Chapter 5

Synthesis of chromen-4-one and bis-chromen-4-one derivatives and its applications

5.1 Introduction

Flavonoids are a group of naturally occurring compounds. They are widely distributed as secondary metabolites and found in fruits, vegetables and certain beverages. Flavonoids family members include flavones, flavanes, flavonols, anthocyanidines and catechins. Chromen-4-one commonly known as flavones has a wide spectrum of biological activities. Chromen-4-ones (flavones) have been found to possess antioxidant, anticancer and anti-inflammatory properties [1-3]. The design of liquid crystals including heterocyclic rings has allowed the preparation of a great variety of mesogenic compounds with interesting properties. Efforts have been made in modifying naturally occurring flavonoid products for some viable social relevant properties [4].

Chromen-4-one derivatives have got fluorescence properties which can detect cysteine intracellular which indicated the potential utility in liquid-crystalline-based sensors [5-7]. It is found that simple heterocyclic core, routine terminal alkyl chains and a variety of connecting moieties are not sufficient to introduce liquid crystalline (LC) properties. There are very rare reports in literature on chromen-4-one derivatives with mesogenic properties. Hirose et al. for the first time in 1989 synthesized 6-(4-n-alkoxybenzoyloxy)-flavone compound **1** (**Fig-5.1**) exhibiting nematic phase [8].

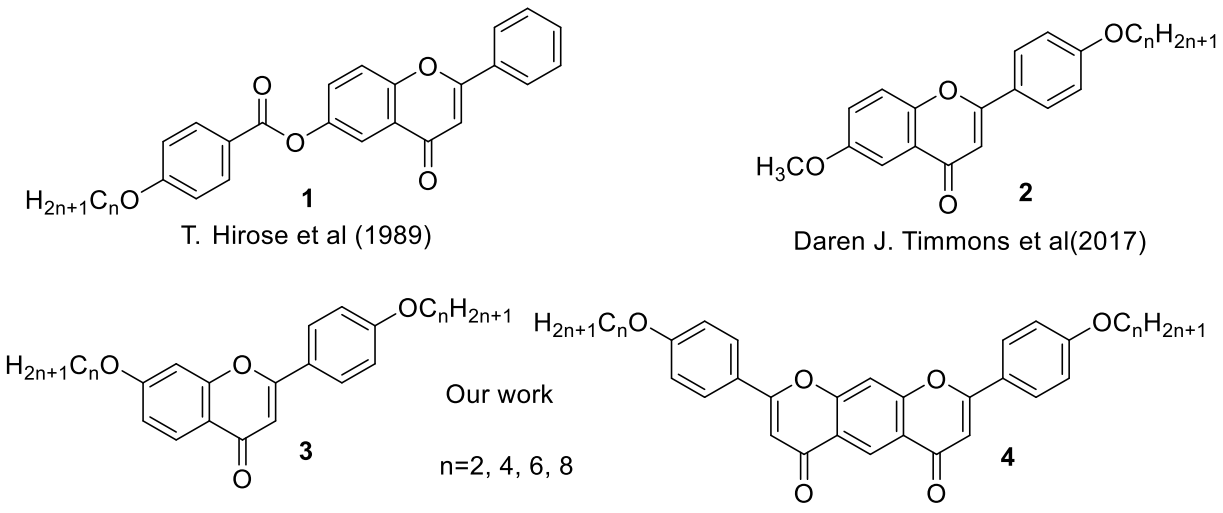


Figure-5.1 Design of chromen-4-one derivative for liquid crystalline property

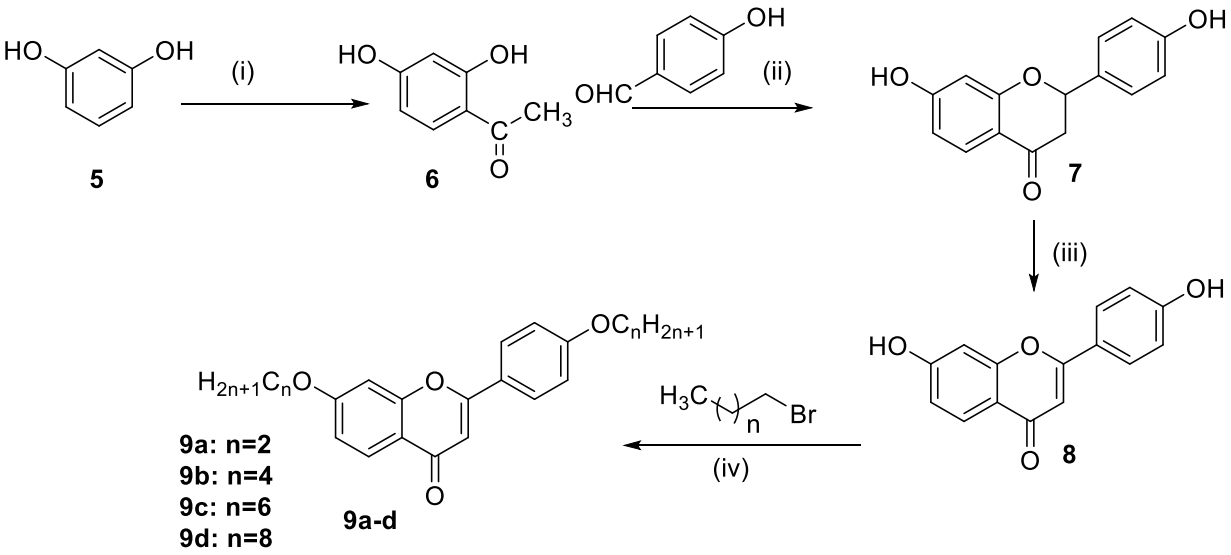
Timmons et al synthesized series of flavones with substitution on 4′-and 6- positions of compound **2** (**Fig-5.1**) which gave nematic and smectic phase [9]. Mohammad et al reported dimers of isoflavone with smectic and nematic mesophase [10]. In our previous work on

chromen-2-one containing chalcone, imine linkages with alkoxy group showed excellent mesomorphic properties, present work includes synthesis of chromen-4-one and bischromen-4-one derivatives **3** and **4** (**Fig-5.1**) for their application as liquid crystals

5.2 Results and discussion

5.2.1 Chemistry

2,4-dihydroxy acetophenone **6** was prepared from resorcinol by using standard method given by Killelba et al. [11] Reaction of 2,4-dihydroxy acetophenone **6** with 4-hydroxy benzaldehyde was carried out in ethanol using catalytic amount of piperidine and acetic acid to give flavanone **7 (Scheme-1)**. Compound **7** was purified by column chromatography and its structure was confirmed by ^{1}H-NMR. Compound **7** was oxidized to flavone using I_2 /DMSO to give compound **8**. Compound **8** was alkylated with different *n*-alkyl bromides using K_2CO_3 in N,N-dimethyl formamide (DMF) to give compounds **9a-d**. (**Scheme-1)**.



Reagent and conditions:- (i) Gla. AcOH/ $ZnCl_2$, 10-15 min, heat (ii) Ethanol, pyrrolidone, 2-3 drops acetic acid, 78-80^{o}C, 48hrs (iii) I_2/DMSO, 120^{o}C, 3hrs (iv) K_2CO_3, DMF, 80^{o}C, Reflux

Scheme-1 Synthesis of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one derivatives

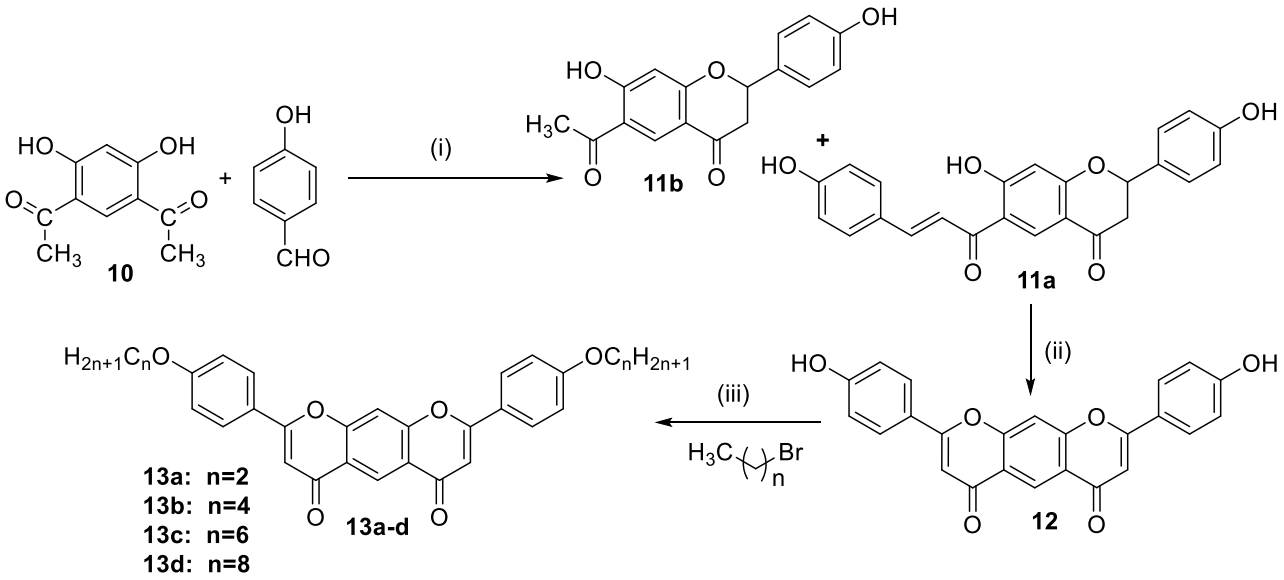
^{1}H-NMR of compound **7** (**Fig-5.2.1**) showed two doublets of doublet at δ 2.62 and 3.10 for one proton each indicated 3rd position protons of flavone ring. Doublet of doublet at δ 5.42 for one proton indicated 2nd position proton. Aromatic protons of flavanone ring were observed at δ 6.33, 6.50 and 7.64 ppm, while protons of 4-hydroxyphenyl ring were observed as doublet at δ 6.78 and 7.31 ppm with coupling constant value (*J*=8.8 Hz) indicated ortho coupled

protons. In ^{13}C-NMR spectrum of compound **7** (**Fig-5.2.2**), two aliphatic carbons are observed at δ 43 and 79 ppm for flavanone ring. Peaks from δ 102-164 are for aromatic carbons and carbonyl carbon peak was observed at 190 ppm. The IR spectrum of compounds **8** (**Fig-5.3.1**) exhibited one broad band in the range of 3214 cm^{-1} for O-H stretching vibrations and another strong band at 2929 cm^{-1} for C-H Stretching vibrations. Carbonyl stretching frequency of ketone for chromen-4-one was observed at 1630 cm^{-1}. ^{1}H-NMR of compound **8** (**Fig-5.3.2**) showed peak for proton at 3rd position of flavone ring at δ 6.28 ppm and seven aromatic protons were observed in region of δ 6.40-8.14 ppm, -OH proton was observed at 13.5 ppm. In ^{13}C-NMR for compound **8 (Fig-5.3.3)** peaks from δ 102-162 were observed for all 13 aromatic carbons. Carbonyl carbon peak was observed at 176 ppm.

Formation of compounds **9a-d** was confirmed by ^{1}H, ^{13}C-NMR, IR and Mass analysis. In general IR spectrum of compound **9a-d** showed bands from 3058-2956 cm^{-1} for C-H stretching, band at 1637 cm^{-1} observed for carbonyl stretching and bands at 1250-1110 cm^{-1} observed for C-O stretching vibrations. ^{1}H NMR of compound **9a-d** showed triplets from δ 0.99-1.04 for six protons of two terminal methyl groups, peaks from δ1.51-1.87 indicated methylene protons of different alkoxy group, triplet in range from δ 4.04-4.11 ppm is for –OCH_2 protons attached at 7th and 4th position. Singlet Peak around δ 6.7 ppm is for proton at 3rd position of flavone ring. Multiplet from δ 6.95-7.03 ppm is for protons of aromatic ring at 2nd position of chromen-4-one. Doublet at δ 7.86 and 8.12 ppm is observed for 5th and 6th position of flavone ring. In ^{13}C NMR of compound **9b (Fig-5.5.3)** exhibited peaks for aliphatic methyl carbons from δ 13.91-31.27 and peaks for methylene carbons next to oxygen were observed at 68.08 and 68.50 ppm. Peaks for aromatic carbons were observed from δ 100-163 while carbonyl carbon of chromen-4-one was observed at 178 ppm.

Resorcinol on acylation with acetic anhydride and $ZnCl_2$ gave 1,1'-(4,6-dihydroxy-1,3-phenylene)diethanone **10** (**Scheme 2**). Compound **10** on reaction with two equivalents of 4-hydroxy benzaldehyde in ethanol using catalytic amount of pyrrolidine and acetic acid gave mixture of two products **11a** and **11b** on TLC which were separated by column chromatography.

The formation of compound **11a** was confirmed by IR, ^{1}H NMR, ^{13}C NMR and the ESI-Mass of **11a** (**Fig-5.8.4**) showed M+H peak at 403.1. While ESI-MS of compound **11b** (**Fig-5.9.1**) showed M+H peak at 299.09 thus proved formation of monoreacted compound **11b.**



Reagent and conditions: (i) EtOH, Pyrrolidine, AcOH, 78-80 ^{o}C, Reflux, 20 hrs (ii) I_2 , DMSO, 3hr reflux (iii) K_2CO_3, DMF, rt, 16hr reflux

Scheme-2 Synthesis of 2,8-bis(4-hydroxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione derivatives

The IR spectrum of compounds **11a** (**Fig-5.8.1**) exhibited one broad band in the range of 3381-3158 cm^{-1} for O-H stretching vibrations. Carbonyl stretching frequency for ketone of chalcone was observed at 1675 cm^{-1} and for chromen-4-one was observed at 1635 cm^{-1}. ^{1}H NMR of compound **11a (Fig-5.8.2)** exhibited three doublets of doublet at δ 2.78, 3.28 and 5.61 ppm for one proton each indicated protons at 3rd and 2nd positions respectively. Aromatic protons of 4-hydroxy phenyl ring and olefinic protons were observed as doublets in region of δ 6.81, 6.85, 7.35 and 7.80 ppm. Protons of 5th and 8th position of flavanone ring were observed at δ 6.52 and 8.62 ppm. Phenolic protons were observed at δ 9.62, 10.21 and 13.56 ppm. In ^{13}C NMR of compound **11a (Fig-5.8.3)** exhibited sharp peaks for aliphatic carbons of flavanone ring at δ 43.47 and 79.79, peaks for aromatic carbons were observed from 104-168 ppm. carbonyl carbon of chromen-4-one ring and chalcone were observed at δ 190 and 193 ppm respectively.

Compound **11a** was subjected to oxidation/ oxidative cyclization using catalytic amount of I_2 (0.2 equivalent) in DMSO to give compound **12** (**Scheme-2**) with high yield of 92%. Further compound **12** was alkylated using alkyl bromides with K_2CO_3 in DMF to give compounds **13a-d**. ^{1}H-NMR of compound **12** (**Fig-5.10.2**) showed singlet at δ 6.86 for two protons, indicated flavone ring protons at 3rd position. While two singlets at δ 8.05 and 8.57 ppm,

indicated protons at 5th and 8th position. Protons of 4-hydroxyphenyl rings were observed as doublet at δ 6.95 and 7.98 ppm with coupling constant (*J*=8.8 Hz) indicated ortho coupled protons.

In general the IR spectrum of compound **13a-d** showed bands from 3077-2856 cm^{-1} for C-H stretching vibrations. Here disappearance of broad band indicated alkylation of free –OH has occurred. Band at 1640 cm^{-1} indicated carbonyl stretching frequency and band at 1250-1050 cm^{-1} indicated C-O stretching vibrations. ^{1}H-NMR of compound **13a-d** showed peaks in range from δ 1.00-2.19 for aliphatic protons of alkyl chain, triplet at 4.06-4.09 ppm is observed for methylene protons of alkoxy group. Aromatic protons of flavones were observed in region from δ 6.72 to 9.07 ppm. ^{13}C-NMR of compound **13b-d** showed peaks from 14-68 ppm for aliphatic carbons. Peak from δ 105-163 ppm corresponds to aromatic carbons. Peak at 177 ppm is for carbonyl carbon of chromone.

Figure-5.2.1 ^{1}H-NMR Spectrum of 7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one (**7**) in DMSO-d_6

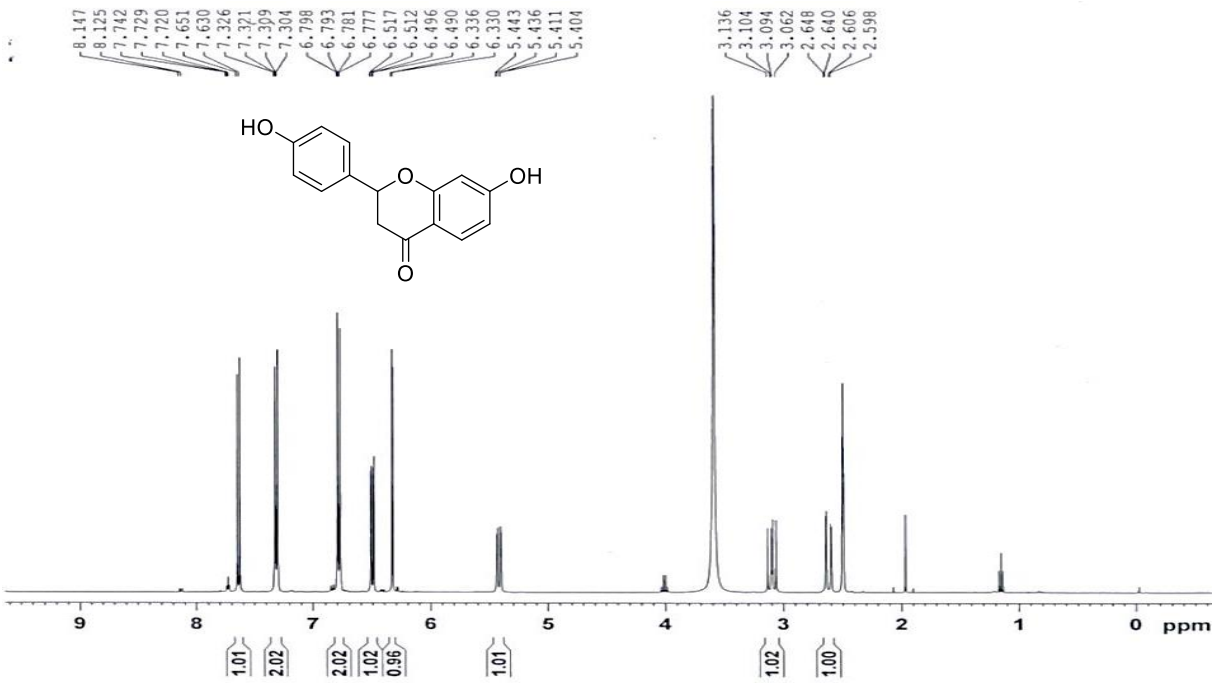


Figure-5.2.2 ^{13}C-NMR Spectrum of 7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one (**7**) in DMSO-d_6

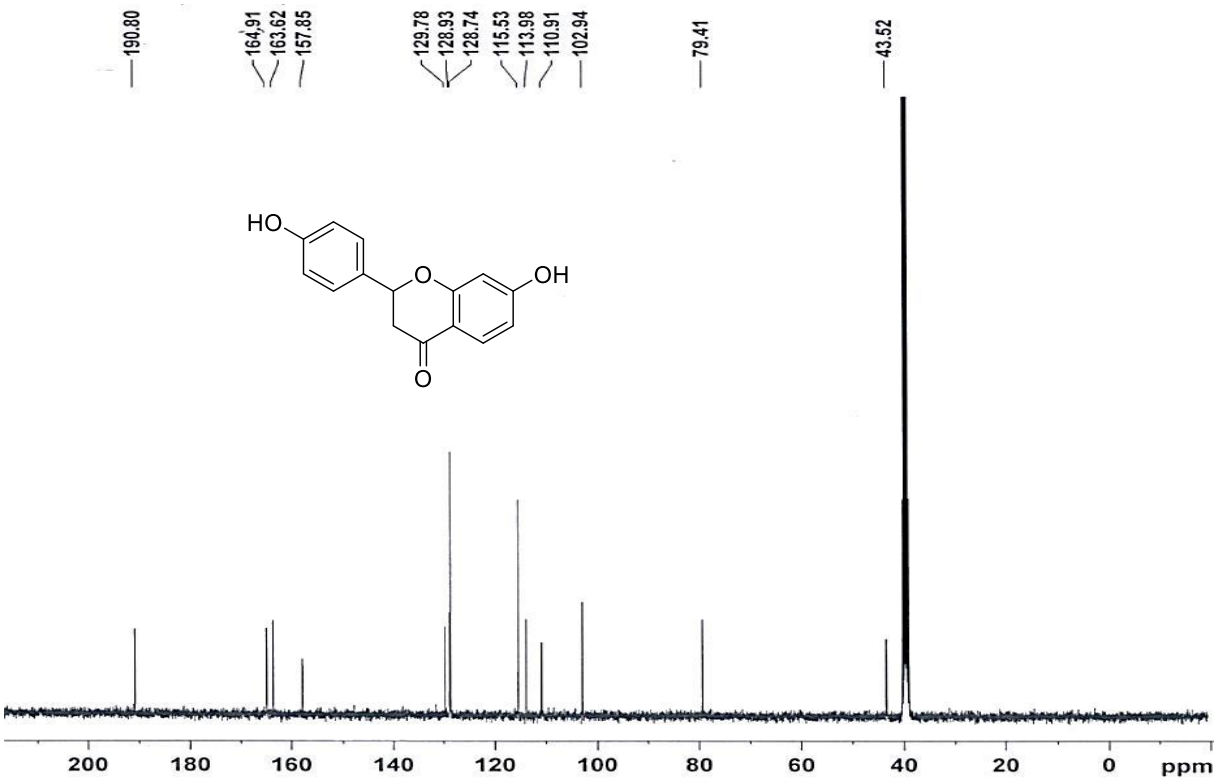


Figure-5.3.1 IR spectrum of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (**8**)

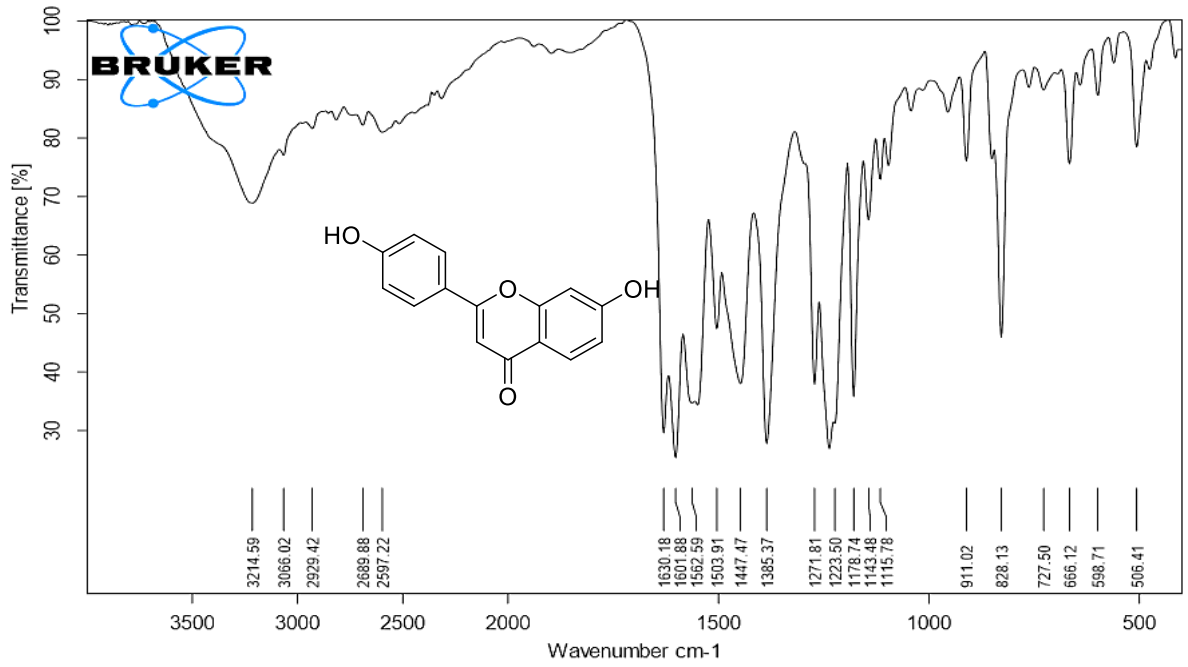


Figure-5.3.2 ^{1}H-NMR spectrum of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (**8**) in DMSO-d_6

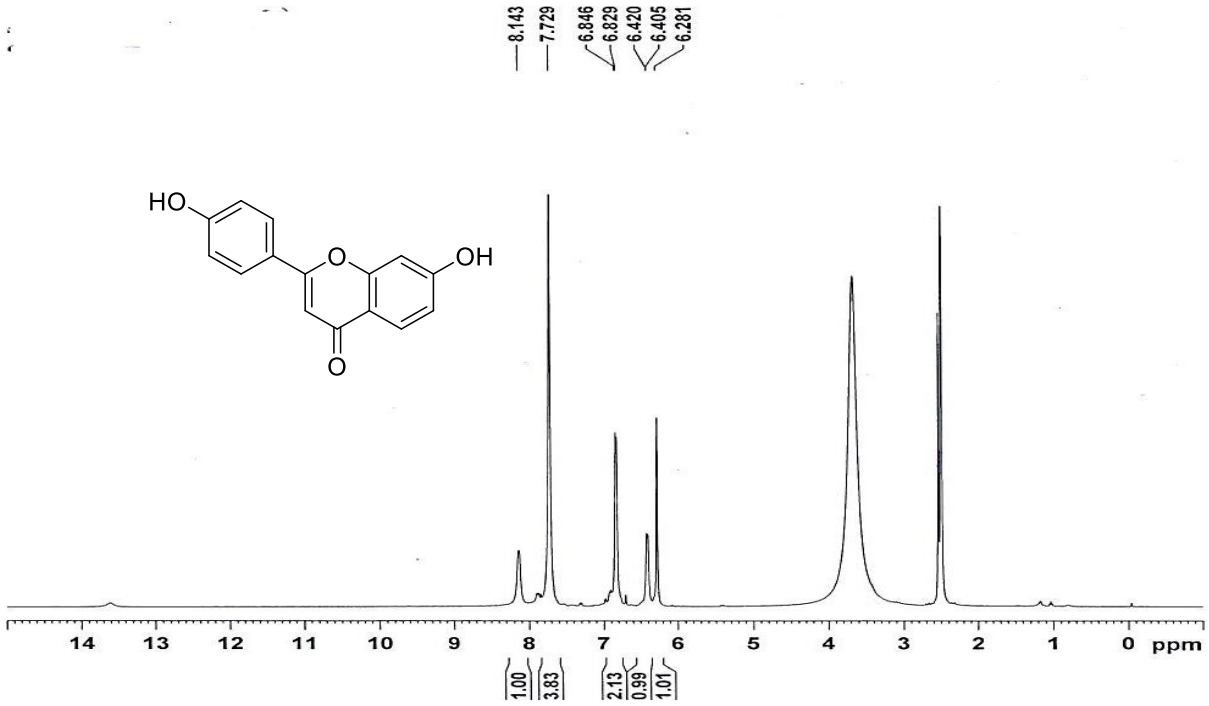


Figure-5.3.3 ^{13}C-NMR spectrum of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (**8**) in DMSO-d_6

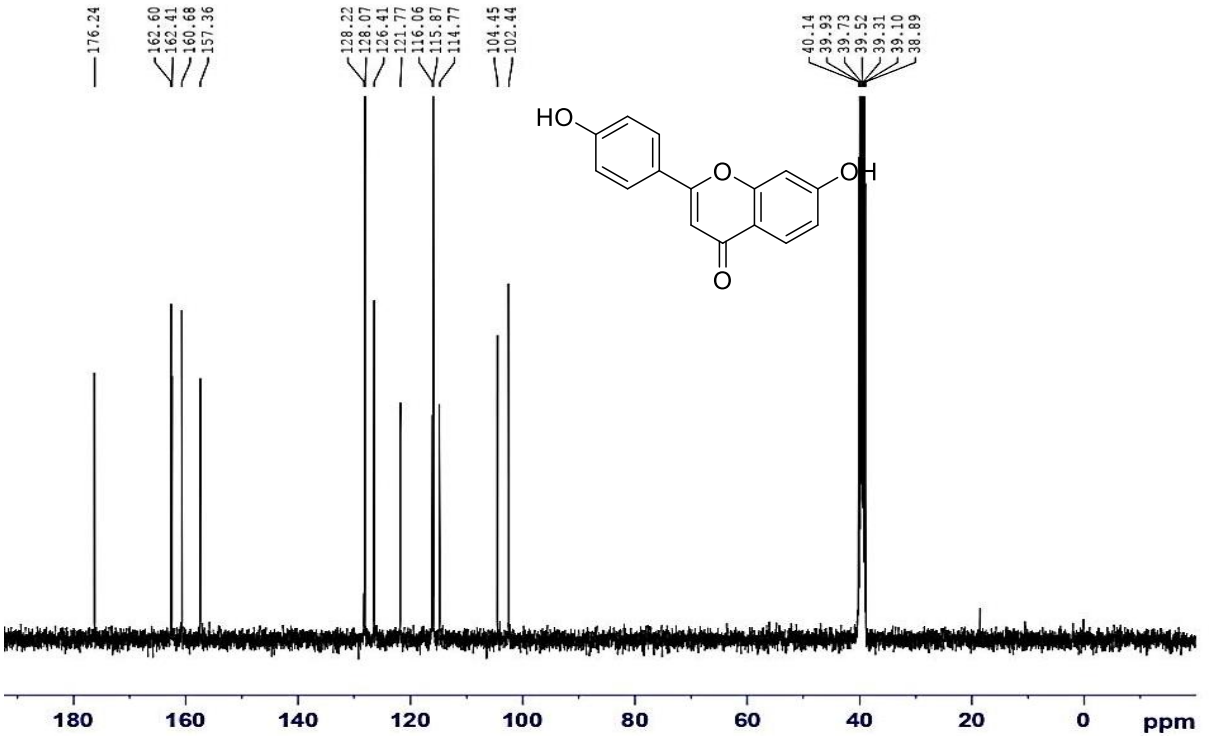


Figure-5.3.4 ESI-MS spectrum of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (**8**). M+H peak at 255.06

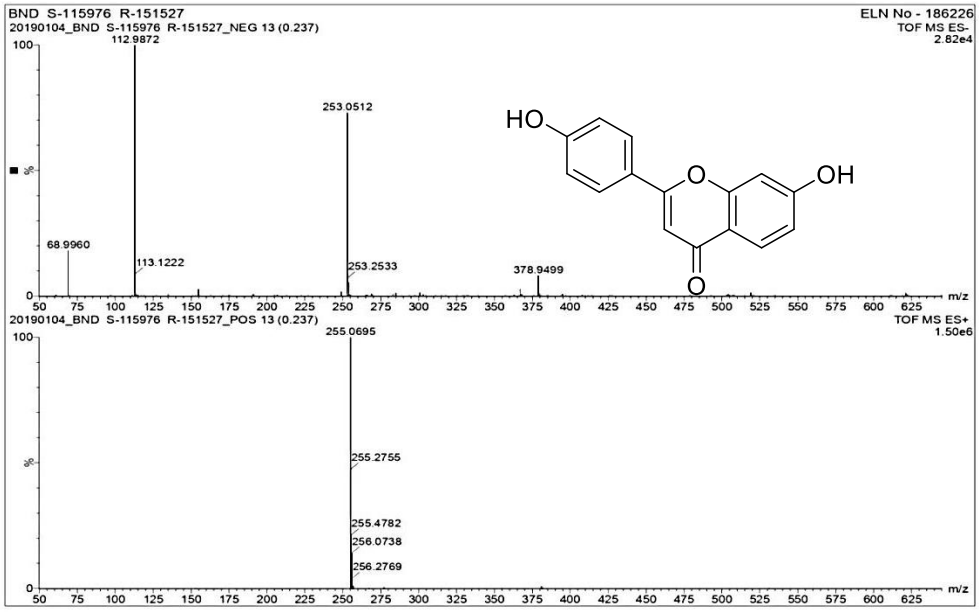


Figure-5.4.1 IR spectrum of 7-ethoxy-2-(4-ethoxyphenyl)-4H-chromen-4-one (**9a**)

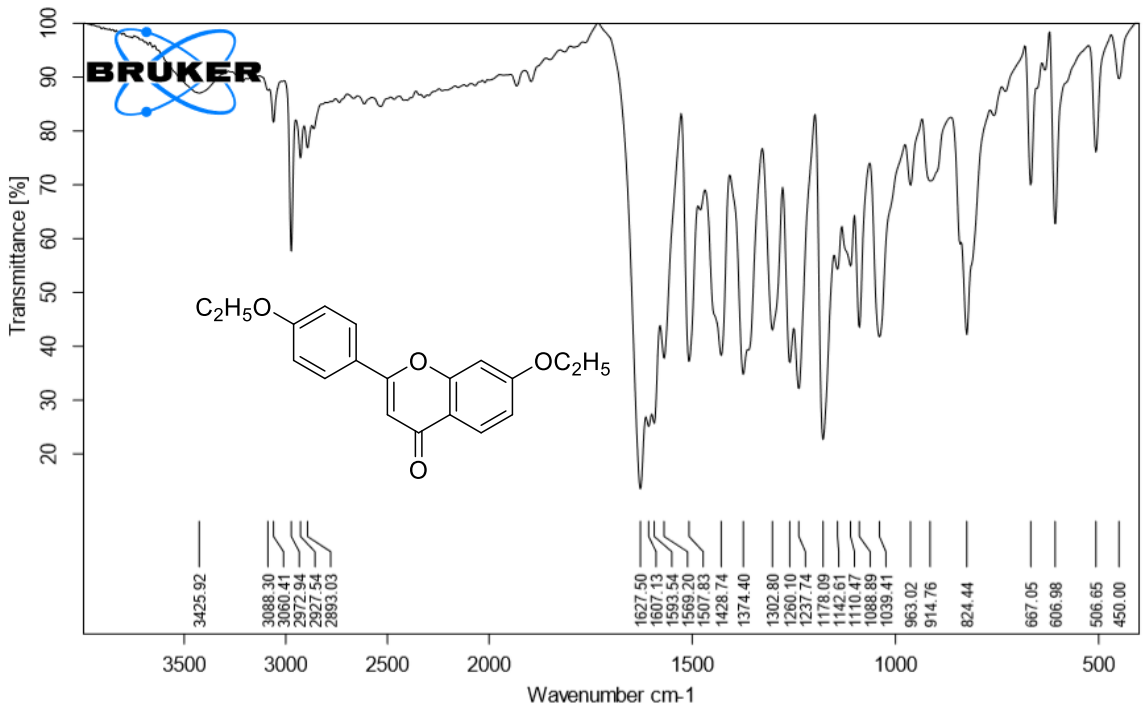


Figure-5.4.2 ^{1}H-NMR spectrum of 7-ethoxy-2-(4-ethoxyphenyl)-4H-chromen-4-one (**9a**) in $CDCl_3$

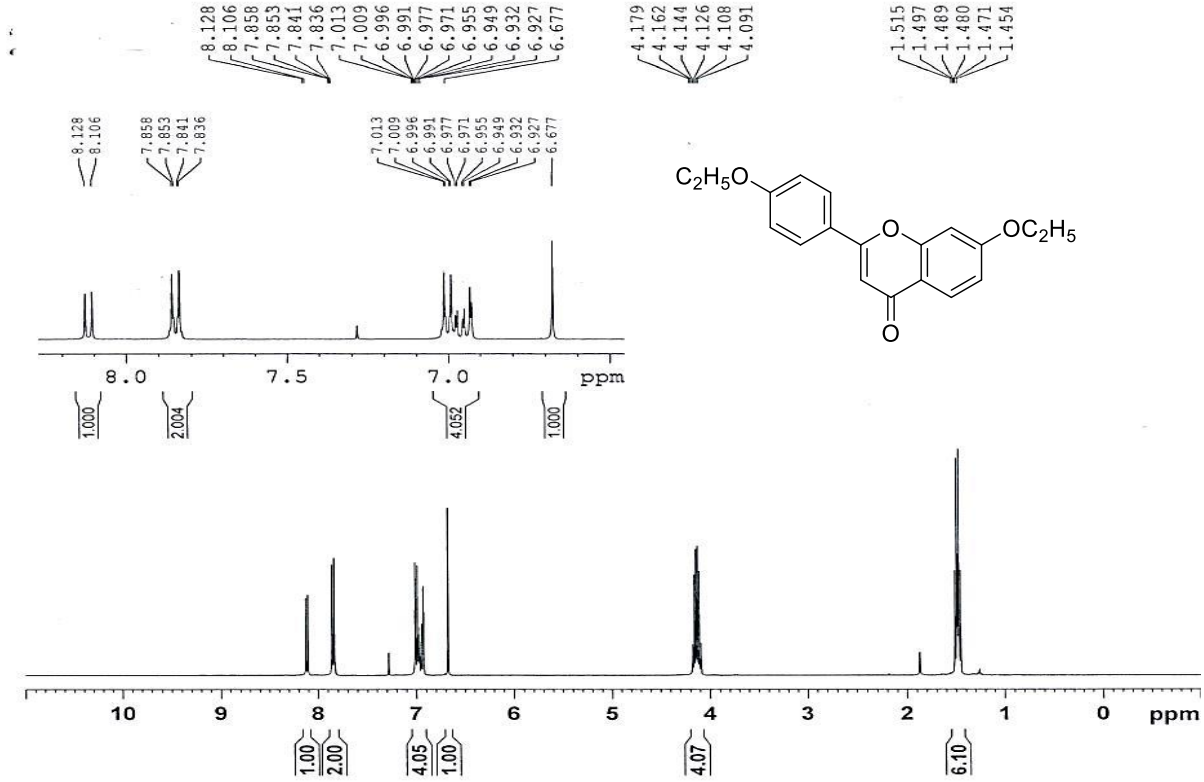


Figure-5.5.1 IR spectrum of 7-butoxy-2-(4-butoxyphenyl)-4H-chromen-4-one (**9b**)

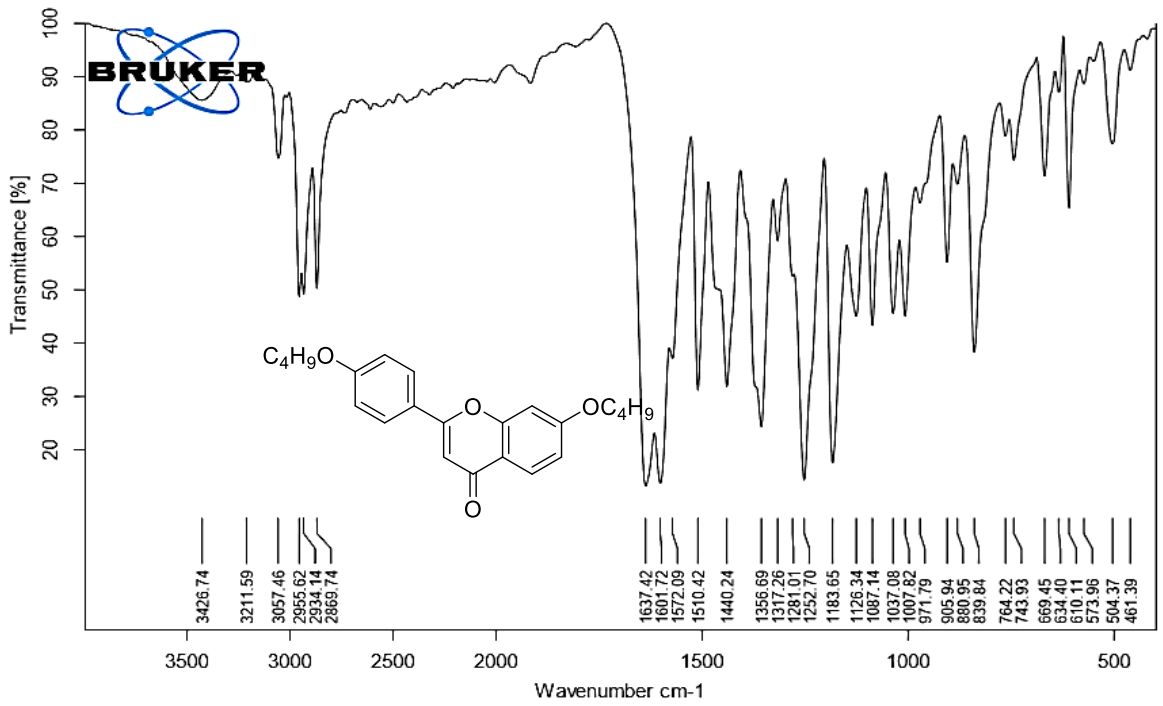


Figure-5.5.2 ^{1}H-NMR spectrum of 7-butoxy-2-(4-butoxyphenyl)-4H-chromen-4-one (**9b**) in $CDCl_3$

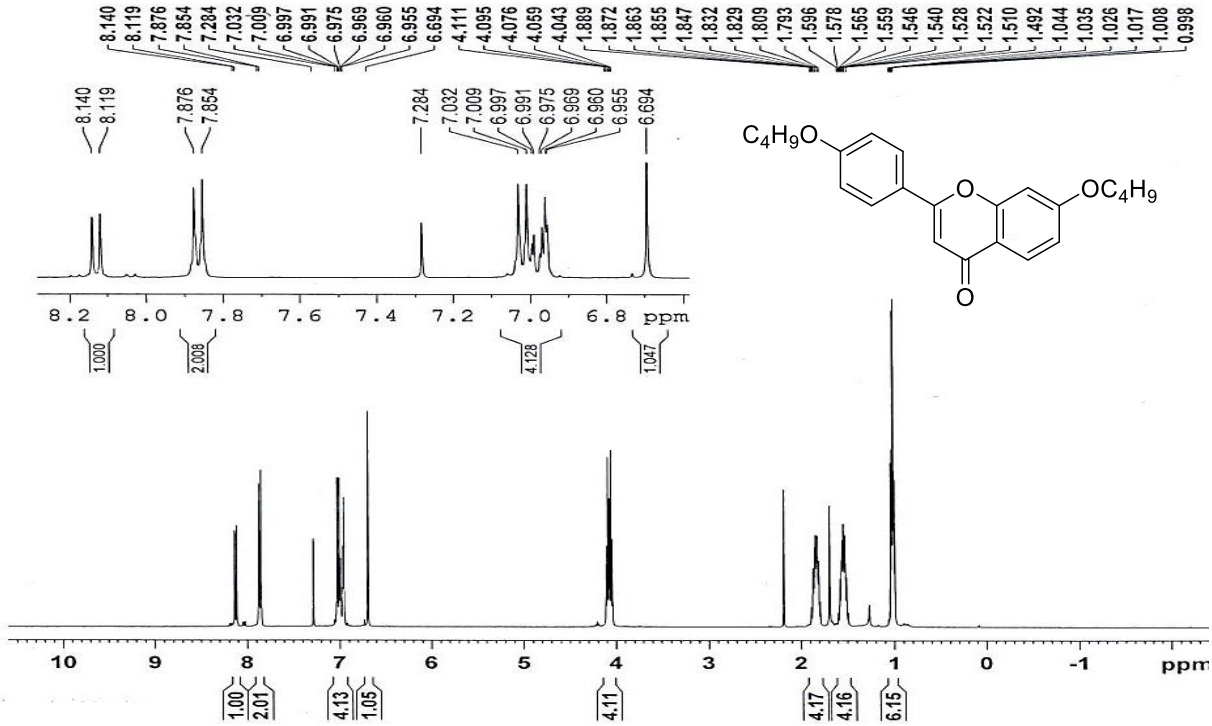


Figure-5.5.3 ^{13}C-NMR spectrum of 7-butoxy-2-(4-butoxyphenyl)-4H-chromen-4-one (**9b**) in $CDCl_3$

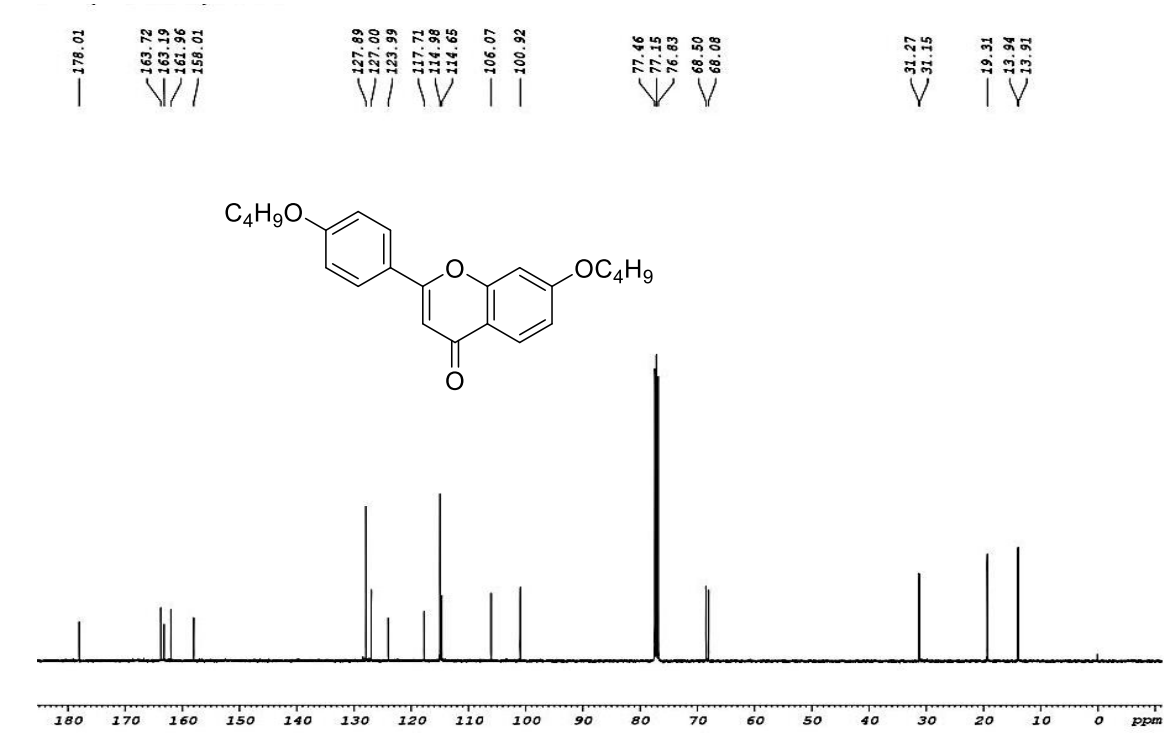


Figure-5.5.4 ESI-MS spectrum of 7-butoxy-2-(4-butoxyphenyl)-4H-chromen-4-one (**9b**)
M+H peak at 367.17

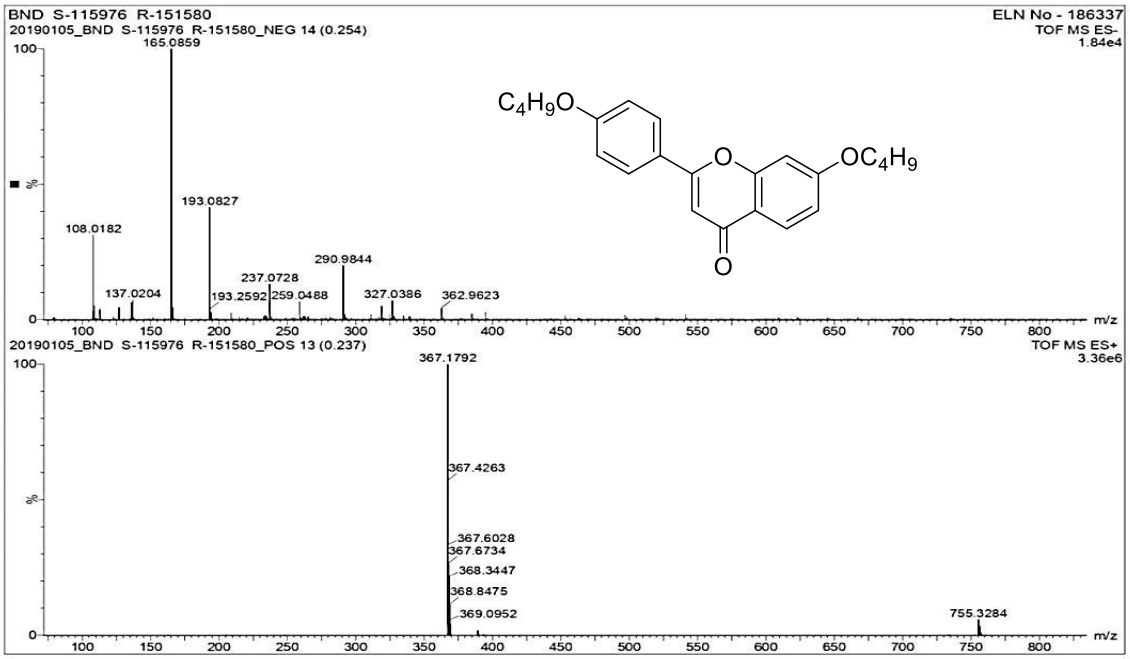


Figure-5.6.1 IR spectrum of 7-(hexyloxy)-2-(4-(hexyloxy)phenyl)-4H-chromen-4-one (**9c**)

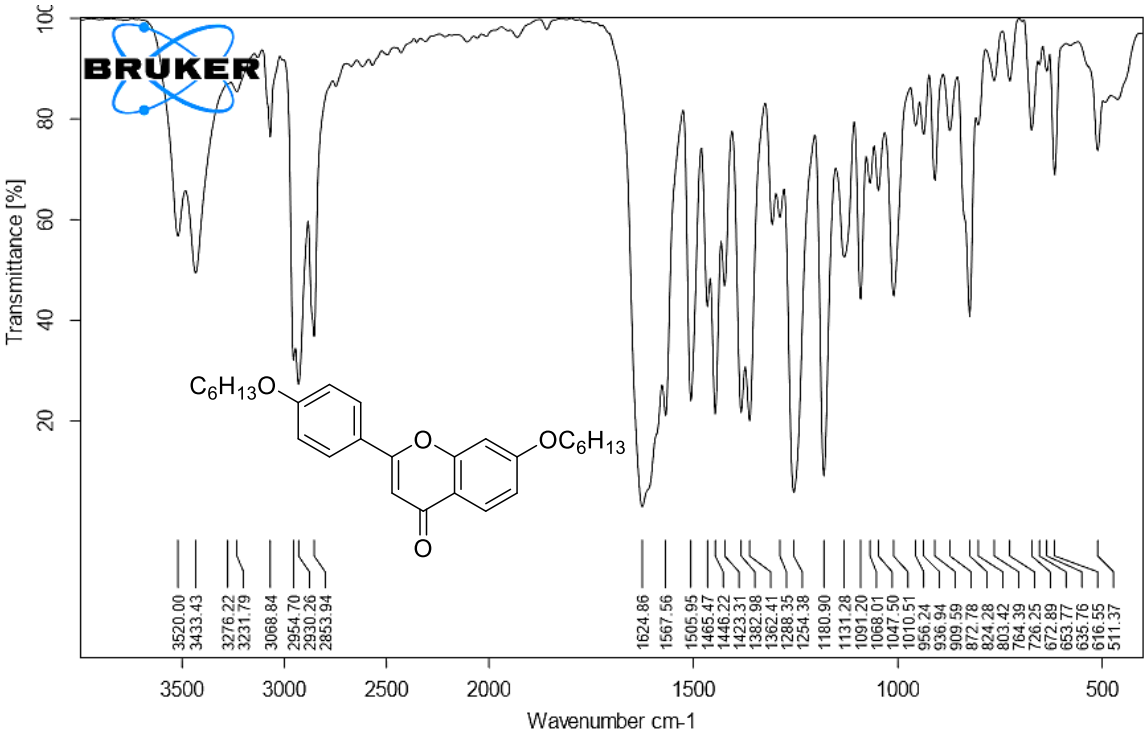


Figure-5.6.2 ^{1}H-NMR spectrum of 7-(hexyloxy)-2-(4-(hexyloxy)phenyl)-4H-chromen-4-one (**9c**) in $CDCl_3$

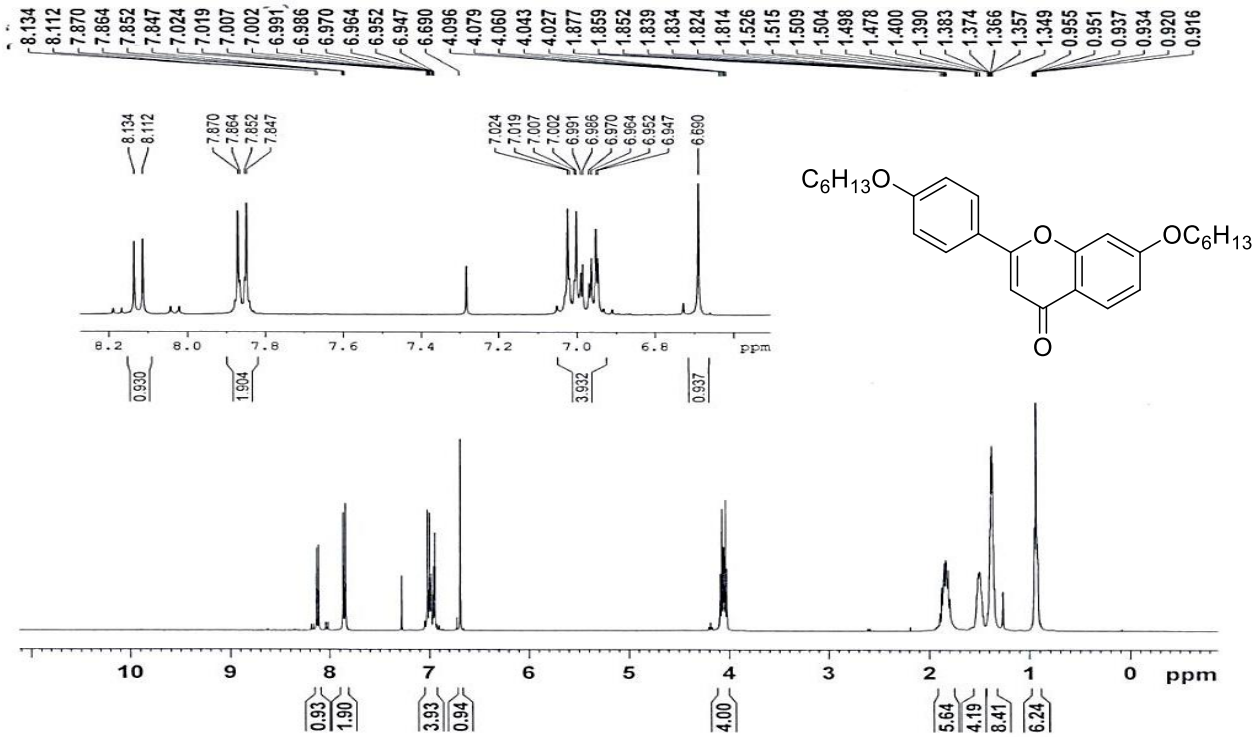


Figure-5.6.3 ^{13}C NMR spectrum of 7-(hexyloxy)-2-(4-(hexyloxy)phenyl)-4H-chromen-4-one (**9c**) in $CDCl_3$

Figure-5.7.1 IR spectrum of 7-(Octyloxy)-2-(4-(octyloxy)phenyl)-4H-chromen-4-one (**9d**)

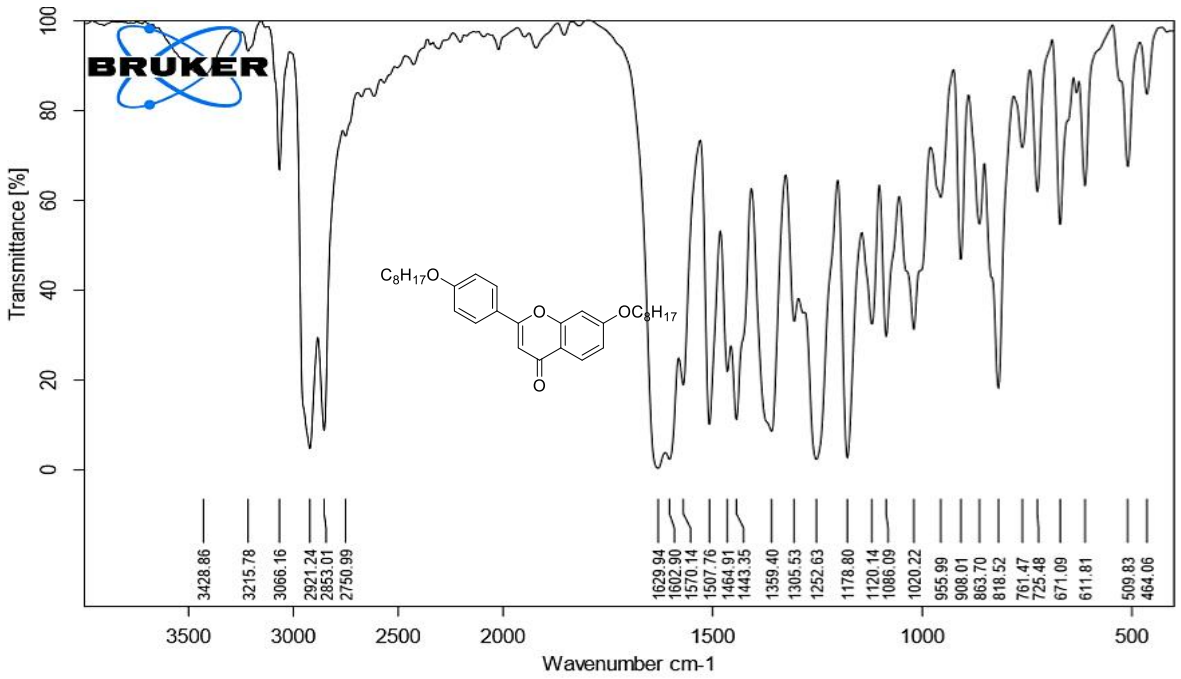


Figure-5.7.2 ^{1}H-NMR spectrum of 7-(Octyloxy)-2-(4-(octyloxy)phenyl)-4H-chromen-4-one (**9d**) in $CDCl_3$

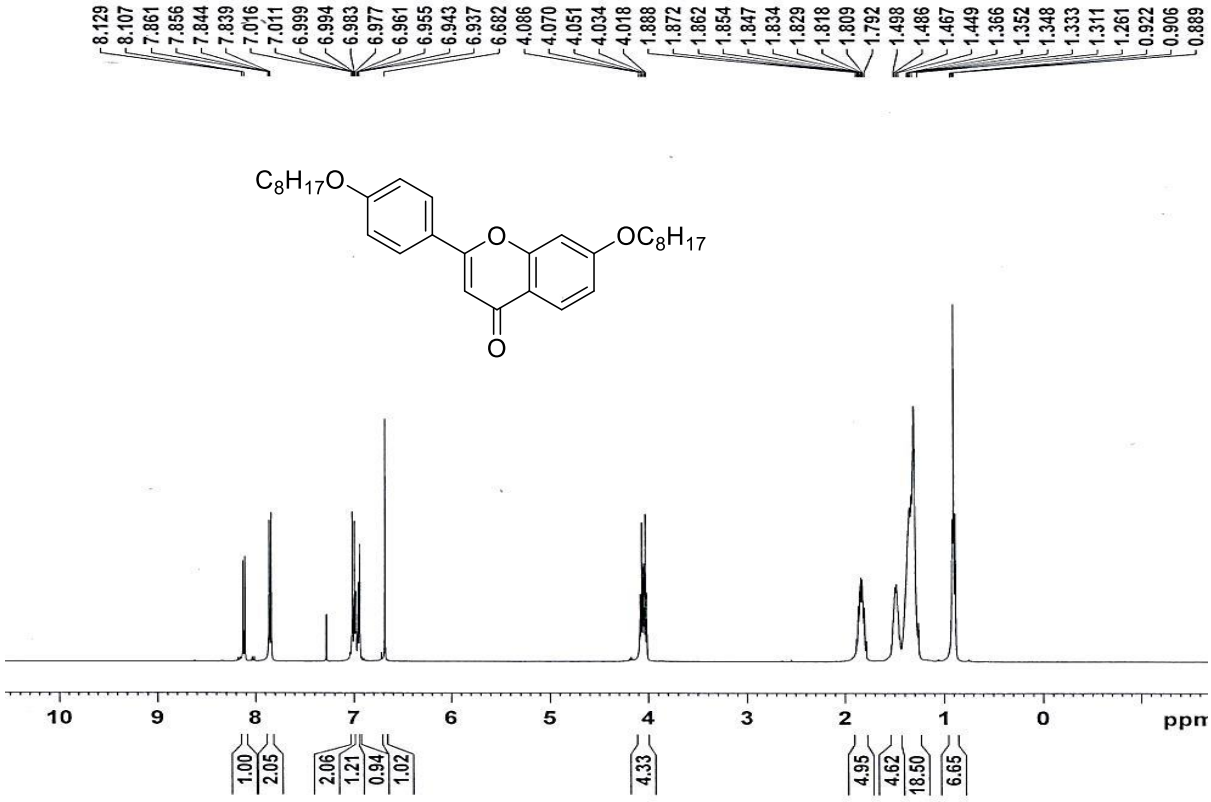


Figure-5.7.3 ^{13}C-NMR spectrum of 7-(Octyloxy)-2-(4-(octyloxy)phenyl)-4H-chromen-4-one (**9d**) in $CDCl_3$

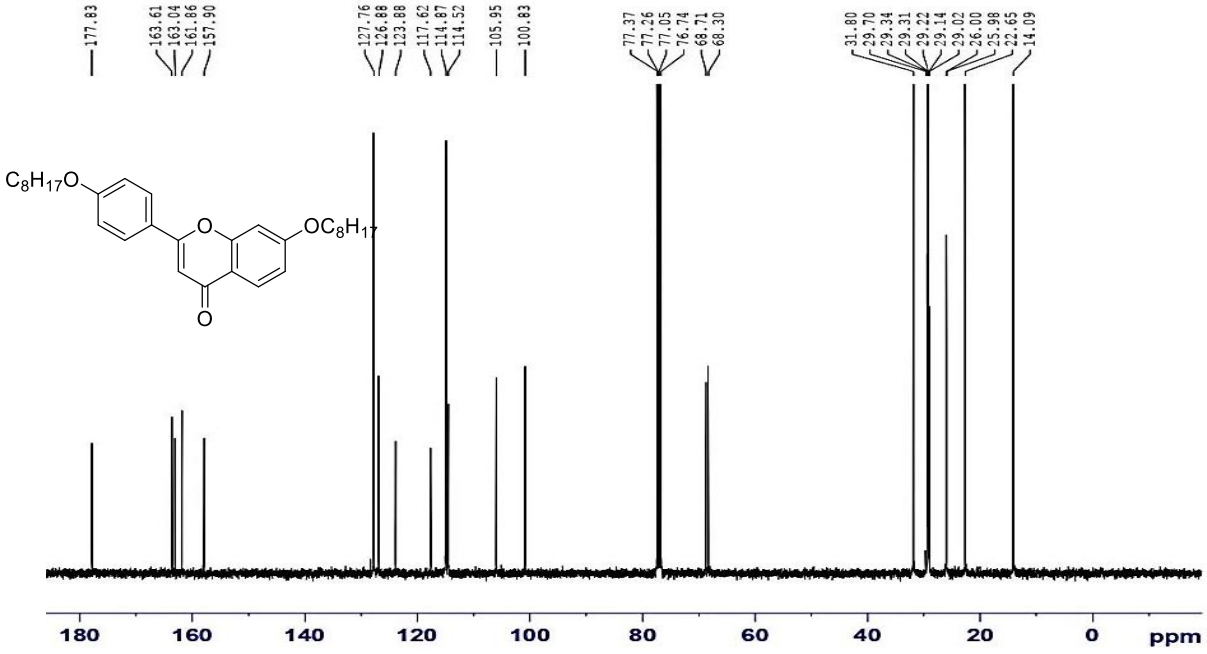


Figure-5.7.4 ESI-MS spectrum of 7-(Octyloxy)-2-(4-(octyloxy)phenyl)-4H-chromen-4-one (**9d**) M+H peak at 479.31

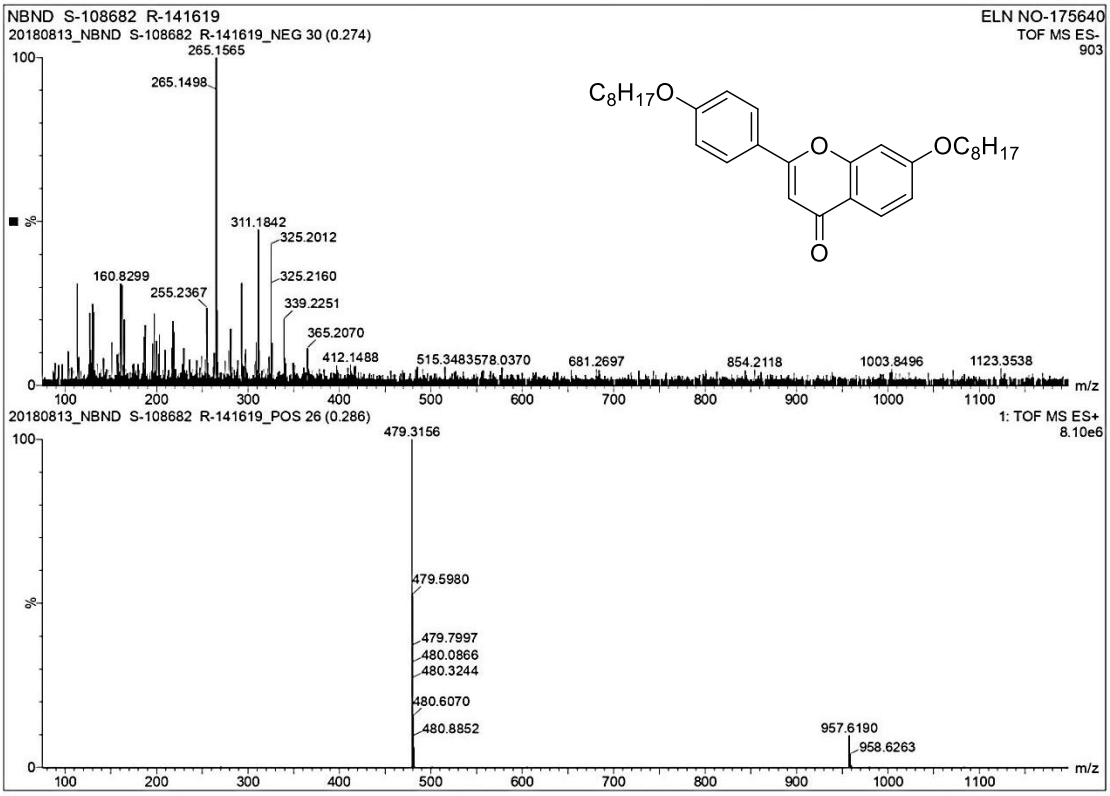


Figure-5.8.1 IR spectrum of (E)-7-hydroxy-2-(4-hydroxyphenyl)-6-(3-(4-hydroxyphenyl) acryloyl) chroman-4-one (**11a**)

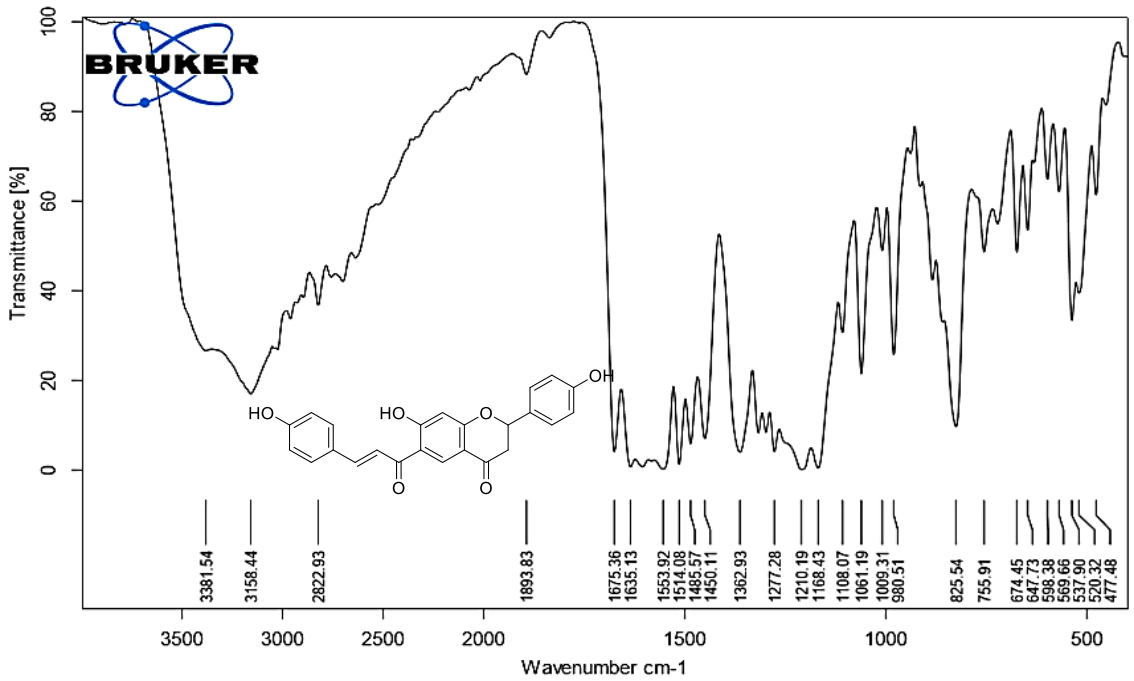


Figure-5.8.2 ^{1}H-NMR spectrum of (E)-7-hydroxy-2-(4-hydroxyphenyl)-6-(3-(4-hydroxyphenyl) acryloyl) chroman-4-one (**11a**) in DMSO-d_6

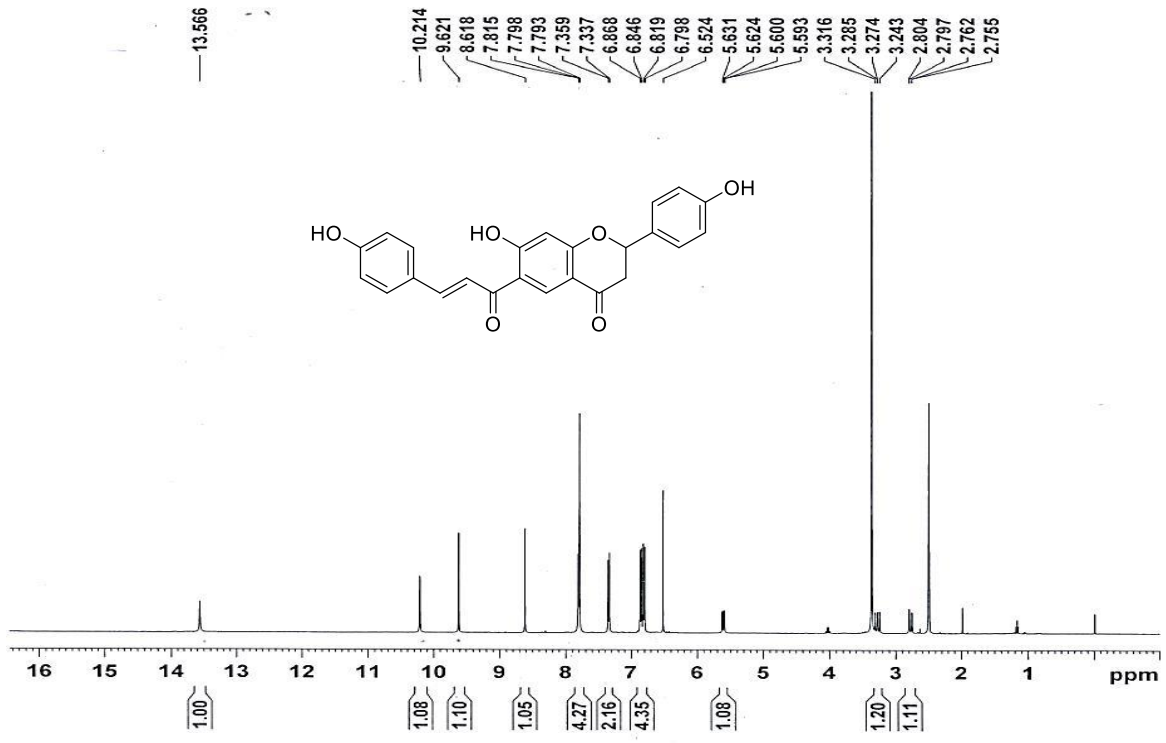


Figure-5.8.3 ^{13}C-NMR spectrum of (E)-7-hydroxy-2-(4-hydroxyphenyl)-6-(3-(4-hydroxyphenyl) acryloyl) chroman-4-one (**11a**) in DMSO-d_6

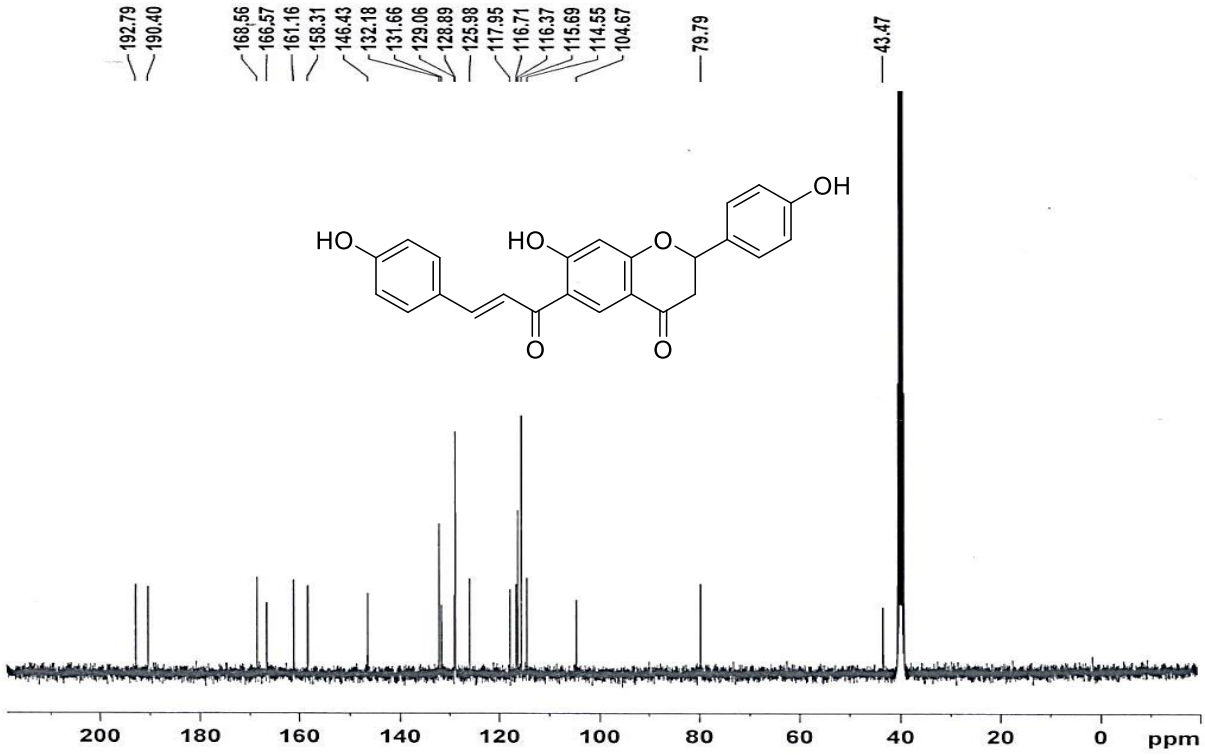


Figure-5.8.4 ESI-MS spectrum of (E)-7-hydroxy-2-(4-hydroxyphenyl)-6-(3-(4-hydroxyphenyl) acryloyl) chroman-4-one (11a) M+H peak at 403.10

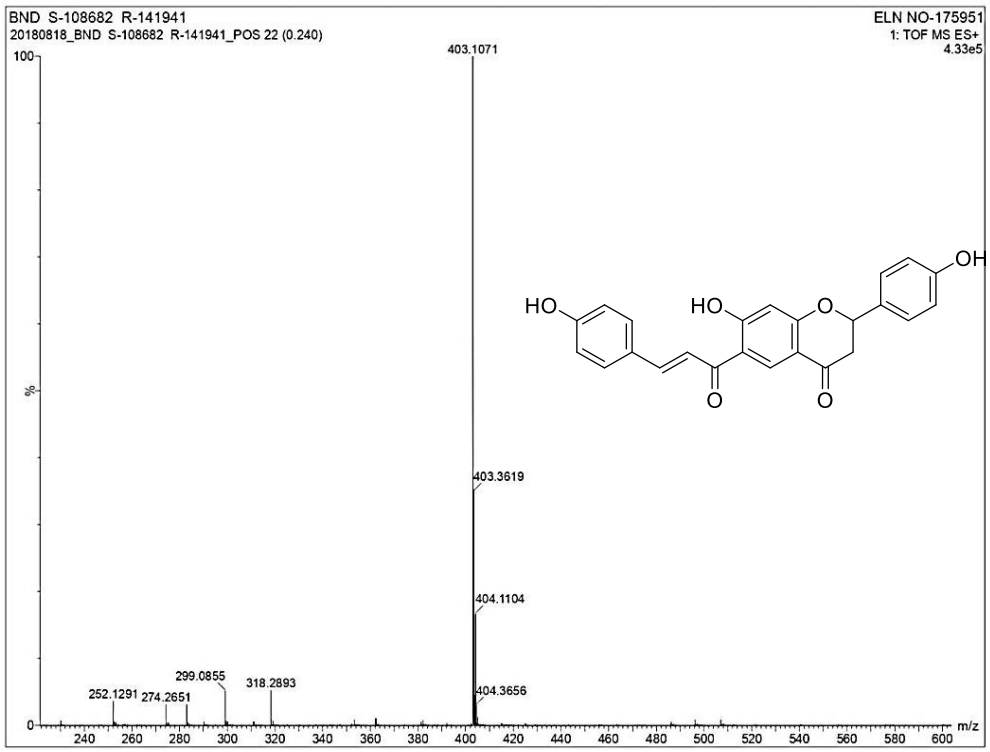


Figure-5.9.1 ESI-MS spectrum of 6-acetyl-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one (**11b**) M+H peak at 299.09

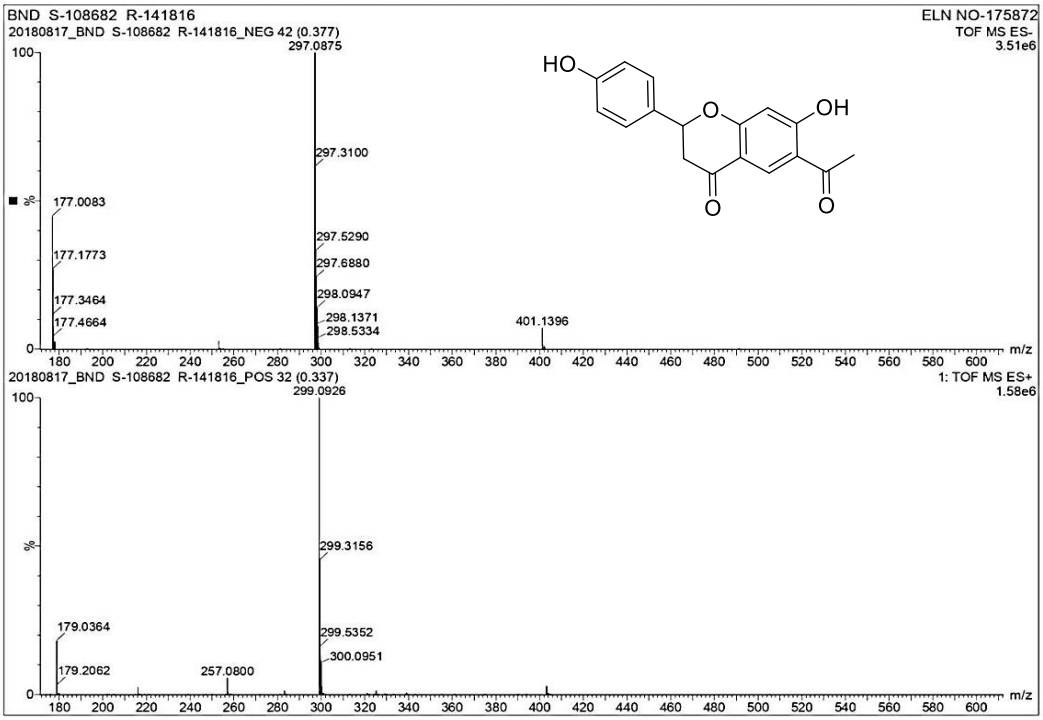


Figure-5.10.1 IR spectrum of 2,8-bis(4-hydroxyphenyl)pyrano[3,2-g]chromene-4,6-dione (12)

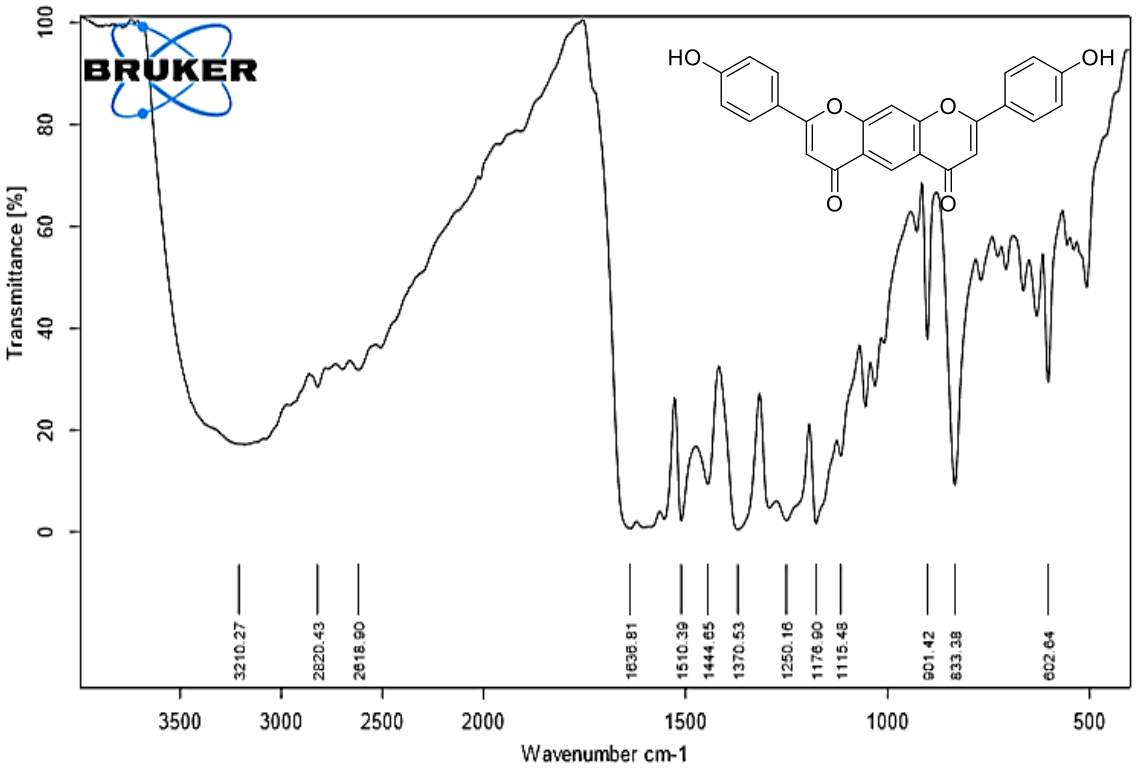


Figure-5.10.2 ^{1}H-NMR spectrum of 2,8-bis(4-hydroxyphenyl)pyrano[3,2-g]chromene-4,6-dione (**12**) in DMSO-d_6

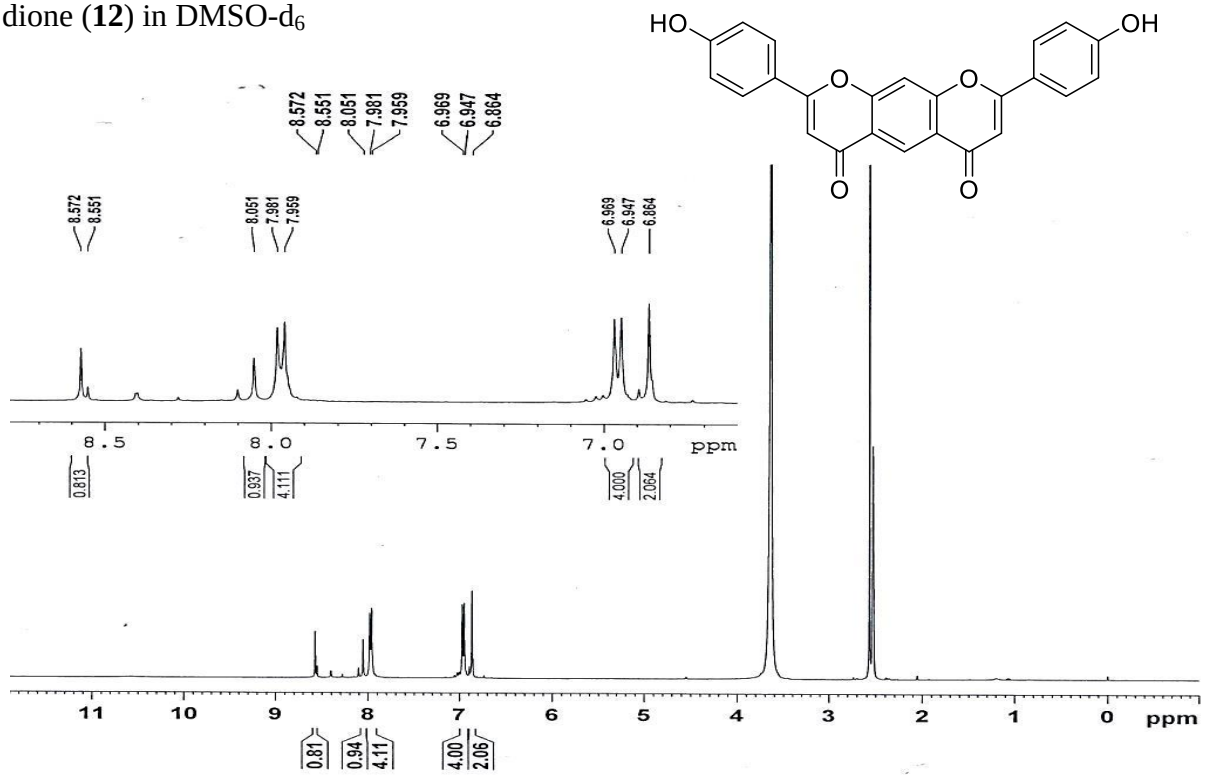


Figure-5.10.3 ESI-MS spectrum of 2,8-bis(4-hydroxyphenyl)pyrano[3,2-g]chromene-4,6-dione (12) M+H peak at 399.08

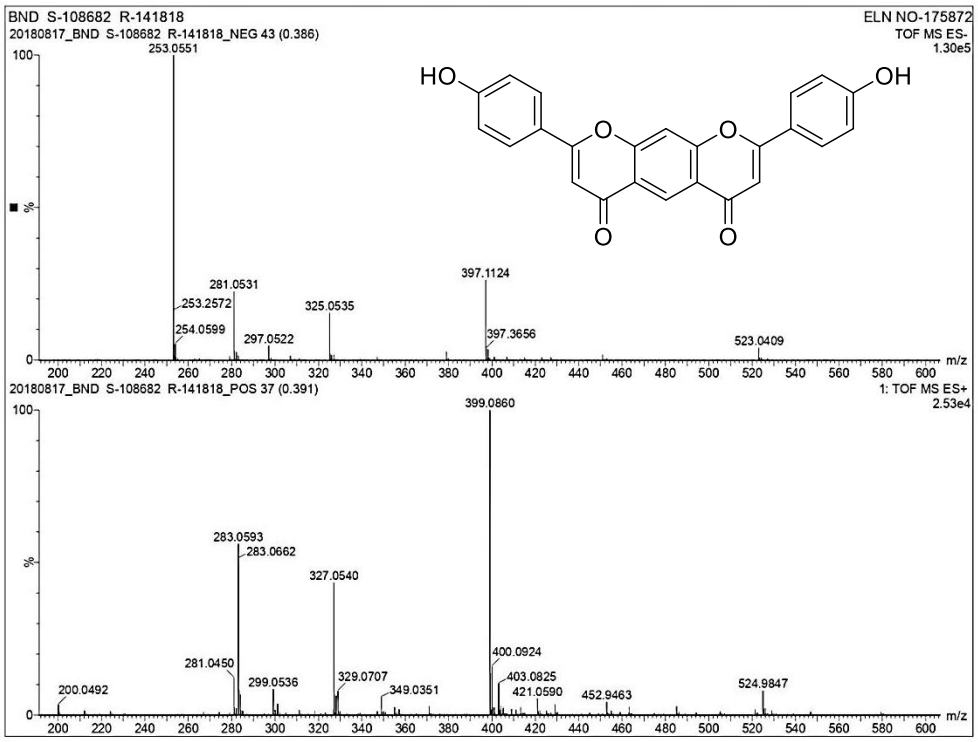


Figure-5.11.1 IR spectrum of 2,8-bis(4-ethoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13a**)

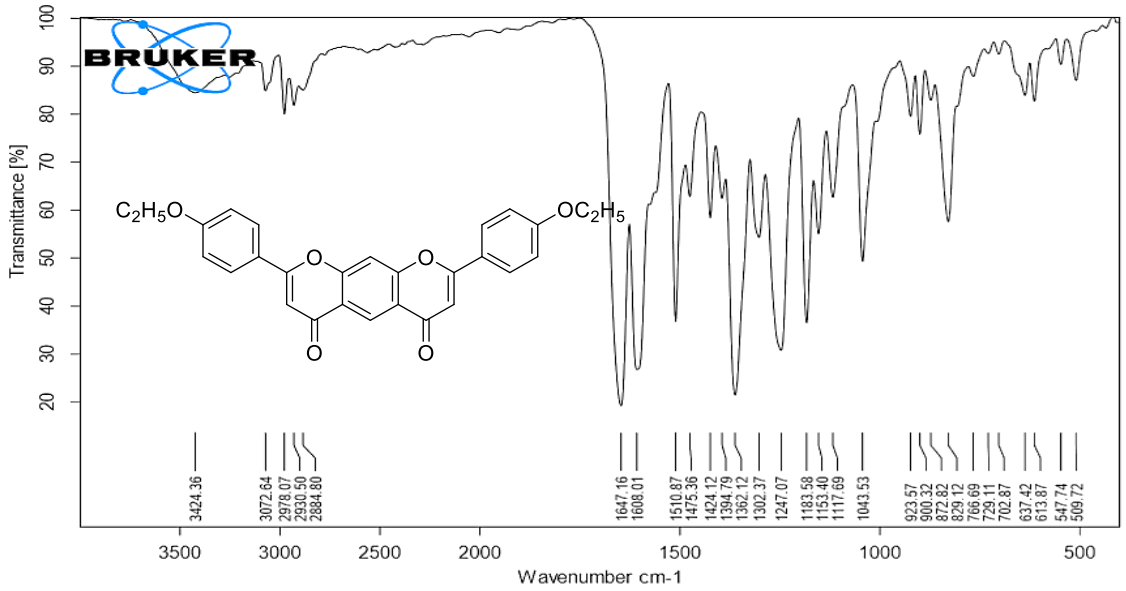


Figure-5.11.2 ^{1}H-NMR spectrum of 2,8-bis(4-ethoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13a**) in DMSO-d_6

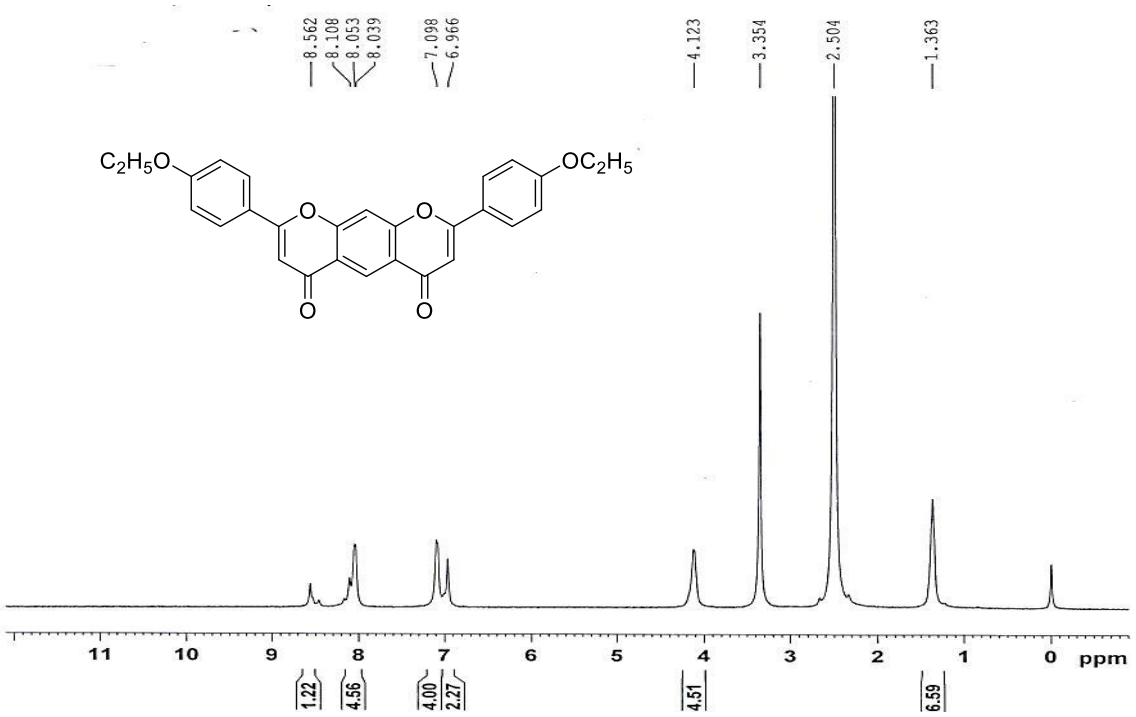


Figure-5.12.1 IR spectrum of 2,8-bis(4-butoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13b)

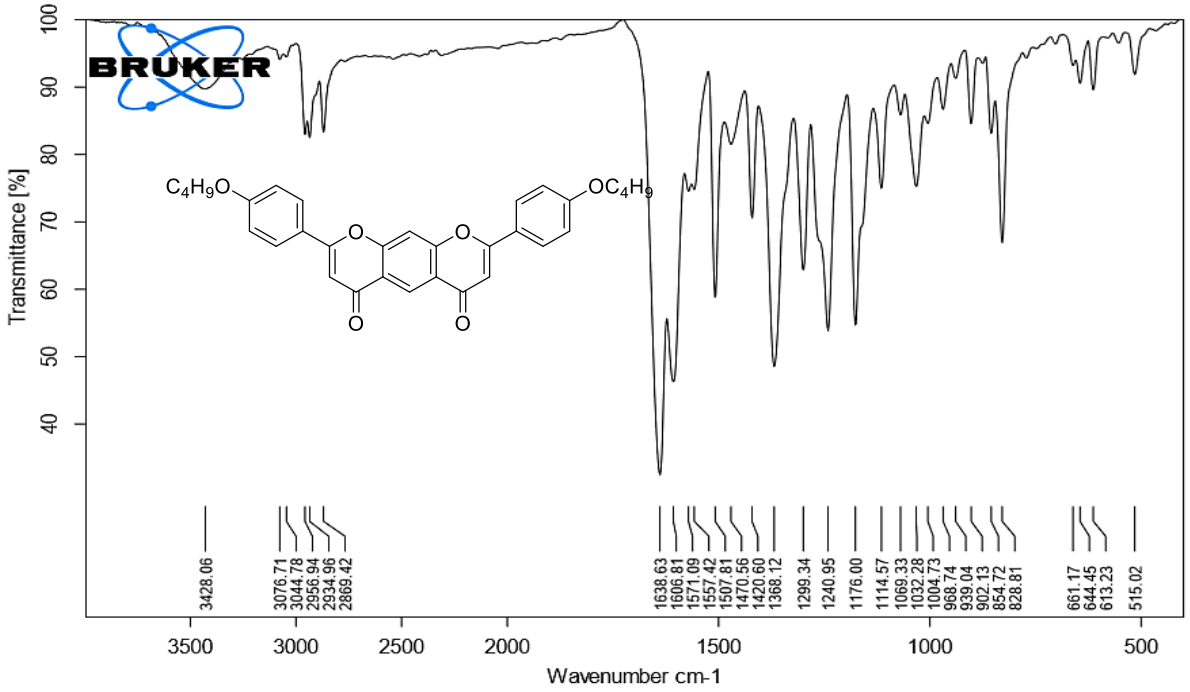


Figure-5.12.2 ^{1}H-NMR spectrum of 2,8-bis(4-butoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13b**) in $CDCl_3$

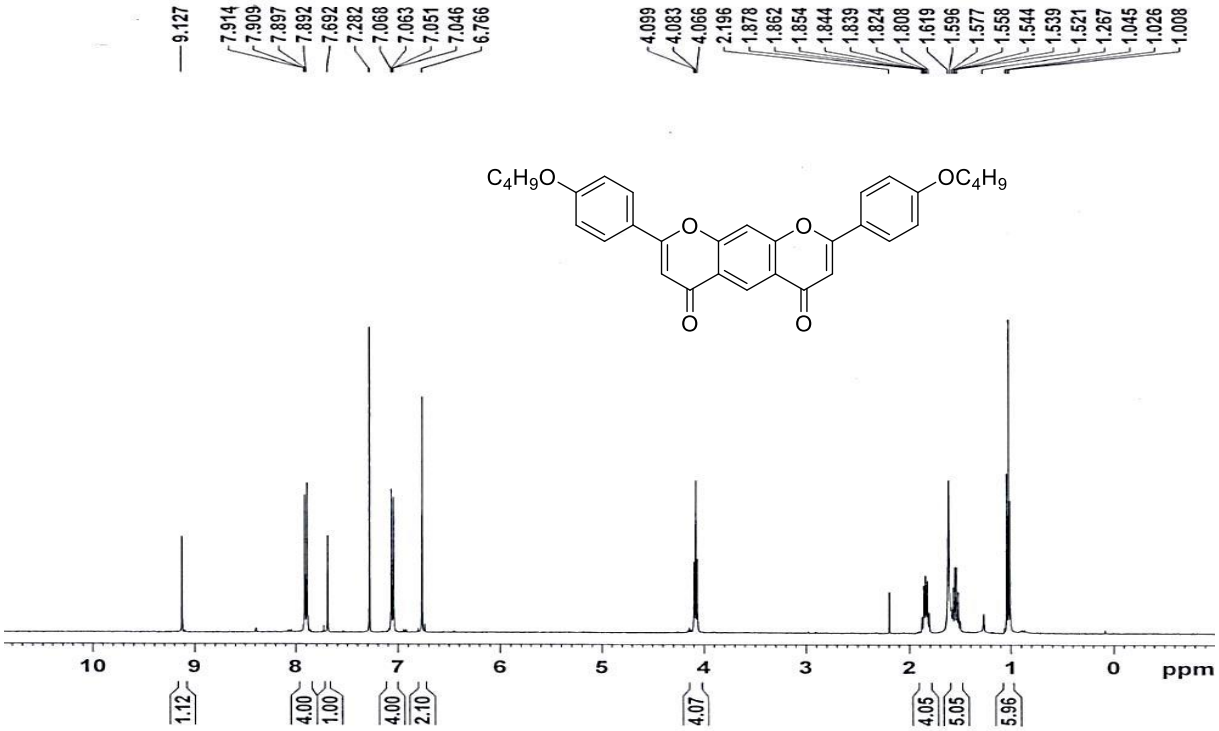


Figure-5.12.3 ^{13}C-NMR spectrum of 2,8-bis(4-butoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13b**) in $CDCl_3$

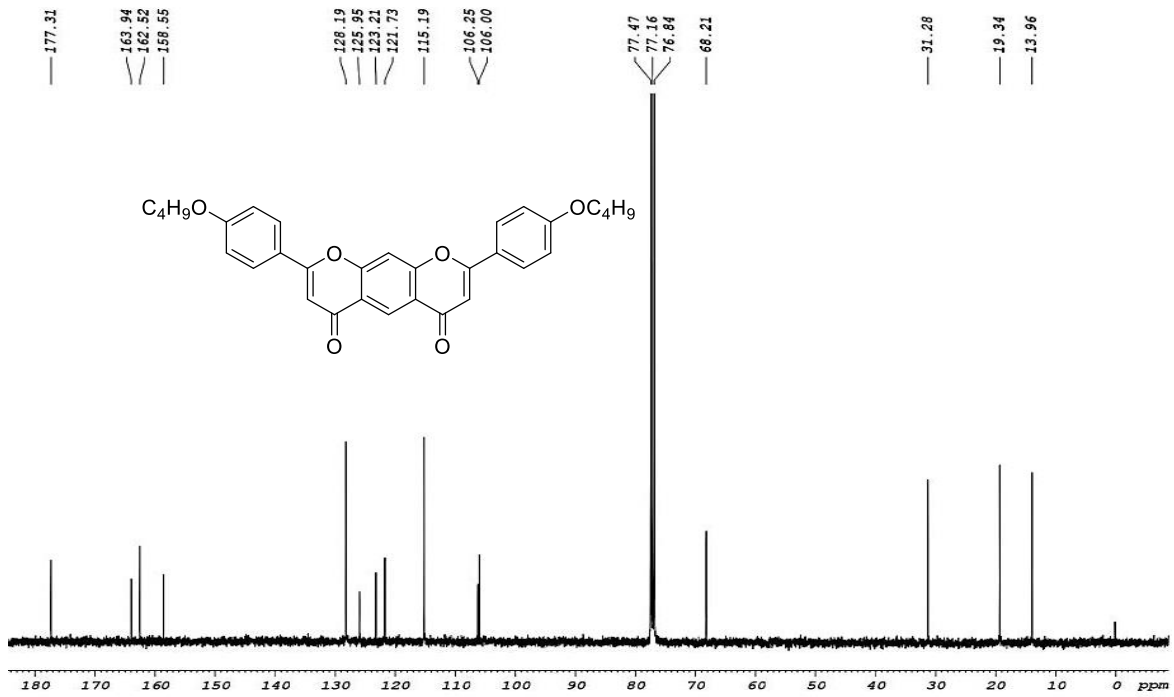


Figure-5.13.1 IR spectrum of 2,8-bis(4-(hexyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13c)

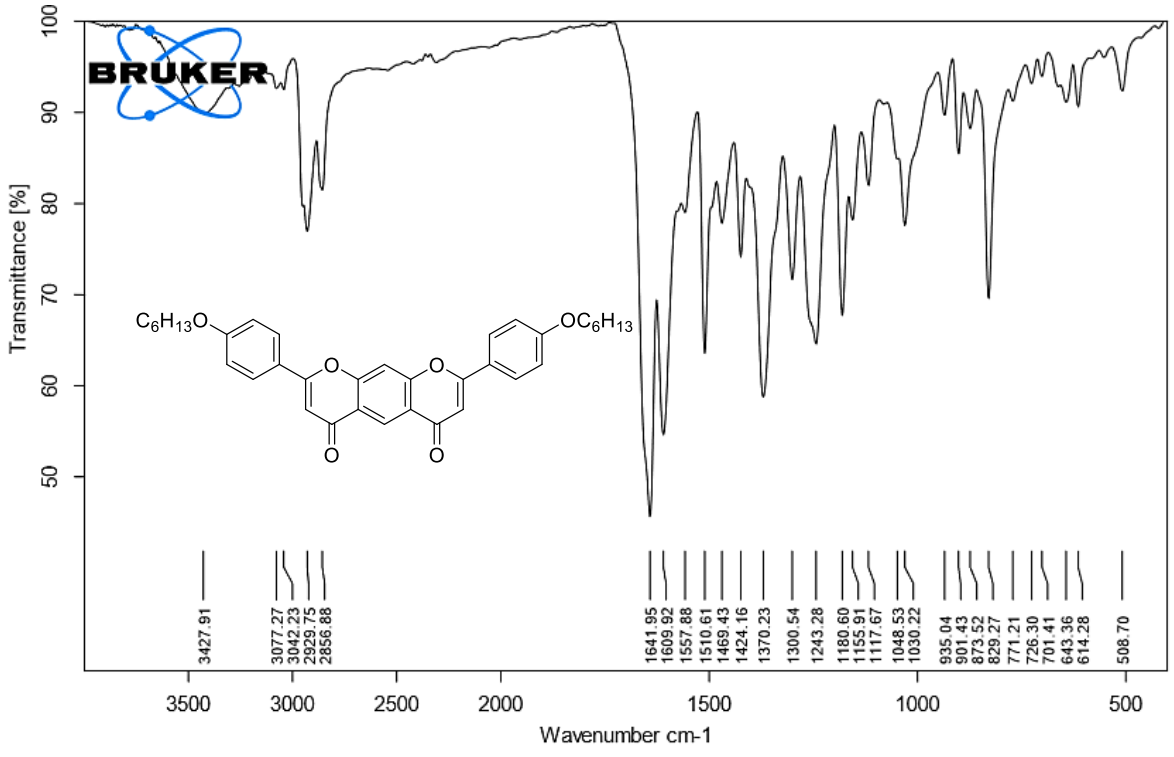


Figure-5.13.2 ^{1}H-NMR spectrum of 2,8-bis(4-(hexyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13c**) in $CDCl_3$

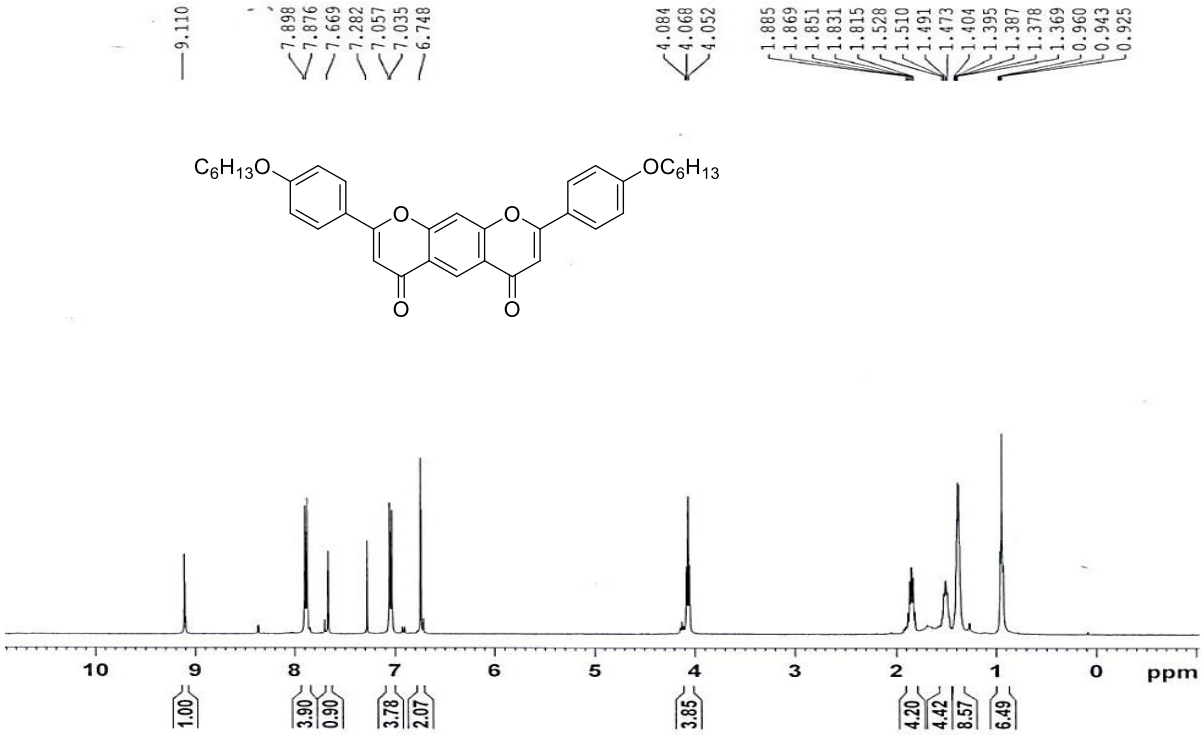


Figure-5.13.3 ^{13}C-NMR spectrum of 2,8-bis(4-(hexyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13c**) in $CDCl_3$

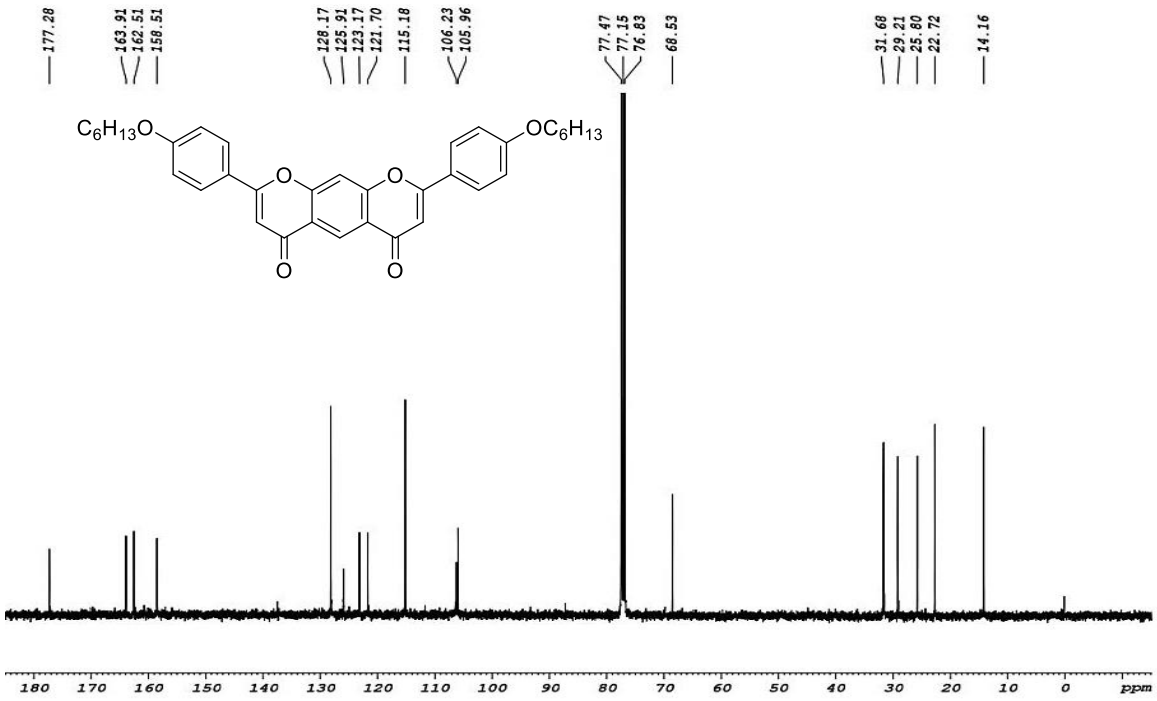


Figure-5.14.1 IR spectrum of 2,8-bis(4-(octyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13d**)

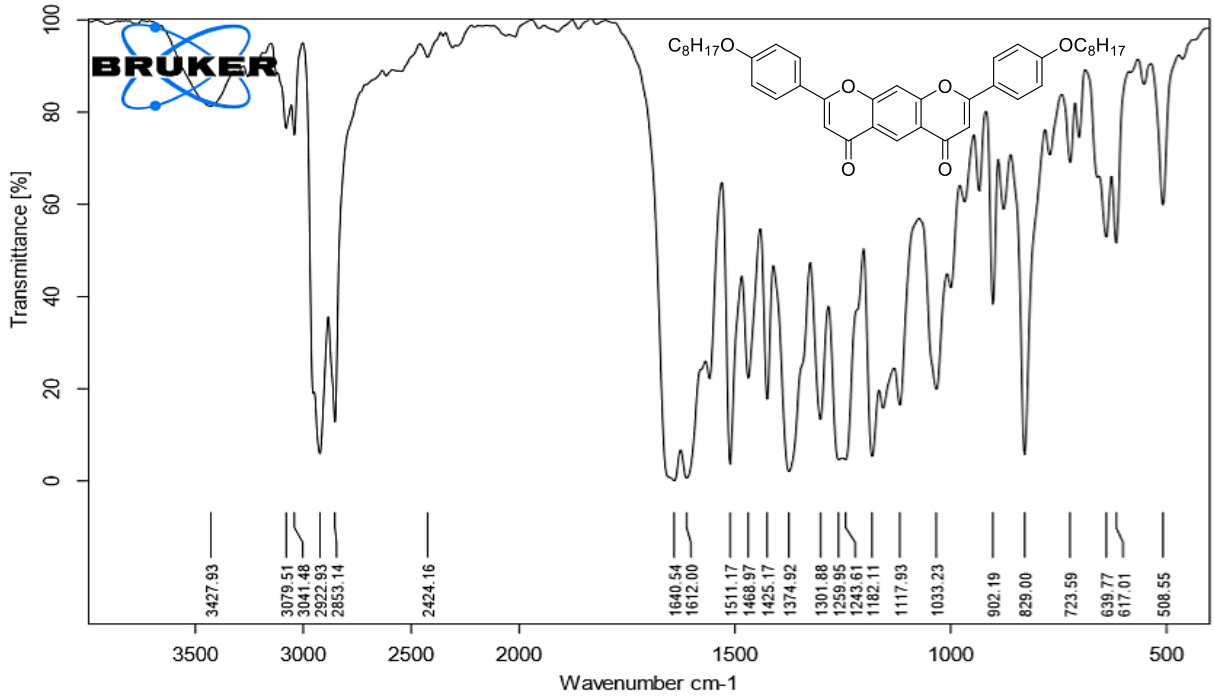


Figure-5.14.2 ^{1}H-NMR spectrum of 2,8-bis(4-(octyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13d**) in $CDCl_3$

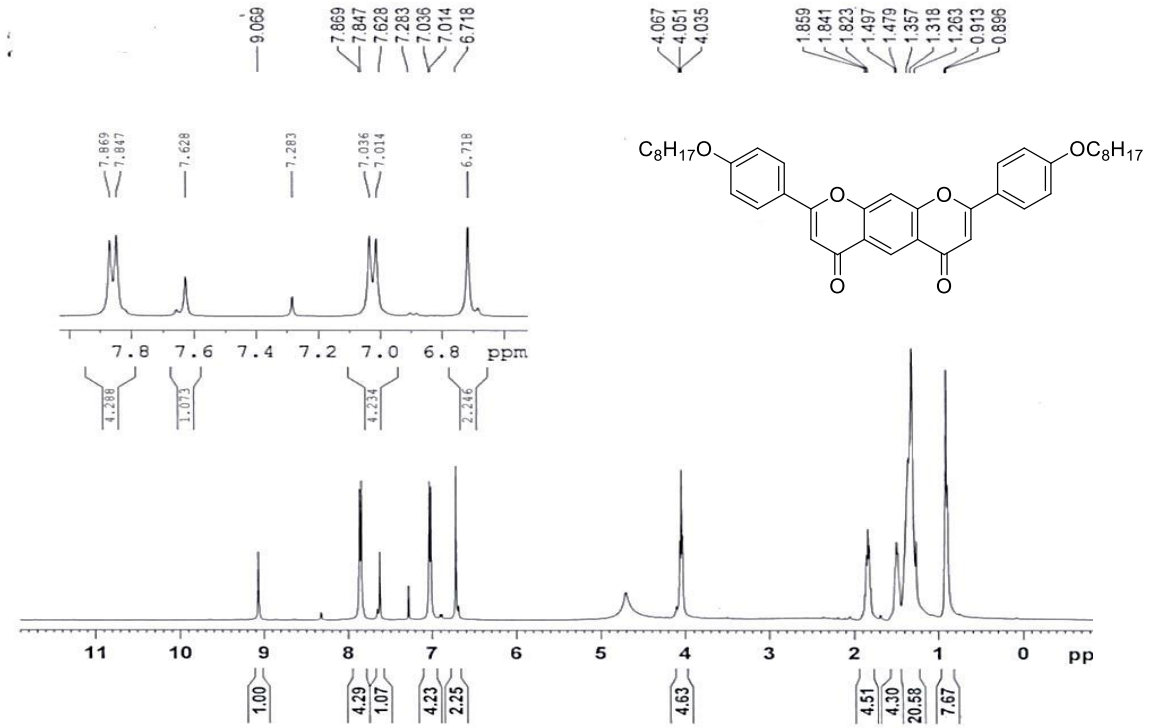


Figure-5.14.3 ^{13}C-NMR spectrum of 2,8-bis(4-(octyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13d**) in $CDCl_3$

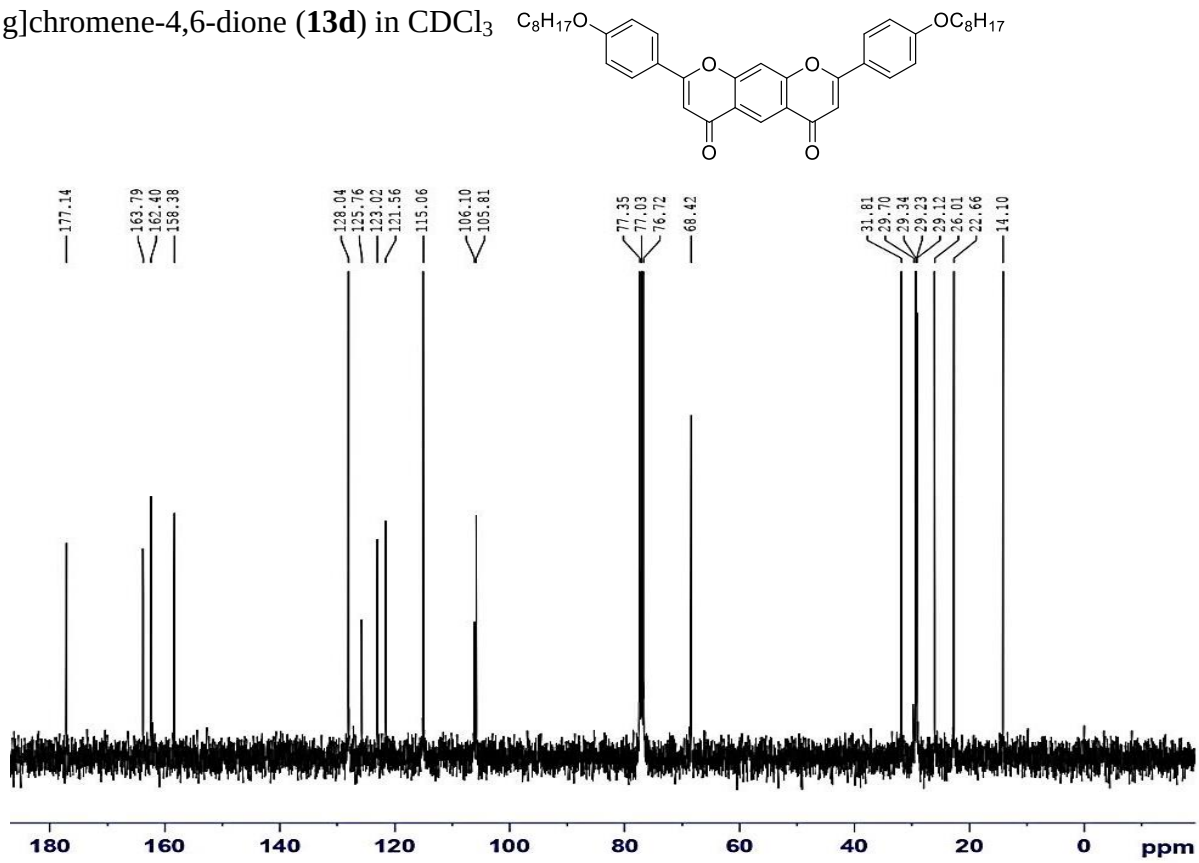
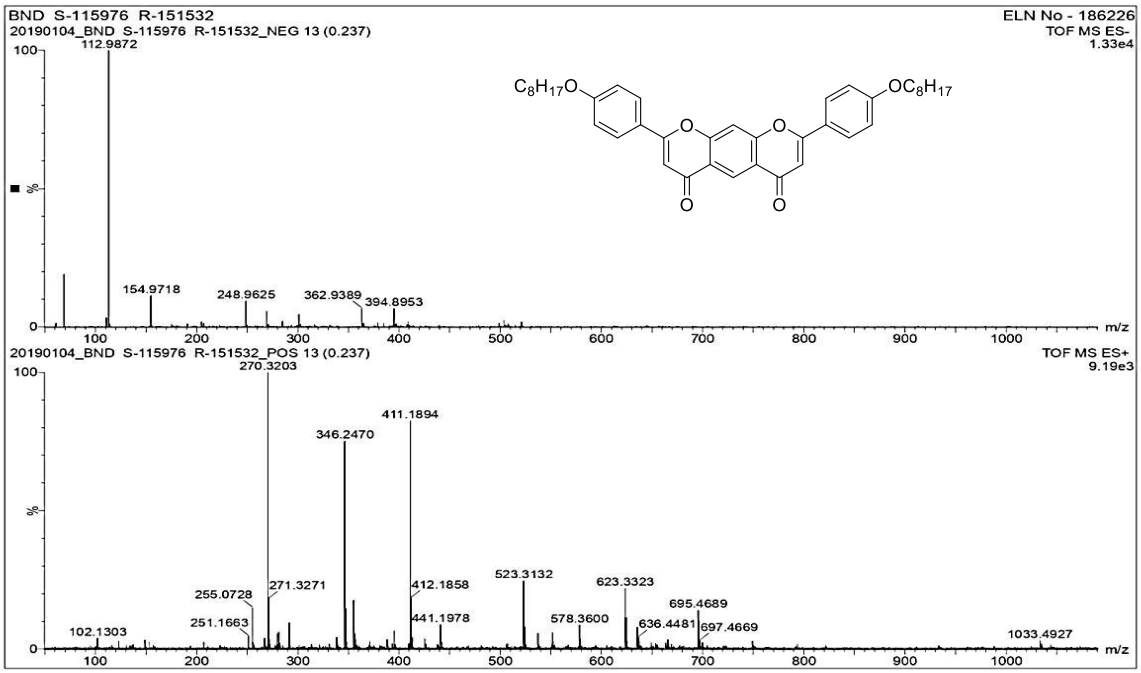


Figure-5.14.4 ESI-MS spectrum of 2,8-bis(4-(octyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**13d**) M+H peak at 623.33



5.2.2 Studies for mesogenic properties

Long alkyl chain containing compounds with rigid structure usually show liquid crystalline properties for liquid phase transitions. The compounds containing long alkyl chain **9a-d** and **13a-d** were chosen for liquid crystal phase study. Compounds were screened for phase transition temprature by differential scanning calorimetry which showed one sharp peak for crystalline to isotropic liquid phase with no phase transition.

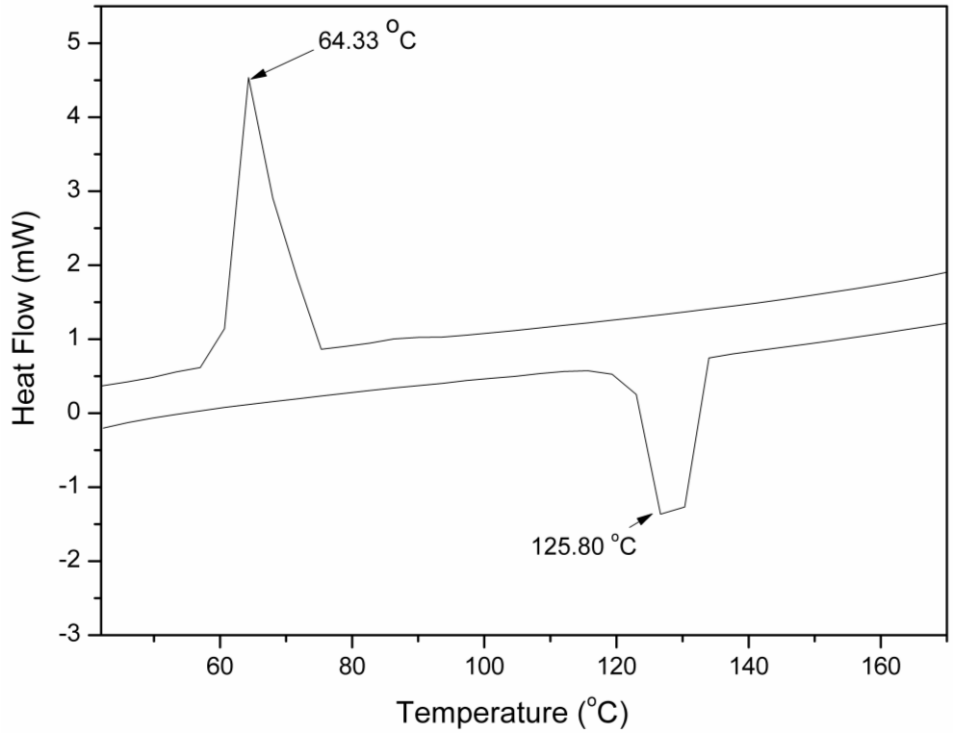
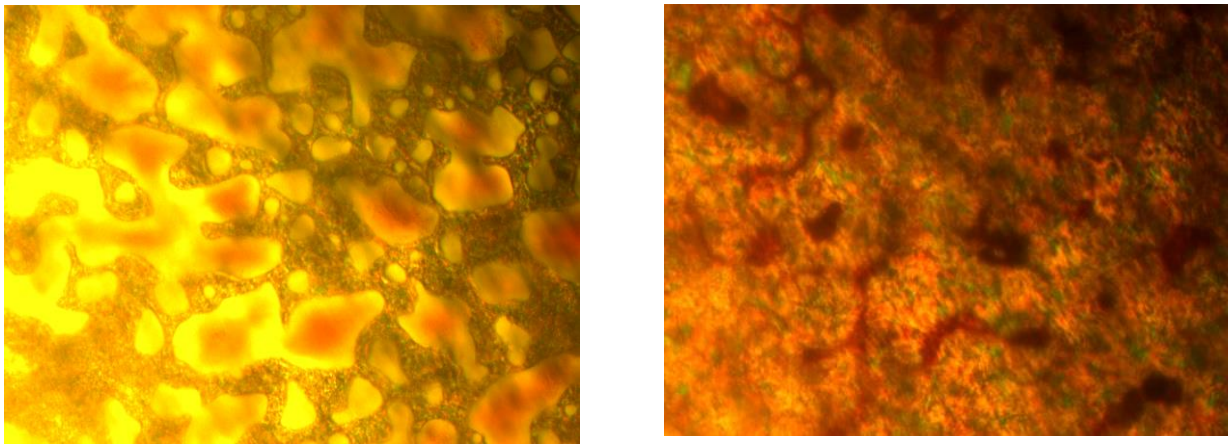


Figure-5.15: DSC of compound **9b** showing sharp melting point at 125.80 ^{o}C and crystallization at 64.33 ^{o}C

To confirm the findings polarizing optical microscope was used to observe photographs of compounds. Initially these compounds were subjected to heating rate of 20 ^{0}C/ min and 10 ^{0}C/ min to find phase transition between solid and liquid phase. Further, these compounds were studied at slower rate of heating and cooling rate of 5^{0}C/min and 2^{0}C/min to find the phase transition under POM observation.

Crystal changed to dark region isotropic during heating run, this observation indicated direct melting of the crystal phase to isotropic liquid phase. No liquid crystal texture was observed during cooling process, on cooling compounds directly crystallized into a stable state of crystal without any transitions within the crystal region, which is also supported by DSC studies.



(a) (b)

Figure-5.16 POM image of compound **9c** in heating (a) shows direct melting (92.2 ^{o}C) of compound and cooling (b) goes to crystallization (65.8 ^{o}C) with no phase

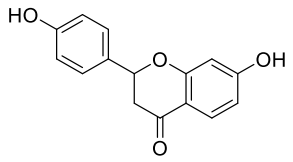
5.3 Conclusion

Synthesis of *n*-alkoxy derivatives of flavone and bisflavones is carried out for liquid crystalline properties. Compounds **9a-d** and **13a-d** were studied for liquid crystalline properties, by DSC studies and POM studies but didn't show any phase transition while going from crystalline solid to Isotropic liquid phase (melting). This may be due to very high melting temperatures of compound **13a-d**. Since melting points of compounds **13a-d** were very high and solubility of compounds was very poor and not showing liquid crystalline phases higher n-alkoxy derivatives were not synthesized. Flavone derivatives can show either anticancer activity or antioxidant activity. Since the solubility of these compounds **9a-d** and **13a-d** was very poor in DMSO, the anticancer activity as well as antioxidant activity was not observed.

5.5 Experimental

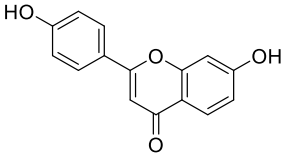
Reagent grade chemicals and solvents were purchased from commercial supplier and used after purification. TLC was performed on silica gel F254 plates (Merck). Acme's silica gel (60-120 mesh) was used for column chromatographic purification. All reactions were carried out in nitrogen atmosphere. Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX 1 spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 400 spectrometer (400 MHz) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. *J* values are in Hz. Mass spectra were determined by ESI-MS, using a Shimadzu LCMS 2020 apparatus. Elemental analyses were recorded on Thermosinnigan Flash 11-12 series EA. DSC, POM

Synthesis of 7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one (7)



To a solution of compound **6** (5.0 g, 32.894 mmol, 1 eq) in ethanol (50 mL) pyrrolidine (1.5 mL) was added followed by acetic acid (1.0 mL) and the reaction mixture was stirred for 10 min at room temperature. To this reaction mixture, 4-hydroxybenzaldehyde (4.0 g, 32.894 mmol,1 eq) was added and resulting mixture was refluxed at 78-80 ^{o}C for 48 h in an oil bath. The completion of reaction was checked by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and poured into ice water. The solid separated out was filtered, washed with cold water and dried. The product obtained was purified by column chromatography using pet ether:ethyl acetate (8:2) to (5:5) to give compound **7**. Yield: 60%, Melting point: 196-198 ^{o}C ^{1}H NMR **(**DMSO, 400 MHz) δ ppm : 2.63 (dd, *J*= 16.8, 3.2 Hz, 1H), 3.10 (dd, *J*= 16.8, 12.8 Hz, 1H), 5.42 (dd, *J*= 12.8, 2.8 Hz, 1H), 6.33 (d, *J*=2.4 Hz, 1H), 6.50 (dd, *J*=8.4, 2.0 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J* =8.8 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 43.52, 79.41, 102.94, 110.91, 113.98, 115.53, 128.74, 128.93, 129.78, 157.85, 163.62, 164.91, 190.80.

Synthesis of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (8)

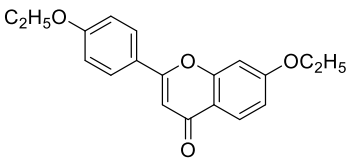


To a clear solution of compound **7** (3.0 g, 11.718 mmol, 1.0 eq) in DMSO (15 mL) I_2 (0.298 g, 1.172 mmol, 0.1 eq) was added and the reaction mixture was heated at 120 ^oC for 4-5 h in an oil bath. The completion of reaction was checked by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and poured into ice water. The reaction mixture was quenched by slow addition of saturated sodium thiosulphate solution. The solid separated out was filtered, washed with cold water and recrystallized from ethanol to give compound **8**. Yield: 50.33%, Melting point: > 250 ^oC; IR(KBr): 3214, 3066, 2929, 1630, 1601, 1562, 1503, 1447, 1385, 1271, 1223, 1178, 1143, 1115, 911, 828, 666 cm^{-1}, ^1H NMR (DMSO, 400 MHz) ppm: 6.28 (s, 1H), 6.41 (d, *J*=6.0 Hz 1H), 6.83 (d, *J*=6.8 Hz, 2H) 7.73 (s, 4H), 8.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 102.44, 104.45, 114.77, 115.87, 116.06, 121.77, 126.41, 128.07, 128.22, 157.36, 160.68, 162.41, 162.60, 176.24; $[M+H]^+$: 255.07

General method for alkylation of 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (9a-d)

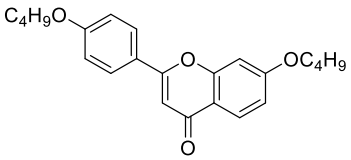
A mixture of compound **8** (1.968 mmol, 1.0 eq) and anhydrous potassium carbonate (4.92 mmol, 2.5 eq) in N,N-dimethyl formamide (DMF) (10.0 mL) was stirred for 10 min at rt. To this mixture, alkyl bromide (4.33 mmol, 2.2 eq) was added and resulting mixture was refluxed at 80 ^oC for 12 h. The completion of reaction was checked by TLC. After completion of reaction, reaction mixture was poured into crushed ice. The solid separated out was filtered, washed with cold water and recrystallized from ethanol to give compounds **9a-d**.

7-ethoxy-2-(4-ethoxyphenyl)-4H-chromen-4-one (9a)



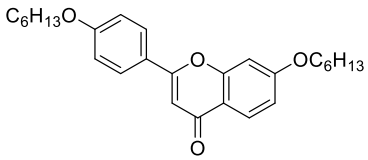
Color: light brown; Yield: 68.2%; M.P: 148-150 ^oC; IR(KBr): 3425, 3088, 3060, 2972, 2927, 1627, 1607, 1569, 1507, 1428, 1374, 1302, 1260, 1178, 1142, 1110, 1088, 1039, 963, 824, 667, 606 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) ppm: 1.45-1.51 (t, 6H), 4.09-4.18 (t, 4H), 6.67 (s, 1H), 6.92 (d, *J*=2.0 Hz, 1H), 6.97 (dd, *J*=8.8, 2.4 Hz, 1H), 6.99-7.01 (m, *J*=8.8, 1.6 Hz, 2H), 7.84 (d, *J*=8.8 Hz, 2H), 8.11 (d, *J*=8.8 Hz, 1H)

7-butoxy-2-(4-butoxyphenyl)-4H-chromen-4-one (9b)



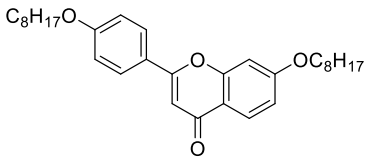
Color: light brown; Yield: 71.5%; M.P: 124-126 ^{o}C; IR(KBr): 3426, 3211, 2955, 2934, 2869, 1637, 1601, 1572, 1440, 1356, 1317, 1252, 1183, 1126, 1087, 1037, 1007, 971, 905, 839, 764, 669, 634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) ppm: 1.0-1.04 (t, 6H), 1.51-1.59 (m, 4H), 1.79-1.89 (m, 4H), 4.04-4.11 (t, 4H), 6.70 (s, 1H), 6.96 (d, *J*=2.0 Hz, 1H), 6.98 (dd, *J*=8.8, 2.4 Hz, 1H), 7.03 (d, *J*=8.8 Hz, 2H), 7.86 (d, *J*=8.8 Hz, 2H), 8.13 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.91, 13.94, 19.31, 31.15, 31.27, 68.08, 68.50, 100.92, 106.07, 114.65, 114.98, 117.71, 123.99, 127.00, 127.89, 158.01, 161.96, 163.19, 163.72, 178.01. $[M+H]^{+}$: 367.18 (M.W= 366.48)

7-(hexyloxy)-2-(4-(hexyloxy)phenyl)-4H-chromen-4-one (9c)



Color: off white; Yield: 64.9%; M.P: 90-92^{o}C; IR(KBr): 3520, 3433, 3276, 3231, 3068, 2954, 2930, 2853, 1624, 1567, 1505, 1465, 1362, 1288, 1254, 1180, 1131, 1068, 1010, 956, 909, 824, 726, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) ppm: 0.92-0.95 (t, 6H), 1.35-1.40 (m, 8H), 1.48-1.53(m, 4H), 1.81-1.88 (m, 4H), 4.03-4.10 (t, 4H), 6.69 (s, 1H), 6.95 (d, *J*=2.0 Hz, 1H), 6.98 (dd, *J*=8.4, 2.0 Hz, 1H), 7.01 (d, *J*=8.8 Hz, 2H), 7.86 (d, *J*=8.8 Hz, 2H), 8.12 (d, *J*=8.8 Hz, 1H); ^{13}C NMR($CDCl_3$, 100 MHz): 14.14, 22.70, 25.76, 25.79, 29.09, 29.21, 31.63, 31.67, 68.42, 68.83, 100.94, 106.06, 114.69, 115.00, 117.70, 123.98, 127.01, 127.92, 158.04, 161.98, 163.25, 163.75, 178.07.

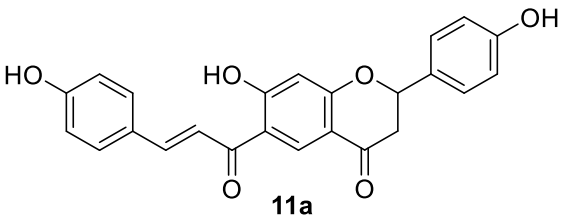
7-(Octyloxy)-2-(4-(octyloxy)phenyl)-4H-chromen-4-one (9d)



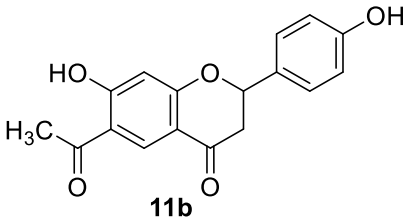
Color: off white, Yield: 60.12%, M.P: 56- 58 ^{o}C, IR (KBr): 3066, 2921, 2853, 1630, 1603, 1570, 1507, 1443, 1359, 1253, 1179, 1120, 1086, 1020, 956, 908, 864, 818, 761, 725, 671, 611 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) ppm: 0.89-0.92 (t, *J*=6.4 Hz, 6H), 1.26-1.37 (m, 16H), 1.45-1.50 (m, 4H), 1.79-1.89 (m, 4H), 4.02-4.09 (t, 4H), 6.68 (s,1H), 6.94 (d, J=2.4 Hz, 1H),

6.98 (dd, *J*= 8.8, 2.4 Hz, 1H), 7.01 (d, *J*=8.8 Hz, 2H), 7.85 (d, *J*=8.8 Hz, 2H), 8.11 (d, *J*=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 14.09, 22.65, 25.98, 26.00, 29.02, 29.14, 29.22, 29.31, 29.34, 29.70, 31.80, 68.30, 68.71, 100.83, 105.95, 114.52, 114.87, 117.62, 123.88, 126.88, 127.76, 157.90, 161.86, 163.04, 163.61, 177.83; $[M+H]^+$: 479.31

Synthesis of (E)-7-hydroxy-2-(4-hydroxyphenyl)-6-(3-(4-hydroxyphenyl) acryloyl)chroman-4-one (11a) and 6-acetyl-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-one (11b)



11a

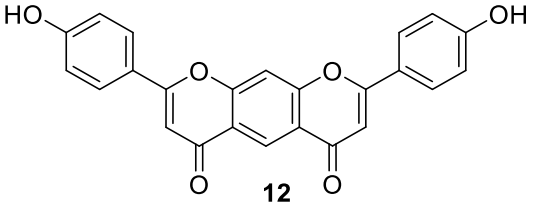


11b

To a clear solution of compound **10** (5.0 g, 25.77 mmol) in ethanol (50 mL), 4-hydroxybenzaldehyde (6.3 g, 51.54 mmol, 2.0 eq) was added. To this mixture, pyrrolidine (2.0 mL) and acetic acid (2.0 mL) were added to the flask and refluxed at 78-80 ^{o}C for 48 h. The completion of reaction was checked by TLC. The reaction mixture was poured into cold water and the product was filtered and dried. The crude compound was purified by column chromatography to give compound **11a** (eluted out in 30:70 ethylacetate:pet.ether) and compound **11b** (eluted out in 50:50 ethylacetate:pet.ether).

(E)-1-(7-hydroxy-2-(4-hydroxyphenyl)chroman-6-yl)-3-(4-hydroxyphenyl)prop-2-en-1-one (11a) Color: Light yellow, Yield: 25%, M. P: 242-244 ^{o}C; IR (KBr) : 3381-3158 (br), 2823, 1675, 1635, 1554, 1514, 1486, 1450, 1363, 1277, 1210, 1168, 1108, 1061, 980, 826, 756, 674, 647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm : 2.78 (dd, *J*=16.8,2.8 Hz, 1H), 3.28 (dd, *J*=16.8, 12.4 Hz, 1H), 5.61 (dd, *J*=12.4, 2.8 Hz, 1H), 6.5 (s, 1H), 6.80-6.87 (m, 4H), 7.35 (d, *J*=8.8 Hz, 2H), 7.79-7.81(m, 4H), 8.62 (s, 1H), 9.62 (s, 1H), 10.21 (s, 1H), 13.57 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz): 43.47, 79.79, 104.67, 114.55, 115.69, 116.37, 116.71, 117.95, 125.98, 128.89, 129.06, 131.66, 132.18, 146.43, 158.31, 161.16, 166.57, 168.56, 190.40, 192.79; $[M+H]^+$=403.10, (M.W= 402)

Synthesis of 2,8-bis(4-hydroxyphenyl)pyrano[3,2-g]chromene-4,6-dione (12)



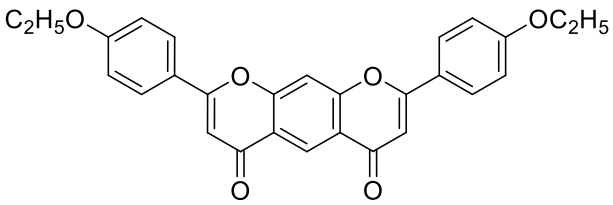
12

To a clear solution of compound **11a** (0.5 g, 1.24 mmol) in DMSO (5 mL) in round bottom flask, I_2 (0.063g, 0.248 mmol, 20 mol%) was added. The mixture was heated at 130^o C for 4 hours. The completion of reaction was checked by TLC. The reaction mixture was allowed to cool to room temperature and then it was poured onto crushed ice. The reaction mixture was quenched by slow addition of sodium thiosulfate solution. The precipitated solid was filtered by suction, dried, boiled in ethanol and filtered hot to give compound **12**. Color: light brown, Yield: 92%, M.P > 300 ^{o}C; IR (KBr) : 3210 (br), 2820, 2619, 1637, 1510, 1445, 1371, 1250, 1177, 1115, 901, 833, 603 cm^{-1} (DMSO, 400 MHz) δ ppm : 6.86 (s, 2H), 6.95 (d, *J*=8.8 Hz, 4H), 7.97 (d, *J*=8.8 Hz, 4H), 8.05 (s, 1H), 8.56 (s, 1H); $[M+H]^+$=399.08

General method for synthesis of (13a-d): by alkylation of 2,8-bis(4-hydroxyphenyl)pyrano[3,2-g]chromene-4,6-dione (12)

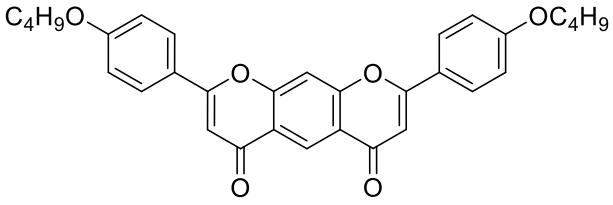
To a solution of compound **12** (0.2 g, 0.5 mmol, 1 eq) in anhydrous DMF (10 mL), anhydrous K_2CO_3 (0.185 g, 1.25 mmol, 2.5 eq) was added and then the reaction mixture was stirred for 15min to obtain a clear orange solution. To this, alkyl bromides (1.1 mmol, 2.2 eq) were added to the stirred solution dropwise. The reaction mixture was heated at 68-70 ^{o}C for 16h. The completion of reaction was checked by TLC. The reaction mixture was cooled to room temperature and poured into ice cold water to give solid. The solid was filtered with vacuum and dried. The solid was dissolved in DCM (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give compounds **13a-d** as yellow solid.

2,8-bis(4-ethoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13a)



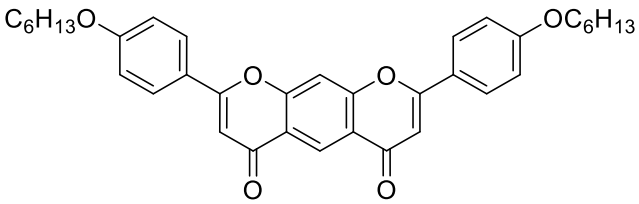
Color: off white; Yield : 76.4 %, M. P : 260-262^{o}C; IR(KBr): 3072, 2978, 2930, 2884, 1647, 1608, 1510, 1475, 1394, 1302, 1247, 1184, 1118, 1043, 923, 900, 872, 766, 702, 637, 547 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm : 1.36 (br s, 6H), 4.12 (br s, 4H), 6.97 (s, 2H), 7.10 (s, 4H), 8.04-8.11(m, 5H), 8.56 (s, 1H).

2,8-bis(4-butoxyphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13b)



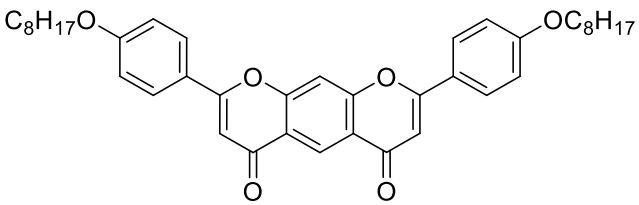
Color: off white; Yield : 58.8%, M. P : 228-230^{o}C; IR(KBr): 3076, 3045, 2956, 2934, 2869, 1638, 1606, 1571, 1557, 1507, 1420, 1368, 1299, 1240, 1176, 1114, 1069, 1004, 902, 854, 828, 661, 613 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm : 1.03 (t, *J*=7.6 Hz, 6H), 1.52-1.62 (m, 4H), 1.81-1.88 (m, 4H), 4.08 (t, *J*=6.4 Hz, 4H), 6.76 (s, 2H), 7.06 (d, *J*=8.8 Hz, 4H), 7.69 (s, 1H), 7.90 (d, *J*=8.8 Hz, 4H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 13.96, 19.34, 31.28, 68.21, 106.00, 106.25, 115.19, 121.73, 123.21, 125.95, 128.19, 158.55, 162.52, 163.94, 177.31

2,8-bis(4-(hexyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13c)



Color: light brown; Yield : 65.2 %, M. P : 218-220 ^{o}C; IR(KBr): 3077, 3042, 2929, 2856, 1641, 1609, 1557, 1510, 1469, 1424, 1370, 1243, 1180, 1155, 1117, 1048, 1030, 935, 901, 873, 829, 726, 643 cm^{-}1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm : 0.94 (t, *J*=6.8 Hz, 6H), 1.37-1.40 (s, 8H), 1.47-1.53 (m, 4H), 1.81-1.88 (m, 4H), 4.06 (t, *J*=6.4 Hz, 4H), 6.75 (s, 2H), 7.04 (d, *J*=8.8 Hz, 4H), 7.67 (s, 1H), 7.88 (d, *J*=8.8 Hz, 4H), 9.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 14.16, 22.72, 25.80, 29.21, 31.68, 68.53, 105.96, 106.23, 115.18, 121.70, 123.17, 125.91, 128.17, 158.51, 162.51, 163.91, 177.28

2,8-bis(4-(octyloxy)phenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (13d)



Color: white; Yield : 68 %, M. P : Above 256-258 ^{o}C; IR (KBr): 3079,3041, 2923, 2853, 1641, 1612, 1511, 1469, 1425, 1375, 1302, 1260, 1244, 1182, 1118, 1033, 902, 829, 640,617 cm^{-1}; ^{1}H ($CDCl_3$, 400 MHz) δ ppm : 0.89-0.92 (t, *J*=6.8 Hz, 6H), 1.26-1.36 (m, 16H), 1.48-1.50 (m, 4H), 1.82-1.86 (m, 4H), 4.05 (t , *J*=6.4Hz, 4H), 6.72 (s, 2H), 7.02 (d, J=8.8 Hz, 4H), 7.63 (s, 1H), 7.85 (d, *J*=8.8 Hz, 4H), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 14.10, 22.66, 26.01, 29.12, 29.23, 29.34, 29.70, 31.81, 68.42, 105.81, 106.10, 115.06, 121.56, 123.02, 125.76, 128.04, 158.38, 162.40, 163.79, 177.14; $[M+H]^{+}$ 623.33, (M.W= 622.33)

5.5 References

[1] J.A. Seijas, M.P. Vazques-Tato, R. Carballido-Reboredo, *J. Org. Chem*. **2005**, *70*, 2855.

[2] E. Middleton, C. Kandaswamy, T.C. Theohardes, *Pharmacol. Rev.* **2000**, *52*, 673.

[3] K. Suresh Babu, T. Haribabu, J. Madhusudana Rao, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 221.

[4] Q. Wang, X. Ge, X. Tian, Y. Zhang, J. Zhang, P. Zhang, *Biomed Rep*. **2013**, *1*, 697

[5] J. Zhang, Y. Lv, W. Zhang, H.Ding, R. Liu, Y. Zhao, G, Zhang, Z. Tian, *Talanta*. **2016**, *146*, 41.

[6] B. Liu, J. Wang, G. Zhang, R. Bai, Y. Pang, *ACS Appl Mater Interfaces.* **2014**, *6*, 4402.

[7] H.T. Srinivasa, H. N. Harishkumar, B.S. Palakshamurthy, *J Mol Struc.* 1131, 2017, 97.

[8] T. Hirose, K. Tsuya, T. Nishigaki, E. Idaka, S. Yano, *Liq Cryst.* **1989**, 4, 653.

[9] D. J. Timmons, A. J. Jordan, A. A. Kirchon, N. S. Murthy, T. J. Siemers, D. P. Harrison, C. Slebodnick, *Liq Cryst.* **2017**, *44*, 1436.

[10] A. T. Mohammad, H. T. Srinivasa, R. Y. Alrawi, *liq cryst*, **2019**, DOI: 10.1080/02678292.2019.1622045

[11] J. R. Killelba, H. G. Lindwall, *J. Am. Chem. Soc.*, **1948**, *70* , 428.