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GREEN AND EFFECTUAL SYNTHESIS AND CHARACTERIZATION OF AMINO CHROMENE PRODUCTS WITH ADD ALKYL TAIL

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Abstract

The reaction between substituted 4-hydroxy benzaldehyde, active methlyene compounds and/or resorcinol yield amino chromene derivatives. Structures of these compounds were established upon the basis of IR, 1HNMR, 13CNMR, and MASS data. Keywords: 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] antihypotensive[8] 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 temperature[3] *etc*., 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 amino chromenes by taking alkylated aldehyde and malonitrile. Currently, many investigations are going on.[12, 13, 14]

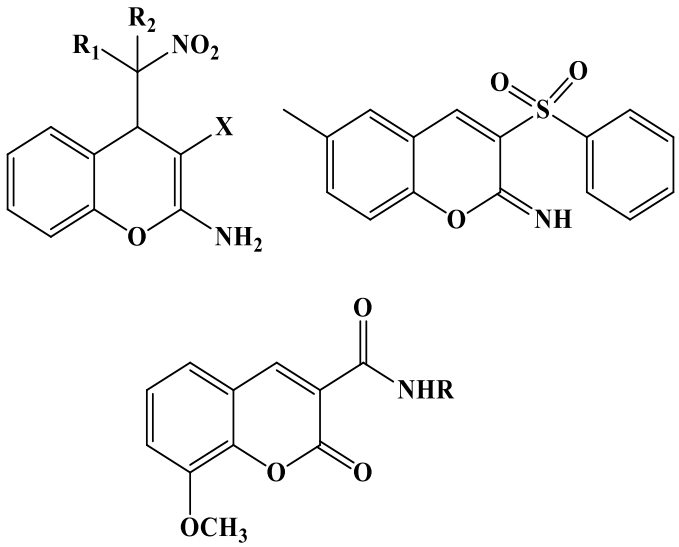

Figure 1. Examples for different chromene derivatives

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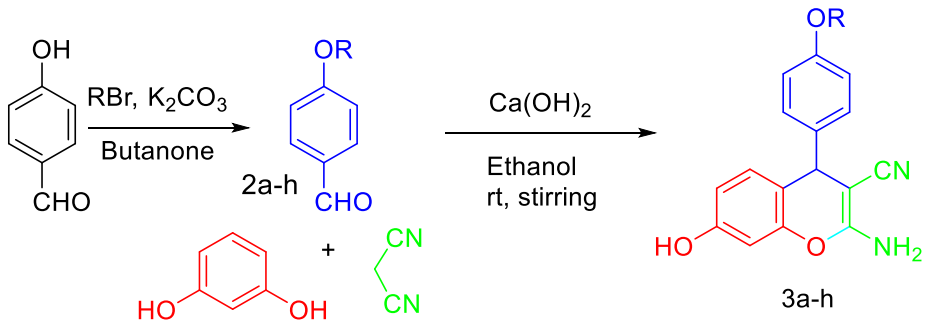
2. Results and Discussion

Various potential catalysts were tested for the direct synthesis o 4c by the model reaction of 4-alyloxy benzoldehyde(1mmol), malononitrile(1mmol) and resorcinol(1mmol) in ethanol at room temperature using calcium hydroxide as green catalyst for this reaction.

Table 1



S.No	R	Yield %	Melting point ºC
1.	ethooxy	80	192
2.	butyloxy	82	202
3.	heptyloxy	85	168
4.	octyloxy	87	162
5.	decyloxy	86	182
6.	dodecyloxy	87	152

Initially the aldehydes react with malononitrile in knoevenagel condensation reaction than undergo Michael addition to give target product. From the result of yield we found $Ca(OH)_2$ was found to be an excellent low-loading (5–10 mol%) catalyst for the synthesis of amino chromene derivatives

3.Experimental

^{1}H NMR spectra were recorded using Bruker (300MHz) spectrometer. For the ^{1}H NMR spectra, the chemical shifts are reported in ppm relative to $SiMe_4$(TMS) as an internal standard and coupling constants are presented in Hz. Infrared spectra were recorded on JASCO- FTIR spectrometer(4000-400cm^{-1}); the spectral positions are given in wave numbers (cm^{-1}). Electrospray ionization mass spectrometry (ESI-MS) analysis was performed in the negative ion mode on a liquid chromatography-ion trap mass spectrometer (LCQ Fleet, Thermo Fisher Instruments Limited, US). Spectra of these compounds were given in supplementary information. The DPPH radical scavenging activity of the compounds was measured according to the method of Blios.[20] The assay of nitric oxide ($NO^{\cdot}$) scavenging activity is measured based on method reported.[21] The ability of the compounds to scavenge hydrogen peroxide was determined using the method available in literature.[22] The superoxide anion radical ($O_2^{\cdot-}$) scavenging assay was based on the capacity of the complexes to inhibit formazan formation by scavenging the superoxide radicals generated in the riboflavin-light-NBT system.[23]

4. Conclusion

A series of 2-amino-7-hydroxy-4-(4-(alkyloxy) phenyl)-4H-chromene-3-carbonitrile have been synthesized using calcium hydroxide as efficient and green catalyst. The structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR and mass spectroscopic techniques.

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4.1 General procedure for the synthesis of 4-alkoxy benzaldehyde: 2a-h

A mixture of 4-hydroxy benzaldehyde (10mmol, 1eq) 1-bromoalkane (15mmol, 1.5eq), anhydrous K_2CO_3 (15mmol, 1.5eq) and butanone 20ml, the catalytic amount of KI was added to the mixture was refluxed for 4 hours. Reaction mixture was concentrated, poured into water and extracted with dichloromethane (DCM) (20ml x 2). The combined organic layer was washed with brine and over anhydrous Na_2SO_4. Evaporation of solvent furnished a brown colored mass which was purified by column chromatography on 60-120 mesh silica gel. Elution with a mixture of ethyl acetate–pet ether (1:9) furnished the pure light yellow oily liquid.[24]

4.2 General procedure for the preparation of 4- alkoxy benzoic acid: 3a-h

The 4-alkoxy benzaldehyde (1g) was dissolved in butanone (20ml) and jones reagent (1.7g CrO_3, 2 ml H_2SO_4 and 6 ml H_2O) was slowly added to this mixture and stirred for 1 hour. After 1 hour, to this mixture water was added slowly. The white precipitate was filtered; it was washed with water and recrystallized by ethanol give pure product.[24]

4.3 General procedure for the preparation of 4-formyl-3-hydroxyphenyl-4-(alkoxy) benzoate: 4a-h

A stirred solution of 4- alkoxy benzoic acid (1eq), 2, 4-dihydroxy benzaldehyde (1.1eq), N, N-Dicyclohexyl carbodiimide (DCC) (3eq) and catalytic amount of (DMAP) dimethyl amino pyridine in (DCM) dichloro methane solution was added at the room temperature, mixture was vacuum created and stirred for overnight under N_2 atmosphere. The precipitate N, N-dicyclohexyl urea was filtered off. The filtrate was diluted with (20ml) DCM and washed with water and dried over anhydrous Na_2SO_4. Evaporate solvent by vacuum pump and puried by column chromatography 60-120 mesh silica gel. Elution with a mixture of (1:9) ethyl acetate–pet ether furnished the pure a product. The product was recrystallized from CH_2Cl_2-acetonitrile to obtain a white solid.[24]

4.4 2-amino-7-hydroxy-4-(4-(alkoxy) phenyl)-4H-chromene-3-carbonitrile: 5a-h

A mixture of resorcinol (1.0mmol), 2-(4-methoxybenzylidene), malononitrile (1.5 mmol), and $Ca(OH)_2$(1.0mmol) in 5mL of methanol was stirred at room temperature for 5 min. After completion of the reaction monitored by TLC, the crude was washed with ethyl acetate, dissolved with THF and filter to separate the catalyst. Solvent was removed from filtrate gave the pure product.

4.4a 2-amino-7-hydroxy-4-(4-(ethoxy) phenyl)-4H-chromene-3-carbonitrile (5a)

Mp: 192ºC; **Y**=80%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3479.70 **(**NH_2), 3271.38(OH), 2931.90 Alphatic (C-H), 2189.28 (C≡N), 1641.48 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.05(s, 1H, ArOH), 7.07(d, *J*=9.0Hz, 2H, ArH), 6.80(d, *J*=9.0Hz, 2H, ArH), 6.74(d, *J*=9.0Hz, 1H, ArH), 6.53-6.48(m, 2H, ArH), 5.16(s, 2H, NH_2), 4.56(s, 1H, CH), 3.89(t, *J*=6.0Hz, 2H, OCH_2), 1.75-1.70(m, 2H, CH_2), 1.42-1.30(m, 8H, CH_2), 0.88(t, *J*=6.0Hz, 3H, CH_3); **^{13}CNMR (75 MHz DMSO-d_6):**159.5, 158.0, 157.0, 149.0, 137.4, 129.9, 128.7, 120.3, 114.5, 113.9, 112.8, 102.8, 67.9, 60.2, 31.4, 29.1, 25.5, 22.4, 13.8; **MS** (EI): *m/z*=351.22(M^+).

4.4b 2-amino-4-(4-(butyloxy) phenyl)-7-hydroxy-4H-chromene-3-carbonitrile (5b)

Mp: 202ºC; **Y**=82%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3423.76 **(**NH_2), 3292.60(OH), 2924.18 Alphatic (C-H), 2189.28 (C≡N), 1645.33 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.00(s, 1H, ArOH), 7.07(d, *J*=9.0Hz, 2H, ArH), 6.80(d, *J*=9.0Hz, 2H, ArH), 6.74(d, *J*=9.0Hz, 1H, ArH), 6.53-6.48(m, 2H, ArH), 5.16(s, 2H, NH_2), 4.56(s, 1H, CH), 3.89(t, *J*=6.0Hz, 2H, OCH_2), 1.75-1.70 (m, 2H, CH_2), 1.41-1.30(m, 6H, CH_2), 0.88(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**159.5, 158.0, 157.1, 149.0, 137.4, 129.9, 128.7, 120.3, 114.5, 113.9, 112.8, 102.6, 67.9, 60.2, 31.4, 29.1, 25.6, 22.4, 13.8; **MS** (EI): *m/z*=365.21(M^+).

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4.4c 2-amino-4-(4-(heptyloxy) phenyl)-7-hydroxy-4H-chromene-3-carbonitrile (5c)

Mp: 168ºC; **Y**=85%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3425.69 **(**NH_2), 3221.23(OH), 2924.18 Alphatic (C-H), 2187.35 (C≡N), 1647.26 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.06(s, 1H, ArOH), 7.09(d, *J*=9.0Hz, 2H, ArH), 6.81(d, *J*=9.0Hz, 2H, ArH), 6.74(d, *J*=9.0Hz, 1H, ArH), 6.54-6.49(m, 2H, ArH), 5.28(s, 2H, NH_2), 4.56(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.76-1.69 (m, 2H, CH_2), 1.42-1.25(m, 8H, CH_2), 0.88(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**159.37, 157.7, 156.7, 148.7, 137.3, 129.6, 128.4, 120.4, 114.2, 113.6, 112.5, 102.5, 67.6, 59.2, 31.4, 28.9, 28.6, 25.6, 22.2, 13.8; **MS** (EI): *m/z*=378.35(M^+).

4.4d 2-amino-7-hydroxy-4-(4-(octyloxy) phenyl)-4H-chromene-3-carbonitrile (5d)

Mp: 162ºC; **Y**=87%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3425.69 **(**NH_2), 3286.81(OH), 2918.40 Alphatic (C-H), 2189.28 (C≡N), 1643.41 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.02(s, 1H, ArOH), 7.09(d, *J*=9.0Hz, 2H, ArH), 6.81(d, *J*=9.0Hz, 2H, ArH), 6.72(d, *J*=9.0Hz, 1H, ArH), 6.54-6.49(m, 2H, ArH), 5.17(s, 2H, NH_2), 4.57(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.79-1.70 (m, 2H, CH_2), 1.43-1.29(m, 10H, CH_2), 0.90(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**159.4, 157.7, 156.7, 148.8, 137.3, 129.7, 128.5, 120.4, 114.2, 113.6, 112.5, 102.6, 67.6, 59.4, 31.4, 29.0, 28.9, 25.7, 22.3, 13.8; **MS** (EI): *m/z*=393.32(M^+).

4.4e 2-amino-4-(4-(decyloxy) phenyl)-7-hydroxy-4H-chromene-3-carbonitrile (5e)

Mp: 182ºC; **Y**=86%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3481.63 **(**NH_2), 3271.38(OH), 2918.40 Alphatic (C-H), 2191.21 (C≡N), 1643.41 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6): δ=** 9.29(s, 1H, ArOH), 7.08(d, *J*=9.0Hz, 2H, ArH), 6.80(d, J=9.0Hz, 2H, ArH), 6.77(d, *J*=9.0Hz, 1H, ArH), 6.51-6.45(m, 2H, ArH), 5.93(s, 2H, NH_2), 4.54(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.83-1.69(m, 2H, CH_2), 1.43-1.12 (m, 14H, CH_2), 0.87(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**159.2, 157.0, 156.2, 148.2, 137.0, 128.9, 127.8, 119.0, 113.6, 113.0, 111.7, 101.8, 66.9, 57.7, 30.8, 28.6, 28.3, 28.3, 24.8, 21.6, 13.1; **MS** (EI): *m/z*=420.91(M^+).

4.4f 2-amino-4-(4-(dodecyloxy) phenyl)-7-hydroxy-4H-chromene-3-carbonitrile (5f)

Mp: 150ºC; **Y**=87%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3481.63 **(**NH_2), 3261.74(OH), 2918.40 Alphatic (C-H), 2191.21 (C≡N), 1643.41 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.19(s, 1H, ArOH), 7.59(d, *J*=9.0Hz, 2H, ArH), 7.09(d, *J*=9.0Hz, 2H, ArH), 6.81(d, *J*=9.0Hz, 1H, ArH), 6.53-6.48(m, 2H, ArH), 5.62(s, 2H, NH_2), 4.56(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.76-1.72(m, 2H, CH_2), 1.43-1.14(m, 22H, CH_2), 0.88(t, J=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**159.5, 157.7, 156.8, 148.8, 137.3, 129.7, 128.5, 120.4, 114.2,113.67, 112.5, 102.4, 67.6, 59.4, 31.5, 29.3, 29.2, 29.1, 29.0, 25.7, 22.3, 13.8; **MS** (EI): *m/z*=447.40(M^-).

4.4g 2-amino-4-(4-(hexadecyloxy) phenyl)-7-hydroxy-4H-chromene-3-carbonitrile (5g)

Mp: 143ºC; **Y**=86%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3481.63 **(**NH_2), 3265.59(OH), 2918.40 Alphatic (C-H), 2191.21 (C≡N), 1645.33 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.06(s, 1H, ArOH), 7.09(d, *J*=9.0Hz, 2H, ArH), 6.81(d, *J*=9.0Hz, 2H, ArH), 6.75(d, *J*=9.0Hz, 1H, ArH), 6.55-6.49(m, 2H, ArH), 5.35(s, 2H, NH_2), 4.57(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.77-1.72(m, 2H, CH_2), 1.43-1.26(m, 26H, CH_2), 0.88(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**158.9, 156.8, 156.0, 148.0, 136.8, 128.7, 127.5, 119.6, 113.3, 112.8, 111.5, 101.6, 66.7, 57.5, 30.6, 28.3, 28.1, 28.0, 24.8, 21.3, 12.9; **MS** (EI): *m/z*=476.83(M^+).

4.4h 2-amino-7-hydroxy-4-(4-(tetradecyloxy) phenyl)-4H-chromene-3-carbonitrile (5h)

Mp: 126ºC; **Y**=86%; white solid; **IR, ν_{max} (KBr, cm^{-1}):** 3338.89 **(**NH_2), 3221.23(OH), 2920.32 Alphatic (C-H), 2218.21 (C≡N), 1604.83 (-C=C-); **^{1}H NMR(300 MHz**, **DMSO-d_6):** δ= 9.06(s, 1H, ArOH), 7.09(d, *J*=9.0Hz, 2H, ArH), 6.81(d, *J*=9.0Hz, 2H, ArH), 6.75(d, *J*=9.0Hz, 1H, ArH), 6.55-6.49(m, 2H, ArH), 5.34(s, 2H, NH_2), 4.57(s, 1H, CH), 3.90(t, *J*=6.0Hz, 2H, OCH_2), 1.77-1.72(m, 2H, CH_2), 1.43-1.26(m, 26H, CH_2), 0.88(t, *J*=6.0Hz, 3H, CH_3); **^{13}C NMR (75 MHz DMSO-d_6):**158.2, 157.0, 156.2, 148.2, 137.0, 128.9, 127.8, 119.8, 113.6, 113.0, 111.7, 101.8, 66.9, 57.8, 30.8, 28.6, 28.4, 28.3, 28.2, 25.0, 21.6, 13.9; **MS** (EI): *m/z*=504.85(M^+).

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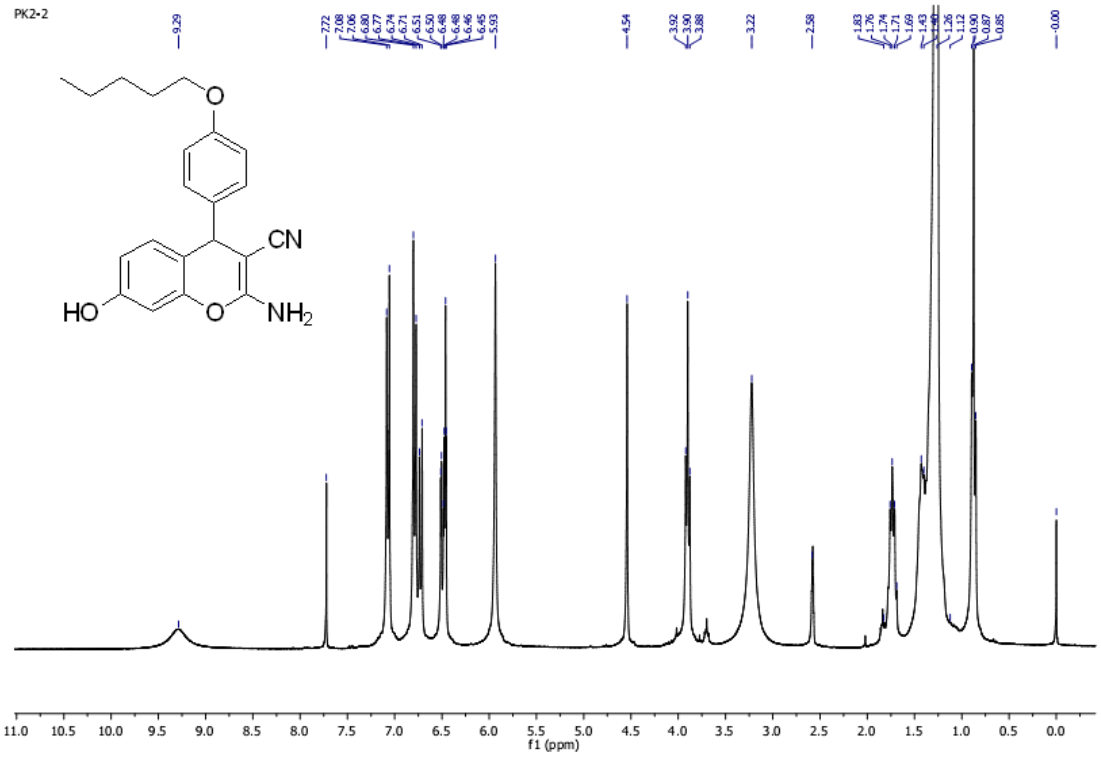
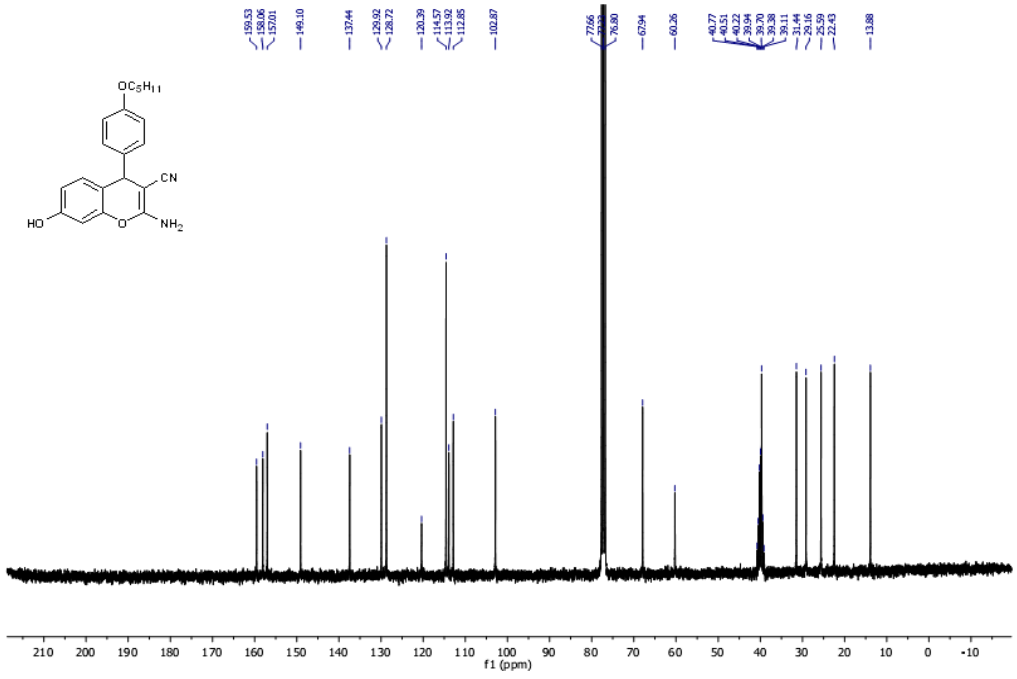


[1]H NMR spectrum of 2-amino-7-hydroxy-4-(4-(pentyloxy)phenyl)-4H-chromene-3-carbonitrile



[13]C NMR spectrum of 2-amino-7-hydroxy-4-(4-(pentyloxy)phenyl)-4H-chromene-3-carbonitrile

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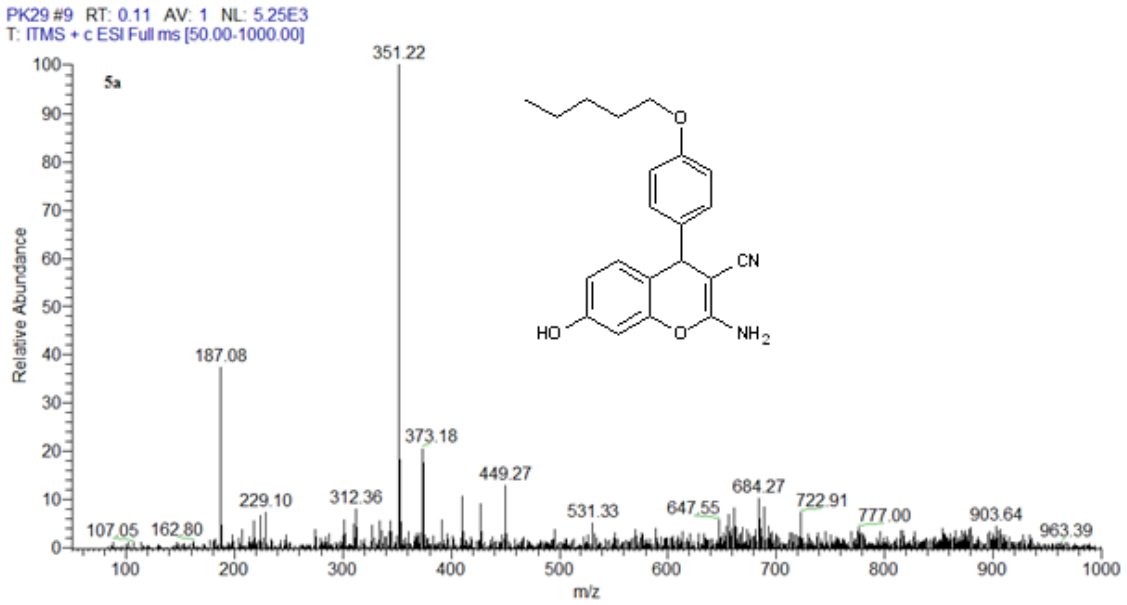

ESI-Mass spectrum of 2-amino-7-hydroxy-4-(4-(pentyloxy) phenyl)-4H-chromene-3-carbonitrile