Drug design based on pentaerythritol tetranitrate reductase: synthesis and antibacterial activity of Pogostone derivatives

Biao Wang,[†a] Wei Huang,[†b] Jin Zhou,[a] Xue Tang,[a] Yang Chen,[b] Cheng Peng[*ab] and Bo Han[*a]

[a] *State Key Laboratory Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China. E-mail: hanbo@cdutcm.edu.cn.*

[b] *Ministry of Education Key Laboratory of Standardization of Chinese Medicine, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China. E-mail: pengchengchengdu@126.com.*

[†] *These authors contributed equally to this work.*

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1. Molecular docking

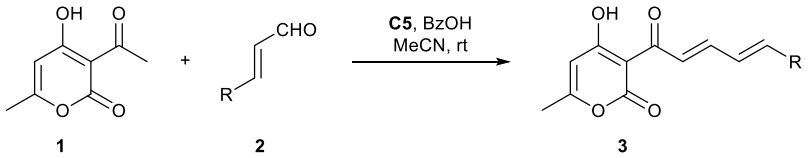
Molecular docking was performed using the CDOCKER program embedded in the Accelrys Discovery Studio 3.5 package (DS 3.5). The Pogostone structure was generated by DS 3.5, and then minimized using the CHARMM27 force field. The crystal structure of PETNR (scPDB: P71278) was used for docking. The binding site was defined to be the interaction residues Thr24, Leu26, Tyr66, Trp100, His182, Tyr184 and Tyr349; the radius was 10 Å. Automated molecular docking was performed using the "partial flexibility" CDOCKER tool in DS 3.5 in the presence of zinc cofactor. The best molecular docking results were identified based on docking scores and binding free energy. DS 3.5 was used to identify and visualize hydrogen bonds as well as hydrophobic, hydrophilic and coordination interactions with amino acid residues in the enzyme active site.

2. Chemistry

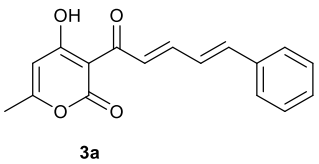
2.1 General Information

NMR data were obtained for ^{1}H at 400 MHz and for ^{13}C at 100 MHz, or for ^{1}H at 600 MHz and for ^{13}C at 150 MHz. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as internal standard with solvent resonance in $CDCl_3$. Mass spectra were recorded using electrospray ionization on a Q-TOF instrument. Column chromatography was performed on a silica gel (200-300 mesh) using an eluent of ethyl acetate and petroleum ether. TLC was performed on glassbacked silica plates; products were visualized using UV light. Melting points were determined on a Mel-Temp apparatus.

2.2 General Procedure for the Synthesis of Pogostone derivatives 3

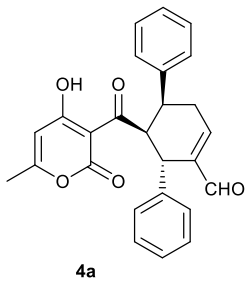


To dehydroacetic acid **1** (50.4 mg, 0.3 mmol), amine catalyst **C5** (35.9 mg, 0.06 mmol), benzoic acid (14.7mg, 0.12 mmol) and MeCN (1.5 mL) in a standard glass vial with stir bar was added α,β-unsaturated aldehyde **2** (0.36 mmol in 0.5 mL MeCN). The reaction mixture was stirred at room temperature until the reaction was completed based on TLC. The reaction mixture was concentrated, and the residue was purified by flash chromatography on a silica gel (Petroleum ether / Ethyl Acetate = 7:1) to give the Pogostone derivatives **3** which were dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry.



3a

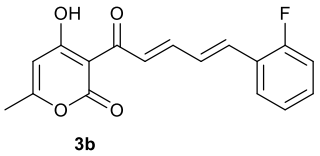
4-hydroxy-6-methyl-3-((2*E*,4*E*)-5-phenylpenta-2,4-dieno-yl)-2*H*-pyran-2-one (3a): yellow solid, 72.6 mg, 86% yield, m.p. 168-172 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 15.0 Hz, 1H), 7.77 (dd, *J* = 15.0, 10.2 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 6.6 Hz, 1H), 7.11 (dd, *J* = 15.6, 10.2 Hz, 1H), 7.05 (d, *J* = 15.6 Hz, 1H), 5.95 (s, 1H), 2.27 (s, 3H) ppm . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 183.4, 168.4, 161.2, 146.7, 143.4, 135.9, 129.6, 128.9, 127.6, 127.4, 126.3, 102.6, 99.3, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{14}O_4$+Na: 305.0790, found: 305.0792.



4a

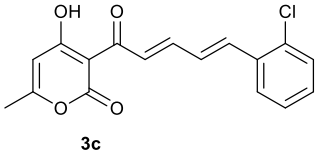
(1'*S*,2'*S*,3'*S*)-2'-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-carbonyl)-1',2',3',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carbaldehyde (4a): white solid, 11.2 mg, 9% yield, m.p. 121-124 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.41 (d, *J*

= 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.18 (dd, *J* = 15.2, 7.2 Hz, 4H), 7.08 (d, *J* = 7.2 Hz, 2H), 5.86 (s, 1H), 4.79 (s, 1H), 4.26 (s, 1H), 3.37-3.31 (m, 2H), 3.01-2.95 (m, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6, 192.7, 181.7, 169.1, 160.8, 152.8, 141.5, 141.3, 139.9, 128.6, 128.4, 128.3, 127.6, 126.8, 126.7, 101.7, 99.7, 53.0, 40.0, 36.7, 31.1, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{26}H_{22}O_5$+Na: 437.1365, found: 437.1364.



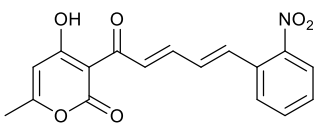
3b

3-((2*E*,4*E*)-5-(2-fluoro-phenyl)penta-2,4-dieno-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3b): yellow solid, 72.9 mg, 81% yield, m.p. 189-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 15.2 Hz, 1H), 7.75 (dd, *J* = 14.8, 9.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.34-7.28 (m, 1H), 7.19-7.06 (m, 4H), 5.95 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 183.3, 168.5, 161.2, 160.9 (d, J_{CF} = 251.3 Hz), 146.5, 135.3 (d, J_{CF} = 3.3 Hz), 130.9 (d, J_{CF} = 8.6 Hz), 129.6 (d, J_{CF} = 5.6 Hz), 127.9 (d, J_{CF} = 3.0 Hz), 127.1, 124.4 (d, J_{CF} = 3.5 Hz), 124.0 (d, J_{CF} = 11.7 Hz), 116.1 (d, J_{CF} = 21.9 Hz), 102.5, 99.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}FO_4$+Na: 323.0696, found: 323.0700.



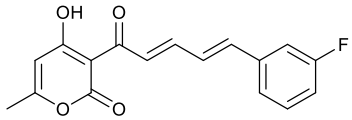
3c

3-((2*E*,4*E*)-5-(2-chloro-phenyl)penta-2,4-dieno-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3c): yellow solid, 74.6 mg, 79% yield, m.p. 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 14.8 Hz, 1H), 7.79 (dd, *J* = 15.2, 10.8 Hz, 1H), 7.68 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.47 (d, *J* = 15.6 Hz, 1H), 7.40 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.31-7.24 (m, 2H), 7.08 (dd, *J* = 15.6, 10.4Hz, 1H), 5.95 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 183.3, 168.6, 161.2, 146.1, 138.5, 134.4, 133.9, 130.3, 130.1, 129.5, 127.4, 127.1, 127.0, 102.5, 99.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}ClO_4$+Na: 339.0400, found: 339.0397.



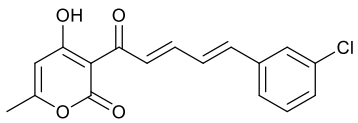
3d

4-hydroxy-6-methyl-3-((2*E*,4*E*)-5-(2-nitrophenyl)penta-2,4-dienoyl)-2*H*-pyran-2-one (3d): yellow solid, 78.4 mg, 80% yield, m.p. 193-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 14.8 Hz, 1H), 7.78-7.71 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.55-7.47 (m, 2H), 7.06 (dd, *J* = 15.6, 11.2 Hz, 1H), 5.97 (s, 1H), 2.29 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 183.1, 168.8, 161.2, 148.1, 145.0, 136.8, 133.3, 132.0, 131.5, 129.5, 128.8, 128.4, 125.0, 102.4, 99.5, 20.7 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}NO_6$+Na: 350.0641, found: 350.0638.



3e

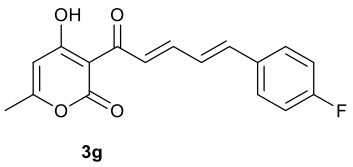
3-((2*E*,4*E*)-5-(3-fluorophenyl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3f): yellow solid, 73.8 mg, 82% yield, m.p. 199-202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 15.2 Hz, 1H), 7.73 (dd, *J* = 15.2, 10.4 Hz, 1H), 7.37-7.27 (m, 2H), 7.20 (d, *J* = 10.0 Hz, 1H), 7.09 (dd, *J* = 15.6, 10.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 15.6 Hz, 1H), 5.96 (s, 1H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 183.3, 168.6, 163.1 (d, J_{CF} = 245.0 Hz), 161.2, 145.8, 141.6 (d, J_{CF} = 2.8 Hz), 138.2 (d, J_{CF} = 7.6 Hz), 130.4 (d, J_{CF} = 8.3 Hz), 128.6, 127.3, 123.4 (d, J_{CF} = 2.8 Hz), 116.3 (d, J_{CF} = 21.3 Hz), 113.8 (d, J_{CF} = 21.9 Hz), 102.5, 99.4, 20.7 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}FO_4$+Na: 323.0696, found: 323.0698.



3f

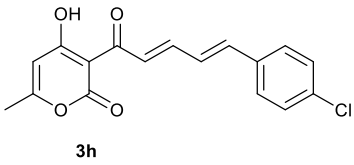
3-((2*E*,4*E*)-5-(3-chlorophenyl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3f): yellow solid, 76.8 mg, 81% yield, m.p. 165-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 14.8 Hz, 1H), 7.71 (dd, *J* = 14.8, 10.8 Hz, 1H), 7.48 (s, 1H), 7.38-7.29 (m, 3H), 7.09 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 5.95 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 192.3, 183.3, 168.6, 161.2, 145.7, 141.3, 137.8, 134.9, 130.1, 129.3, 128.7, 127.4, 127.4, 125.6, 102.5, 99.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}ClO_4$+Na: 339.0400, found: 339.0401.



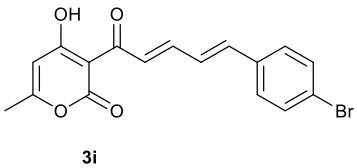
3g

3-((2*E*,4*E*)-5-(4-fluorophenyl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3g): yellow solid, 75.6 mg, 84% yield, m.p. 189-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.70 (m, 2H), 7.50-7.47 (m, 2H), 7.08-7.00 (m, 4H), 5.94 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 183.3, 168.5, 163.4 (d, J_{CF} = 249.3 Hz), 161.2, 146.4, 141.9 (d, J_{CF} = 0.9 Hz), 132.2 (d, J_{CF} = 3.4 Hz), 129.3 (d, J_{CF} = 8.2 Hz), 127.2 (d, J_{CF} = 2.4 Hz), 126.4 (d, J_{CF} = 0.8 Hz), 116.0 (d, J_{CF} = 21.8 Hz), 102.6, 99.3, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}FO_4$+Na: 323.0696, found: 323.0701.



3h

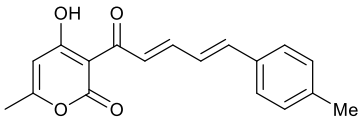
3-((2*E*,4*E*)-5-(4-chlorophenyl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3h): yellow solid, 82.8 mg, 87% yield, m.p. 174-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 15.2 Hz, 1H), 7.72 (dd, *J* = 15.2, 10.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.06 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.98 (d, *J* = 15.2 Hz, 1H), 5.95 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 183.3, 168.5, 161.2, 146.1, 141.6, 135.3, 134.5, 129.2, 128.7, 127.9, 126.9, 102.5, 99.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}ClO_4$+Na: 339.0400, found: 339.0399.



3i

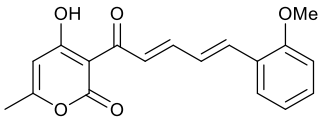
3-((2*E*,4*E*)-5-(4-bromophenyl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3i): yellow solid, 92.1 mg, 85% yield, m.p. 179-182 °C. ^{1}H NMR (400

MHz, $CDCl_3$): δ = 7.84 (d, *J* = 15.2 Hz, 1H), 7.71 (dd, *J* = 15.2, 10.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.96 (d, *J* = 15.2 Hz, 1H), 5.94 (s, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 183.3, 168.5, 161.2, 146.1, 141.7, 134.9, 132.1, 128.9, 128.0, 127.0, 123.6, 102.5, 99.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{13}BrO_4$+Na: 382.9895, found: 382.9893.



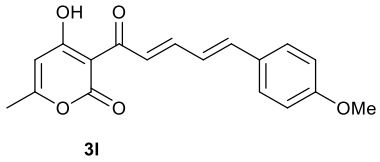
3j

4-hydroxy-6-methyl-3-((2*E*,4*E*)-5-(*p*-tolyl)penta-2,4-dienoyl)-2*H*-pyran-2-one (3j): yellow solid, 66.4 mg, 75% yield, m.p. 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 14.4 Hz, 1H), 7.75 (dd, *J* = 14.4, 8.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.09-6.99 (m, 2H), 5.92 (s, 1H), 2.36 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 183.4, 168.3, 161.2, 147.2, 143.7, 140.0, 133.3, 129.7, 127.6, 126.5, 125.7, 102.6, 99.3, 21.3, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{18}H_{16}O_4$+Na: 319.0946, found: 319.0941.



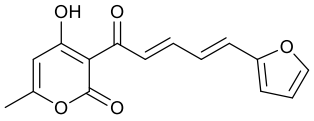
3k

4-hydroxy-3-((2*E*,4*E*)-5-(2-methoxyphenyl)penta-2,4-dienoyl)-6-methyl-2*H*-pyran-2-one (3k), yellow solid, 70.1 mg, 75% yield, m.p. 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 2.0 Hz, 1H), 7.79 (s, 1H), 7.53 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.20-7.13 (m, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.92 (s, 1H), 3.89 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 183.5, 168.2, 161.3, 157.8, 148.2, 139.0, 130.9, 128.1, 128.0, 125.4, 124.9, 120.8, 111.1, 102.7, 99.3, 55.5, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{18}H_{16}O_5$+Na: 335.0895, found: 335.0897.



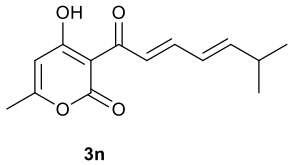
3l

4-hydroxy-3-((2*E*,4*E*)-5-(4-methoxyphenyl)penta-2,4-dienoyl)-6-methyl-2*H*-pyran-2-one (3l): yellow solid, 71.7 mg, 77% yield, m.p. 152-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.72 (m, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.03-6.93 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.92 (s, 1H), 3.84 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 183.5, 168.1, 161.3, 161.0, 147.5, 143.5, 129.3, 128.8, 125.4, 125.0, 114.4, 114.4, 102.7, 99.2, 55.4, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{18}H_{16}O_5$+Na: 335.0895, found: 335.0894.



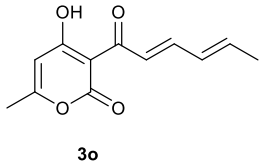
3m

3-((2*E*,4*E*)-5-(furan-2-yl)penta-2,4-dienoyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (3m), yellow solid, 59.5 mg, 73% yield, m.p. 178-181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 14.8 Hz, 1H), 7.70 (dd, *J* = 15.2, 11.2 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 6.98 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 6.47 (q, *J* = 1.6 Hz, 1H), 5.93 (s, 1H), 2.26 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 183.4, 168.3, 161.2, 152.3, 146.3, 144.4, 129.5, 126.1, 125.8, 113.2, 112.5, 102.6, 99.3, 20.6 ppm. HRMS (ESI): *m/z* calculated for $C_{15}H_{12}O_5$+Na: 295.0582, found: 295.0580.



3n

4-hydroxy-6-methyl-3-((2*E*,4*E*)-6-methylhepta-2,4-dienoyl)-2H-pyran-2-one (3n): pale yellow, 36.7 mg, 49% yield, m.p. 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1H), 5.47 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.29 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.36 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.19 (dd, *J* = 17.6, 8.4 Hz, 1H), 2.25 (s, 3H), 2.11 (dq, *J* = 13.6, 6.8 Hz, 1H), 0.79 (dd, *J* = 12.4, 6.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.5, 180.6, 168.9, 160.4, 140.9, 124.4, 101.3, 100.2, 51.1, 37.3, 30.8, 22.4, 22.3, 20.7 ppm. HRMS (ESI): *m/z* calculated for $C_{14}H_{16}O_4$+Na: 271.0946, found: 271.0948.



3o

3-((2E,4E)-hexa-2,4-dienoyl)-4-hydroxy-6-methyl-2H-pyran-2-one (3o): yellow solid, 29.3 mg, 44% yield, *Z*/*E* ratio 2.5:1, m.p. 85-87 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72-7.53 (m, 2H), 6.51-6.29 (m, 2H), 5.92 (s, 1H), 2.26 (s, 3H), 1.92 (d, *J* = 6.0 Hz, 2H), 1.84 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 183.3, 168.3, 161.2, 147.2, 143.1, 131.2, 124.2, 102.5, 99.2, 20.6, 19.1 ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{12}O_4$+Na: 243.0633, found: 243.0634.

3. Procedure for in vitro minimum inhibitory concentration assay

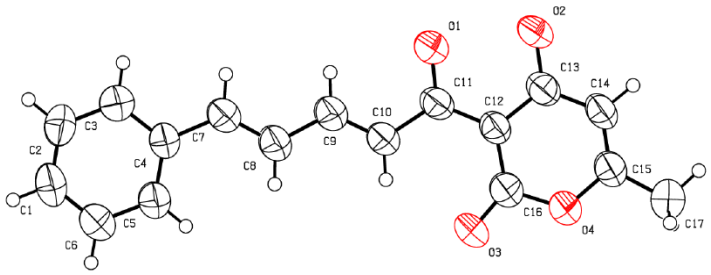
Bacteria

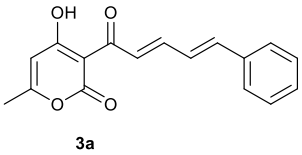
E. coli ATCC, 25922, *E. coli* CMCC 44102, *S. aureus* ATCC 25923, *S. aureus* CMCC 26003, MRSA ATCC 43300 and MRSA ATCC 33591 were cultured in the trypticase soy broth at 37 ºC.

In vitro MIC assay

The MIC of each compound was determined using a standard broth microdilution assay consistent with the guidelines of the Clinical Laboratory Standards Institute. Stock solutions of test compounds were diluted in a 2-fold series to achieve the desired concentrations. The MIC was defined as the lowest concentration of the chemical that inhibited the development of visible bacterial growth after incubation at 37 ºC for 18-24 h.

4. Crystal Data of 3a

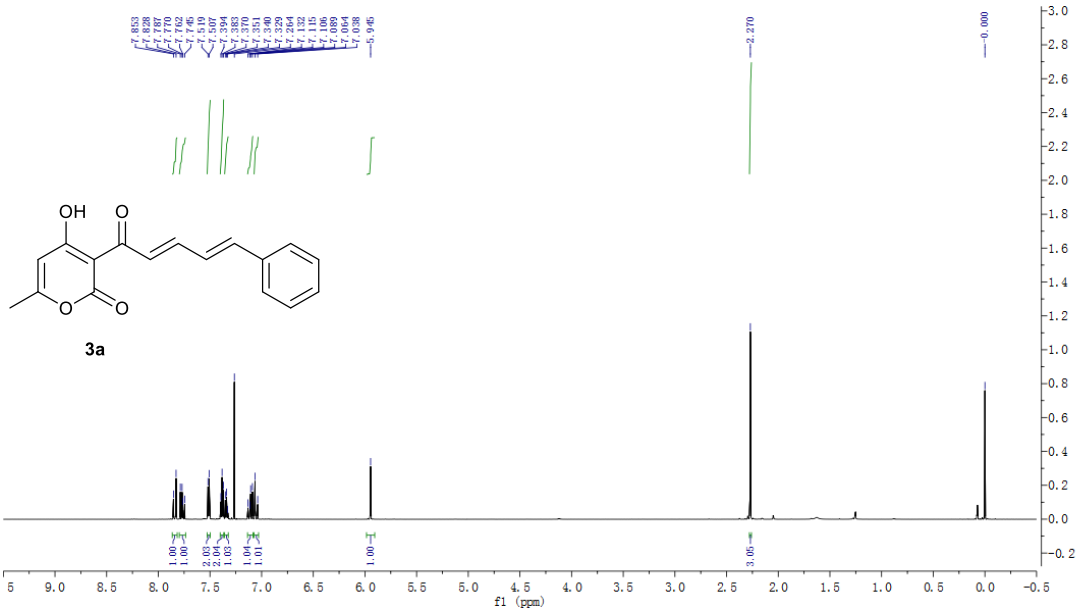


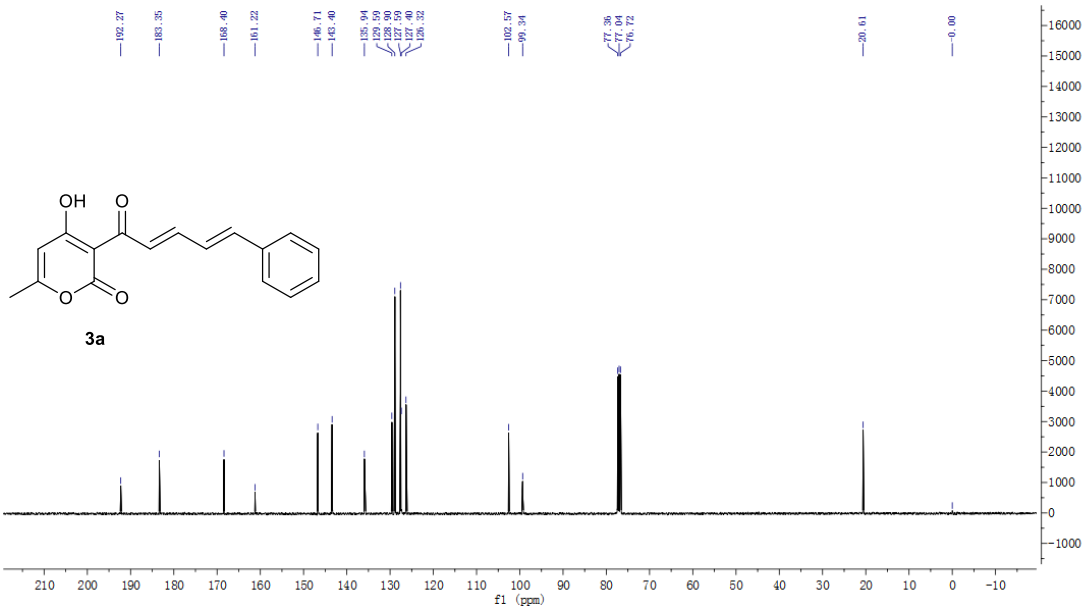


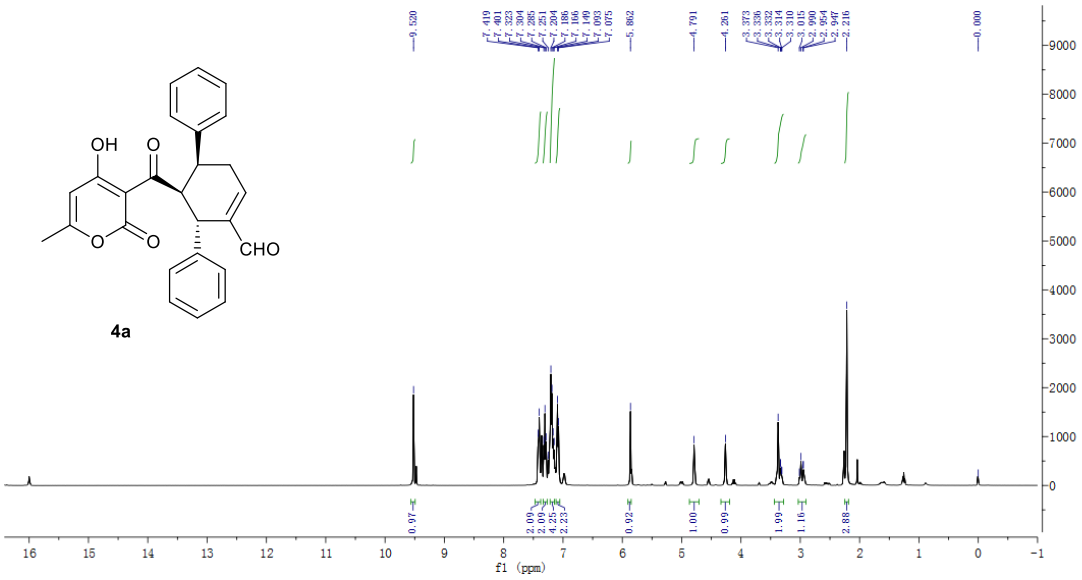
ORTEP Drawing of compound **3a**.

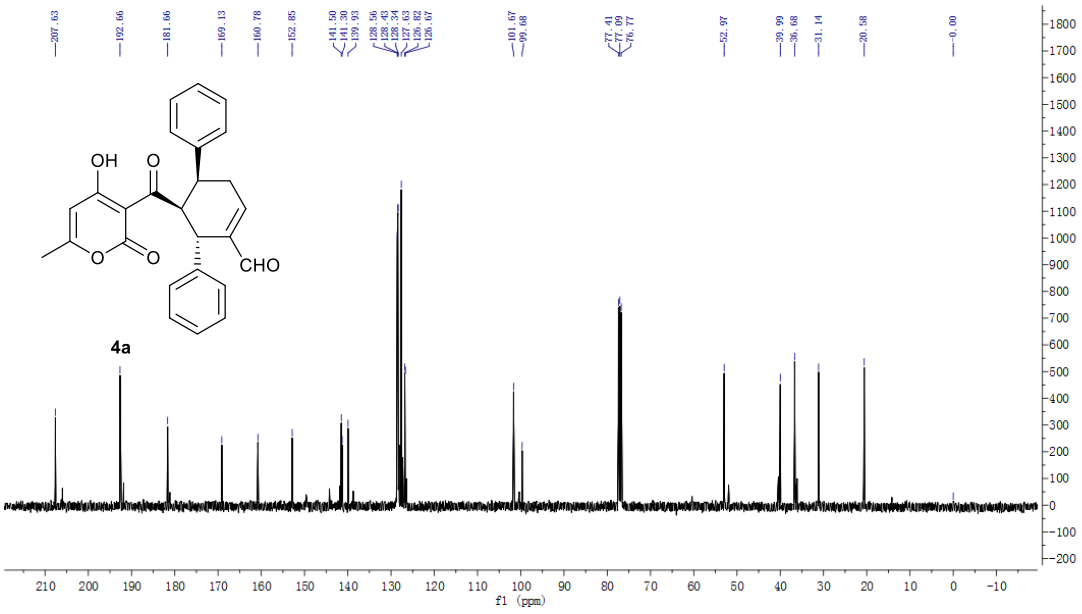
Empirical formula	$C_{17}H_{13}O_4$
Formula weight	281.27
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	6.9865(17)
b/Å	8.511(2)
c/Å	11.9757(18)
α/°	88.053(17)
β/°	77.077(18)
γ/°	84.50(2)
Volume/Å^3	690.8(3)
Z	2
ρ_{calc}g/cm^3	1.352
μ/mm^{-1}	0.797
F(000)	294.0
Crystal size/mm^3	0.1 × 0.1 × 0.05
Radiation	Cu Kα (λ = 1.5418)
2Θ range for data collection/°	7.58 to 134.48
Index ranges	-8 ≤ h ≤ 7, -10 ≤ k ≤ 9, -12 ≤ l ≤ 14
Reflections collected	4008
Independent reflections	2420 [R_{int} = 0.0291, R_{sigma} = 0.0588]
Data/restraints/parameters	2420/0/192
Goodness-of-fit on F^2	0.999
Final R indexes [I>=2σ (I)]	R_1 = 0.0789, wR_2 = 0.2226
Final R indexes [all data]	R_1 = 0.1414, wR_2 = 0.2941
Largest diff. peak/hole / e Å^{-3}	0.29/-0.28

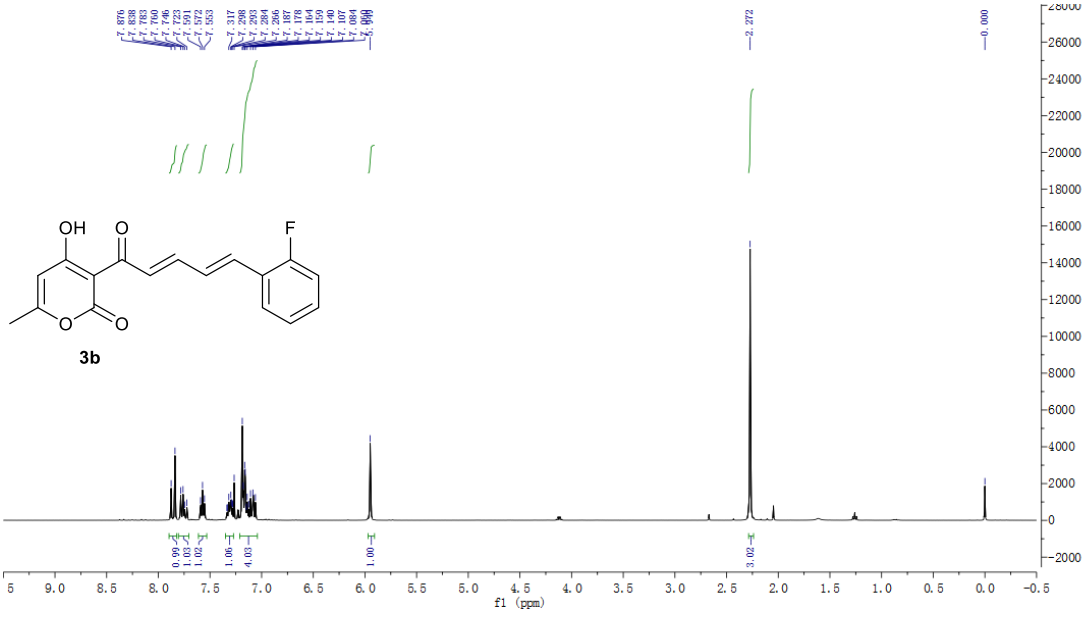
5. NMR Spectra of the Pogostone derivatives 3

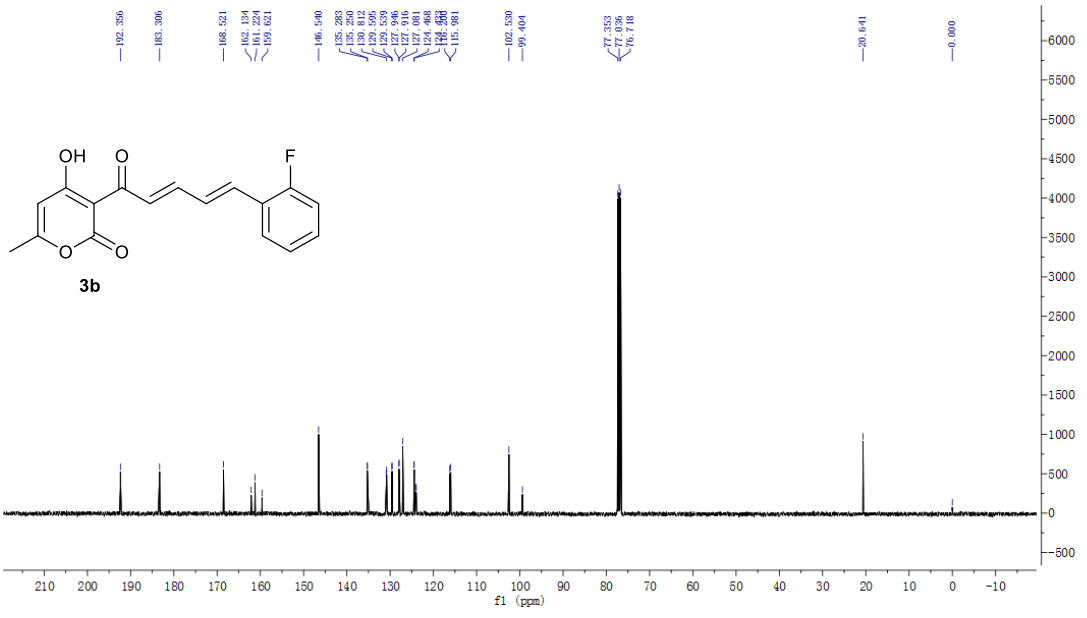


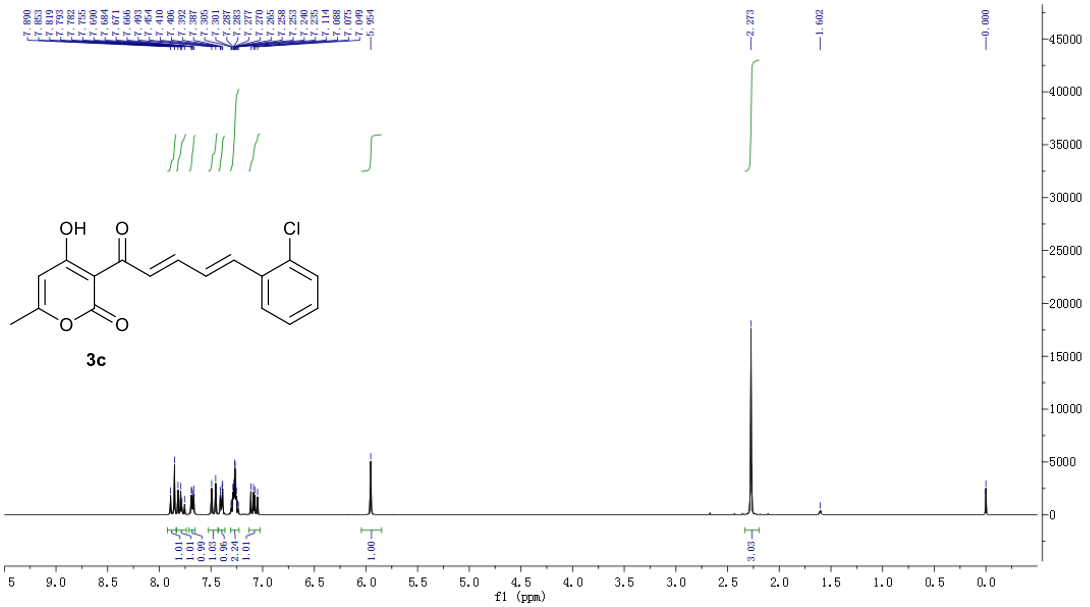


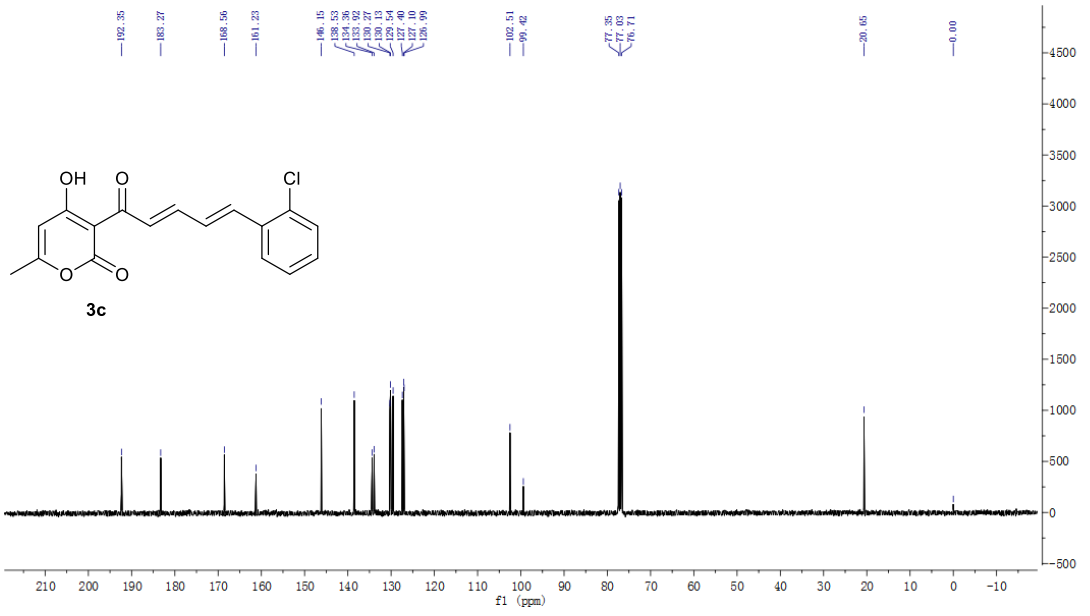

OH
O
O
O
CHO
4a
f1 (ppm)

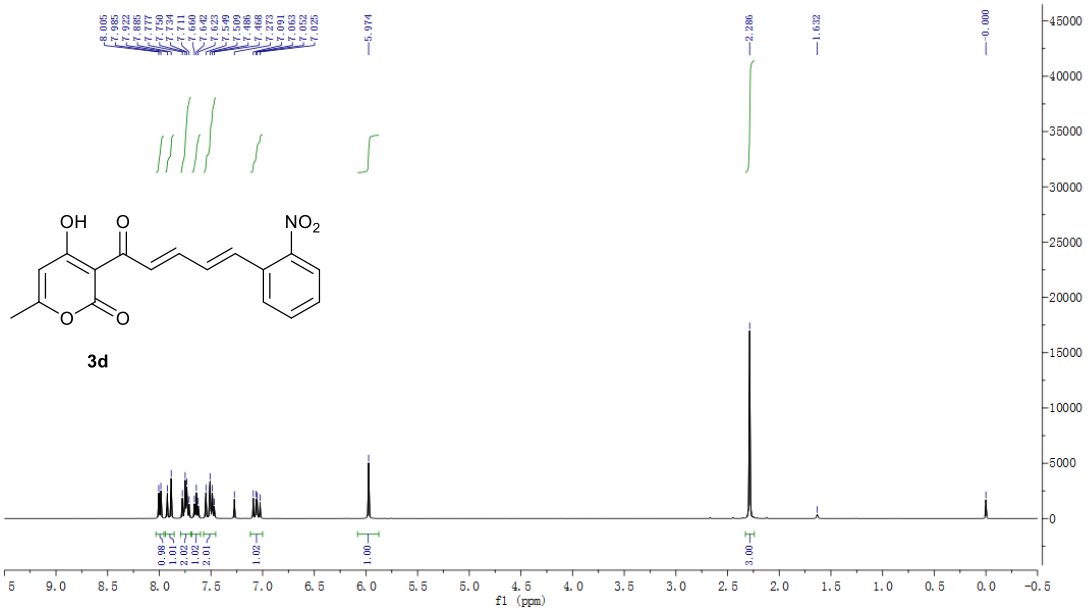

OH
O
O
O
CHO
4a
f1 (ppm)


OH
O
F
O
O
3b
f1 (ppm)


OH
O
F
O
O
3b
f1 (ppm)


OH
O
Cl
O
O
3c
f1 (ppm)


OH
O
Cl
O
O
3c
f1 (ppm)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O
NO2
O
O
3d
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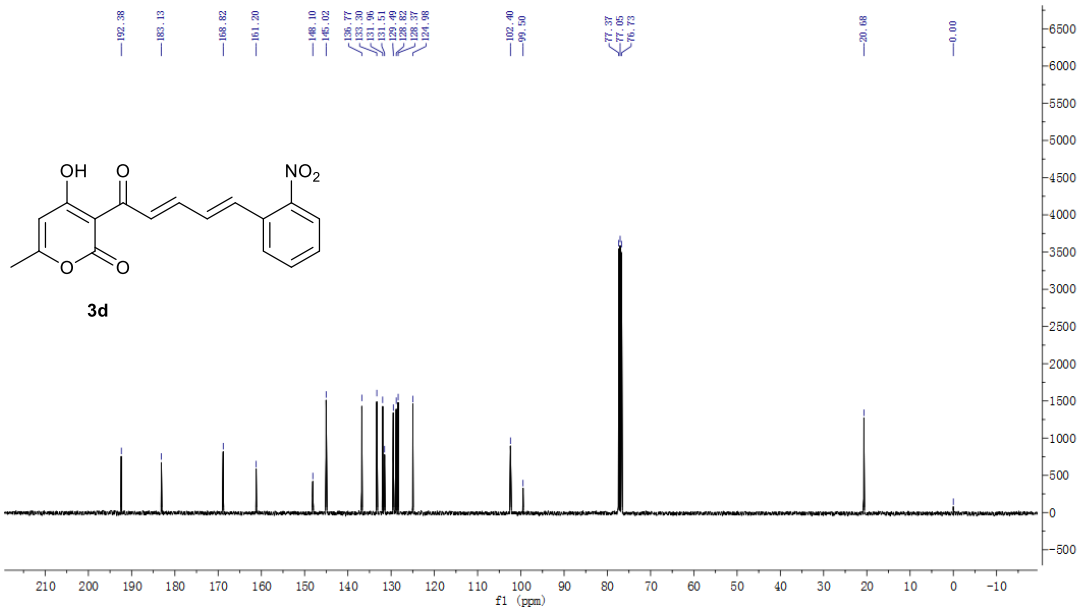
7.995
7.932
7.885
7.777
7.750
7.734
7.711
7.660
7.642
7.623
7.569
7.509
7.486
7.468
7.273
7.091
7.063
7.052
7.025
5.974
2.286
1.632
0.000
0.98
1.01
2.02
1.02
2.01
1.02
1.00
3.00
f1 (ppm)


OH
O
NO2
O
O
3d
192.38
183.13
168.82
161.20
148.10
145.02
136.77
133.30
131.96
131.51
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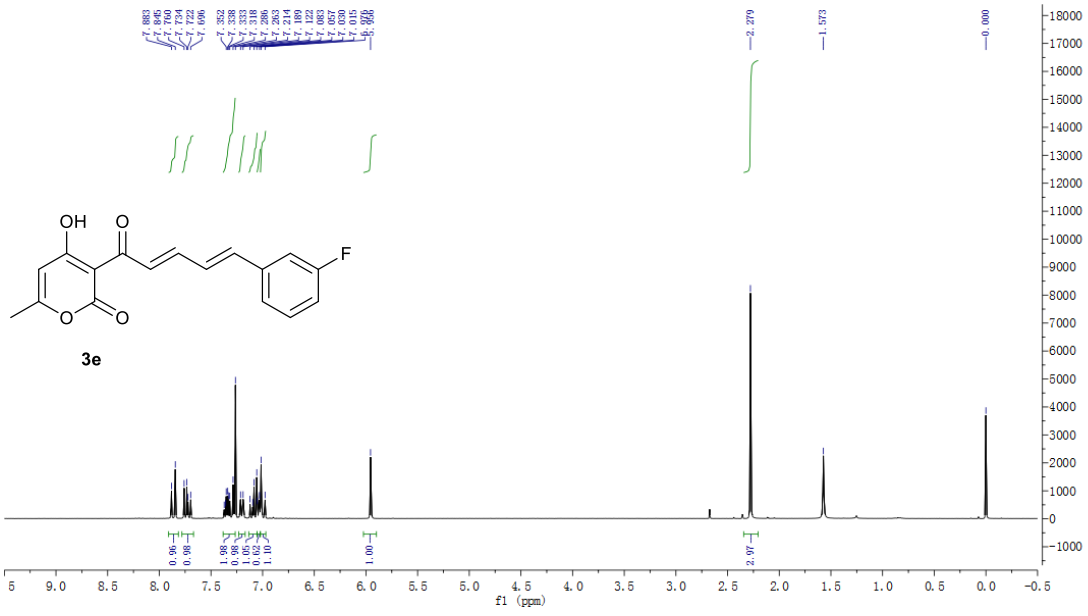
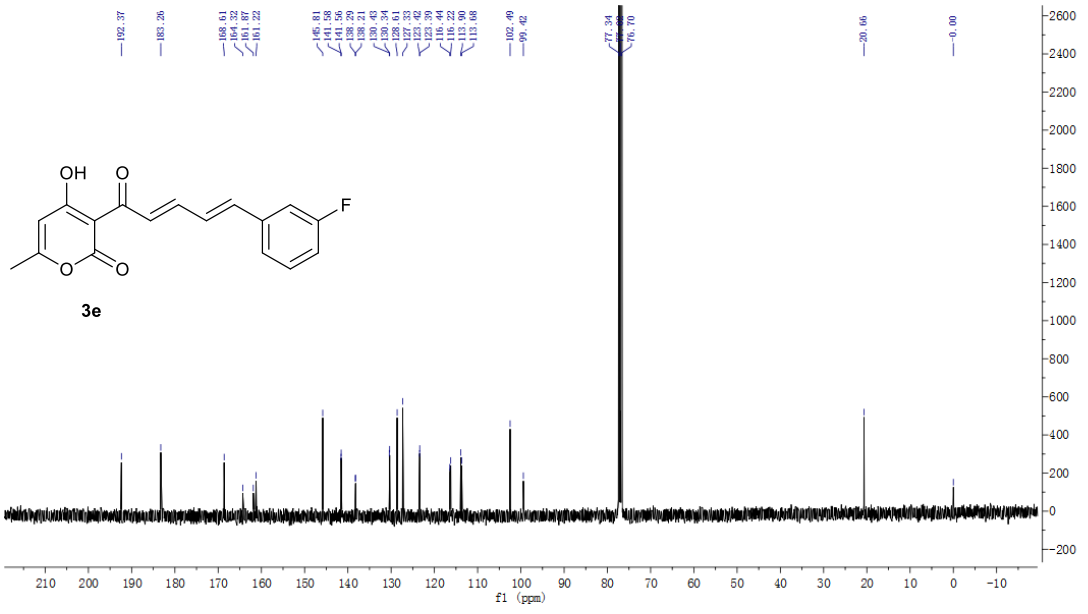
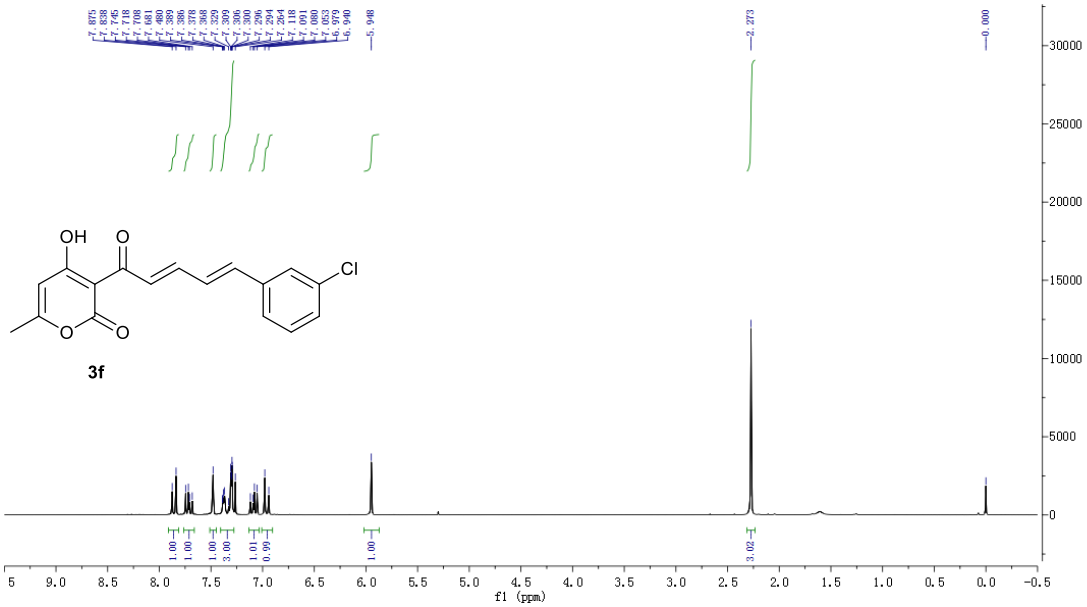
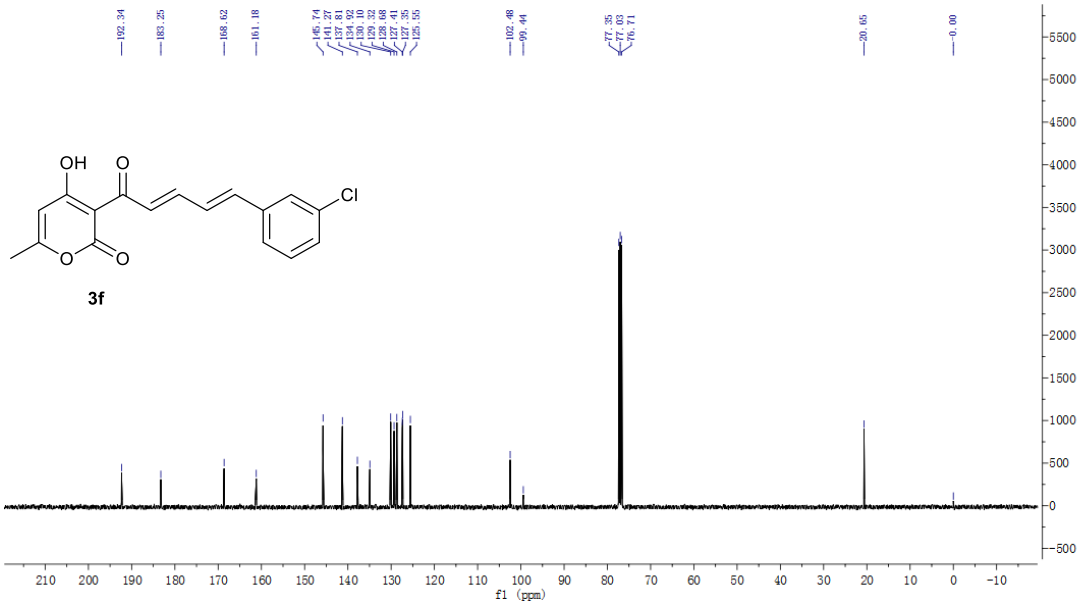
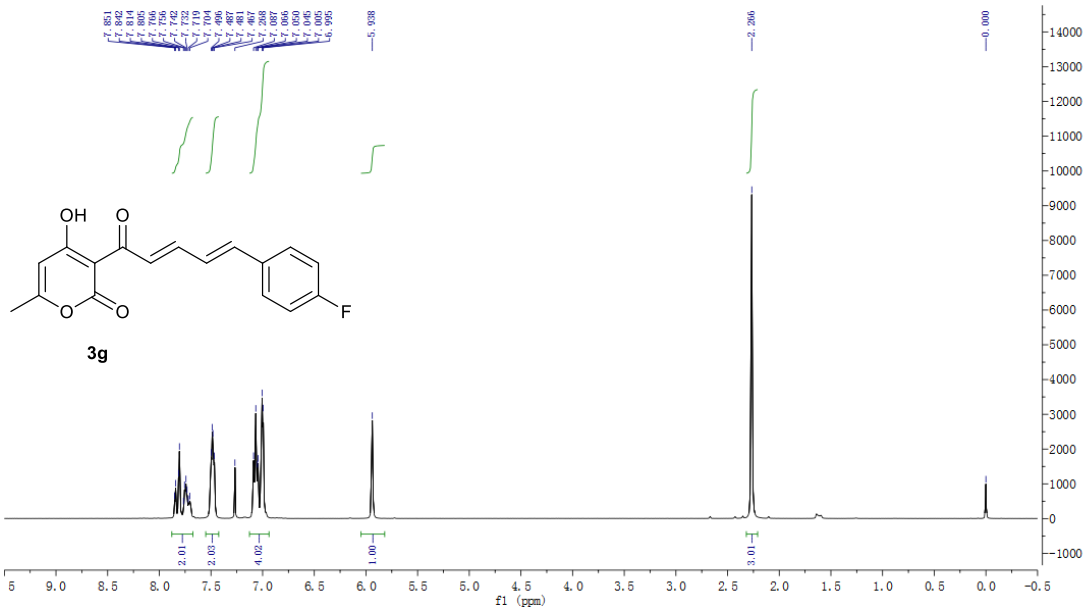
77.05
76.73
20.68
0.00
f1 (ppm)


OH
O
F
O
O
3e
f1 (ppm)


OH
O
F
O
O
3e
f1 (ppm)


OH
O
Cl
O
O
3f
f1 (ppm)


OH
O
Cl
O
O
3f
f1 (ppm)


OH
O
O
O
F
3g
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7.842
7.814
7.805
7.766
7.756
7.742
7.732
7.719
7.704
7.496
7.487
7.481
7.467
7.268
7.087
7.066
7.050
7.045
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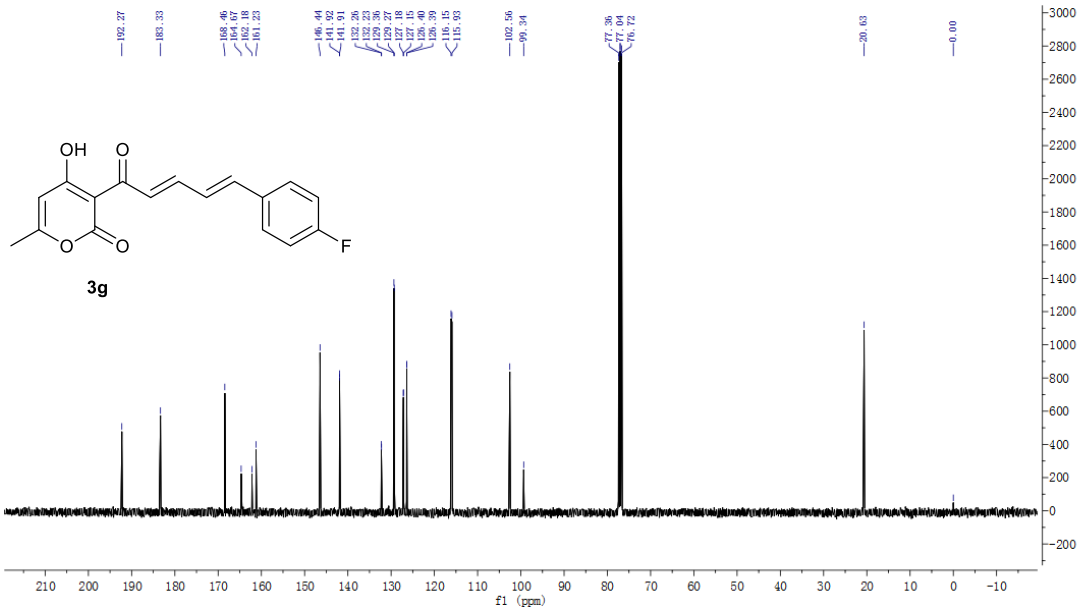
5.938
2.266
0.000
2.01
2.03
4.02
1.00
3.01
f1 (ppm)


OH
O
O
O
F
3g
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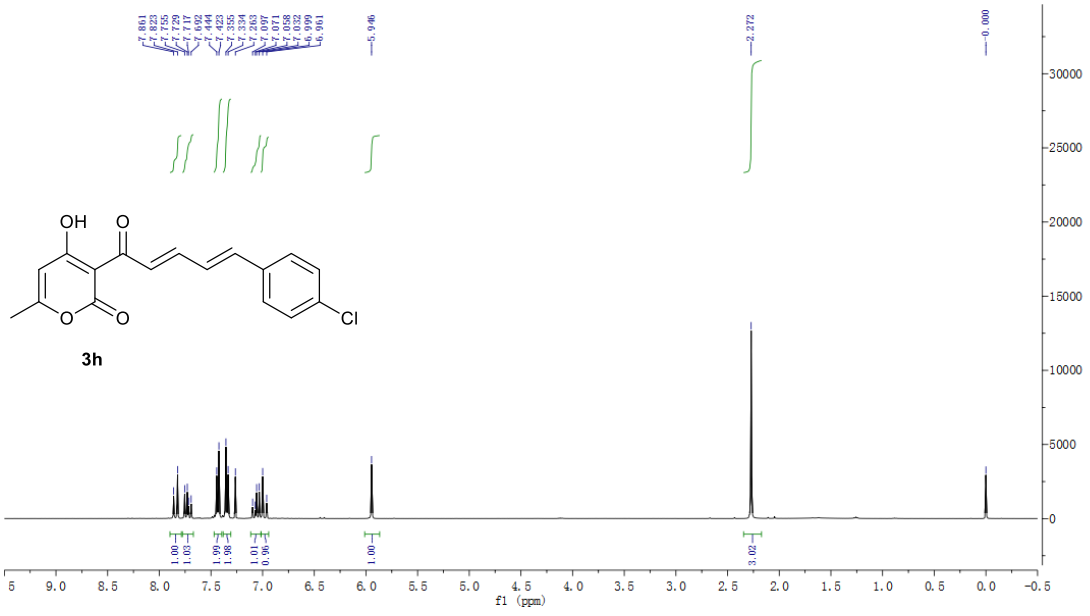
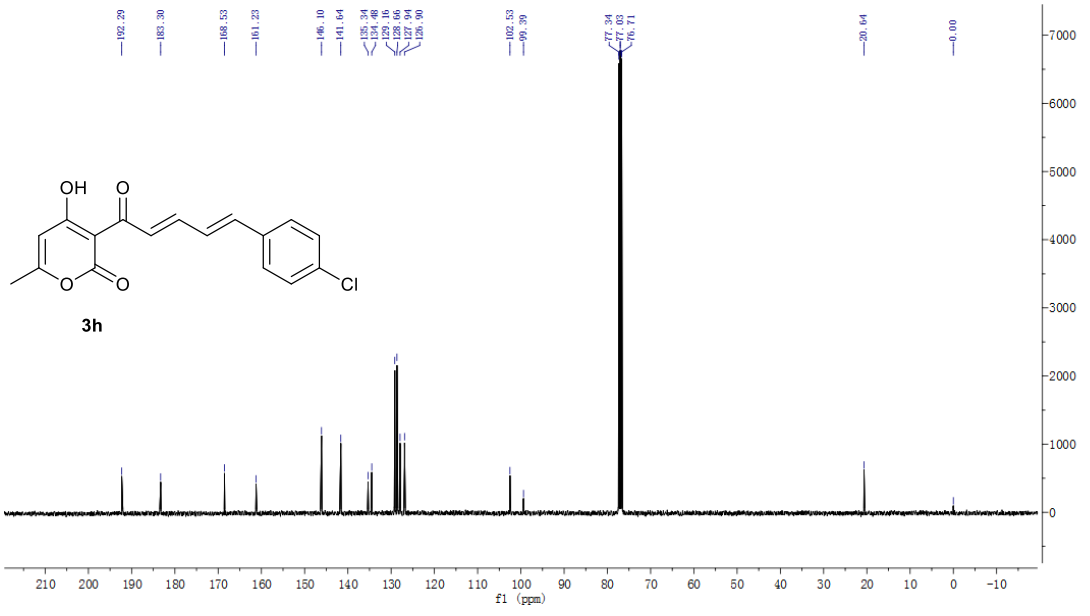
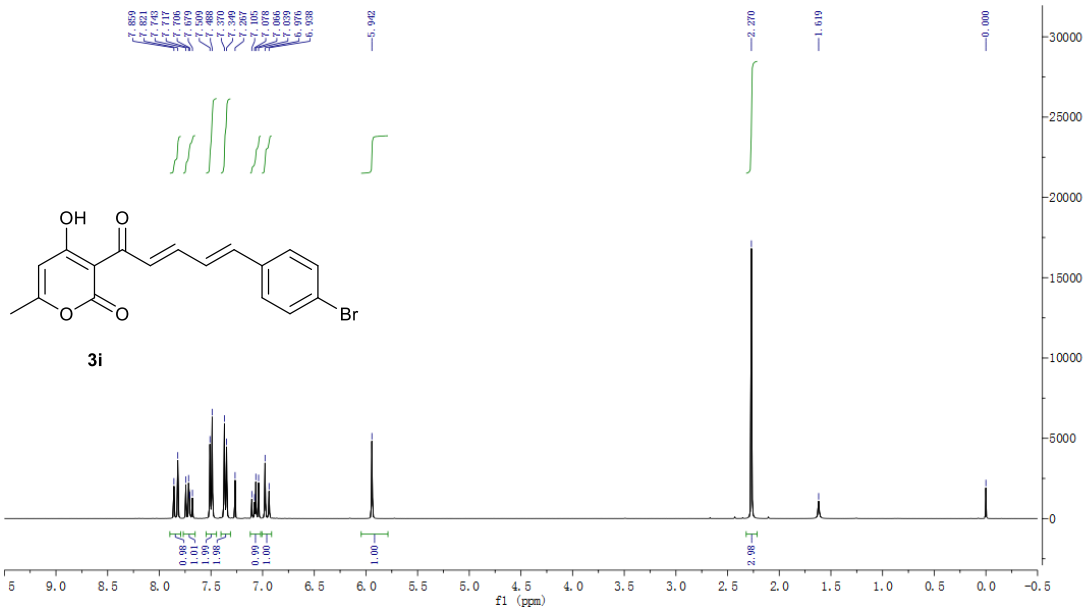
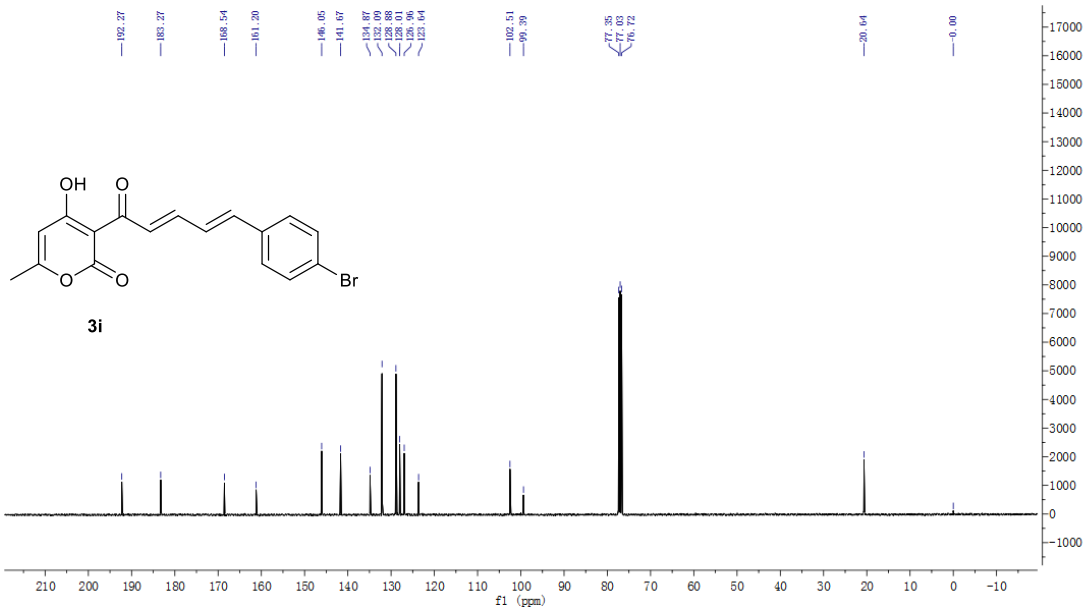
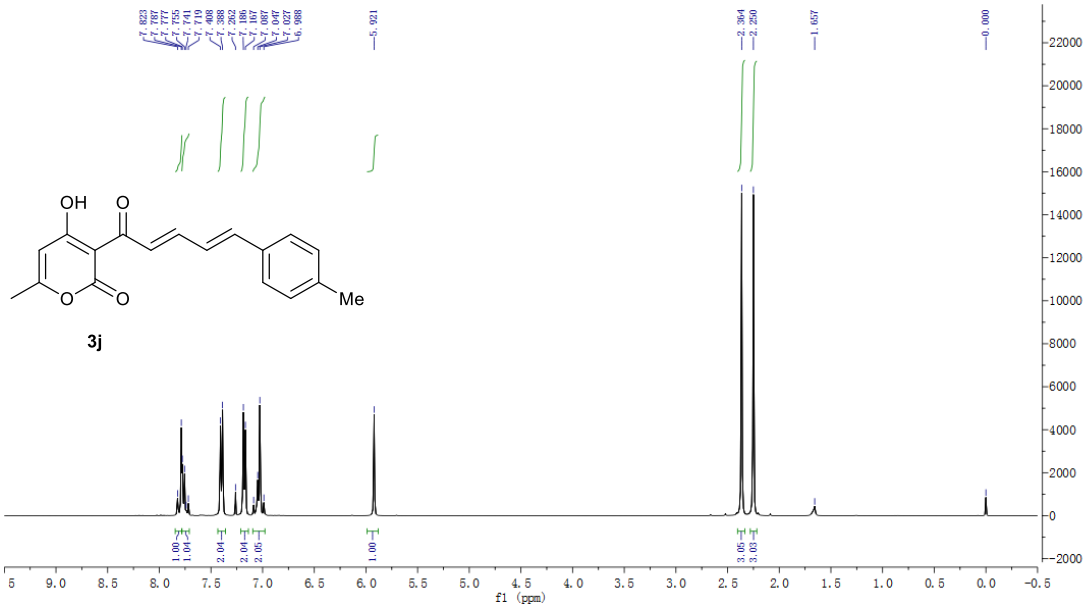
183.33
168.46
164.67
162.18
161.23
146.44
141.92
141.91
132.26
132.23
129.36
129.27
127.18
127.15
126.40
126.39
116.15
115.93
102.56
99.34
77.36
77.04
76.72
20.63
0.00
f1 (ppm)

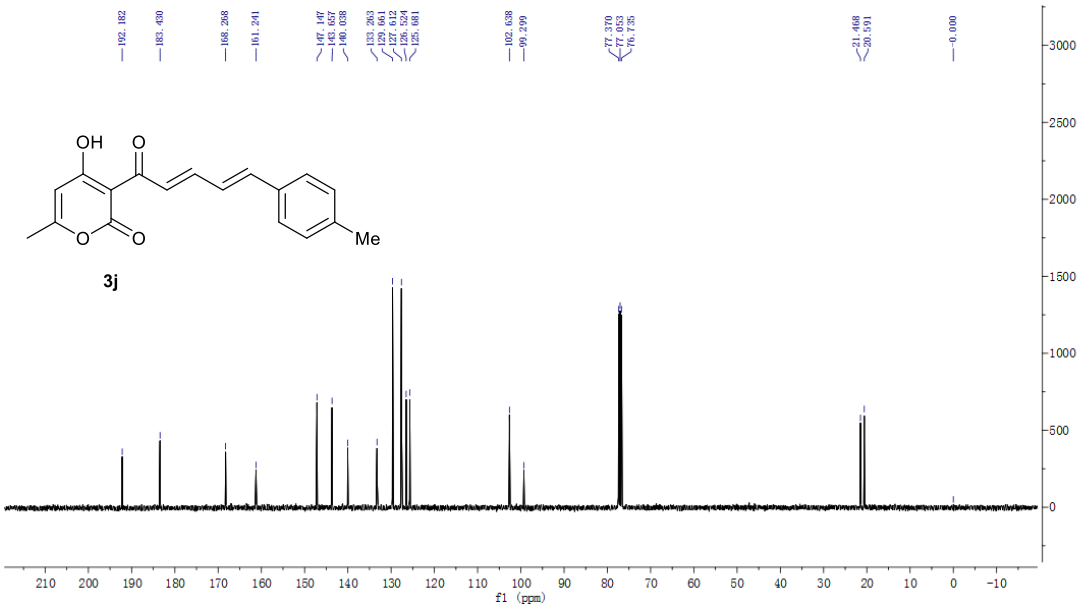

7.861
7.823
7.755
7.729
7.717
7.660
7.444
7.423
7.355
7.334
7.303
7.097
7.071
7.058
7.032
6.999
6.961
5.946
2.272
0.000
OH
O
O
O
Cl
3h
1.00
1.03
1.99
1.98
1.01
0.96
1.00
3.02
f1 (ppm)

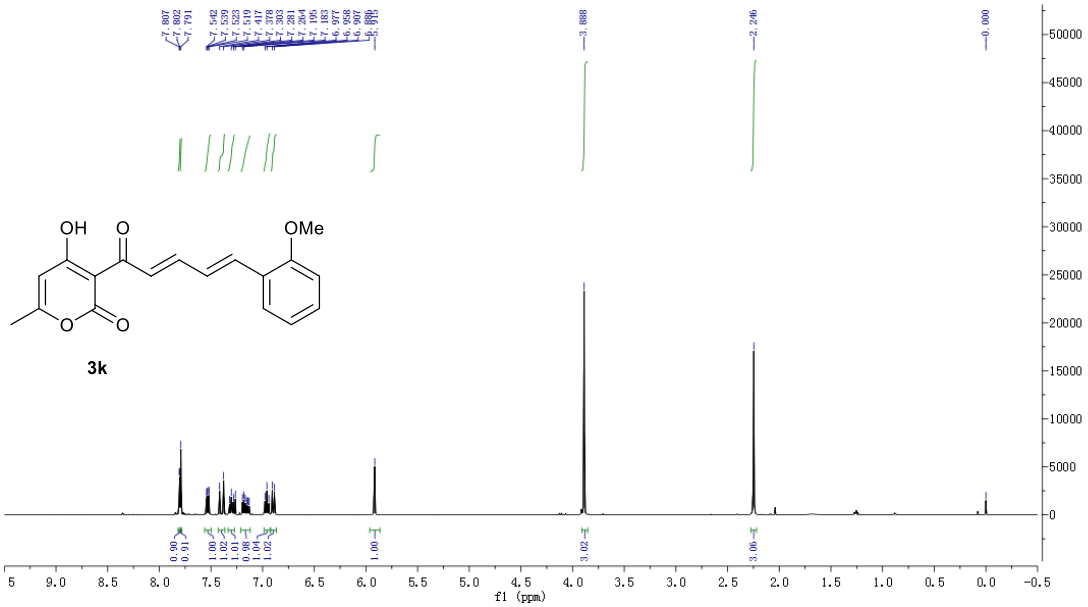

192.29
183.30
168.53
161.23
146.10
141.64
135.34
134.48
129.16
128.66
127.64
126.90
102.53
99.39
77.34
77.03
76.71
20.64
0.00
OH
O
O
O
Cl
3h
f1 (ppm)

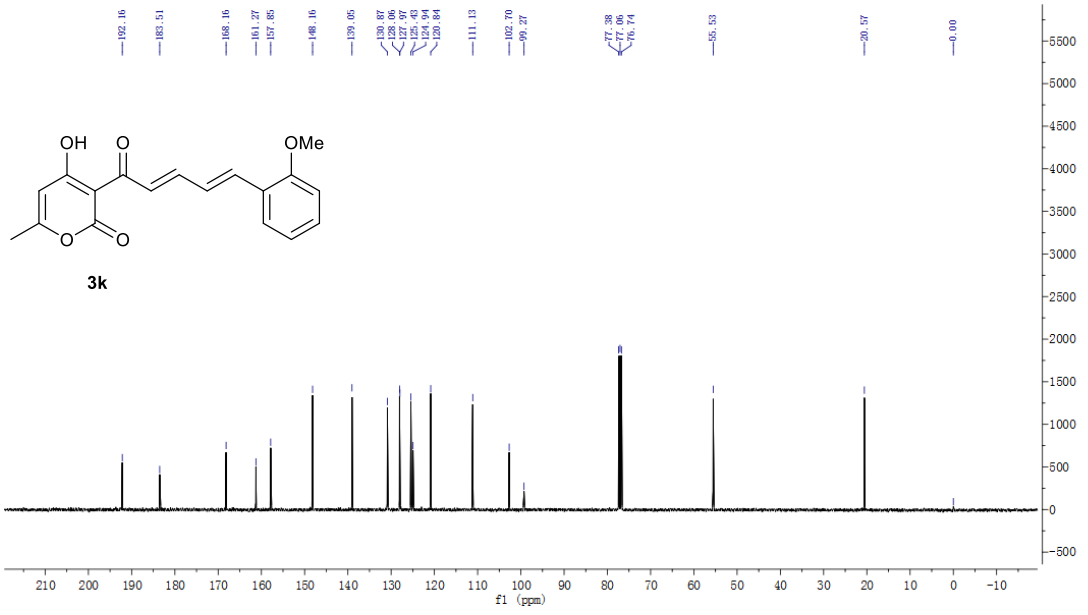

OH
O
O
O
Br
3i
f1 (ppm)

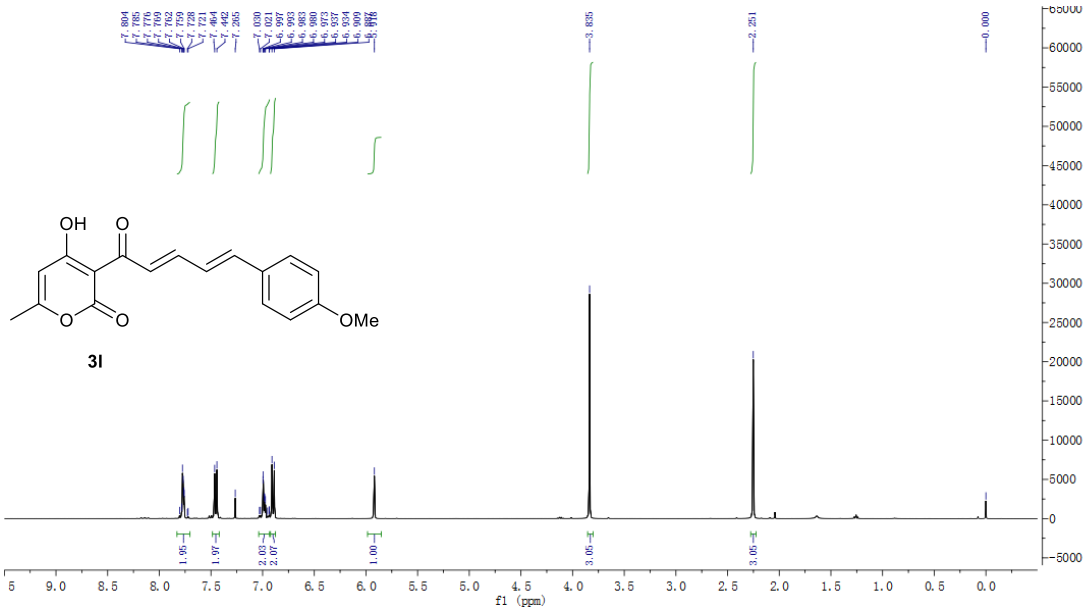

OH
O
O
O
Br
3i
f1 (ppm)

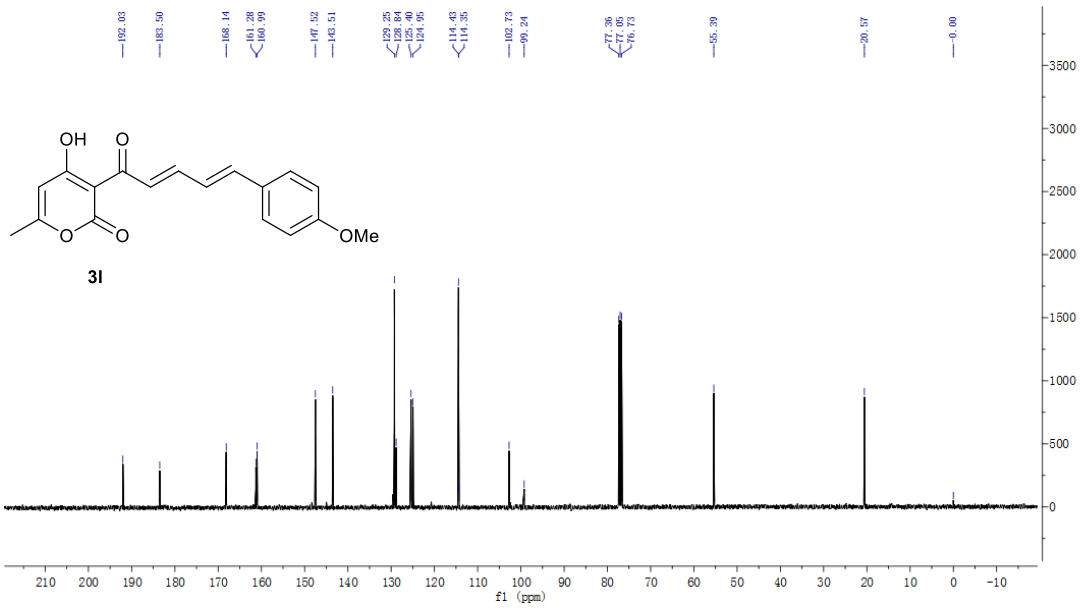

OH
O
O
O
Me
3j
7.823
7.797
7.777
7.755
7.741
7.719
7.408
7.388
7.262
7.186
7.107
7.087
7.047
7.027
6.988
5.921
2.364
2.250
1.657
0.000
1.00
1.04
2.04
2.04
2.05
1.00
3.05
3.03
f1 (ppm)

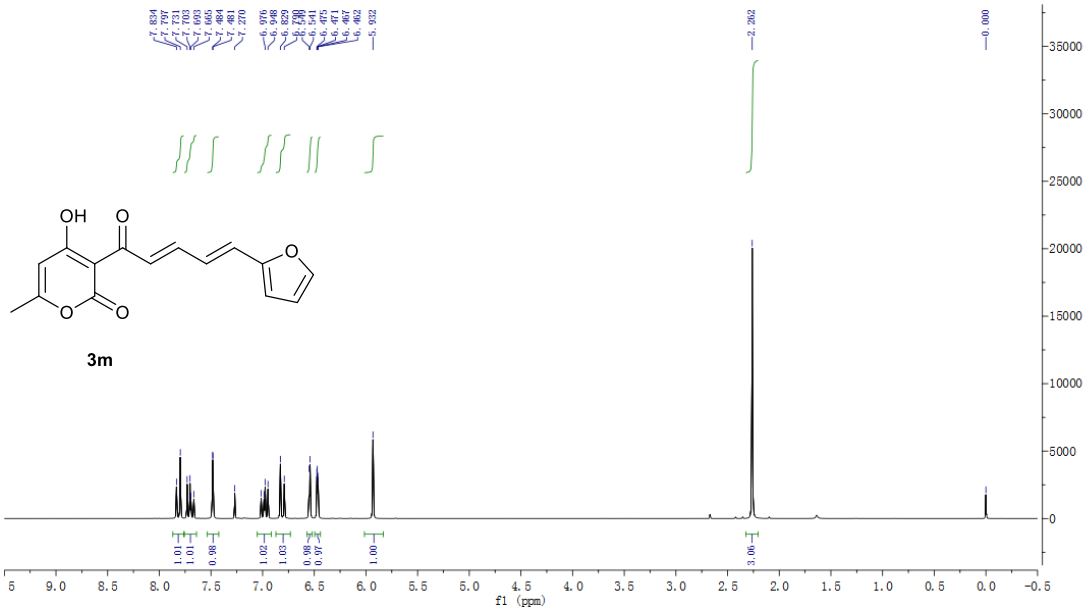

OH
O
O
O
Me
3j
192.182
183.430
168.268
161.241
147.147
145.657
140.038
133.263
129.661
127.613
126.524
125.681
102.638
99.299
77.370
77.053
76.735
21.468
20.591
0.000
f1 (ppm)

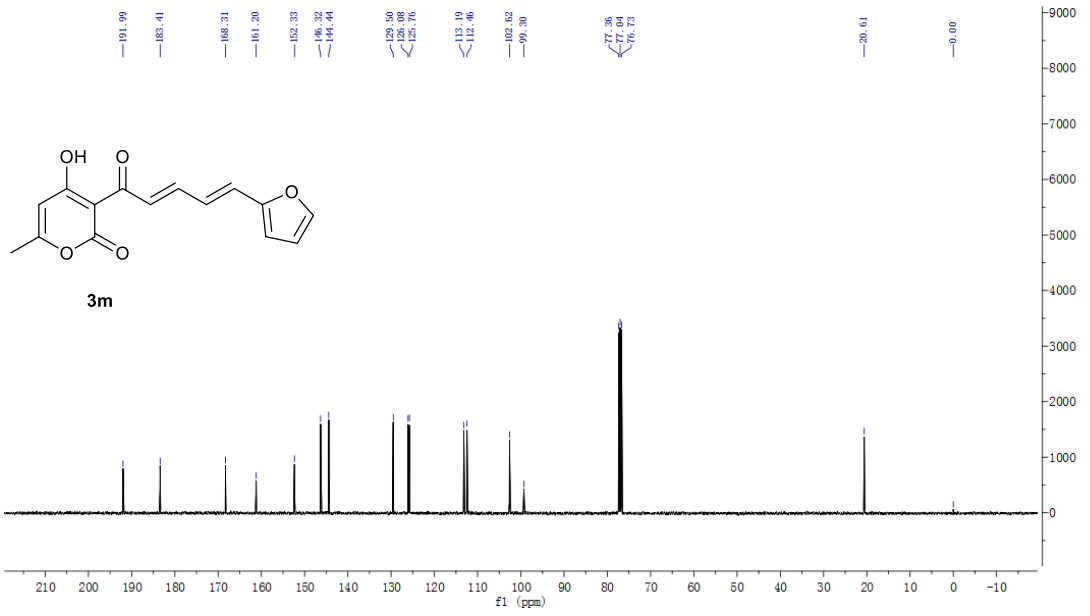

OH
O
OMe
O
O
3k
f1 (ppm)

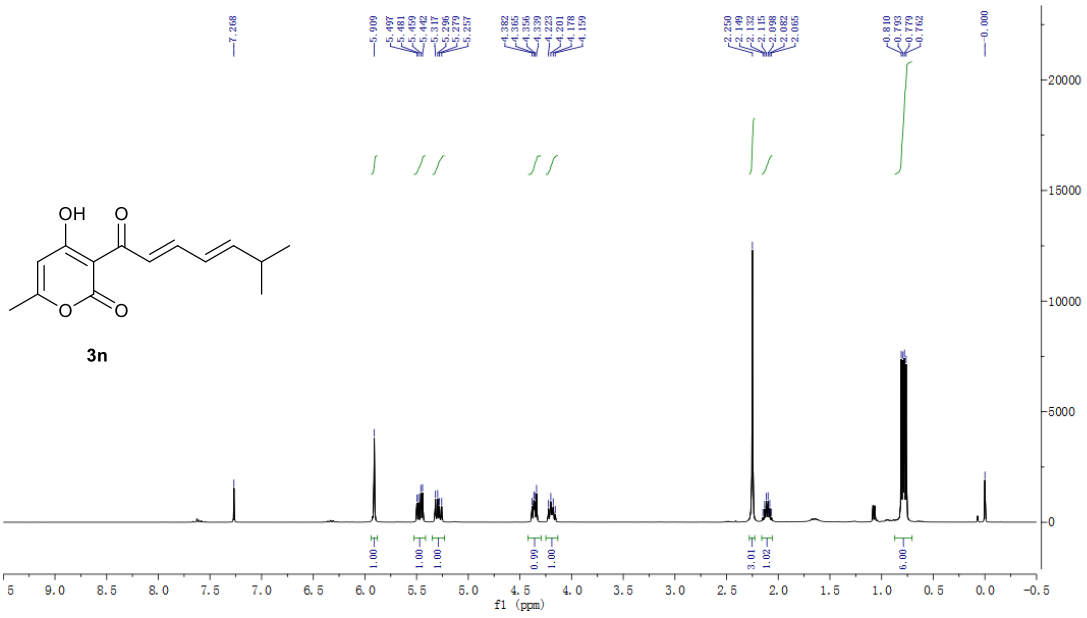

OH
O
OMe
O
O
3k
f1 (ppm)

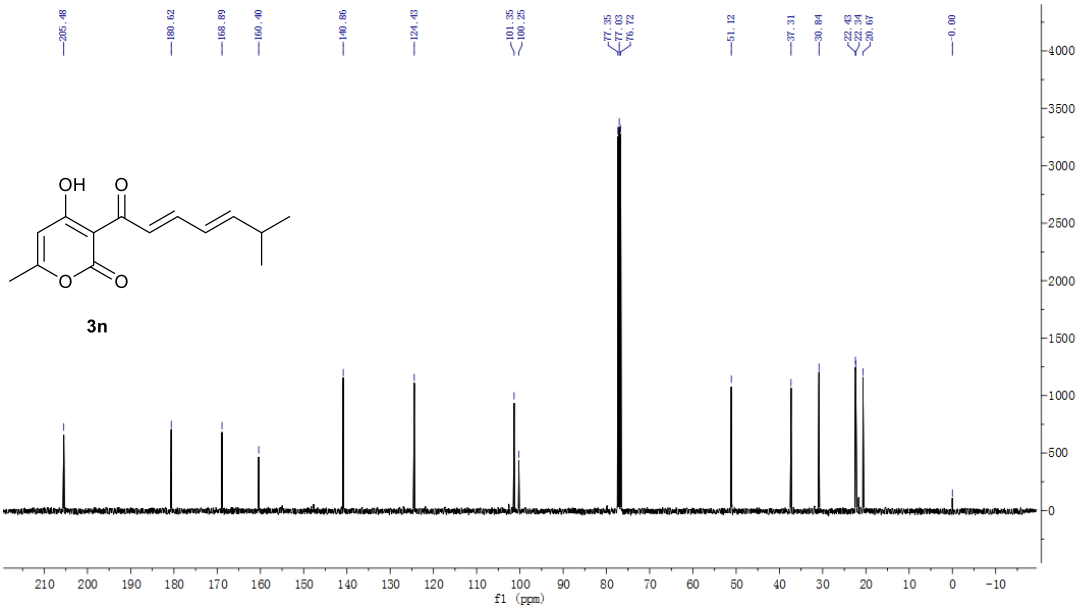

OH
O
O
O
OMe
3l
f1 (ppm)

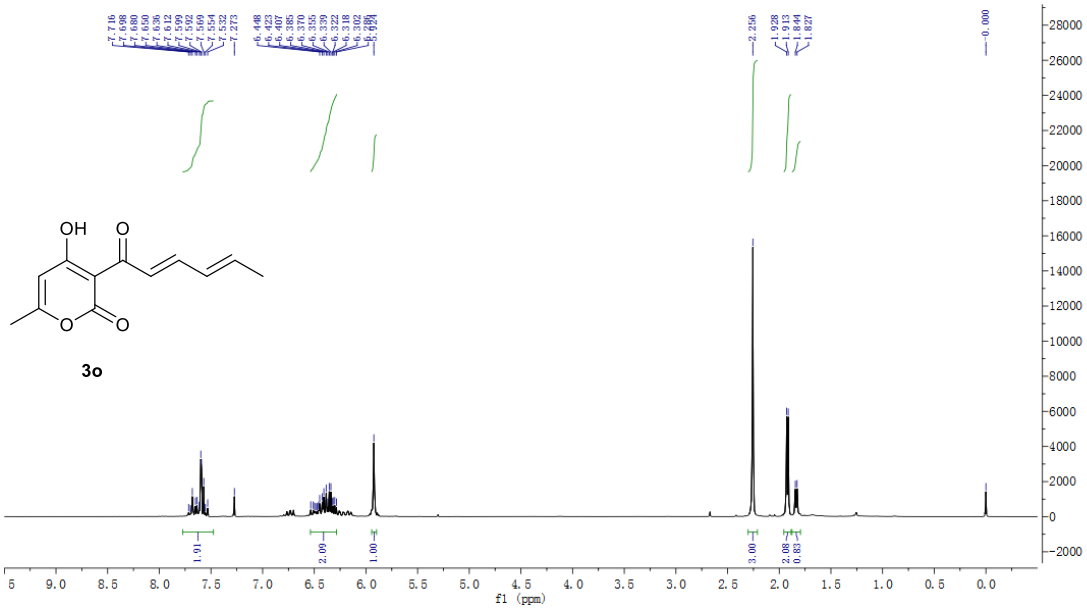

OH
O
O
O
OMe
3l
f1 (ppm)

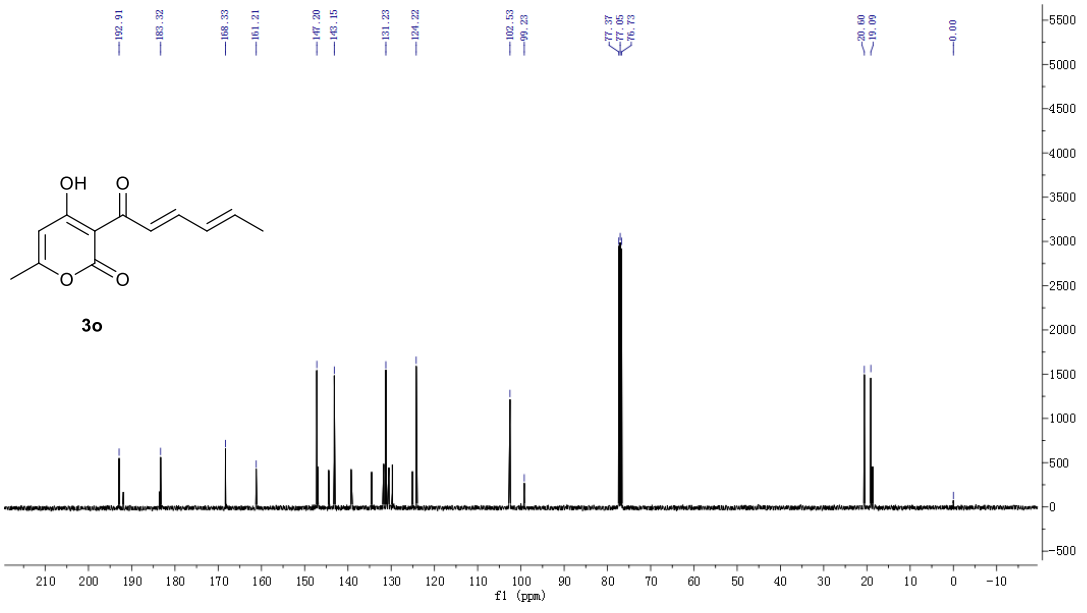

OH
O
O
O
O
3m
7.834
7.797
7.731
7.703
7.665
7.484
7.481
7.270
6.976
6.948
6.829
6.541
6.475
6.471
6.467
6.462
5.932
2.262
0.000
1.01
1.01
0.98
1.02
1.03
0.98
0.97
1.00
3.06
f1 (ppm)


OH
O
O
O
O
3m
191.99
183.41
168.31
161.20
152.33
146.32
144.44
129.50
126.08
125.76
113.19
112.46
102.62
99.30
77.36
77.04
76.73
20.61
0.00
f1 (ppm)


7.268
5.909
5.497
5.481
5.459
5.442
5.337
5.296
5.279
5.257
4.382
4.365
4.356
4.339
4.223
4.201
4.178
4.159
2.250
2.149
2.132
2.115
2.098
2.082
2.065
0.810
0.793
0.779
0.762
0.000
OH
O
O
O
3n
f1 (ppm)


205.48
180.62
168.89
160.40
140.86
124.43
101.35
100.25
77.35
77.03
76.72
51.12
37.31
30.84
22.43
22.34
20.67
0.00
OH
O
O
O
3n
f1 (ppm)


OH
O
O
O
3o
f1 (ppm)


OH
O
O
O
3o
f1 (ppm)