

Biological activity of substituted novel 6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one.

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Abstract:

The field of biomedical analogs of podophyllotoxin is still in its infancy, but the explosion of interest in these molecules as inherently active therapeutic agents is increasing. There is growing interest in the design and synthesis of novel biocompatible analogs. The series of novel substituted podophyllotoxin derivatives were synthesized under mild conditions with satisfactory yield. The recorded results of lipid peroxidation with treated samples were increasing with increasing concentration. Auto dock server analysis of the these analogs structure showed that the compounds were shown to interact with the proteins involved in Bcl-xL mediated pathway with inhibition constant of 0.000149 and 0.000584 for 5G and 5C respectively.

Keywords: [Podophyllotoxin](#), Cyclolignan, docking study, Auto dock, chick chorioallantoic membrane.

INTRODUCTION:

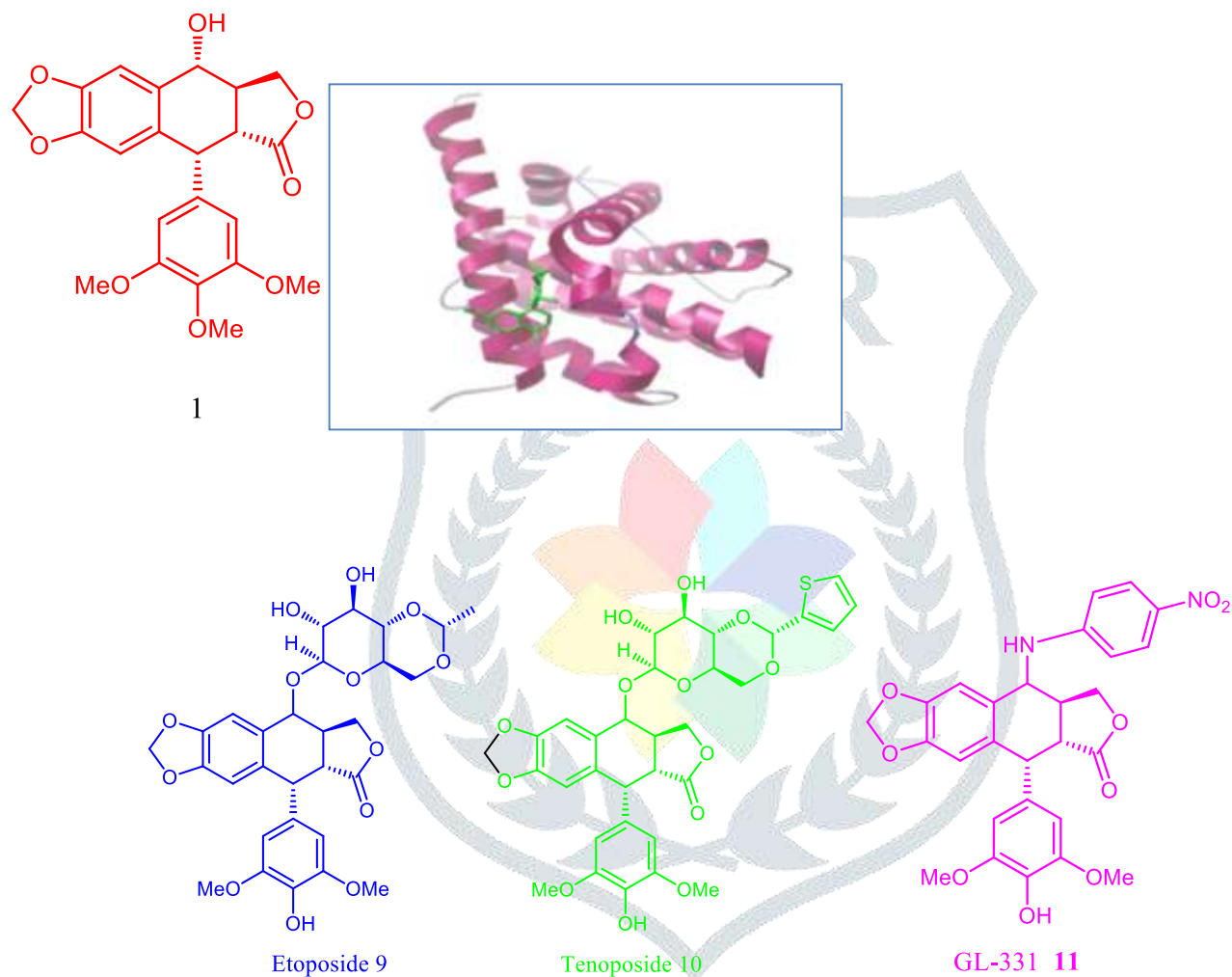
Podophyllotoxins are important natural products in the armamentarium of antineoplastic and antiviral agents. The biological assessment of podophyllotoxin (1) was followed by discovery of its mode of action and culminated in the synthesis of the anticancer drugs etoposide (2) and teniposide (3). The long journey from podophyllotoxin to (2 and 3) illustrates the fascinating development of clinically useful anticancer drugs from natural product prototypes through chemical modification. It is particularly distinctive that structural variation of podophyllotoxin caused a radical change in the mechanism of action. Today, several new analogs have emerged as potential drugs for several diseases.

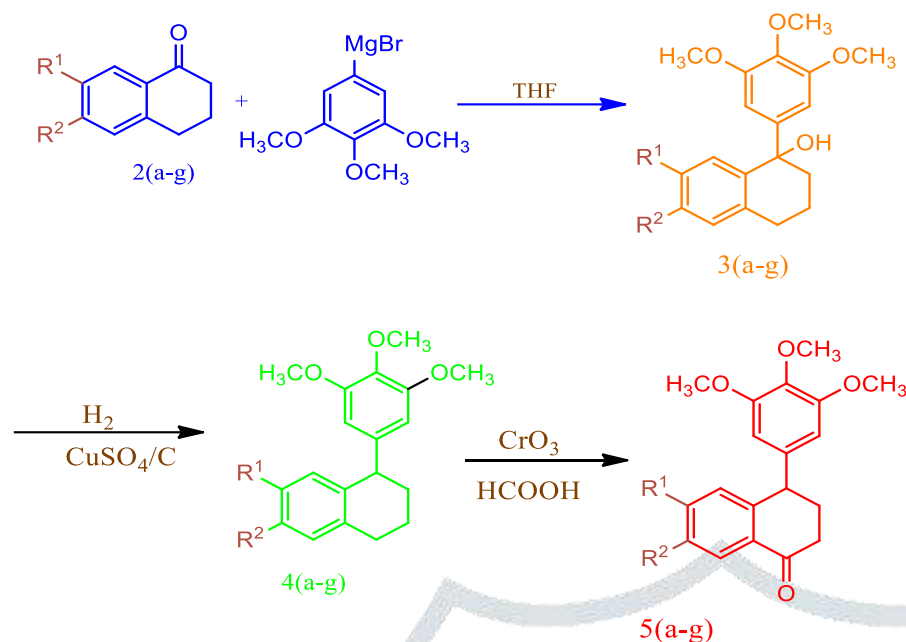
Podophyllotoxin (1), a naturally occurring aryltetralin lignan, holds a unique position among natural products having been known for approximately 1000 years from its first application in folk medicines to its most recent developments in antitumor agents.¹⁻⁸ due to its remarkable biological activity and extensive use in traditional medicine, Podophyllotoxin(1) has remained an important starting point in the development of new therapeutic agents.

The latter are included in a wide variety of cancer chemotherapy protocols. Due to these biological activities, lignans, and especially cyclolignans, have been the objective of numerous studies focused to prepare better and safer anticancer drugs. It is well accepted from structure-activity studies in this field that the trans-lactones are more potent as antineoplastics than the cis-lactones. The configuration of the D ring is an important factor for high cytotoxic activity, but also a quasi-axial arrangement of the E ring is necessary. On this basis, studies on lignans have been addressed to modify the lactone moiety and prepare analogs with heteroatoms at different positions of the cyclolignan skeleton. Our group has been working during the last few

years on chemical synthesis of podophyllotoxin and analogs and we have prepared a large number of cyclolignan derivatives some of which display potent antiviral, immunosuppressive and cytotoxic activities. We have reported several new cytotoxic agents with nitrogen atoms, we are preparing mainly new compounds by modifications of the A and E cyclolignan-rings.

Chemistry





Scheme 1: protocol for the synthesis of aryl tertalone 1(a-g)

Where	R ¹	R ²
a	OCH ₃	OCH ₃
b	H	OH
c	H	CH ₃
d	H	Cl
e	H	H
f	H	OCH ₃
g	H	NH ₂

General procedure for the synthesis of 6, 7-substituted 4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5a-g)

A Grignard reaction was used to prepare 3(a-g). An oven dried three-necked flask outfitted with a reflux condenser, dropping funnel and magnetic stirrer. Approximately 1/4th of an aliquot of 1-bromo-3, 4, 5-trimethoxybenzene (10mmol) in 5ml of anhydrous THF was added to a mixture of magnesium turnings (10mmol) in 2.5ml of anhydrous THF with a small piece of iodine. As soon as the reaction mixture becomes colourless the remaining 1-bromo-3, 4, 5-trimethoxybenzene solution was added drop wise to the solution under a mild condition, stirring was then continued for 1-hour at 60°C temperature. A solution of 3, 4, 5-trimethoxyphenyl magnesium bromide (10mmol) was added slowly to the 6, 7-substituted-3, 4-dihydronaphthalen-1(2H)-one **2(a-g)** (8.35mmol) in 2.5ml anhydrous THF solution at 60°C. After complete addition, the solution was allowed to stir at room temperature for another 20min, a saturated ammonium

chloride solution(10ml) was added to hydrolyze the adduct at 0°C and the mixture was stirred for 10min. The two layers were separated and the aqueous layer was extracted with ether (10ml in three portions), the combined organic layer was washed with brine solution and dried over MgSO₄ and filtered. The filtrate was concentrated in vacuum and the residue was purified by column chromatography gave 93.67% yield.

6, 7-substituted-1- (3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-1-ol **3(a-g)** (0.01 mole) was subjected to hydrogenation over 10% CuSO₄-C in ethanol-formic acid (35:1.25 v/v) mixture. The catalyst was filtered off and the filtrate was distilled to remove ethanol and the residue was extracted with ether. The ether extract was washed with water and dried to give the crude product which was purified by column chromatography over silica gel using petroleum ether to give a product in 86.90%.

To a stirred solution of compound 6, 7-Substituted-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene (0.01mole) **4a** in formic acid (14ml) was added with stirring at 0°C followed by chromium (VI) oxide (0.01mole) in water was added. The reaction mixture was stirred at 0-5°C for 7hr. After completion of the reaction, it was decomposed by pouring the reaction mixture into ice-water and extracted with ether. The ether extract was washed with water, sodium carbonate solution and again with water, dried over magnesium sulfate and recrystallized using ethanol to give a dark brown gummy solid in around 85.18%.

6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5a)

It was prepared by the oxidation of 8-(3, 4, 5-trimethoxyphenyl)-5, 6, 7, 8-tetrahydronaphthalen-2-ol(0.01mmole) **4a** with chromium (VI) oxide (0.01mmole) in formic acid to give a brown semi solid in 82.18%.

IR: 1697-1699 (C=O), 3009-3128(Ar-CH);

¹H NMR (CDCl₃): δppm 1.89–2.78 (4 H, m, CH₂), 3.94 (15 H, s, OCH₃), 4.43 (1 H, t, CH), 6.67(2 H, dd, Ar-H), 7.12-7.59 (2 H, dd, Ar-H);

^{13}C NMR(CDCl_3): δ ppm 31.4(C_3), 37.4(C_2), 45.6(C_4), 56.7($\text{C}-\text{C}_6, \text{C}_7, 4^3, 4^5\text{-OCH}_3$), 60.5($\text{C-}4^4\text{-OCH}_3$), 106.7($\text{C-}4^2, 4^6$), 109.2(C_5), 110.5(C_8), 127.3(C_9), 133.8(C_{10}), 136.7($\text{C-}4^4$), 137.3($\text{C-}4^1$), 147.5(C_7), 153.4($\text{C-}4^3, 4^5$), 154.9(C_6), 198.0(C_1);

MS, m/z : 372.25 (M^+), 373.41(M^++1);

Anal. Calcd. For $\text{C}_{21}\text{H}_{24}\text{O}_6$: C, 67.73; H, 6.50 O, 25.78 Found: C, 67.75; H, 6.51 O, 25.79 %.

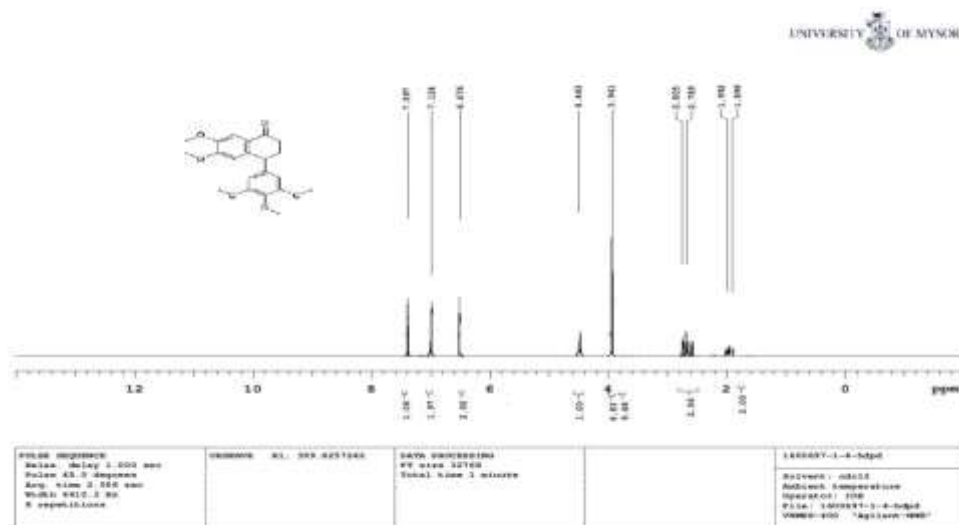


Figure 4.10: ^1H NMR spectra of 6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5a)

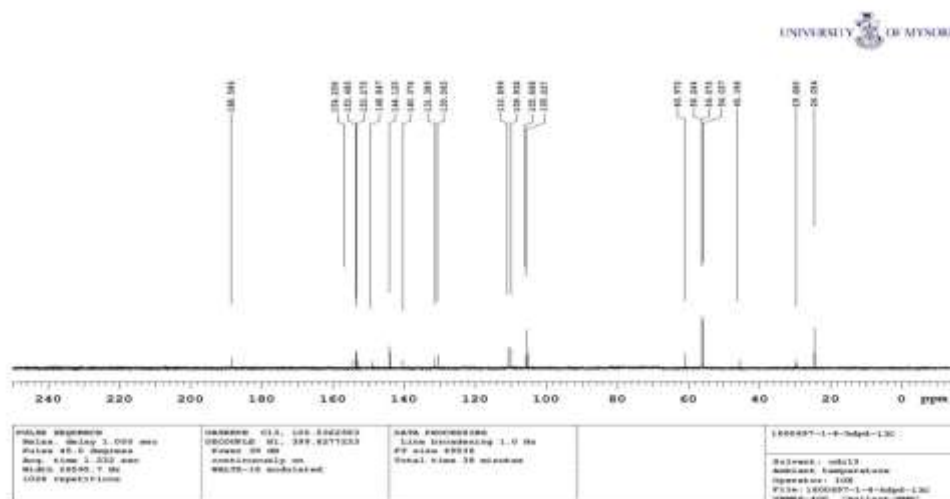


Figure 4.11: ^{13}C NMR spectra of 6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5a)

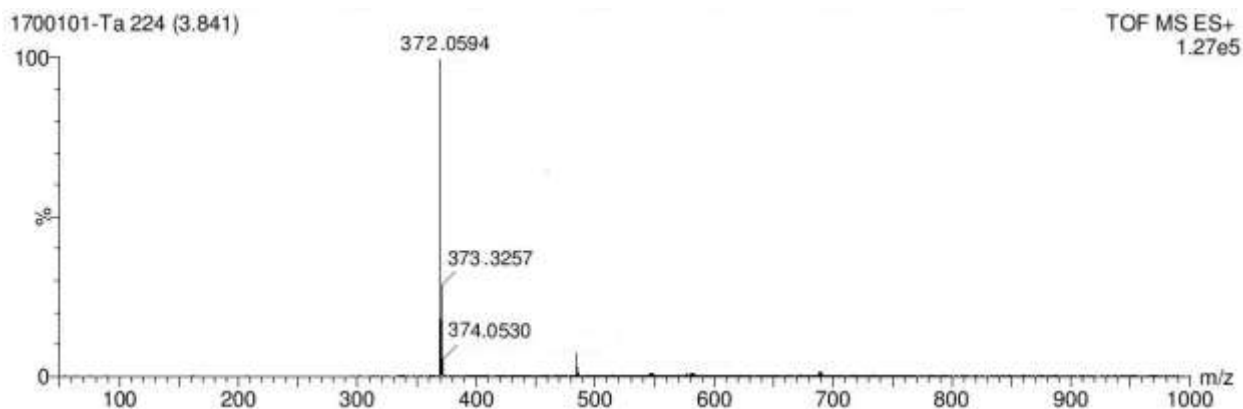


Figure 4.12: mass spectra of 6,7-dimethoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5a)

6-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5b)

It was prepared by the oxidation of 8-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (0.01 mmole) **4b** with chromium (VI) oxide (0.01 mmole) in acetic acid to give a brown semi solid in 82.18%.

IR: 1677-1710 (C=O), 3018–3139 (Ar-CH);

^1H NMR (CDCl_3): δ ppm 2.29–2.82 (4 H, m, CH_2), 3.92 (9 H, s, OCH_3), 3.98–4.02 (1 H, t, CH), 5.63 (1H, s, OH), 7.21–7.98 (5 H, m, Ar-H);

^{13}C NMR (CDCl_3): δ ppm 31.2 (C_3), 37.5 (C_2), 45.9 (C_4), 56.2 ($\text{C}-4^3$, 4^5-OCH_3), 60.8 ($\text{C}-4^4\text{-OCH}_3$), 106.6 ($\text{C}-4^2$, 4^6), 113.3 (C_7), 120.6 (C_5), 126.6 (C_9), 130.7 (C_8), 136.7 ($\text{C}-4^4$), 137.3 ($\text{C}-4^1$), 141.9 (C_{10}), 153.4 ($\text{C}-4^3$, 4^5), 161.9 (C_6), 198.4 (C_1);

MS, m/z : 330.16 (M^+), 331.16 (M^++1);

Anal. Calcd. For $\text{C}_{19}\text{H}_{20}\text{O}_5$: C, 69.53; H, 6.15 O, 24.36 Found: C, 69.56; H, 6.14 O, 24.39 %.

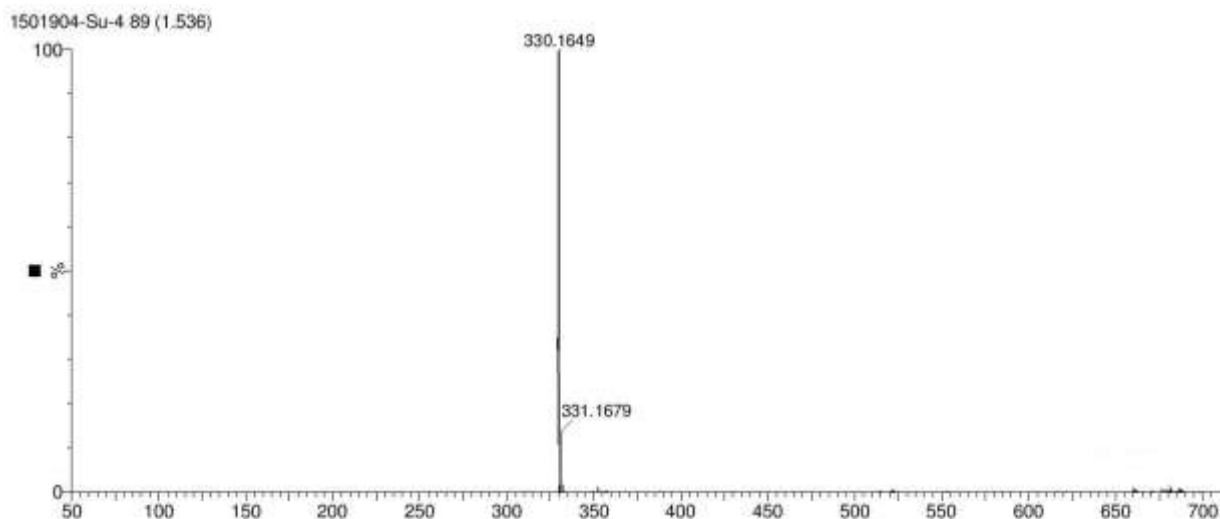


Figure 4.15: mass spectra of 6-hydroxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5b)

6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5c)

It was prepared by the oxidation of 7-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (0.01mmole) **4c** with chromium (VI) oxide (0.01mmole) in formic acid to give brown gummy solid in 87.98%.

IR: 1695-1712 (C=O), 3025–3138 (Ar-CH);

¹H NMR (CDCl₃): δppm 1.89–2.80 (4 H, m, CH₂), 2.36 (3 H, s, CH₃), 3.83(9H, s, OCH₃), 4.23-4.44 (1 H, t, CH), 6.67–7.87 (4 H, m, Ar-H);

¹³C NMR(CDCl₃): δppm 21.6(CH₃), 31.3(C₃), 37.6(C₂), 45.5(C₄), 56.3(C-4³, 4⁵-OCH₃), 60.9(C-4⁴-OCH₃), 106.7(C-4², 4⁶), 125.2(C₈), 126.4(C₇), 128.0(C₅), 131.4(C₉), 136.7(C-4⁴), 137.3(C-4¹), 140.4(C₁₀), 143.3(C₆), 153.4(C-4³, 4⁵), 198.1(C₁);

MS, *m/z*: 326.15 (*M*⁺), 327.16(*M*⁺+1);

Anal. Calcd. For C₂₀H₂₂O₄: C, 73.60; H, 6.79 O, 19.61 Found: C, 73.61; H, 6.75 O, 19.69 %.

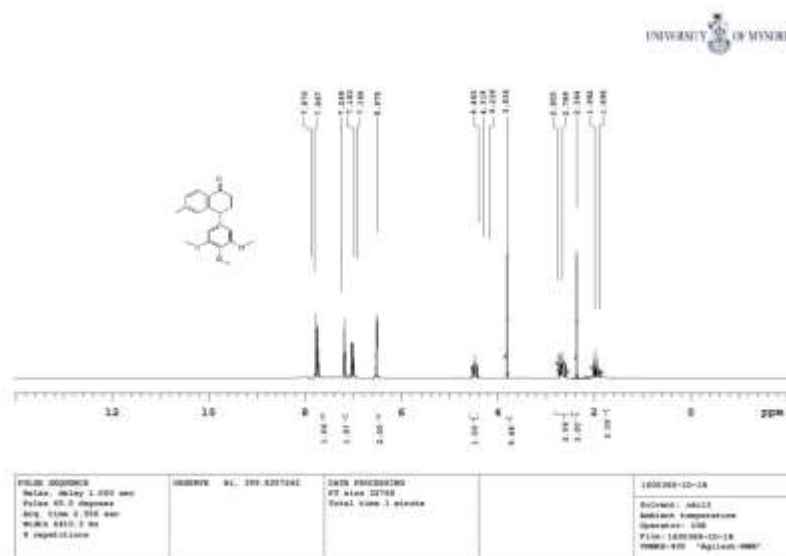


Figure 4.16: ¹H NMR spectra of 6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5c)

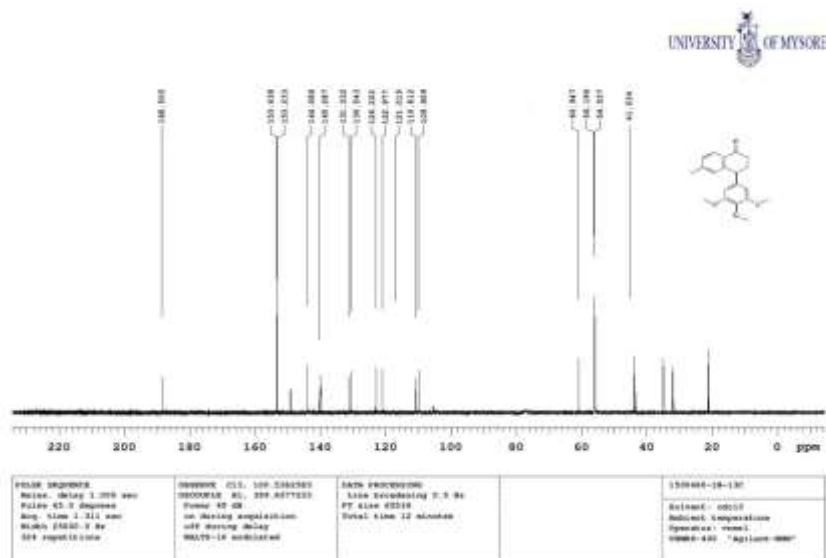


Figure 4.17: ¹³C NMR spectra of 6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5c)

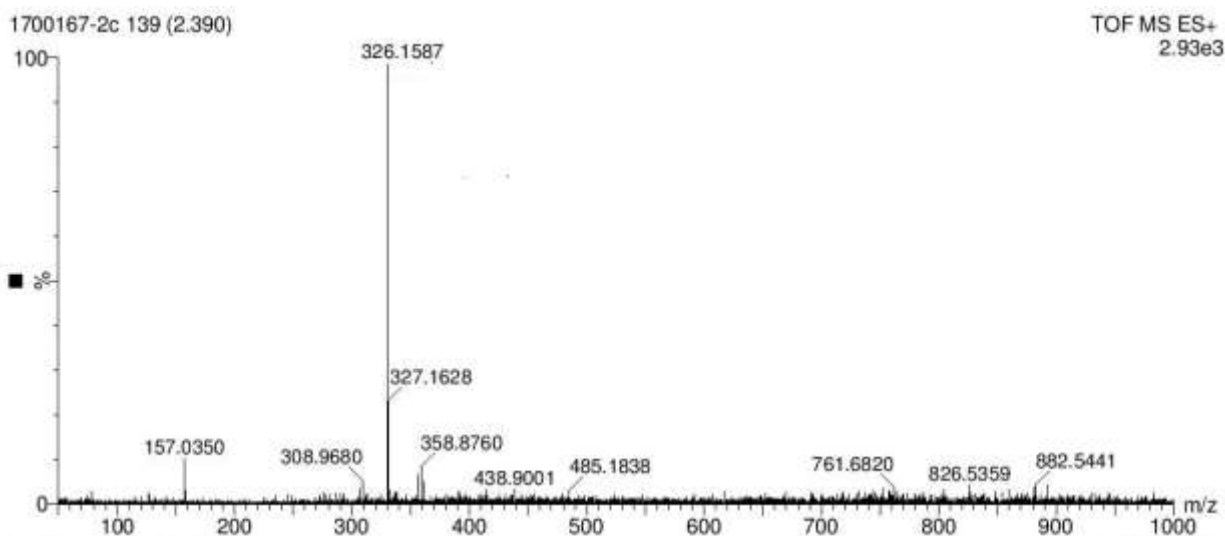


Figure 4.18: mass spectra of 6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5c)

6-chloro-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5d)

It was prepared by the oxidation of 7-chloro-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (0.01 mmole) **4d** with chromium (VI) oxide (0.01 mmole) in formic acid to give brown semi solid in 82.18%.

IR: 1685-1701 (C=O), 3020–3128 (Ar-CH);

$^1\text{H NMR}$ (CDCl_3): δ ppm 2.29- 2.82 (4 H, m, CH_2), 3.90-3.92 (9H, s, OCH_3), 4.06-4.09 (1 H, t, CH), 6.83–8.19 (5 H, m, Ar-H);

$^{13}\text{C NMR}$ (CDCl_3): δ ppm 31.6(C_3), 37.5(C_2), 45.1(C_4), 56.3($\text{C}-4^3$, 4^5-OCH_3), 60.9($\text{C}-4^4\text{-OCH}_3$), 106.9($\text{C}-4^2,4^6$), 126.2(C_7), 127.9(C_5), 130.7(C_8), 132.1(C_9), 136.4($\text{C}-4^4$), 137.7($\text{C}-4^1$), 139.3(C_6), 141.9(C_{10}), 153.4($\text{C}-4^3$, 4^5), 195.8(C_1);

MS, m/z : 347.27 (M^+), 345.19($M^+ + 2$);

Anal. Calcd. For $\text{C}_{19}\text{H}_{19}\text{ClO}_4$: C, 65.80; H, 5.52; Cl 10.22; O, 18.45 Found: C, 65.81; H, 5.55; Cl 10.20; O, 18.49 %.

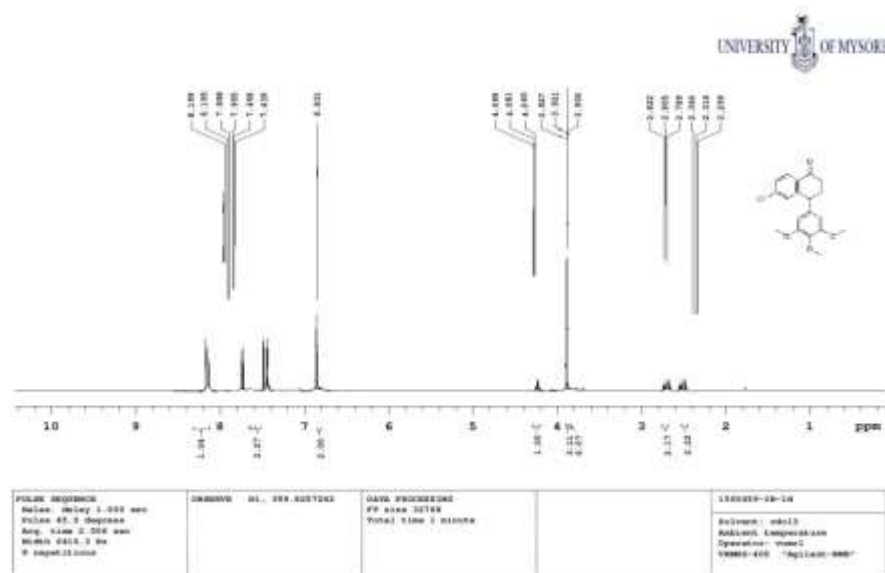


Figure 4.19: ^1H NMR spectra of 6-chloro-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5d)

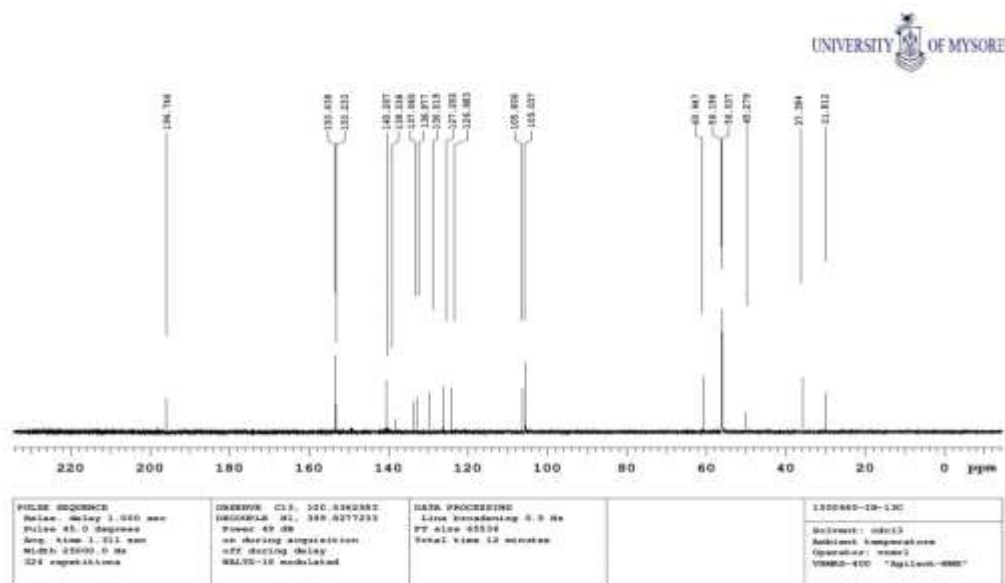


Figure 4.20: ^{13}C NMR spectra of 6-chloro-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5d)

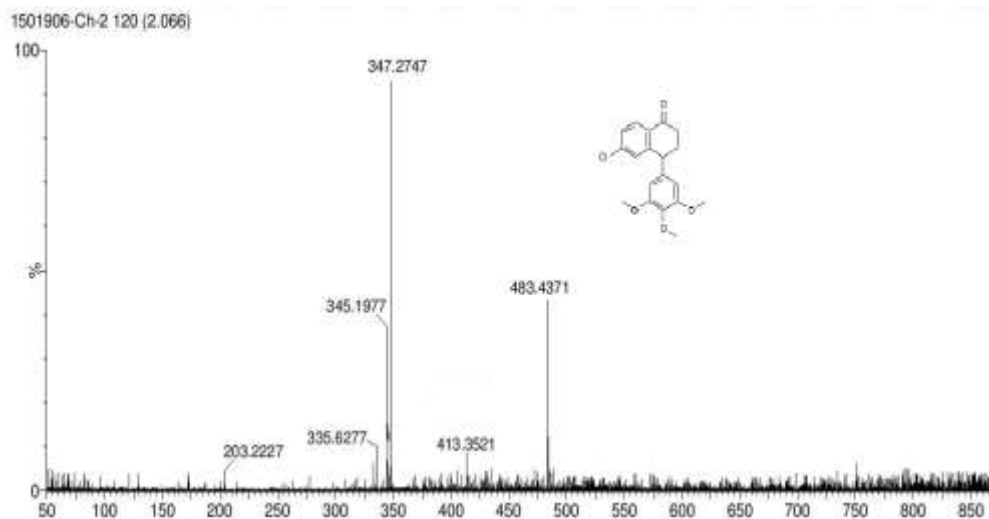


Figure 4.21: mass spectra of 6-chloro-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5d)

4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5e)

It was prepared by the oxidation of 1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene (0.01 mmole) **4e** with chromium (VI) oxide (0.01 mmole) in formic acid to give brown semi solid in 82.98%.

IR: 1691-1698 (C=O), 3023–3125 (Ar-CH);

$^1\text{H NMR}$ (CDCl_3): δ ppm 2.62–2.70 (4 H, m, CH_2), 3.80-3.91 (9H, s, OCH_3), 4.06-4.10 (1 H, t, CH), 6.52 (2 H, dd, Ar-H), 7.33-7.83 (6 H, m, Ar-H);

$^{13}\text{C NMR}$ (CDCl_3): δ ppm 31.4 (C_3), 37.6 (C_2), 45.6 (C_4), 56.5 ($\text{C}-4^3$, 4^5-OCH_3), 60.8 ($\text{C}-4^4\text{-OCH}_3$), 106.1 ($\text{C}-4^2, 4^6$), 126.1 (C_7), 128.1 (C_5, C_8), 133.6 (C_6), 134.0 (C_9), 136.7 ($\text{C}-4^4$), 137.3 ($\text{C}-4^1$), 140.5 (C_{10}), 153.4 ($\text{C}-4^3$, 4^5), 198.0 (C_1);

MS, m/z : 312.1 (M^+), 313.1 (M^++1);

Anal. Calcd. For $\text{C}_{19}\text{H}_{20}\text{O}_4$: C, 73.06; H, 6.45 O, 20.49. Found: C, 73.07; H, 6.43, O, 20.50%.

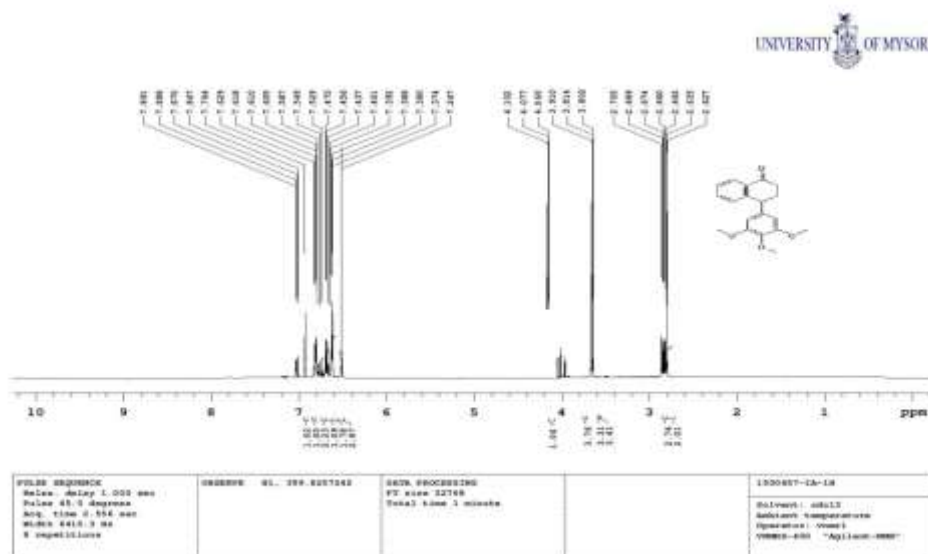


Figure 4.22: ^1H NMR spectra of 4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5e)

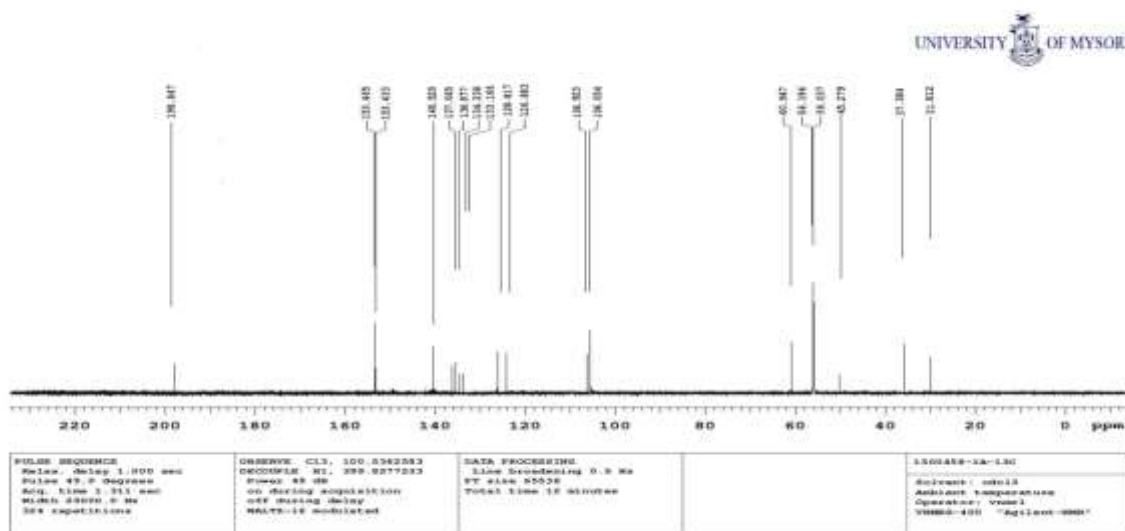


Figure 4.23: ^{13}C NMR spectra of 4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5e)

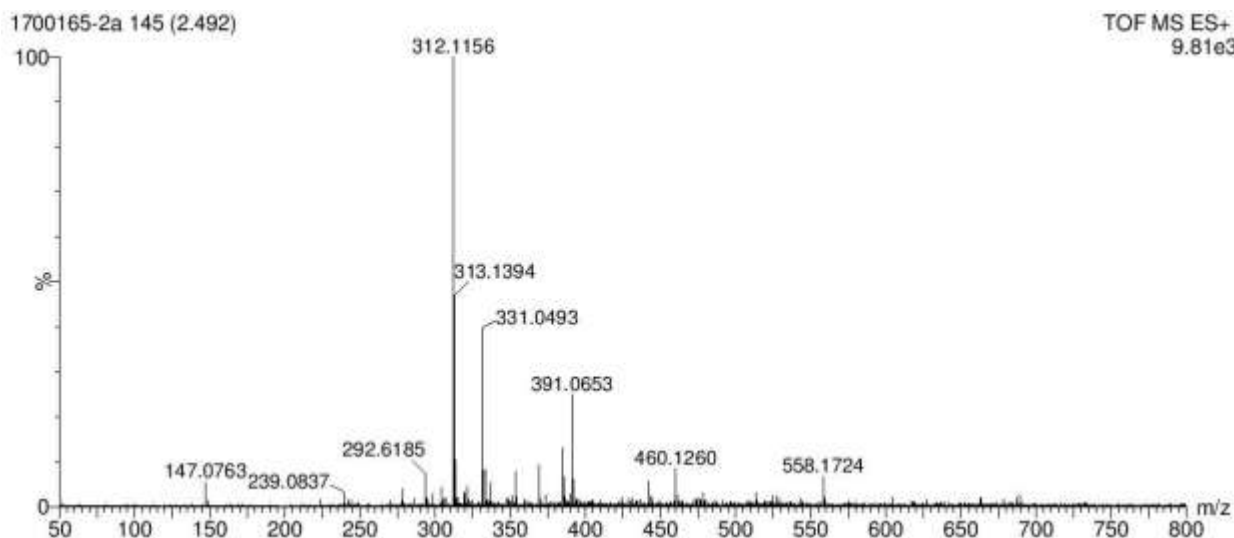


Figure 4.24: mass spectra of 4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5e)

6-methoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5f)

It was prepared by the oxidation 7-methoxy-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene (0.01mmole) **4f** with chromium (VI) oxide (0.01mmole) in formic acid to give brown semi solid in 85.48%.

IR: 1687-1701 (C=O), 3018–3139 (Ar-CH);

^1H NMR (CDCl_3): δ ppm 1.95–2.66 (4 H, t, CH_2), 3.90(12H, s, OCH_3), 4.04-4.12 (1 H, t, CH), 6.62(2 H, dd, Ar-H), 6.85 –8.28(3 H, m, Ar-H);

^{13}C NMR(CDCl_3):: δ ppm 31.4(C_3), 37.4(C_2), 45.9(C_4), 55.8($\text{C}_6\text{-OCH}_3$), 56.8(C-4^3 , 4^5-OCH_3), 60.9($\text{C-4}^4\text{-OCH}_3$), 106.7(C-4^2 , 4^6), 104.6(C_5), 111.9(C_7), 126.5(C_9), 130.5(C_8), 136.7(C-4^4), 137.5(C-4^1), 141.5(C_{10}), 153.6(C-4^3 , 4^5), 165.9(C_6), 198.0(C_1);

MS, m/z : 342.15 (M^+), 343.23(M^++1);

Anal. Calcd. For $\text{C}_{20}\text{H}_{22}\text{O}_5$: C, 70.16; H, 6.49 O, 23.36 Found: C, 70.17; H, 6.45 O, 23.39 %.

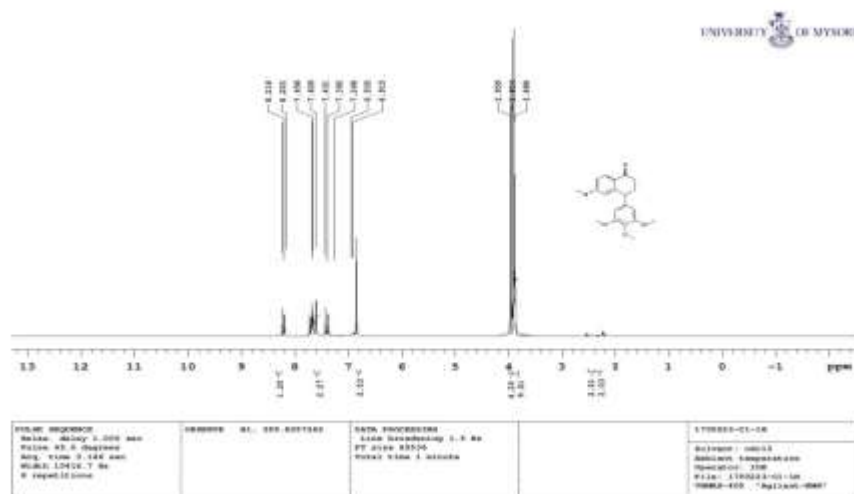


Figure 4.25: ^1H NMR spectra of 6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5f)

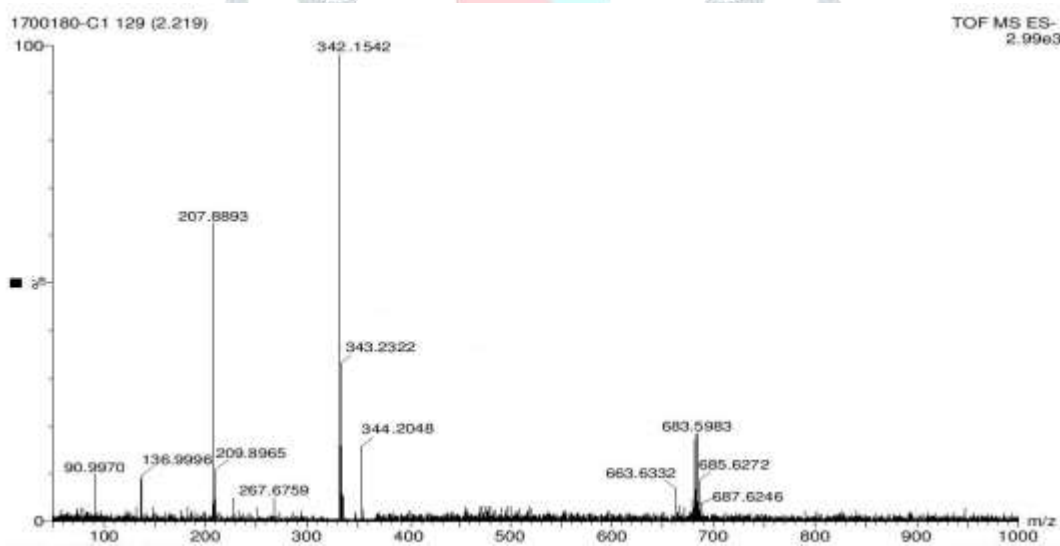


Figure 4.26: mass spectra of 6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5f)

6-amino-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (5g)

It was prepared by the oxidation 7-amino-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (0.01mmole) **14g** with chromium (VI) oxide (0.01mmole) in ac formic acid to give brown semi solid in 85.48%.

IR: 1687-1698(C=O), 3022–3139 (Ar-CH), 3350-3360(NH);

^1H NMR (CDCl_3): δ ppm 1.95–2.66 (4 H, t, CH_2), 3.91(9 H, s, OCH_3), 4.01-4.06 (1 H, t, CH), 6.67-7.39(6 H, m, Ar-H);

^{13}C NMR(CDCl_3): δ ppm 31.4(C_3), 37.4(C_2), 45.9(C_4), 56.1($\text{C}-4^3$, 4^5-OCH_3), 60.9($\text{C}-4^4\text{-OCH}_3$), 106.7($\text{C}-4^2$, 4^6), 111.6(C_7), 115.1(C_5), 124.0(C_9), 130.1(C_8), 136.7($\text{C}-4^4$), 137.3($\text{C}-4^1$), 141.3(C_{10}), 153.3(C_6), 153.4($\text{C}-4^3$, 4^5), 198.3(C_1);

MS, m/z : 327.00 (M^+), 328.87(M^++1);

Anal. Calcd. For $\text{C}_{19}\text{H}_{21}\text{NO}_4$: C, 69.71; H, 6.47; O, 19.55 Found: C, 69.72; H, 6.46; O, 19.56 %.

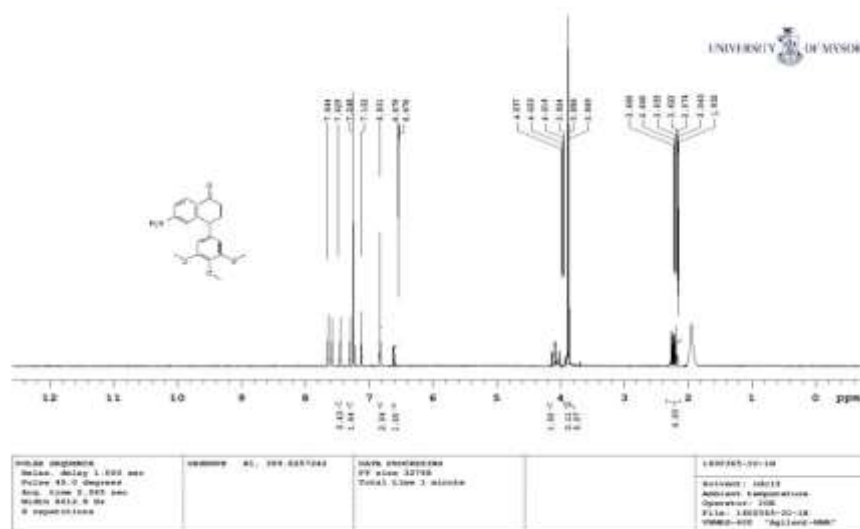


Figure 4.27: ^1H NMR spectra of 6-amino-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5g)

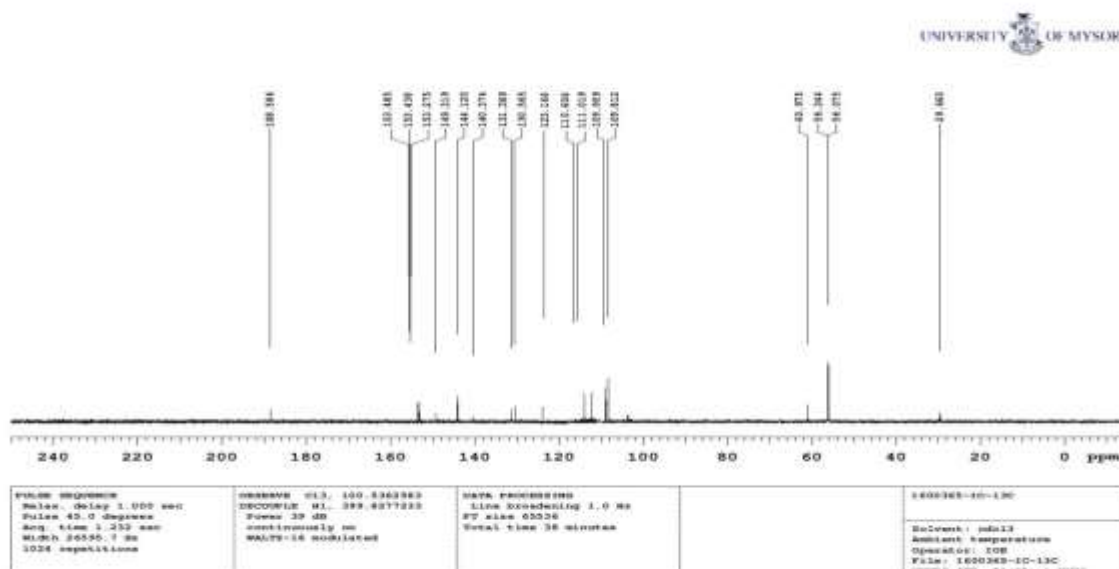


Figure 4.28: ^{13}C NMR spectra of 6-amino-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5g)

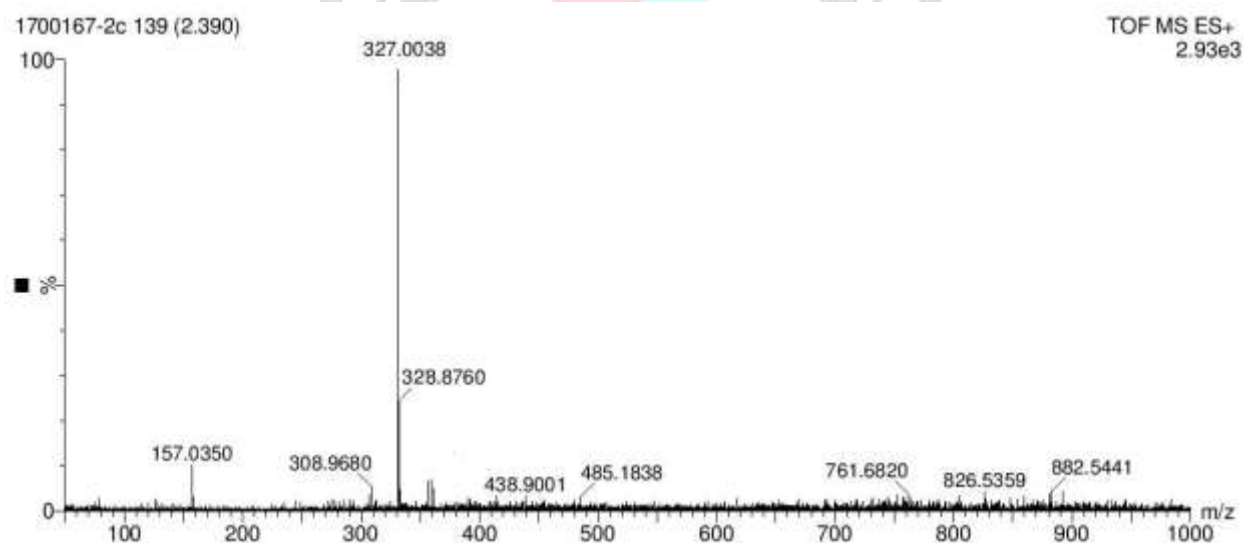


Figure 4.29: mass spectra of 6-amino-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (5g)

Docking studies: Auto doc server was used for docking studies of **5(a-g)**. The [6 methyl-4-(3, 4, 5-trimethoxyphenyl) 3, 4 dihydronaphthalenelactone-1(2H) one (**5C**) and [6 amino 4(3, 4,5-trimethoxy phenyl) 3, 4 dihydronaphthalenelactone-1(2H) one (**5G**). The structure of the target Bcl-xL (B-cell lymphoma-extralarge) was obtained from Protein Data Bank PDB. The binding energy and inhibition constants were identified.

Docking studies: auto dock server analysis of 6 methyl-4-(3, 4, 5-trimethoxyphenyl) 3, 4 dihydronapfthalenelactone-1(2H) one (**5C**) and 6 amino 4(3, 4,5-trimethoxy phenyl) 3, 4 dihydronapfthalenelactone-1(2H) one (**5G**) revealed that these synthesized compounds functions through Bcl-xL mediated pathway.

Compounds	Binding energy	Inhibition constant
6 methyl-4-(3, 4, 5-trimethoxyphenyl) 3, 4 dihydronapfthalen-1(2H) one (5C)	-4.68	0.000584
6 amino 4(3, 4,5-trimethoxy phenyl) 3, 4 dihydronapfthalen-1(2H) one (5G)	-5.22	0.000149

Table: Inhibition constants of 5C and 5G compounds.

5C

5G

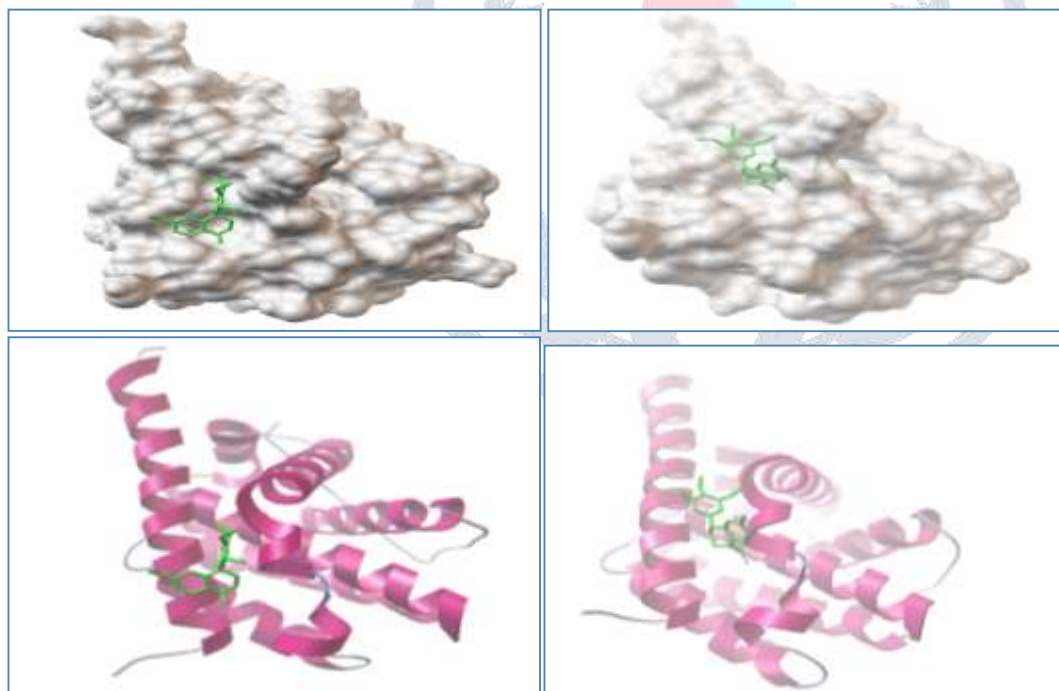


Fig: Auto dock server analysis of 5C and 5G.

Biological activity

Materials and methods

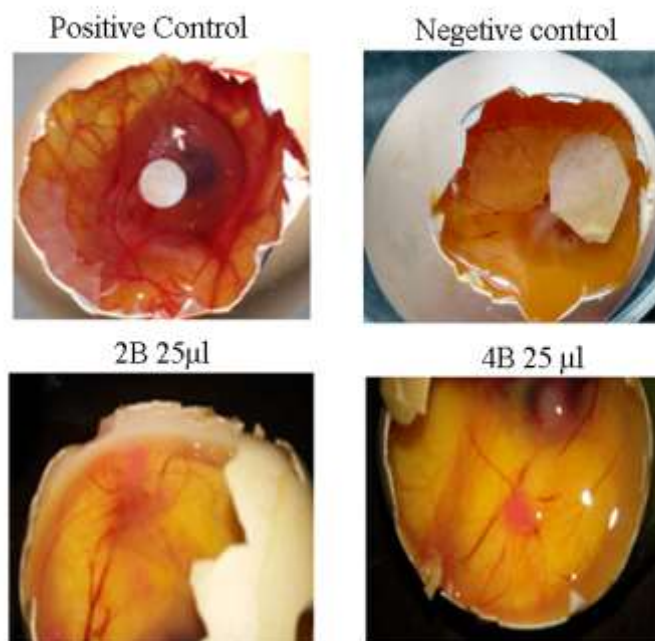
Chick chorioallantoic membrane (CAM) Assay

In order to validate the angiogenic effect of 6-methyl-4-(3, 4, 5-trimethoxyphenyl)-3, 4- dihydronaphthalen-1(2H)-one (**5c**) and 6-amino-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one (**5g**) CAM assay was performed as described previously. Briefly, chick fertilized eggs were incubated for 8 day at 37⁰C in a humidified atmosphere. On the 3rd day of incubation, a single window was opened in the egg shell after removal of 2-3ml of albumen to detach the developing CAM from the shell. The window was sealed with a glass of the same dimension, and the eggs were returned to the incubator. On day 10 of incubation, under sterile conditions within a laminar-flow hood, CAMs were treated with 6 methyl-4-(3, 4, 5-trimethoxyphenyl)-3,4-dihydronapfthalenelactone-1(2H)one absorbed by 1mm³ sterilized blotting paper and placed on top of the growing CAM. Blotting paper containing vehicle alone (PBS buffer) was used as negative controls. After 72h of incubation blood vessels were photographed with a digital camera at 20x magnification. Quantification of angiogenesis was carried out in digitized images by measuring the total blood vessels length using Image J 1.44 (National institute of Health, USA). Measures were performed by three experiments in a circle centred on filter disk that represents 50% of the total CAM surface.

Results:

Chick chorioallantoic membrane (CAM) Assay

In non-tumor context chorioallantoic membrane (CAM) of the chick embryo provides a unique model for investigating the process of new blood vessel formation and vessel responses to antiangiogenic agents. Using this model, we examined the *in vivo* antiangiogenic activity of 6 - amino 4(3, 4, 5-trimethoxy phenyl) 3, 4 dihydronaphthalene-1(2H) one] (**5G**) and 6 - methyl4-(3, 4, 5-trimethoxyphenyl) 3, 4 dihydronaphthalene-1(2H) one (**5C**). Formation of new blood vessels either in presence of positive control was evident in our results as shown in Fig respectively. The CAM treated with 6 amino 4(3, 4,5-trimethoxy phenyl) 3, 4 dihydronaphthalene-1(2H) one (**5G**) and 6-methyl-4-(3, 4, 5-trimethoxyphenyl) 3, 4 dihydronapfthalene-1(2H) one **5C** showed significant decrease in neo-vascularization.



The CAM assay

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