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REVIEW ON POTENTIAL ACTIVITY OF SYNTHETIC COUMARINS AS ANTI-INFLAMMATORY AGENTS

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***Abstract*:**

Inflammation is a defense mechanism used by body tissues to protect them against stimuli that they perceive to be harmful, such as pathogens, damaged cells, and irritants. The most common treatments for inflammation are nonsteroidal anti-inflammatory drugs (NSAIDs). Coumarin and its derivatives have some basic pharmacological properties like anti-inflammatory, anti-coagulant, antibacterial, antifungal, anti-HIV, antioxidant, antidepressants, antidiabetic, anti-allergic, anti-cancer, anti-proliferative, and antiviral. The purpose of this review is to investigate the synthetic scheme of novel coumarin derivatives that have been reported to have COX-1, COX-2, and TNF-alpha inhibitor activity. Various of the compounds described have also undergone in-vivo testing. Also, we performed in-silico study of various lead compounds originated from mentioned synthetic strategies against 4PH9 and 2AZ5 receptor.

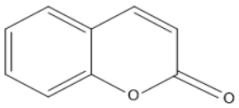
Keywords:

Coumarins, Inflammation, NSAIDs, Cyclooxygenase, TNF-Alpha

INTRODUCTION:

A fundamental immune system response is inflammation which aims to protect and maintain tissue homeostasis during tissue injury or pathogenic infection. Redness, pain, swelling, heat and loss of function are the symptoms of inflammation. However, inflammation can lead to life-threatening conditions [1,2]. Inflammation can be classified into two types: Acute inflammation can be caused due to the damage of tissue which occurs because of trauma, invasion of microbes, or noxious compounds. It starts quickly, in short span of time it becomes severe and its symptoms can last for few days. Another type is chronic inflammation which can also termed as slow, long-term inflammation which last for long periods of times generally from months to years. The cause of the injury and the body's capacity to heal and repair the harm are the main determinants of the extent and results of chronic inflammation [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common treatments used in inflammation. Also, these medications are widely useful all over the world [4]. Indomethacin exhibit a potent anti-inflammatory action and it is also used as an antipyretic and analgesic agent to treat various medical conditions [5]. The history of anti-inflammatory dated back to 1900's when aspirin was developed but depends upon doses, it usually causes gastric upset and in higher dosage it delays the process of child birth and in overdose may harms the kidney [6]. Looking forward, the improvement of new, safer NSAIDs is utmost important, as most current NSAIDs have critical aspect effects, which include gastrointestinal (GI) toxicity and cardiotoxicity, hepatic injury, renal damage, gastric injuries that might cause gastric ulceration later which may even lead to death [1,7]. Inflammation is a factor in a number of diseases, including diabetes mellitus (DM), neoplasms, neurodegenerative illnesses, and other serious conditions [8]. Cyclooxygenase (COX), an enzyme that primarily activates the formation of prostaglandins (PGs) from arachidonic acid and NSAIDS works by suppressing COX enzyme. Cyclooxygenase has two isotypes, one of which is COX-1 (constitutive), while the other is COX-2 (inducible) [9]. Most frequently, inflammatory mediators such plasma proteases, arachidonic acid metabolites (like PGE2 and leukotrienes), histamine, serotonin, nitric oxide, cytokines (including lipoxins, interleukins 1-16, and tumor necrosis factor-a), and chemokines are targeted in order to reduce inflammation [1]. Numerous medications, including indomethacin, ibuprofen, naproxen, etc., have already been documented to treat inflammation [10].

Coumarins is recognized as a naturally occurring polyphenolic compound. This ring is composed of fused benzene and a-pyrone rings due to which it is also termed as 1,2-benzopyrone. The pharmacological properties of coumarin and its derivatives include **anti-inflammatory**, antimicrobial, antifungal, anti-HIV, antioxidant, anti-allergic, antidepressant, antidiabetic, anti-cancer, anti-proliferative, and antiviral properties [11,12]. Coumarin derivatives can be developed by a variety of processes, including the Witting reaction, Perkin reaction, Pechmann reaction, Claisen rearrangement and Knoevenagel condensation [13]. Several studies have shown that coumarin derivatives can block the cyclooxygenase and lipoxygenase pathways of the arachidonate metabolism [14]. The lipoxygenase, cyclooxygenase and T-alpha (Tumor Necrosis Factor -alpha) enzymes, as well as the suppression of prostaglandin formation, are the main causes of the anti-inflammatory effect of coumarin derivatives. Numerous new coumarin compounds have anti-inflammatory properties. They function by reducing tissue edema, by changing the actions of certain enzymes, including cyclooxygenase and lipoxygenase, and by preventing the production of free radicals [15].



COUMARIN

In this article, we evaluate various synthetic strategies to develop a library of newer coumarin derivatives that have potent anti-inflammatory activity.

Fig. 1: SYNTHETIC SCHEME [1]

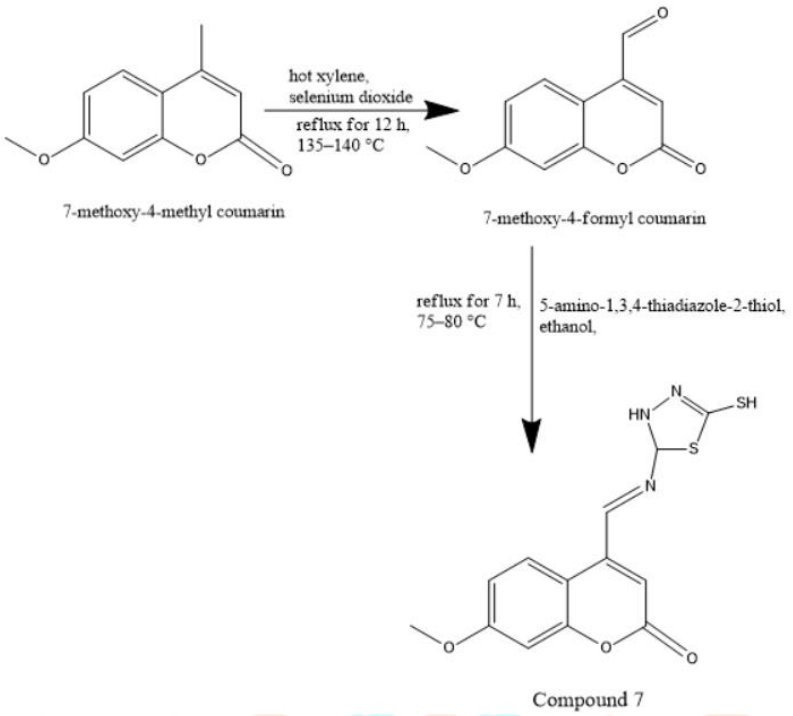


TABLE 1: NOMENCLATURE OF SYNTHESIZED COMPOUNDS [1]

S. No.	Compound	IUPAC NOMENCLATURE	Reference
1.	5	[(E)-[(7-hydroxy-2-oxo-2H-chromen-4-yl)methylidene]amino]thiourea	[1]
2.	6	4-[(E)-[(4-acetylphenyl)imino]methyl]-7-methoxy-2H-chromen-2-one	
3.	7	7-methoxy-4-[(E)-[(5-sulfanyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)imino]methyl]-2H-chromen-2-one	
4.	8	4-[(E)-[(7-methoxy-2-oxo-2H-chromen-4-yl)methylidene]amino]benzoic acid	

Shokhan J. Hamid et.al., 2022 has reported a series of 7-hydroxy-4-methylcoumarin and 7-methoxy-4-methyl-coumarin derivatives as shown in Fig. 1 that were synthesized and docked concerning the COX-2 enzyme inhibitor as target which leads to potent and effective anti-inflammatory drugs. A series of compounds was synthesized by mixing 7-hydroxy-4-formyl coumarin and 7-methoxy-4-formyl coumarin with different compounds to form 4 derivatives of Schiff bases. According to the data analyzed, compound 5 and 8 shows a lesser rate of inhibition relative to the standard compound (5 = 84.7– 87.4% and 8 = 86–88.35%). But, **compound 7** i.e.: 7-methoxy-4-[(E)-[(5-sulfanyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)imino]methyl]-2H-chromen-2-one seems to become a most potent derivative as it has the highest predicted binding affinity, the strongest correlation between concentration and percentage of protein denaturation, the lowest P-value (0.014), and significantly more potent protein denaturation inhibition than ibuprofen, also their cytotoxicity test were performed. Although also, compound 6 shows potent anti-inflammatory effect and has more binding affinity as compared to the standard compound, but not taken into consideration due to some side effects. The IUPAC nomenclature of the various synthesized compounds is shown in TABLE -1 [1].

Fig. 2 SYNTHETIC SCHEME [16]

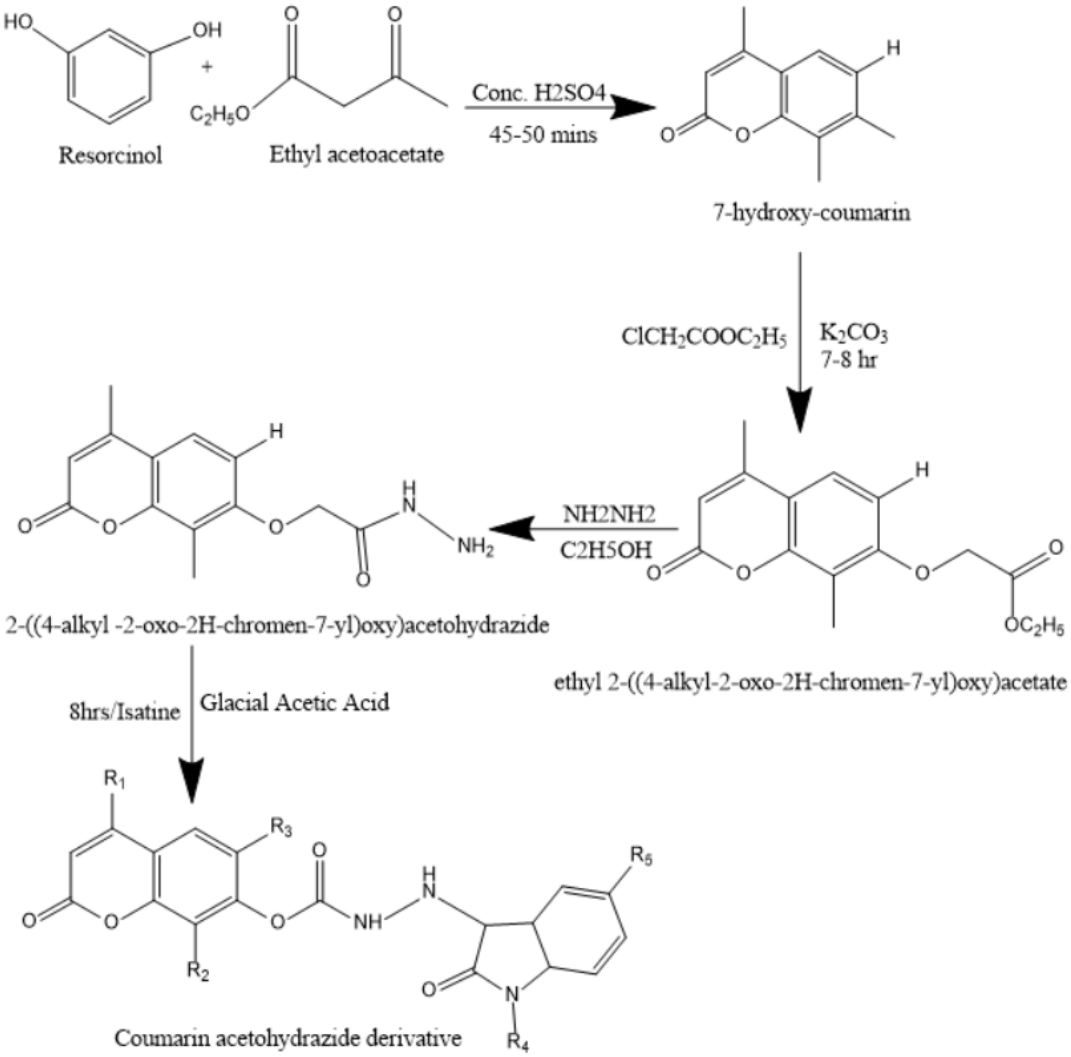
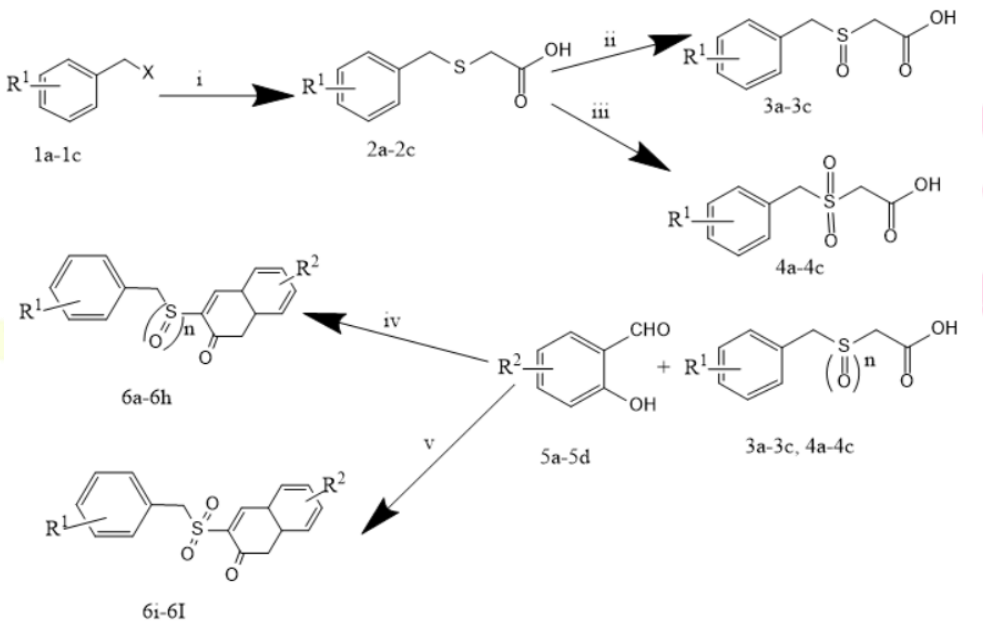


TABLE 2- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [16]

S. No.	Product code	R_1	R_2	R_3	R_4	R_5	Reference
1.	M5N	CH_3	CH_3	H	H	NO_2	[16]
2.	C1M	CH_3	H	H	H	Cl	
3.	P1M	CH_3	H	H	CH_3	H	
4.	P5N	CH_3	H	H	H	NO_2	

Adsule Prajakta V. et.al, 2021 have proposed the designing and synthetic scheme to derive the substituted coumarin acetohydrazide derivatives as shown in Fig. 2 exhibiting anti-inflammatory & anticonvulsant property. In this, 12 coumarin derivatives were screened in-silico against the COX-I enzyme coupled with flurbiprofen (PDB: 3PGH), synthesized and tested for their anti-inflammatory efficacy using the carrageenan-induced hind paw edema method, also comparative study is done taking celecoxib as standard. As a result of their study compound M5N, C1M, P1M, P5N (69.32% to 77.96%) exhibited highest inhibitory effect. Out of these mainly **compound M5N** i.e. (Z)-2-((4,8-dimethyl-2-oxo-2H-chromen-7-yl)oxy)-N-(5-nitro-2-oxoindolin-3-ylidine) acetohydrazide, which is NO2 substituted isatin showed the most potent anti-inflammatory activity among other substituted compounds. The substitution of the various product code is shown in TABLE -2 [16].

Fig. 3: SYNTHETIC SCHEME [17]



Reagents and conditions: (i) $HSCH_2COOH$, NaOH, CH_3OH, rt, 1-2 h, (ii) H_2O_2, NaOH, H_2O, rt,4h, (iii) H_2O_2, CH_3COOH, 55 °C, 5h ; (iv) EDCI, DMAP, CH3CN,rt; (v) CH_3COONa, $(CH_3CO)_2O$, 110 °C, 0.5 h.

TABLE 3- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [17]

S. No.	Compound	Substitution	Reference
1	1a	R^1 = 3-OCH_3, X = Cl	[17]
2	1b	R^1 = 4-OCH_3, 3-NO_2, X = Br	
3	1c	R^1 = 4-Br, X = Br	
4	2a, 3a, 4a	R^1 = 3-OCH_3	
5	2b,3b,4b	R^1 = 4-OCH_3, 3-NO_2	
6	2c, 3c, 4c	R^1 = 4-Br	
7	5a	R^2 = 4,6-$(OCH3)_2$	
8	5b	R^2 = 5-OCH_3	
9	5c	R^2 = 4-OCH_3	
10	5d	R^2 = 5-Br	
11	6a	R^1 = 3-OCH_3, R2 = 5,7-$(OCH_3)_2$, n = 1	[17]
12	6b	R^1 = 4-Br, R2 = 6-OCH_3, n = 2	
13	6c	R^1 = 4-Br, R2 = 6-OCH_3, n = 1	
14	6d	R^1 = 4-Br, R2 = 5,7-$(OCH_3)_2$, n = 2	
15	6e	R^1 = 4-Br, R2 = 5,7-$(OCH_3)_2$, n = 1	
16	6f	R^1 = 4-OCH_3, 3-NO_2, R^2 = 5,7-$(OCH_3)_2$, n = 1	
17	6g	R^1 = 4-OCH_3, 3-NO_2, R^2 = 7-OCH3, n = 1	
18	6h	R^1 = 3-OCH_3, R^2 = 6-Br, n = 1	
19	6i	R^1 = 3-OCH_3, R^2 = 5,7-$(OCH3)_2$, n = 2	
20	6j	R^1 = 4-OCH_3, 3-NO_2, R^2 = 5,7-$(OCH_3)_2$	
21	6k	R^1 = 4-OCH_3, 3-NO_2, R^2 = 7-OCH_3	
22	6I	R^1 = 3-OCH_3, R^2 = 6-Br	

Wang Tao et.al., 2020 created and evaluated a series of various derivatives of 3-Substituted Coumarins as shown in Fig. 3 as Anti-Inflammatory Agents. All of the substances in this investigation exhibit COX-1 and COX-2 inhibitory activity, which was assessed through in vitro and in vivo studies on the effects on the production of TNF-α, which is generated by LPS in RAW 264.7 macrophages, on cyclooxygenase, and on mice models of xylene-induced ear swelling. As a result, most of the derivatives could able to repress the TNF-α release and proven a potent COX-1 inhibitory effect at 10μM concentration. Although **6h and 6l** proved to have maximum inhibitory effects against COX-2 with 33.48% and 35.71% inhibition rates respectively. Derivatives with maximum potency of inhibition against COX-2 enzyme but have lesser inhibitory property against COX-1 were prove to have ideal anti-inflammatory properties as it would not contribute to the side effects, like gastric and renal damage. In comparison to the usual medication indomethacin, 6l showed to be the most potent compound at 10 mg/kg dose and would be taken as a lead compound for further investigation. The substitution of various synthesized compounds is shown in TABLE -3 [17].

Fig. 4: SYNTHETIC SCHEME [18]

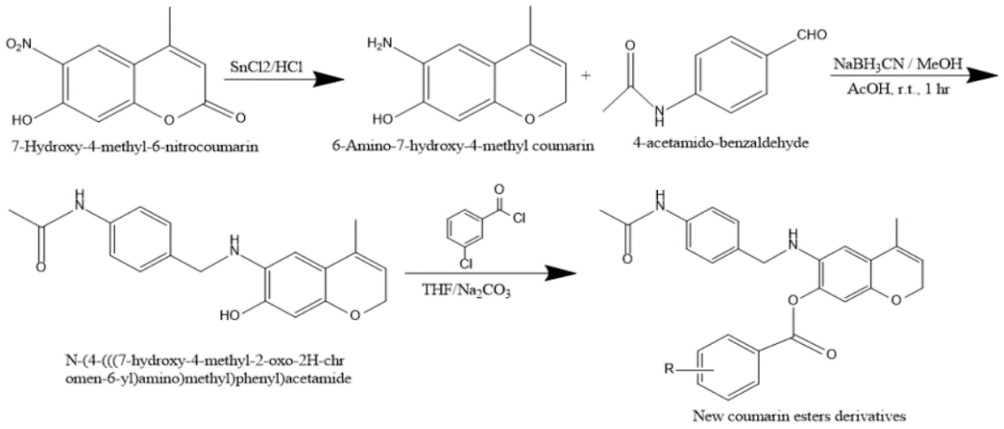


TABLE 4- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [18]

S. No.	Compound	Substitution	Reference
1.	1	R = H	[18]
2.	5	R = 3-NO_2	
3.	6	R = 4-Cl	
4.	7	R = 4-F	
5.	8	R = 4-Br, 2-F	

Wablia Reem Al et.al., 2018 synthesized some newer Coumarin esters compounds, as shown in Fig. 4 and in order to evaluate their anti-inflammatory properties, they also conducted in-vivo studies using the formalin-induced hind paw edema method and in-vitro studies using the suppression of albumin denaturation and Red Blood Cells (RBCs) membrane stability method. All the synthesized derivatives exhibit more potent effect than the parent compound 3 and standard compound Celecoxib. In their particular study they used multiple hydrophobic groups in benzoyl chloride derivatives which aims to enhance the lipophilicity and hence leads to increase the bioavailability of the synthesized compounds. As a result, derivatives 1, 5, 6, 7 and 8 exhibit remarkable anti-inflammatory effect. Out of which **compound 6** i.e.: 6-((4-acetamidobenzyl)amino)-4-methyl-2-oxo-2H-chromen-7-yl-4-chlorobenzoate exhibits most potent effect and would be taken as lead for further consideration. The substitution of various synthesized compounds is shown in TABLE -4 [18].

Fig. 5 SYNTHETIC SCHEME [19]

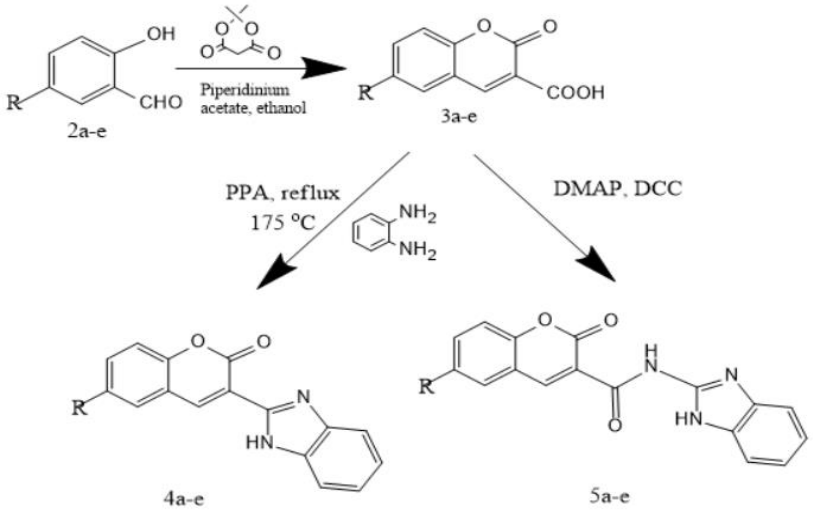


TABLE 5- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [19]

S. No.	Compound	Substitution(R)	Reference
1.	A	-H	[19]
2.	B	$-OCH_3$	
3.	C	-Br	
4.	D	-Cl	
5.	E	$-NO_2$	

Radha Krishan Arora, et.al., 2014 developed many novel compounds of coumarin–benzimidazole (4a–e and 5a–e) (as shown in Fig. 5 which have been screened for their anti-inflammatory activity and antioxidant activity. They considered indomethacin as the standard drug. This article describes the synthesis of a number of benzimidazole derivatives by coupling coumarin at the 3-position with benzimidazole at the 2-position using a single bond (series 4) or an amide linkage (series 5). According to the results, it is discovered that compounds 4c, 4d, and 5a demonstrate strong anti-inflammatory activity (inhibition values of 45.45%, 46.75%, and 42.85%, respectively, compared to indomethacin's inhibition value of 54.54%). However, series 4 exhibited better anti-inflammatory activity as compare to the series 5. Also, **compound 4d** i.e.: 3-(1H-Benzo[d]imidazol-2-yl)-6-chloro-2H-chromen-2-one and **5a** i.e.: N-(1H-Benzoimidazol-2-yl)-2-oxo-2H-chromen-3-carboxamide would be further taken as lead compounds as it showed most potent activity and as their ulcer index is low (0.67 and 0.75, respectively), compared to indomethacin's ulcer index score of 3.17, it has been demonstrated to be safe for the gastric mucosa. The substitution of various synthesized compounds is shown in TABLE -5 [19].

Fig. 6 SYNTHETIC SCHEME [13]

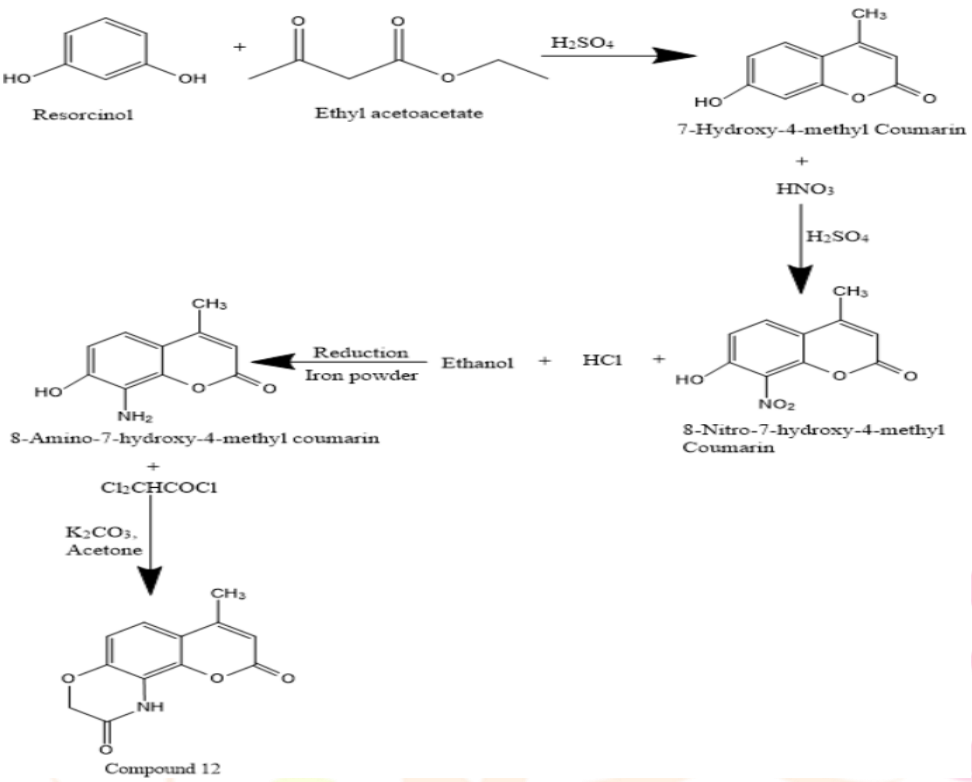


TABLE 6- NOMENCLATURE OF SYNTHESIZED COMPOUNDS [13]

S. No.	Compound	IUPAC NOMENCLATURE	Reference
1.	7	6-methyl-2-[p-benzoate]-8H-pyrano [2, 3-e] benzoxazol-8-ones	[13]
2.	8	6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8-ones	
3.	12	3-chloro-7-methyl-9H-pyrano [2, 3-e] benzo-1, 4-oxazine-2, 9-Dione	

Subhangankar Nandy et al., 2012 has created the novel derivatives of coumarins as shown in Fig. 6 and their characterization is done by IR and 1H NMR spectra, as anti-inflammatory agents and also these derivatives has been screened with biological evaluations. Ibuprofen was identified to be standard drug in this investigation. A series of thirteen compounds was synthesized, and the in-vivo activity has been performed. After 3 hours of carrageenan induction, data analysis indicates that compounds 7, 8, and 12 show larger rates of inhibition ($P<0.001$), when compared with the standard drug ibuprofen. However, time dependent studies showed that **compound 12** exhibits most potent anti-inflammatory activity because of the presence of chlorine at position 3, methyl group at position 7 on aromatic ring. The IUPAC Nomenclature of various synthesized compounds is shown in TABLE -6 [13].

Fig. 7: SYNTHETIC SCHEME [20]

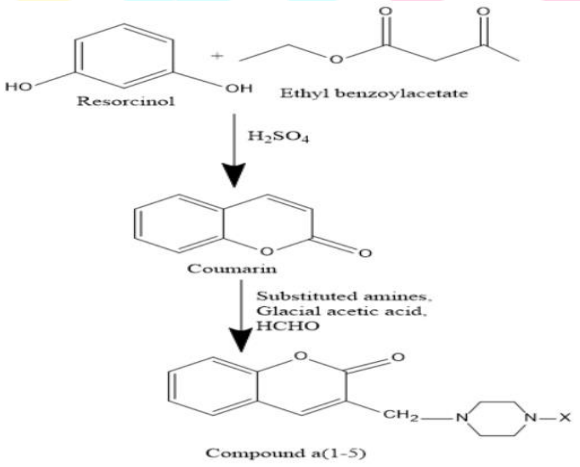


TABLE 7- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [20]

S. No.	Compound	Substitution (X)	Reference
1.	a1	$-C_{14}H_{12}FNO_3$	[20]
2.	a2	$-C_{13}H_{12}FNO_3$	
3.	a3	$-C_{14}H_{12}F_2N_2O_3$	
4.	a4	-H	
5.	a5	$-CH_3$	

Selvam et al., 2010 developed novel compounds of coumarin, as shown in Fig. 7 also their characterization and pharmacological evaluation were done as analgesic and anti-inflammatory agent. In this, a rat paw oedema model caused by carrageenan was used to study the anti-inflammatory activity and the comparative study were done between reference drug diclofenac and the synthesized derivatives. As a result, it is found that **compounds a5** i.e.: 3-((4-methylpiperazin-1-yl) methyl)-2H-chromen-2-one exhibited more potent effect at 400 mg/kg. The substitution of various synthesized compounds is shown in TABLE -7 [20].

Fig. 8 SYNTHETIC SCHEME [21]

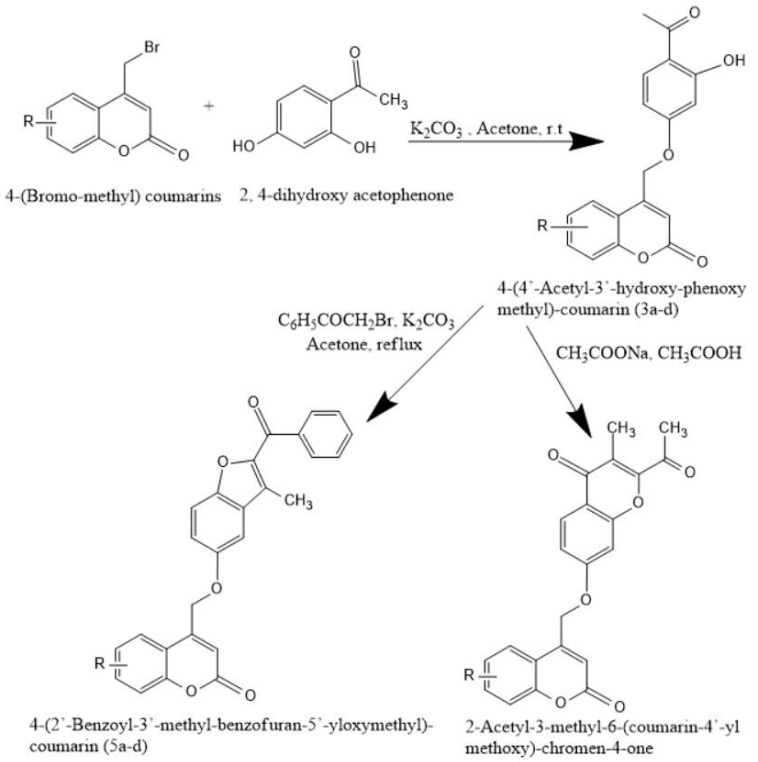


TABLE 8- SUBSTITUTION OF SYNTHESIZED COMPOUNDS [21]

S. No.	Compound	Substitution (R)	Reference
1.	A	6-CH3	[21]
2.	B	5,6-Benzo	
3.	C	6-OCH3	
4.	D	6-Cl	

Ghate M. et.al, 2005 synthesized some novel derived bi heterocyclic coumarinyl ethers derivatives as shown in Fig. 8 and evaluated their analgesic and anti-inflammatory efficacy by in-vivo study. To synthesize these derivatives various reactions are used such as Pechmann cyclization, Kostanecki synthesis, Boyd method of synthesis. In this carrageenan induced model is used to evaluate the anti-inflammatory activity. As compare to indomethacin taken as a reference, derivatives 4d, 5a, 5b, 5c and 5d proved to have satisfactory anti-inflammatory effect. In these derivatives, it is found that substitution of methoxy and chloro in coumarin ring increases the anti-inflammatory effect. As a result, benzofuranyl ethers **5a-5d derivatives** of coumarins were found to be exhibit more potent effect in all other derivatives due to change of aromatic nucleus into heterocyclic moiety. Also, the acute toxicity (LD50) of all the derivatives is found to be lesser than Indomethacin. The substitution of various synthesized compounds is shown in TABLE -8 [21].

IN-SILICO DOCKING STUDIES OF POTENT COMPOUNDS AGAINST 4PH9 AND 2AZ5 RECEPTOR

Many coumarin ring-based derivatives have already been created and tested for their improved pharmacological characteristics and decreased adverse effects. Also, we conducted the in-silico study of various lead compounds originated from above mentioned schemes against 4PH9 and 2AZ5 PDB-id via AutoDock vina software which aims to review the potency of various derivatives as Anti-inflammatory agents, so that it would be selected for the further research. In TABLE- 9, we have shown the calculated binding affinity scores along with some more properties of the compounds.

TABLE 9- CALCULATION OF BINDING AFFINITY AGAINST 4PH9 AND 2AZ5 RECEPTOR

Code	Binding Affinity Against - 4PH9 (kcal/mol)	Binding Affinity against - 2AZ5 (kcal/mol)	H- bond Donar	H- bond Acceptor	Molecular Mass (g/mol)	Synthetic Accessibility	Lipinski rule	Reference
Scheme-1								
Compound-7	-9.5	-7.2	2	5	321.37	3.94	Yes	1
Scheme-2								
Compound-M5N	-11.4	-10.2	3	8	426.38	5.0	Yes	16
Scheme-3								
Compound- 6i	-9.3	-7.6	0	6	390.45	4.71	Yes	17
Compound- 6k	-9.2	-7.8	0	6	405.42	4.63	Yes	
Compound- 6j	-9.3	-7.5	0	8	435.45	4.81	Yes	
Compound- 6I	9.5	-7.6	0	4	409.29	4.51	Yes	
Scheme-4								
Compound-6	11.1	-9.8	2	4	462.92	3.70	Yes	18
Scheme-5								
Compound- 4d	-10.5	-9.0	1	3	296.71	2.66	Yes	19
Compound- 5a	-9.6	-8.9	2	6	350.29	2.98	Yes	
Scheme- 6								
Compound-12	-9.6	-7.9	1	4	231.20	2.73	Yes	13
Scheme- 7								
Compound-a5	-9.5	-8.0	0	4	258.32	3.07	Yes	20
Scheme-8								
Compound - a	-12.1	-9.8	0	5	424.44	3.78	Yes	21
Compound - b	-12.3	-11.2	0	5	460.48	3.88	Yes	
Compound - c	-12.0	-9.2	0	6	440.44	3.85	Yes	
Compound - d	-10.8	-9.7	0	5	444.86	3.67	Yes	
Standard-1								
Ibuprofen	-7.5	-6.5	1	2	206.28	1.92	Yes	
Standard-2								
Indomethacin	-9.7	-7.6	1	3	343.80	2.45	Yes	

CONCLUSION:

Most of the anti-inflammatory agents have major side effects like cardiotoxicity, hepatic injury, renal damage, gastric injuries that might cause gastric ulceration, etc. But, coumarin-ring based derivatives were prove to have ideal anti-inflammatory properties as it would not contribute to the side effects, like gastric and renal damage in comparison to the usual medications available. Even, many of the coumarin derivatives shows more potent activity as their ulcer index is low compared to indomethacin's ulcer index score so these would be ideally safe for the gastric mucosa. Also, it is found that the acute toxicity (LD50) of most of derivatives is lesser than the standard ones, so it would definitely cause lesser side effects.

This article contains a number of ideas that generate a huge interest in further investigation, resulting in the continued development of coumarin based structures using novel method as an anti-inflammatory agent. The main focus of this review is on the several coumarin derivative schemes that each contribute in a unique way to various pharmacological areas.

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DECLARATIONS:

Ethical Approval
N/A

Competing interests
N/A

Authors' contributions
Sakshi Gupta prepared the main manuscript.

Anita Singh and Amrita Verma Pargaien prepared the figures and tables.

Sakshi Gupta and Komalpreet Kaur performed the docking studies.

All authors reviewed the manuscript.

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All data generated or analysed during this study are included in this published article.

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