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# ANTIOXIDANT ACTIVITIES OF IMINOCHROMENE DERIVATIVES WITH ADD ALKYL TAIL: SYNTHESIS AND CHARACTERISATION

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**Abstract**

The reaction between substituted 4-hydroxy benzaldehyde, active methlyene compounds imino chromene derivatives. Structures of these were established upon the basis of IR, 1HNMR, 13CNMR, and MASS data. In vitro, antioxidants activities of these compounds against super oxide anion radical, nitric oxide radical, DPPH radical and hydrogen peroxide were evaluated and compared with standard natural antioxidants ascorbic acid.

**Key words:** chromenes, imines, amines, antioxidants

## Introduction

Multicomponent reactions (MCRS) are reactions where numerous reactants involved in single synthetic operation and give new compounds.1 This type of reactions avoids purification process and often wide variety of complex molecule in a single step, inturn it is very useful for saving solvent and reagents. Among many heterocyclic compounds, chromenes are very important due to its biological activity such as antioxidants,2 anticancer,anti-microbial, 3 anti-inflammatory,4 anti-HIV,5 and anti-tumor,6 alzimer disease, 7 antihypotensive8 and antileishmanial.9 There are many reports shown that synthesis of different chromene derivatives and its applications (Figure 1).1, 10, 11 A Knoevenagel condensation is the reaction between salicylaldehyde with active methylene compounds followed by intramolecular cyclisation to give imino derivatives 11. As per reports, different products are obtained by control of a solvent, ratio of reagents and temperature3etc., Due to importance of these chromene derivatives, numerous green approaches have been developed under distinct conditions like thermal heating, microwave, ultrasonic, electrochemical, infrared, and solvent free conditions. We could not find many reports on variation of an alkyl side chain to see the effect on antioxidant properties of chromene derivatives. So we are motivated to synthesis imino and amino chromenes by taking alkylated aldehyde and malonitrile. Currently, many investigations are going on effect of free radicals in biological systems such as lipids, DNA and protein, also create many diseases like atherosclerosis, neurodegenerative disease, rheumatoid arthritis, age related disease, cancer initiation and tumor.12, 13, 14 It is necessary to keep a proper level of natural antioxidant such as vitamin E, C and glutathione in a biological system in order to avoid serious health problems.15, 16, 17 All these health problems are caused by action of free radical oxygen (ROS) and reactive nitrogen (RNS) species, commonly known as (RSs).18, 19

## Results and Discussion

### Antioxidant activities

In the present study, antioxidant potential of synthesized 3-cyano-2-imino-2H-chromen-7-yl 4-(alkyloxy)benzoate (6a-h) were studied using DPPH, NO•,O2-•, H2O2 radical scavenging

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Table II. Antioxidant activity of chromene derivatives (6a-h)

| | $IC_{50}(\mu M)$ | | | |
|---|---|---|---|---|
| **SNo** | **Entry** | **DPPH** | **NO•** | **$O_2^{-\bullet}$** | **$H_2O_2$** |
| 1 | Vitamin C | 32.52±0.11 | 55.00±0.12 | 52.00±0.56 | 43.00±0.65 |
| 2 | 6a | 27.16±0.41 | 22.48±0.41 | 35.04±0.49 | 42.48±0.82 |
| 3 | 6b | 27.95±0.32 | 24.62±0.03 | 31.96±0.38 | 35.67±0.15 |
| 4 | 6c | 27.93±0.36 | 27.72±0.36 | 31.08±0.40 | 34.88±0.38 |
| 5 | 6d | 28.75±0.18 | 27.37±0.92 | 28.90±0.11 | 33.17±0.54 |
| 6 | 6e | 28.11±0.22 | 27.23±0.23 | 30.83±0.92 | 33.15±0.45 |
| 7 | 6f | 30.65±0.38 | 27.28±0.53 | 29.76±0.36 | 29.76±0.43 |
| 8 | 6g | 31.04±0.58 | 29.13±0.35 | 28.48±0.53 | 30.60±0.82 |
| 9 | 6h | 31.04±0.45 | 33.72±0.18 | 27.96±0.13 | 26.89±0.22 |

technique by spectrophotometrically. Radical scavenging activities of all derivatives weredetermined from the interacting ability of derivatives with DPPH, NO•,O2-•, H2O2 radicals. The antioxidant activities were expressed as 50% inhibitory concentration values in Table 2,

Figure 2, and compared with that of standard ascorbic acid. The hydrogen donating ability of amines and imine groups present as part of all synthesized derivativesin the series 5a-h and 6a-h might be responsible for their antioxidantproperties. LowerIC50valuegivesbetterradical-scavengingactivity.Fromthetable,itwasclearthatalmostallthecompounds were shownradicalscavengingactivitiesinDPPH•assay.Itwasimportanttonotethat6a,6band6c

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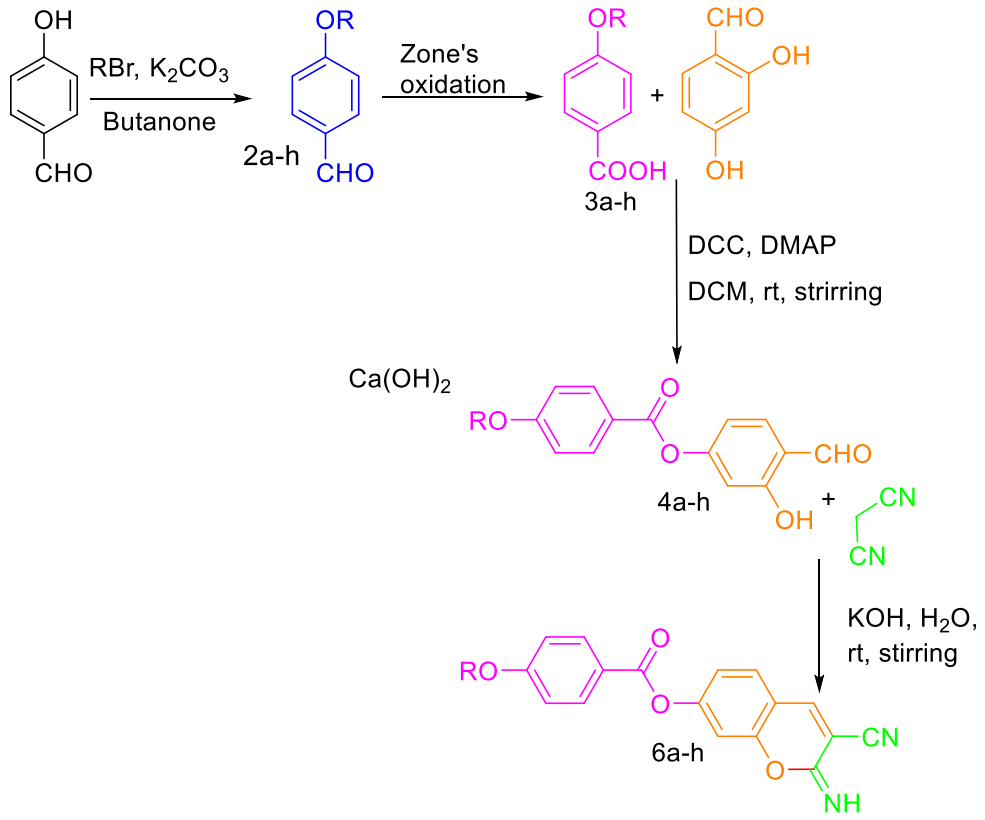


R= $C_5H_{11}$, $C_6H_{13}$, $C_7H_{15}$, $C_8H_{17}$, $C_{10}H_{21}$,$C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$

Scheme 1. Synthetic procedures for series5 and 6

shownbetter DPPH scavenging activitythanvitaminCwithIC50values27.16,27.95and27.93µMrespectively.TheDPPH•activitiesoftestedwerefoundtobeinthedecreasingorderof6a,6c,6b,6e,6d,6f, 6g and6h. We can find in caseof NO•radicalscavenging activities, compound 6a and 6b have very low IC50 values are 22.48 and 24.52 µM respectively. The decreasing orders of antioxidant activityof these compounds were 6a, 6b, 6e, 6d, 6c, 6f, 6g and 6h. TheresultsoftheNO•assaywereexpressedasIC50valuesinTable2revealedthat6h,6g showedbettersuper oxide radicalscavengingactivitythannaturalantioxidantvitaminCwithIC50of27.96,and28.48µMrespectively.Surprisingly,IC50valuesofallsynthesizedderivativeswerelowerthanIC50VitaminC.Thesuperoxide anion radicalscavengingactivitiesoftestedwasfoundtobeinthedecreasingorderof6h, 6g,6d,6f,6e,6c,6b,6aandVitaminC.Thehydrogenperoxideradicalscavengingactivitiesoftestedwasfoundtobeinthedecreasingorderof6h,6f,6g,6e,6d,6c,6b,6aandVitaminC.

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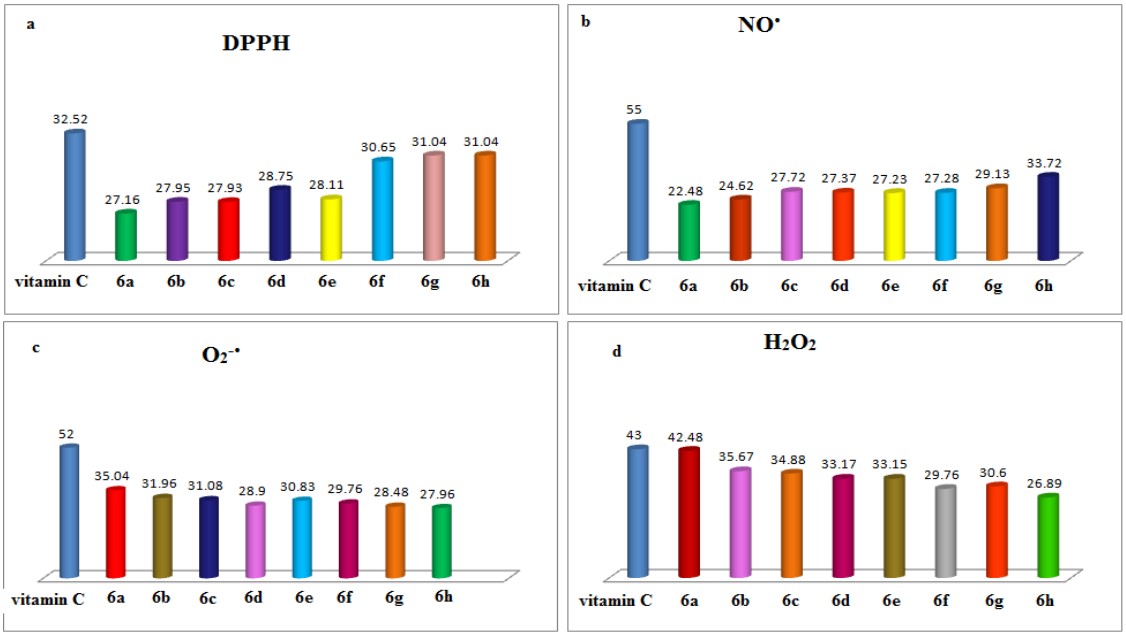


Fig.2.Antioxidant activity of 6a-h in IC50 values

**Experimental**

1HNMRspectrawererecordedusingBruker(300MHz)spectrometer.Forthe1HNMRspectra,thechemicalshiftsarereportedinppmrelativetoSiMe4(TMS)asaninternalstandardandcouplingconstantsarepresentedinHz.InfraredspectrawererecordedonJASCO-FTIRspectrometer(4000-400cm-1);thespectralpositionsaregiveninwavenumbers(cm-1).Electrosprayionizationmassspectrometry(ESI-MS)analysiswasperformedinthenegativeionmodeonaliquidchromatography-iontrapmassspectrometer(LCQFleet,ThermoFisherInstrumentsLimited,US). Spectra of these compounds were given in supplementary information. TheDPPHradicalscavengingactivityofthecompoundswasmeasuredaccordingtothemethodofBlios.20Theassayofnitricoxide(NO·)scavengingactivityismeasuredbasedonmethodreported.21Theabilityofthecompoundstoscavengehydrogenperoxidewasdeterminedusingthemethodavailableinliterature.22 Thesuperoxideanionradical(O2-·)scavengingassaywasbasedonthecapacityofthecomplexestoinhibitformazanformationbyscavengingthesuperoxideradicalsgeneratedintheriboflavin-light-NBTsystem.23

**3.5 General procedure for the preparation of 3-cyano-2imino-2H-chromen-7-yl-4(pentyloxy) benzoate: 6a-h**

To a stirred solution of 4-formyl-3-hydroxy phenyl 4-(pentyloxy)benzoate (0.08 Mol, 1eq) and malononitrile (0.081 Mol, 1eq) in water (50 mL) was added excess amount of KOH. The resulting mixture was stirred for 5 min at room temperature. The formed precipitate was isolated by filtration and washed with ethanol to get pure product as yellow solid and was recrystallized from ethanol to obtain a white solid.

**3.5a 3-cyano-2-imino-2H-chromen-7-yl 4-(methyloxy) benzoate (6a)**

Mp: 170ºC; Y=70%;white solid;IR, vmax(KBr, cm-1):3433.85(NH), 2227.98 (C≡N), 1602.66 (-C=C-), 1724 (C=O), 3058Ar(C-H), 2883.69Alphatic (C-H); 1H NMR( 300MHz, DMSO-d6): δ= 8.58 (1H, s, -C=NH ), 8.04 (d, J=9.0Hz, 2H, ArH), 7.76 (d, J=9.0Hz, 1H, ArH), 7.61 (s, 1H, C=CH), 7.27-7.25 (m, 2H, ArH), 6.93 (d, J=9.0Hz, 2H, ArH), 3.98 (t, J=6.0Hz, 2H,O-CH2), 1.78-1.69 (m, 2H, CH2), 1.38-1.32 (m, 4H, CH2) 0.85 (t, J=9.0Hz, 3H, -CH3);13C-NMR (75 MHz, DMSO-d6): 164.08, 156.53, 155.29, 152.43, 132.51, 130.86, 119.97, 115.01, 114.59, 110.72, 101.69, 68.37, 28.63, 28.00, 22.30, 14.02;MS(EI): m/z=377.17(M+).

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**3.5b 3-cyano-2-imino-2H-chromen-7-yl 4-(penyloxy) benzoate (6b);**

Mp: 132ºC; Y=75%;white solid;IR, νmax(KBr, cm-1):3446.64(NH),2227.98 (C≡N), 1609.06 (-C=C-), 1733.80 (C=O), 3058Ar(C-H), 2874.50Alphatic (C-H);1H NMR( 300MHz, DMSO-d6):δ=8.59 (1H, s, C=NH ) 8.12 (d, J=9.0Hz, 2H, ArH), 7.8 (d, J=6.0Hz,1H, ArH), 7.58 (s, 1H, C=CH), 7.36 (m, 2H, ArH), 7.02 (d, J=6.0Hz, 2H, ArH), 4.09 (t, J=6.0Hz, 2H,O-CH2), 1.83 (m, 2H, CH2), 1.50 (m, 6H), 0.93 (t, J=6.0Hz, 3H, -CH3); 13CNMR(75 MHz, DMSO-d6): 161.26, 157.01, 140.04, 137.21, 124.68, 119.28, 115.44, 73.09, 58.44, 36.10, 33.60, 31.22, 30.21, 27.16, 18.71; MS (EI): m/z=391.50(M+).

**3.5c 3-cyano-2-imino-2H-chromen-7-yl 4-(pentyloxy) benzoate (6c);**

Mp: 140ºC; Y=85%;white solid;IR, νmax(KBr, cm-1): 3456.24(NH), 2227.98 (C≡N), 1613.86 (-C=C-), 1738.60 (C=O),3058Ar(C-H), 2883.69Alphatic (C-H);1H NMR( 300MHz, DMSO-d6): δ=8.69 (1H, s, C=NH ), 8.15 (d, J=9.0Hz, 2H, ArH), 7.87 (d, J=6.0Hz,1H, ArH), 7.70 (s, 1H, C=CH), 7.39 (m, 2H, ArH),7.06 (d, J=9.0Hz, 2H, ArH), 4.10 (t, J=6.0Hz, 2H,OCH2), 1.86 (m, 2H, CH2) 1.51 (m ,9H), 0.93 (t, J=6.0Hz, 3H, CH3);13CNMR(75 MHz, DMSO-d6):164.27, 163.66, 156.80, 156.10, 155.55, 132.58, 130.06, 125.06, 120.17, 120.01, 114.70, 114.64, 111.05, 102.39, 68.52, 31.71, 29.05, 28.96, 25.91, 22.54, 13.98; MS(EI):m/z= 405.17(M+).

**3.5d 3-cyano-2-imino-2H-chromen-7-yl 4-(heptyloxy) benzoate (6d);**

Mp: 120ºC; Y=80%;white solid;IR, νmax(KBr, cm-1): 3437.05(NH), 2227.81 (C≡N), 1725.81 (-C=C-), 1610.60 (C=O).3078.80Ar(C-H), 2874.10Alphatic (C-H);1H–NMR( 300MHz, DMSO-d6): δ= 8.69 (1H, s, C=NH) 8.13 (d, J=9.0Hz, 2H, ArH), 7.86 (d, J=9.0Hz,1H, ArH), 7.72 (s, 1H, -C=CH), 7.37-7.35 (m, 2H, ArH), 7.03 (d, J=9.0Hz, 2H, ArH), 4.08 (t, J=6.0Hz, 2H,OCH2), 1.85-1.80 (m, 2H, CH2) 1.49-1.30 (m,10H), 0.89 (t, J=6.0Hz, 3H, CH3); 13C NMR(75 MHz, DMSO-d6):164.30,163.68, 156.82, 156.10, 155.58, 151.04, 132.60, 130.04, 120.19, 120.02, 115.47, 114.66, 113.47, 111.08, 102.45, 68.54, 31.77, 29.28, 25.96, 22.61, 14.02;MS(EI):m/z= 442.25(M+).

**3.5e 3-cyano-2-imino-2H-chromen-7-yl 4-(nonanyloxy) benzoate (6e);**

Mp: 116ºC; Y=80%;white solid;IR, νmax(KBr, cm-1): 3437.05(NH), 2226.38 (C≡N), 1612.26 (-C=C-), 1737(C=O), 3078.80Ar(C-H), 2862.90Alphatic (C-H).1H NMR (300MHz, DMSO-d6): δ= 8.61 (1H, s, C=NH ), 8.13 (d, J=9.0Hz, 2H, ArH), 7.82 (d, J=6.0Hz,1H, ArH), 7.60 (s, 1H, -C=CH), 7.36-7.35 (m, 2H, ArH), 7.02(d, J=9.0Hz, 2H, ArH), 4.07 (t, J=6.0Hz, 2H,O-CH2), 1.85-1.78 (m, 2H, CH2) 1.48-1.28(m,14H, CH2), 0.88 (t, J=6.9Hz, 3H, CH3);13CNMR(75 MHz, DMSO-d6): 164.44, 164.03, 163.95, 159.66, 155.67, 133.05, 132.92, 120.36, 115.07, 111.09, 102.01, 68.80, 32.18, 29.83, 29.59, 29.37, 26.28, 22.98, 14.63;MS (EI):m/z= 447.33(M+).

**3.5f 3-cyano-2-imino-2H-chromen-7-yl 4-(undecyloxy) benzoate (6f);**

Mp: 124ºC; Y=75%;white solid;IR, νmax(KBr, cm-1):3427.45(NH), 2227.98 (C≡N), 1613.86 (-C=C-), 1738.60 (C=O).3048.42 Ar(C-H), 2842.11Alphatic (C-H); 1HNMR(300 MHz, DMSO-d6) δ=8.66 (1H, s, C=NH ), 8.13 (d, J=9.0Hz, 2H, ArH), 7.84 (d,J=6.0Hz,1H, ArH), 7.68 (s, 1H, -C=CH), 7.37-7.36 (m, 2H, ArH), 7.03 (d, J=9.0Hz, 2H, Ar), 4.07 (t, J=6.0Hz, 2H,O-CH2), 1.85-1.80 (m, 2H, CH2) 1.48-1.27 (m,18H), 0.88 (t, J=6.0Hz, 3H, -CH3); 13C NMR(75 MHz, DMSO-d6): 164.44, 164.03, 163.95, 159.66, 155.67, 133.05, 132.92, 120.36, 115.07, 111.09, 102.01, 68.80, 32.18, 29.83, 29.59, 29.37, 26.28, 22.98, 14.63;MS(EI):m/z= 475.33(M+).

**3.5g 3-cyano-2-imino-2H-chromen-7-yl 4-(tridecyloxy) benzoate (6g);**

Mp: 108ºC; Y=80%;white solid;IR, νmax(KBr, cm-1): 3435.45(NH), 2226.38 (C≡N), 1602.66 (-C=C-), 1737 (C=O), 3048.42 (Ar(C-H), 2874.10 Alphatic (C-H).1H NMR (300MHz, DMSO-d6): δ= 8.60 (1H, s, C=NH ), 8.05 (d, J=9.0Hz, 2H, ArH), 7.77 (d, J=6.0Hz,1H,ArH), 7.64 (s, 1H, -C=CH), 7.28-7.26 (m, 2H, ArH), 6.95 (d, J=9.0Hz, 2H, ArH), 3.99 (t, J=6.0Hz, 2H,O-CH2), 1.77-1.72 (m, 2H , -(CH2)-) 1.40-1.18 (m, 22H), 0.80 (t,

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J=6.0Hz, 3H, -CH3 ).13C-NMR(75 MHz, DMSO-d6): 168.87, 161.31, 160.08, 157.12, 137.24, 135.60, 124.65, 119.78, 119.40, 115.43, 106.47, 73.18, 36.51, 34.26, 34.16, 33.93, 33.93, 33.69, 30.59, 27.27, 18.82; MS(EI):m/z= 503.33(M+).

**3.5h 3-cyano-2-imino-2H-chromen-7-yl 4-(hexadecyloxy) benzoate (6h);**

Mp: 143ºC; Y=70%;white solid;IR, vmax(KBr, cm-1):3437.05(NH), 2227.98 (C≡N), 1604.26 (-C=C-), 1738.60(C=O), 3058 (Ar(C-H), 2862.90 Alphatic (C-H). 1H NMR (300MHz, DMSO-d6): δ= 8.67 (1H, s, -C=NH ), 8.13 (d, J=9.0Hz, 2H, ArH), 7.92 (d,J=9.0Hz,1H, ArH), 7.69 (s, 1H, -C=CH), 7.36-7.34 (m, 2H, ArH), 6.99 (d, J=9.0Hz, 2H, ArH), 4.07 (t, J=6.0Hz, 2H,O-CH2), 1.82-1.80 (m, 2H, (CH2)-) 1.46-1.16 (m, 26H), 0.87 (t, J=6.0Hz, 3H, (-CH3 ).13CNMR(75 MHz, DMSO-d6): 168.87, 161.31, 160.08, 157.12, 137.24, 135.60, 124.65, 119.78, 119.40, 115.43, 106.47, 73.18, 36.51, 34.26, 34.16, 33.93, 33.93, 33.69, 30.59, 27.27, 18.82;MS(EI):m/z= 531.33(M+).

**Conclusion**

Aseriesof3-cyano-2-imino-2H-chromen-7-yl 4-(alkyloxy) benzoatehavebeensynthesized.Thestructureswereconfirmedby1H-NMR,13C-NMR,FT-IRandmassspectroscopictechniques.Thecompoundsexhibitedexcellentradicalscavengingactivitiesagainstsuperoxideanionradical,nitricoxideradical,DPPHradicalandhydrogenperoxide.Among all the derivatives 6a,6c(DPPH),6a, 6b (NO•), 6g, 6h (O2-•), 6h, 6f (H2O2)having better free radical scavenging ability. Basedontheresult,itisclearthatthesecanbeusedasgoodantioxidantinthefieldofmedicinalandfoodindustry.

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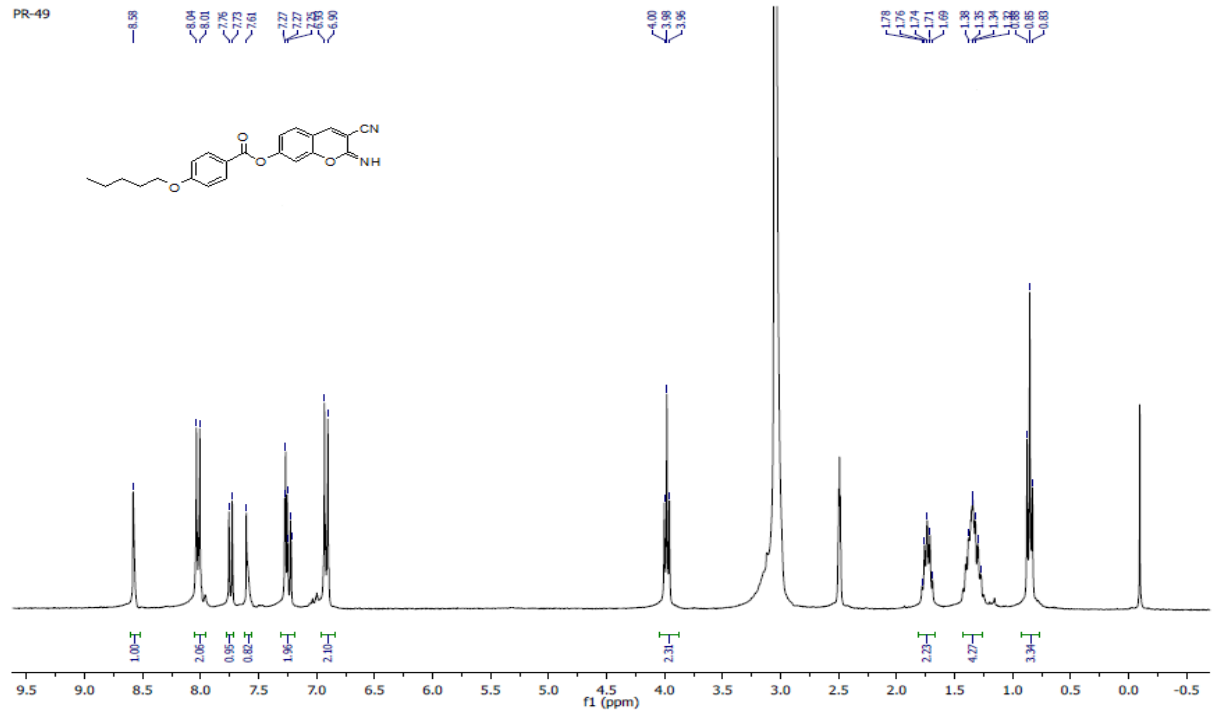


[1]H-NMR of 3-cyano-2-imino-2H-chromen-7-yl 4-(pentyloxy) benzoate (6a)

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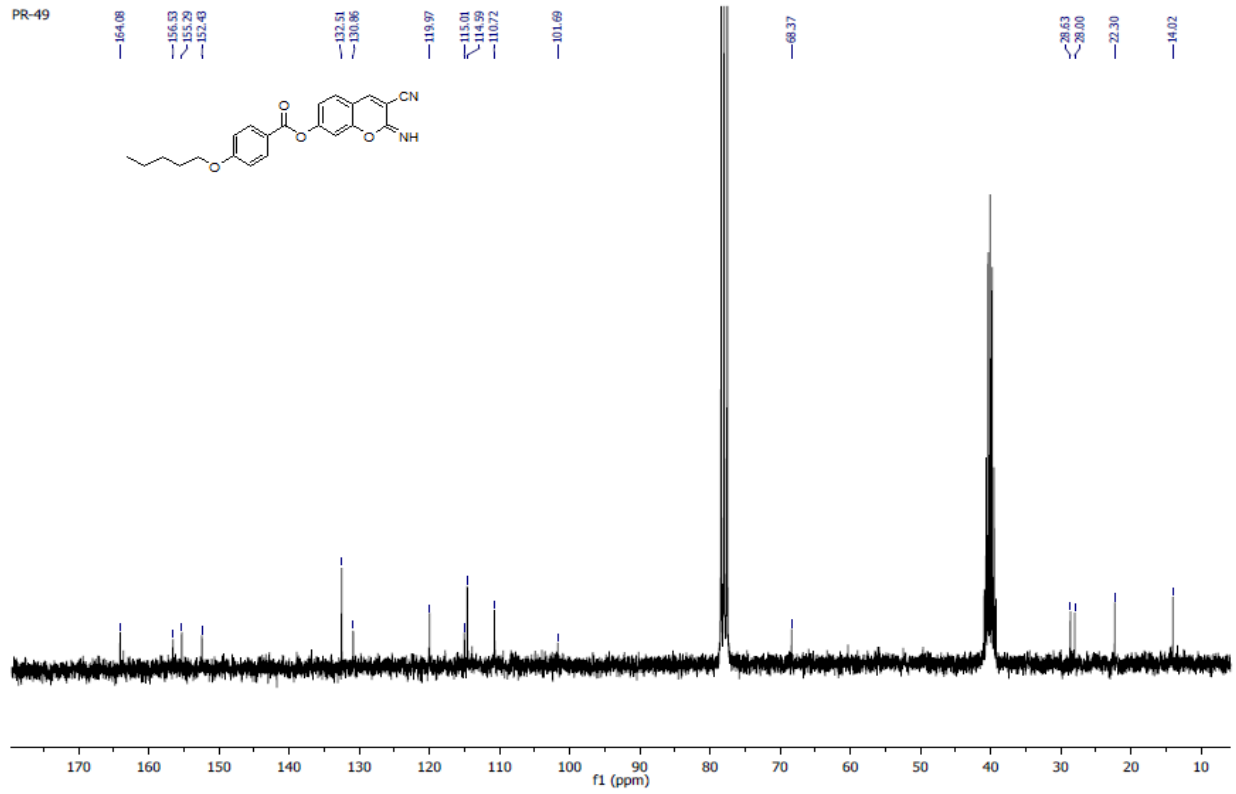


$^{13}$C-NMR of 3-cyano-2-imino-2H-chromen-7-yl 4-(pentyloxy) benzoate (6a)