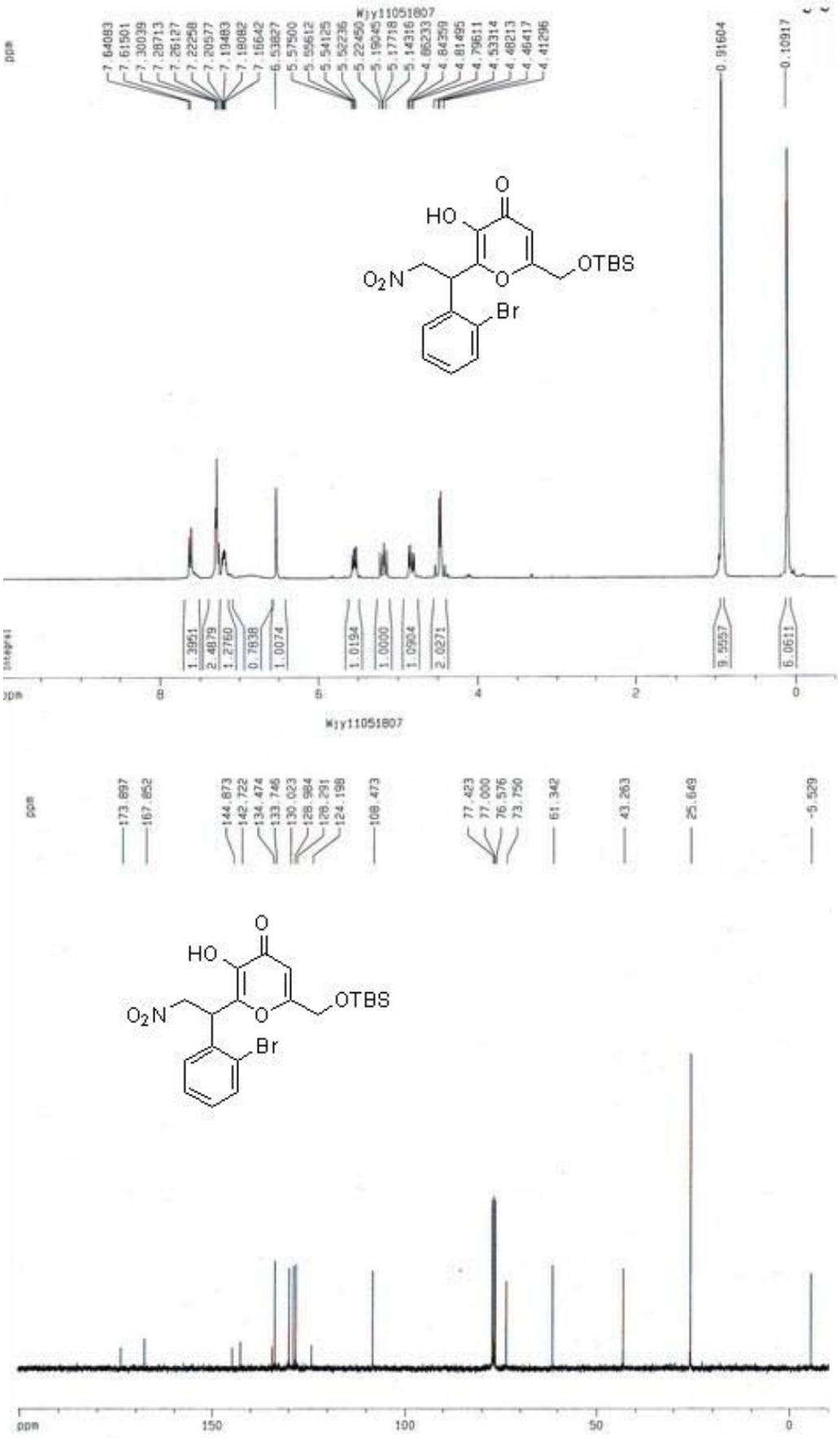


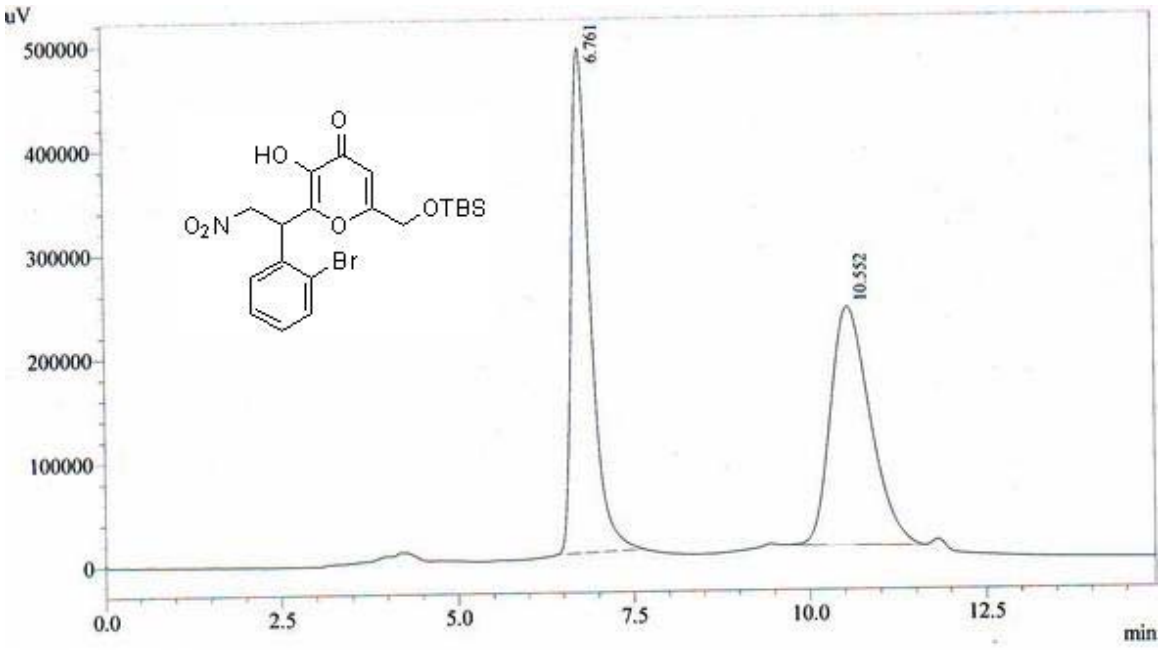
1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.661	43123169	2019973	91.583	95.519
2	9.498	3963471	94771	8.417	4.481
Total		47086640	2114744	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4j**

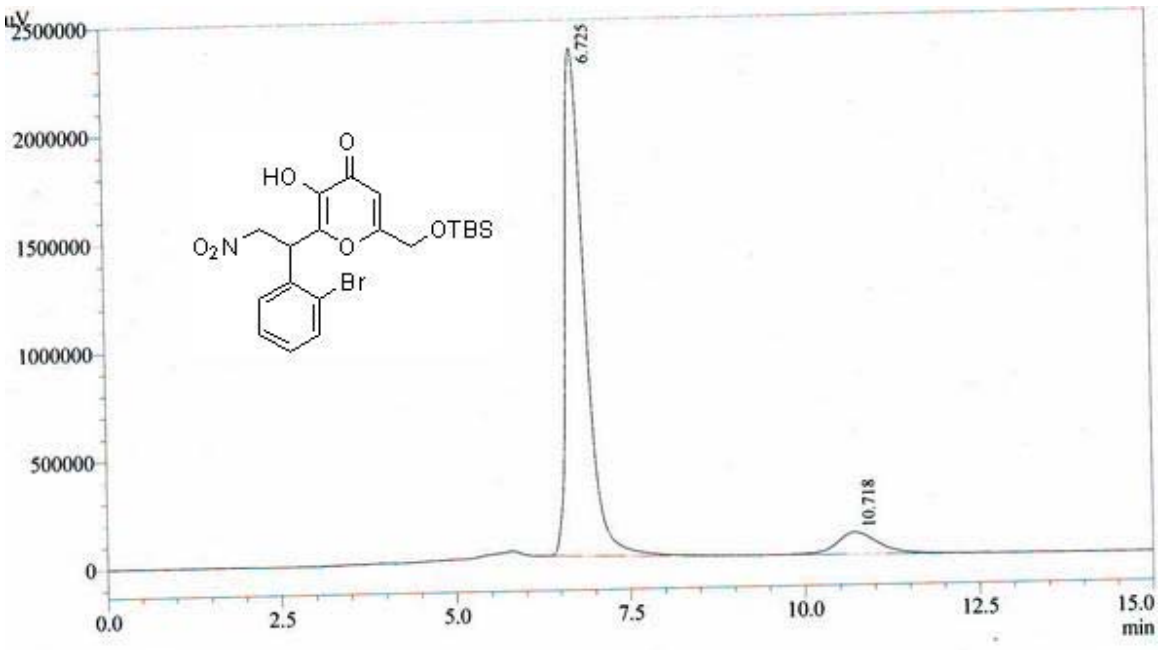




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.761	9057411	485540	50.408	67.935
2	10.552	8910815	229173	49.592	32.065
Total		17968226	714713	100.000	100.000

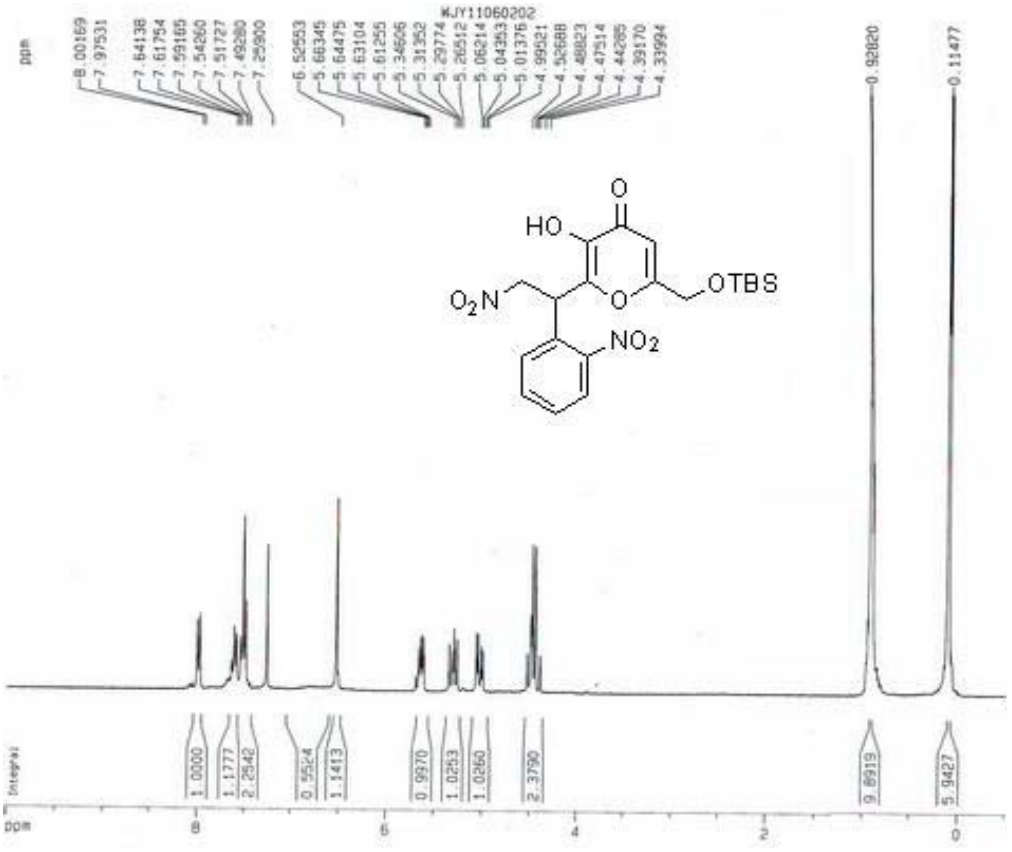


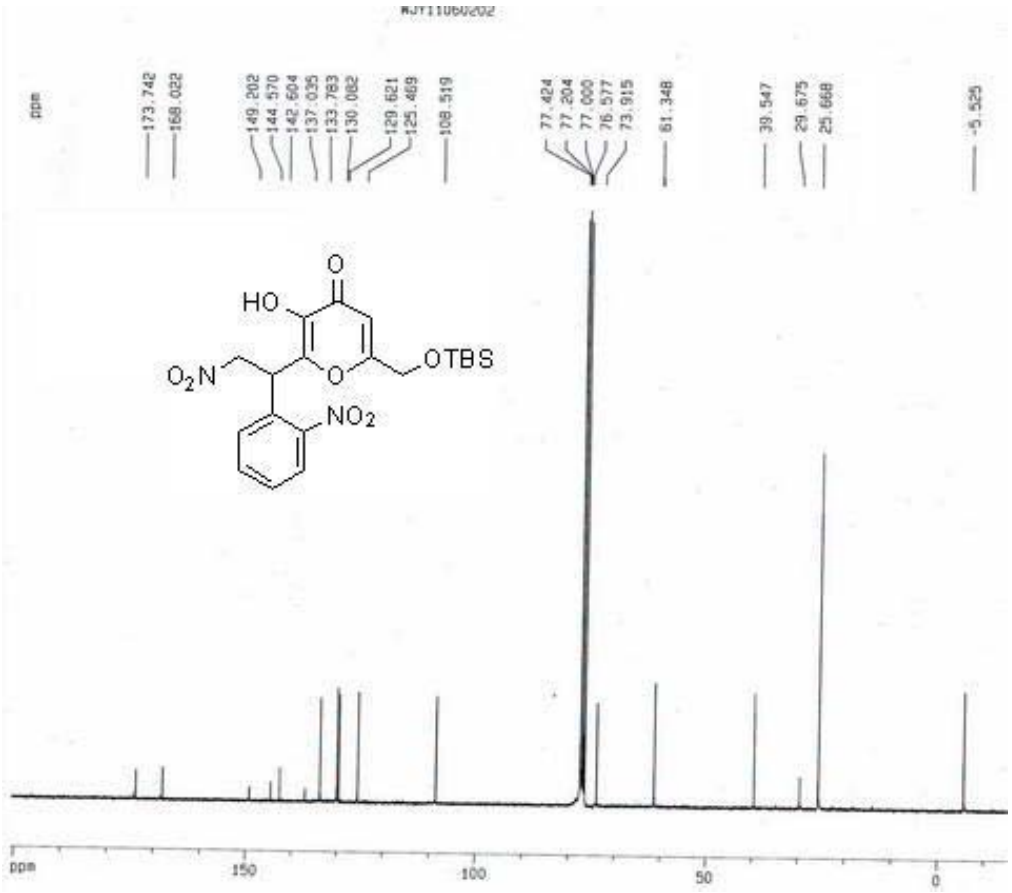
1 Det.A Ch1 / 254nm

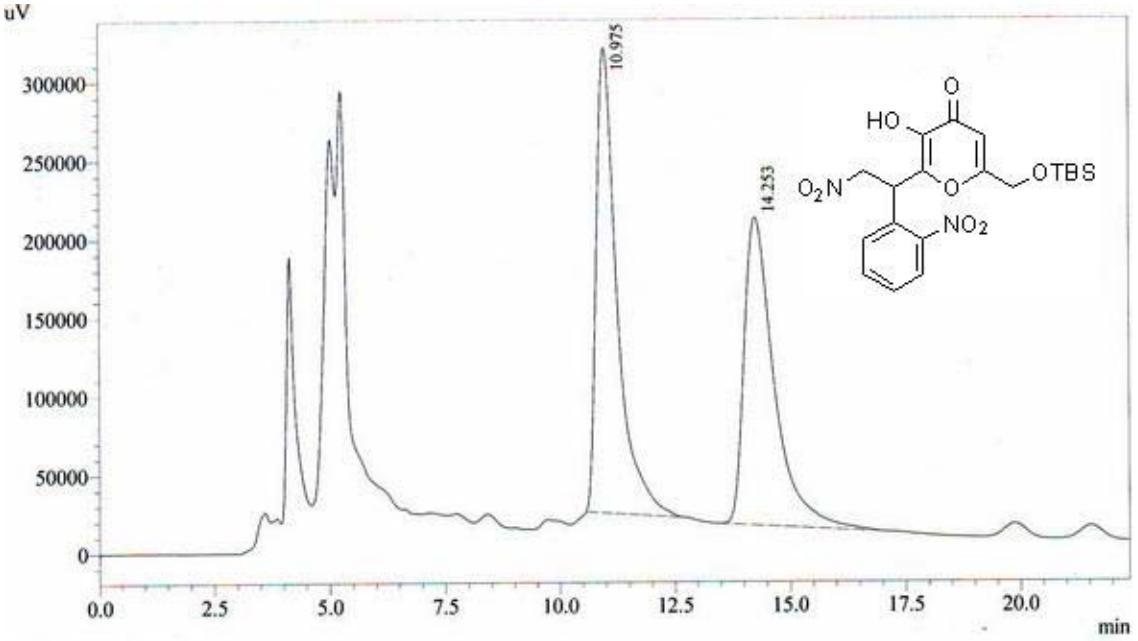
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.725	45780195	2344893	91.710	95.880
2	10.718	4138401	100758	8.290	4.120
Total		49918596	2445650	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4k**



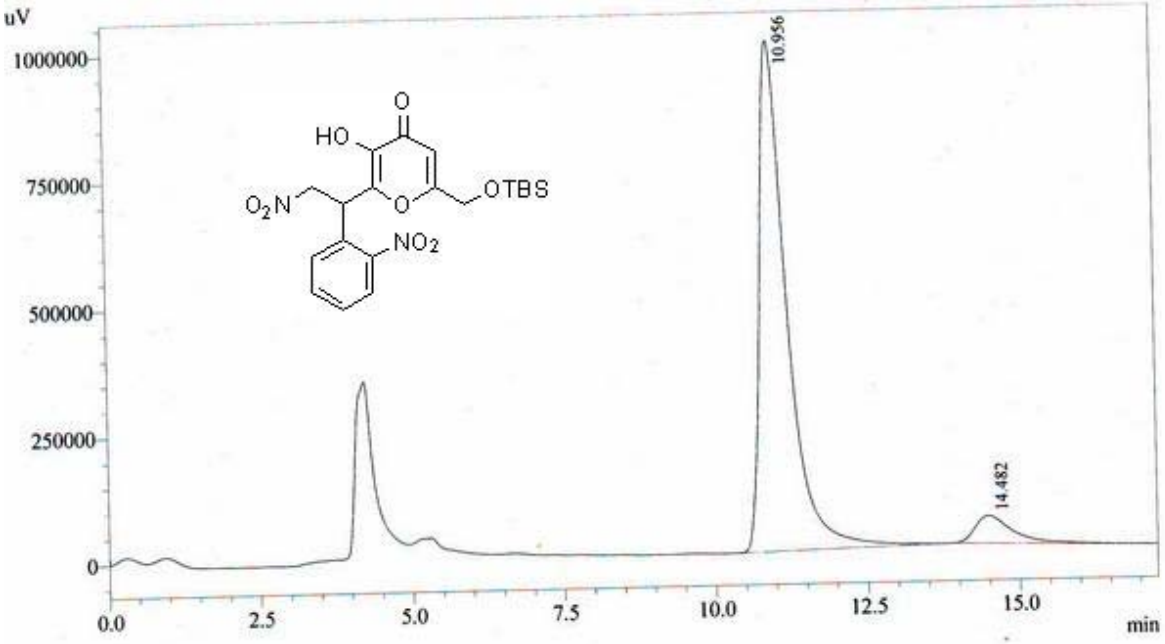




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.975	9322694	295944	51.344	60.221
2	14.253	8834618	195487	48.656	39.779
Total		18157312	491431	100.000	100.000

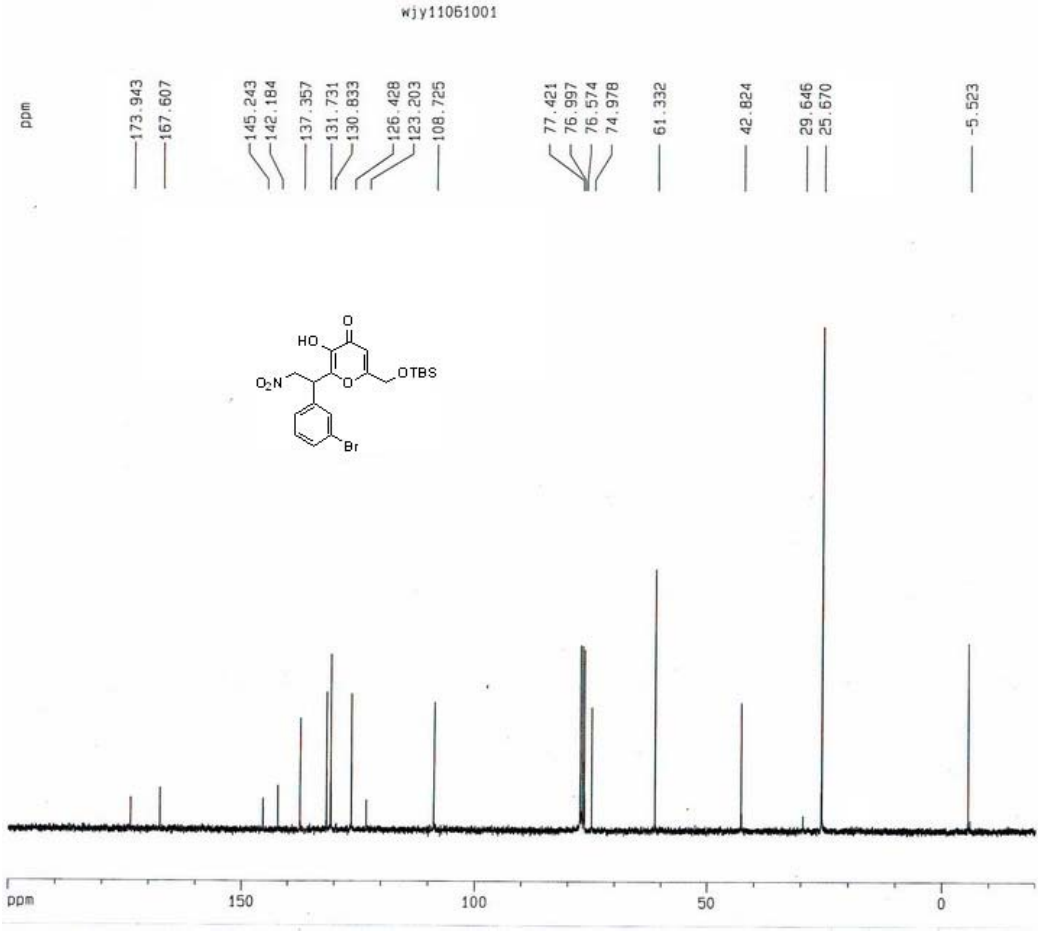


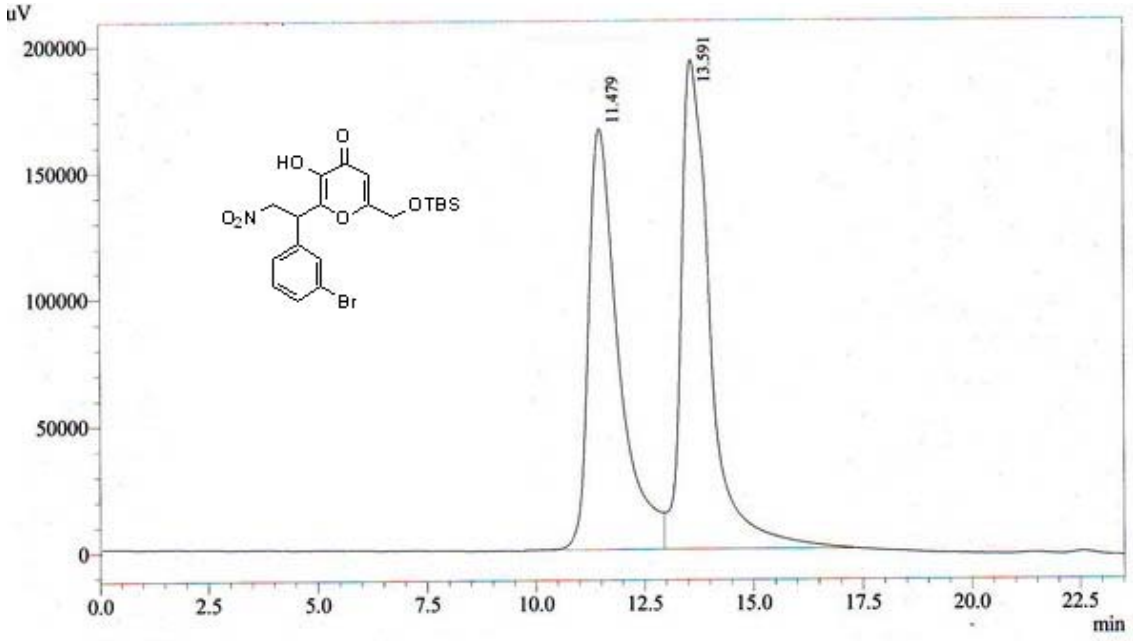
1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.956	31167466	1004989	93.134	94.895
2	14.482	2297616	54060	6.866	5.105
Total		33465082	1059049	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4**

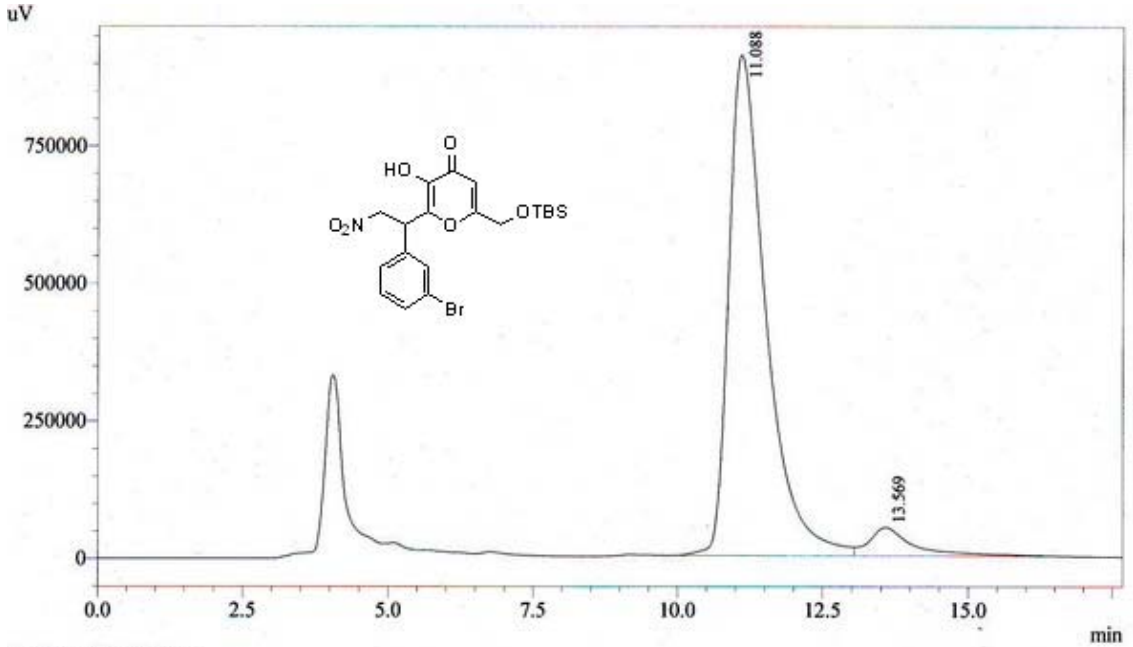




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.479	8009670	166188	47.129	46.259
2	13.591	8985598	193068	52.871	53.741
Total		16995268	359256	100.000	100.000

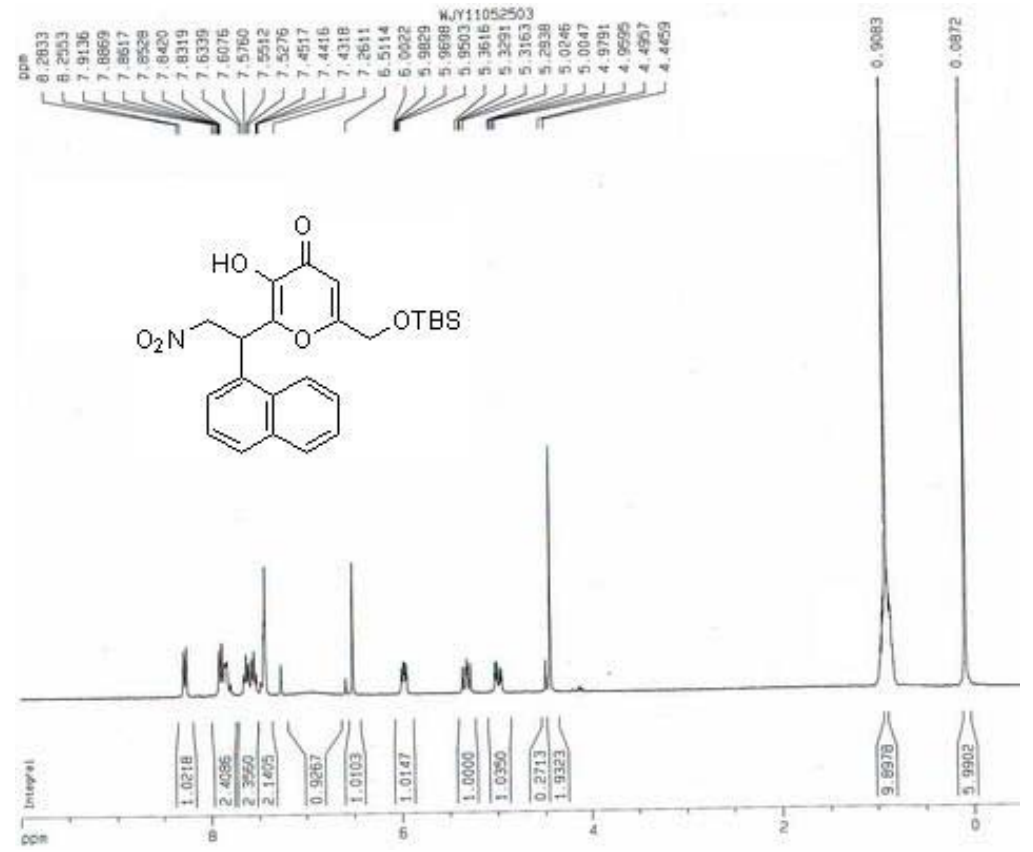


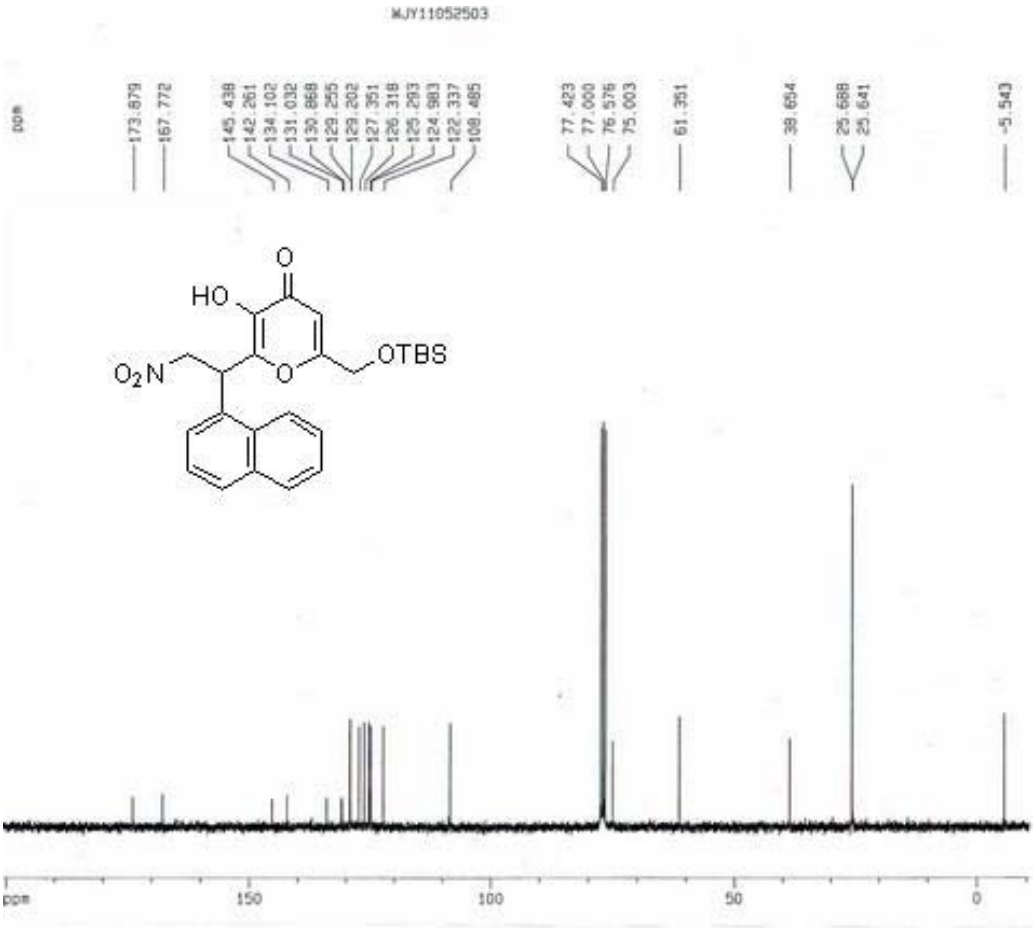
1 Det.A Ch1 / 254nm

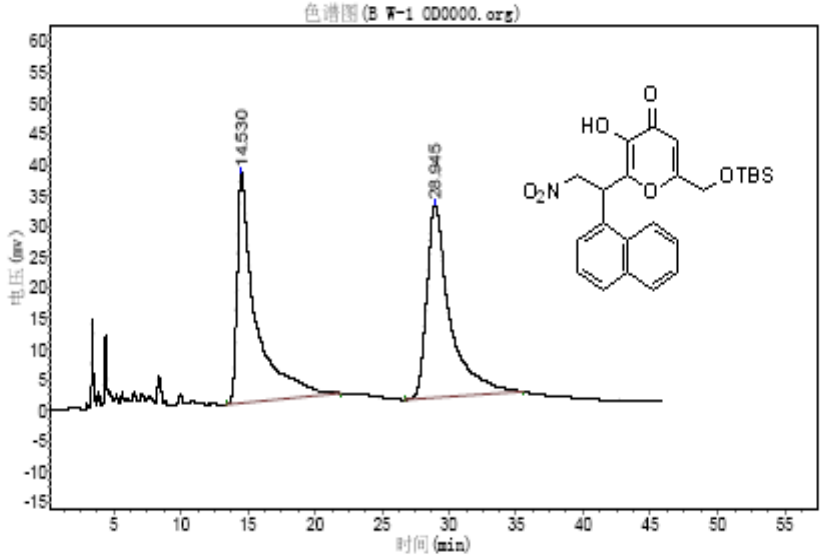
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.088	40557120	910954	93.694	94.648
2	13.569	2729827	51506	6.306	5.352
Total		43286947	962460	100.000	100.000

^{1}H NMR, ^{13}C NMR and HPLC of **4m**

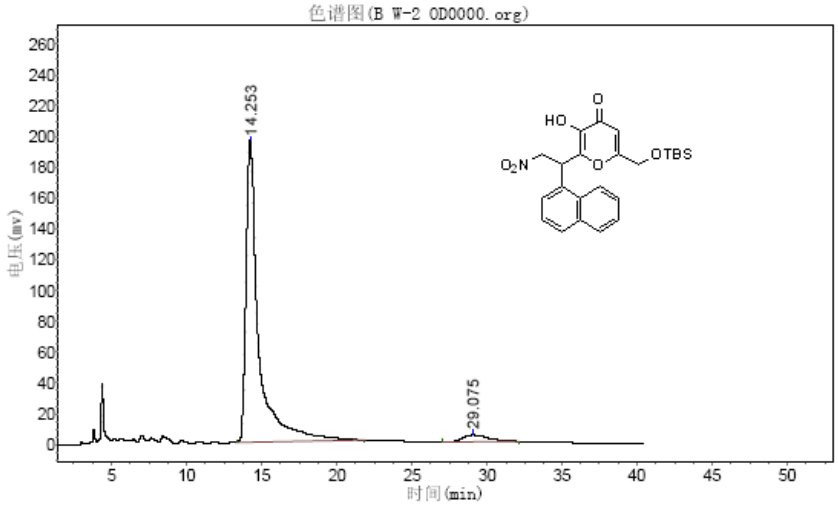






分析结果表

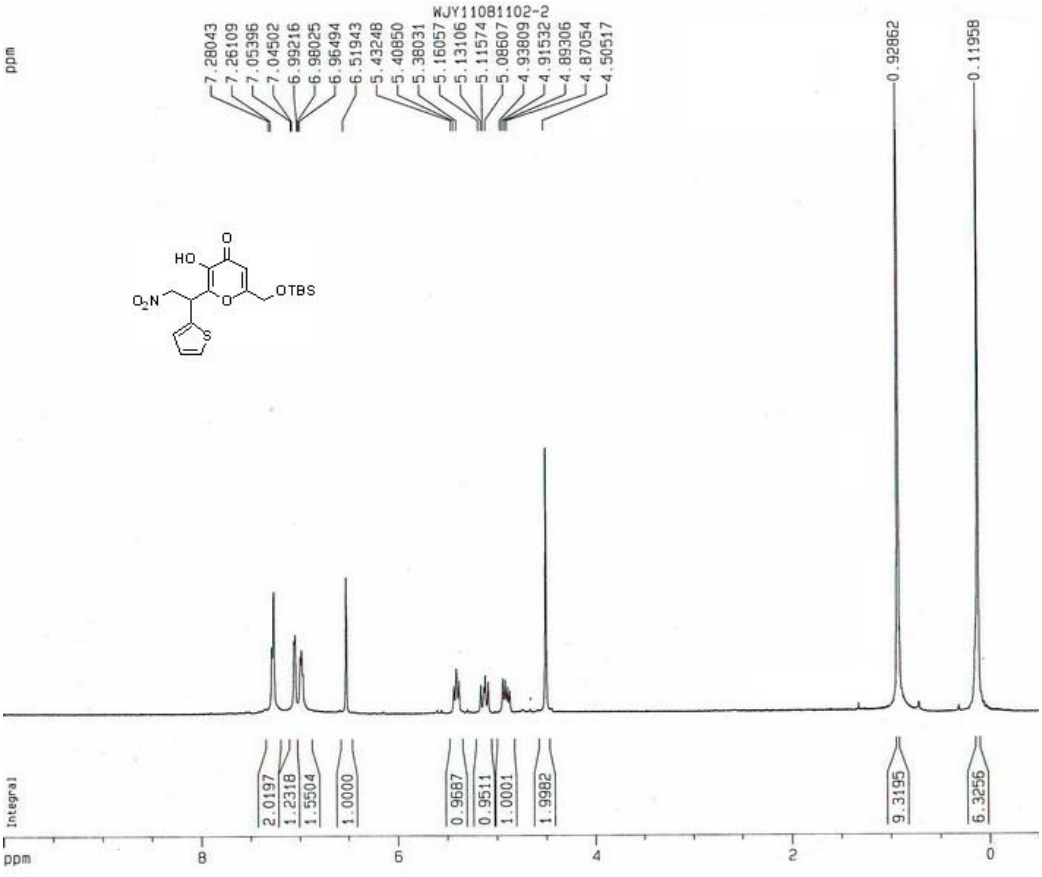
峰号	峰名	保留时间	峰高	峰面积	含量
1		14.530	37593.359	3628739.500	49.0518
2		28.945	31284.275	3769034.250	50.9482
总计			68877.635	7397773.750	100.0000

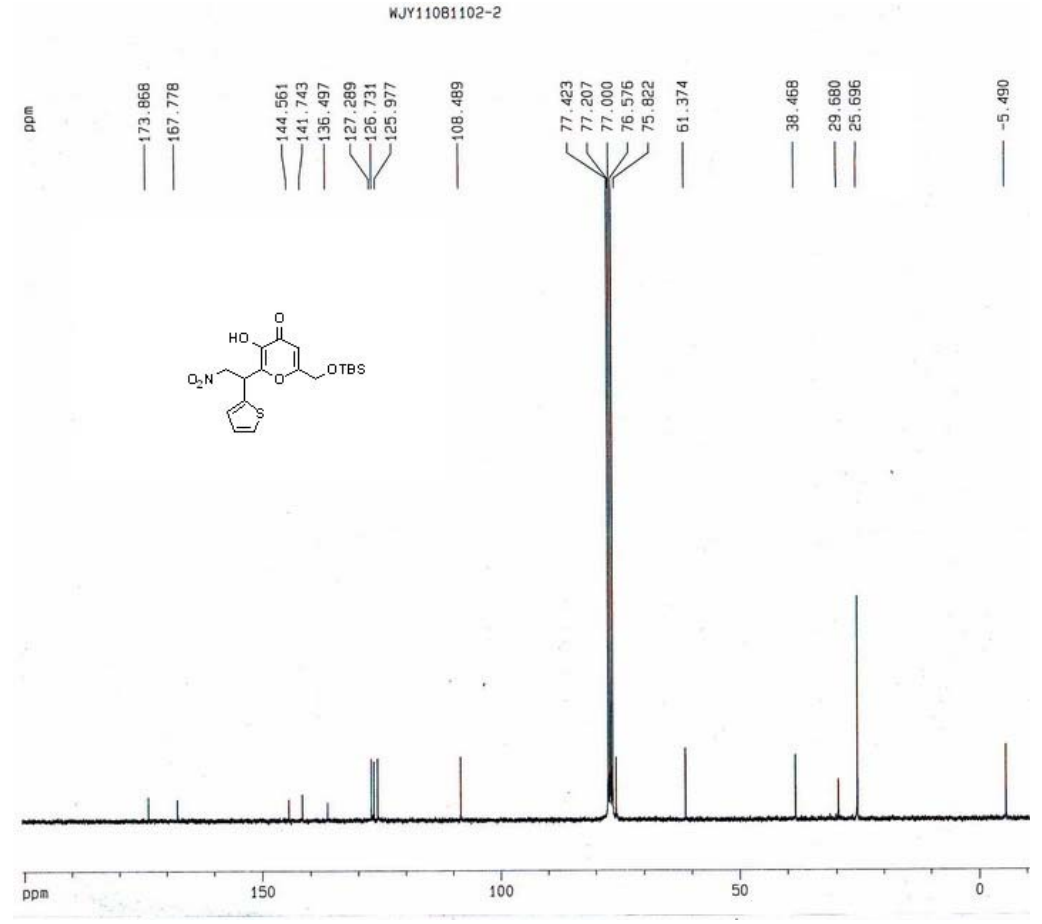


分析结果表

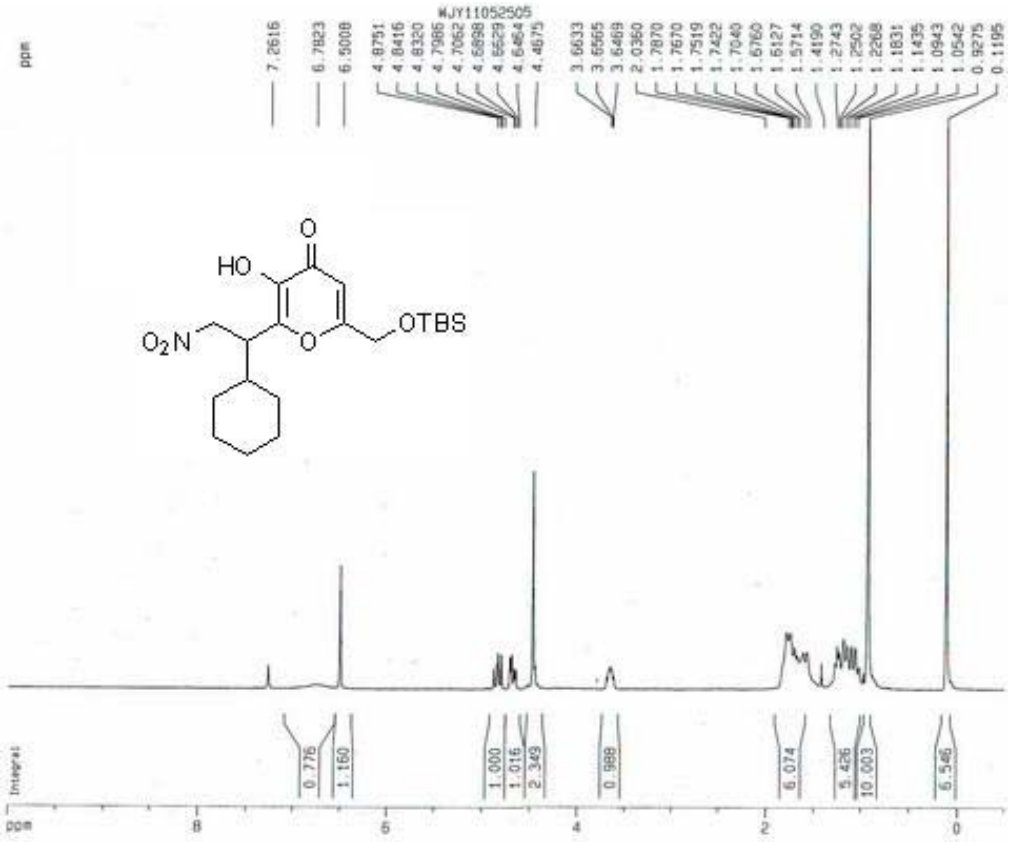
峰号	峰名	保留时间	峰高	峰面积	含量
1		14.253	195938.297	11442531.000	95.4052
2		29.075	4770.081	551079.063	4.5948
总计			200708.377	11993610.062	100.0000

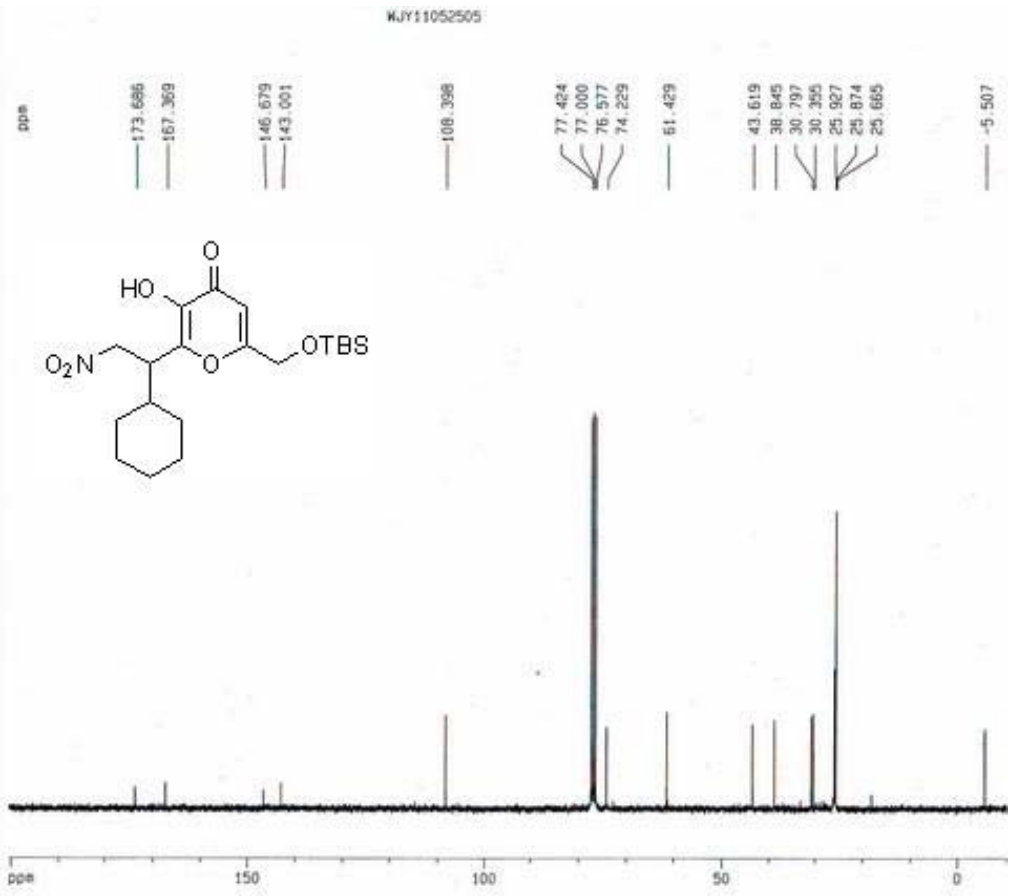
^{1}H NMR, ^{13}C NMR and HPLC of **4n**



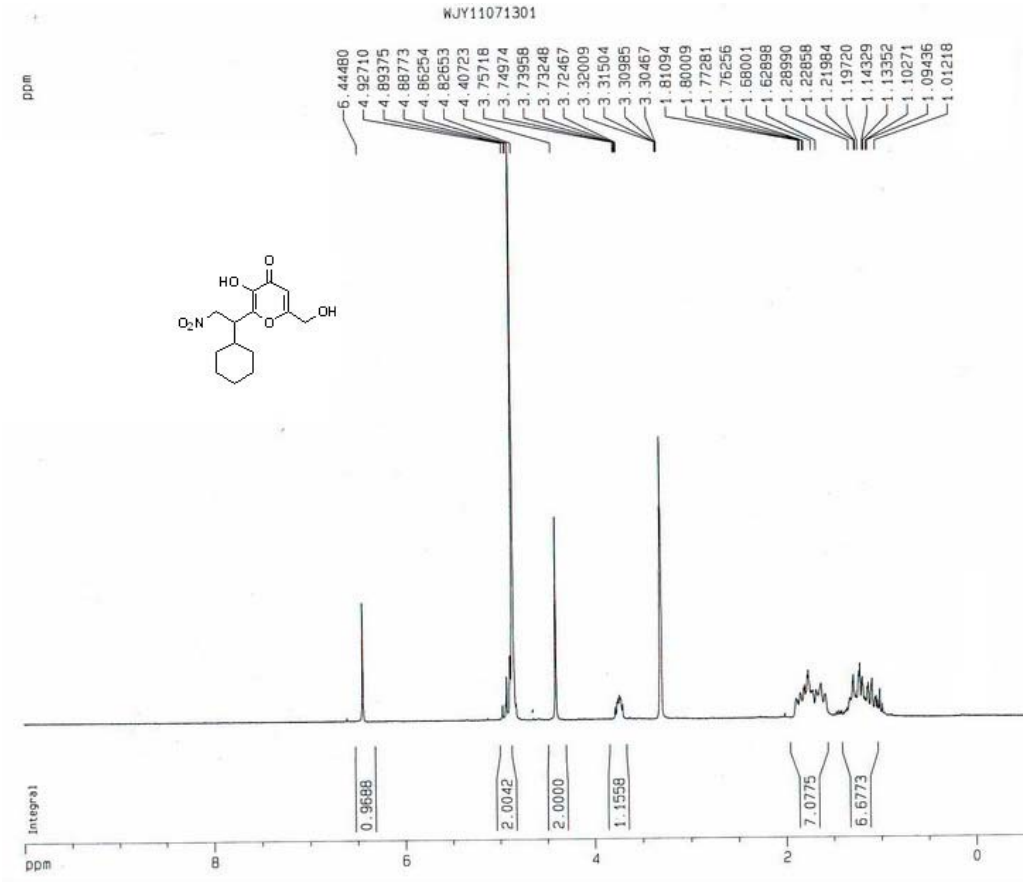


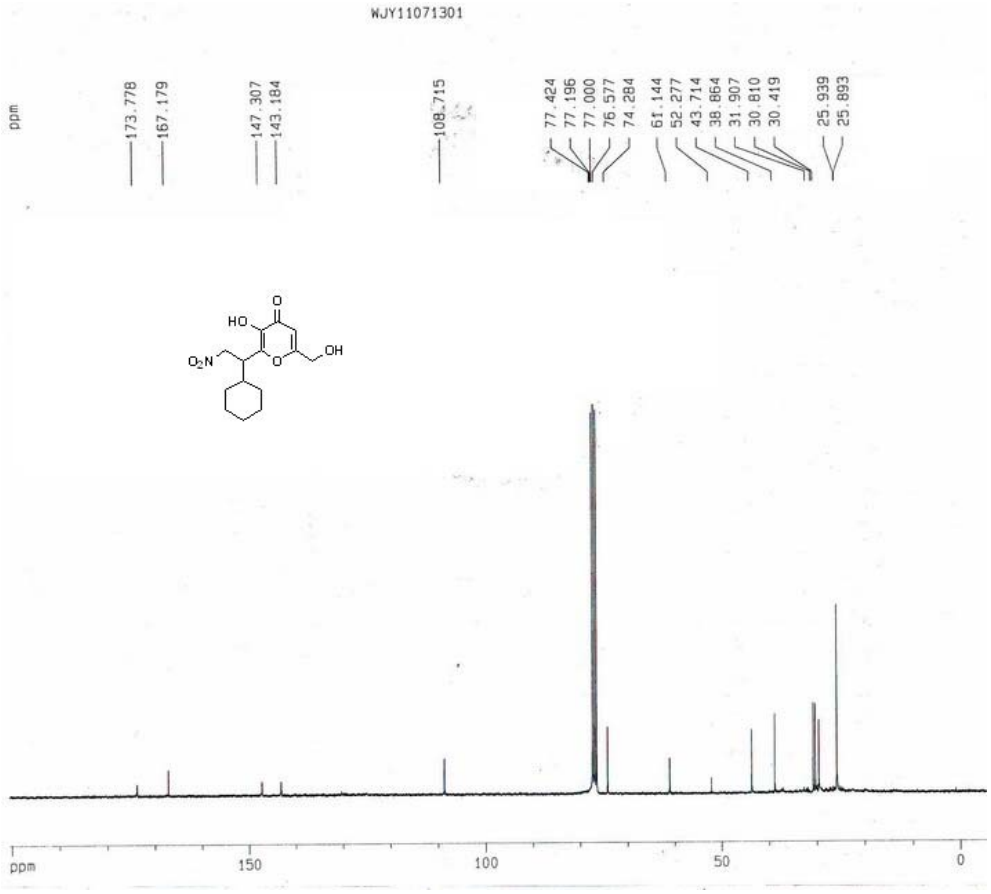
^{1}H NMR, ^{13}C NMR of **4o**

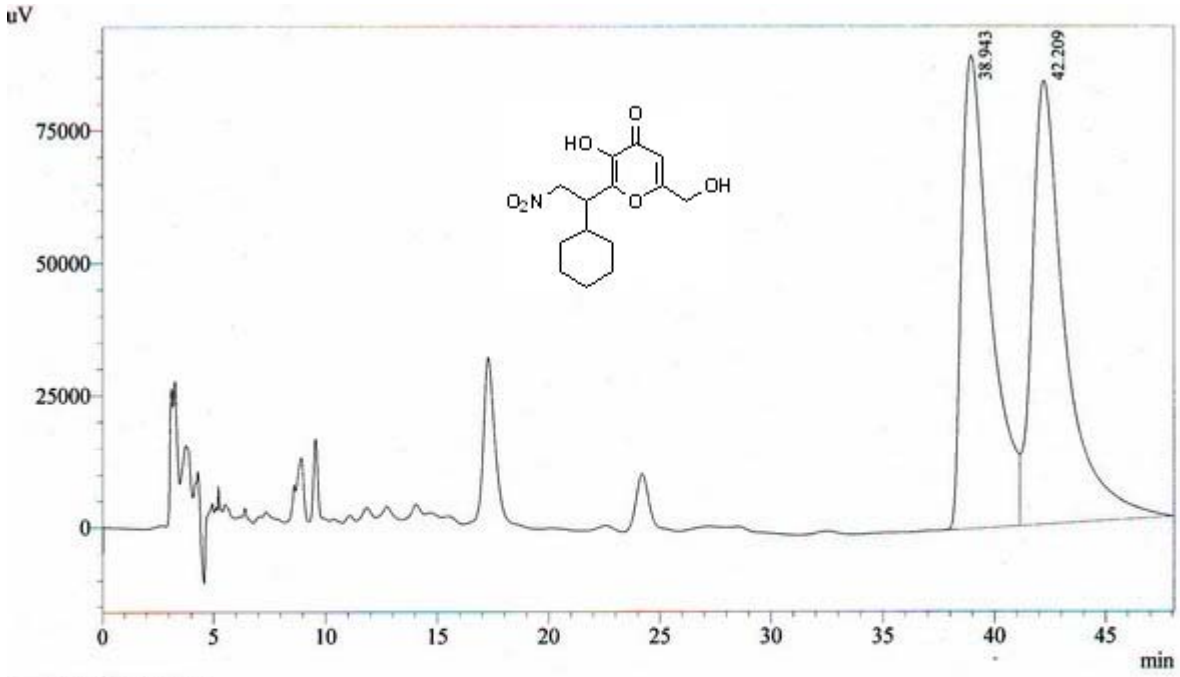




^{1}H NMR, ^{13}C NMR and HPLC of **8**



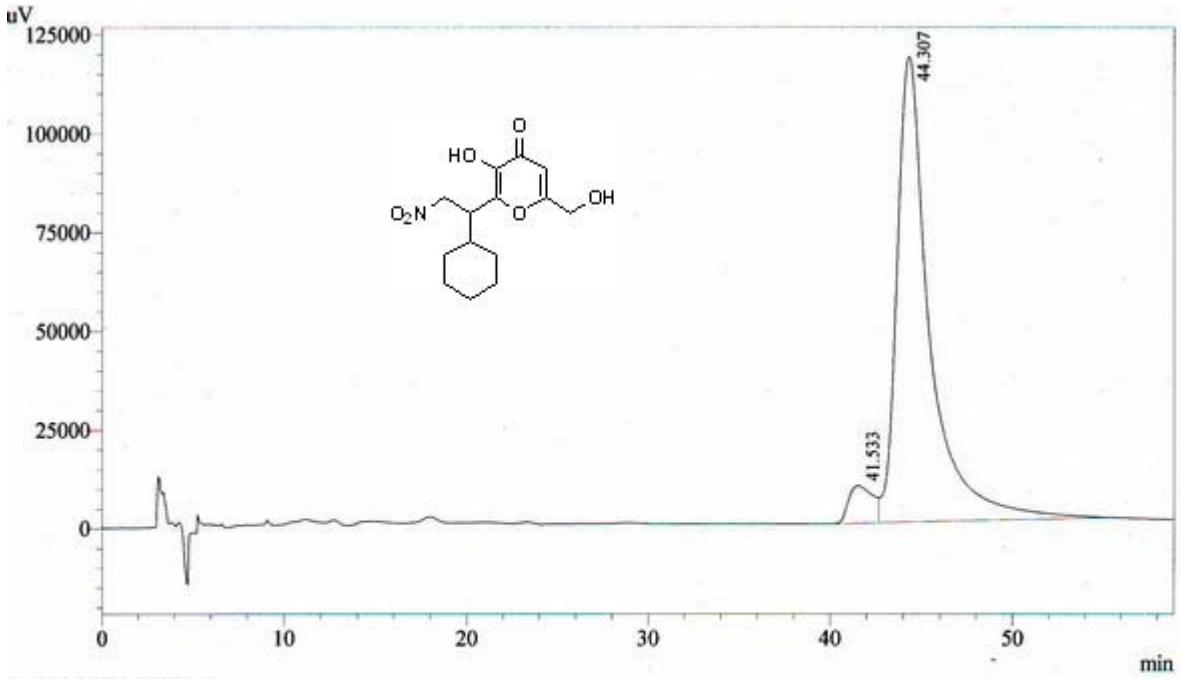




1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	38.943	7935540	89408	47.634	51.619
2	42.209	8723827	83800	52.366	48.381
Total		16659367	173208	100.000	100.000

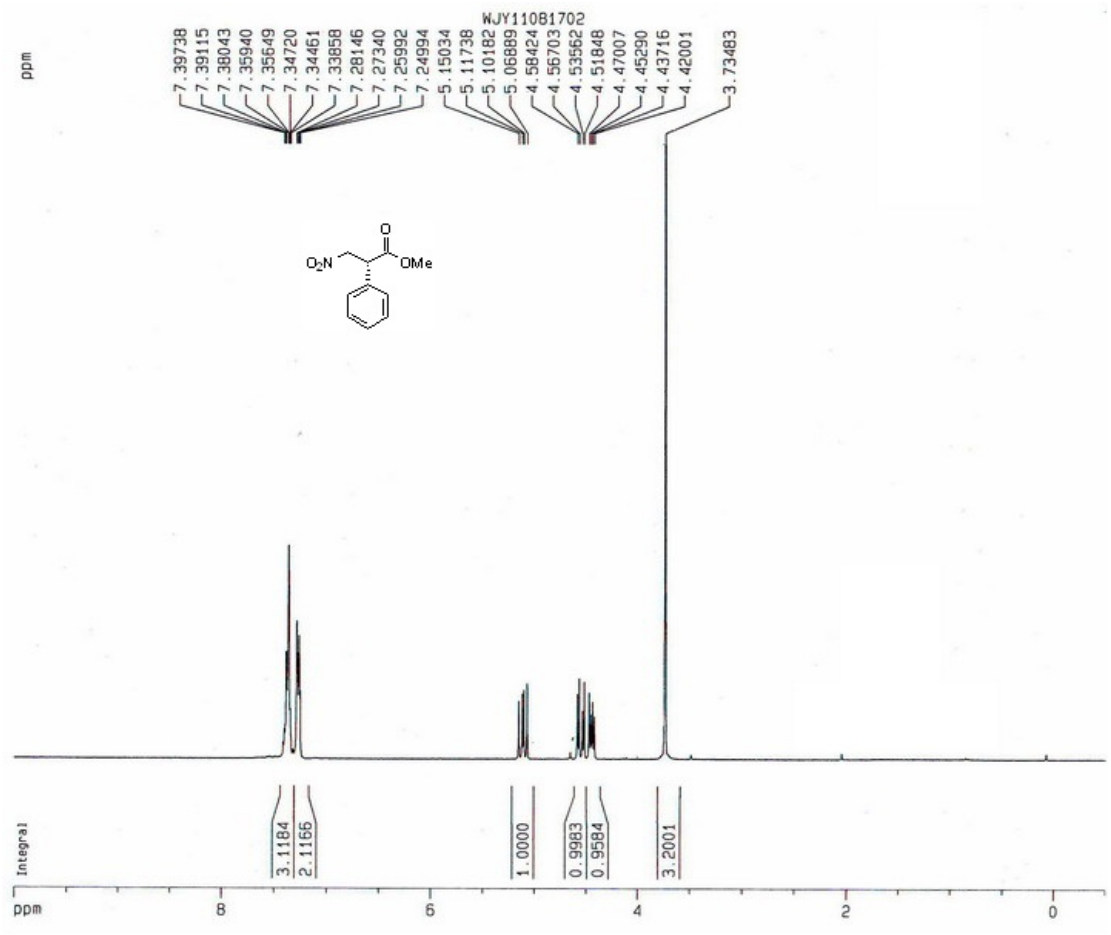


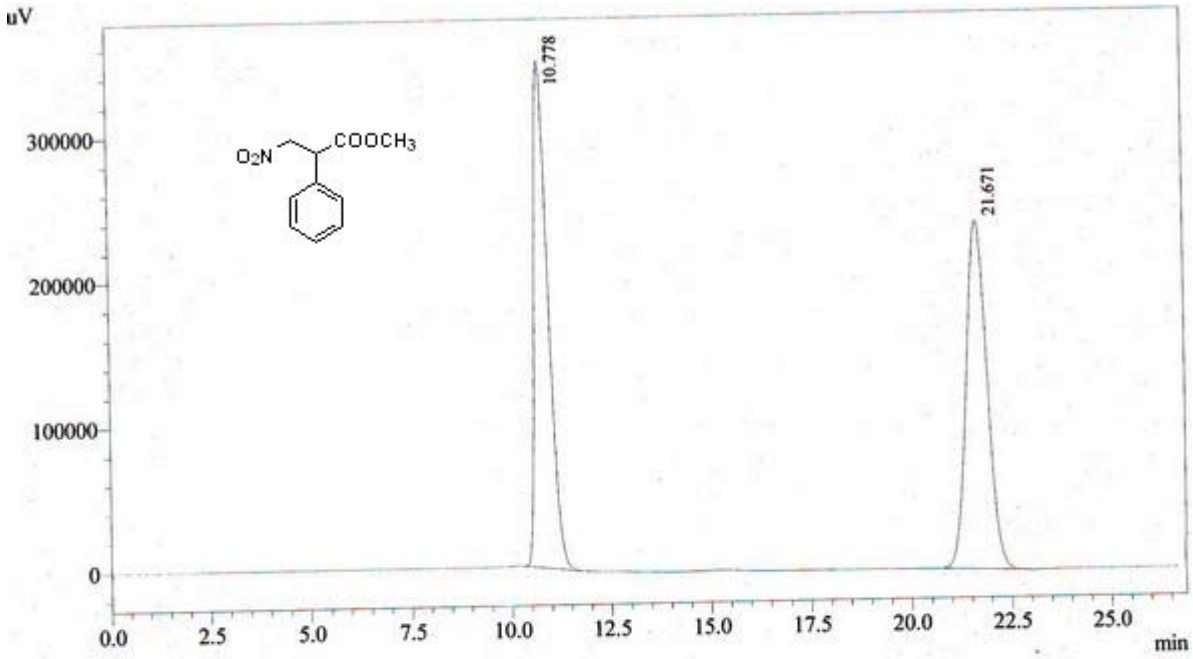
1 Det.A Ch1 / 254nm

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	41.533	874620	9552	5.595	7.504
2	44.307	14758524	117739	94.405	92.496
Total		15633144	127291	100.000	100.000

^{1}H NMR and HPLC of **6**

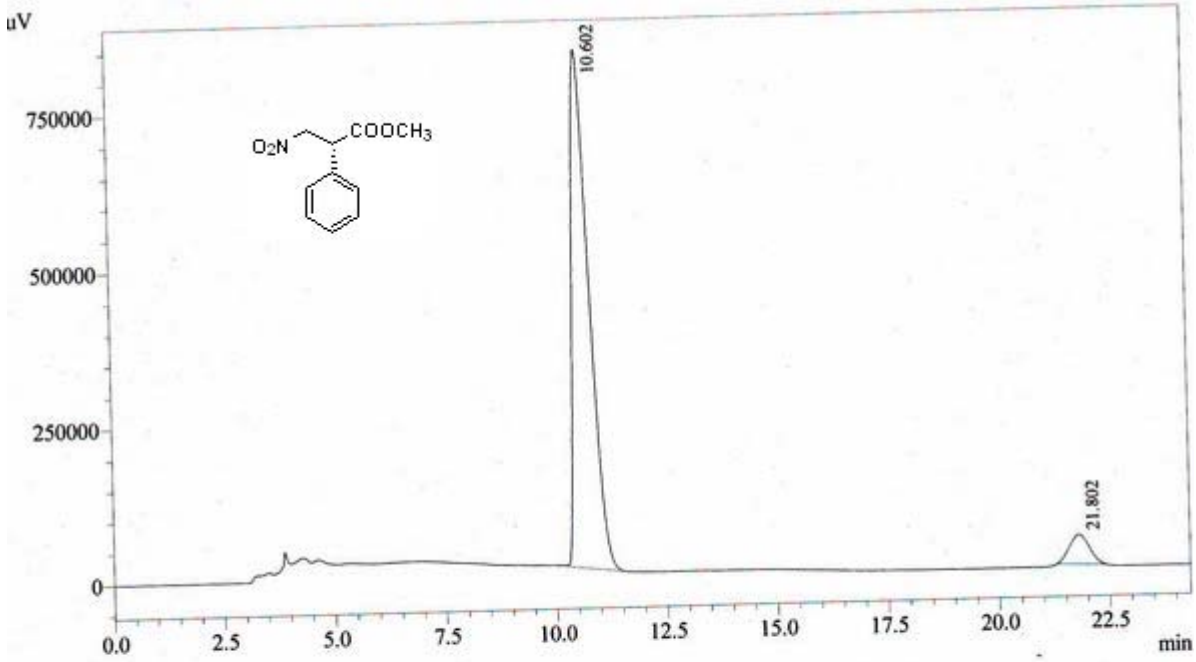




1 Det.A Ch1 / 235nm

Detector A Ch1 235nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.778	8525244	349758	49.369	59.214
2	21.671	8743068	240908	50.631	40.786
Total		17268312	590665	100.000	100.000



1 Det.A Ch1 / 235nm

Detector A Ch1 235nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.602	22093693	830049	93.710	94.646
2	21.802	1483082	46951	6.290	5.354
Total		23576775	877000	100.000	100.000