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Advancements in the Field of Medicinal Chemistry with a Focus on the Therapeutic Properties of Coumarin and its Derivatives

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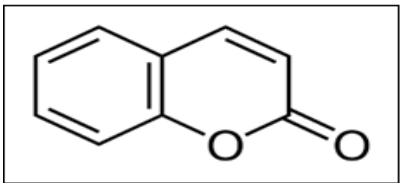
Abstract:- Researchers frequently utilize naturally occurring coumarins, which exhibit a broad range of actions like antioxidant effects, anti-inflammatory capabilities, anticancer potential, MAO-B inhibiting characteristics, and antimicrobial attributes, as a foundation for the development of innovative synthetic and semi-synthetic therapeutic agents based on coumarin. Oxygen-containing heterocyclic compounds are prevalent in both natural and synthetic substances. Coumarins are widely recognized as prominent heterocycles, characterized by the presence of a single oxygen atom within their ring structures. These compounds serve as versatile scaffolds with numerous applications, such as anti-HIV agents, pain relievers, antihistamines, insecticides, dyes, herbicides, sensitizers, fragrances, ingredients in cosmetics, and additives in the food industry. Because of their wide-ranging uses in both manufacturing and pharmaceutical industry sectors, numerous Chemists have exhibited significant interest in these substances. This review aims to emphasize various approaches for harnessing the interactions involving the coumarin moiety, which stands out as one of the most effective classes of heterocycles. Special emphasis has been placed on exploring the potential of coumarins as a vital scaffold in drug development, along with their usefulness as fluorescent markers for tasks like prodrug activation, metal sensing, and diagnostics This review brings together various research findings concerning the creation of diverse coumarin hybrids and categorizes them according to their therapeutic applications. Within this context, we conduct an examination of the current trends and pertinent subjects pertaining to coumarin and its derivative compounds.

Keywords:- *Coumarin, Heterocycle, Therapeutic uses.*

I. INTRODUCTION

For quite a considerable duration, coumarins have been recognized as fragrant components within perfumes due to their sweet aroma[1]. There are roughly 700 naturally occurring coumarin structures documented across more than 100 plant families, and this number continues to grow[2]. Coumarins, constituting a significant category of organic heterocycles, find applications in various domains of science and technology[3]. From a chemical perspective, coumarins, specifically 2H-1-benzopyran-2-one belongs to the lactone subgroup. Coumarin, which is also known as 1,2-benzopyrone or o-hydroxycinnamic acid-8-lactone, falls under this classification. Natural coumarins can be classified into six primary groups, namely: simple coumarins, furanocoumarins, pyranocoumarins (comprising both linear and angular variants), dihydrofuranocoumarins, phenylcoumarins, and bicoumarins.[4]

The initial discovery of the pure parent coumarin compound took place in 1820 when it was isolated from the tonka bean (Dipteryx odorata) by Vogel.[5] Various methodologies have since been developed for synthesizing coumarins, incorporating reactions such as the Perkin reaction, Knoevenagel condensation, Pechmann condensation, Wittig reaction, Baylis-Hillman reaction, Claisen rearrangement, and also Vilsmeier-Haack and Suzuki cross-coupling reactions.[6]



These compounds are part of the flavonoid category of secondary metabolites in plants, and they exhibit a range of biological activities, typically characterized by their low toxicity. In addition to their clinically established anticoagulant and antithrombotic effects, various natural and synthetic derivatives based on coumarin have also been discovered to possess:

Anticancer[7-10], anti-HIV, antimicrobial[11-12], antioxidant reagents[13], dyes[14,] sensitizers[15], and anti-inflammatory[16-17], antituberculosis[18] , anti-influenza , anti-Alzheimer[19-22] , antiviral and antihyperlipidemic activities[23], etc.

In recent years the molecular hybridization strategy has surfaced as a novel approach involving the fusion of two or more pharmacophores within a single molecular scaffold to create multifunctional hybrid molecules. The versatility of coumarins as a foundational structure in drug design is

pivotal, highlighting its significant role as a scaffold for fluorescent probes utilized in the detection of metals, enzymes, and biomaterials.[24-27] These fluorescent probes exhibit significant imaging potential for the diagnosis of various medical conditions.

Coumarin derivatives are well-known for their substantial fluorescence within the visible light spectrum, significant Stokes shift, high quantum yield of photoluminescence, and satisfactory solubility. This has led to their widespread exploration and notable commercial importance as organic fluorescent materials.[28-32]

II. LITERATURE REVIEW

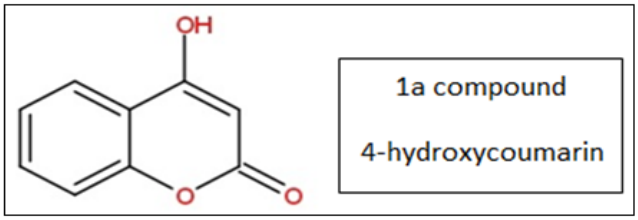
➢ *Coumarin as Anti-Oxidant:*

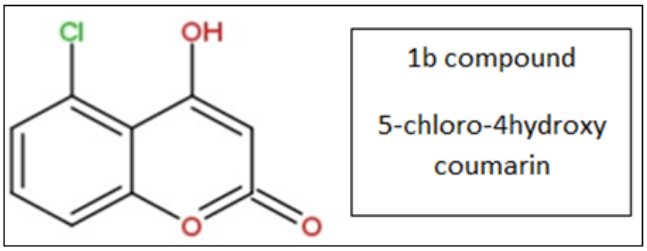
R.M. Patel et.al.2011 The study unveiled various coumarin compounds through DPPH, superoxide, and nitric oxide free radical scavenging techniques, assessing their in-vitro antioxidant properties. The primary focus of this research was to utilize coumarin scaffolds as a foundation for the development of new antioxidant agents. Specifically, the investigation involved evaluating the in-vitro antioxidant activity of 4-hydroxy, 5-chloro-4-hydroxy, and 7-hydroxy-4-methyl coumarin derivatives. The IC50 value was employed to quantify the effectiveness of these compounds. The results indicated that compounds **1a and 1b** displayed notable antioxidant activity when compared to ascorbic acid. This suggests that these compounds hold therapeutic potential in mitigating the effects of aging and oxidative stress associated with degenerative diseases.[33]

Table 1 Inhibitory Concentrations(IC_{50}µM/ml) of Coumarin Compounds

Compound no.	Inhibitory Concentration(IC_{50} µM/ml)		
	DPPH	SO	NO
1a	8.172±0.1123	6.227±0.1223***	7.496±0.1449***
1b	6.975±0.76***	7.21±0.987***	7.143±0.1138***
Ascorbic acid (standard)	8.21±0.1002	20.72±0.1135	30.01±0.3376

IC_{50} coumarin compounds when compared to ascorbic acid, ***P<0.001 vs. ascorbic acid



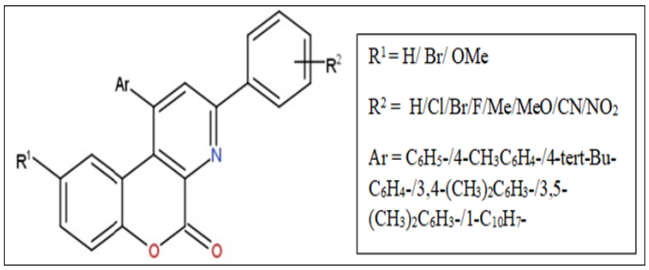


A.Khan et.al, 2012 reported a three-component reaction was employed to synthesize pyridol [2,3-c] coumarin derivatives, utilizing molecular iodine as a catalyst in one-pot Povarov reactions. This reaction involved a variety of 3-aminocoumarin, aromatic aldehyde, and phenylacetylenes, all without the need for any additional co-oxidant, resulting in satisfactory yields. Among the synthesized compounds, **2a, 2b, 2c, 2d, 2e, 2f,** and **2g** exhibited heightened potency. These compounds were subsequently characterized using a range of spectroscopic techniques. Notably, the products could be easily isolated in excellent yields without requiring any aqueous work-up process, chromatographic separation, or the involvement of a metal catalyst. Importantly, this protocol demonstrates environmentally friendly characteristics.[34]

Table 2 Synthesis of Substituted Pyrido[2,3-c] Coumarin Derivatives using Povarov Reaction

Entry	Product	Time(h)	Yield[b](%)
1.	2a	3	78
2.	2b	3	81
3.	2c	3	78
4.	2d	2	77
5.	2e	2	76
6.	2f	2	78
7.	2g	2	76

The reactions were carried out with 3-aminocoumarin(1.0 mmol),aromatic aldehydes(1.0 mmol), and phenylacetylene(1.5 mmol) in the presence of 10 mol 5 of iodine in 4ml of CH3CN under reflux conditions.



M.Ristic et.al., 2021 A novel method was devised to synthesize an azine derivative containing a coumarin moiety, which exhibited antioxidant properties. Comprehensive spectral characterization of these azine derivatives was conducted, encompassing the thorough characterization of H1 and 13C-NMR spectra, in addition to the analysis of 2D-NMR spectra (including 1H-1H COSY, NOESY, HSQC, and HMBC).

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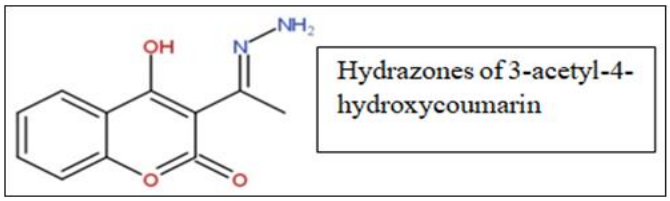
To assess the antioxidant activity of both the corresponding hydrazone and azine compounds, the DPPH method was employed. The hydrazone derivatives demonstrated significant antioxidant activity, while the azine compound displayed good antioxidant potential, having IC50 values of **11.69 µM and 216.60** µM, respectively.[35]

Table 3 DPPH free Scavenging Activity (IC_{50}, µM) of Compounds

Compound	IC_{50}(µM)
3a	11.69
3b	216.60
Ascorbic acid	7.82



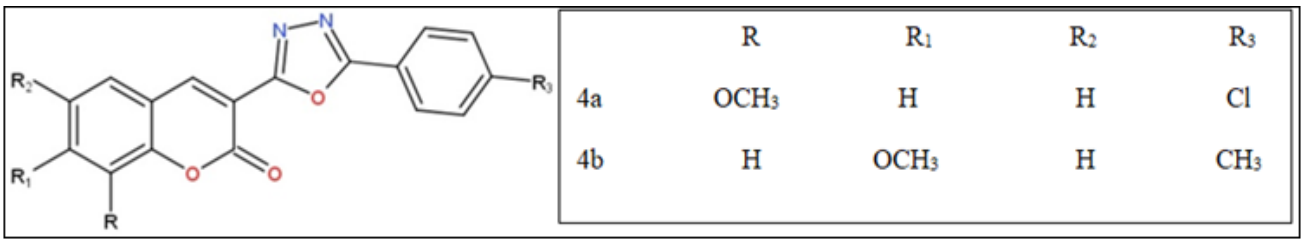
V.C.Basappa et.al., 2021 A method was developed to synthesize a series of compounds that combine coumarin with 1,3,4-oxadiazole analogues, and their antioxidant activity was investigated. The synthesis process employed green chemistry principles, involving the use of alkylated aldehydes and hydrazine hydrate derivatives, in conjunction with grinding methods in the presence of iodine to promote cyclization. The synthesized compounds were subjected to spectroscopic characterization methods, including IR, 1H NMR, 13C NMR, and LCMS.

The antioxidant properties of the synthesized compounds, as well as standard antioxidants, were assessed using DPPH and hydroxyl radical scavenging assays. Among the synthesized compounds, **4a and 4b** demonstrated the most effective radical scavenging activity, making them the top-performing antioxidants in this series.[36]

Table 4 The Antioxidant Activity in the Synthesized Series of Compounds.

Compound	DPPH radical scavenging IC_{50} (µM)	Hydroxyl radical scavenging IC_{50} (µM)
4a	19.47±1.28	32.62±0.98
4b	17.19±0.81	28.51±1.41
AA	23.80±1.21	-
BHA	-	36.05±1.68

Values are mean ± SD of three replicates (n=3); Ascorbic acid and Butylated hydroxyl anisole-----positive controls.



E.Gerasimova et.al., 2021 Highlighted in the study were instances of coumarin derivatives exhibiting antioxidant and anti-radical characteristics. The assessment of these various compounds involved investigations into their mechanisms of action, encompassing electron transfer, hydrogen atom transfer, and metal chelation mechanisms. Specifically, the study examined their antioxidant activity through electron-transfer mechanisms, establishing a correlation between AOC (Antioxidant Capacity) and antioxidant potential.

Furthermore, the compounds in the series displayed a capacity to inhibit the generation reactions of peroxyl radicals and ARC (Antiradical Capacity), indicating a reduction in their effectiveness. In summary, the synthetic derivatives of coumarin demonstrated significant potential as antioxidants, while natural coumarin derivatives proved to be potent exogenous antioxidants.[37]

M.R.Antonijevic 2021 synthesized coumarin-hydroxybenzohydrazide derivatives using an eco-friendly one-pot method and evaluated their antioxidant properties. We conducted spectroscopic characterizations of the synthesized compounds using techniques such as IR and NMR. Purity analysis for all the compounds was accomplished using the HPLC technique and elemental microanalysis.

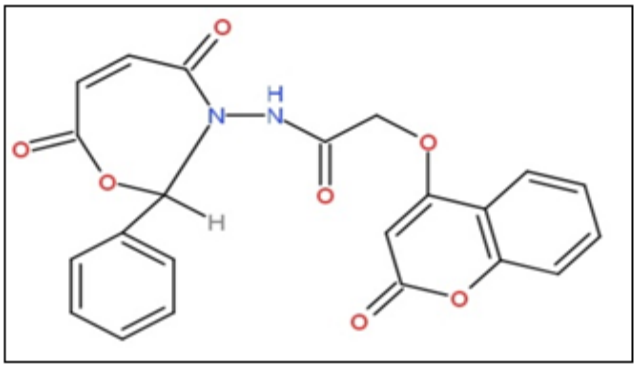
We employed a DFT (Density Functional Theory) approach to explore the mechanism of antioxidant activity. Compounds 5a, 5b, and 5c exhibited favorable yields and high purity as determined by HPLC. Conversely, compounds 3d and 3e demonstrated significant oxidant activity. During the synthesis process, compounds 5c, 5b, and 5a displayed enhanced reactivity. Notably, compound 5d showcased the highest antioxidative potential due to its lowest H-L (Highest Occupied Molecular Orbital - Lowest Unoccupied Molecular Orbital) value. Among all the compounds, compounds **5b and 5c** exhibited the most impressive antioxidant activity.[38]

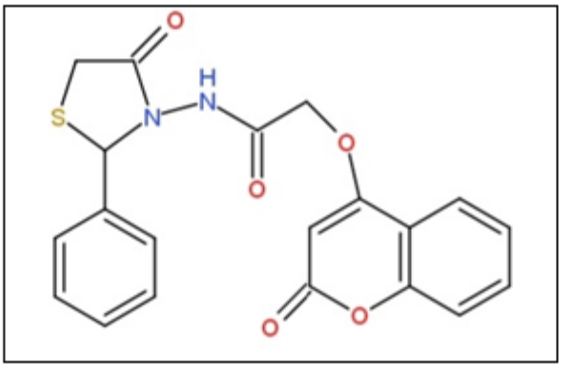
Table 5 In vitro DPPH Antioxidant Activity of Synthesized Products

Compound	IC_{50} (µM)
5b	2.9 ± 0.1
5c	12.9 ± 0.4
NDGA	1.7 ± 0.1
Quercetin	1.9 ± 0.1

A.A.H.Kadhum et.al., 2011 disclosed the synthesis of two coumarin derivatives showing antioxidant activity. The compounds N-(4,7-dioxo-2-phenyl-1,3-oxazepin-3(2H,4H,7H)-yl)-2-(2-oxo-2H-chromen-4-yloxy)acetamide and N-(4-oxo-2-phenylthiazolidin-3-yl)-2-oxo-2H-chromen-4-yloxy) acetamide were assessed in comparison to the established antioxidant ascorbic acid. Various methods, including DPPH, hydrogen peroxide, and nitric oxide radical assays, were employed for evaluation. They were successively characterized by various spectroscopic techniques and elemental analysis method.

Compounds **6a and 6b** demonstrated favorable yields and underwent screening for in-vitro antioxidant activity across various methods. The antioxidant activity of these compounds was evaluated based on two proposed mechanisms. In comparison to ascorbic acid, the compounds exhibited enhanced properties, and their initial antioxidant activity assessments were conducted.[39]



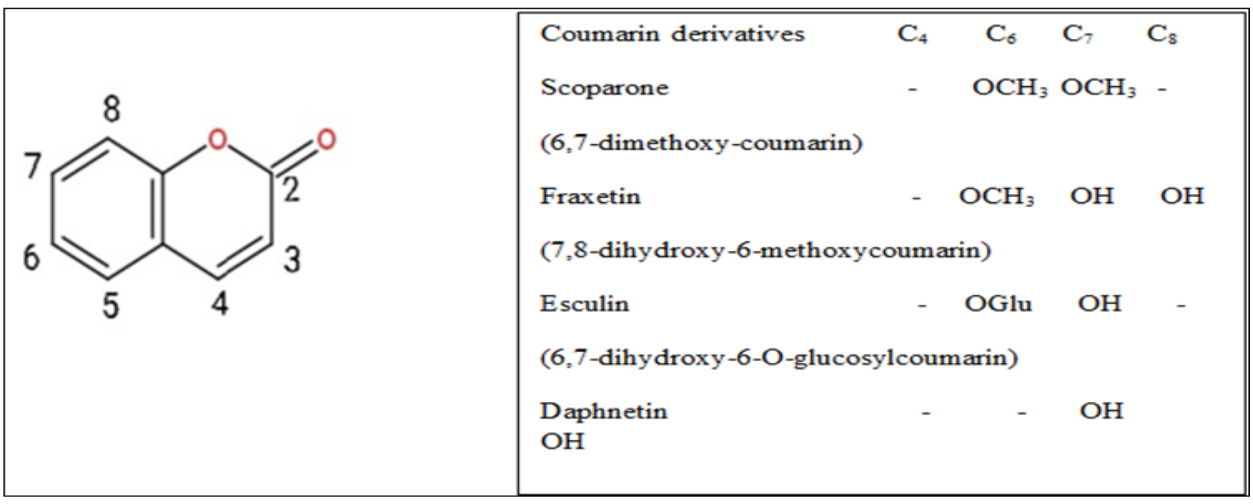


A.Witaicenis et.al., 2013 reported plant-derived derivatives of coumarin with several therapeutic effects including antioxidant and intestinal anti-inflammatory activity. Lipid peroxidation and DPPH assays were used to determine the antioxidant activity of the plant derived coumarin. Scopoletin, scoparone, fraxein, 4-methyl-umbeliferone, esculin, and daphnetin were scrutinized to investigate potential correlations between intestinal anti-inflammatory activity and antioxidant activity. The best protective result was given by when treated with esculin, scoparone and daphnetin. The consumption of coumarin and food rich in couamrin derivatives can procure the anti-inflammatory disease and antioxidant activity was related to intestinal anti-inflammmatory activity.[40]

Table 6 Coumarin Derivatives Effect on Lipid Peroxidation and Free Radical(DPPH) Scavenging Assay

Compound	lipid peroxidation ($IC_{50\text{-}\mu}M$)[a]	DPPH ($EC_{50\text{-}\mu}M$)[b]
Scoparone	inactive	0.192
Esculin	inactive	0.141
Daphnetin	24.12	0.280
Quercetin(reference)	5.73	0.148

[a]IC_{50} = 50% inhibitory concentration.
[b]IC_{50} = effective concentration to scavenging 50% of DPPH

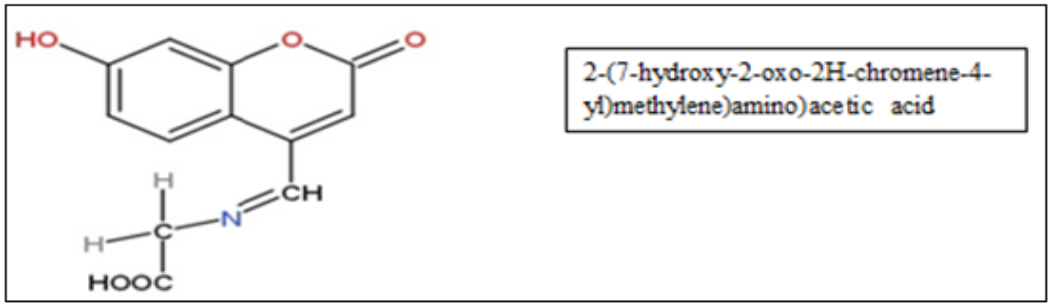


➢ *Coumarin as Anti-Microbial:*

D.M.Hussein et.al, 2017 the synthesis pertaining to 7-hydroxy-4-methyl-coumarin was documented, followed by an assessment of its antibacterial properties. The structures of the Schiff bases were characterized by FT-IR, ^{13}CNMR, and MS. The compound was synthesized by oxidation of methyl group at C4 of coumarin nucleus by using oxidizing agent SeO_2. The title coumarin derivatives were tested for their preliminary antibacterial activity using serial dilution method and by determining their minimum inhibitory concentration (MIC). We conducted antibacterial assessments against two Gram-positive and two Gram-negative bacteria, recording their minimum inhibitory concentrations (MICs). Compound **7a** exhibited the highest antibacterial activity against Gram-positive bacteria such as Staphylococcus aureus and Micrococcus leteus, as well as Gram-negative E. coli. The synthesized derivatives were further examined through DFT calculations.[41]

Table 7 Minimum Inhibitory Concentration of Coumarin Derivatives

Compound no	Staphylococcus aureus(G^{+ve}) Conc.µg/ml	Micrococcus luteus(G^{+ve}) Conc.µg/ml	Escherichia coli (G^{-ve}) Conc. µg/ml
7a	40	40	31



S.Mamidala et.al, 2020 reported a single-step, three-component synthesis of a range of coumarin-based thiazoles was carried out using microwave irradiation, followed by an assessment of their antibacterial activity and molecular docking studies. Structures of all synthesized compounds were characterized by spectroscopic technique ^{1}H &^{13}C NMR, FTIR, Mass) and analytical data. Compound **8a** was found to potent antibacterial activity with the standard against *S.aureus.*[42]

Table 8 The Antibacterial Activity of the Target Coumarin Based Thiazoles

Entry	Compound	MIC(µg/ml)*S.aureus*
1	8a	3

Standard: **Novobiocin**

S.N.Esfahani et.al, 2021 reported 3D –QSAR Studies, synthesis of a series of coumarin isoxazol sulfonamide hybrid compounds with their antibacterial effects. Several sulfonamides hybrids were synthesized and assayed for inhibition of bacterial development. The samples obtained were produced in good yield and were characterized by FT-IR, CHN, ^{13}C-NMR, ^{1}H-NMR and with melting point techniques. The effect of compound efficacy was through 3D-QSAR which is easy, cost-effective, and high throughout screening method.

9a and 9b among all synthesized sulfonamide hybrid shown highest effect against gram negative and gram positive bacteria based on the pMIC. The 3D-QSAR demonstrated in model is useful for developing new antibacterial agents were confirmed in the experimental assays. The work proposes here a computational-driven strategy for designing and discovering new sulfonamide scaffold for bacteria inhibition.[43]

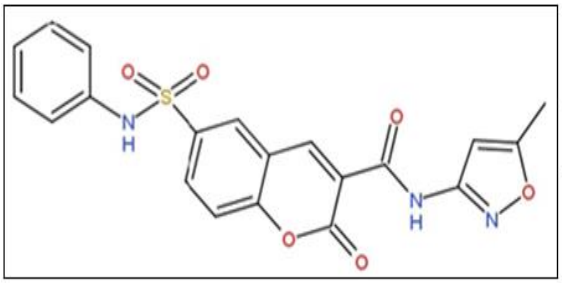
Table 9 Prediction of Biological Activity to Prediction Set

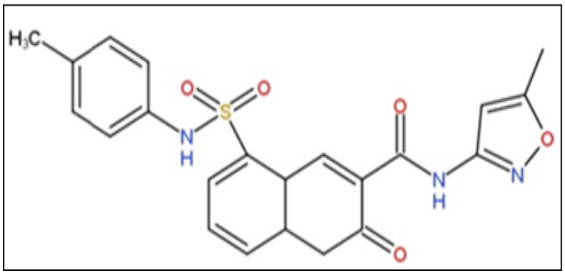
Predicted PMIC(pMIC = -log(MIC))		
Compound no	pMIC S. aureus	pMIC E.coli
9a	4.2	4.3
9b	4.3	4.4

Table 10 Minimum Inhibitory Concentrations in µg/ml of Compounds

Compound no	E.coli	S. aureus
9a	64	128
9b	32	128

Reference drug is **Muller-Hinton agar**





B.Manjunatha et.al., 2021 reported The production of azo dyes based on coumarin-benzothiazole was achieved. The structures of these newly synthesized dyes were analyzed using spectroscopic techniques such as IR, NMR, and HRMS. Computational studies were conducted to investigate the optimized molecular geometry and reactive parameters, providing a deeper understanding of the molecular properties. All the synthesized dyes were studied through molecular electrostatic potential and reduced density gradient. The energy gaps of synthesized compounds were carried through the diffuse reflectance study. Many of the properties of dyes were studied using DFT techniques. A positive solvatochromic behavior in absorption and emission study was exhibited by the synthesized dyes. Compound **10a, 10b, 10c and 10d** were potent against the bacteria. The synthesized compounds were tested for their pharmacological activity against mycobacterium tuberculosis (H37 RV strain). Enoyl-ACP reductase was used for performing molecular docking studies.[44]

Table 11 Antimycobacterial Activity of Synthesized Coumarin Dyes

Sl. No	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	10a	S	S	S	S	S	S	S	R
2	10b	S	S	S	S	S	S	S	R
3	10c	S	S	S	S	S	S	S	R
4	10d	S	S	S	S	S	S	S	R

S- sensitive; r- resistant; strain used: **M.Tuberculosis** (H_{37} RV strain): ATCC No- 27294.

The standard values for the Anti-TB test which was performed. Isoniazid- 1.6µg/ml, Ethambutol-3.2 µg/ml, Pyrazinamide- 3.125 µg/ml, Rifampicin- 0.8 µg/ml, Streptomycin- 0.8 µg/ml.

F.A.Qais et.al., 2021 disclosed the novel drug targets quorum sensing and biofilm inhibitors against gram negative bacteria. The potency The effect of coumarin was evaluated against quorum sensing-regulated characteristics in Gram-negative bacteria. The synthesis of the violacein pigment in Chromobacterium violaceum was inhibited by coumarin. The highest sub minimum inhibitory concentration of the virulence the activity of the *Serratia marcescens* MTCC 97 factor was inhibited by over 50% -5.7 to -8.1 kcal $mol^{-1}$are the energy bindings derived from docking investigations. Compound **11a, 11b, 11c** showed the good potency. Coumarin bound to the proteins' active site, resulting in the formation of a stable complex with the tested protein. Coumarin showed a good potency in opposition to the virulence factor of gram Gram-negative bacteria that have the potential to be developed into effective inhibitors of quorum sensing and biofilm formation.[45]

Table 12 Molecular Docking Values for the Interaction of Coumarin with Different Proteins using AutoDock Vina.

S. No.	PDB ID	Protein name	Binding energy (kcal mol^{-1})	Binding constant (M^{-1})
11a	IRO5	LasI	-5.7	1.5×10^4
11b	1KZF	EsaI	-6.6	6.9×10^4
11c	2UV0	LasR	-8.1	8.7×10^5

N.H.Metwally et.al., 2022 developed a range of coumarin derivatives bearing benzothiazole moieties were synthesized and subsequently evaluated for their antimicrobial effectiveness, the compounds were tested against Gram-positive bacteria, specifically *S. aureus* and *S. mutans*, as well as Gram-negative bacteria including E. coli, P. aeruginosa, and K. pneumonia. The synthesized compounds were characterized by ^{1}H NMR, IR, MS and elemental analysis. The fluorescence properties of the synthesized compounds showed high absorption band ranging from 347 to 366nm, which are caused by the π-π* electronic transition. The best potency against both the types of bacteria was compound **12a**. Compound 13a showed high activity of (25 ± 0.6) towards *S. aureus* than the reference drug ampicillin (22 ± 0.1).[46]

A.R.Nesaragi et.al., 2021 reported one-pot synthesis of compounds combining coumarin and benzoxazole with 1,2,3-triazoles was conducted under microwave conditions showing antimicrobial activity evaluated Through molecular docking and in silico ADME (Absorption, Distribution, Metabolism, and Excretion) investigations. The compounds were produced using both conventional and microwave irradiation methods to create antimicrobial agents. Docking studies revealed robust interactions involving binding with the enzyme N-myristoyl transferase, showing exceptional C-score values. The synthesized compounds were assessed for their antimicrobial potency against the fungi *Candida albicans* and *Aspergillus niger*, as well as the gram-positive bacterium *Bacillus subtilis* and the gram-negative bacterium *Pseudomonas aeruginosa*. Compounds **13a and 13b** have Remarkable antimicrobial efficacy was observed against all tested microorganisms, with minimum inhibitory concentrations (MICs) falling within the range of 3.12 to 6.25 µg/ml, surpassing the performance of commercially available drugs.[47]

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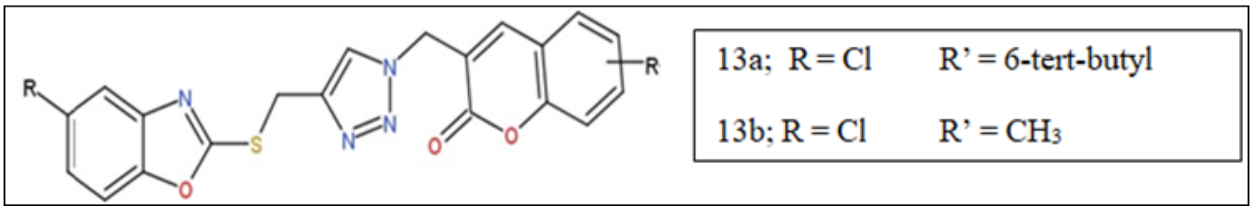
Table 13 Docking Score of the Title Compounds on Enzyme N-Myristoyl Transferase

Entry no	C score[a]	Crash score[b]	Polar score[c]	D score[d]	PMF score[e]	G score[f]	Chem score[g]
13a	7.29	-2.31	2.01	-165.329	-54.653	-307.125	-34.035
13b	6.59	-1.05	2.80	-173.854	-69.145	-252.162	-35.438
Fluconazole	5.60	-0.94	0.44	-123.137	-87.301	-197.923	-10.249
4CAW Ligand	9.22	-1.65	0.98	-177.948	-76.945	-313.307	-38.593

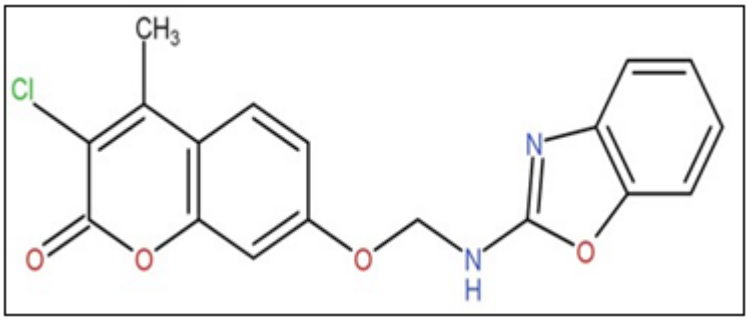


➢ *Coumarin as Anti-Cancer:*

A.F-aguilar et. al.2021 reported design, synthesis of 2-aminobenzoxazole-appended coumarin as potent and selective inhibitors of tumor-associated carbonic anhydrase. Useful SARs were obtained when substituents on C-3 and C-4 position of coumarin scaffold and benzoxazole moiety, linker connecting both the units were linked. CA inhibition study of tumor associated CAs IX and XII showed a good selectivity. The CAs activity was determined by the docking calculations. The chlorine atom on C-3 of the coumarin showed the strongest antiproliferative activity within the low micro-molar range for the panel of tumor cell lines when tested. The lead compound **14a** exhibited GI_{50} values within low micromolar range having good selectivity for the control drugs.[48]

Table 14 GI_{50} Values for the Antiproliferative Activity

Compound	A549(Lung)	HBL-100(Breast)	HeLa(Cervix)	SW1573(Lung)	T-47D(Breast)	WiDr(Colon)	BJ-hTert
14a	2.6 ± 0.5	5.1 ± 1.4	3.9 ± 0.7	3.1 ± 0.5	4.3 ± 0.1	4.2 ± 0.5	>100
5 Fluorouracil	2.2 ± 0.3	4.4 ± 0.7	16 ± 5	3.3 ± 1.2	43 ± 16	49 ± 7	5.5 ± 0.5
CDDP	4.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.5	2.7 ± 0.4	17 ± 3	26 ± 4	14 ± 2



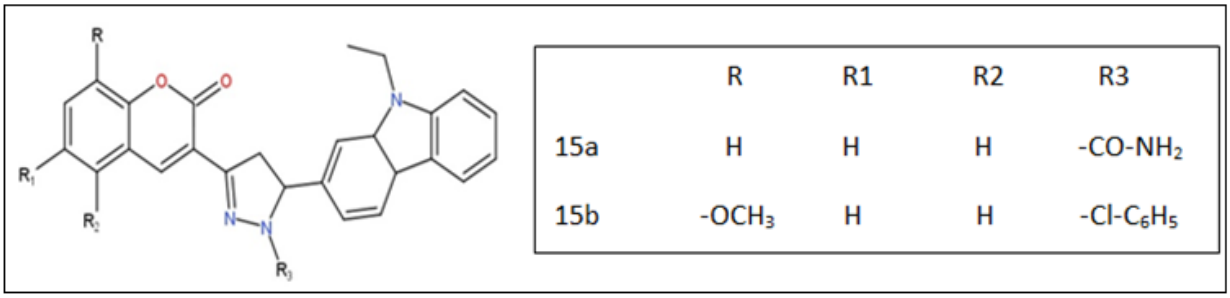
M.Patel et.al., 2021 reported the production of innovative pyrazoline structures derived from coumarin and carbazole, showcasing potential anticancer properties, along with molecular docking investigations.

The synthesized compounds underwent characterization through FT-IR, DEPT, methods involving proton NMR, carbon NMR, and mass spectrometry. In the cytotoxicity assessment, all the produced compounds underwent testing against HeLa and NCL-H520 cell lines, and NRK-52E cell lines. The remarkable cytotoxic effectiveness of the two compounds was examined, revealing their potential to halt the cell cycle in the G0 and G1 phases, and induce apoptosis in both cell lines. The high docking score inhibited by their CDK2 rationalization of the two potent candidates through molecular docking studies.

This study gives potent information for developing valuable and structurally designing the coumarin hybrid as best cancer therapeutic agents. **15a and 15b** are the most active compounds and exhibits their promising potent anticancer activity.[49]

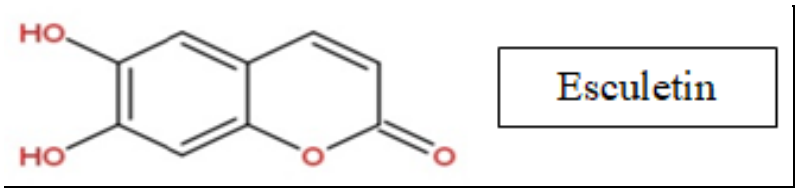
Table 15 Cytotoxicity of Compounds Assessed using HeLa, NCI-H520, and NRK-52E Cell Lines.

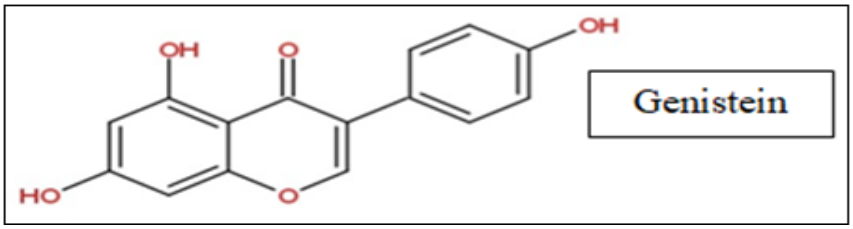
Compounds	IC_{50}, µM		
	HeLa	NCI-H520	NRK-52E
15a	12.59±0.10	11.26±0.45	28.37±1.29
15b	11.36±0.24	9.13±0.08	24.16±1.73
Cis-platin	7.75±0.42	10.41±1.35	12.93±0.40
5-Fluorouracil	55.72±2.10	8.36±0.45	46.68±3.79



	R	R1	R2	R3
15a	H	H	H	$-CO-NH_2$
15b	$-OCH_3$	H	H	$-Cl-C_6H_5$

A.Lacy et.al.,2004 reported the research on coumarin compounds aimed to investigate their potential therapeutic applications in cancer treatment.. The effect of coumarin and there derivatives compounds were investigated on a panel of cell lines. Two cell lines, specifically MCF-7 (representing breast carcinoma) and A549 (representing lung carcinoma). Cytosensor microphysiometer was used as biosensor for analysis of cell-viability and microtitre assays.The release of Cyclin D1 is inhibited by 7-hydroxycoumarin.Cell cycle progression and growth are inhibited by Esculetin which induces G1 phase arrest in HL-60 leukaemia cells that results in the inhibition of retinoblastoma protein phosphorylation. This study shows the therapeutic activity ranging from treatment of leukemia and HIV treatment in patients. **Genisten and esculetin** demonstrated the most robust inhibitory impact on cell growth.[50]





➢ *Coumarin as Anti-Inflammatory*

C.Sproll and co-worker 2007 described analytical method of coumarin in food safety assessment by using HPLC technique. It has shown that TDI value can be reached by consuming staple foods like breakfast cereals and bakery products. It has found that bakery products and breakfast cereals contains good amount of coumarin.

The highest concentration of cookies with cinnamon flavors was found to be **88mg/kg**. coumarin concentration in liqueurs, vodka, mulled with their anti-inflammatory activity.[51]

L.Kambanis et.al., 2021 reported a novel coumarin based photoliable protecting group for iterative one pot on rapid nature of diselenide-selenoester ligation reaction. A new photolabile protective group, DEAMC (7-dimethylamino-3-methyl coumarin), was created for safeguarding the side chain of selenocysteine. This protection can be removed by subjecting it to LED irradiation at 450nm.

Deprotection of the DEAMC group can be achieved gently and without the need for additional reagents, utilizing visible light. This approach holds the potential to facilitate the iterative synthesis of larger polypeptides and proteins in a one-pot assembly method.

The synthesis of 60- and 80- residue MUC1 (mucin-1) polypeptides showcased the power of the new synthetic strategies on unmatched time scales. Finally the iterative DSL approach to access ApoCIII, a aggregation-prone protein and poorly aqueous soluble protein in just 2 to 4 hours over 4 steps.[52]

D.H Litina et.al., 2007 synthesised series of coumarin analogues as potential fluorescent zinc sensors and evaluated there biological functions such as anti-inflammatory and antioxidant properties. All the synthesized compounds were synthesized by UV and TLC. Using carrageenin-induced raw paw of odema model the effect of inflammation of synthesized compounds were studied. Compound **16a, 16b, 16c and 16d** were found to be most potent in the series of synthesized compound, these compounds inhibited the soyabean inhibiting lipoxygenase and neutralizing superoxide anion radicals. The observed reduction in activity appeared to be linked to anti-inflammatory properties. The compounds lipophilicity was determined by their R_M values.[53]

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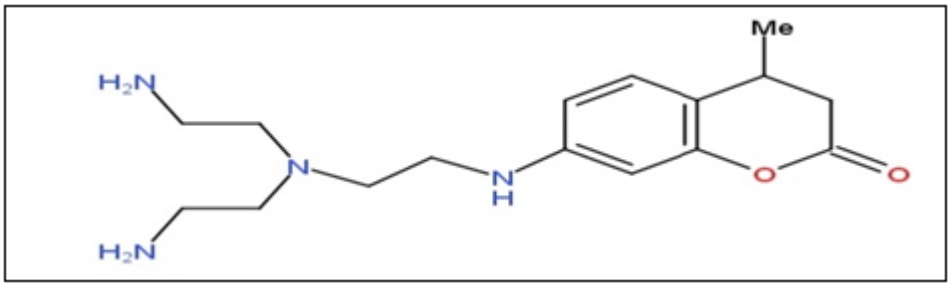
Table 16 Interaction with %Superoxide Radical Scavenging Activity(PMS %); % with DPPH (RA %)

	RA%				
Compound	**0.1mM 20 min**	**0.1mM 60 min**	**0.2mM 20 min**	**0.2mM 60 min**	**PMS% 0.1mM**
16a	7.5	1.1	11	11.4	61.5
16b	6.1	2	3.3	11.5	50
16c	11.2	4.2	4.1	5	80.8
16d	40.8	40.1	25.8	82.5	no
NDGA	81	82.6	80	80	nt
BHT	31.3	60	52.7	78	nt
Caffeic acid	nt	nt	nt	nt	45.7
Coumarin	4.9	21	nt	nt	88.9

NDGA(Nordihydroguaiaretic acid); BHT(butylated hydroxytoluene); nt: not tested; no: no action under the experimental conditions.

Table 17 Lipophilicity measurements included experimentally determined Rm values and clog P values. The evaluation criteria encompassed the percentage of inhibition in induced carrageenin rat paw edema (CPE %) and the in vitro percentage inhibition of soybean lipoxygenase (LOX).

Compound	**MgVol***	**clog P***	**R_M^+(±SD)**	**CPE(%)0.01 mmoles/kg**	**LOX(%0.1 mM)**
16a	324.42	2.33	-0.707(0.041)	26.5**±1.3	55.6
16c	390.48	1.40	-0.501(0.027)	64*±3.9	68.7
16d	289.42	1.05	-0.568(0.027)	nt	92.4
Coumarin	146.15	nt	nt	30.2**±1.8	15.1
NDGA		nt	nt	nt	83.7



III. COUMARIN AS ANTI-VIRAL AGENTS

S.Mishra et.al., 2020 reported coumarin as antiviral agent. Coumarin being a natural compound have a potential therapeutic value possessing attributes related to stability, solubility, and minimal toxicity, there is substantial evidence demonstrating its inhibitory role against many different viruses namely HIV, Influenza, enterovirus 71 and coxsackievirus A16. The mechanism of action may involve inhibition of proteins which is important for viruses entry, replication, and infection, or the modulation of cellular pathways such as the mammalian target of rapamycin. (Akt-Mtor), nuclear factor of kappalight chain enchancer of activated B-cells, and anti oxidative pathways that includes the nuclear factor erythroid 2-related factor 2. Its concluded with potential molecular mechanisms targeting influenza virus, HIV virus, hepatitis virus, dengue virus, and chikungunya virus..[54]

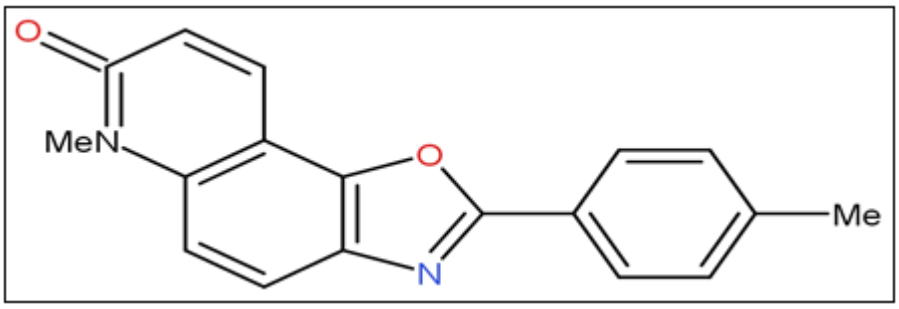
IV. COUMARIN AS OTHERS

K.C. Majumdar et al. (2012) revealed a highly effective method for the catalyst-free production of oxazole derivatives with coumarin, quinoline, and pyridine attachments through direct intramolecular carbon-oxygen bond formation mediated by a base. Reaction conditions were very simple and products were obtained in good yield in the absence of a transition metal catalyst, good for environmental and used on large-scale for suitable industrial application. When the intramolecular cyclization of o-bromoamides reaction was performed with minimum of 1.5 equiv Cs2CO3 in DMSO at 130°C in 5h the desired yield was obtained to be 93%. The oxazole derivatives with heterocycle attachments were acquired with increased yields through the nucleophilic addition of amide, forming the C-O bond.[55]

Table 18 Optimization of Intramolecular Cyclization

Entry	**Base**	**Solvent**	**Temp (°C)**	**Time (h)**	**Yield [b] (%)**
17a	CS_2CO_3 [a]	DMSO	130 °C	5	93

a Base used 1.5 equiv., b Isolated yields.

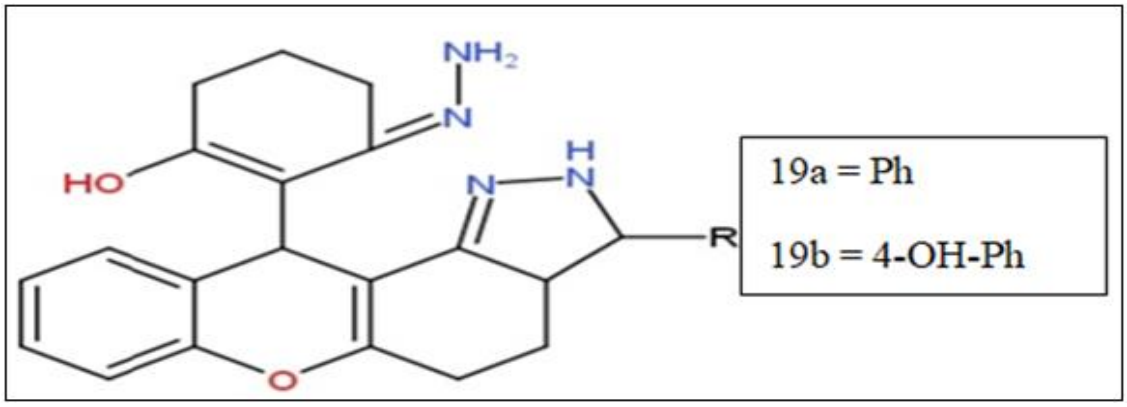


N.Kumar et.al., 2020 performed an environmentally friendly and solvent-free synthesis of a novel coumarin-based compound with solvatochromic properties, suitable for applications in visualizing liquid crystal displays (LFPs) and organic light-emitting diodes (OLEDs). The CTFTs determined to show excellent solvatochromic behavior when treated with solvents namely polar protic and polar aprotic. The strong excitation peaks of CTFTs were found at 407 nm and 431 nm. Cyan blue at 407nm and greenish blue at 431nm luminescence of CTFTs derivatives were exhibited in both liquid as well as solid state. The coumarin thiophene fluorescent tags we produced underwent characterization using various analytical methods, including Fourier-transform infrared spectroscopy, proton nuclear magnetic resonance spectroscopy, mass spectrometry, X-ray diffraction analysis, and UV-visible and photoluminescence spectrometry. It was explored the use of CTFTs (Coumarin Thiophene Fluorescent Tags) as a novel approach for visualizing latent fingerprints on different non-porous surfaces. This research demonstrated the potential application of CTFTs for flat-panel displays and fingerprint visualization.[56]

S.Chidambaram et.al., 2020 reported production of new coumarin analogs was carried out, and their interactions with the SARS-CoV-2 protein were investigated through molecular docking. These analogs were characterized using various methods including FT-IR, 1H and 13C NMR, elemental analysis, and mass spectrometry. The main protease COVID-19 major inhibitors The recommended compounds originating from medicinal plants include Calanolide A, Collinin, Inophyllum A, Mesuol, Isomesol, Pteryxin, Rutamarin, Seselin, and Suksdorfin.. Inophullum A the natural coumarin analogue tested by molecular docking showed the good binding energy inhibition potential of -8.4kcal/mol. 3D modules were biochemical interactions of the compounds were examined through predictions conducted using the SWISS MODEL web server and the AutoDock Vina tool. All the protein inhibitor accessed the target protein with negative dock energy. **18a and 18b** the synthetic coumarin analogues both showed the best binding energy inhibition potential of -7.9 kcal/mol. Drug like compounds were evaluated that passes the Lipinski's Law of 5 with 0 violations.[57]

Table 19 Docking Scores for Analogs of Coumarin, both Natural and Synthetic.

Main protease of SARS coronavirus (PDB ID: 5N50)			
	Bindin affinity (kcal/mol)	**No. of H-bonds**	**H-bonding residues**
Inophyllum A	-8.4	1	Cys145
18a	-7.9	0	-
18b	-7.9	1	His163



B.Jiang et.al., 2020 revealed the development of a luminescent sensor using coumarin-encapsulated MOF for the identification of picric acid within aqueous environments, this luminescent metal-organic framework (MOF) sensor demonstrates efficient functionality in detecting aromatic nitro compounds existing in water. It has the ability to quantitatively detect picric acid in natural water within the range of 0-100 µM. The C-CAU-10 sensor was synthesized using a solution immersion method, featuring a quantum yield of luminescence at 34.92% and a specific surface area of 649.7544 m3 g-1 with a defined pore size.

This sensor proves efficient for the luminous identification of picric acid in deionized water, as well as in river and tap water settings. Notably, the quenching of picric acid is particularly prominent, underscoring the C-CAU-10 sensor's proficiency in picric acid detection.[58]

B.S.Chinta et.al., 2021 described trapping of a HDDA-Benzene by coumarin (5,6-Benzo-2-pyrone) new mode of aryne reactivity with coumarins. Coumarin and o-benzene under a [4+2] cycloaddition followed by a cheletropic ejection of CO_2 to cafford conjugated polyaromatic scaffolds. DFT computation provided additional mechanism for some elementary steps which are involved in the class of transformation to help understand the difference in reactivity between 2-pyrone and the slower trapping agent, coumarin. Viability of coumarin was shown when coumarin reacted with o-benzene.[59]

V. CONCLUSION

Coumarins, belonging to the category of heterocyclic compounds, have sparked significant interest in the present day. Consequently, the extraction and structural analysis of new derivatives, coupled with the advancement of innovative synthetic techniques and exploration of their biological properties, have become subjects of increasing importance for numerous research teams. Hence, it holds significance to emphasize that the investigation of this subject and the formulation of fresh synthetic approaches remain among the forefront areas of research. It is of even greater significance to underscore that ongoing metabolic studies concerning the biotransformation of coumarin and its derivatives represent an emerging field of research.

Attempts were undertaken to offer a summary of the present status of knowledge concerning simple coumarins and their analogs, primarily focusing on recent developments. As expected, the literature reveals numerous unanswered questions that warrant further exploration. We also made efforts to scour the literature published within the specified timeframe, but encountered several challenges in locating certain references or categorizing topics due to their lack of clarity. We extend our apologies to authors who, for various reasons, were not mentioned in this work.

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