# SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL COUMARIN DERIVATIVES AS ANTI-INFLAMMATORY ACTIVITY

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## ABSTRACT

Coumarins are described as α-benzopyrones. New and known coumarin subsidiaries have been synthesized or confined from regular sources. This research focuses on synthesis and biological evaluation of some novel coumarin derivatives for its anti-inflammatory potential by using diverse types of in-vivo models to confirm its actual anti-inflammatory potential after long term (21 days) treatment of novel coumarin derivatives. Albino rats of either sex weighing 150–200 g will be obtained from the Animal House, Department of Pharmacy, IIMT University, Meerut (UP) India. The animals are maintained in proper conditions, at room temperatures of 25 ± 1°C with 12-hour light/dark cycle. Novel coumarins were developed by standard procedure and evaluated by FTIR, NMR & using carrageenan induced paw edema. Rats were divided in 5 groups; Group 1: rats are given only normal saline each day for 21 days, Group 2: rats are given carrageenan (2%) intradermally for 21 days, Group 3: rats are given carrageenan (2%) + indomethacin (10mg/kg/day, p.o.) for 21 days, Group 4: rats are given carrageenan (2%) + all the novel coumarin derivatives (200mg/kg/day, p.o.) for 21 days and Group 5: rats are given carrageenan (2%) + all the novel coumarin derivatives (400mg/kg/day, p.o.) for 21 days. As the results indicate that synthesized novel coumarins derivatives exhibited significant anti-inflammatory activity at both the doses. The response was noted as dose-dependent (100mgkg & 200mg/kg). Maximum inhibition was recorded in the dose of 200mg/kg of coumarins when given with carrageenan. This action might be produced through involvement in suppression of prostaglandins, cytokines responsible for edema and inflammation, in fact. In conclusion, novel coumarin derivatives might be much significant in reducing the inflammation and counter it.


**Keywords:** coumarins, anti-inflammatory, benzopyrones, FT-IR, prostaglandins

## INTRODUCTION

Coumarins are described as α-benzopyrones. New and known coumarin subsidiaries have been synthesized or confined from regular sources. Coumarins show different distinctive target proteins and enzymes (Detsi et al. 2017). Coumarins belongs to the benzopyrones family (Katsori & Dimitra, 2014). They demonstrate various pharmacological properties such as antitumor, anti-hypertension, antiseptic and analgesic (pain-killer) as well as toxicity including phototoxic and carcinogenic properties (Gerrard, 2014). The majority of coumarins are found in higher plants, with the Rutaceae and Umbelliferae being the largest sources (Keating et al. 1997). By making some modifications in the structure of coumarin and introducing other functional groups, researchers have synthesized more complex and novel coumarin derivatives with more extensive applications and high performance (Wu et al. 2020).

High oestrogen levels caused by in situ synthesis have been linked to the growth of tumours in endocrine-dependent tissues. Estrogens are only produced in tissues, and the aromatase and sulfatase processes are involved in their production (Hamelers et al. 2003).

### *Chemistry of Coumarins*

Coumarin is found as white crystalline solid and smell as vanilla-like, having a note of 'freshly mowed hay.' They are frequently available in various herbal compounds like sweet clover, lavender oil, woodruff, tonka beans and in various edible plants-strawberries and celery (Al- Majedy et al. 2017; Gerrard, 2014).

Molecular formula: C9H6O2

Molecular weight: 146.14

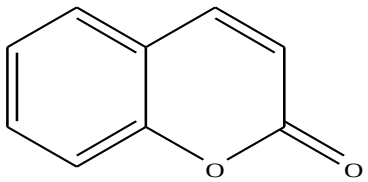



**Fig. 1 Structure of coumarin**

IUPAC name: 2H-chromen-2-one

Numerous members of these plant families are extensively utilized as spices and vegetables in human nutrition or medicines (Matern et al. 1999).

On the basis of above literature survey, I found a little and limited data that demonstrates the anti-inflammatory effect of some coumarins derivatives. So, this research focuses on synthesis and biological evaluation of some novel coumarin derivatives for its anti-inflammatory potential by using diverse types of in-vivo models to confirm its actual anti-inflammatory potential after long term (21 days) treatment of novel coumarin derivatives.

## MATERIALS AND METHODS

### Experimental requirements

Carrageenan, Formalin, Photo-spectrometer, Indomethacin,Water-bath, distilled water, Ethanol, Wistar albino rats (either sex), rotatory evaporator, weighing machine and ethanol.

### Synthesis of Coumarins

In a beaker, 7.5 mL of concentrated H2SO4 is cooled down below 100°C. 1.6 gm of resorcinol is dissolved in 2.3ml of ethyl acetoacetate and thoroughly mixed. The mixture is then stirred for 3-5 hours. When the crude coumarin separated, it is placed into crushed ice. Then there came the crude product. Dry product was filtered-off. After the substituted amines is added, the dry product is collected (Akira et al. 2001).

Coumarins can be made via a variety of techniques, including the Perkin reaction, Knoevenagel condensation, Pechmann condensation, Wittig reaction, Baylis-Hillman reaction, Claisen rearrangement, Vilsmeier-Haack and Suzuki cross-coupling reactions.

Some reactions are depicted as below-

#### *Synthesis of novel coumarin derivatives*

In an RBF, equimolar (0.01mol) amounts of coumarin and several substituted amines were ingested. The RBF was filled with 50 mL glacial acetic acid and 1 mL formaldehyde, which was then refluxed for 3-7 hours on a steam bath dependent on the substituted amines (both primary & secondary). After drying, the product was recrystallized (Zhao et al. 2012).

In DMF (10ml), a catalytic quantity of anhydrous K2CO3 was added to a suspension of maltol (0.01mol) and substituted 4-bromomethyl coumarins (0.03mol). At 65°C, the mixture was refluxed with stirring for 150–240 minutes. The reaction's progress was kept track of by TLC (n-hexane/ethyl acetate 1:1 eluent). The reaction is complete when it is completed. The mixture was chilled with crushed ice, then neutralized with 10 mL of 5% HCl and separated. From chloroform, the solid was filtered, washed with water, dried, and recrystallized (Zhuo et al. 2016).

#### *Procedure of synthesis for C1*

7-(hydroxymethyl)-3-oxo-3,4-dihydronaphthalene-e-carboxylic acid was made reacted with acetic anhydride to get the 7-[(acetyloxy)methyl]-3-oxo-3,4-dihydronaphthalene-2-carboxylic acid as intermediate. This intermediate gives the desired coumarin derivative as phenyl 6-[(acetyloxy)methyl]-2-oxo-2H-1-benzopyran-3-carboxylate upon reaction with phenol or pyridine.

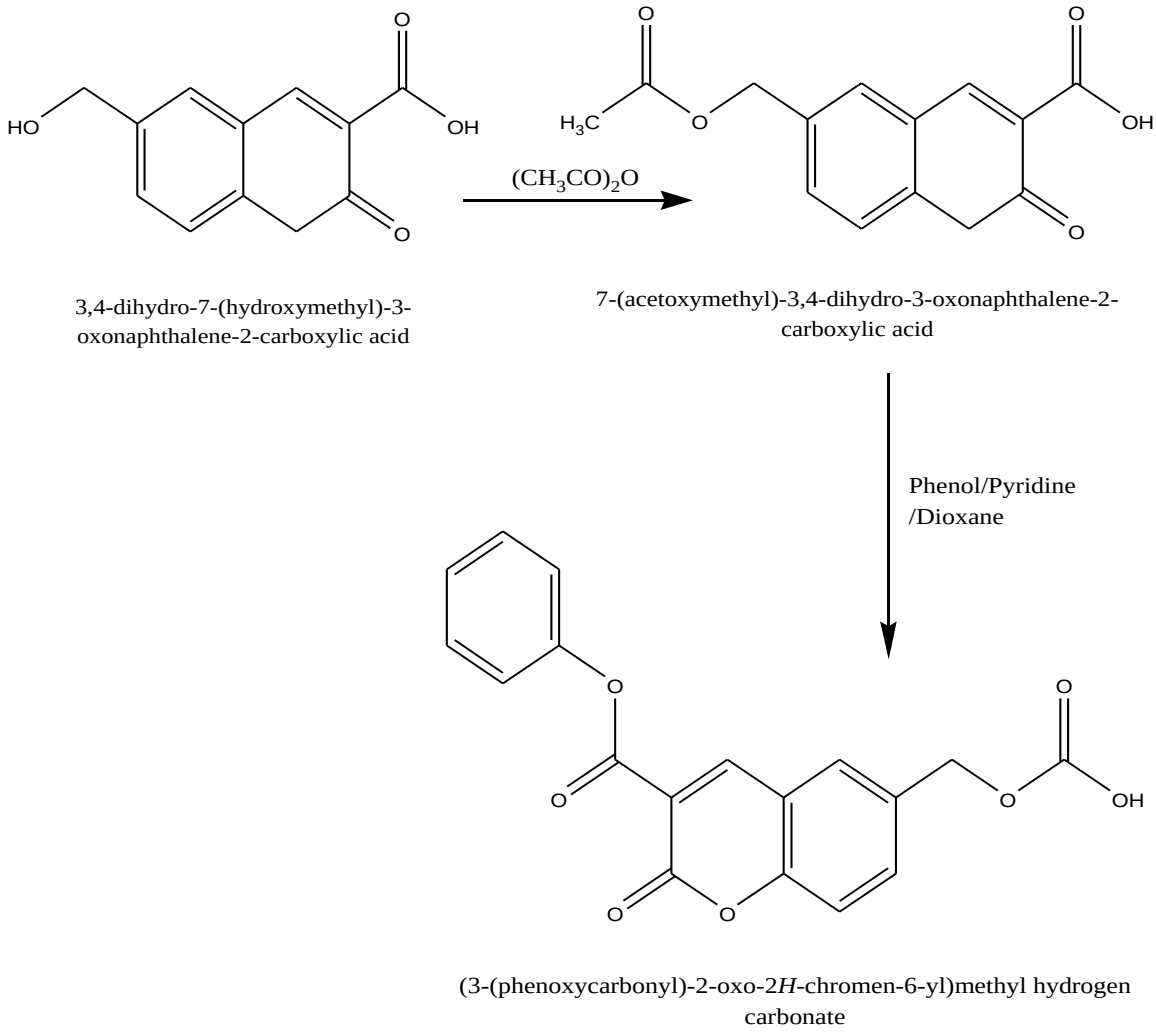
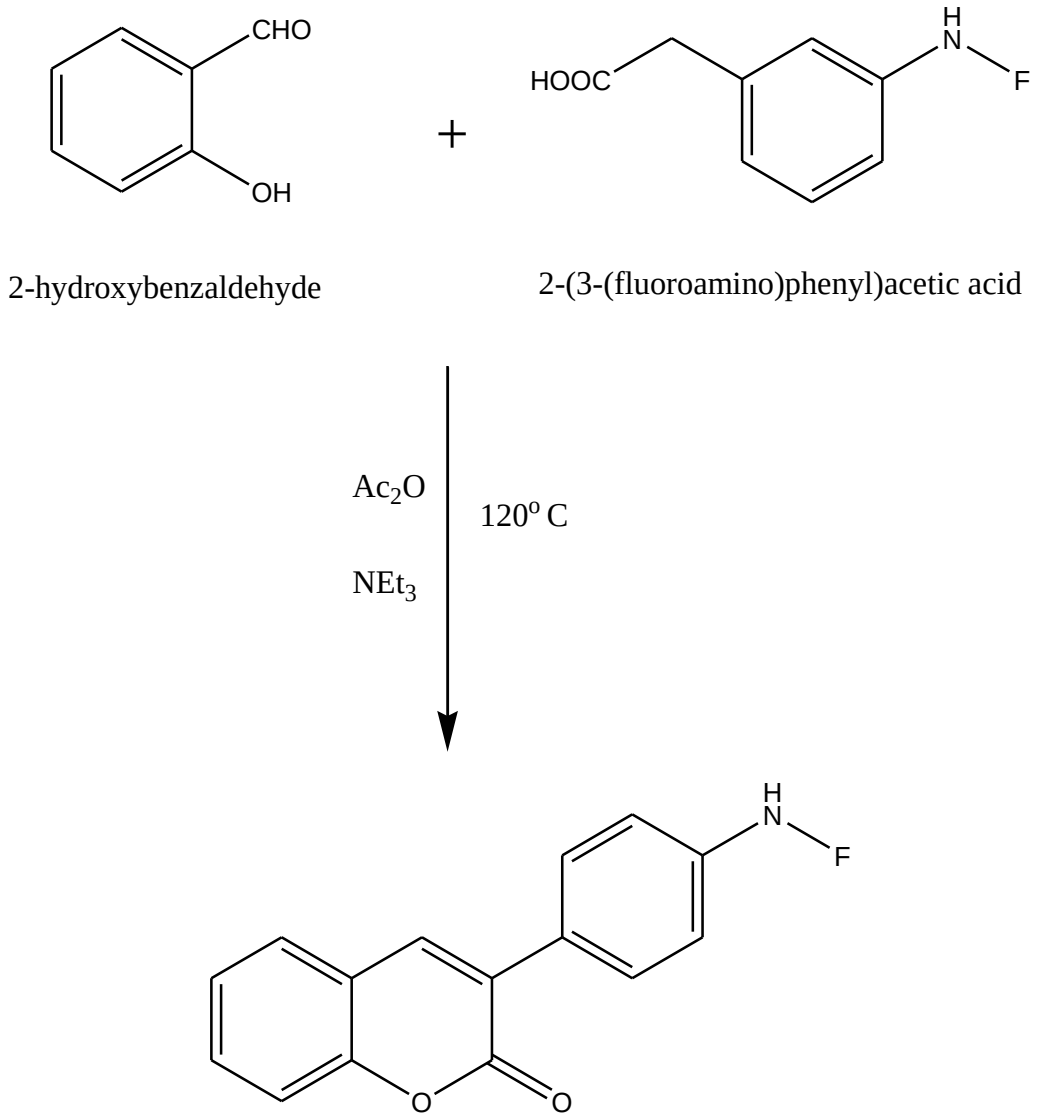



**Fig 2. Synthesis of coumarin derivative C1 (Scheme 1)**

***Procedure of synthesis for C2***

In order to get the coumarin derivative for Scheme 2 the compound 2-hydroxybenzaldehyde was made reacted with [3-(fluoroamino)phenyl]acetic acid in presence of acetic anhydride and tri-ethylamine at 120˚C that produced the desired coumarin derivative named as N-[4-(3-oxo-3,4-dihydronaphthalen-2-yl)phenyl]hypofluorous amide.




2-hydroxybenzaldehyde

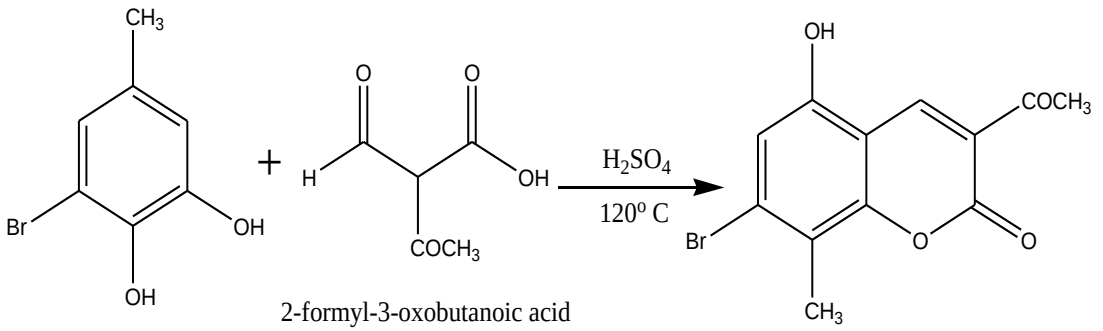
2-(3-(fluoroamino)phenyl)acetic acid

3-(4-(fluoroamino)phenyl)-2*H*-chromen-2-one

**Fig 3. Synthesis of coumarin derivative C-2 (Scheme 2)**

***Procedure of synthesis for C3***

In this procedure, 3-bromo-5-methylbenzene-1,2-diol was made reacted with 2-formyl-3-oxobutanoic acid in the presence of Sulfuric acid at 120ºC for some period of time to obtain the desired derivative of coumarin as 2-acetyl-7-bromo-5-hydroxy-8-methyl-2H-chromen-2-one.




3-bromo-5-methylbenzene-1,2-diol

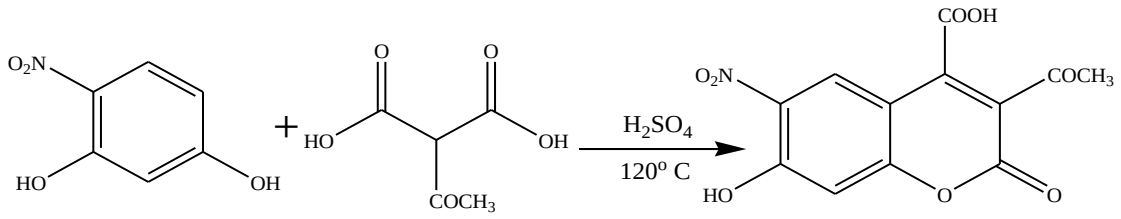
2-formyl-3-oxobutanoic acid

3-acetyl-7-bromo-5-hydroxy-8-methyl-2*H*-chromen-2-one

**Fig 4. Synthesis of coumarin derivative C-3 (Scheme 3)**

***Procedure of synthesis for C4***

In synthesis of compound C3, 4-nitrobenzen-1,3-diol was used as starting reagent to get the desired coumarin derivative. In this process, 4-nitrobenzen-1,3-diol was made reacted with 2-acetylmalonic acid in the presence of sulfuric acid at the temp. of 120ºC. Thus, the desired coumarin derivative was obtained as 3-acetyl-7-hydroxy-6-nitro-2-oxo-2H-chromene-4-carboxylic acid as final product.




4-nitrobenzene-1,3-diol

2-acetylmalonic acid

3-acetyl-7-hydroxy-6-nitro-2-oxo-2*H*-chromene-4-carboxylic acid

**Fig 5. Synthesis of coumarin derivative C-3 (Scheme 4)**

***Procedure of synthesis for C5***

2-methylphenol was used in the synthesis of coumarin derivative C5. In this procedure, 2-methylphenol was made reacted with 3-hydroxypropanoic acid in the presence of conc. Sulfuric acid to produce 7-hydroxy-8-methyl-2H-chromen-2-one as intermediate. This intermediate was further made reacted with 4-chlorobenzenamine to get the final derivative as 3-(4-aminophenyl)-7-hydroxy-8-methyl-2H-chromen-2-one (C5).

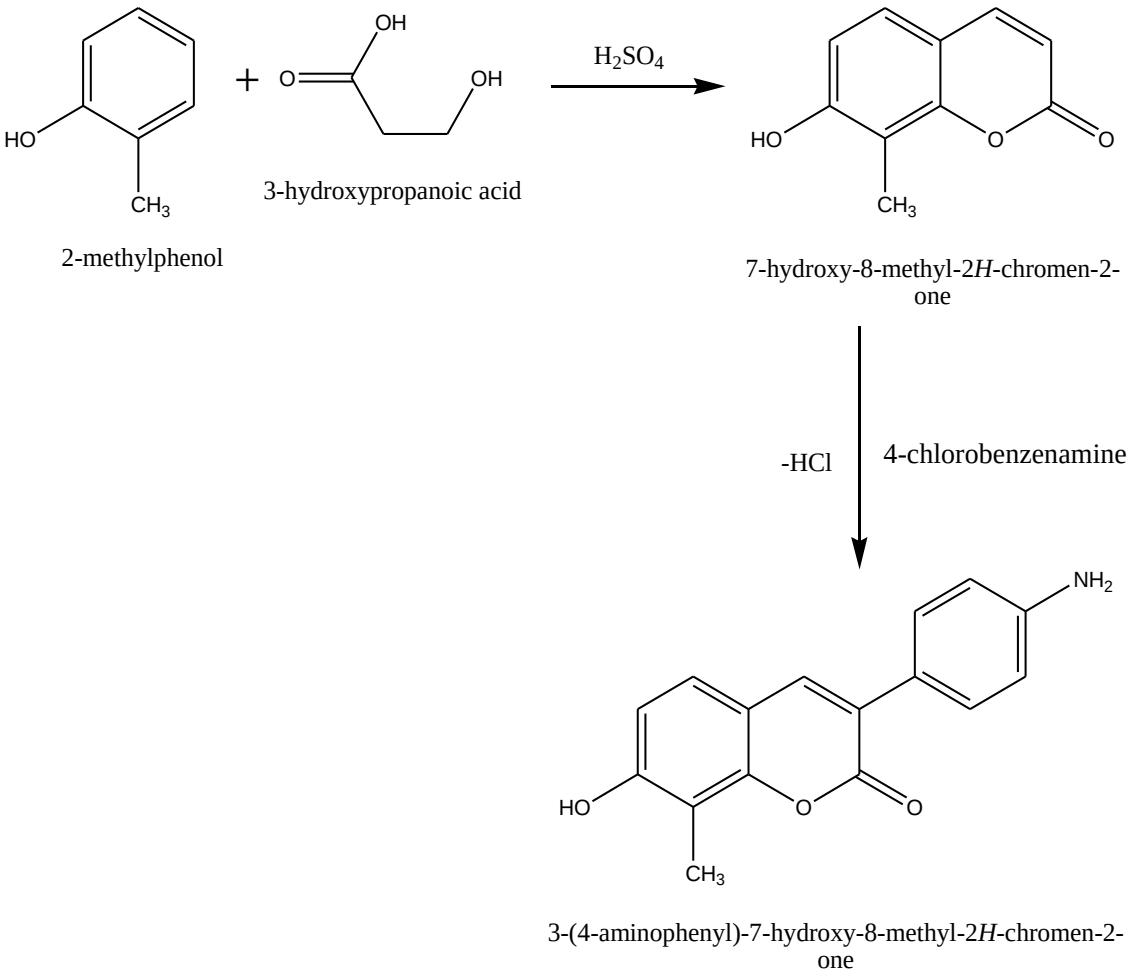



**Fig 6. Synthesis of coumarin derivative C-3 (Scheme 5)**

***Procedure of synthesis for C6***

The 5-chloro-2-hydroxybenzaldehyde on reaction with phenyl-1H-pyrrol-2yl-propandioate in presence of ethanol &Phenyliodinediacetateat 30-40˚C produced 1H-pyrrol-2-yl-7-chloro-3-oxo-3,4-dihydronaphthalene-2-carboxylate as intermediate product. In presence of this intermediate product get converted into desired novel coumarin derivative with the name as 1H-pyrrol-2-yl-7[(acetyloxy)methyl]-3-oxo-3,4-dihydronaphthalene-2-carboxylate.

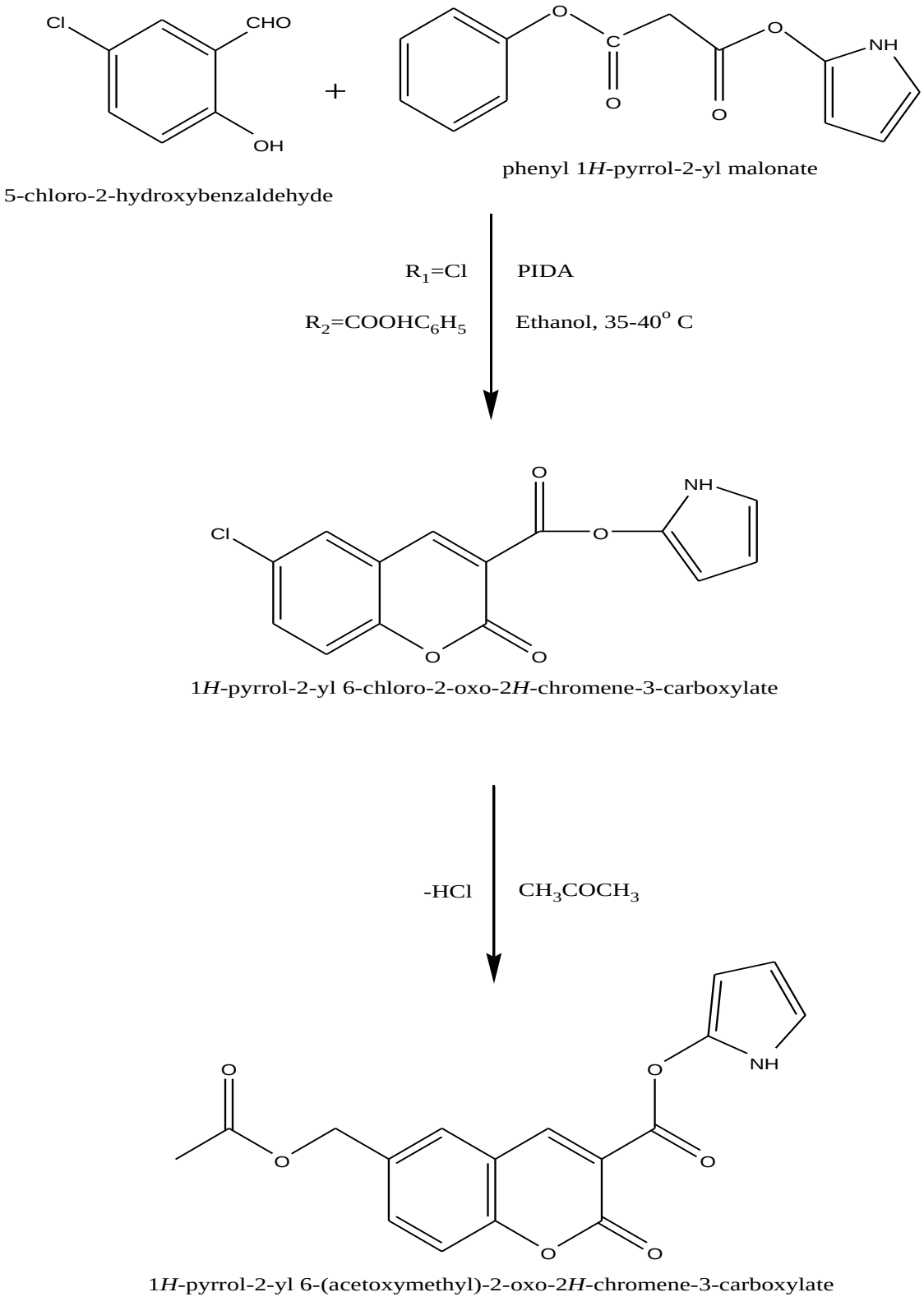
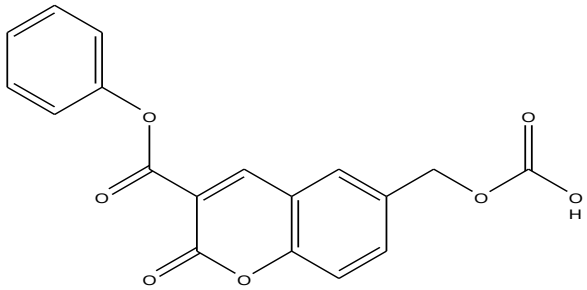
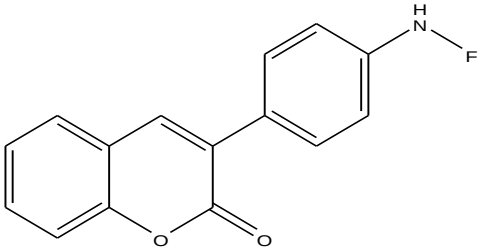
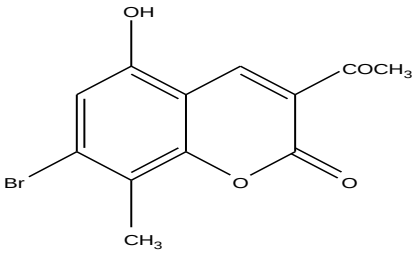
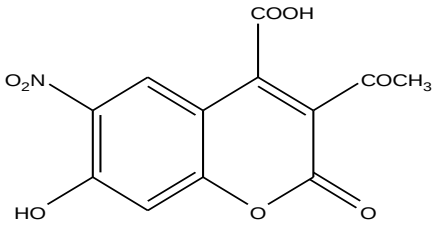
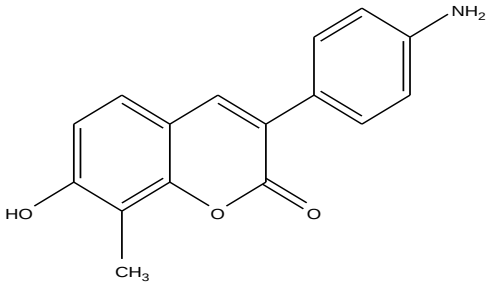
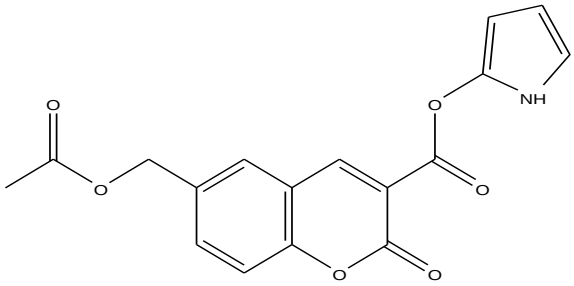



**Fig 7. Synthesis of coumarin derivative C-5 (Scheme 6)**

**Table 1. Structures of synthesized compounds**

| Code | Structure of synthesized compound | IUPAC Name |
|---|---|---|
| **C1** |  | (3-(phenoxycarbonyl)-2-oxo-2H-chromen-6-yl)methyl hydrogen carbonate |
| **C2** |  | 3-(4-(fluroamino)phenyl)-2H-chromen-2-one |
| **C3** |  | 3-acetyl-7-bromo-5-hydroxy-8-methyl-2H-chromen-2-one |
| **C4** |  | 3-acetyl-7-hydroxy-6-nitro-2-oxo-2H-chromen-4-carboxylic acid |

| | | |
|---|---|---|
| **C5** |  | 3-(4-aminophenyl)-7-hydroxy-8-methyl-2H-chromen-2-one |
| **C6** |  | 1H-pyrol-2-yl-6-(acetoxymethyl)-2-oxo-2H-chromen-3-carboxylate |

**Identification of physical properties**

***Melting point determination***

Melting point determination: Thiel's melting point tube was used to determine the melting point of an organic compound (capillary tube method). The most important and straightforward means of distinguishing one compound from another is to determine its melting point.

***Thin Layer Chromatography (Rf value)***

TLC stands for thin layer chromatography and is used in synthetic chemistry to infer the production of a molecule based on its Rf value, which varies depending on the compound. It also aids in confirming the reaction's progress.

**Preparation of animals**

Albino rats of either sex weighing 150–200 g will be obtained from the Animal House, Department of Pharmacy, IIMT University, Meerut (UP) India. The animals are maintained in proper conditions, at room temperatures of 25 ± 1°C with 12-hour light/dark cycle. The relative humidity is maintained at 44-56%, and are fed with standard rodent diet and water ad libitum. Animals will keep on fasting but free access to water up to 1 h before the induction of paw edema (Bhajoni et al. 2016).

**Experimental protocols**

All the rats are divided into four groups (n=6) as followings-

Group 1: rats are given only normal saline each day for 21 days.

Group 2: rats are given carrageenan (2%) intradermally for 21 days.

Group 3: rats are given carrageenan (2%) + indomethacin (10mg/kg/day, p. o.) for 21 days.

Group 4: rats are given carrageenan (2%) + all the novel coumarin derivatives (200mg/kg/day, p. o.) for 21 days.

Group 5: rats are given carrageenan (2%) + all the novel coumarin derivatives (400mg/kg/day, p.o.) for 21 days.

**Evaluation parameter**

***Carrageenan- induced paw edema***

The rats were divided into 4 groups, each weighing 180–220 g. The studied chemicals were given intra-peritoneally in the dose of 0.01 mmol/kg (body weight), suspended in the water added few drops of Tween 80 and pulverized in a mortar before use. The right foot pad received 0.1 ml of carrageenan (2%) intradermally, with the left paw served as a control. Simultaneously with the phlogistic agent, indomethacin (the reference medication) was given intraperitoneally. Both hind paws are diagnosed, just above the ankle joint and recorded for the volume of inflammation. The medication treatments are repeated at 5, 10, 15, and 21 days (Christos et al. 2005).

**RESULTS AND DISCUSSION**

Novel Coumarin derivatives (C1-C6) were developed by following scheme. The procedure was followed as conventional procedures for the coumarin synthesis, already mentioned in materials and methods section. After synthesis, all the derivatives undergone evaluation of physical parameters in terms of % yield, melting point and molecular weight.

**Identification of physical properties**

***Melting point determination***

Melting point determination: Thiel's melting point tube was used to determine the melting point of an organic compound (capillary tube method). The most important and straightforward means of distinguishing one compound from another is to determine its melting point.

***Thin Layer Chromatography (Rf value)***

TLC stands for thin layer chromatography and is used in synthetic chemistry to infer the production of a molecule based on its Rf value, which varies depending on the compound. It also aids in confirming the reaction's progress.

All the synthesized derivatives of coumarin were tested for their physical properties. Various profiles i. e., percentage yield, melting point, molecular weight and functional groups attached with were tested. C4 demonstrated for its highest % yield as 81.51 and lowest was seen in C2 as 63.21. Melting point was estimated as 180ºC for C1 and

highest was found in compound C6 as 248ºC. Highest melting point indicates about the strongest density of the compound. Molecular weight was also found significant in the analogues of coumarin developed. Molecular weight was found as 295.51, 311.37 and 325.61 for C4, C5 and C6 respectively. Maximum Rf was seen in C-6 as 83. The following table summarized physical properties of all the compounds.

**Table. Physical properties of synthesized coumarin derivatives (C1-C6)**

| Compound | Yield (%) | Rf Value | Melting point | Molecular weight |
|---|---|---|---|---|
| C1 | 72.34 | 0.68 | 180ºC | 195.21 |
| C2 | 63.21 | 0.73 | 195ºC | 256.21 |
| C3 | 67.72 | 0.82 | 217ºC | 276.42 |
| C4 | 81.51 | 0.79 | 235ºC | 295.51 |
| C5 | 79.47 | 0.67 | 189ºC | 311.37 |
| C6 | 75.61 | 0.83 | 248ºC | 325.61 |

### *Infrared Spectroscopy*

Infrared spectroscopy (IR) is one of the most essential methods for determining different functional groups and probable chemical structures. The main benefit of IR over other techniques is that it easily produces fingerprints (1300-650 cm-1) of molecules' structure (functional group, associating with one other). There are no two compounds with the same fingerprint region. This method is based on the molecular vibration of the chemical, which causes each bond to vibrate at a particular frequency, which corresponds to the IR frequency. As a result, IR spectra of each bond will be created. On a Jasco V410, FTIR spectra were obtained in KBr powder.

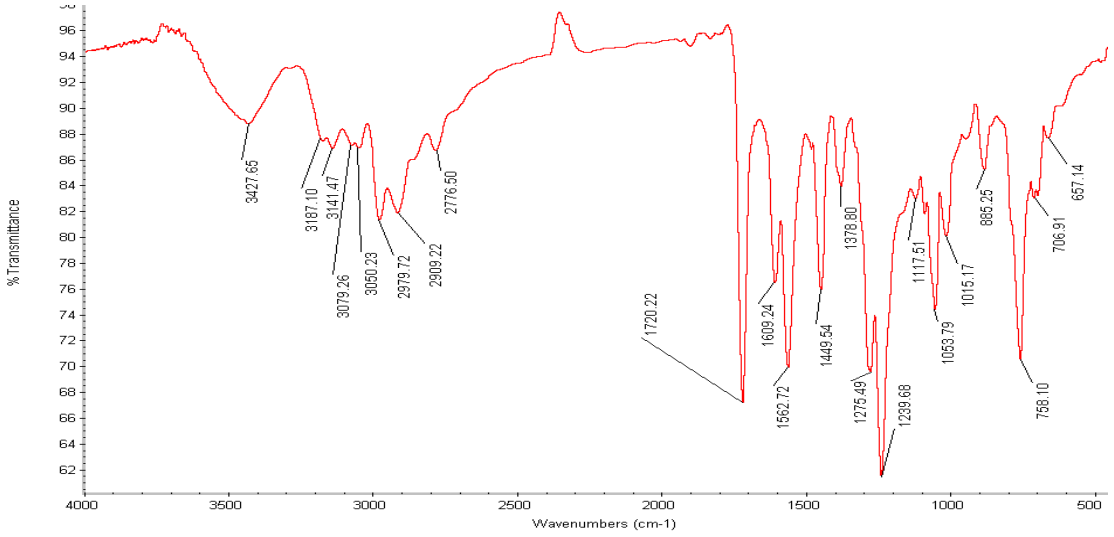



**Fig 8. IR Spectrum (C-1)**

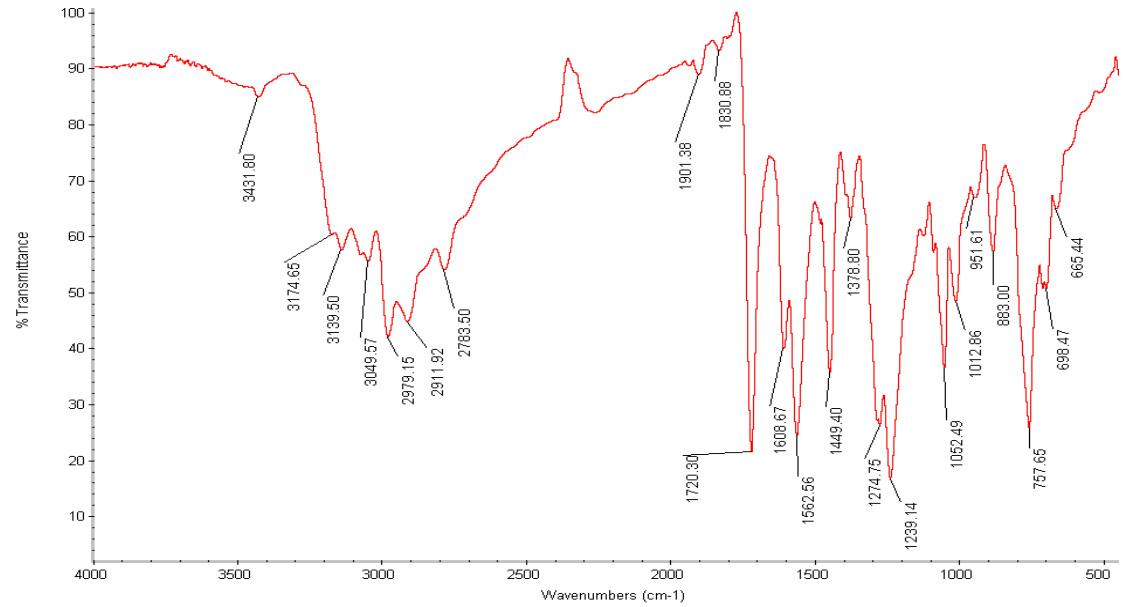



**Fig 9. IR Spectrum (C-2)**

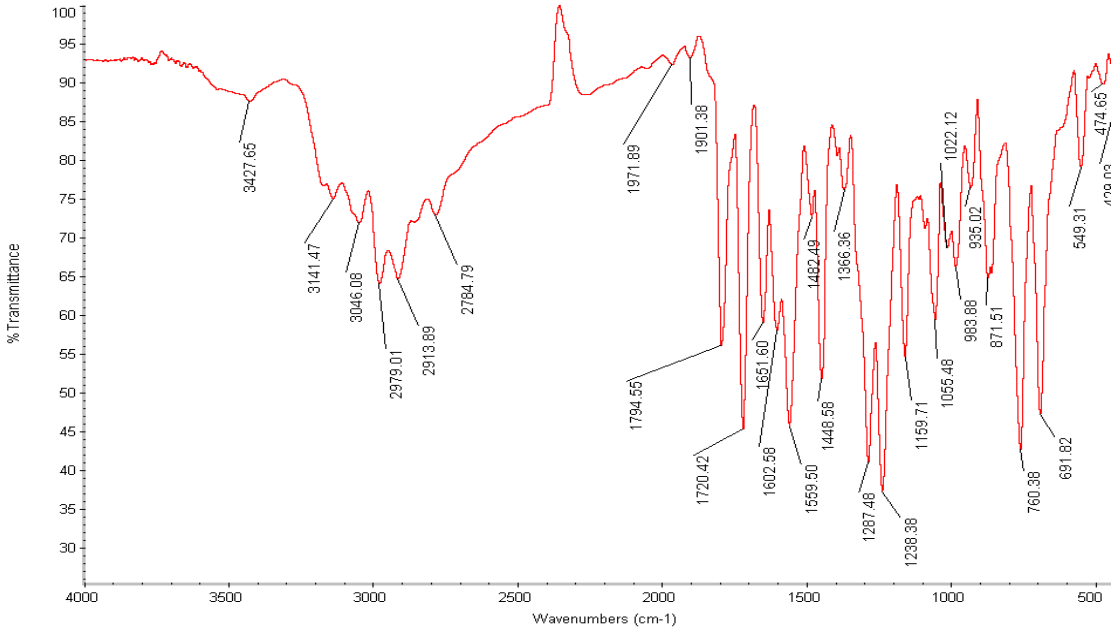



**Fig 10. IR Spectrum (C-3)**

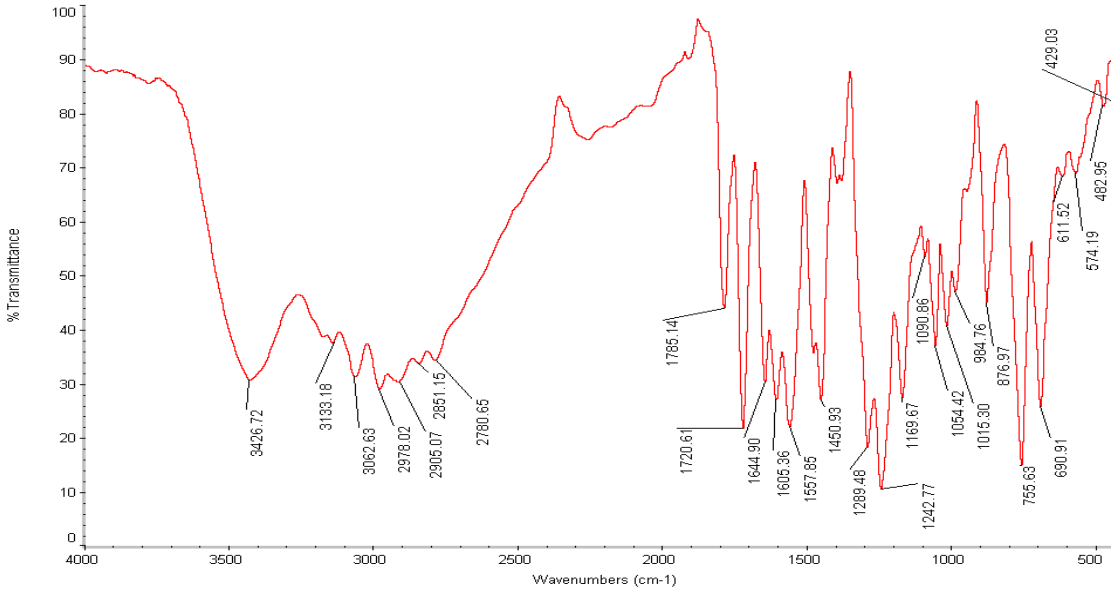



**Fig 11. IR Spectrum (C-4)**

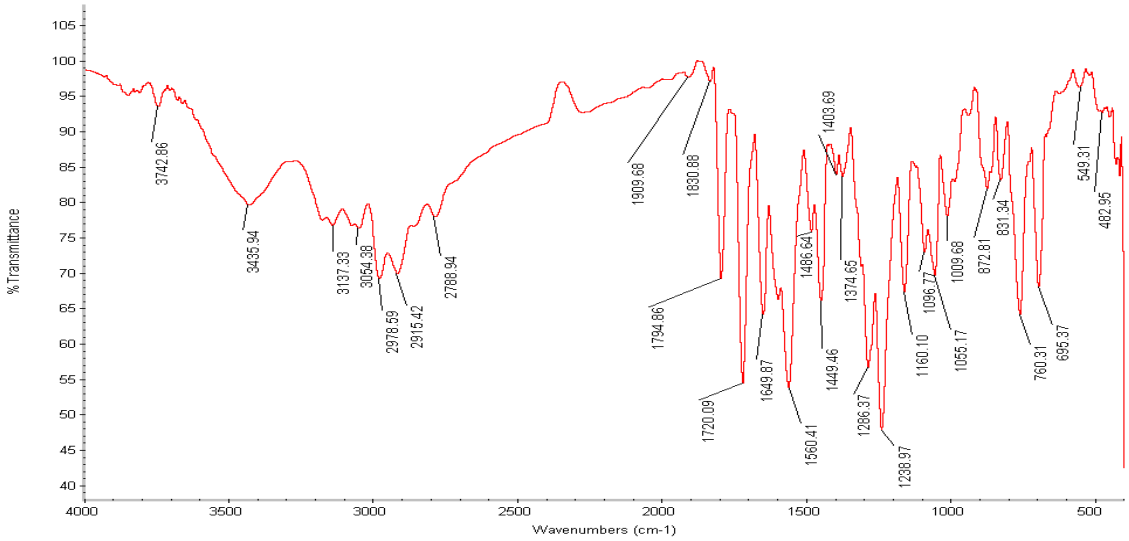



**Fig 12. IR Spectrum (C-5)**

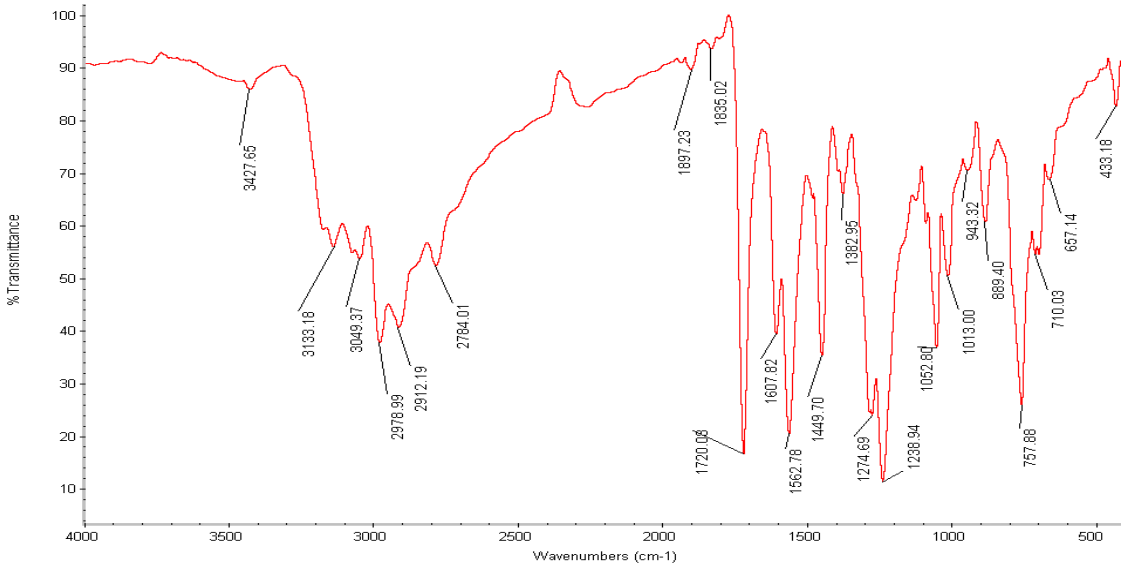



**Fig 13. IR Spectrum (C-6)**

***NMR Spectroscopy***

By exposing a substance to two magnetic forces, one fixed and the other fluctuating at a radio frequency, the interaction between matter and electromagnetic forces can be seen. The sample detects energy at a certain combination of fields, and absorption is detected as a change in single developed by a radio frequency detector and amplifier. The magnetic dipolar character of a spinning nucleus can be linked to this absorption energy. Nuclear Magnetic Resonance is the name for this technology. This method is beneficial for determining the molecule's structure. A Bruker Ultraspec 500MHz/ AMX400MHz spectrometer was used to measure 1H- NMR spectra in CDCl3 and d6-DMSO.

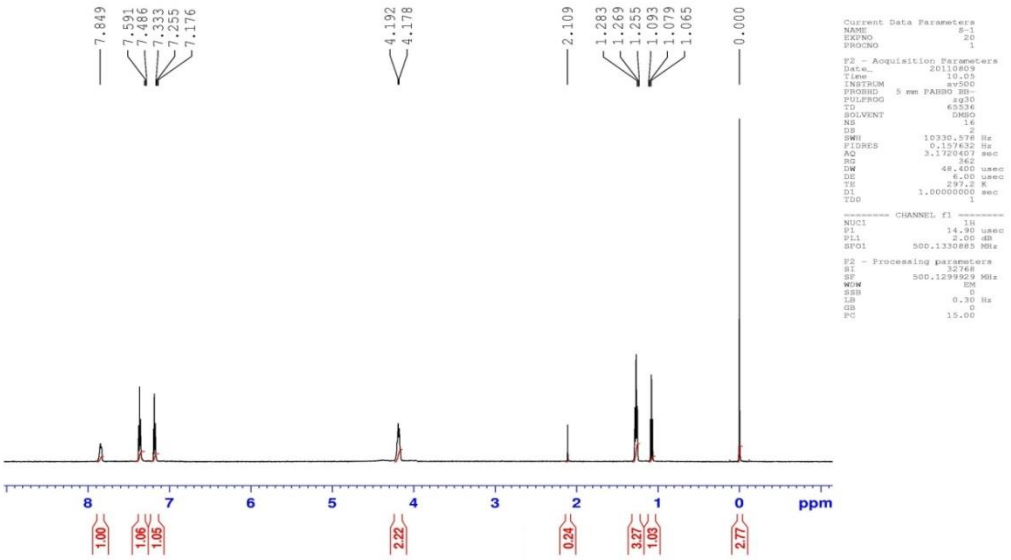



**Fig 14. NMR Spectrum (C-1)**

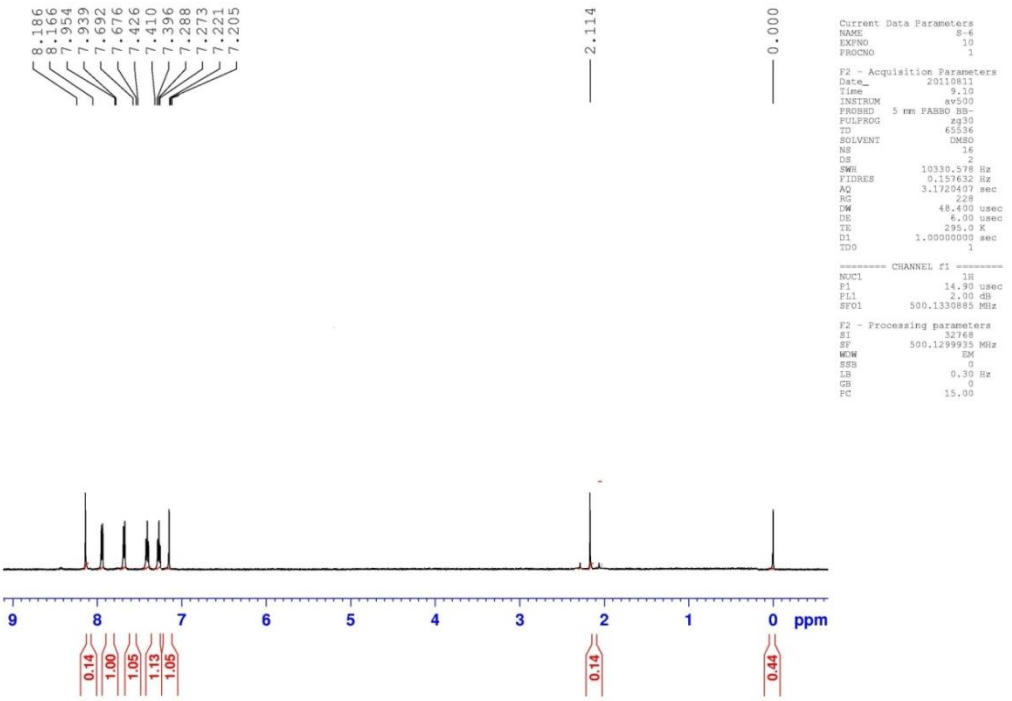



**Fig 15. NMR Spectrum (C-2)**

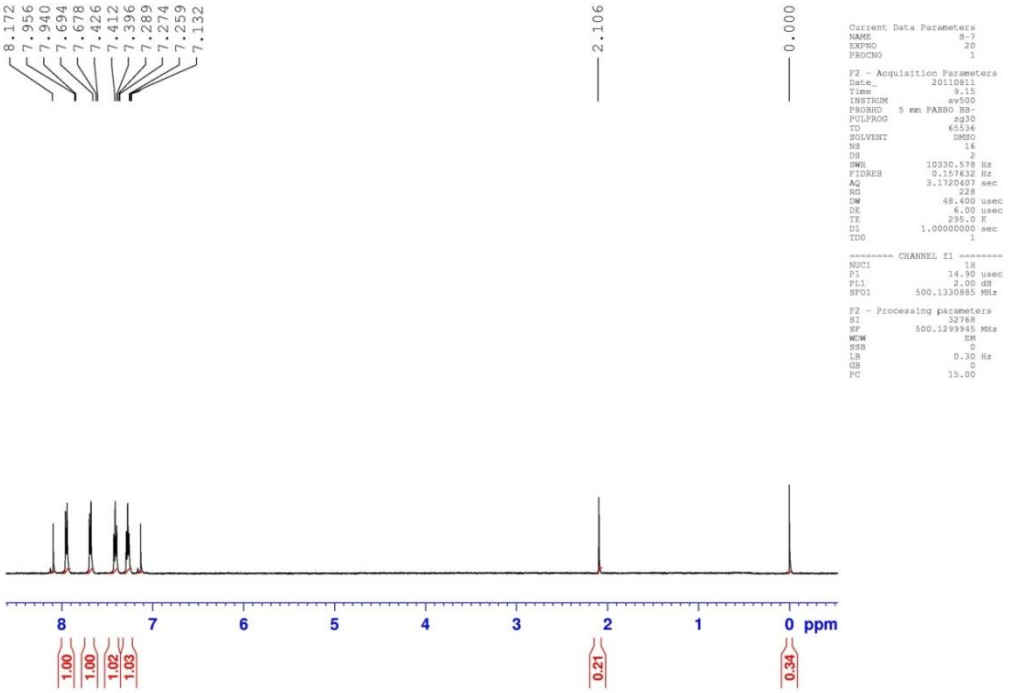



**Fig 16. NMR Spectrum (C-3)**

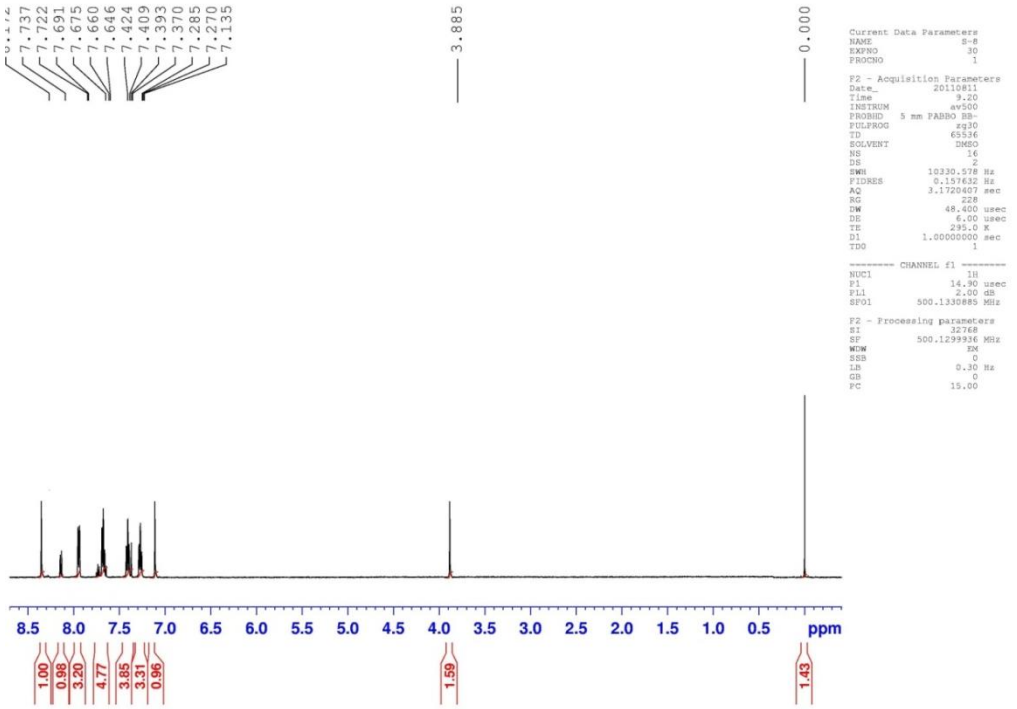



**Fig 17. NMR Spectrum (C-4)**

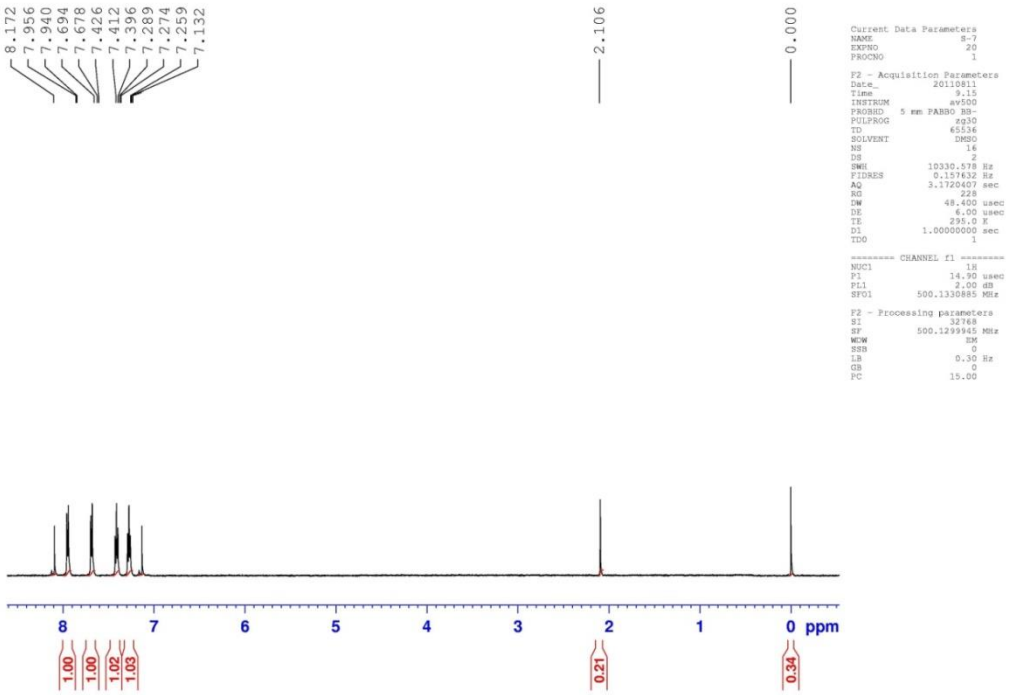



**Fig 18. NMR Spectrum (C-5)**

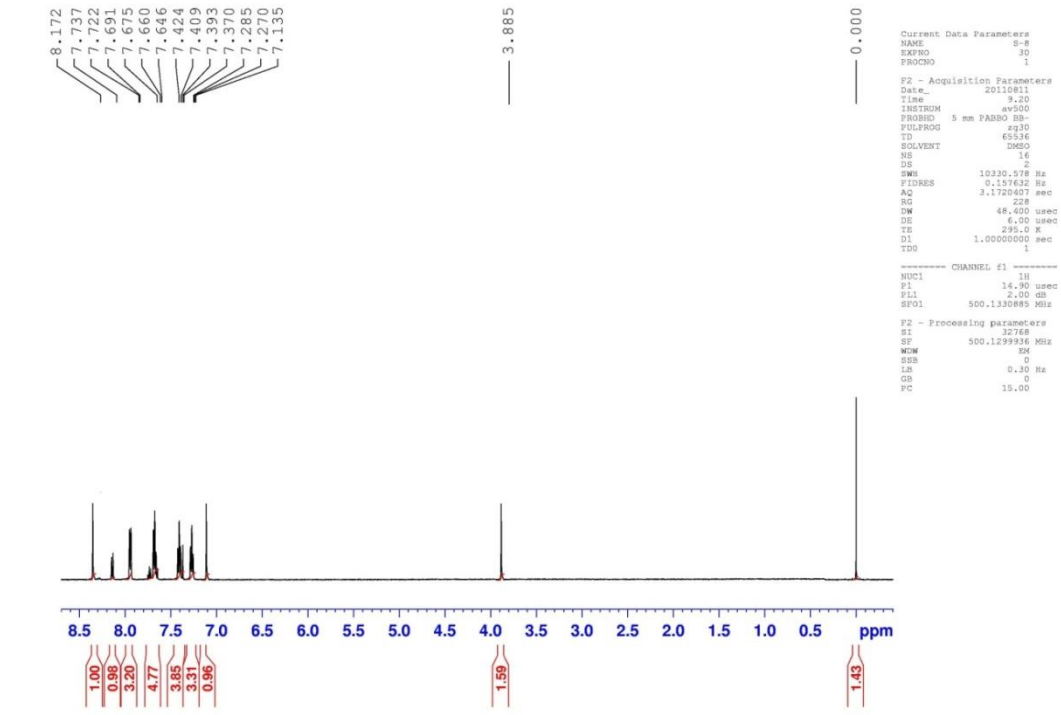



**Fig 19. NMR Spectrum (C-6)**

**Carrageenan induced paw edema**

All the coumarin derivatives (C1-C6) were evaluated for anti-inflammatory effect by using carrageenan induced paw edema model. In this method, carrageenan (2%) was given to group 1 in the dose of 0.1 ml for 21 days on daily basis. After completion of treatment time, they all were evaluated after 30, 60, 120 and 180 minutes for reduction in paw edema. The activity was estimated at 100mg/kg and 200mg/kg separately. Indomethacin was given in the dose of 10mg/kg b. w. of rats.

Compound C1, C2, C3, C4, C5 and C6 showed the volume of left hind paw as 2.32±0.41, 2.10±0.51, 2.41±0.09, 2.36±0.03, 2.37±0.20 and 2.28±0.11 respectively when observed at the dose of 100mg/kg, whereas indomethacin treated group showed 2.10±0.32 and control group 2.85±0.12, after 30 min of treatment. It showed that all the synthesized compounds exhibited significantly anti-inflammatory potential when compared with standard and control group.

**Table 2. Volume of left hind paw in control (1ml), standard (10mg/kg) and coumarin derivatives (C1-C6) at 100mg/kg**

| Compounds | Dose (mg/kg) | Volume of left hind paw (Mean± SEM) | | | |
|---|---|---|---|---|---|
| | | 30 min | 60 min | 120 min | 180min |
| Carrageenan (2%) | 0.1 ml | 2.85±0.12** | 3.57±0.08*** | 4.21±0.31** | 4.77±0.07** |
| Indomethacin + Carrageenan | 10 | 2.10±0.32)** | 2.40±0.16** | 2.77±0.42** | 3.42±0.09** |
| C1 + Carrageenan | 100 | 2.32±0.41** | 2.72±0.19** | 3.71±0.40** | 3.91±0.14*** |
| C2 + Carrageenan | 100 | 2.10±0.51** | 2.36±0.17** | 3.14±0.17*** | 3.76±0.06** |
| C3 + Carrageenan | 100 | 2.41±0.09*** | 2.70±0.04*** | 3.89±0.06** | 3.92±0.04** |
| C4 + Carrageenan | 100 | 2.36±0.03*** | 2.62±0.08** | 3.29±0.12** | 3.73±0.37** |
| C5 + Carrageenan | 100 | 2.37±0.20** | 2.69±0.31** | 3.16±0.29** | 3.67±0.27** |
| C6 + Carrageenan | 100 | 2.28±0.11*** | 2.91±0.26** | 3.43±0.05*** | 3.86±0.30** |

Significance Level= *

Values were given in Mean ± S.E.M. and found statistically significant at P<0.05, compared to control (n=6).

Compound C1, C2, C3, C4, C5 and C6 showed the volume of left hind paw as 2.23±0.02, 2.10±0.51, 2.56±0.14, 2.25±0.13, 2.47±0.26 and 2.20±0.09 respectively when observed at the dose of 200mg/kg, whereas indomethacin treated group showed 2.13±0.12 and control group 2.72±0.32, after 30 min of treatment. It showed that all the synthesized compounds exhibited significantly anti-inflammatory potential when compared with standard and control group.

**Table 3. Volume of left hind paw in control (1ml), standard (10mg/kg) and coumarin derivatives (C1-C6) at 200mg/kg**

| Compounds | Dose (mg/kg) | Volume of left hind paw (Mean± SEM) | | | |
|---|---|---|---|---|---|
| | | 30 min | 60 min | 120 min | 180min |
| Carrageenan (2%) | 0.1 ml | 2.72±0.32** | 3.47±0.18** | 4.22±0.32** | 4.71±0.16*** |
| Indomethacin + Carrageenan | 10 | 2.13±0.12*** | 2.51±0.19** | 2.52±0.17*** | 3.59±0.25** |
| C1 + Carrageenan | 200 | 2.23±0.02*** | 2.822±0.10** | 3.63±0.52** | 3.9 1±0.14** |
| C2 + Carrageenan | 200 | 2.10±0.51** | 2.36±0.17** | 3.14±0.19** | 3.54±0.12*** |
| C3 + Carrageenan | 200 | 2.56±0.14** | 2.68±0.06*** | 3.79±0.26** | 4.20±0.23** |
| C4 + Carrageenan | 200 | 2.25±0.13** | 2.69±0.13*** | 3.53±0.31** | 3.42±0.31** |
| C5 + Carrageenan | 200 | 2.47±0.26*** | 2.50±0.08*** | 2.94±0.23** | 3.62±0.24** |
| C6 + Carrageenan | 200 | 2.20±0.09** | 2.73±0.36** | 3.27±0.15*** | 4.41±0.23** |

Significance Level= *

Values were given in Mean ± S.E.M. and found statistically significant at P<0.05, compared to control (n=6).

**% Inhibition of Inflammation**

The % inhibition was recorded in all the treated animals. It was found maximum in the indomethacin treated group as a sign of potent COX (cyclooxygenase) inhibitor. All the synthesized compounds (C1-C6) also demonstrated better % inhibition. Indomethacin

itself showed % inhibition as 78.73. Compound C1, C2, C3, C4, C5 and C6 showed % inhibition as 64.42±0.42, 64.89±0.08, 67.32±0.51, 69.82±0.21, 71.22±0.27 and 68.11±0.31 respectively.

**Table 4. % Inhibition of Indomethacin and C1-C6**

| Compound | % Inhibition (Mean ± SEM) |
|---|---|
| Indomethacin | 78.73±0.31 |
| C1 | 64.42±0.42 |
| C2 | 64.89±0.08 |
| C3 | 67.32±0.51 |
| C4 | 69.82±0.21 |
| C5 | 71.22±0.27 |
| C6 | 68.11±0.31 |

When compared anti-inflammatory activity among all compounds, C-5 was found excellent moiety in terms of maximum % inhibition comparable to standard group. Novel coumarins derivatives synthesized successfully and exhibited significant anti-inflammatory activity at both the doses used. The response was noted as dose-dependent. Maximum inhibition was recorded in the dose of 200mg/kg of coumarins.

This action might be due to involvement in suppression of prostaglandins, cytokines responsible for edema and inflammation, in fact. It may be assumed that these derivatives blocked COX and LOX enzymes.

## CONCLUSION

As the results indicate that synthesized novel coumarins derivatives exhibited significant anti-inflammatory activity at both the doses. The response was noted as dose-dependent (100mgkg & 200mg/kg). Maximum inhibition was recorded in the dose of 200mg/kg of coumarins when given with carrageenan. This action might be produced through involvement in suppression of prostaglandins, cytokines responsible for edema and inflammation, in fact. It may be assumed that these derivatives blocked non-selectively COX and LOX enzymes and thus subside the production of inflammatory mediators & inflammation.

In conclusion, novel coumarin derivatives might be much significant in reducing the inflammation and counter it. As they are obtained from the plant source mainly, so it will become an easiest way to avail widely.

**Future Prospective of Study**

Various coumarin derivatives have been synthesized and evaluated for their pharmacological potentials in different areas such as Diabetes mellitus, Parkinson, Alzheimer, anti-nociceptive, ulcer etc.

It emphasizes on to synthesize and confirm its actual anti-inflammatory potential by using in-vivo models. This research will indicate the highest level of anti-inflammatory effect in the specific coumarin derivative after being compared to all derivatives.

It suggests to isolate and formulate that specific coumarin derivative and develop in desired dosage form to avail the highest potency and intrinsic activity. It also needed to further researchers to affirm its mode of action for anti-inflammatory response. Due to easy availability of coumarins (natural sources) its production would be cost effective and will available among all even economy class patients.

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Nil.

**CONFLICT OF INTEREST**

Authors have declared for none conflict of interest.

**REFERENCES**

1. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol.* 2001;2:675–680.

2. Al- Majedy, Yasameen, Ahmed Al-Amiery, Abdul Amir Kadhum, Abu Bakar Mohamad. Antioxidant Activity of Coumarins, Sys Rev Pharm., 2017; 8(1): 24-30.

3. Bhajoni et al. Evaluation of the Antiulcer Activity of the Leaves of Azadirachta indica: An Experimental Study. Integrative Medicine International, 2016; 3:10–16.

4. Christos A. Kontogiorgis,KyriakosSavvoglou& Dimitra J. Hadjipavlou-Litina. Anti-inflammatory and antioxidant evaluation of novel coumarin derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry, 2005; 21(1): 21-29.

5. Detsi A, Christos K, Dimitra H L. Coumarin derivatives: an updated patent review (2015-2016), 2017; 27(11): 1201-1226.

6. Gerrard A. Coumarins, Encyclopedia of Toxicology, Third Edition, 2014.

7. Hamelers I, Schaik R, Sussenbach JS, Steenbergh PH. *Cancer Cell Int.* 2003;3:10.

8. Katsori A M, Dimitra H L. Coumarin derivatives: an updated patent review (2012 – 2014). Experts Opinion on Therapeutic Patents, 2014; 24(12): 1323-1347.

9. Keating G, O' Kennedy R. The Chemistry and Occurrence of Coumarins. Coumarins: Biology, Applications and Mode of Action. (Eds: O' Kennedy R, Thornes RD), Chichester, John Wiley & Sons, 1997; 23-66.

10. Matern Ulrich, P L, Dieter Kreusch. Biosynthesis of Coumarins. Comprehensive Natural Products Chemistry, 1999; 1: 623-637.

11. Wu Yi, J Xu, Y Liu, Y Zeng, G Wu. A Review on Anti-Tumor Mechanisms of Coumarins. Front. Oncol., 2020; 10:592853.

12. Zhao D, Islam MN, Ahn BR, Jung HA, Kim BW and Choi JS: In-vitro antioxidant and anti-inflammatory activities of Angelica decursiva. Archives of Pharmacal Research, 2012;35:179-92.

13. Zhou Y, Hong Y, Huang H. Triptolide Attenuates Inflammatory Response in Membranous Glomerulo-Nephritis Rat via Downregulation of NF-κBSignaling Pathway. *Kidney and Blood Pressure Res.* 2016;41:901–910.