

Bronsted acid-type biosurfactant for heterocyclization: a green protocol for benzopyran synthesis

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Supporting Information

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-S1-

General: All chemicals were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined on DBK programmable melting point apparatus and are uncorrected. Infrared spectra were measured with a Bruker FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC (300 MHz for ¹H NMR and 300 MHz for ¹³C NMR) spectrometer using CDCl₃ as solvent. Chemical shifts are expressed in δ parts per million (ppm) values with tetramethylsilane (TMS) as the internal reference and coupling constants are expressed in Hertz (Hz). Mass spectra were recorded on Shimadzu (QP 2010 GCMS). Equiptronics (Model EQ-664A) digital auto ranging conductivity meter was used for the measurement of critical micellar concentration. Optical micrograph was taken using ordinary light microscope (Leica DM 2000) under 100x magnifications.

Typical procedure for synthesis of 9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydroxanthren-1-one:

In a 25 mL round bottom flask, salicylaldehyde (1.1 mmol), 5,5-dimethyl 1,3-cyclohexanedione (2.2 mmol) were placed in lemon extract:water (6 mL, 1:1, v/v) and reaction mixture was stirred at 80°C temperature in preheated oil-bath till the completion of reaction as indicated by TLC (ethylacetate:hexane 4:6). The solid products was separated by simple filtration through a Buckner funnel, washed with cold water, and recrystalyzed from 96% ethanol (5 mL). The identity of the compound was ascertained on the basis of ¹H NMR, ¹³C NMR, and FT-IR spectroscopy.

-S2-

9-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-Dimethyl-2,3,4,9-tetrahydroxanthen-1-one (Table 3,Entry 1)

Yield: 85 %; mp 215–218 °C; ¹H NMR (300 MHz, CDCl₃): d 10.50(s, 1H, -OH), 7.08–7.16 (m, 1H, Ar-H), 6.93–7.01 (m, 3H, Ar-H), 4.65 (s, 1H, -CH), 2.54 (q, J=17.7, 20.0 Hz, 2H, -CH₂), 2.35 (s, 2H, -CH₂), 2.30(s, 2H, -CH₂), 1.93 (q, J=6.0, 16.4 Hz, 2H, -CH₂), 1.14 (s, 3H, -CH₃), 1.03 (s, 3H, -CH₃), 1.00 (s, 6H, 2-CH₃); ¹³C NMR (300 MHz, CDCl₃): d 200.40, 196.13, 170.53, 168.78, 151.04, 127.98, 127.52, 124.53, 118.31, 115.78, 111.07, 96.20, 50.58, 49.93, 43.24, 41.60, 32.33, 31.02, 29.85, 29.43, 27.79, 27.21,26.42; IR (cm⁻¹): 3153, 2958, 1622, 1488, 1376, 1312, 1233, 1185, 1151, 1077, 1019, 762, 655, 582, 475; MS : 367 (M + 1), 389 (M + Na). Anal. calcd. for C₂₃H₂₆O₄: C, 75.38; H, 7.15; O, 17.46. Found: C, 75.33; H, 7.15; HRMS m/z calcd. for C₂₃H₂₆O₄: 366.0000, found 367.1918(M+H), 389.1737 (M+Na).

-S3-

3-methoxy-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (Table 3,Entry 2)

Yield: 80 %; mp 224-227 °C; ¹H NMR (300 MHz, CDCl₃): d 10.50 (s, 1H, -OH), 7.08–7.21 (m, 1H, Ar-H), 6.93–7.01 (m, 3H, Ar-H), 4.63 (s, 1H, -CH), 2.54 (q, J=17.7, 20.0 Hz, 2H, -CH₂), 2.35 (s, 2H, -CH₂), 2.30 (s, 2H, -CH₂), 1.93 (q, J=6.0, 16.4 Hz, 2H, -CH₂), 3.88 (s, 1H, -OCH₃) , 1.14(s, 3H, -CH₃), 0.93 (s, 9H, 3CH₃); ¹³C NMR (300 MHz, CDCl₃): 200.40, 196.521, 170.554, 168.800, 147.081, 140.658, 125.203, 124.203, 119.760, 118.149, 110.887, 110.370, 56.058, 50.623, 49.930, 43.167, 41.533, 32.288, 30.887, 29.852, 29.051, 27.755 , 27.162, 26.421.

-S3-

-S4-

7-Bromo-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (Table 3,Entry 3)

Yield: 92 %; mp 248-251°C; ¹H NMR (300 MHz, CDCl₃): d 10.15 (s, 1H, -OH), 7.21–7.24 (dd, J=1.9, 6.8 Hz, 1H, Ar-H), 7.08 (s, 1H, Ar-H), 6.87 (d, J=8.7 Hz, 1H, Ar-H), 5.02 (s, 1H, -CH-), 2.28–2.59 (m, 6H, 3-CH₂), 1.95 (s, 2H, -CH₂), 1.33 (s, 3H, -CH₃), 0.99–1.05 (m, 9H, 3-CH₃); ¹³C NMR (300 MHz, CDCl₃ + DMSO): d 195.65, 164.328, 148.794, 130.563, 129.103, 127.741, 116.932, 115.413, 110.34, 50.27, 40.65, 40.33, 40.05, 39.78, 39.22, 38.94, 38.66, 31.35, 31.27, 28.93, 27.56, 26.30; IR (cm⁻¹): 3103, 2963, 1618, 1475, 1374, 1302, 1231, 1178, 1075, 1037, 884, 817, 657, 590, 478; MS : 445 (M⁺), 447 (M+2). Anal. calcd. for C₂₃H₂₅BrO₄: C, 62.03; H, 5.66; Br, 17.94; O, 14.37. Found: C, 62.03; H, 5.65. HRMS m/z calcd for: C₂₃H₂₅BrO₄: 445.0000, found 445.1003 (M)⁺.

-S5-

7-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (Table 3,Entry 5)

Yield: 91 %; mp 232–234 °C; ¹H NMR (300 MHz, CDCl₃): d 10.50 (s, 1H, -OH), 7.09 (dd, J=2.2, 2.6 Hz, 1H, Ar-H), 6.91–6.97 (m, 2H, Ar-H), 4.61 (s, 1H, -CH), 2.52 (q, J= 17.3, 18.5 Hz, 2H, -CH₂), 2.37 (d, J=4.9 Hz, 2H, -CH₂), 2.30 (s, 2H, -CH₂), 1.96 (s, 2H, -CH₂), 1.14 (s, 3H, -CH₃), 1.00–1.05 (m, 9H, 3-CH₃); IR (cm⁻¹): 3102, 2965, 2710, 1624, 1571, 1476, 1374, 1301, 1233, 1179, 1077, 1038, 1015, 879, 819, 657, 618, 591, 549, 469; MS : 401 (M⁺), 403 (M+2). Anal. calcd. for C₂₃H₂₅ClO₄: C, 68.91; H, 6.29; Cl, 8.84; O, 15.96. Found: C, 68.89; H, 6.24. HRMS m/z calcd. for C₂₃H₂₅ClO₄: 400.0000, found 401.1529 (M + H), 423.1328 (M + Na).

-S6-

5-Bromo-7-chloro-9-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-xanthen-1-one (Table 3,Entry 6)

Yield: 90 %; mp 241-243 °C; ¹H NMR (300 MHz, CDCl₃): d 10.34 (s, 1H, -OH), 7.36 (d, J=2.2 Hz, 1H, Ar-H), 6.90 (d, J=2.0 Hz, 1H, Ar-H), 4.60 (s, 1H, -CH), 2.62 (q, J=17.7, 18.5 Hz, 2H, -CH₂), 2.38 (d, J=4.5 Hz, 2H, -CH₂), 2.31 (s, 2H, -CH₂), 1.97 (s, 2H, -CH₂), 1.16 (s, 3H, -CH₃), 1.00–1.05 (m, 9H, 3-CH₃); ¹³C NMR (300 MHz, CDCl₃): d 196.47, 195.10, 163.43, 144.77, 128.68, 127.79, 127.41,

126.35, 112.78, 109.93, 108.78, 94.79, 49.58, 49.03, 39.81, 30.77, 28.24, 26.92, 26.03, 25.64, 25.17; IR (cm⁻¹): 3184, 2940, 1647, 1599, 1452, 1375, 1313, 1257, 1207, 1183, 1150, 1017, 887, 855, 803, 722, 662, 587, 475; MS: 479 (M⁺), 481 (M+2). Anal. calcd. for C₂₃H₂₄BrClO₄: C, 57.58; H, 5.04; Br, 16.65; Cl, 7.39; O, 13.34. Found: C, 57.57; H, 5.04; HRMS m/z calcd. for C₂₃H₂₃ClBrO₄: 478.0000, found 479.0618 (M + H), 481.0602 (M + 2), 501.0421 (M + Na), 503.0415 (M + Na + 2)

-S7-

9-(2-Hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 7)

Yield: 87 %; mp 240-243 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.00 (s, 1H, -OH), 6.80–7.14 (m, 4H, Ar-H), 4.84 (s, 1H, -CH), 1.60–2.40 (m, 12H, 6-CH₂); IR (cm⁻¹): 2951, 2538, 1830, 1641, 1553, 1485, 1421, 1372, 1294, 1235, 1192, 1142, 1071, 993, 924, 850, 773, 564, 493 MS : 311 (M+1). Anal. calcd. for C₁₉H₁₈O₄: C, 73.53; H, 5.85; O, 20.62. Found: C, 73.52; H, 5.84; HRMS m/z calcd. for C₁₉H₁₈O₄: 310.0000, found 311.1295 (M + H), 333.1081 (M + Na).

-S8-

7-Bromo-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 9)

Yield: 88 %; mp 238-240 °C; ¹H NMR (300 MHz): δ 10.75 (s, 1H, -OH), 7.25 (d, J=3.0 Hz, 1H, Ar-H), 7.09 (d, J=2.2 Hz, 1H, Ar-H), 6.89 (dd, J=5.2, 6.0 Hz, 1H, Ar-H), 4.57 (s, 1H, -CH), 1.76–2.85 (m, 12H, 6-CH₂); ¹³C NMR (300 MHz, CDCl₃) : 202.18, 193.99, 167.43, 166.15, 148.45, 129.74, 129.28, 128.61, 126.86, 116.51, 116.10, 115.09, 47.57, 35.57, 35.02, 33.26, 26.02, 22.80, 18.95; IR (cm⁻¹): 3105, 2955, 1640, 1596, 1477, 1374, 1279, 1233, 1186, 1144, 1070, 981, 819, 763, 620, 530, 470; MS : 389 (M⁺) 391 (M + 2); Anal. calcd. For C₁₉H₁₇BrO₄: C, 58.63; H, 4.40; Br, 20.53; O, 16.44, found: C, 58.63; H, 4.39; HRMS m/z calcd. for C₁₉H₁₇BrO₄: 389.0000, found 391.0551 (M + 2).

-S9-

7-Chloro-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 11)

Yield: 94 %; mp 242-244 °C; ¹H NMR (500 MHz, CDCl₃): δ 10.76 (s, 1H, -OH), 7.09 (d, J=6.3 Hz, 1H, Ar-H), 6.91–6.96 (m, 2H, Ar-H), 4.57 (s, 1H, -CH), 1.77–2.81 (m, 12H, 6-CH₂); ¹³C NMR (300 MHz, CDCl₃+DMSO-d₆): 201.86, 193.94, 167.23, 165.96, 147.56, 127.13, 126.76, 125.61, 124.53,

115.52, 110.65, 99.74, 47.08, 35.47, 34.82, 33.05, 26.35, 22.69, 19.03; IR (cm⁻¹): 3110, 2954, 1645, 1596, 1477, 1416, 1375, 1280, 1239, 1188, 1141, 1068, 984, 917, 824, 576, 460; MS : 345 (M⁺), 347 (M + 2). Anal. calcd. for C₁₉H₁₇ClO₄: C, 66.19; H, 4.97; Cl, 10.28; O, 18.56, found: C, 66.18; H, 4.97.

-S10-

5-Bromo-7-chloro-9-(2-hydroxy-6-oxo-cyclohex-1-enyl)-2,3,4,9-tetrahydro-xanthen-1-one (Table 3, Entry 12)

Yield: 91 %; mp 238–240 °C; ¹H NMR (300MHz, CDCl₃): d 10.44 (s, 1H, -OH), 7.30 (d, J=2.6 Hz, 1H, Ar-H), 6.95 (d, J=1.7 Hz, 1H, Ar-H), 5.04 (s, 1H, -CH), 1.93–2.12 (m, 4H, 2-CH₂), 2.25–2.51 (m, 8H, 4CH₂); ¹³CNMR (300MHz, CDCl₃): 195.44, 163.90, 145.45, 129.31, 128.72, 127.93, 110.62, 109.50, 50.29, 40.33, 40.05, 39.77, 39.50, 39.2, 38.94, 38.76, 31.45, 31.3, 28.97, 27.56, 26.69, 26.20, 25.75 29; IR (cm⁻¹): 49, 2887, 2526, 1651, 1560, 1452, 1363, 1279, 1245, 1185, 1133, 1063, 1007, 857, 765, 707, 538, 500, 438; MS: 423 (M⁺), 425 (M+2) Anal. calcd. for C₁₉H₁₆BrClO₄: C, 53.86; H, 3.81; Br, 18.86; Cl, 8.37; O, 15.11, found: C, 53.85; H, 3.81.

-S11-

5-methoxy-2,3-Dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)-cyclopenta[*b*]chromen-1(9H)-one (Table 3, Entry 14)

Yield: 84 %; mp 257-260 °C; ¹H NMR (300 MHz DMSO): 2.29~2.36 (m, 6H, 3CH₂), 2.72~2.74 (m, 2H, CH₂), 3.82 (s, 3H, CH₃O), 4.58 (s, 1H, CH), 6.58~6.60 (m, 1H, ArH), 6.92 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, ArH), 6.99~7.03 (m, 1H, ArH), 11.80 (b, 1H, OH); IR (cm⁻¹): 3438, 3024, 2971, 2939, 1682, 1637, 1579, 1480, 1445, 1380, 1322, 1273, 1255, 1237, 1170, 1125, 1076, 825, 788, 739, 716.

-S12-

7-Bromo-2,3-dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[*b*]chromen-1(9H)-one (Table 3, Entry 15)

Yield: 86 %; mp 280-282°C; ¹H NMR (300 MHz DMSO): 2.26~2.43 (m, 6H, 3CH₂), 2.56~3.34 (m, 2H, CH₂), 5.01 (s, 1H, CH), 7.01~7.24 (m, 2H, ArH), 7.27 (d, J = 8.4 Hz, 1H, ArH), 10.60 (b, 1H, OH); IR (cm⁻¹): 3505, 2932, 2910, 1699, 1653, 1585, 1474, 1383, 1276, 1259, 1240, 1198, 1160, 1126, 1071, 1018, 818, 707, 659.

-S13-

7-nitro-2,3-Dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[*b*]chromen-1(9*H*)-one

(Table 3, Entry 16)

Yield: 89 %; mp 265-268 °C; ¹H NMR (300 MHz DMSO): 2.34~2.41 (m, 6H, 3CH₂), 2.74~2.76 (m, 2H, CH₂), 4.72(s, 1H, CH), 7.41 (d, *J* = 8.8 Hz, 1H, ArH), 7.87 (d, *J* = 2.4 Hz, 1H, ArH), 8.11 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H, ArH), 12.06 (b, 1H, OH). IR (cm⁻¹): 3512, 2943, 2926, 1698, 1656, 1581, 1528, 1481, 1458, 1379, 1277, 1253, 1168, 1134, 1020, 929, 912, 840, 805, 748, 666.

-S14-

7-Chloro-2,3-dihydro-9-(2-hydroxy-5-oxocyclopent-1-enyl)cyclopenta[*b*]chromen-1(9*H*)-one

(Table 3, Entry 17)

Yield: 90 %; mp 271-273 °C; ¹H NMR (300 MHz DMSO): 2.33~2.38 (m, 6H, 3CH₂), 2.71~2.73 (m, 2H, CH₂), 4.60(s, 1H, CH), 7.01 (dd, *J* = 2.4 Hz, *J* = 1.2 Hz, 1H, ArH), 7.18 (d, *J* = 8.8 Hz, 1H, ArH), 7.27~7.30 (m, 1H, ArH), 12.00 (b, 1H, OH); IR (cm⁻¹): 3508, 2935, 2914, 1699, 1654, 1583, 1477, 1409, 1384, 1277, 1259, 1240, 1162, 1126, 1018, 819, 677.

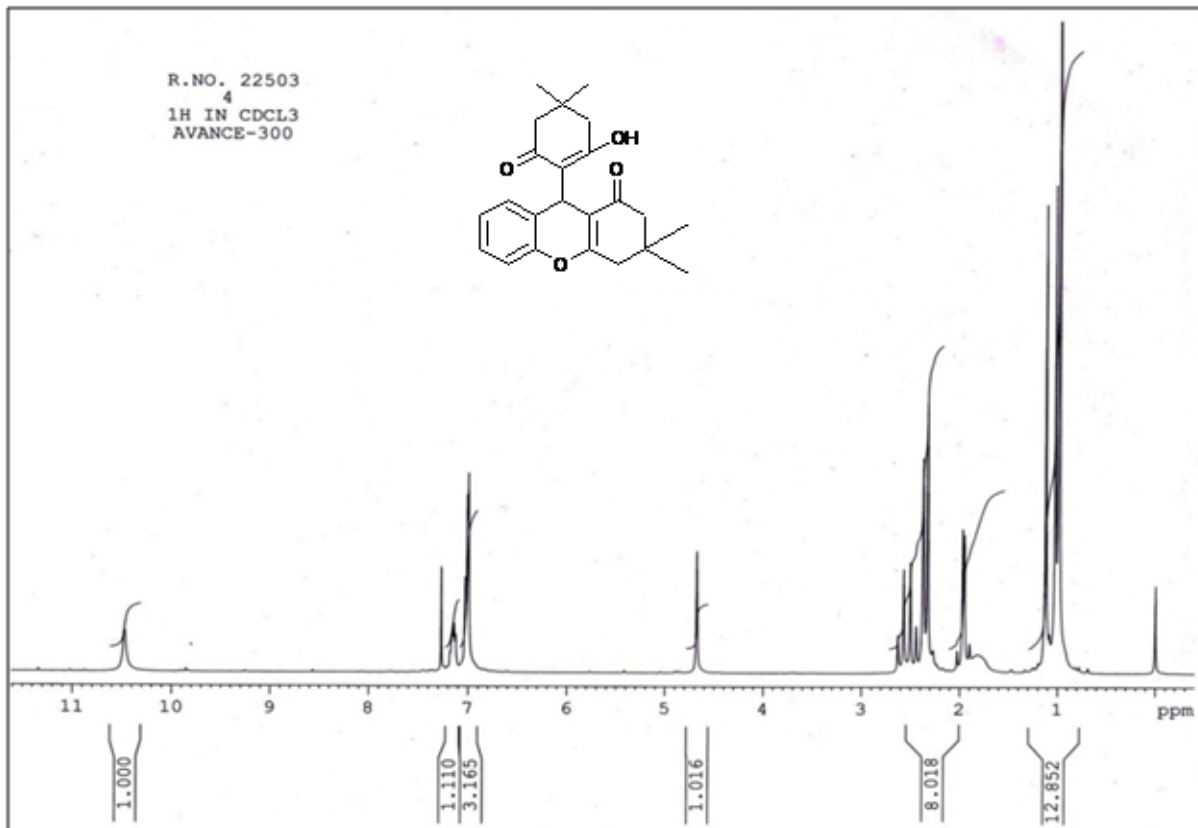
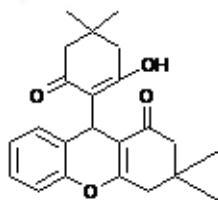
-S15-

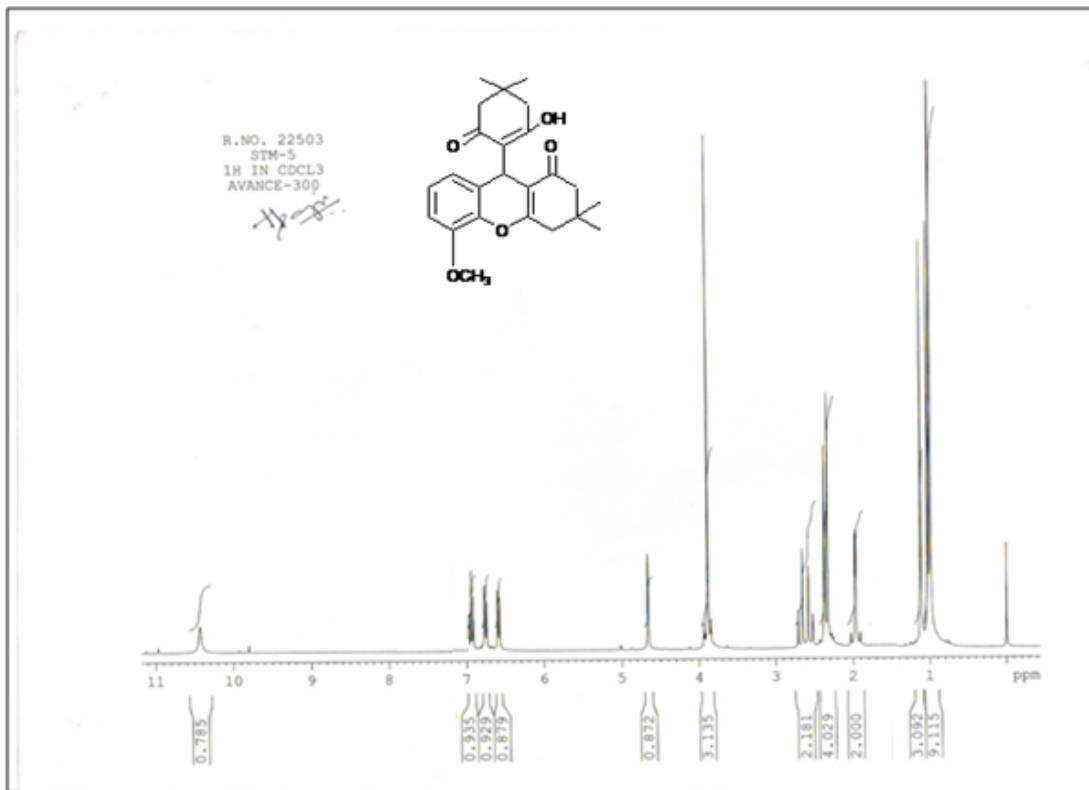
7,8-h-ph-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (3h) (Table 4, Entry 1)

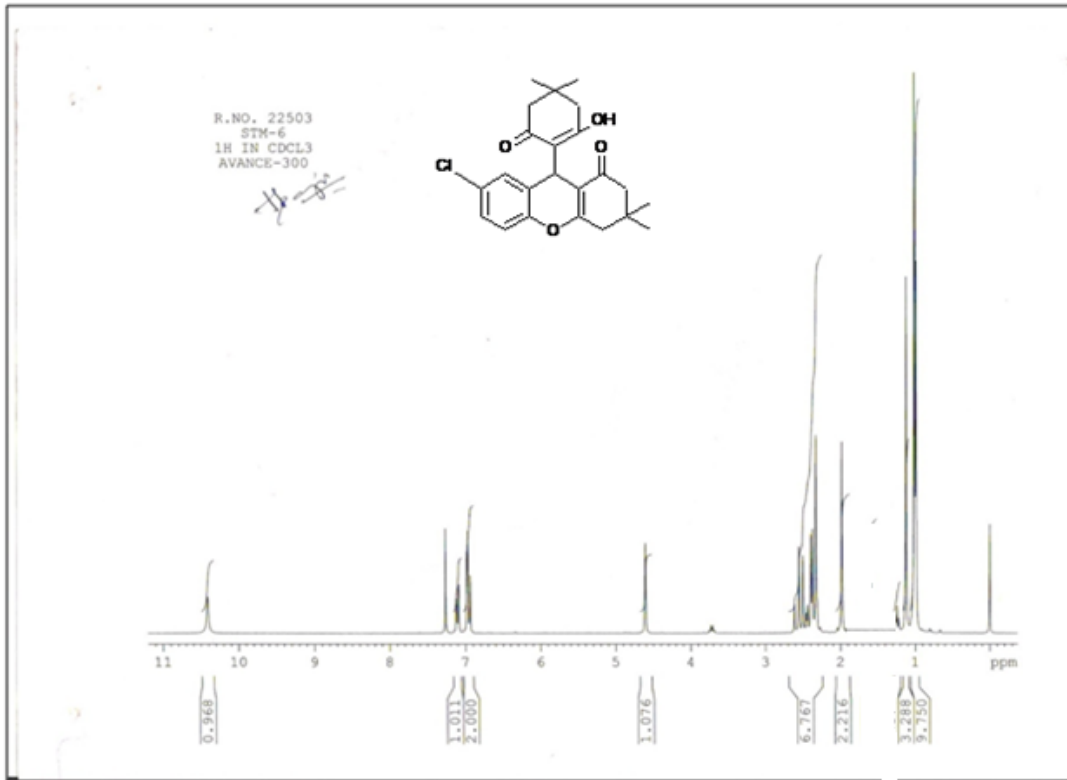
Yield: 95 % mp 235-237 °C. ¹H NMR (300 MHz, CDCl₃) δ = 10.70 (s, 1H, OH), 7.78 (d, 1H, ArH), 7.73 (d, 2H, ArH), 7.48 (t, 1H, ArH), 7.39 (t, 1H, ArH), 7.27 (d, 1H, ArH), 5.27 (s, 1H, CH), 2.68 (AB_q, *J* = 17.6 Hz, 1H, CH₂), 2.57 (AB_q, *J* = 17.6 Hz, 1H, CH₂), 1.96 (AB_q, *J* = 16.4 Hz, 1H, CH₂), 1.83 (AB_q, *J* = 16.4 Hz, 1H, CH₂), 2.36-2.41 (m, 4H, 4CH₂), 1.17 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 0.72 (s, 3H, CH₃) ppm; ¹³C NMR (300 MHz, CDCl₃) δ = 201.11, 196.85, 170.22, 169.09, 148.89, 131.26, 130.96, 158.54, 128.50, 126.71, 124.64, 122.87, 117.68, 116.59, 116.14, 111.08, 50.71, 49.98, 43.18, 41.37, 32.42, 30.62, 29.92, 29.33, 27.10, 26.37, 25.38 ppm; IR (KBr): 3182, 2941, 2862, 1643, 1593, 1464, 1373, 1315, 1261, 1235, 1061, 1026, 888, 813 cm⁻¹.

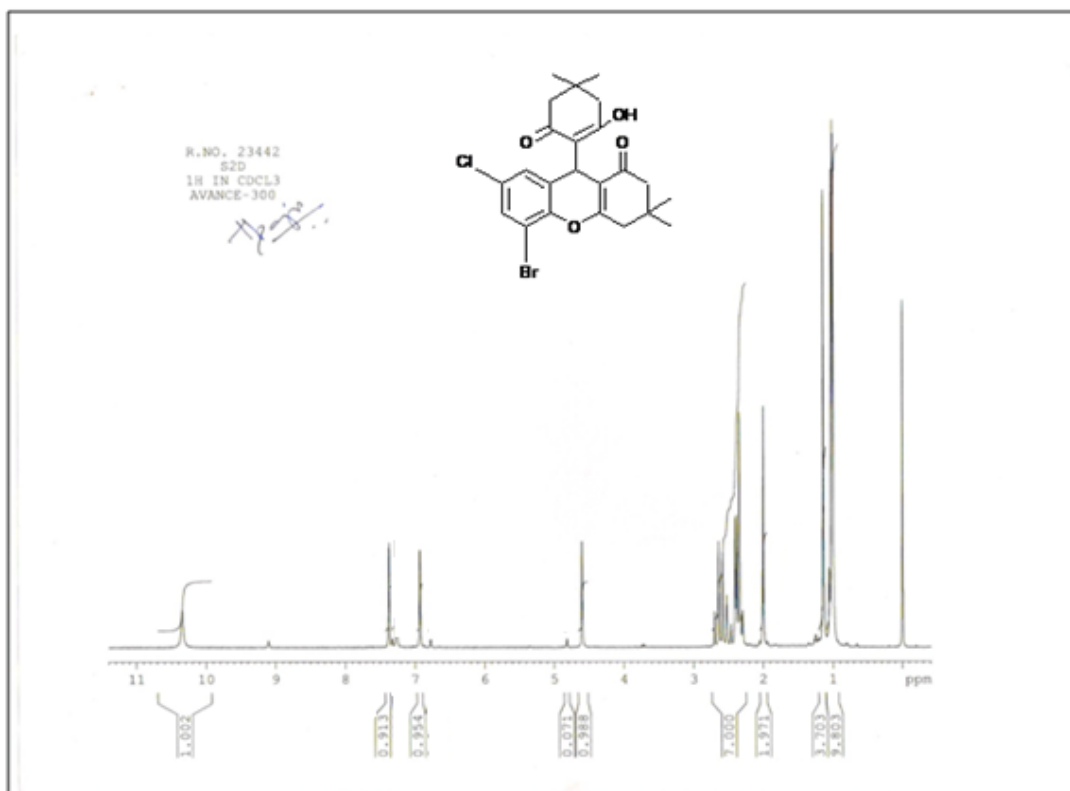
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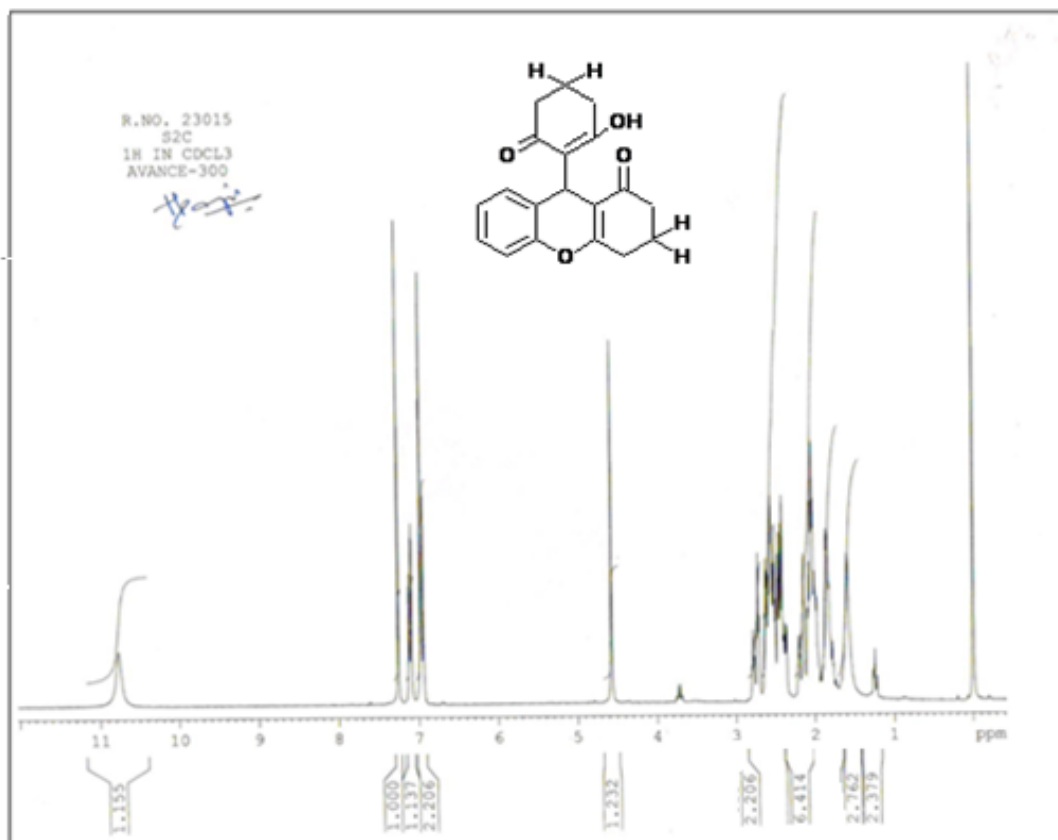
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1H IN CDCL3
AVANCE-300

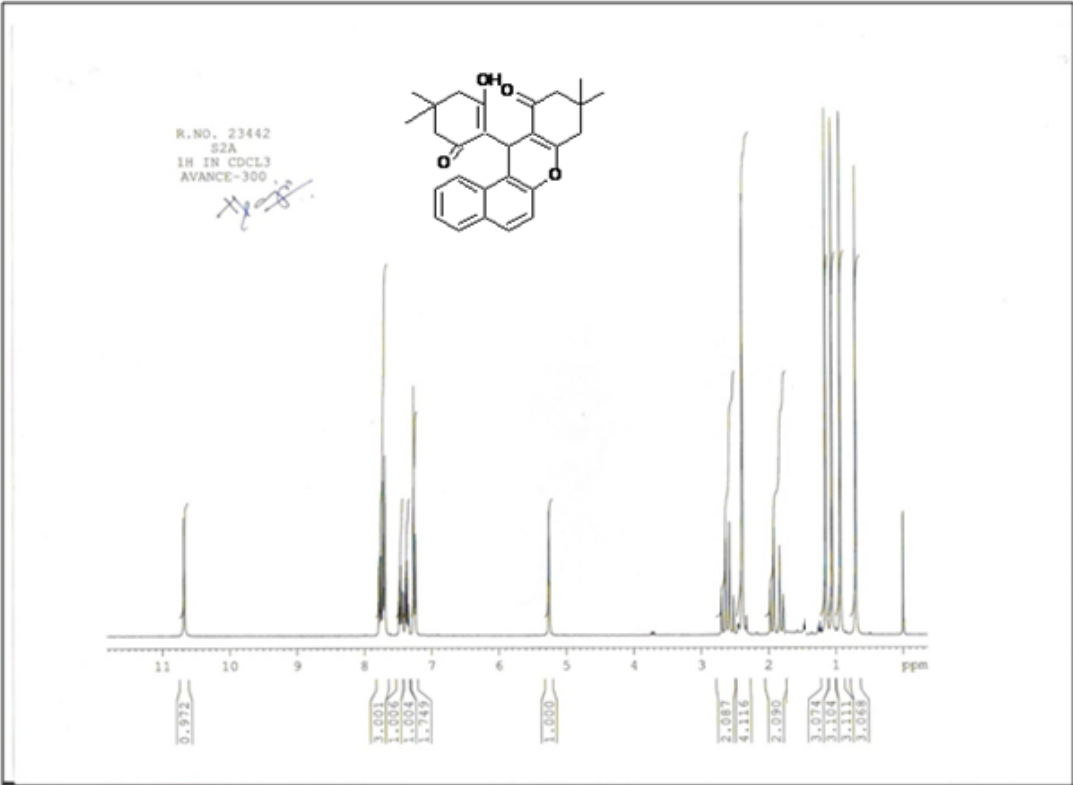


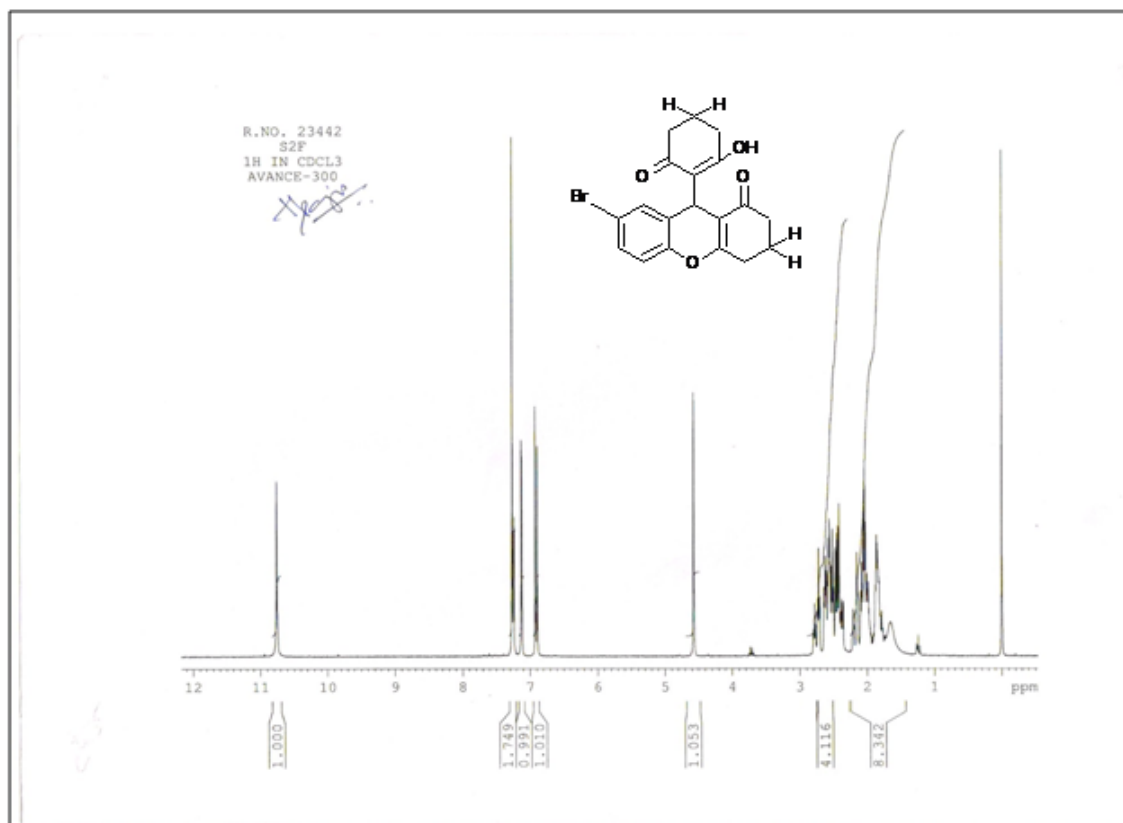


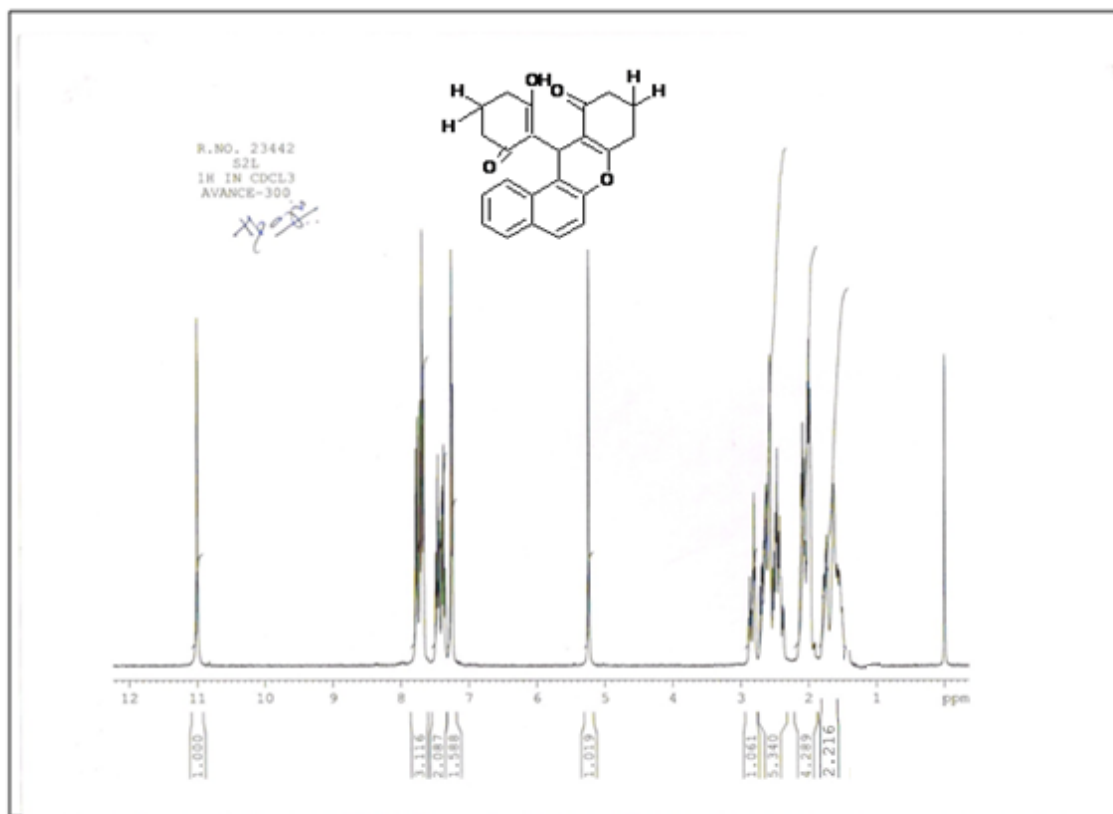


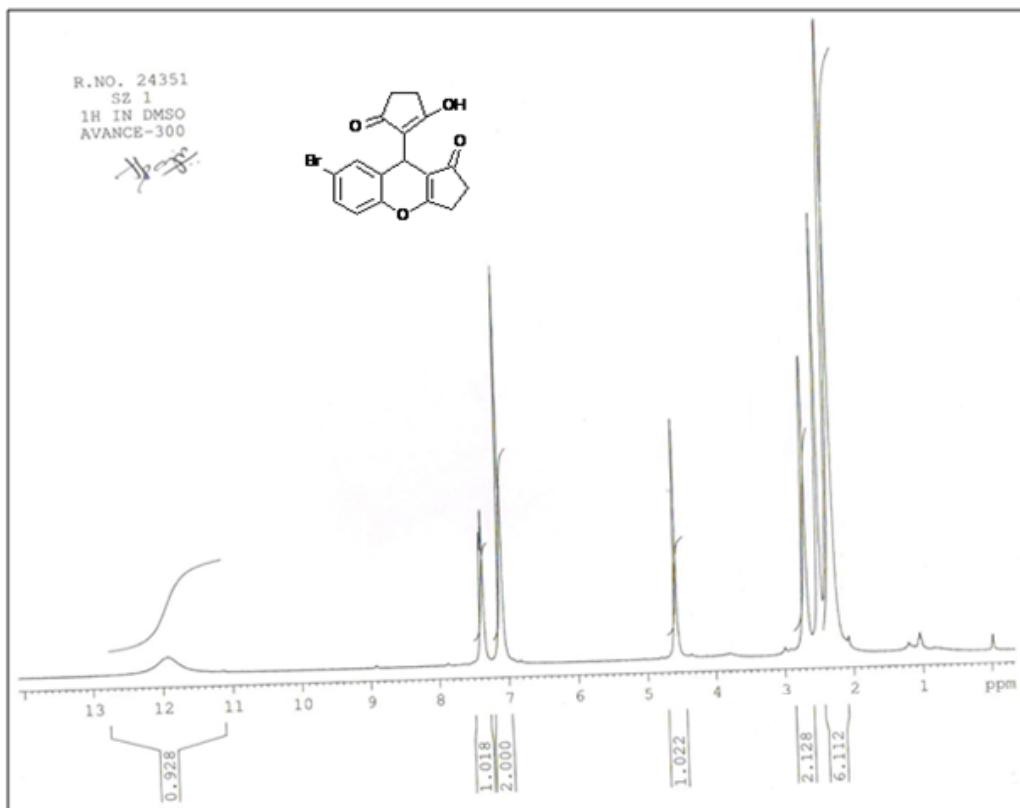








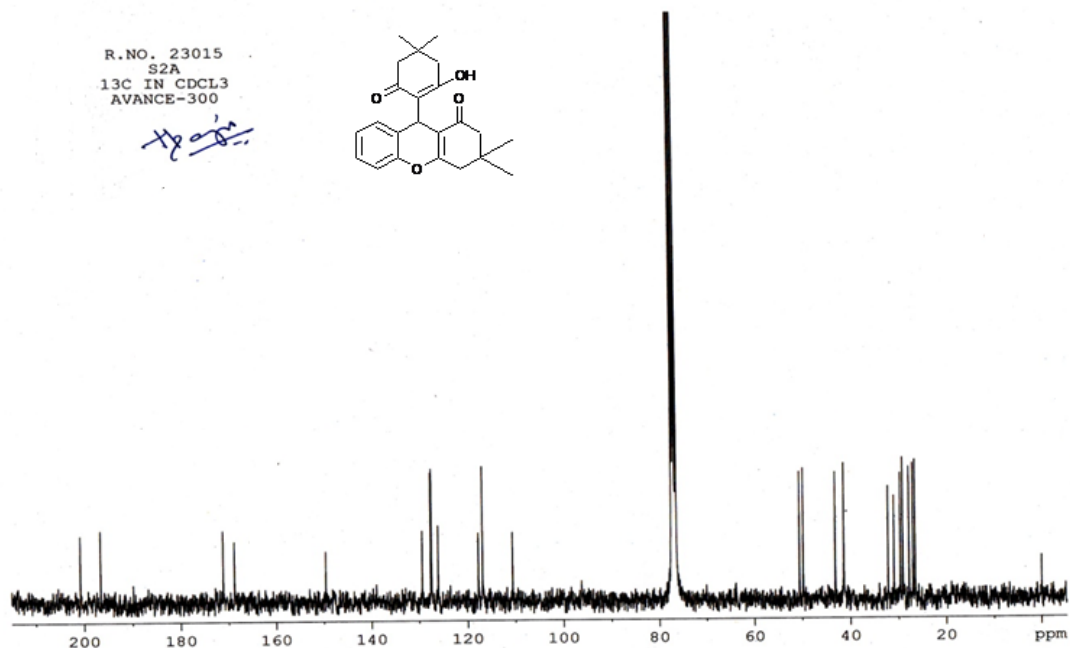
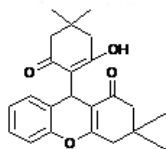


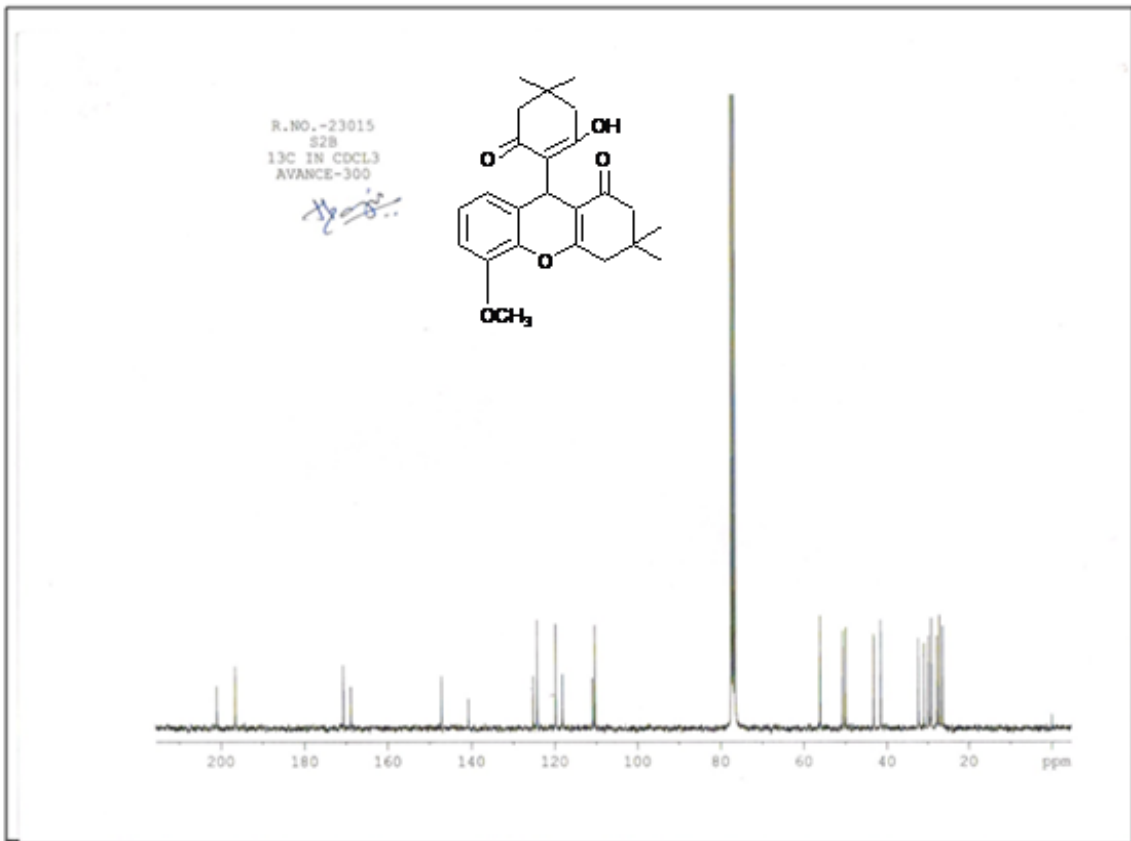


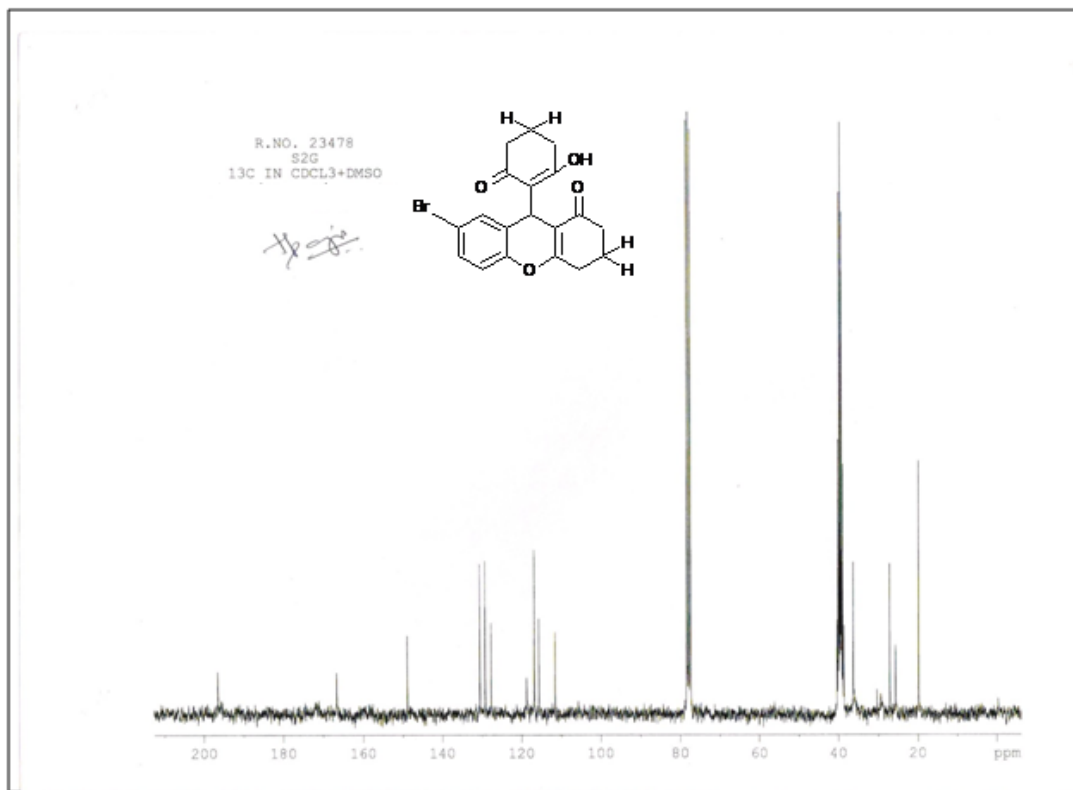
S24-

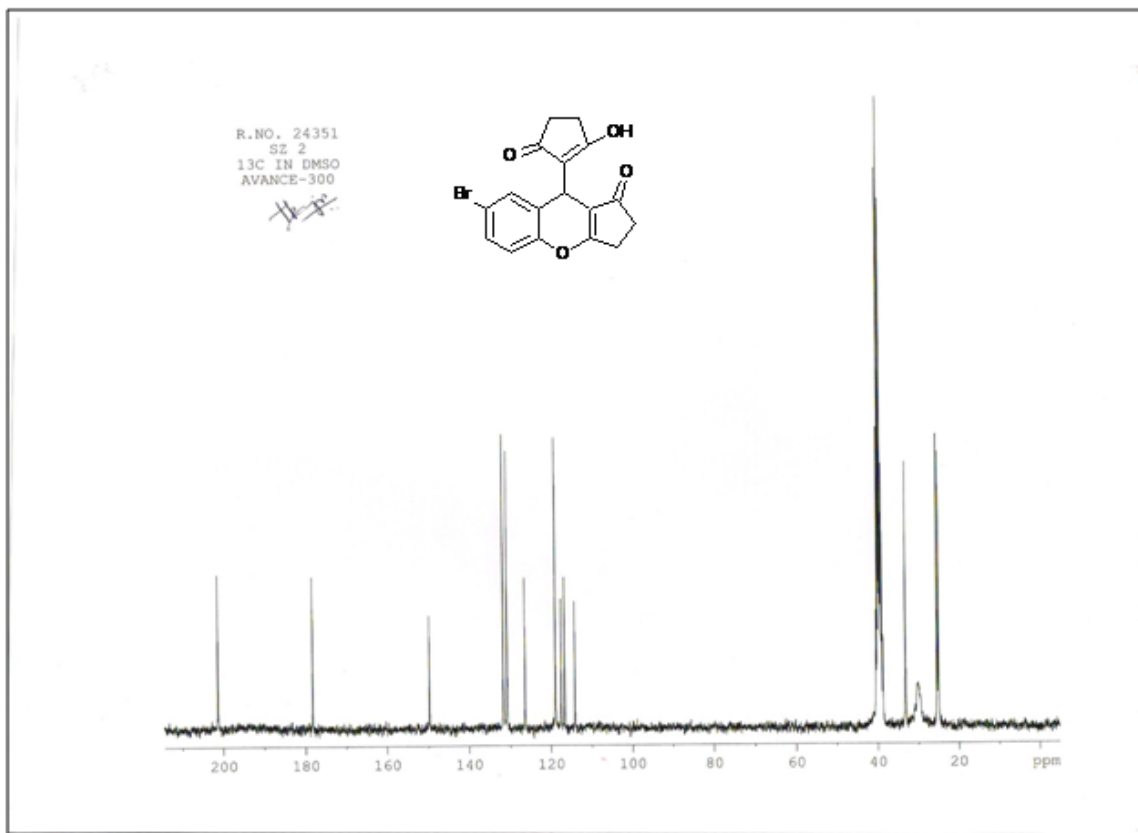
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S2A
13C IN CDCL3
AVANCE-300

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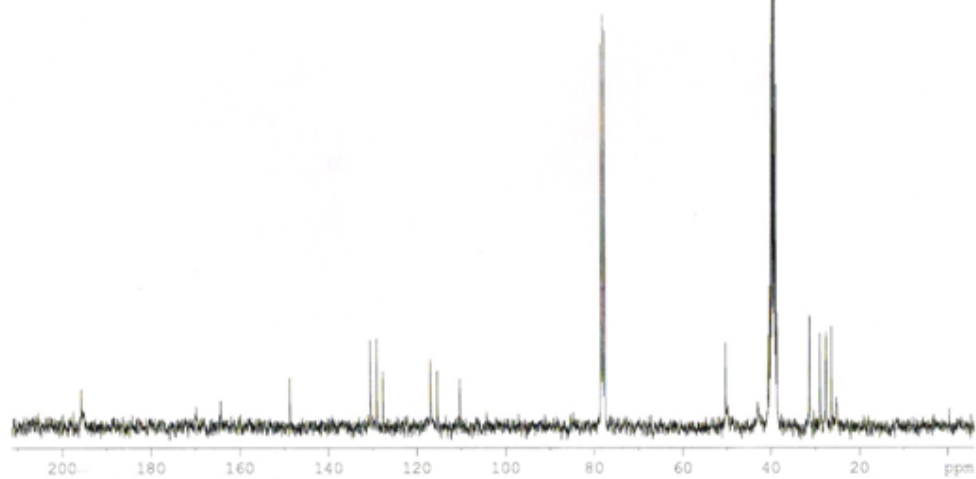
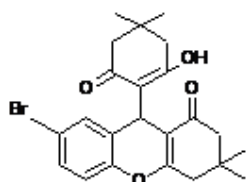






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S21
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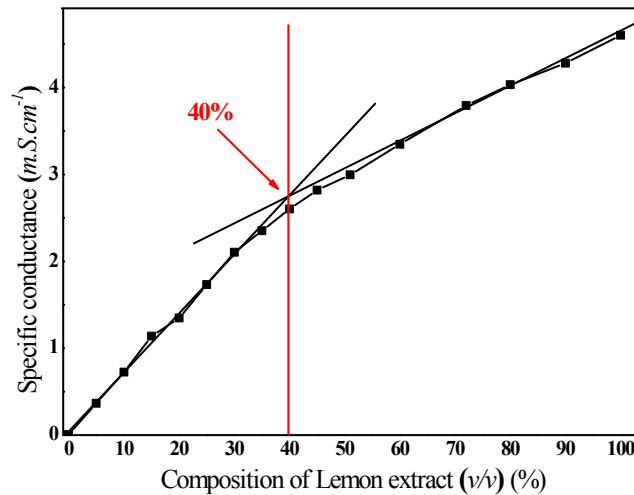
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Determination of Critical micellar concentration (CMC) of lemon extract by conductivity method

-S30-

To maintain better lemon extract:water composition i.e above CMC for this protocol, we employed electrical conductivity method to determine the critical micelle concentration (CMC) of reaction medium. The conductivity experiments were carried using Equiptronics (Model EQ-664 A) digital auto ranging conductivity meter. Different composition of solutions of Lemon extract was prepared in deionized water having specific conductance $7.0 \mu\text{S cm}^{-1}$. A step-by step dilution method was adopted for the measurements of specific conductance of the various compositions to avoid dilution error. The conductance was plotted as a function of percentage composition of lemon extract:water (v/v) and the inflection point gives the value (40 %) of CMC which is indicated in the figure.



-S31-