Radical Directed Regioselective Functionalization of Diverse Alkene Derivatives.

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Supporting information

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Table of Context

Materials and methods:

All reactions were carried in oven-dried glassware with magnetic stirring. Starting material of 2-benzylidene-1,3-indandione were synthesized from aromatic aldehyde (purchased from Avra, HIMEDIA & SRL) and 1,3-indandione (Sigma Aldrich& SRL). Pivalic acid and pyruic acid were purchased from spectrochem and phenylglyoxylic acid was purchased from Alfa Asear. Silver nitrate and potassium peroxydisulfate were purchased from Merck. Acetronitrile was purchased from Ranbaxy. Double distilled water was used. Silica gel 100-200 (code 28112200) mesh size was purchased from SRL. Sodium chloride was purchased from SRL (Assay =99.5%). Melting points were uncorrected. ^{1}H NMR was recorded JEOL NMR Spectrometer (JNM-ECZ600R/S1) 600 MHz and ^{13}C 150 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. High resolution ESI mass spectra were recorded on Q-TOF & MicrOTOF-Q-II mass spectrometer.

Methods:

General Procedure

1. Synthesis of 2-benzylidene-1,3-indandione (1a-h) derivatives

The synthesis of 2-benzylidene-1,3-indandione derivatives were performed by modified procedure of the literature.[1] In the 25 mL RBF, 1,3-indandione (146 mg, 1 mmol), aryl aldehydes (1 mmol), and in methanol was added L-proline (17 mg, 0.15 mmol) and the reaction mixture was reflux for 3 h to 16 h. The completion of the reaction was monitored by Thin Layer Chromatography (TLC). The solvent was removed under reduced pressure. The crude residue was washed with methanol; formation of solid was filtered and dried to afford crude residues. The crude residues were purified by flash chromatography at 10% EtOAc in hexanes.

2. General procedure for the synthesis of peroxo indandione (3a-g) derivatives

A suspension of 2-benzylidene-1,3-indandione derivatives (0.1 mmol) and pivalic acid (41 mg, 0.4 mmol) in H_2O:ACN (1:1 v/v) (2 mL) was stirred at room temperature. $AgNO_3$ (5 mg, 0.03 mmol) and $K_2S_2O_8$ (54 mg, 0.2 mmol) was added to the reaction mixture and allowed to stir till the complete the reaction. After completion, the mixture was quenched with water and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. After drying, the organic layer was filtered, and concentrated under reduced pressure to afford crude reaction of product. The crude mixture was purified by column chromatography at 5% EtOAc in Hexane to afford pure product.

2-(1-(4-bromophenyl)-2,2-dimethylpropyl)-2-(*tert*-butylperoxy)-1*H*-indene-1,3(2*H*)-dione (3a). Yellow liquid, Yield: 68% (31 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.8 Hz, 1H), 7.77-7.74 (m, 1H), 7.71-7.68 (m, 2H), 7.19 (dd, J = 7.8 Hz, 2.4 Hz, 1H), 7.13 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.05 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.84 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 3.34 (s, 1H), 1.03 (s, 9H), 0.99 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.9, 199.6, 141.9, 140.9, 135.9, 135.8, 135.7, 134.8, 131.5, 131.0, 130.2, 122.9, 122.8, 121.0, 87.6, 81.4, 60.2, 35.2, 30.4, 26.3. HRMS (ESI): calcd for $C_{24}H_{27}BrO_4$ [M+Na^+]: 481.0985, found: 481.0986.

2-(*tert*-butylperoxy)-2-(2,2-dimethyl-1-phenylpropyl)-1*H*-indene-1,3(2*H*)-dione(3b). Off-white solid, Yield: 79% (30.2 mg), Mp: 118-121 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1H), 7.69-7.66 (m, 1H), 7.61-7.59 (m, 2H), 7.08 (d, J = 7.8 Hz, 1H), 7.03–7.00 (m, 1H), 6.93 – 6.91 (m, 2H), 6.84 – 6.81 (m, 1H), 3.34 (s, 1H), 1.084 (s, 9H), 1.077 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.1, 199.7, 142.2, 140.8, 136.6, 135.5, 135.3, 133.2, 129.7,

128.0, 127.1, 126.8, 122.7, 122.6, 88.8, 81.2, 60.9, 35.5, 30.7, 26.4. HRMS (ESI): calcd for $C_{24}H_{28}O_4$ [M+NH_4^+]: 398.2326, found: 398.2330.

2-(*tert*-butylperoxy)-2-(2,2-dimethyl-1-(*p*-tolyl)propyl)-1*H*-indene-1,3(2*H*)-dione(3c). Yellowish solid, Yield: 67% (26.6 mg), Mp: 120-122 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1H), 7.69-7.67 (m, 1H), 7.60 (d, J = 4.8 Hz, 2H), 6.90 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 6.82–6.77 (m, 2H), 6.61 (d, J = 7.8 Hz, 1H), 3.30 (s, 1H), 2.08 (s, 3H), 1.09 (s, 9H) 1.07 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.2, 199.7, 142.3, 140.8, 136.4, 135.4, 135.2, 133.3, 133.1, 129.5, 128.6, 127.8, 122.7, 122.5, 88.9, 81.1, 60.5, 35.5, 30.6, 26.4, 20.9. HRMS (ESI): calcd for $C_{25}H_{30}NO_4$ [M+NH_4^+]: 412.2482, found: 412.2503.

2-(tert-butylperoxy)-2-(1-(4-methoxyphenyl)-2,2-dimethylpropyl)-1H-indene-1,3(2H)-dione (3d). Off-white solid, Yield: 72% (29.5 mg), Mp: 101-102 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.8 Hz, 1H), 7.70-7.67 (m, 1H), 7.62-7.61 (m, 2H), 6.95 (dd, J = 2.4 Hz, 9.0 Hz, 1H), 6.83 (dd, J = 3.0 Hz, 9.0 Hz, 1H), 6.55 (dd, J = 3.0 Hz, 8.4 Hz, 1H), 6.37 (dd, J = 3.0 Hz, 8.4 Hz, 1H), 3.61 (s, 3H), 3.30 (s, 1H), 1.09 (s, 9H), 1.07 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.2, 199.8, 158.3, 142.2, 140.8, 135.5, 135.3, 134.3, 130.6, 128.6, 122.7, 122.5, 113.0, 112.8, 88.9, 81.1, 60.0, 55.1, 35.6, 30.6, 26.4. HRMS (ESI): calcd for $C_{25}H_{30}O_5$ [M+Na^+]: 433.1985, found: 433.1997.

2-(*tert*-butylperoxy)-2-(1-(4-chlorophenyl)-2,2-dimethylpropyl)-1*H*-indene-1,3(2*H*)-dione(3e). Off-white solid, Yield: 54% (22.3 mg), Mp: 111-113 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.8 Hz, 1H), 7.76-7.74 (m, 1H), 7.70-7.69 (m, 2H), 7.18 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.04 (dd, J = 7.8 Hz, 2.4 Hz, 1H), 6.91 – 6.89 (m, 2H), 3.35 (s, 1H), 1.03 (s, 9H), 1.00 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.9, 199.7, 141.9, 140.9, 135.9, 135.7, 135.3, 134.4, 132.8, 131.1, 128.0, 127.3, 122.9, 122.7, 87.7, 81.3, 60.1, 35.3, 30.4, 26.3. HRMS (ESI): calcd for $C_{24}H_{27}ClO_4$ [M+NH_4^+]: 432.1936, found: 432.1939.

4-(1-(2-(tert-butylperoxy)-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)-2,2-dimethylpropyl)benzonitrile (3f). white solid, Yield: 60% (24.1 mg), Mp: 112-114 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.2 Hz, 1H), 7.82-7.75 (m, 3H), 7.69 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.43 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.36 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.15 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 3.48 (s, 1H), 0.94 (s, 9H), 0.92 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.5, 199.4, 142.8, 141.6, 141.0, 136.3, 136.1, 133.6, 131.5, 131.1, 130.8, 123.1, 123.0, 118.9, 110.7, 86.3, 81.6, 60.7, 35.0, 30.2, 26.1. HRMS (ESI): calcd for $C_{25}H_{27}NO_4$ [M+Na^+]: 428.1832, found: 428.1831.

2-(*tert*-butylperoxy)-2-(2,2-dimethyl-1-(4-nitrophenyl)propyl)-1*H*-indene-1,3(2*H*)-dione(3g). Off-white solid, Yield: 60% (25.7 mg), Mp: 88-90 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.98-7.94 (m, 2H), 7.84-7.81 (m, 3H), 7.79-7.77 (m, 1H), 7.23 (dd, J = 1.8 Hz, 8.4 Hz, 1H), 3.57 (s, 1H), 0.93 (s, 9H), 0.91 (s, 9H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.5, 199.4, 146.8, 145.0, 141.5, 141.1, 136.4, 136.2, 133.8, 131.2, 123.2, 123.1, 122.8, 122.2, 86.0, 81.6, 60.4, 35.0, 30.2, 26.1. HRMS (ESI): calcd for $C_{24}H_{27}NO_4$ [M+K^+]: 464.1470, found: 464.1471.

3. Synthesis of acetyl indandione (4a-g) derivatives.

A suspension of 2-benzylidene-1,3-indandione derivatives (0.2 mmol) and pyruvic acid (35.2 mg, 0.4 mmol)in 2 mL of H_2O:ACN (1:1 v/v) was stirred at room temperature.$AgNO_3$ (5 mg, 0.03 mmol) and $K_2S_2O_8$ (54 mg, 0.2 mmol) was added to the reaction mixture and allowed to complete the reaction. After completion, the mixture was quenched with water (3 mL) and extract with ethyl acetate (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. After drying, the organic layer was filtered, and concentrated under reduced pressure

to afford crude reaction of product. The crude mixture was purified by column chromatography at 10% to 20%EtOAc in hexanes to afford pure product.

2-(2-oxo-1-phenylpropyl)-1*H*-indene-1,3(2*H*)-dione (4a) Off-white solid, Yield: 85% (47.3 mg), Mp: 115-118 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97-7.92 (m, 2H), 7.83-7.77 (m, 2H), 7.51-7.49 (m, 2H), 7.40-7.38 (m, 2H), 7.34-7.31 (m, 1H), 4.63 (d, J = 3 Hz, 1H), 3.35 (d, J = 3 Hz, 1H), 2.02 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.2, 198.8, 198.7, 142.7, 141.2, 136.3, 135.6, 135.1, 130.3, 129.1, 128.1, 123.3, 123.1, 60.1, 55.6, 28.2. HRMS (ESI): calcd for $C_{18}H_{14}O_3$ [M+Na^+]: 301.0835, found: 301.0840.

2-(2-oxo-1-(*p*-tolyl)propyl)-1*H*-indene-1,3(2*H*)-dione (4b) yellow liquid, Yield: 77% (45.1 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96-7.92 (m, 2H), 7.82-7.77 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 4.60 (d, J = 2.4 Hz, 1H), 3.32 (d, J = 3.0 Hz, 1H), 2.34 (s, 3H), 2.02 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.5, 198.9, 198.8, 142.8, 141.2, 137.8, 135.6, 135.1, 133.2, 130.1, 129.8, 123.3, 123.1, 59.7, 55.6, 28.1, 21.2. HRMS (ESI): calcd for $C_{19}H_{16}O_3$ [M+Na^+]: 315.0992, found: 315.0978.

2-(1-(4-methoxyphenyl)-2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione(4c) Off-white solid, Yield: 67% (41.5 mg), Mp: 106-109 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96-7.91 (m, 2H), 7.82-7.77 (m, 2H), 7.41-7.39 (m, 2H), 6.91-6.90 (m, 2H), 4.58 (d, J = 3 Hz, 1H), 3.80 (s, 3H), 3.33 (d, J = 3.0 Hz, 1H), 2.01 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.5, 198.9, 159.3, 142.8, 141.3, 135.6, 135.1, 131.5, 128.2, 123.3, 123.1, 114.4, 59.3, 55.7, 55.4, 28.0. HRMS (ESI): calcd for $C_{19}H_{16}O_4$ [M+Na^+]: 331.0941, found: 331.0951.

2-(1-(4-nitrophenyl)-2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione (4d) Brownish semi solid, Yield: 53% (34.8 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28-8.27 (m, 2H), 8.00-7.96 (m, 2H), 7.88-7.83 (m, 2H), 7.75-7.73 (m, 2H), 4.74 (d, J = 3.0 Hz, 1H), 3.40 (d, J = 3.0 Hz, 1H), 2.07

(s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.3, 198.2, 197.8, 147.8, 143.4, 142.5, 141.1, 135.9, 135.5, 131.4, 124.2, 123.5, 123.3, 59.2, 55.2, 28.4. HRMS (ESI): calcd for $C_{18}H_{13}NO_5$ [M+H$^+$]: 324.0866, found: 324.0851.

2-(1-(4-chlorophenyl)-2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione (4e) yellow liquid, Yield: 52% (32.8 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98-7.94 (m, 2H), 7.85-7.80 (m, 2H), 7.48-7.46 (m, 2H), 7.38-7.37 (m, 2H), 4.61 (d, *J* = 2.4 Hz, 1H), 3.35 (d, *J* = 3.0 Hz, 1H), 2.04 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 205.6, 198.6, 198.4, 142.6, 141.2, 135.7, 135.3, 134.7, 134.2, 131.7, 129.3, 123.3, 123.2, 59.2, 55.4, 28.1. HRMS (ESI): calcd for $C_{18}H_{13}ClO_3$ [M+Na$^+$]: 335.0445, found: 335.0463.

2-(1-(4-bromophenyl)-2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione (4f) Yellow liquid, Yield: 79% (56.2 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97-7.93 (m, 2H), 7.84-7.79 (m, 2H), 7.53-7.51 (m, 2H), 7.40-7.39 (m, 2H), 4.57 (d, *J* = 3.0 Hz, 1H), 3.33 (d, *J* = 3.0 Hz, 1H), 2.02 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.5, 198.6, 198.4, 142.6, 141.2, 135.7, 135.3, 135.2, 132.3, 132.0, 123.4, 123.2, 122.4, 59.3, 55.4, 28.2. HRMS (ESI): calcd for $C_{18}H_{13}BrO_3$ [M+H$^+$]: 357.0121, found: 357.0144.

2-(1-(Furan-2-yl)-2-oxopropyl)-1*H*-indene-1,3(2*H*)-dione (4g) Brown liquid, Yield: 55% (29.4 mg), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97-7.95 (m, 2H), 7.82-7.81 (m, 2H), 7.413-7.410 (m, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 6.394-6.386 (m, 1H), 4.72 (d, *J* = 3.0 Hz, 1H), 3.48 (d, *J* = 3.0 Hz, 1H), 2.09 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.0, 198.1, 197.8, 149.6, 142.6, 142.5, 141.5, 135.6, 135.3, 123.4, 123.2, 111.3, 110.2, 54.5, 52.2, 27.9. HRMS (ESI): calcd for $C_{16}H_{12}O_4$ [M+Na$^+$]: 291.0628, found: 291.0628.

4. Synthesis of benzoyl indandione (5a):

A suspension of 2-(4-methoxybenzylidene)-1H-indene-1,3(2H)-dione(52 mg, 0.2 mmol) and 2-oxo-2-phenylacetic acid (75 mg, 0.5 mmol) in 2 mL of H_2O:ACN (1:1 v/v) was stirred at room temperature. $AgNO_3$ (10 mg, 0.06 mmol) and $K_2S_2O_8$ (108 mg, 0.4 mmol) was added to the reaction mixture and allowed to stir for further 16 h. After completion of the reaction, the mixture was quenched with water (3 mL)and extract with ethyl acetate (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. After drying, the organic layer was filtered, and concentrated under reduced pressure to afford crude reaction of product. The crude mixture was purified by column chromatography at 20% EtOAc in hexanes to afford pure product.

2-(1-(4-methoxyphenyl)-2-oxo-2-phenylethylidene)-1*H*-indene-1,3(2*H*)-dione (5a) Yellow solid, Yield: 66% (48.9 mg), Mp: 77-79 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.97-7.92 (m, 3H), 7.83-7.74 (m, 5H), 7.54-7.52(m, 1H), 7.44-7.41 (m, 2H), 6.94(d, J = 7.8 Hz, 2H), 3.85 (s, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.1, 189.7, 188.1, 163.2, 159.3, 142.4, 140.0, 135.8, 135.6, 135.5, 133.7, 133.3, 129.1, 128.9, 123.40, 123.36, 123.3, 114.1, 55.6. HRMS (ESI): calcd for $C_{24}H_{16}O_4$ [M+Na^+]: 391.0941, found: 391.0930.

5. Reaction with 1,4-dione (6a-b) derivatives

A suspension of 1,4-dione derivatives (0.4 mmol) and pivalic acid (66 mg, 0.65 mmol) in 2 mL of H_2O:ACN (1:1 v/v) was stirred at room temperature. $AgNO_3$ (10 mg, 0.06 mmol) and $K_2S_2O_8$ (108 mg, 0.4 mmol) was added to the reaction mixture and allowed to stir for further 16 h. After completion of the reaction, the mixture was quenched with water and extract with ethyl acetate (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. After drying, the organic layer was filtered, and concentrated under reduced pressure to afford

crude reaction of product. The crude mixture was purified by column chromatography at 5% EtOAc in hexanes to afford pure product.

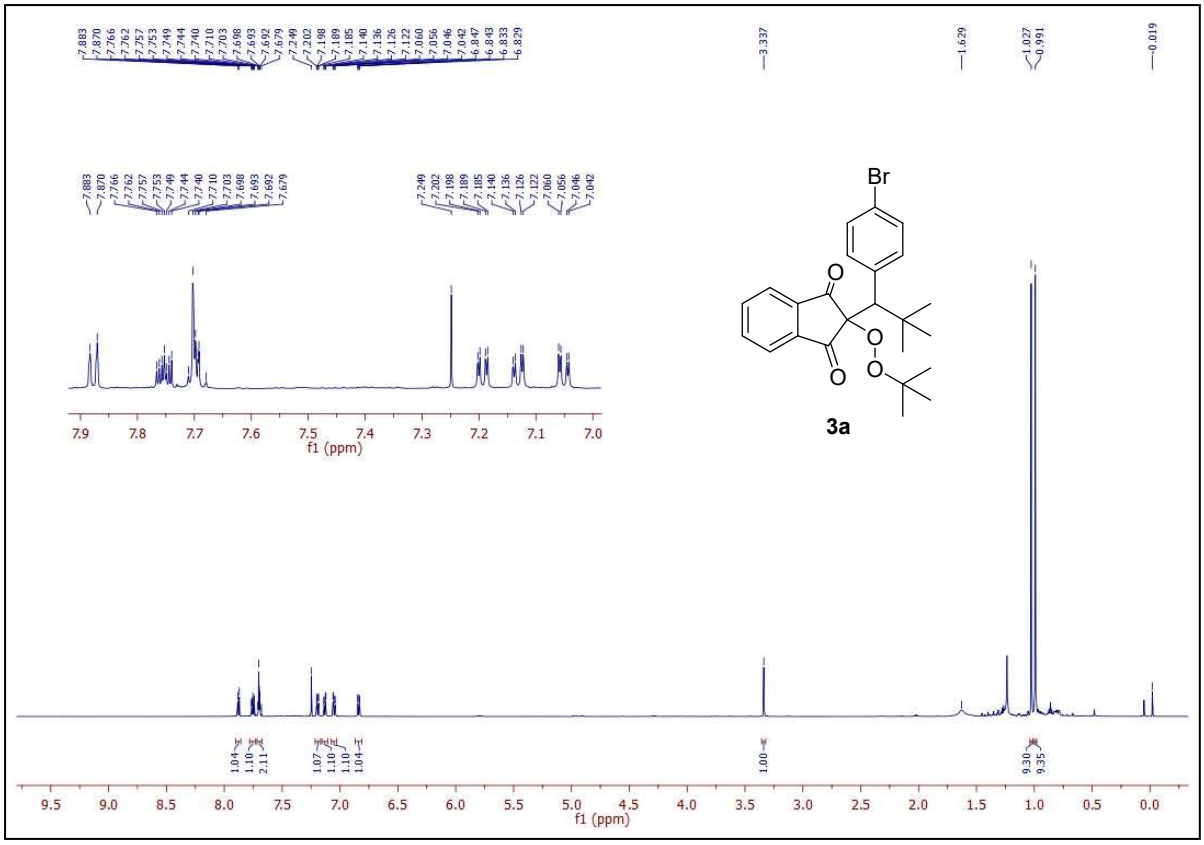
2-(*tert*-butyl)cyclohexa-2,5-diene-1,4-dione (6a)[2] Brownish liquid, Yield: 61% (39.8 mg) (85%)[#] ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.67 (s (br), 2H), 6.58 (s (br), 1H), 1.27 (s, 9H). [#] - yield based on recovery starting material.

2-(tert-butyl)naphthalene-1,4-dione (6b) Yellow solid, Yield: 74% (63.4 mg), (94%)[#], Mp: 73-74 ^{o}C (Lit 76 ^{o}C)[3]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08-8.07 (m, 1H), 8.03-8.01 (m, 1H), 7.73-7.67(m, 2H), 6.83 (s, 1H), 1.36 (s, 9H) ppm. [#] - yield based on recovery starting material.

6. Reaction with TBHP

A suspension of 2-benzylidene-1,3-indandione(23 mg, 0.1 mmol) and pyruvic acid (35 mg, 0.4mmol) in 2 mL of H_2O:ACN (1:1 v/v) was stirred at room temperature. 70% TBHP solution in water (200 µL, 0.02 mmol) and $K_2S_2O_8$ (54 mg, 0.2 mmol) was added to the reaction and allowed for 16 h. After completion of the reaction, the mixture was quenched with water and extract with ethyl acetate (3 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. After drying, the organic layer was filtered, and concentrated under reduced pressure to afford crude reaction of product. The crude mixture was purified by column chromatography at 10% EtOAc in hexanes to afford pure product.

3'-phenylspiro[indene-2,2'-oxirane]-1,3-dione (7). white solid, Yield: 77% (19.3 mg), Mp: 134-136 ^{o}C (Lit 140-143 ^{o}C)[4]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04-8.03 (m, 1H), 7.90-7.84 (m, 3H), 7.59 (dd, J = 7.8 Hz, 1.8 Hz, 2H), 7.40-7.37 (m, 3H), 4.73 (s, 1H) ppm.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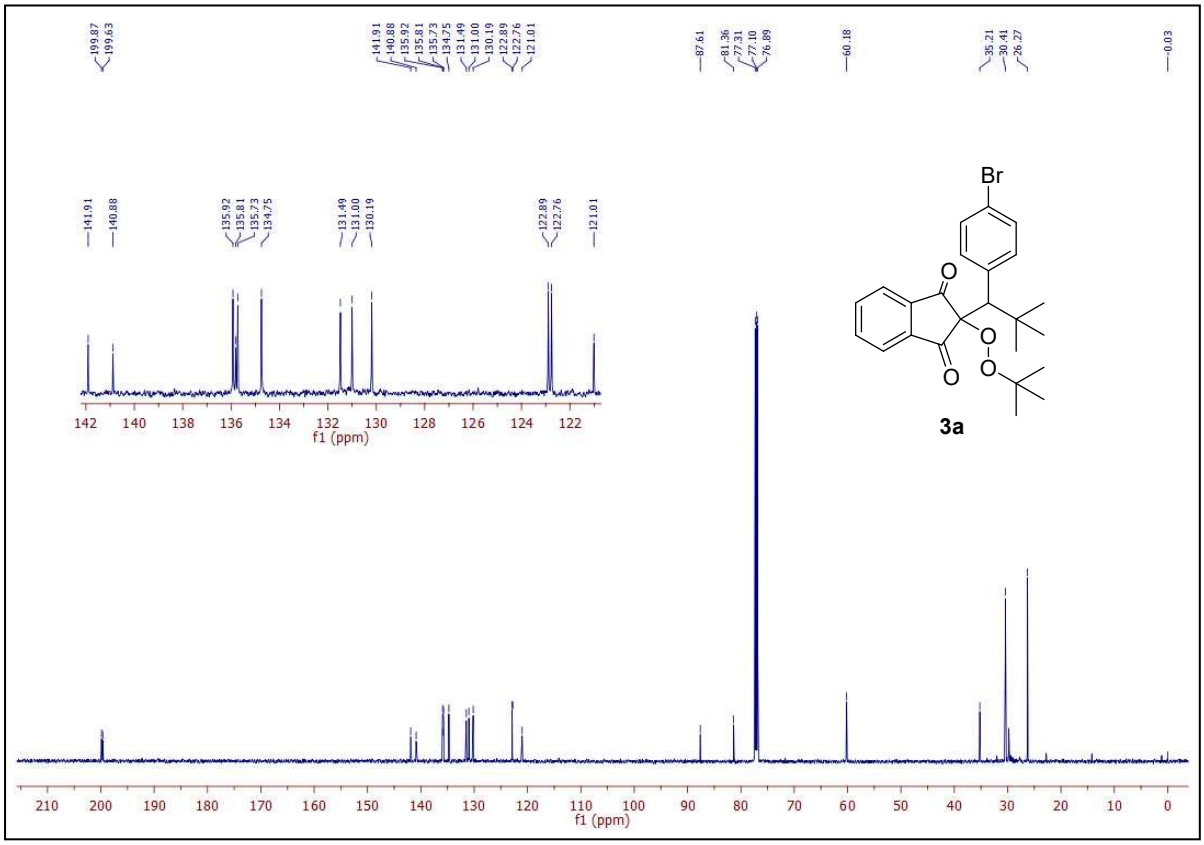
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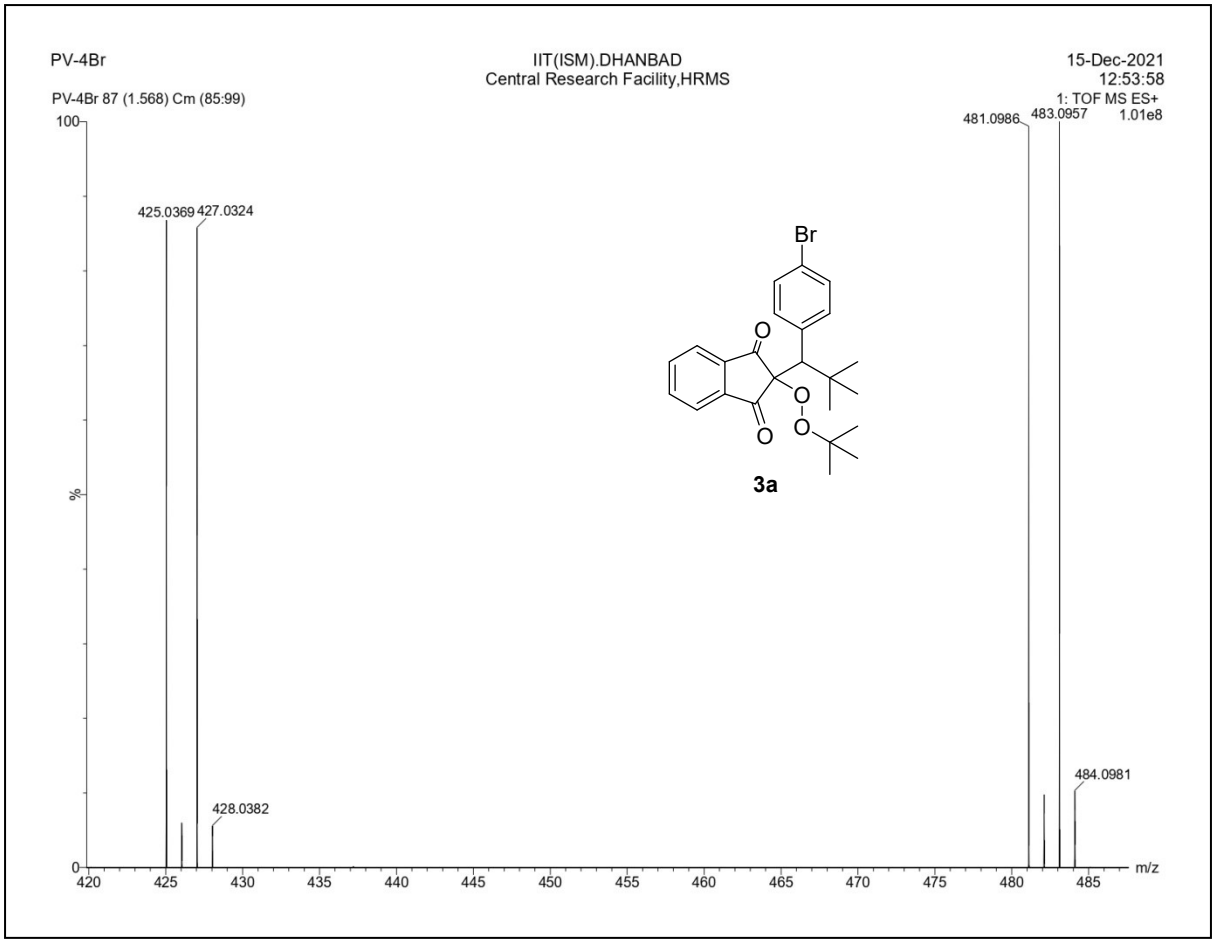
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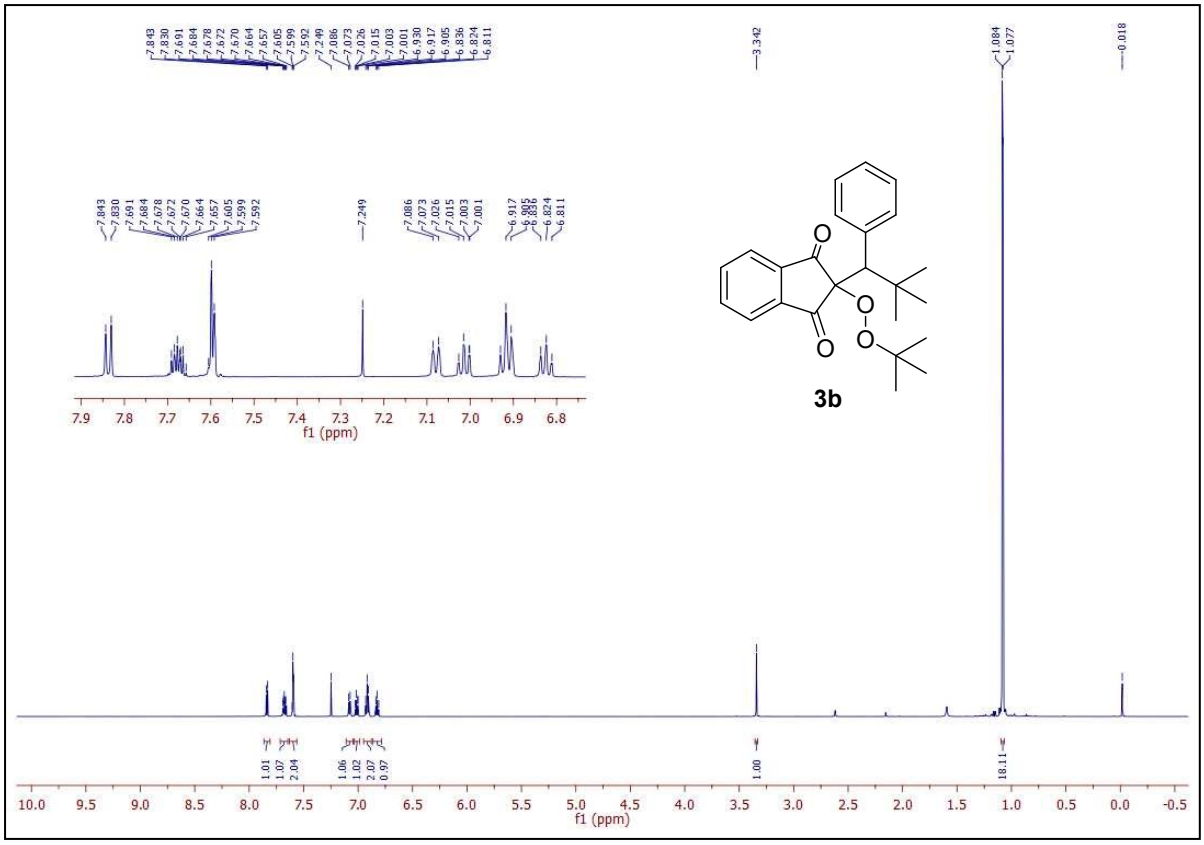
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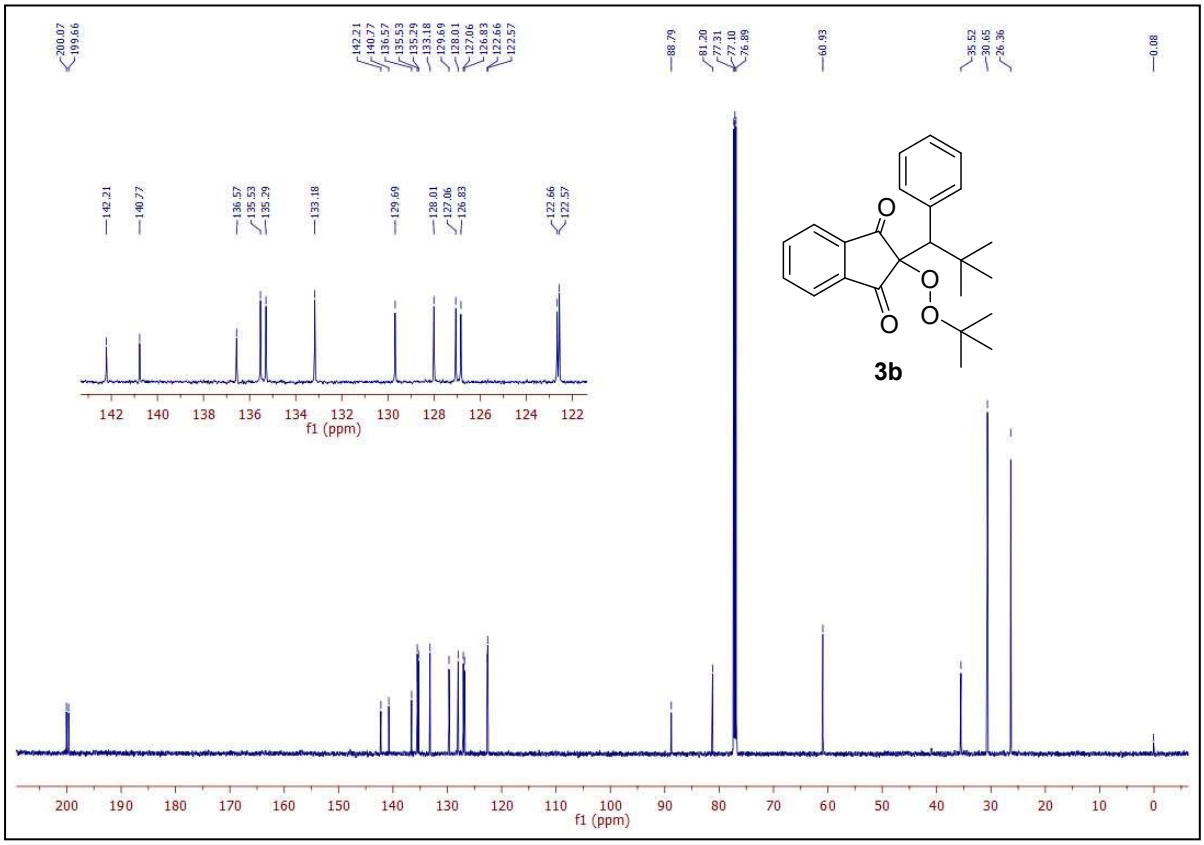
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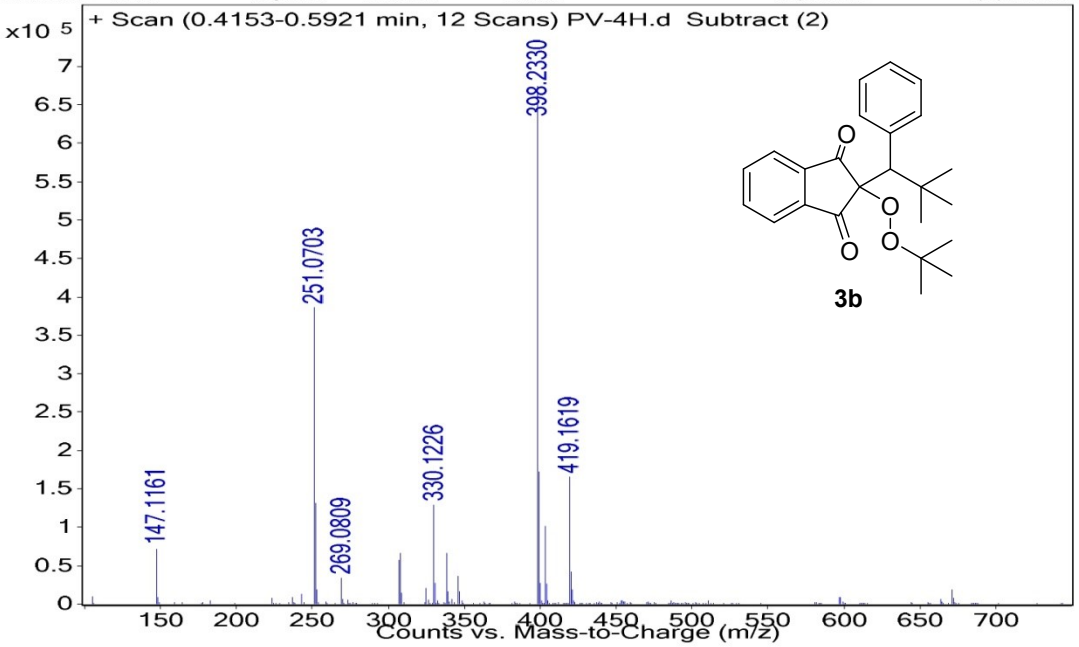
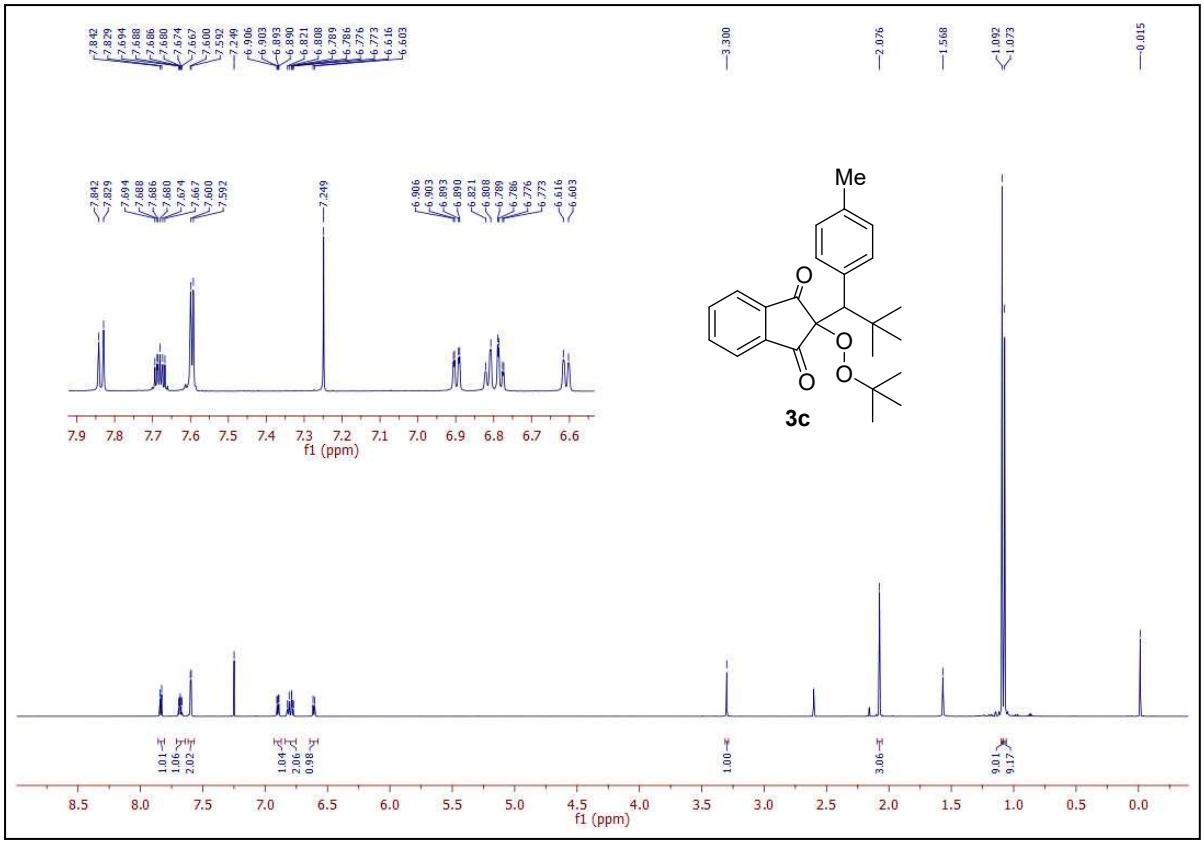
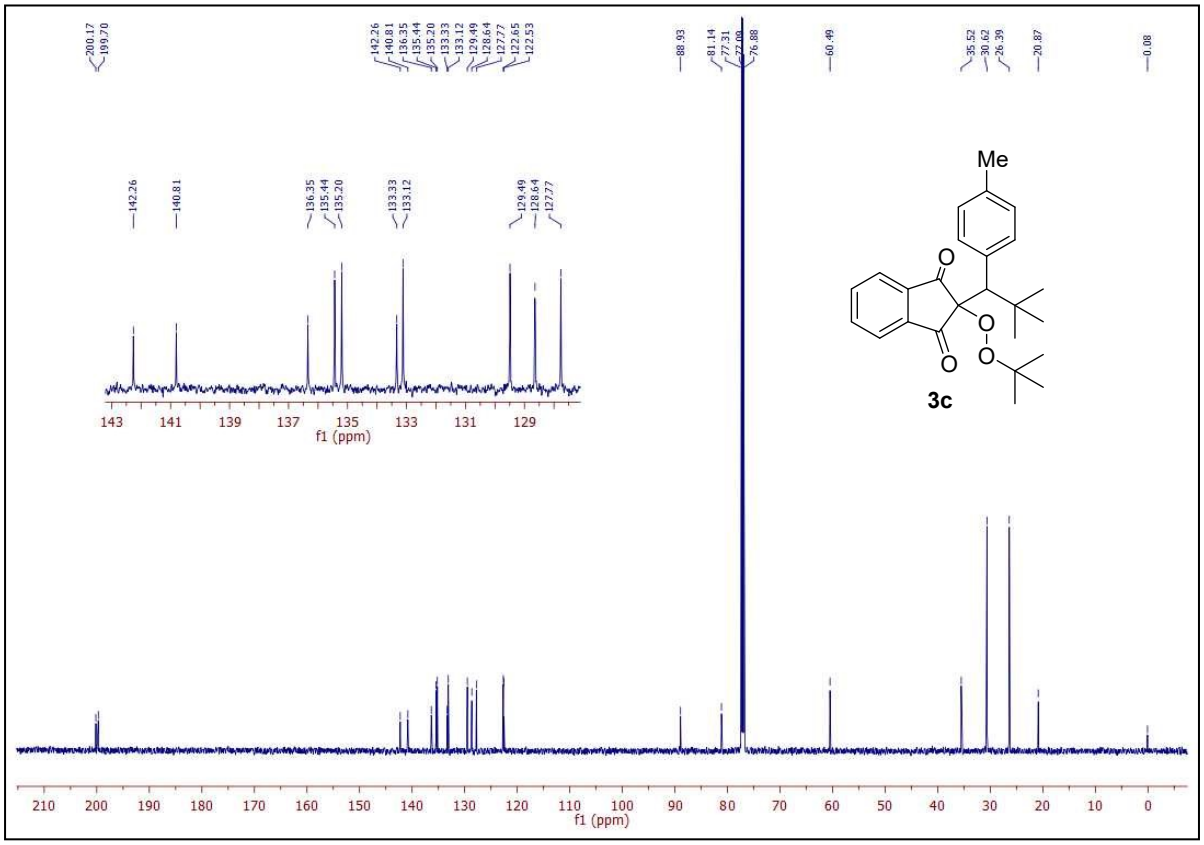
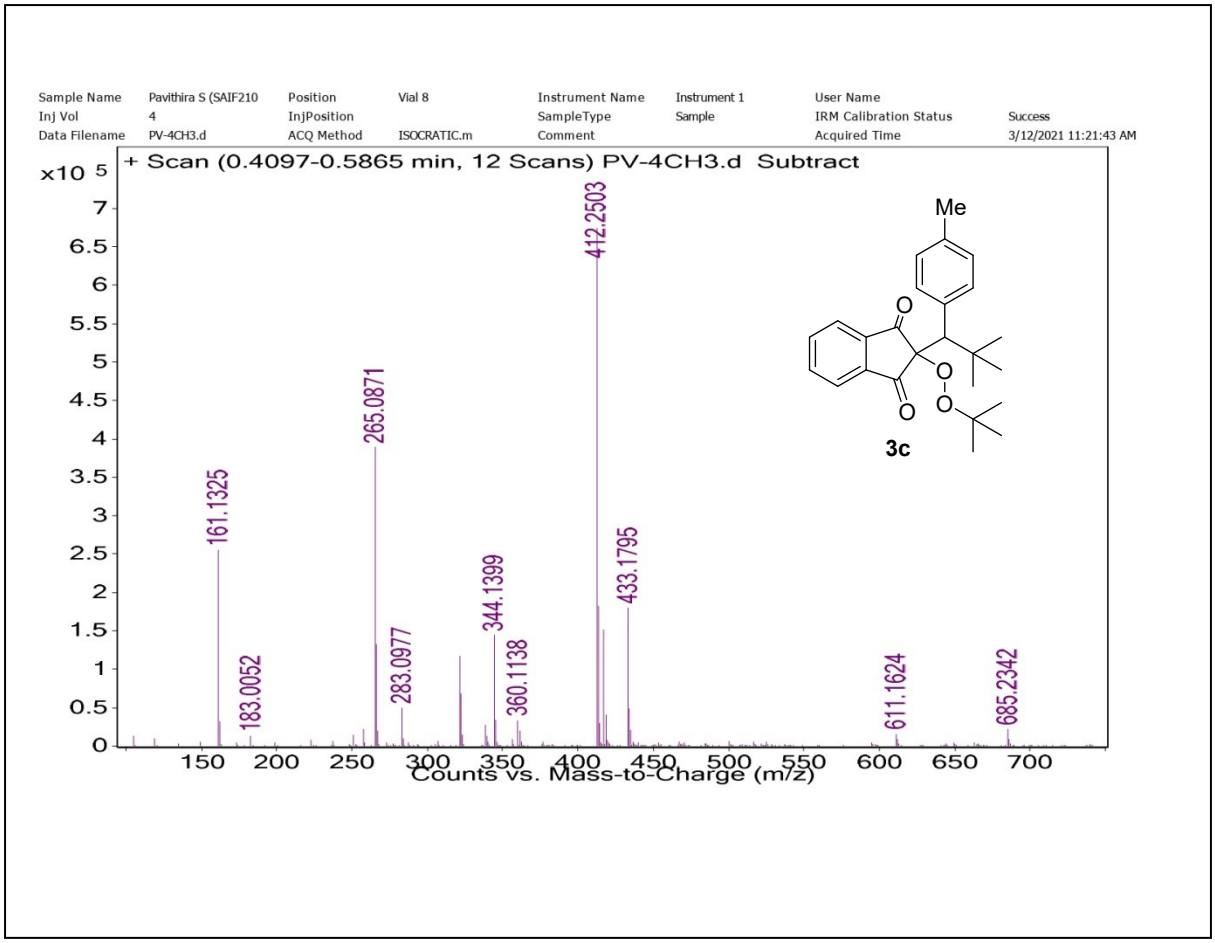
Sample Name	Pavithira S (SAIF210	Position	Vial 7	Instrument Name	Instrument 1	User Name	
Inj Vol	4	InjPosition		SampleType	Sample	IRM Calibration Status	Success
Data Filename	PV-4H.d	ACQ Method	ISOCRATIC.m	Comment		Acquired Time	3/12/2021 11:18:01 AM

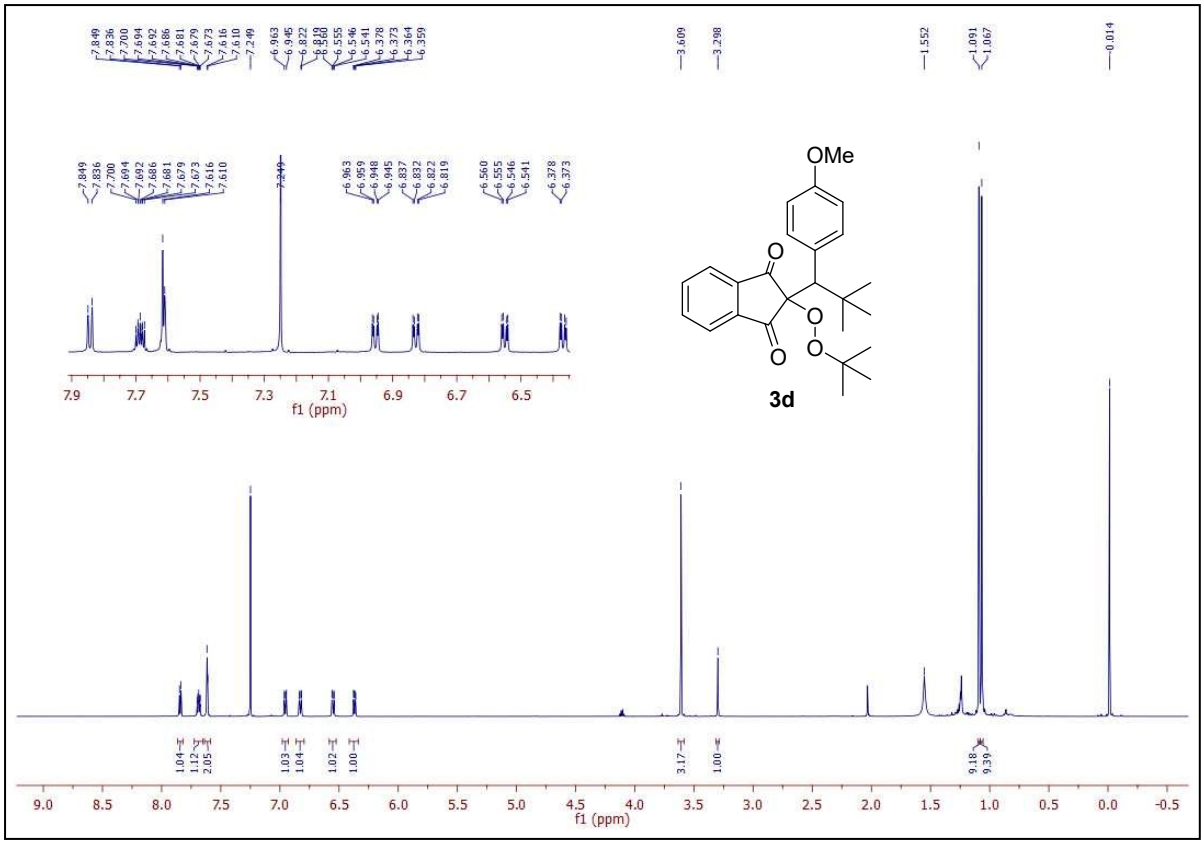


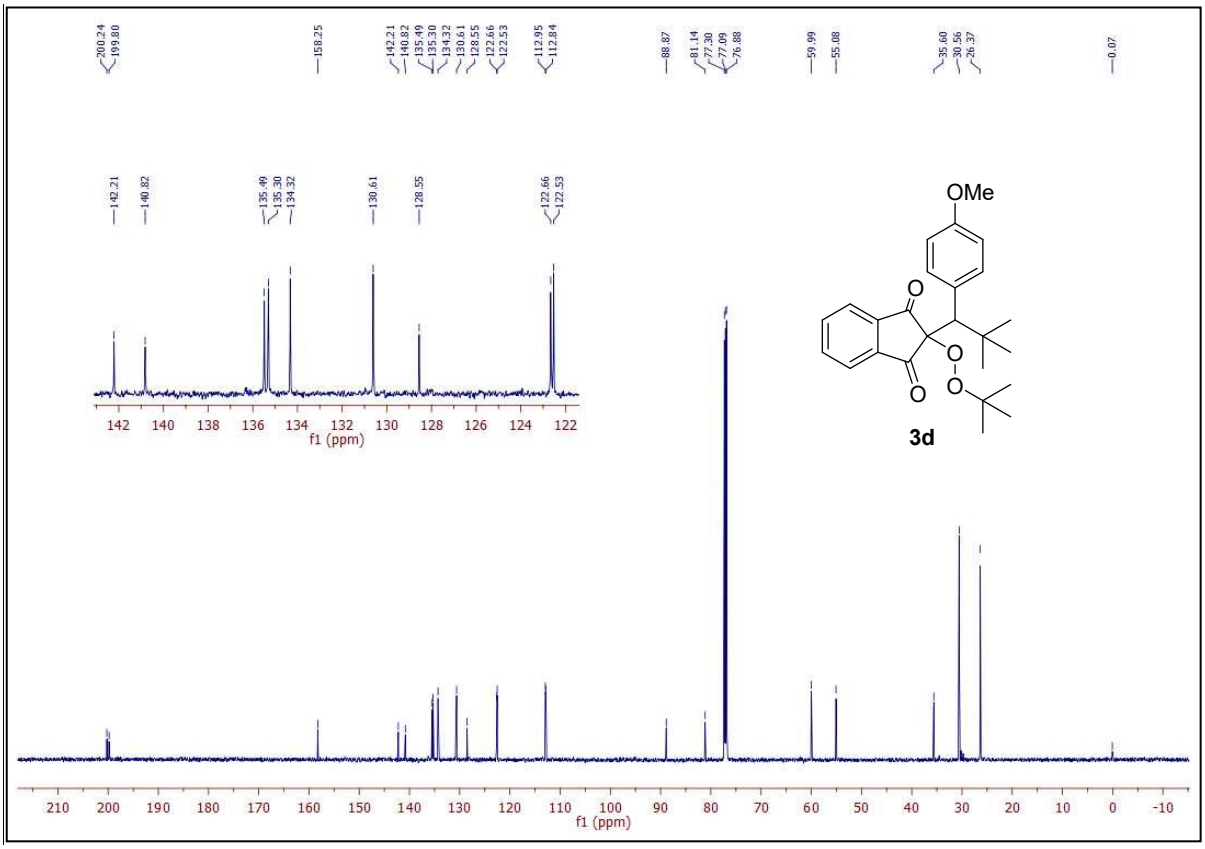
3b

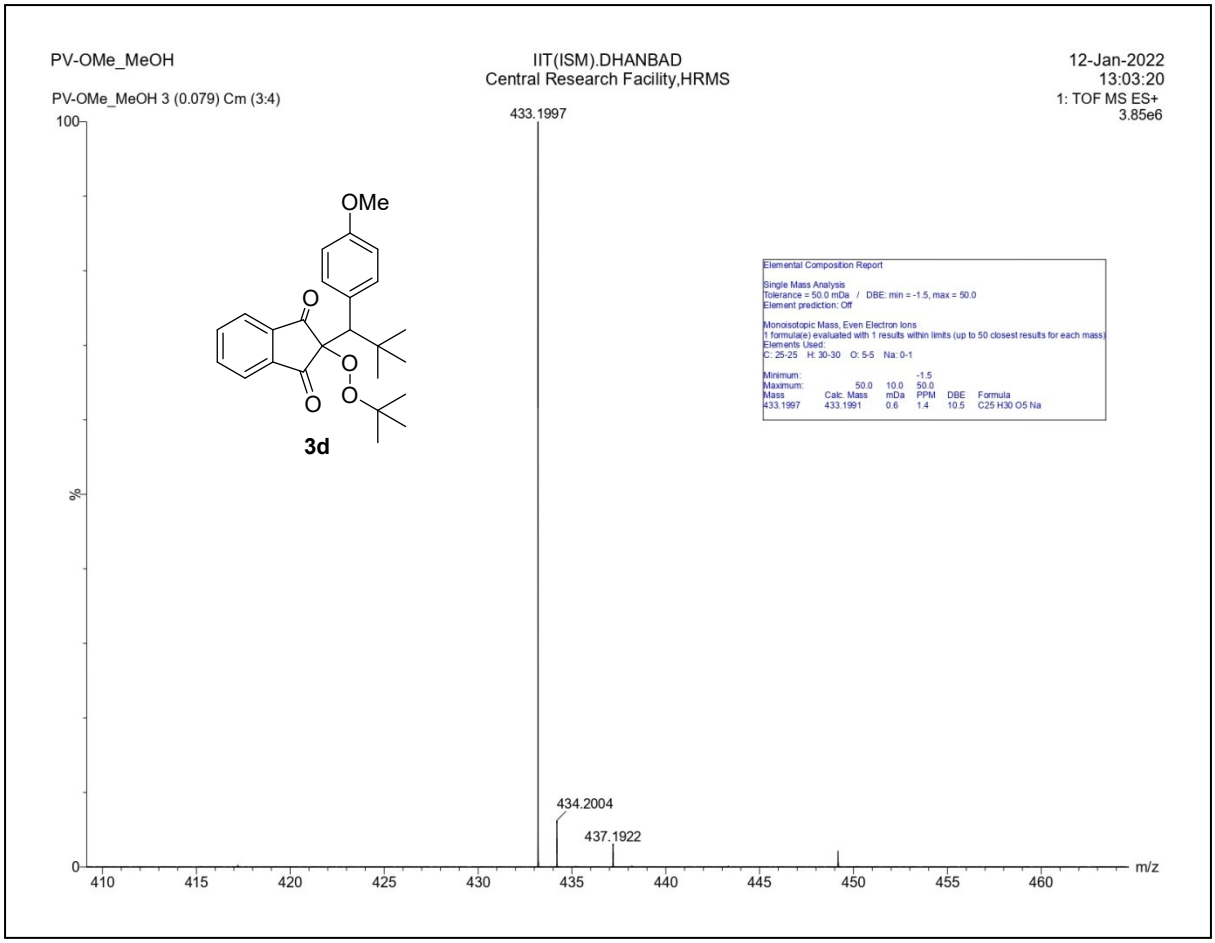

Me
O
O
O
O
3c
f1 (ppm)

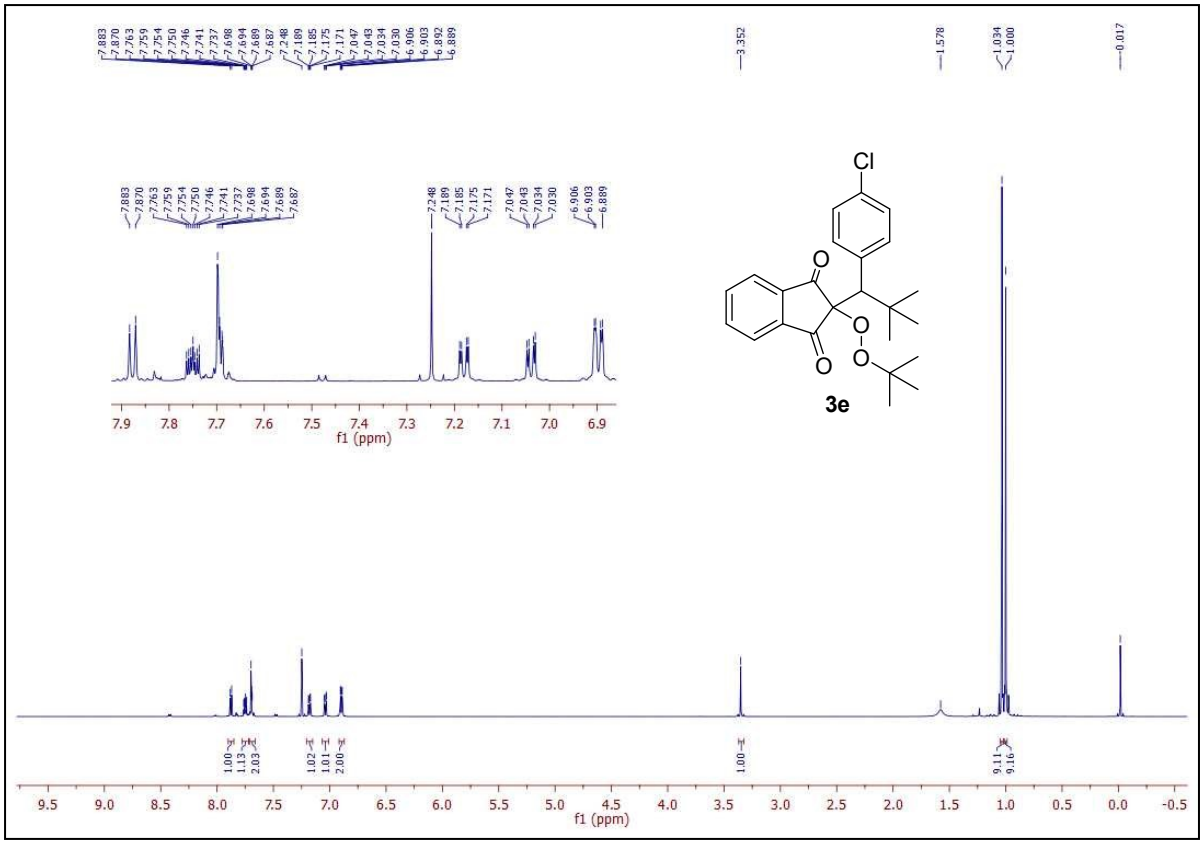

Me
O
O
O
O
3c
f1 (ppm)

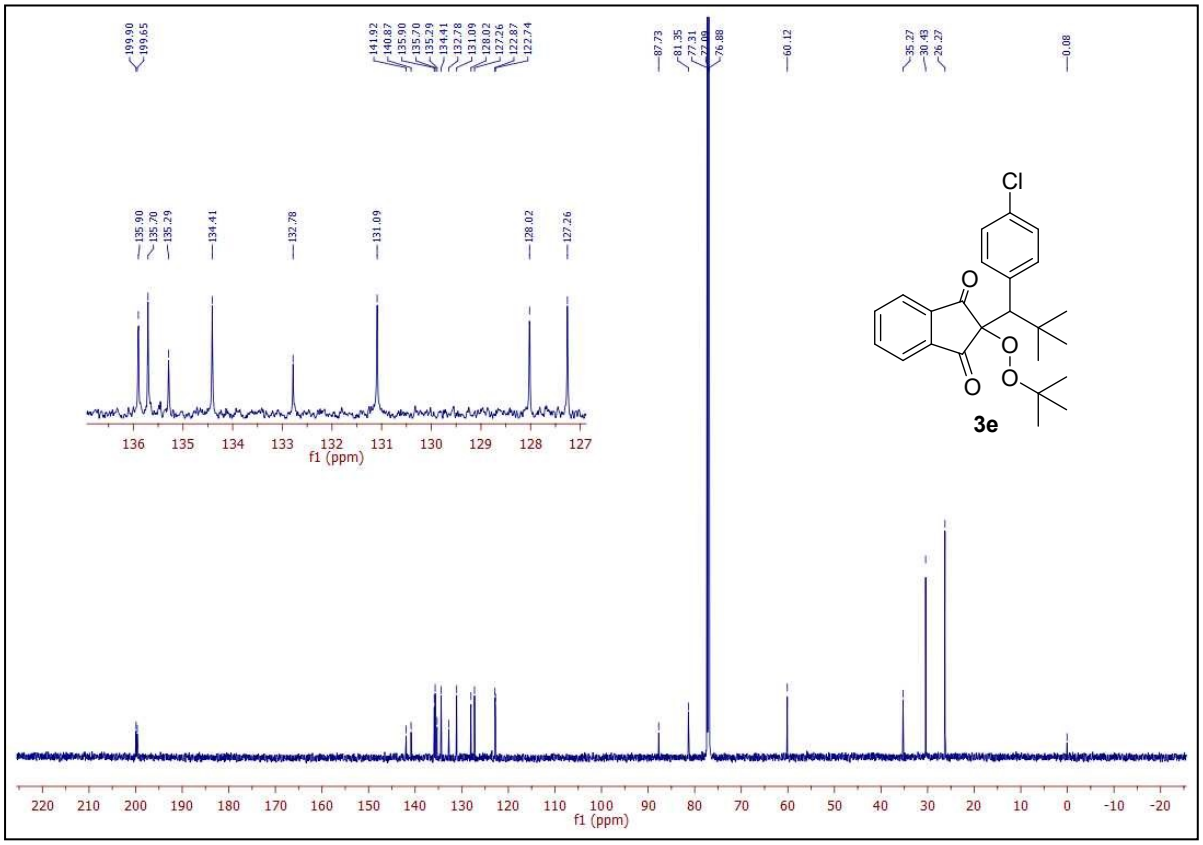

Sample Name Pavithira S (SAIF210 Position Vial 8 Instrument Name Instrument 1 User Name
Inj Vol 4 InjPosition SampleType Sample IRM Calibration Status Success
Data Filename PV-4CH3.d ACQ Method ISOCRATIC.m Comment Acquired Time 3/12/2021 11:21:43 AM
+ Scan (0.4097-0.5865 min, 12 Scans) PV-4CH3.d Subtract
x10 5
412.2503
265.0871
161.1325
433.1795
344.1399
283.0977
360.1138
183.0052
611.1624
685.2342
Me
O
O
O
O
3c
Counts vs. Mass-to-Charge (m/z)


OMe
O
O
O
3d
f1 (ppm)

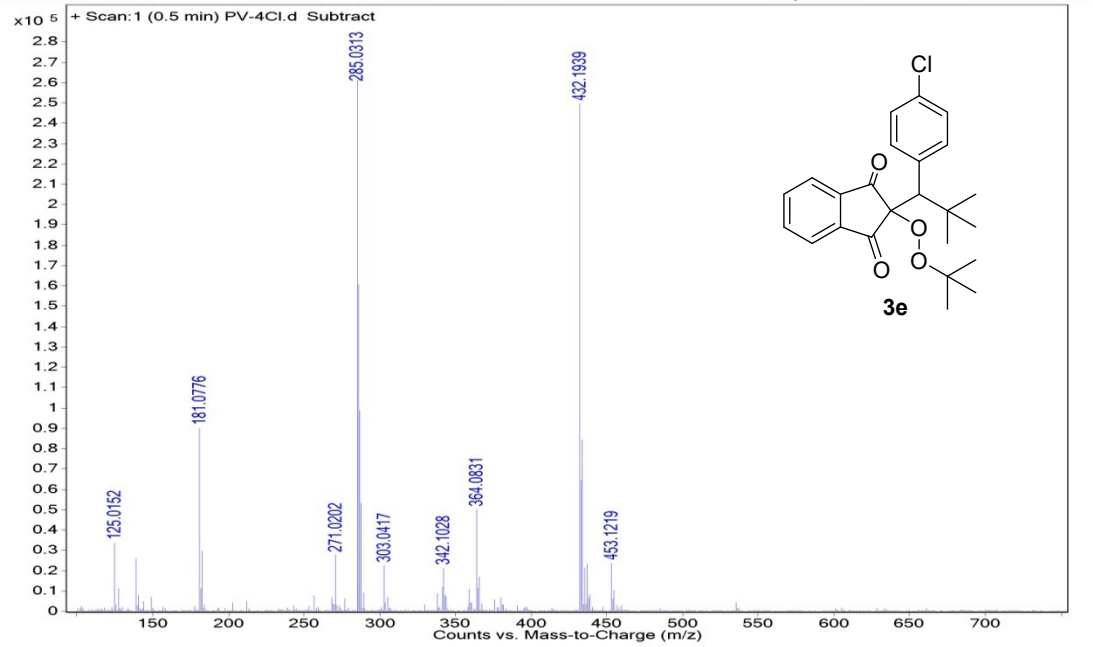

OMe
O
O
O
3d
f1 (ppm)


PV-OMe_MeOH
IIT(ISM).DHANBAD
Central Research Facility,HRMS
12-Jan-2022
13:03:20
PV-OMe_MeOH 3 (0.079) Cm (3:4)
1: TOF MS ES+
3.85e6
433.1997
OMe
O
O
O
O
3d
Elemental Composition Report
Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 25-25 H: 30-30 O: 5-5 Na: 0-1
Minimum: -1.5
Maximum: 50.0 10.0 50.0
Mass Calc. Mass mDa PPM DBE Formula
433.1997 433.1991 0.6 1.4 10.5 C25 H30 O5 Na
434.2004
437.1922
100
%
0
410
415
420
425
430
435
440
445
450
455
460
m/z

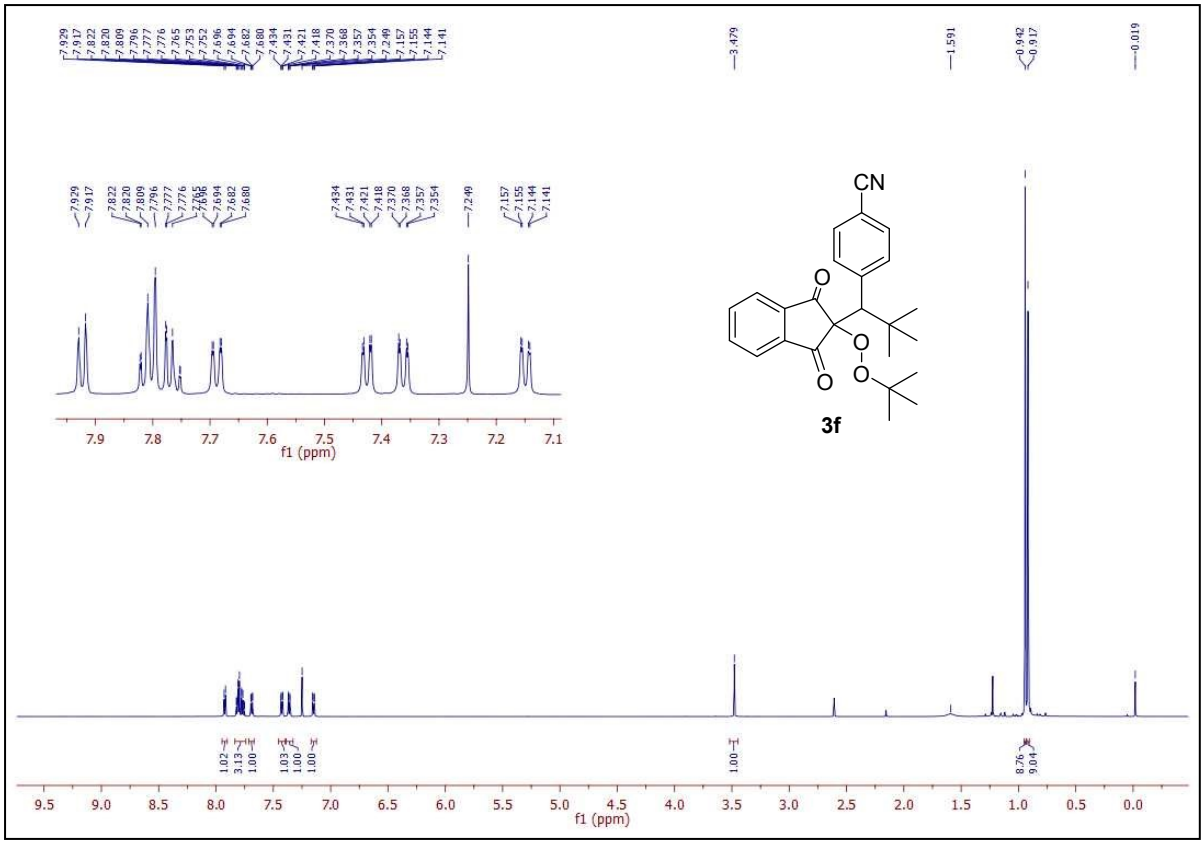

Cl
O
O
O
O
3e
f1 (ppm)

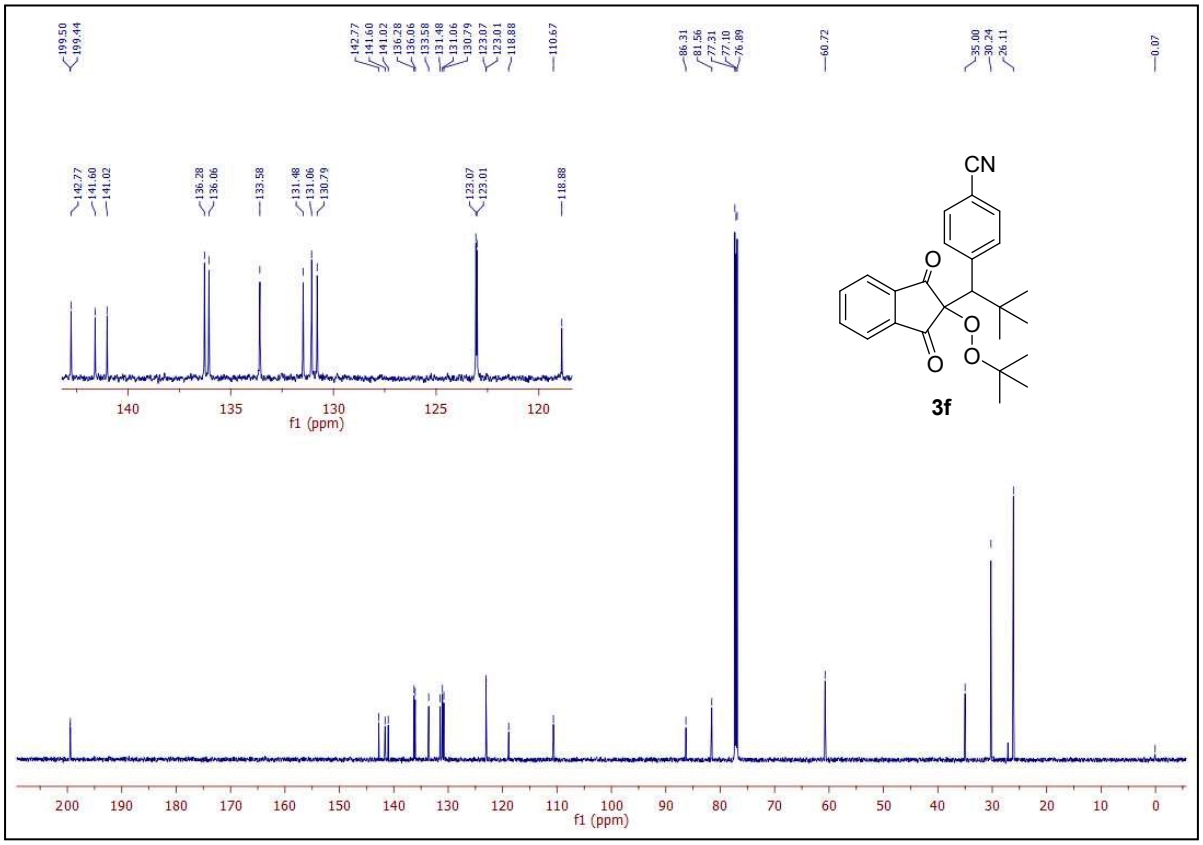

Cl
O
O
O
O
3e
f1 (ppm)

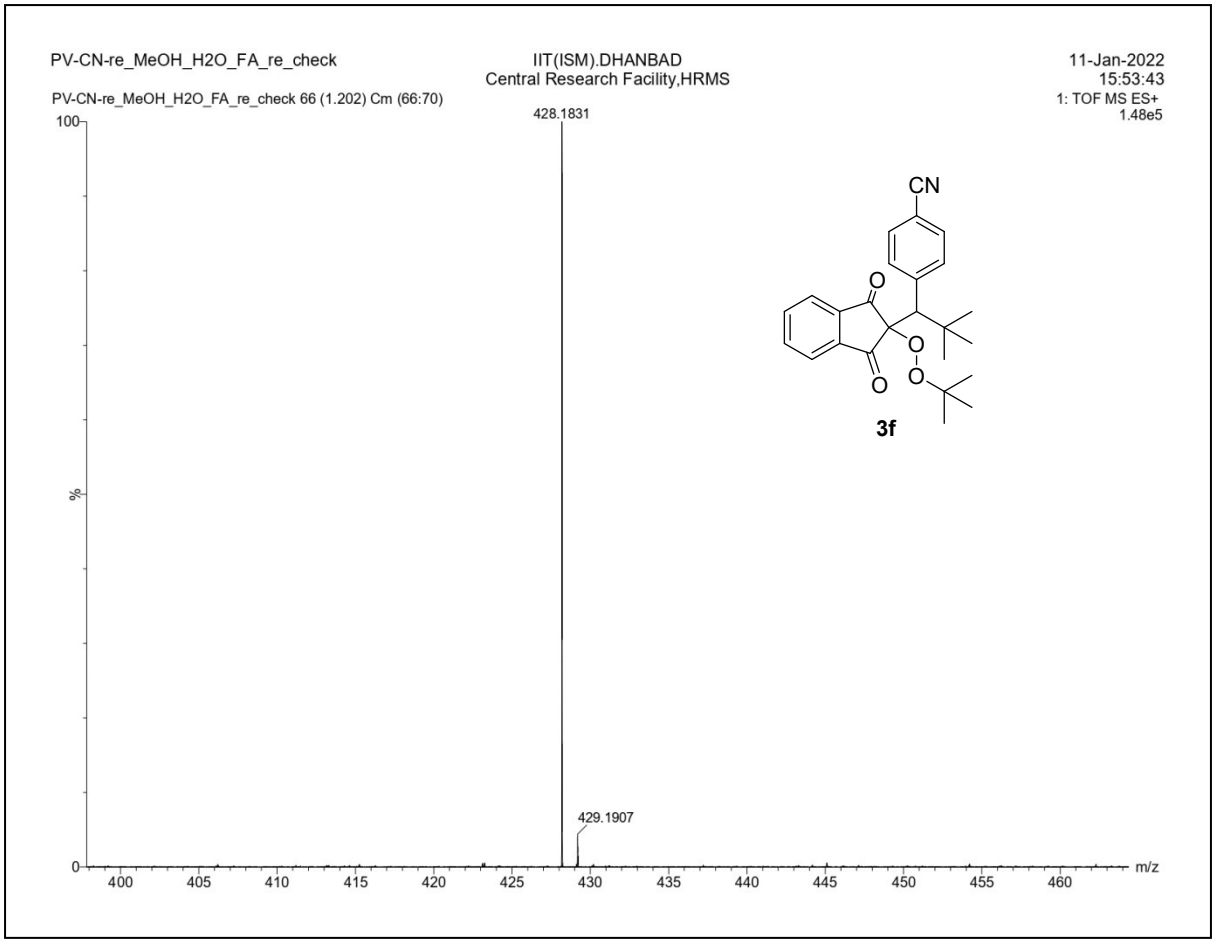
Sample Name	Pavithira S(SAIF2202	**Position**	Vial 59	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	PV-4Cl.d	**ACQ Method**	ISOCRATIC.m	**Comment**		**Acquired Time**	2/16/2022 2:24:08 PM

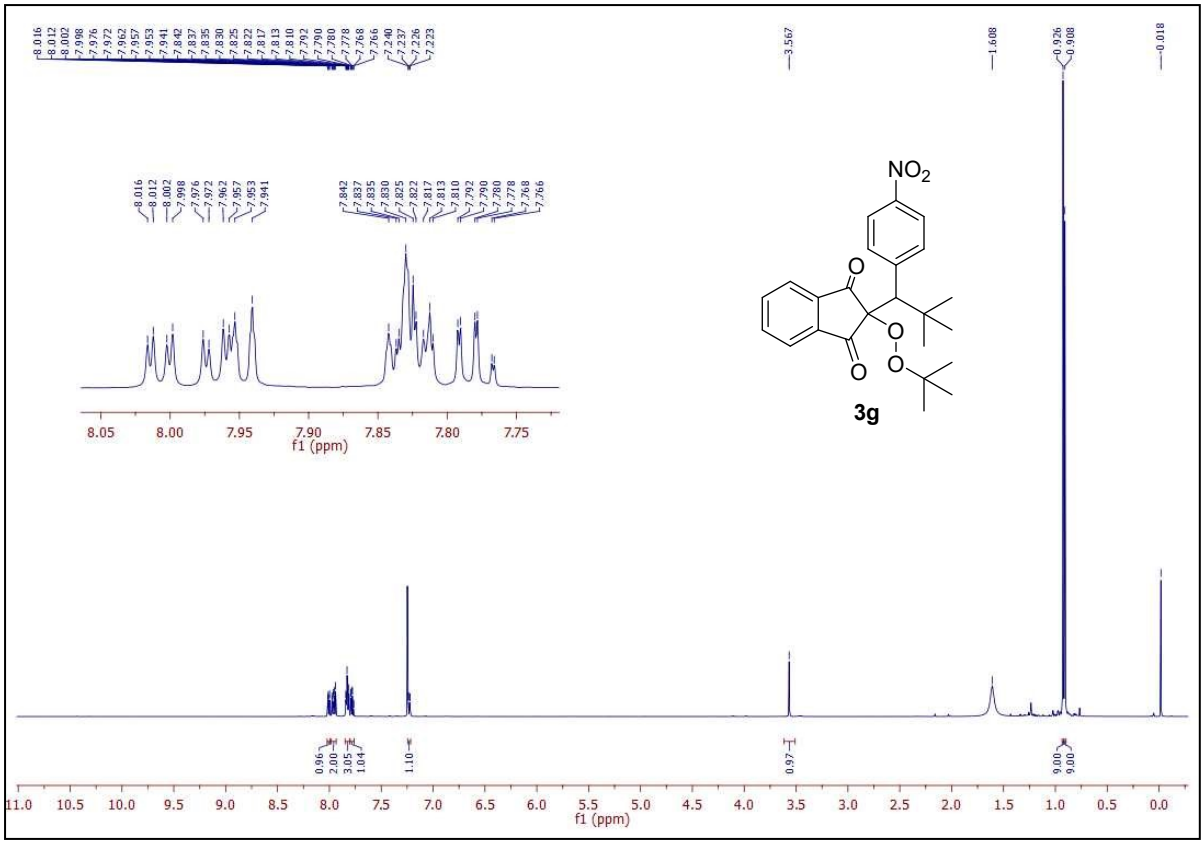


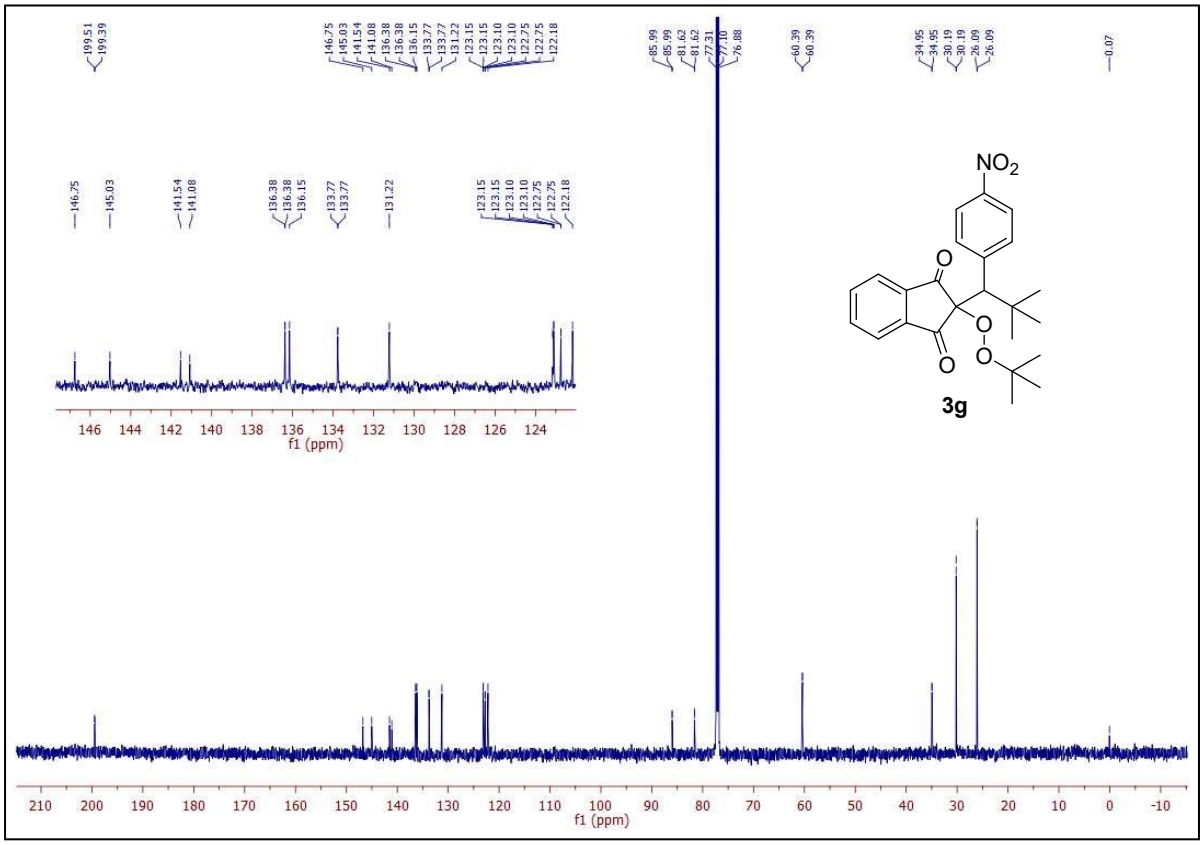
3e

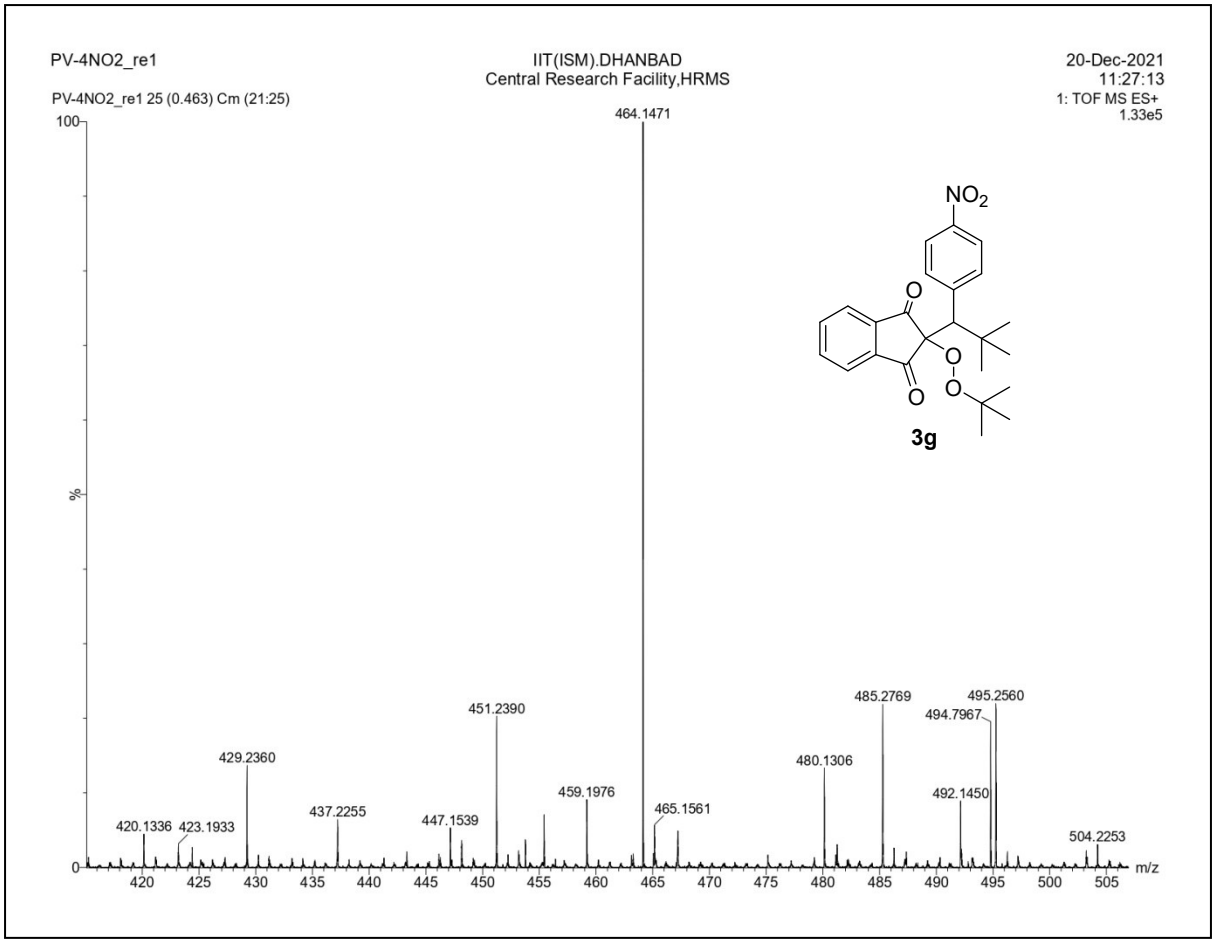

CN
O
O
O
O
3f
f1 (ppm)

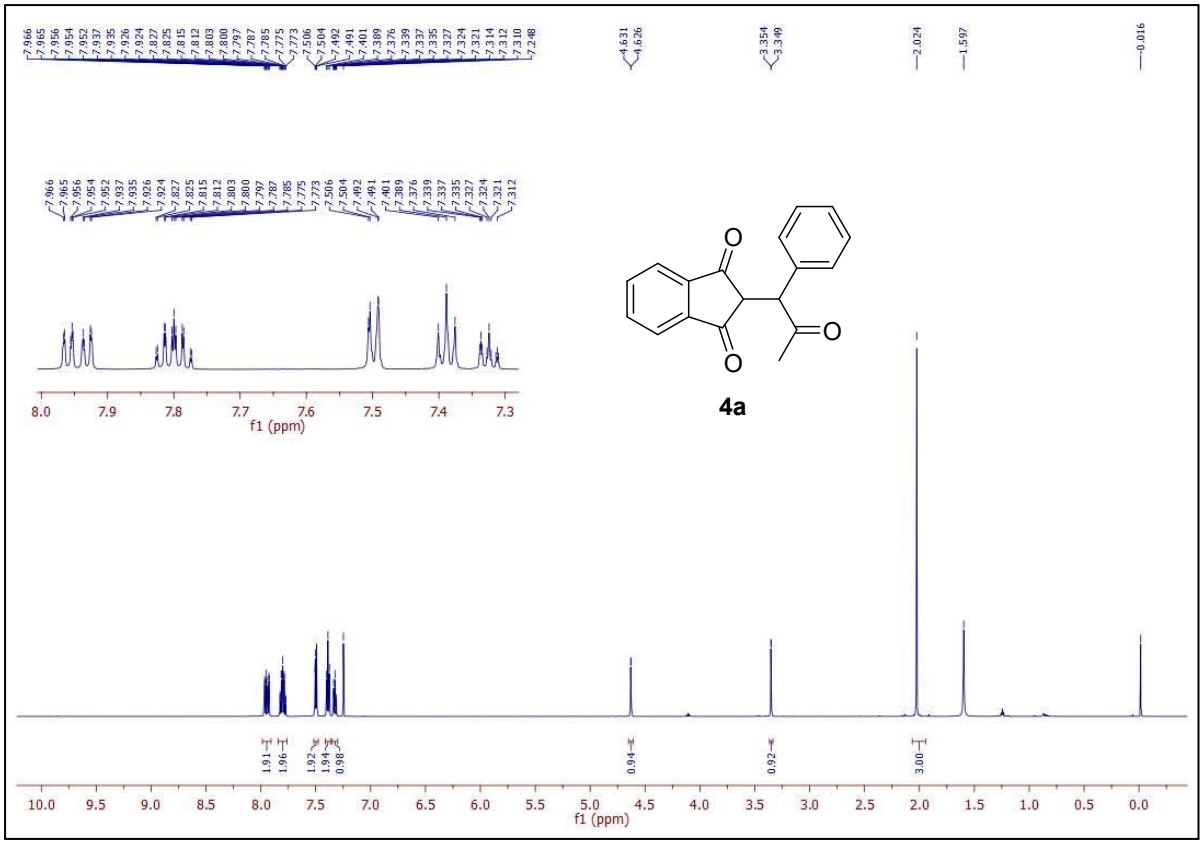

CN
O
O
O
O
3f
f1 (ppm)

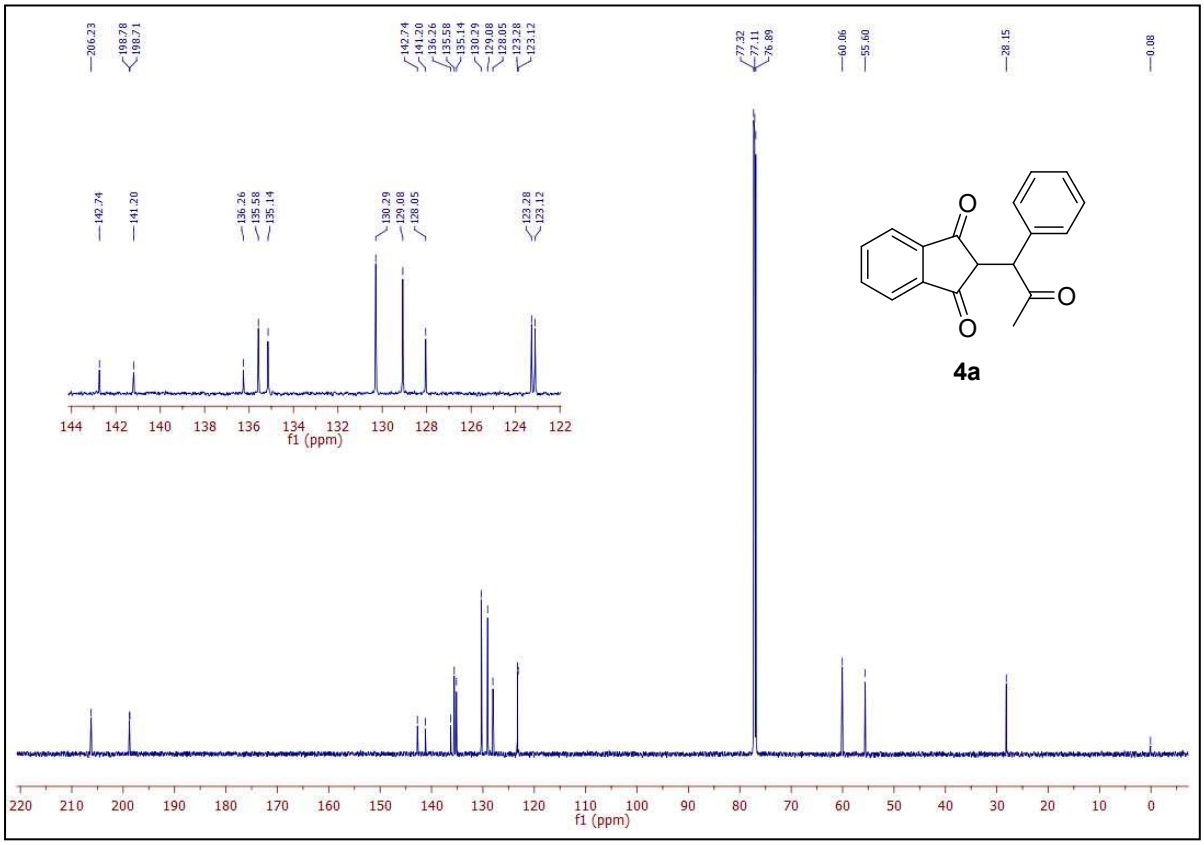

PV-CN-re_MeOH_H2O_FA_re_check
IIT(ISM).DHANBAD
Central Research Facility,HRMS
11-Jan-2022
15:53:43
PV-CN-re_MeOH_H2O_FA_re_check 66 (1.202) Cm (66:70)
1: TOF MS ES+
1.48e5
428.1831
429.1907
100
%
0
400
405
410
415
420
425
430
435
440
445
450
455
460
m/z
CN
O
O
O
O
3f


NO2
O
O
O
O
3g
f1 (ppm)


NO2
O
O
O
O
3g
f1 (ppm)


PV-4NO2_re1
IIT(ISM).DHANBAD
Central Research Facility,HRMS
20-Dec-2021
11:27:13
PV-4NO2_re1 25 (0.463) Cm (21:25)
1: TOF MS ES+
1.33e5
100
%
0
464.1471
451.2390
485.2769
495.2560
494.7967
429.2360
480.1306
459.1976
492.1450
465.1561
437.2255
447.1539
420.1336
423.1933
504.2253
420
425
430
435
440
445
450
455
460
465
470
475
480
485
490
495
500
505
m/z
NO2
O
O
O
O
3g


4a
f1 (ppm)


4a
f1 (ppm)

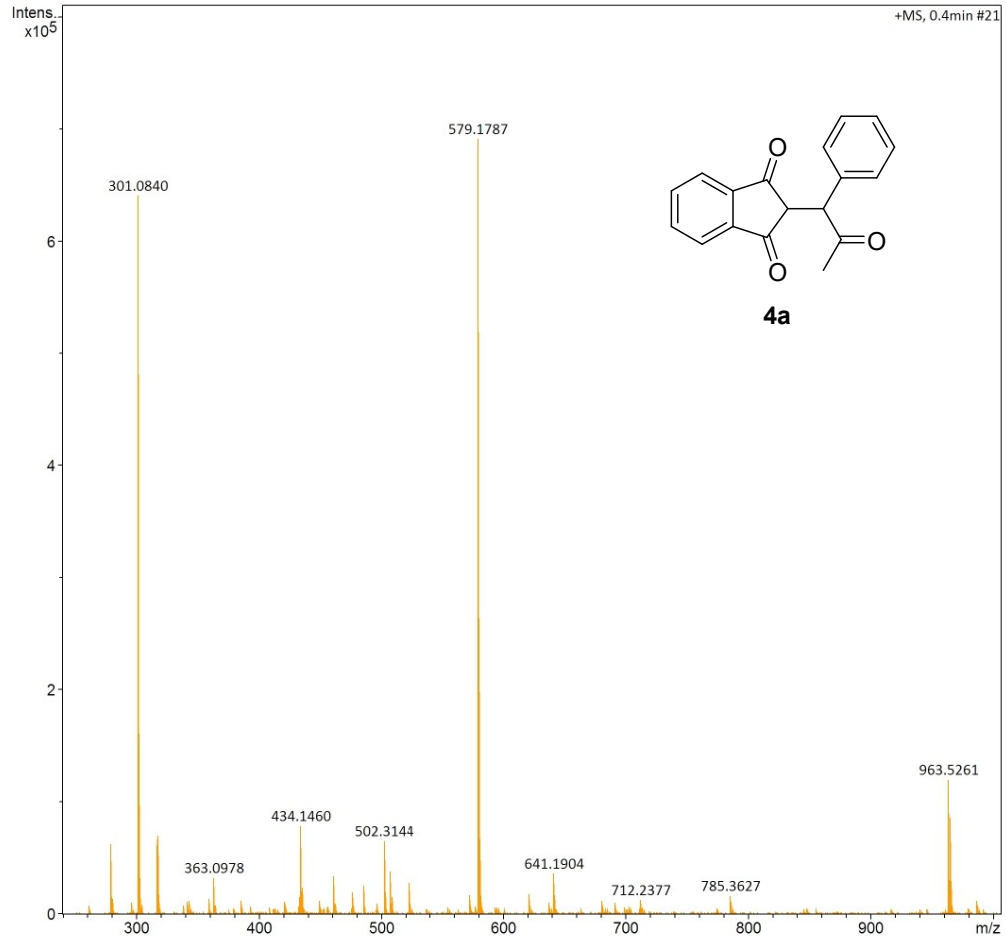
Display Report

Analysis Info

Analysis Name	D:\Data\2021-data\EXTERNAL SAMPLES\NOV\3.d	Acquisition Date	11/15/2021 4:47:19 PM
Method	tune_low.m	Operator	BDAL
Sample Name	3	Instrument	maXis 255552.10138
Comment			

Acquisition Parameter

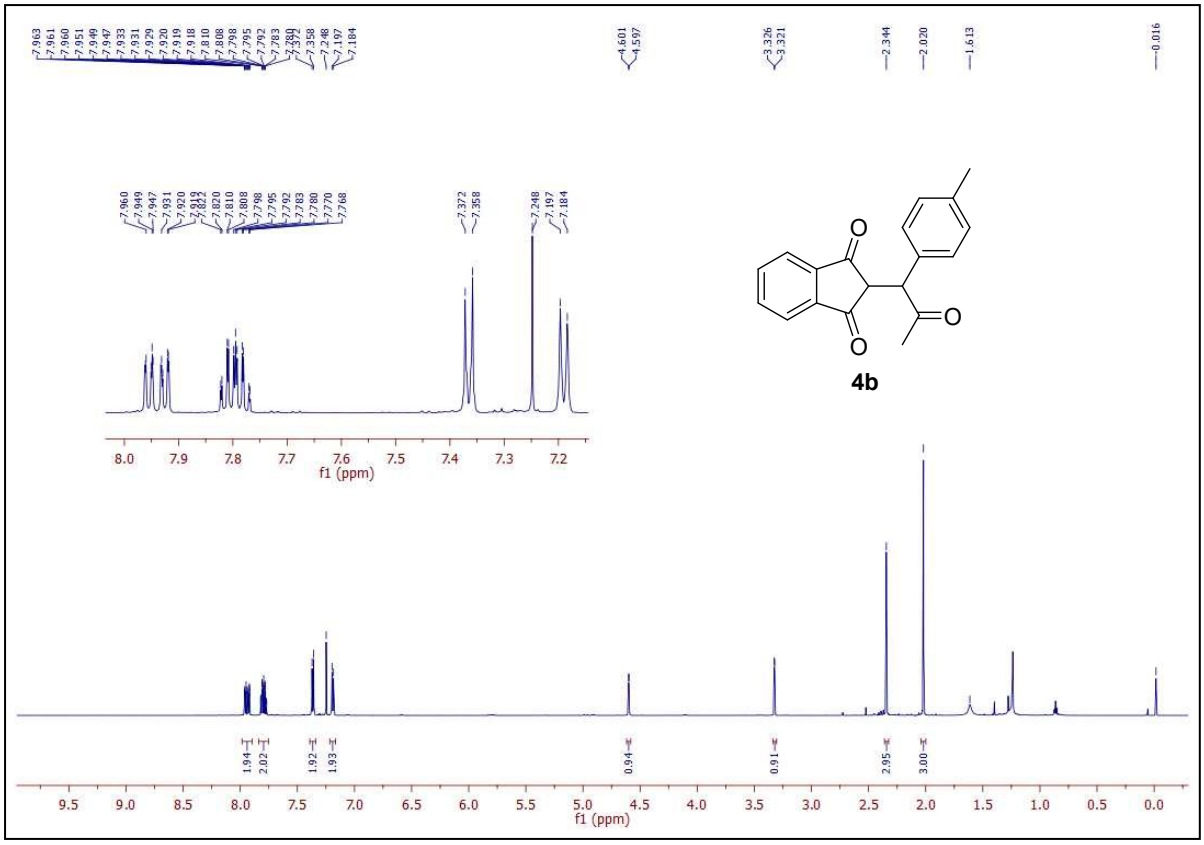
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	2000 m/z	Set Charging Voltage	0 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C

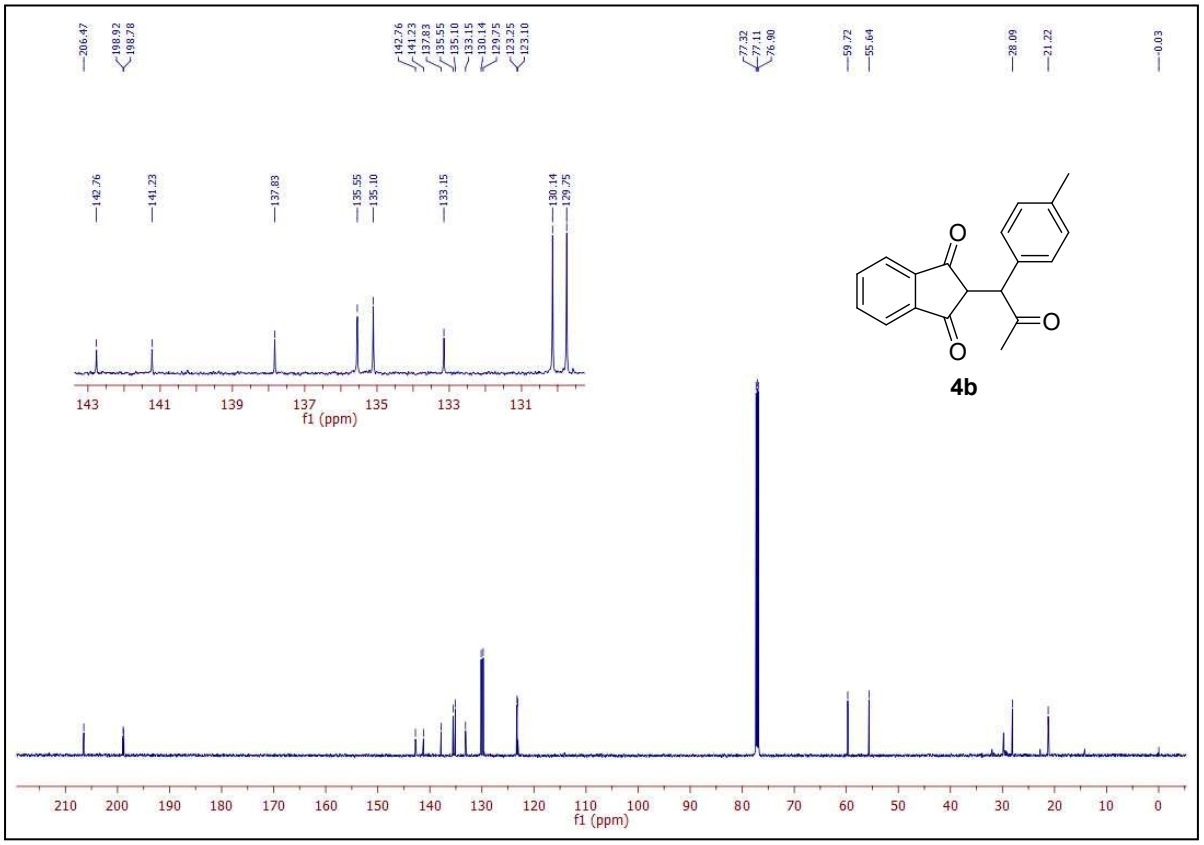


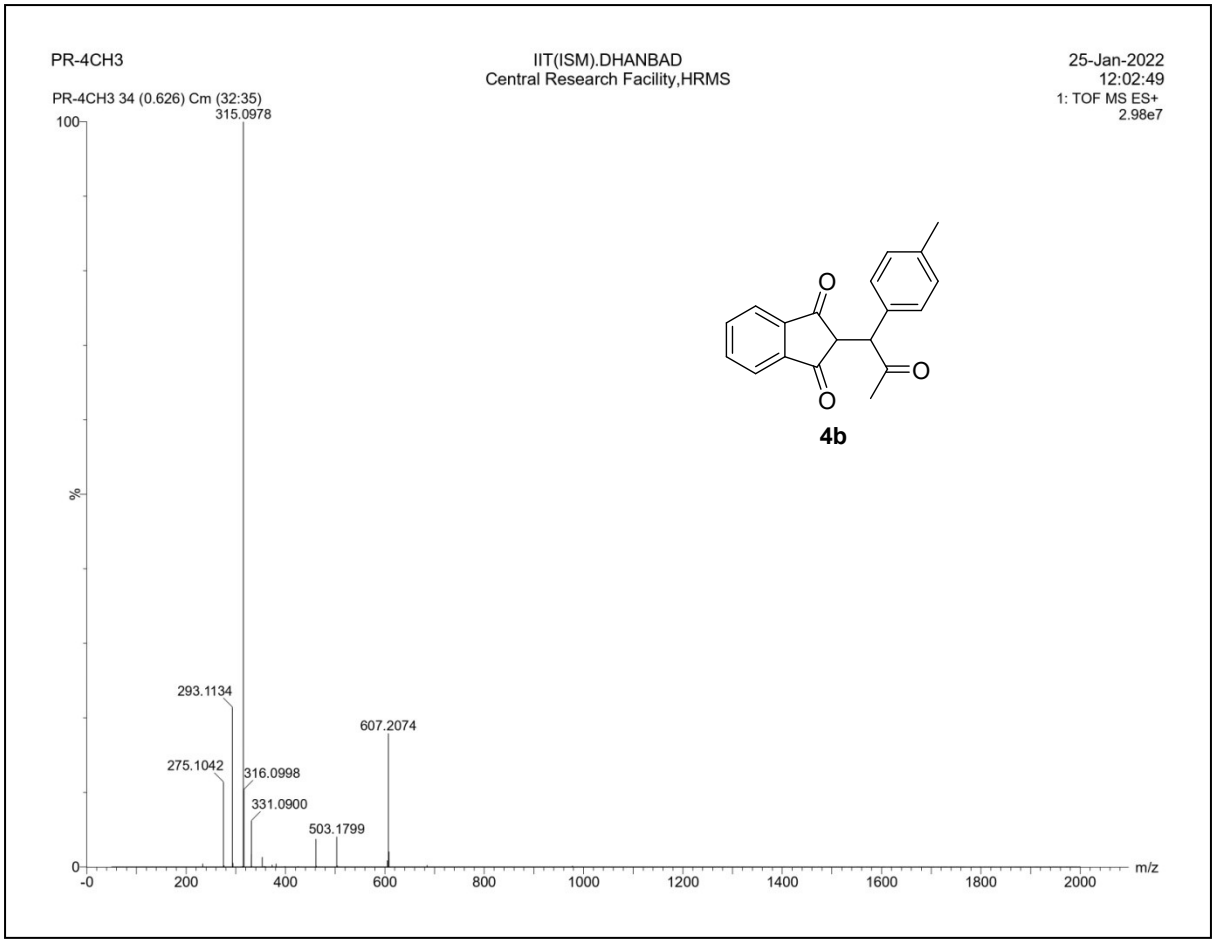
4a

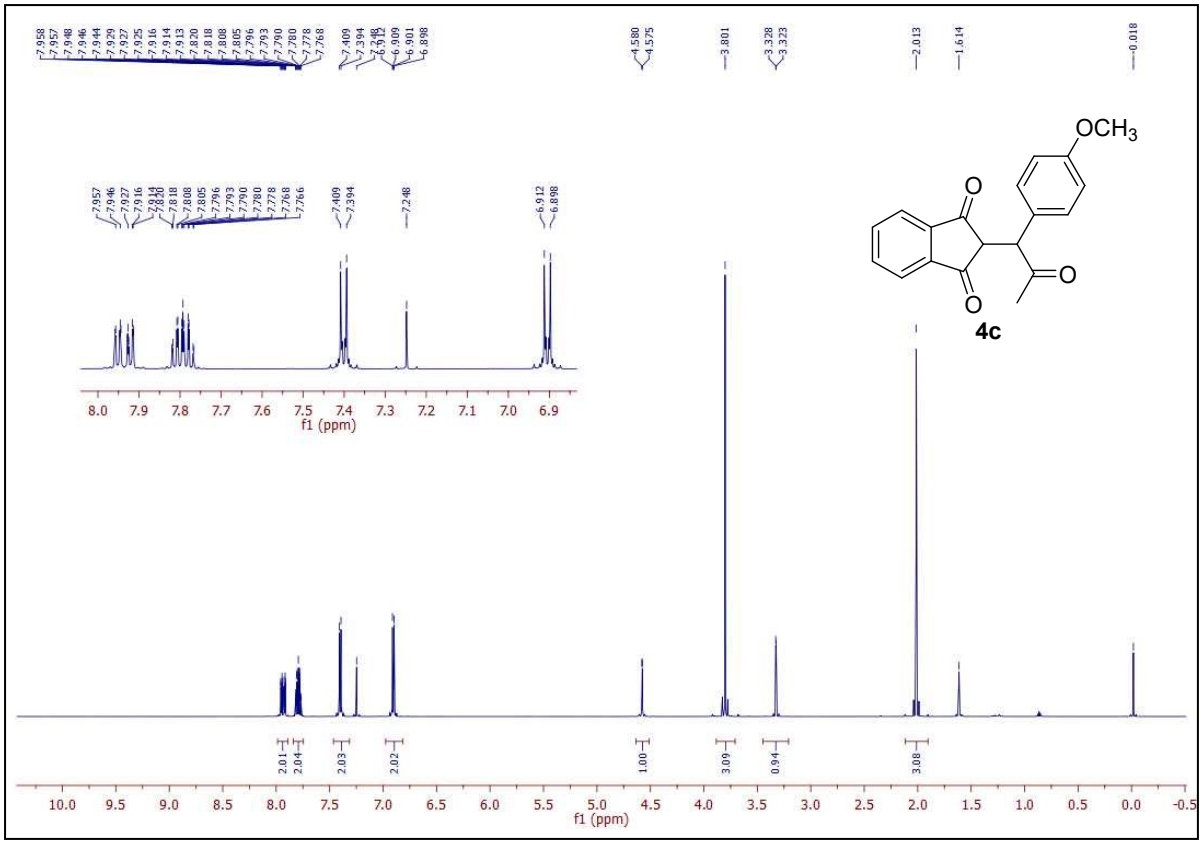
3.d

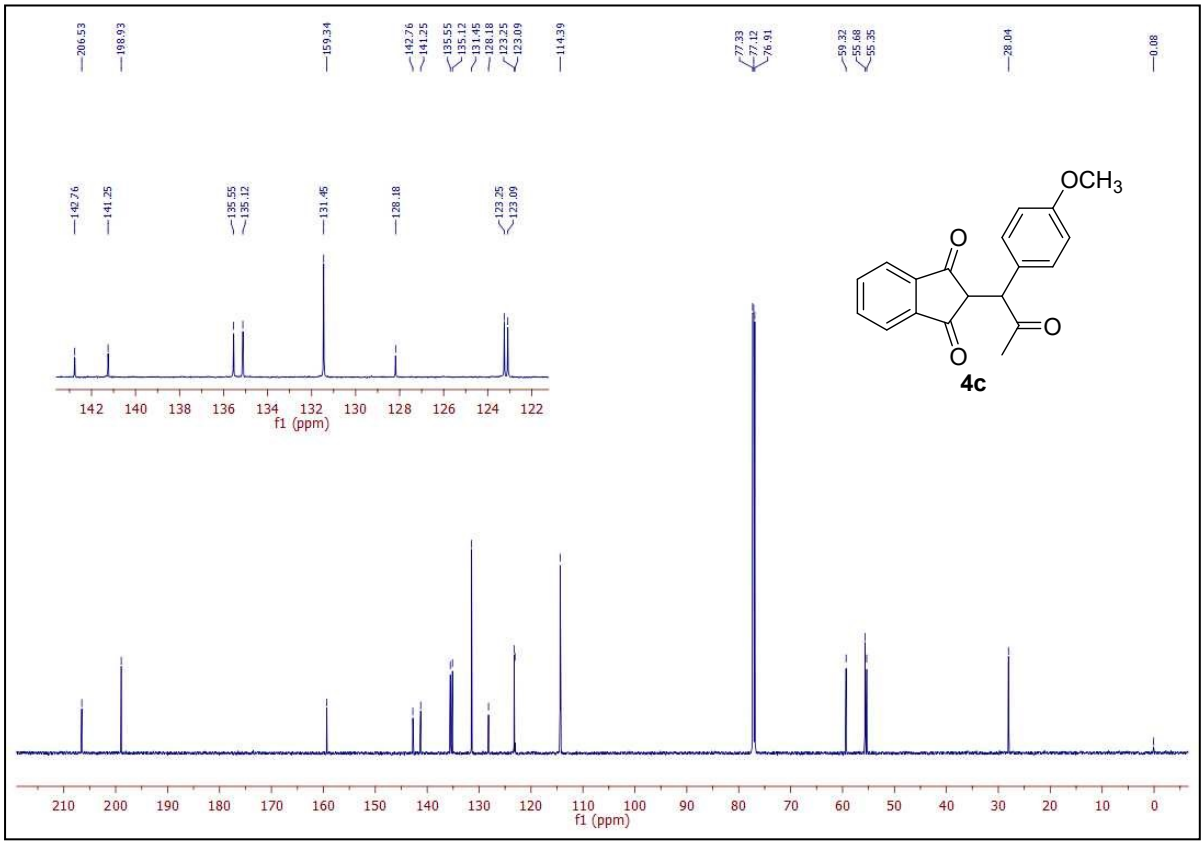
Bruker Compass DataAnalysis 4.2 printed: 11/15/2021 5:03:32 PM by: BDAL Page 1 of 1

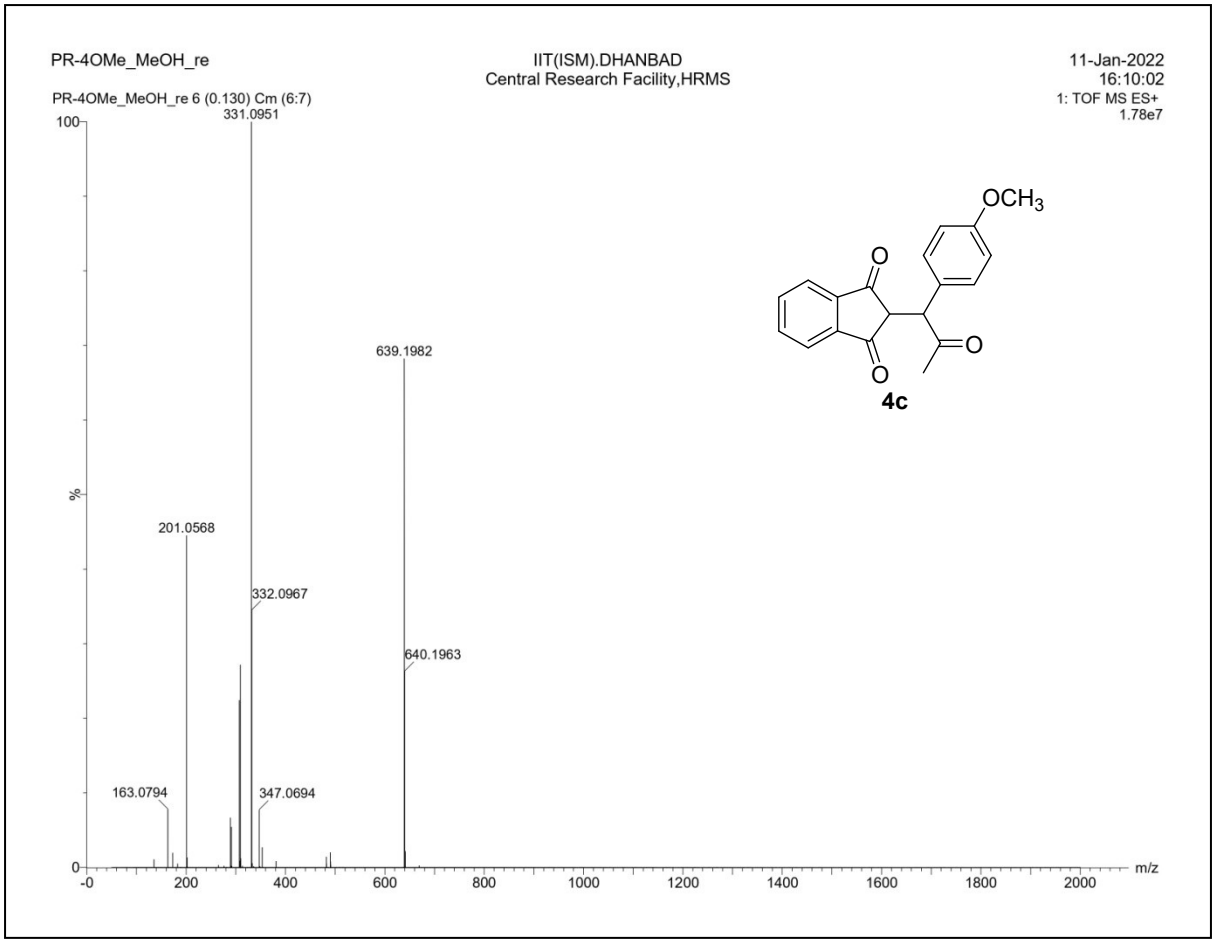

4b
f1 (ppm)

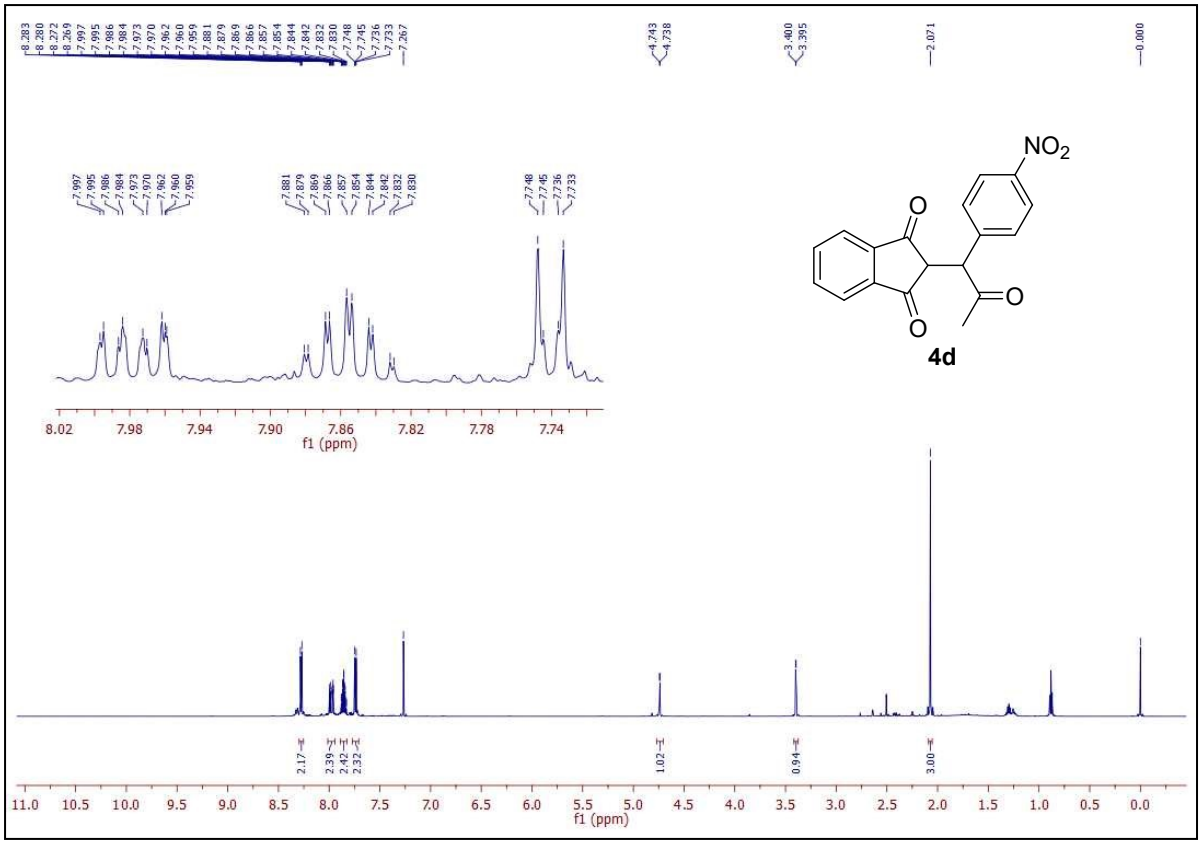

4b
f1 (ppm)

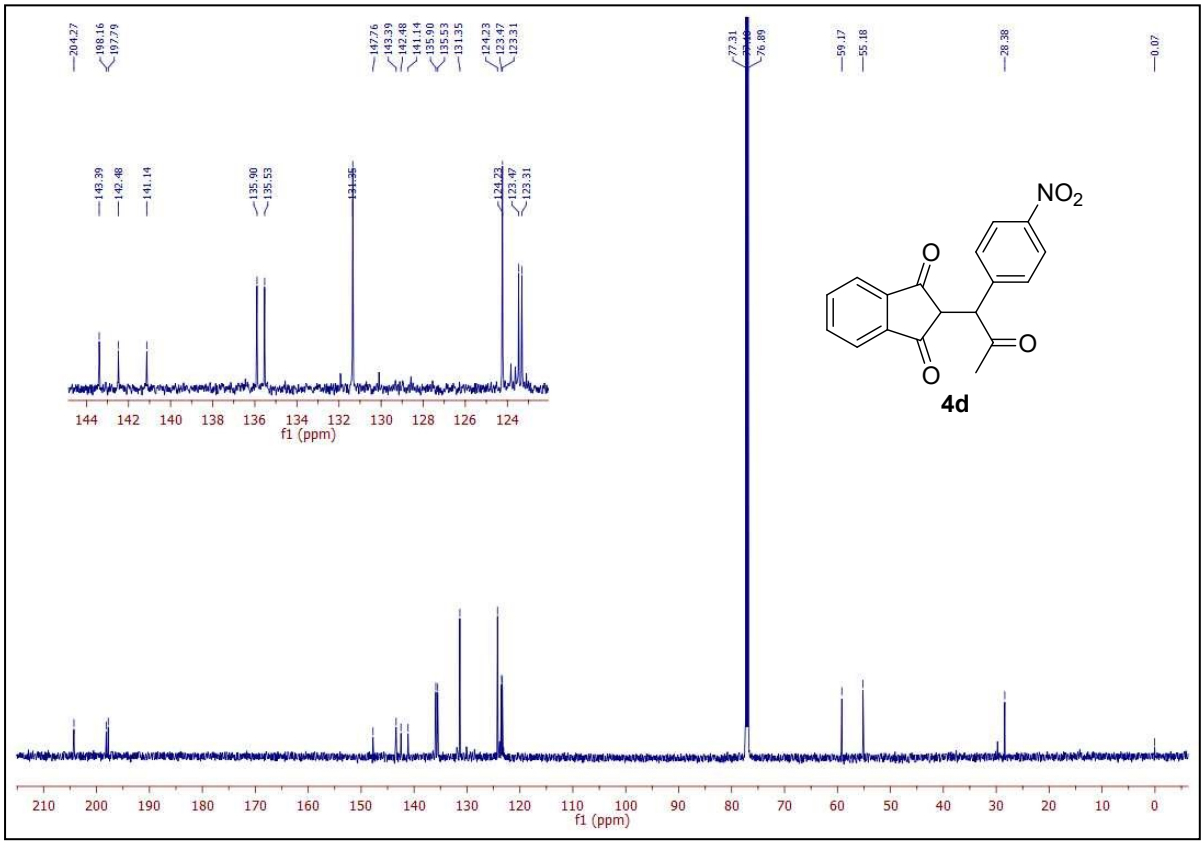

PR-4CH3
IIT(ISM).DHANBAD
Central Research Facility,HRMS
25-Jan-2022
12:02:49
PR-4CH3 34 (0.626) Cm (32:35)
1: TOF MS ES+
2.98e7
315.0978
293.1134
607.2074
275.1042
316.0998
331.0900
503.1799
%
m/z
O
O
O
4b


OCH3
O
O
O
4c
f1 (ppm)

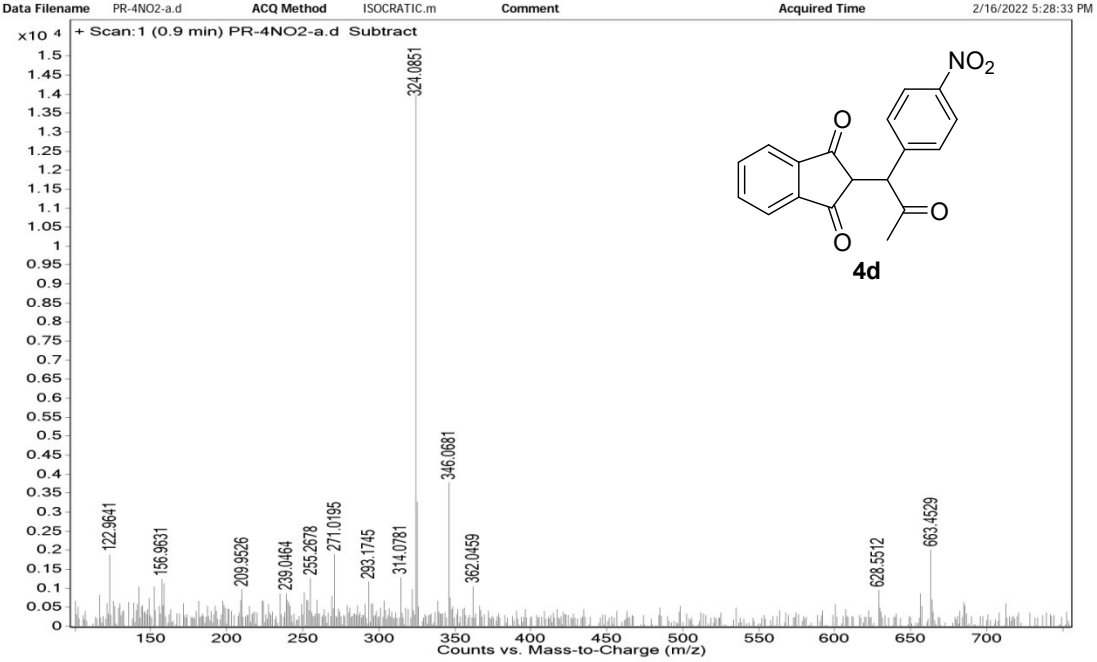

OCH3
O
O
O
4c
f1 (ppm)


PR-4OMe_MeOH_re
IIT(ISM).DHANBAD
Central Research Facility,HRMS
11-Jan-2022
16:10:02
PR-4OMe_MeOH_re 6 (0.130) Cm (6:7)
1: TOF MS ES+
1.78e7
331.0951
639.1982
201.0568
332.0967
640.1963
163.0794
347.0694
100
%
0
-0
200
400
600
800
1000
1200
1400
1600
1800
2000
m/z
OCH3
O
O
O
4c

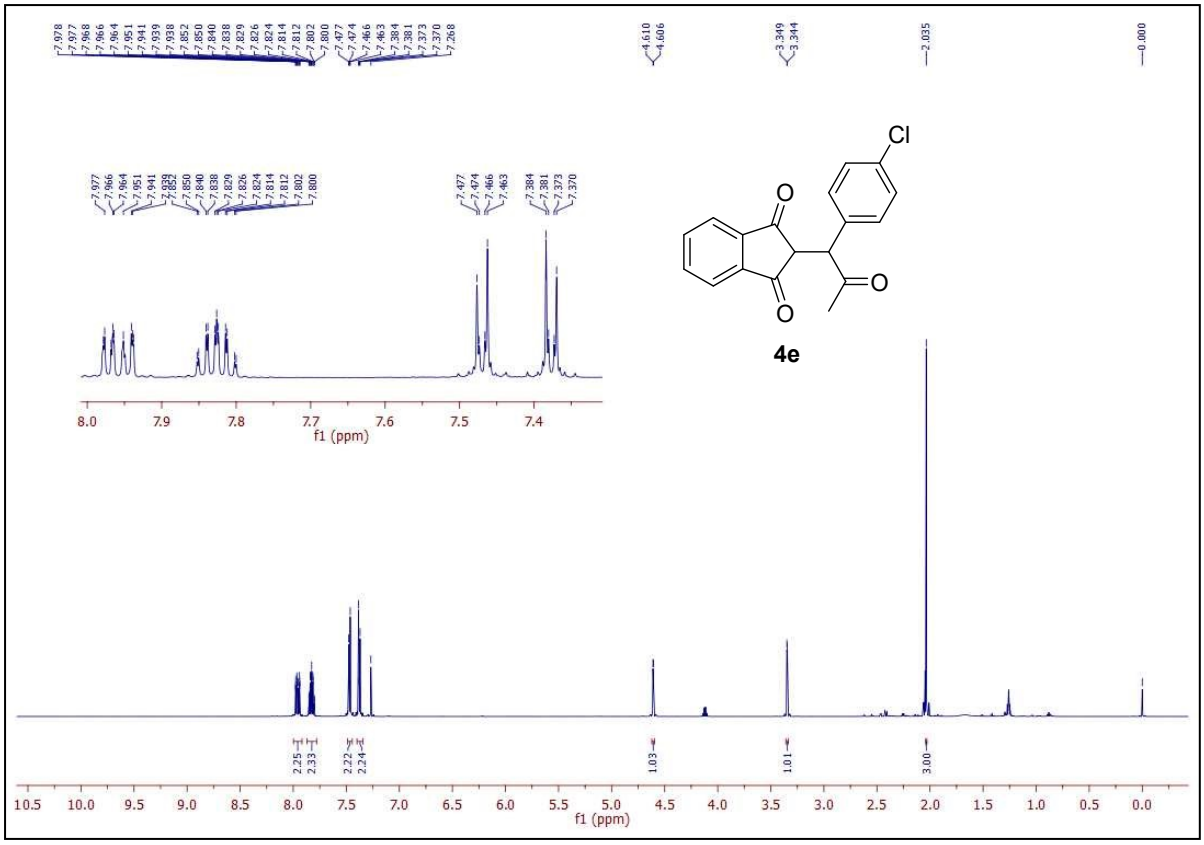

NO2
O
O
O
4d
f1 (ppm)

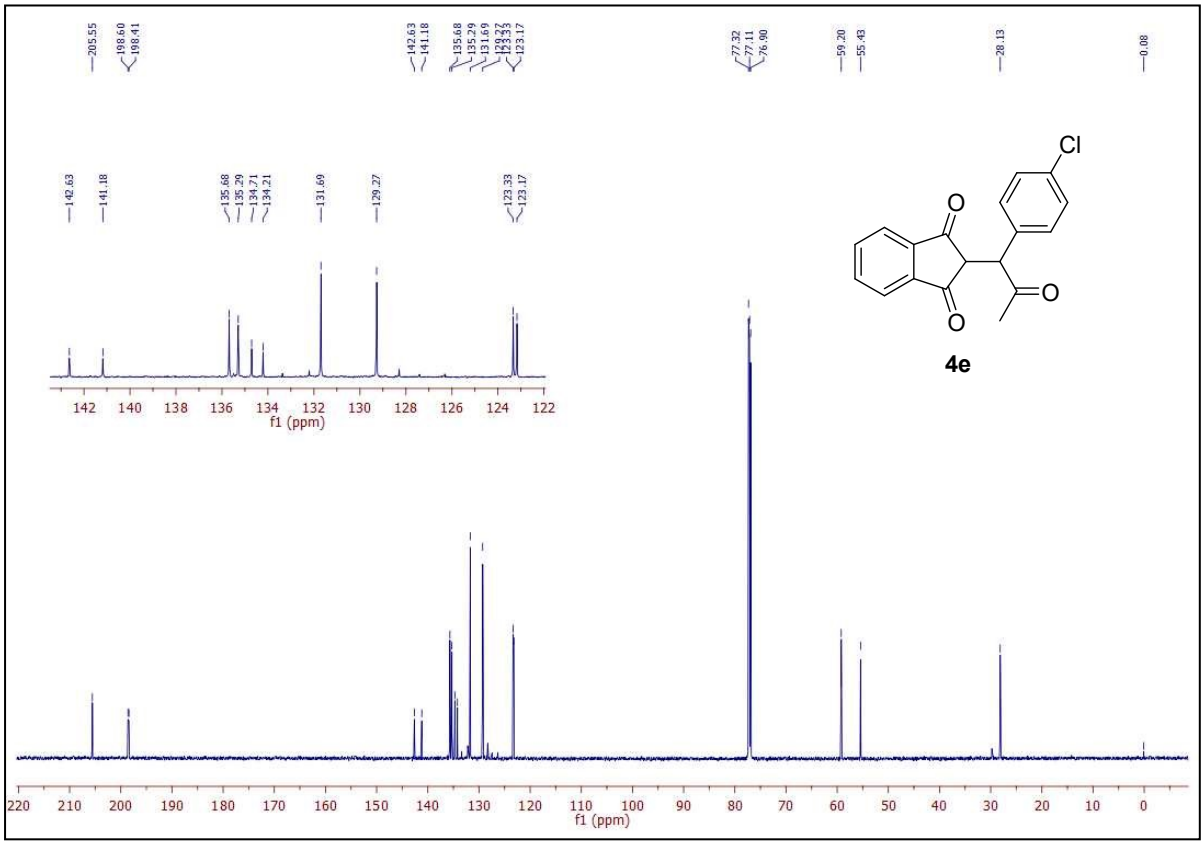

NO2
O
O
O
4d
f1 (ppm)

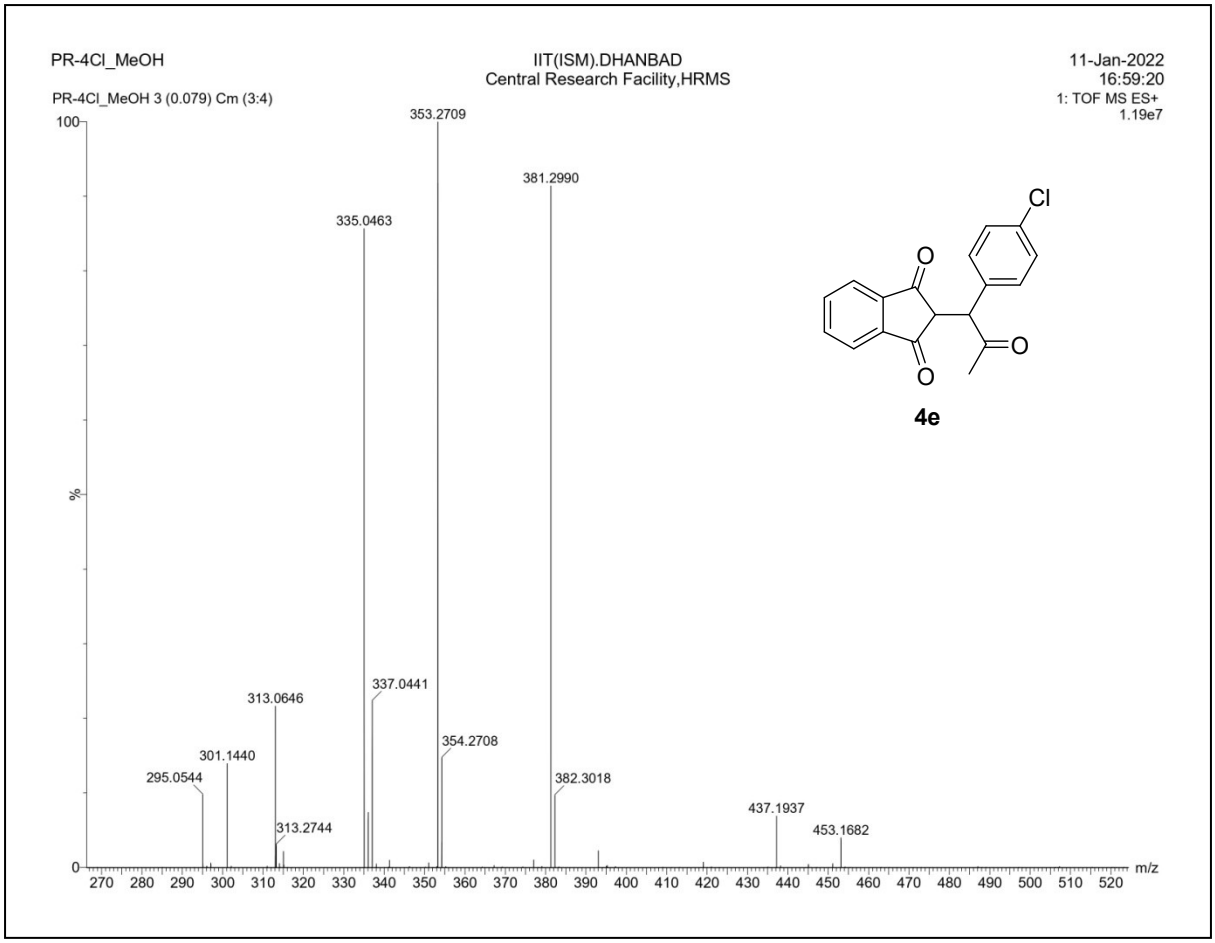
Sample Name	Pavithira S(SAIF2202	**Position**	Vial 60	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	PR-4NO2-a.d	**ACQ Method**	ISOCRATIC.m	**Comment**		**Acquired Time**	2/16/2022 5:28:33 PM

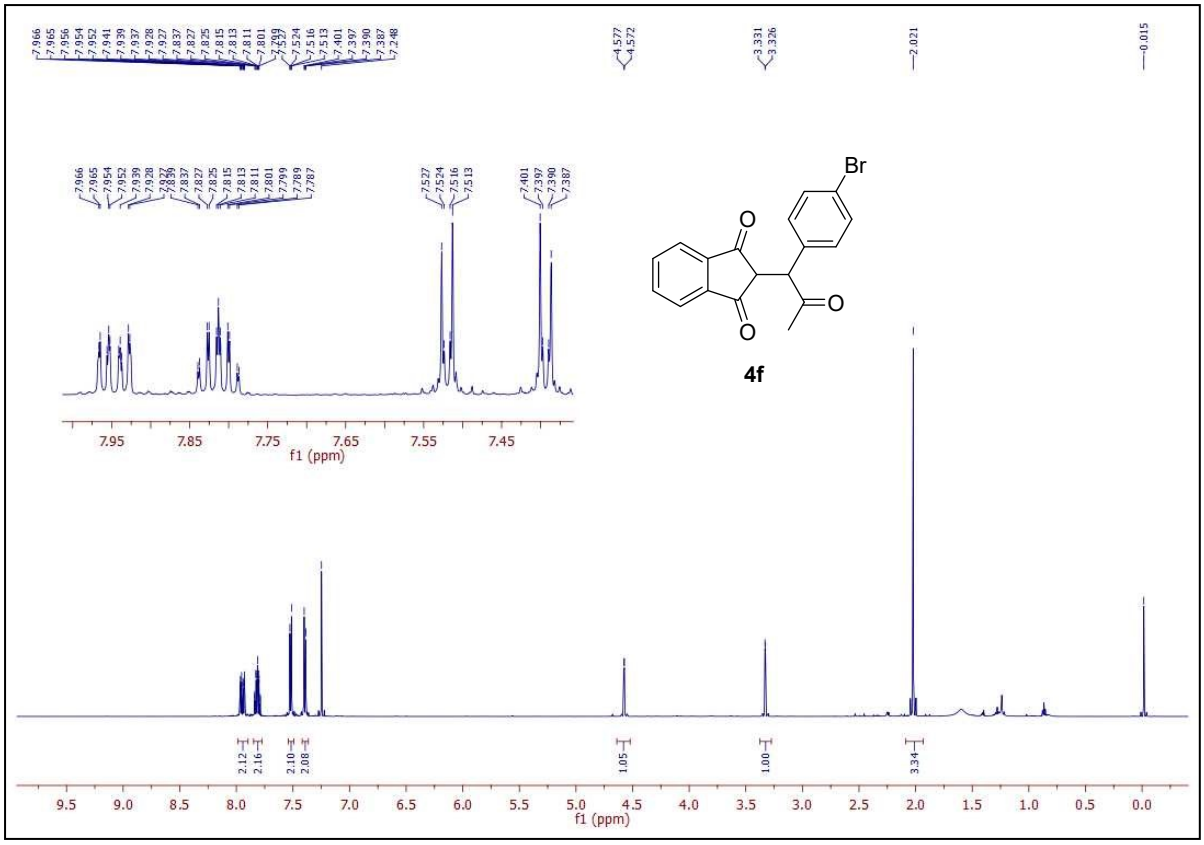


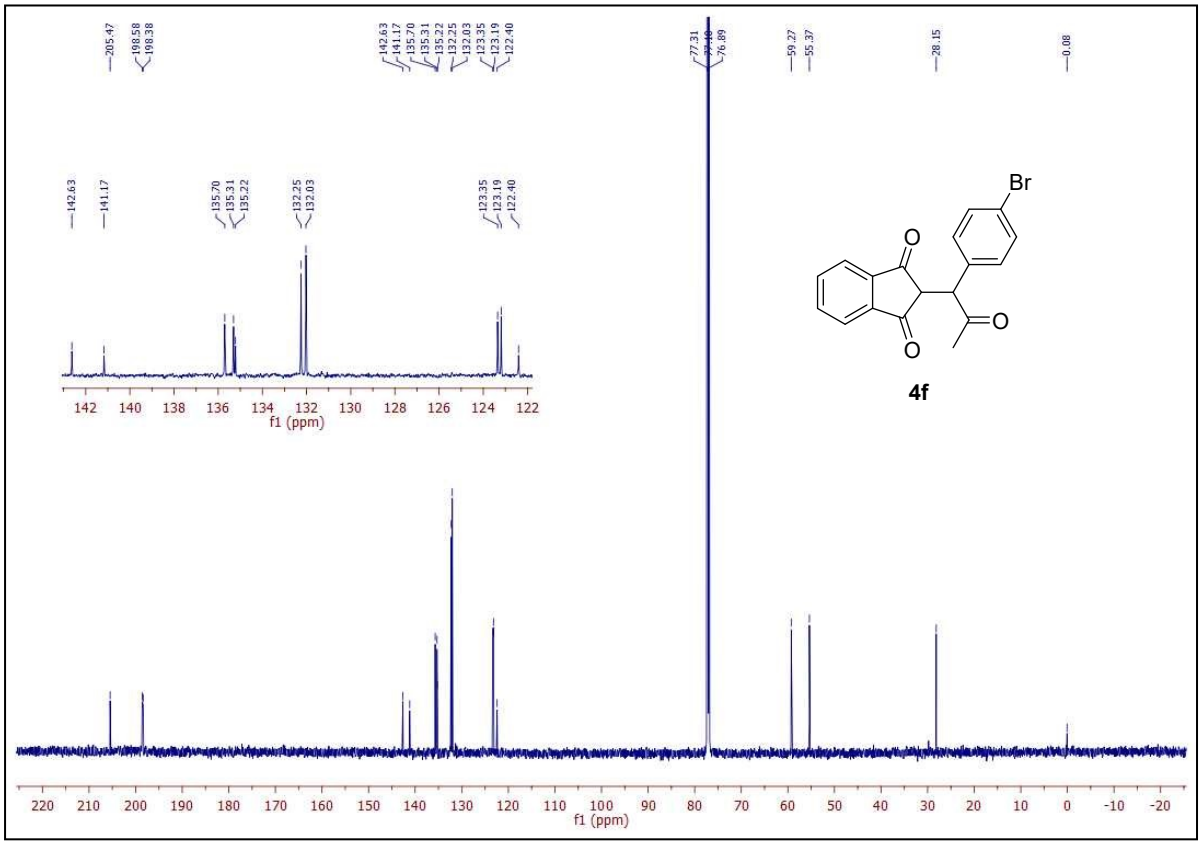
4d

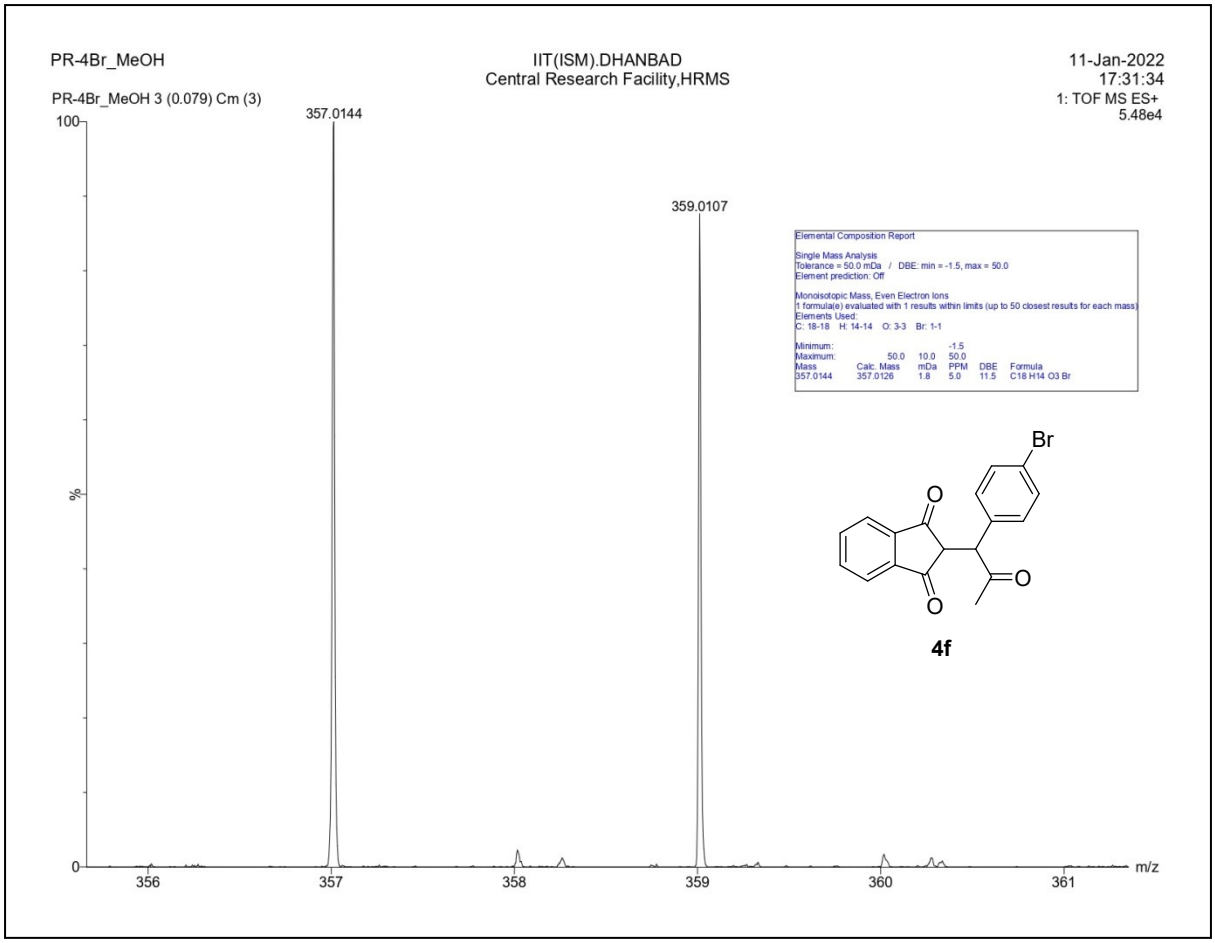

Cl
O
O
O
4e
f1 (ppm)


Cl
O
O
O
4e
f1 (ppm)

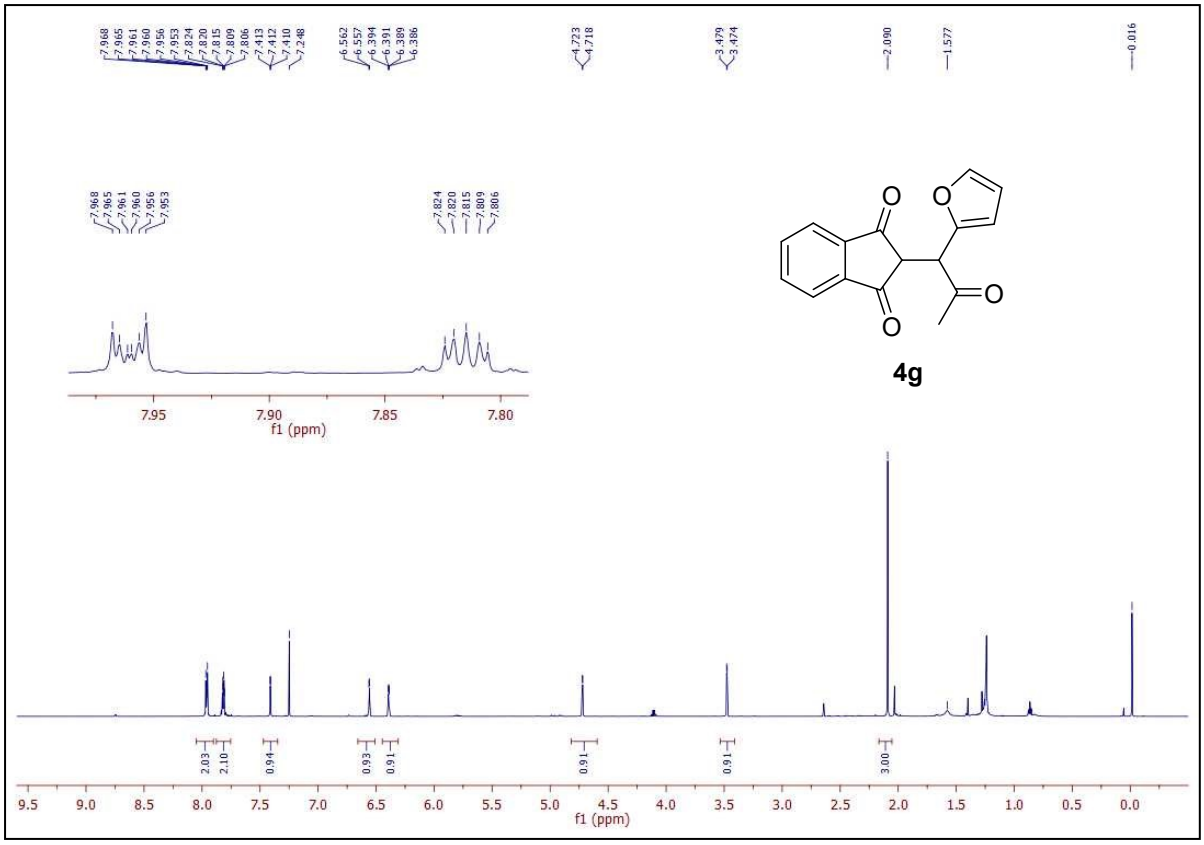

PR-4Cl_MeOH
IIT(ISM).DHANBAD
Central Research Facility,HRMS
11-Jan-2022
16:59:20
PR-4Cl_MeOH 3 (0.079) Cm (3:4)
1: TOF MS ES+
1.19e7
100
%
0
353.2709
381.2990
335.0463
337.0441
313.0646
354.2708
301.1440
295.0544
382.3018
437.1937
453.1682
313.2744
270 280 290 300 310 320 330 340 350 360 370 380 390 400 410 420 430 440 450 460 470 480 490 500 510 520
m/z
Cl
O
O
O
4e

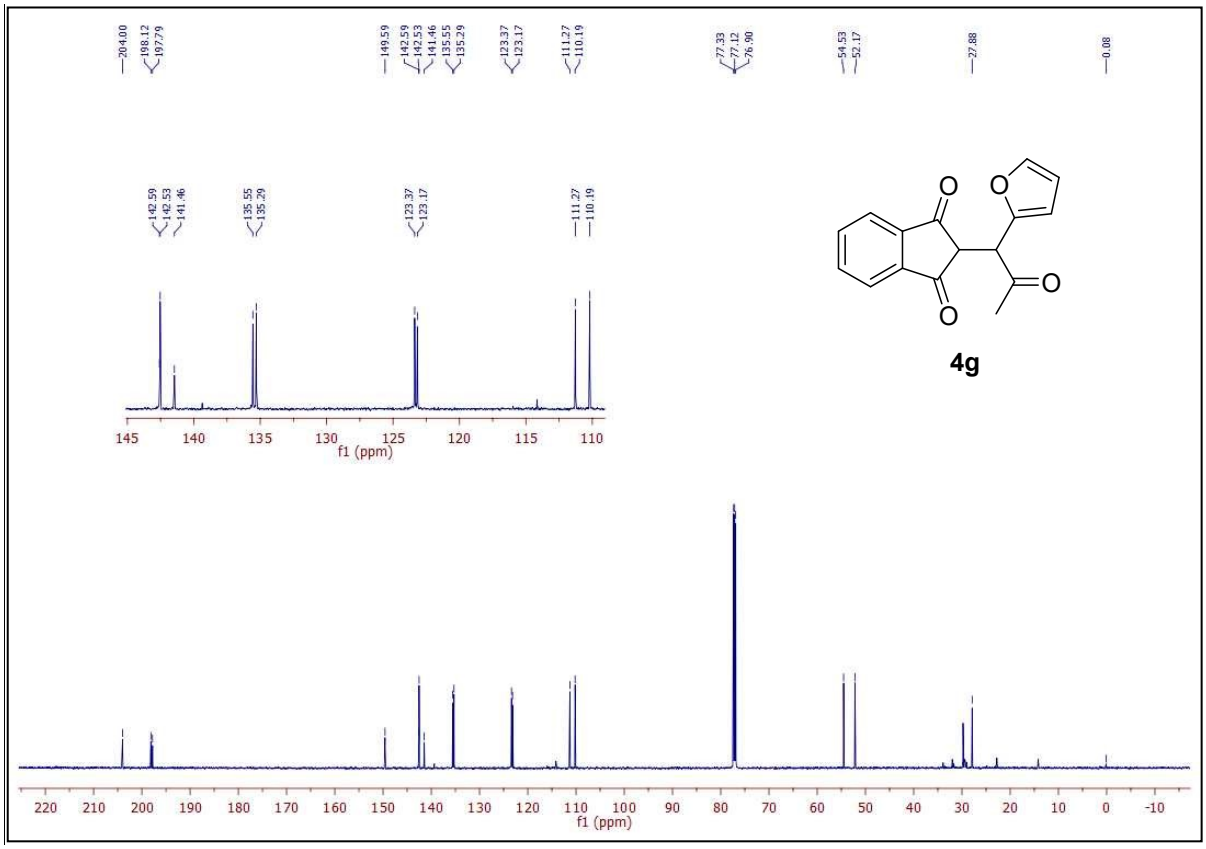

Br
O
O
O
4f
f1 (ppm)


Br
O
O
O
4f
f1 (ppm)

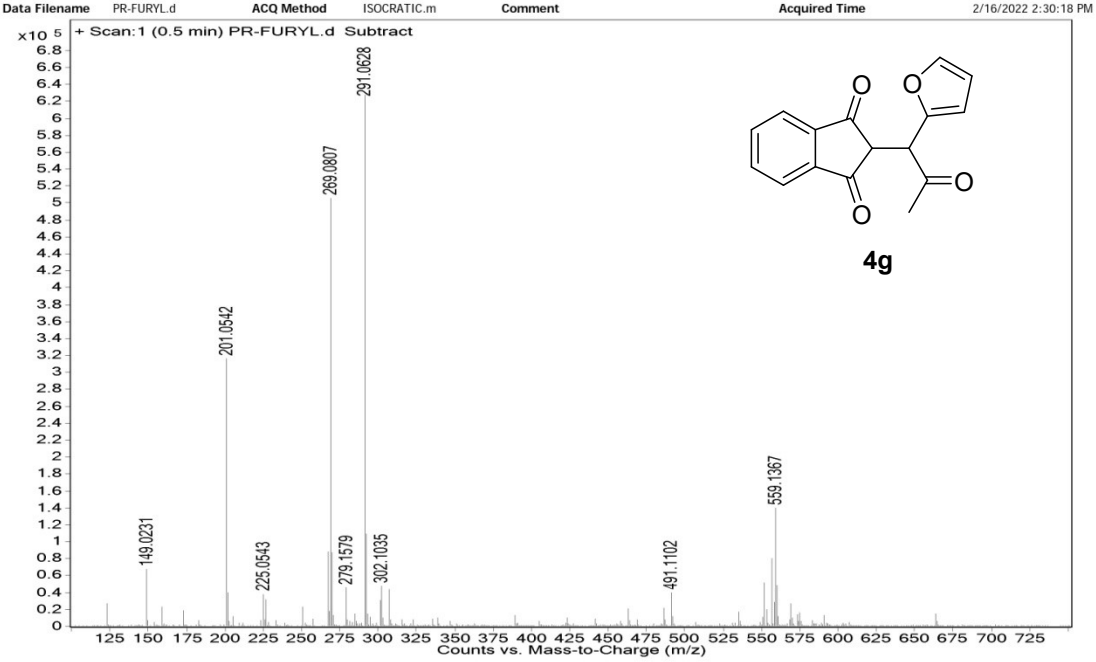

PR-4Br_MeOH
IIT(ISM).DHANBAD
Central Research Facility,HRMS
11-Jan-2022
17:31:34
PR-4Br_MeOH 3 (0.079) Cm (3)
1: TOF MS ES+
5.48e4
100
%
0
357.0144
359.0107
356
357
358
359
360
361
m/z
Elemental Composition Report
Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 18-18 H: 14-14 O: 3-3 Br: 1-1
Minimum: -1.5
Maximum: 50.0 10.0 50.0
Mass Calc. Mass mDa PPM DBE Formula
357.0144 357.0126 1.8 5.0 11.5 C18 H14 O3 Br
Br
O
O
O

4f


7.968
7.965
7.961
7.960
7.956
7.953
7.824
7.820
7.815
7.809
7.806
7.413
7.412
7.410
7.248
6.562
6.557
6.394
6.391
6.389
6.386
4.723
4.718
3.479
3.474
2.090
1.577
0.016
7.95
7.90
7.85
7.80
f1 (ppm)
O
O
O
O
4g
2.03
2.10
0.94
0.93
0.91
0.91
0.91
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


204.00
198.12
197.79
149.59
142.59
142.53
141.46
135.55
135.29
123.37
123.17
111.27
110.19
77.33
77.12
76.90
54.53
52.17
27.88
0.08
145
140
135
130
125
120
115
110
f1 (ppm)
O
O
O
O
4g
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Sample Name	Pavithira S(SAIF2202	**Position**	Vial 61	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	PR-FURYL.d	**ACQ Method**	ISOCRATIC.m	**Comment**		**Acquired Time**	2/16/2022 2:30:18 PM



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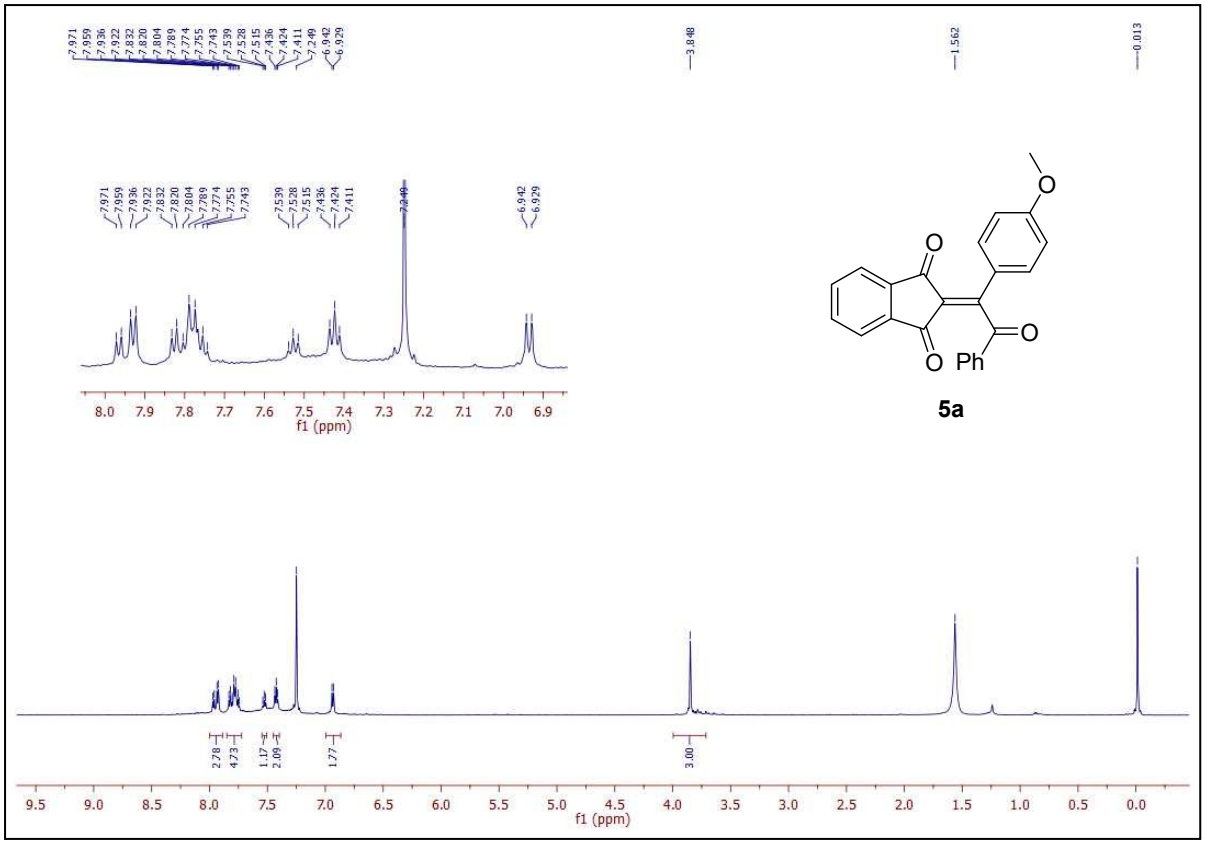
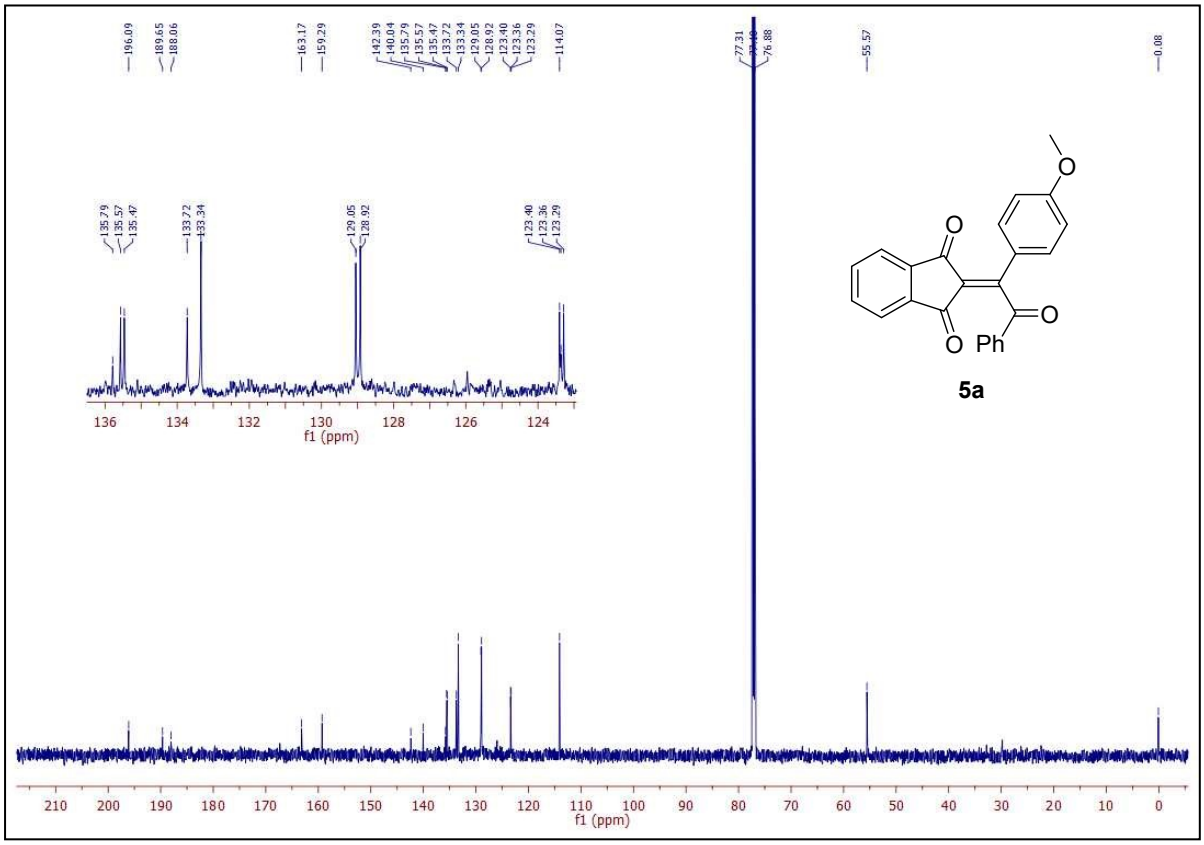
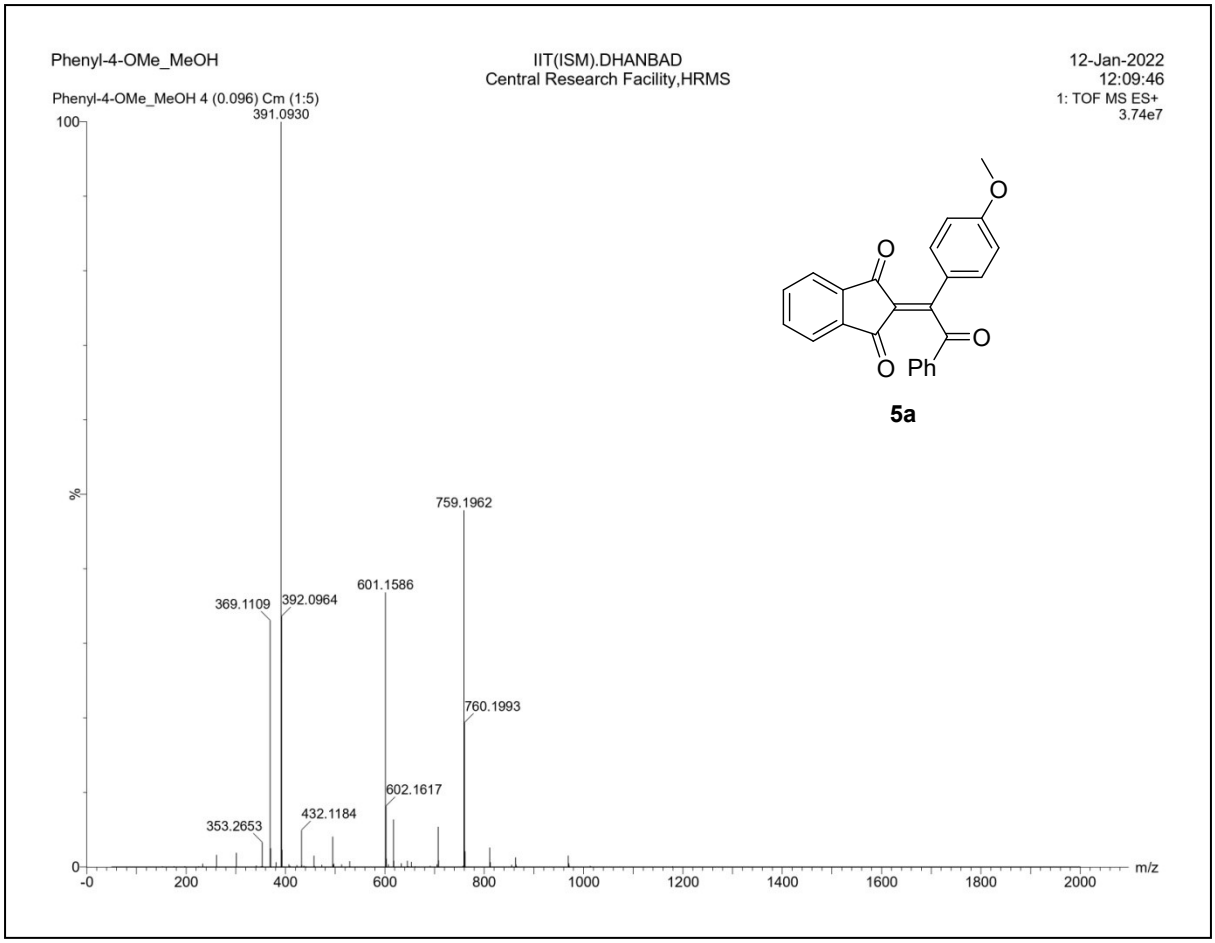


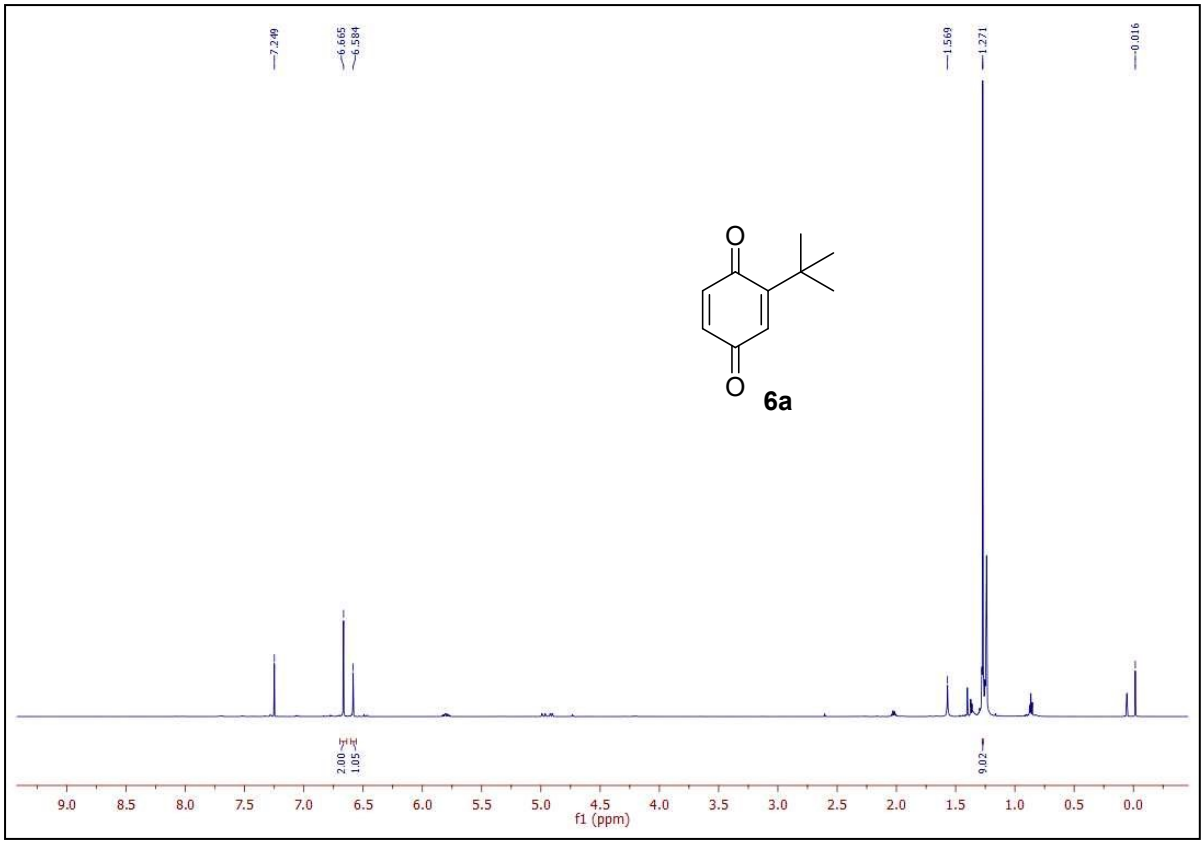
5a

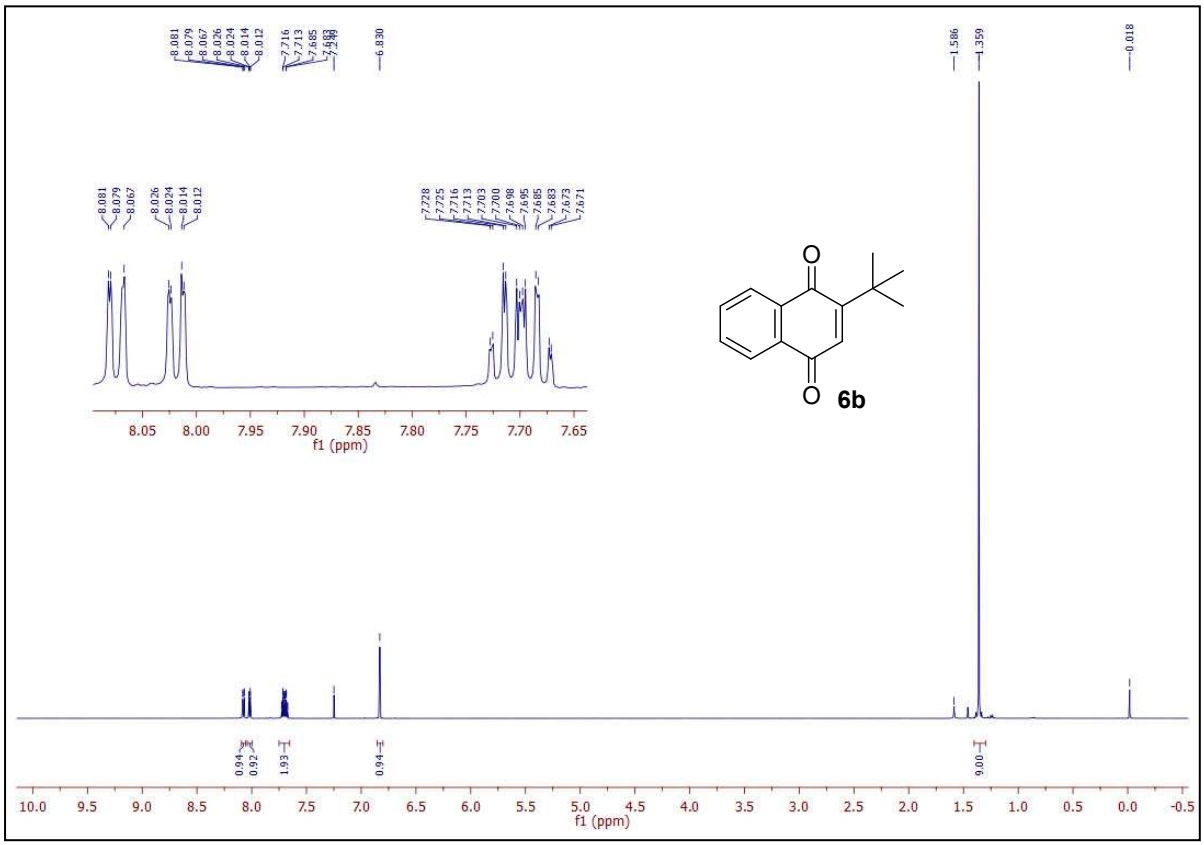


5a


Phenyl-4-OMe_MeOH
IIT(ISM).DHANBAD
Central Research Facility,HRMS
12-Jan-2022
12:09:46
1: TOF MS ES+
3.74e7
Phenyl-4-OMe_MeOH 4 (0.096) Cm (1:5)
391.0930
759.1962
601.1586
369.1109
392.0964
760.1993
602.1617
432.1184
353.2653
%
m/z
O
O
O
O
Ph

5a


7.249
6.665
6.584
1.569
1.271
0.016
O
O
6a
2.00
1.05
9.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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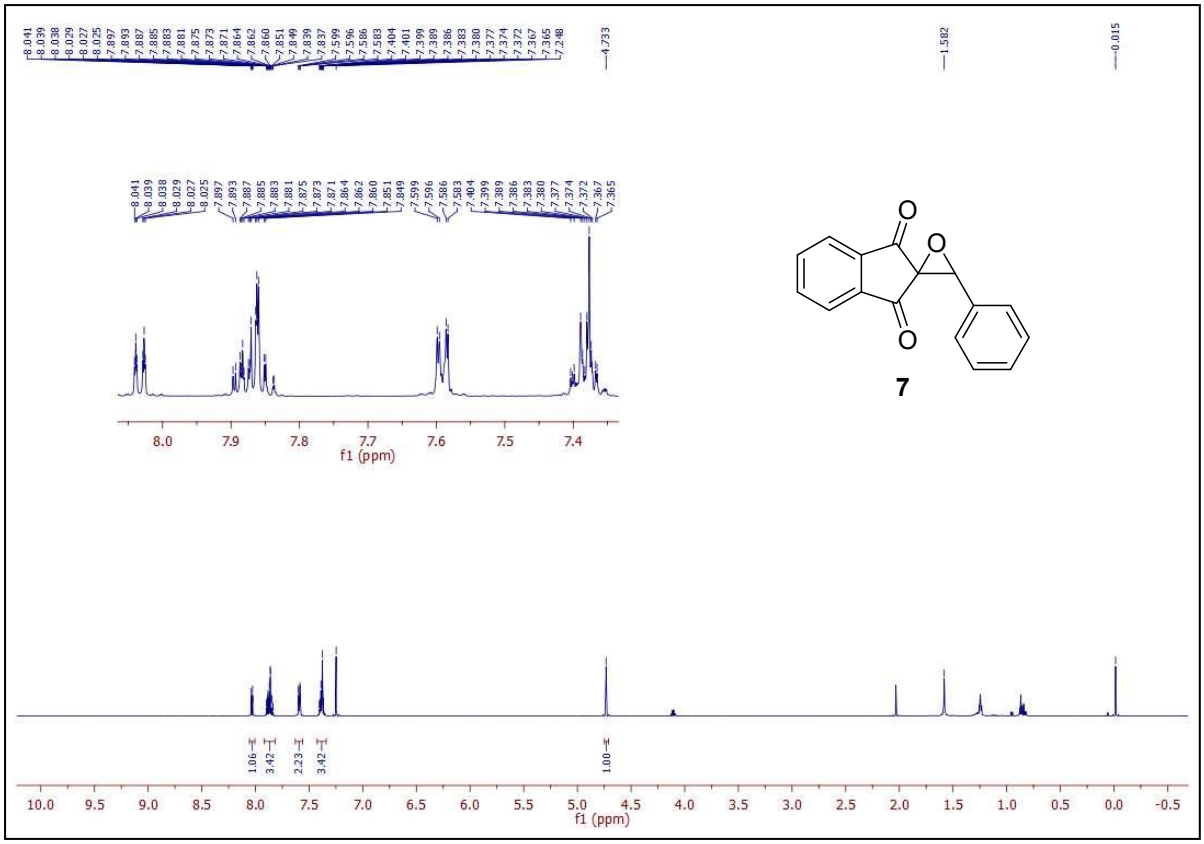
8.079
8.067
8.026
8.024
8.014
8.012
7.716
7.713
7.685
6.830
1.586
1.359
0.018
O
O
6b
8.05 8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65
f1 (ppm)
0.94
0.92
1.93
0.94
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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8.039
8.038
8.029
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7.893
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7.885
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7.881
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7.873
7.871
7.864
7.862
7.860
7.851
7.849
7.839
7.837
7.599
7.596
7.586
7.583
7.404
7.401
7.399
7.389
7.386
7.380
7.377
7.374
7.372
7.367
7.365
7.248
4.733
1.582
0.015
O
O
O
7
8.0
7.9
7.8
7.7
7.6
7.5
7.4
f1 (ppm)
1.06
3.42
2.23
3.42
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

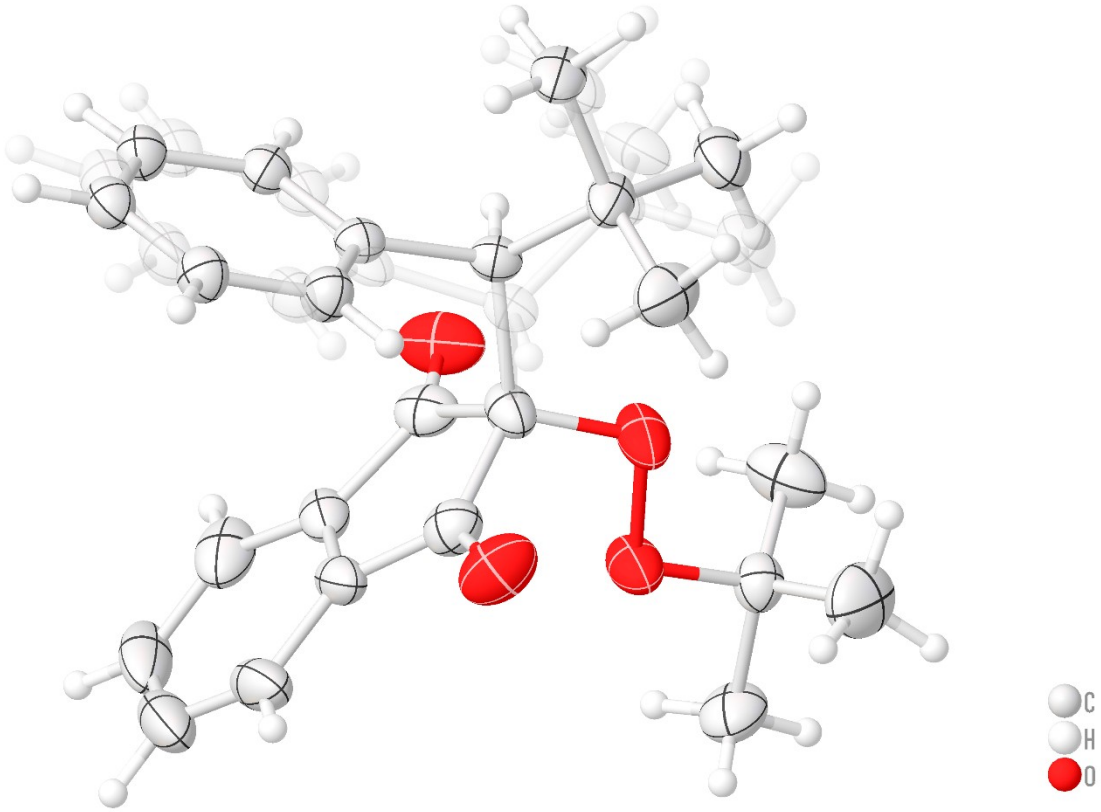
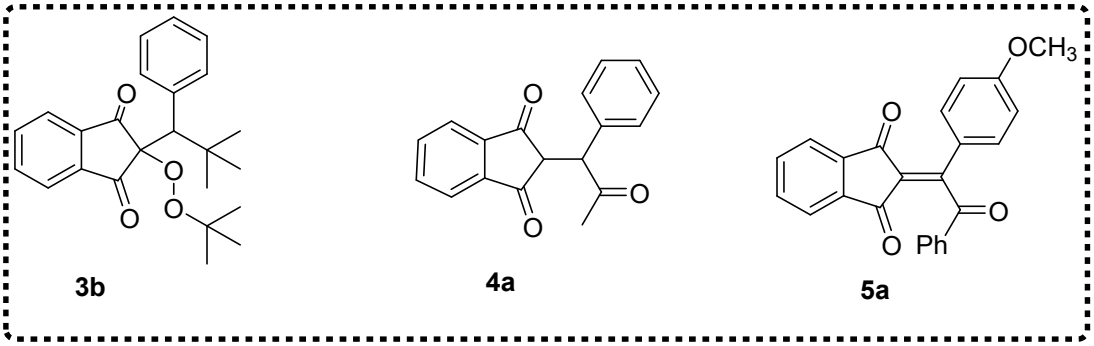


Figure. S1. Disordered structure of **3b** (ORTEP drawn at 25% probability)

In silico studies

The given below molecules were chosen for in silico studies



Prediction of Biological Activity

The bioactivities of the three synthesized compounds were predicted using the PASS (Prediction of Activity Spectra for Substances) online server (way2drug.com/passonloine/predict.php). Currently, this online server predicts more than 4000 kinds of biological activity and provides the probability of being active (Pa) and the probability of being inactive (Pi) for the given molecule. The bioactivity of these compounds with more than 0.8 (Pa) are tabulated.

Table S1: Predicted bioactivity for the synthesized compounds

Pa	Pi	Activity
3b (Peroxygenated derivative)		
0.821	0.015	Antiseborrheic
0.815	0.022	Testosterone17β-dehydrogenase (NADP+) inhibitor
0.820	0.031	CYP2C12 substrate
0.817	0.029	Aspulvinone dimethylallyltransferase inhibitor
4a (Acetylated derivative)		
0.942	0.002	Gluconate 2-dehydrogenase (acceptor) inhibitor
0.920	0.004	Anticoagulant
0.833	0.011	Mucomembranous protector
5a (Benzoylated derivative)		
0.932	0.004	Aspulvinone dimethylallyltransferase inhibitor

0.905	0.011	CYP2C12 substrate
0.894	0.005	Chlordecone reductase inhibitor
0.890	0.004	Feruloyl esterase inhibitor
0.884	0.015	Membrane integrity agonist
0.866	0.006	Gluconate 2-dehydrogenase (acceptor) inhibitor
0.860	0.014	Ubiquinol-cytochrome-c reductase inhibitor
0.833	0.004	3-Hydroxybenzoate 6-monooxygenase inhibitor
0.819	0.016	Antiseborrheic
0.808	0.010	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0.804	0.006	Alkane 1-monooxygenase inhibitor
0.801	0.004	Carminative
0.806	0.009	Aldehyde oxidase inhibitor

Molecular docking

To validate the predicted bioactivity and to see the binding modes of these compounds at the active site of the target proteins, we have performed molecular docking analysis for these compounds with selected protein targets. All the docking calculations were carried out using the Schrodinger software (Schrodinger Release 2021-4 Schrodinger, LLC, New York, 2021) and proteins and ligands were prepared as described in our earlier report.[5] Two target proteins such as Gluconate 2-dehydrogenase from a plant pathogen *Pantoea cypripedii* and cytochrome P450 2C12 (CYP2C12) from *Rattus norvegicus* were selected for molecular docking. The 3D structure of Gluconate 2-dehydrogenase (uniport id: O34213) was retrieved from AlphaFold database[6] and compound **4a** was docked with this protein. Compounds **3b** and **5a** were docked with CYP2C12 protein. The 3D structure of P450 2C12 was built using the structure of CYP2C9 from *Homo sapiens* (PDB ID: 5X23) with SWISS Model server (https://swissmodel.expasy.org). The CYP2C12 and CYP2C9 share 65.81% sequence identity. The active site of Gluconate 2-dehydrogenase was predicted using the sitemap module of the Schrodinger suite, whereas the active site of CYP2C12 was defined based on the losartan drug (used to treat high blood pressure, heart failure and diabetic kidney diseases) complexed with CYP2C9 protein. We noted that losartan drug bound at the three different sites on the CYP2C9 protein. The same sites were used for CYP2C12 protein for docking simulation. For Gluconate 2-dehydrogenase, five active sites were predicted by the sitemap module. The glide XP (extra

precision) module was used for all docking calculations. The glide XP scores for these three compounds at different active sites of Gluconate dehydrogenase and P450 2C12 are summarized in Table S2.

Table S2: Glide XP docking score (in kcal/mol)

Compound	Protein target	Glide XP score
3b	P450 2C12	
	Site 1	-3.767
	Site 2	-2.267
	Site 3	-2.709
4a	Gluconate 2-dehydrogenase	
	Site 1	-7.031
	Site 2	-5.681
	Site 3	-5.796
	Site 4	-5.836
	Site 5	-3.909
5a	P450 2C12	
	Site 1	-4.738
	Site 2	-0.173
	Site 3	-4.533

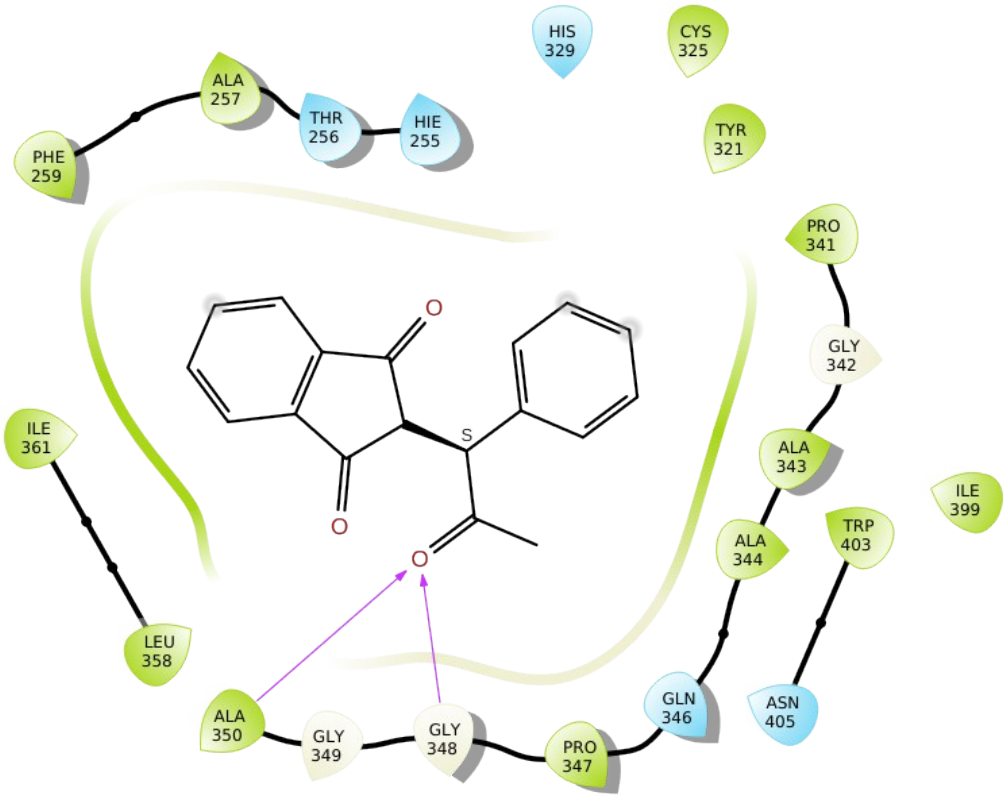


Figure. S2. Binding mode of **4a** at site 1 of Gluconate 2-dehydrogenase.

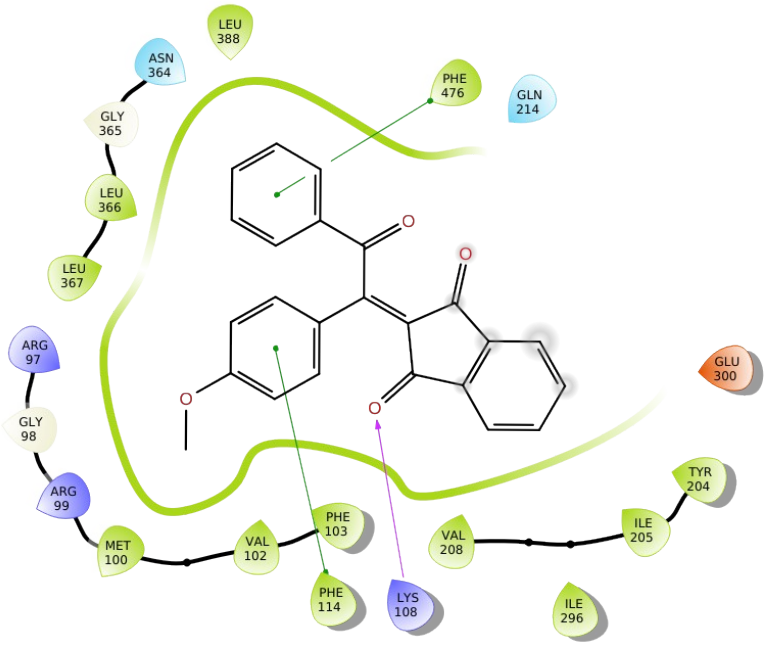


Figure. S3. Binding mode of **5a** at the site 1 of P450 2C12 protein.

References

1 Y. –C. Liou, Y. -A. Lin, K. Wang, J. –C. Yang, Y. –J. Jang, W. Lin and Y. –C. Wu, *Int. J. Mol. Sci.* 2021, **22**, 6251.

2 M. H. Ali, A. Welker, C. A. York, *Synthesis* 2015, **47**, 3207-3211.

3 P. T. Perumal and M. V. Bhatt, *Proc. Indian Acad. Sci. (Chem. Sci).* 1995, **107**, 567-572.

4 A. Russo, A Lattanzi, *Org. Biomol. Chem.*, 2010, **8**, 2633–2638.

5 A. A. Al-Mutairi, K. Alagappan, O. Blacque, M. A. Al-Alshaikh, A. A. El-Emam, M. J. Percino and S. Thamotharan. *ACS Omega,* 2021, **6**, 27026-27037

6 J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, O. Ronneberger, K. Tunyasuvunakool, R. Bates, A. Žídek, A. Potapenko, A. Bridgland, C. Meyer, S. A. A. Kohl, A. J. Ballard, A. Cowie, B. Romera-Paredes, S. Nikolov, R. Jain, J. Adler, T. Back, S. Petersen, D. Reiman, E. Clancy, M. Zielinski, M. Steinegger, M. Pacholska, T. Berghammer, S. Bodenstein, D. Silver, O. Vinyals, A. W. Senior, K. Kavukcuoglu, P. Kohli and D. Hassabis. *Nature*, 2021, **596**, 583-589.