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Review Article

Coumarins: Chemical Synthesis, Properties and Applications

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ABSTRACT

Coumarins are compounds characterized by a benzopyrone structure resulting from the condensation of pyrone and a benzene ring. They are commonly found as secondary metabolites in various plants, microorganisms, and sponges. These metabolites play a crucial role in defence mechanisms, and extensive research has revealed numerous biological activities associated with these compounds. Coumarin and its derivatives show significant potential as candidates for new drugs due to their exceptional biocompatibility and a wide range of biological activities, including antimicrobial, anticancer, antimitotic, antioxidant, anti-inflammatory, and anticoagulant properties. Beyond medicinal applications, the simple and versatile scaffold structures of coumarins have found use in fields such as food production, agriculture, cosmetics, and textiles. This review covers the classification of coumarin and its derivatives, as well as various chemical synthesis methods. Furthermore, it delves into the properties, biological activities, and diverse application areas of coumarins.

Keywords: *Coumarin, Coumarin Derivatives, Classification, Chemical Synthesis, Biological Activity, Applications*

Kumarinler: Kimyasal Sentez, Özellikler ve Uygulamalar

Öz

Kumarinler, piron ve bir benzen halkası arasında meydana gelen kondenzasyon sonucu oluşan benzopiron yapısı ile karakterize edilen bileşiklerdir. Bu metabolitler çeşitli bitkilerde, mikroorganizmalarda ve süngerlerde ikincil metabolitler olarak yaygın olarak bulunurlar. Bu metabolitler, savunma mekanizmalarında önemli bir rol oynarlar ve geniş çapta yapılan araştırmalar bu bileşiklerle ilişkilendirilen çok sayıda biyolojik aktiviteyi ortaya koymuştur. Kumarin ve türevleri, antimikrobiyal, antikanser, antimitotik, antioksidan, antiinflamatuar ve antikoagülan özellikler dahil olmak üzere geniş bir biyolojik aktivite yelpazesine sahip olmaları nedeniyle yeni ilaç adayları olarak önemli potansiyele sahiptirler. Tıbbi uygulamaların ötesinde, kumarinlerin basit ve çok yönlü iskelet yapıları, gıda üretimi, tarım, kozmetik ve tekstil gibi alanlarda kullanım bulmuştur. Bu derleme, kumarin ve türevlerinin sınıflandırılmasını, çeşitli kimyasal sentez yöntemlerini kapsamaktadır. Ayrıca, kumarinlerin özellikleri, biyolojik aktiviteleri ve çeşitli uygulama alanlarına da değinmektedir.

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I. INTRODUCTION

Coumarins (coumarin and its derivatives) are compounds that are formed as a result of the joining of benzene and α-pyrone rings and have a core structure defined as chromen-2-one or benzopyran-2-one [1]. Coumarins, an important member of the polyphenolic compounds class, are characterized by their benzopyrone structure [2]. According to the substituents next to this heterocyclic structure, coumarins; It is divided into 6 different classes: simple coumarins, pyranocoumarins, furanocoumarins, dihydrofuranocoumarin, phenylcoumarin and bicoumarin [3]. Found in the seeds, roots and leaves of many plants, coumarin was first found in high concentration in tonka beans. For this reason, it is named after the French word "Coumarou" meaning tonka bean [4].

More than 1800 coumarin derivatives have been found so far [5]. It has been reported that these coumarins can be found in free form in nature as well as in conjugated form with other compounds such as methyl and sugar [5], [6]. There are studies reporting that coumarins belonging to the benzopyrone family have potential activity against many diseases such as cancer [6]. In addition, coumarins, which are secondary metabolites related to the defence mechanism in living things, have been reported in many articles to have a number of pharmacological properties such as anti-inflammatory, antioxidant, antimicrobial, antidepressant, neuroprotective or antitumoral effects [7].

The heterocyclic systems present in coumarins have led to their widespread adoption as scaffolds in various applications. Moreover, owing to their remarkable biological activities, coumarins have assumed a pivotal role in the development of novel candidate drugs [8]. In the following sections of this paper, we will delve into the classification of coumarin and its derivatives, explore various chemical synthesis methods, and discuss their properties, biological activities, and manifold areas of application.

II. CLASSES OF COUMARINS

Coumarins can be classified in different ways according to their chemical structure, source and synthesis methods.

A. CLASSIFICATION OF COUMARINS BY CHEMICAL STRUCTURE

This classification based on the most common chemical (core) structure of coumarins with 1,2-benzopyrone structure [6], [7].

A. 1. Simple Coumarins

It contains unsubstituted, mono-substituted, di-substituted, tri-substituted, tetra-substituted coumarins (Figure 1). Simple coumarins are divided into the following 5 classes:

a) Isocoumarins: It is an isomer of coumarin formed by the replacement of the carbonyl group and oxygen in the coumarin structure. For example: isocoumarin.
b) Glycosid coumarins: The coumarin ring is formed by bonding with a sugar. For example: esculin, daphnin, skimmin.
c) Pyrone-substituted coumarins: It is a type of coumarin formed by binding different substituents to the pyron ring. For example: warfarin.
d) Benzene-substituted coumarins: They are structures formed by attaching a phenyl group to the coumarin ring. For example: limettin, umbelliferone, osthole.
e) Complex coumarins: It is formed by the bonding of different substituents in both the benzene ring and the pyron ring. For example: novobiocin, alternariol.

Simple coumarins form a new product family called Seskiterpene coumarins by forming C-C bonds [9].

A. 2. Furanocoumarins

It is formed by the bonding of coumarin and furan ring, and there are two types as linear and angular. For example: psoralen, marmelosin, angelicin, isobergapten (Figure 2).

A. 3. Dihydrofuranocoumarins

It is a coumarin derivative formed by the bonding of coumarin and dihydrofuran ring. For example: marmesin, felamidin (Figure 2).

A. 4. Pyranocoumarins

They are compounds that have two types, linear type and angular type, and are formed as a result of the bonding of coumarin and pyran ring. For example: xanthyletin, seselin, visnadin (Figure 2).

A. 5. Phenylcoumarins

It is formed by attaching a phenyl group to the pyron ring in the coumarin ring. For example: isodispar B, mammea A/AB (Figure 2).

A. 6. Bicoumarins

It is formed as a result of the bonding of two coumarin rings. For example: dicoumarol (Figure 2).

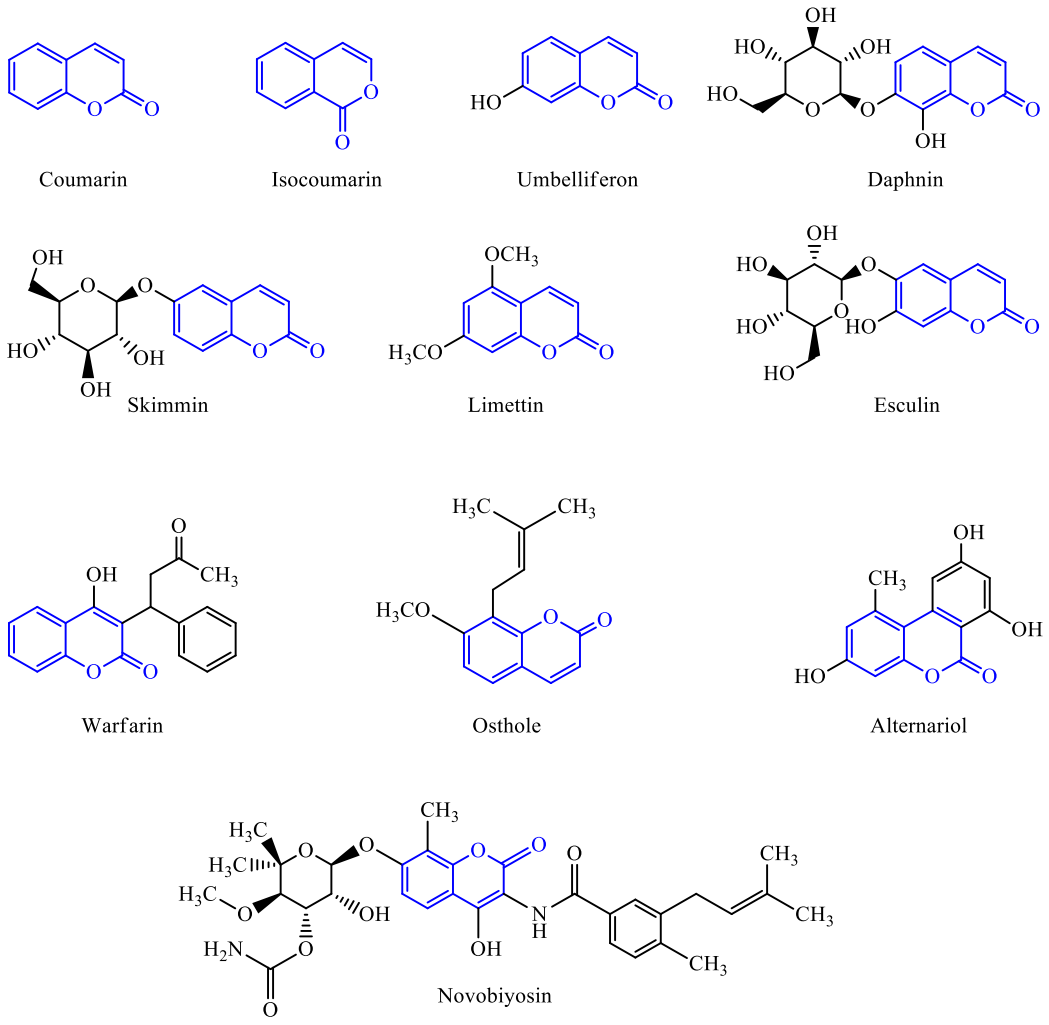


Figure 1. *Chemical Structure of Simple Coumarins.*

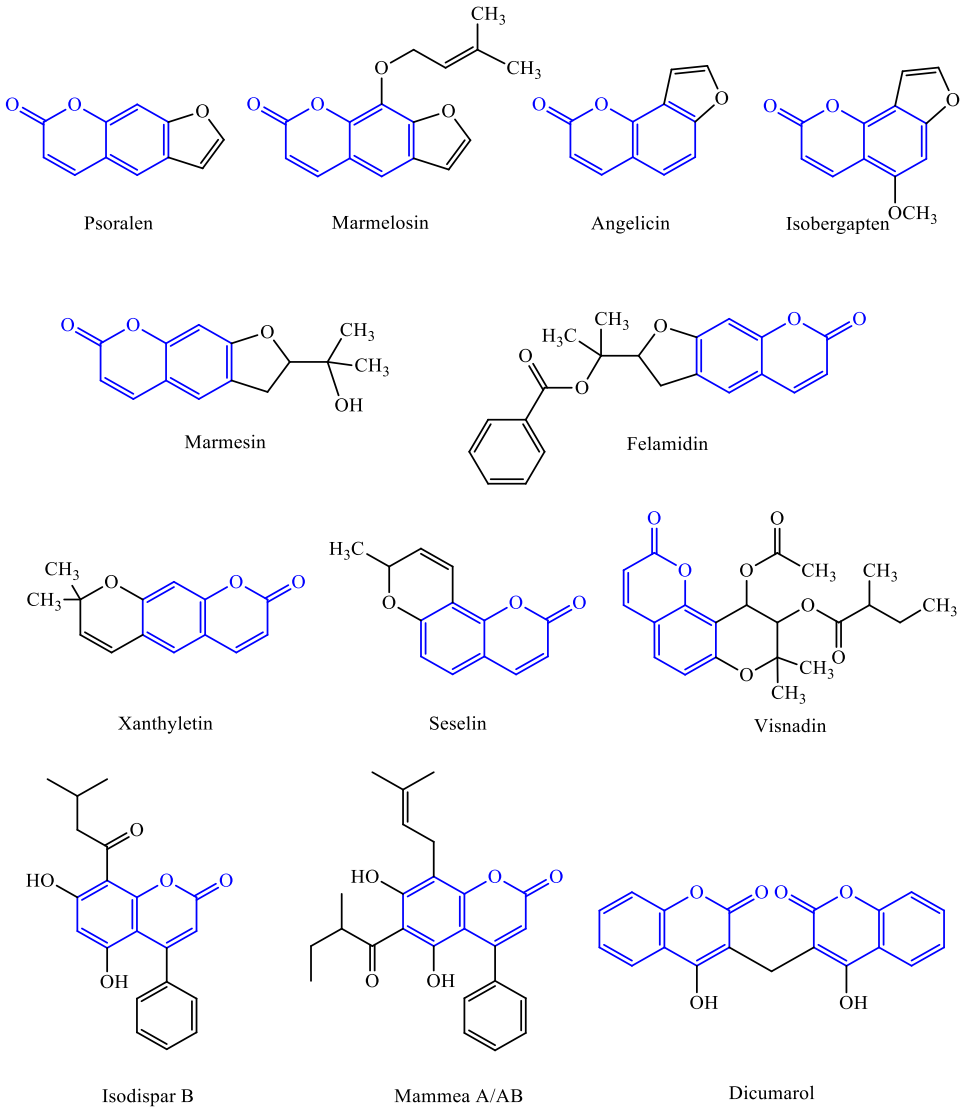


Figure 2. *Chemical Structure of Other Coumarins.*

B. CLASSIFICATION OF COUMARINS BY THEIR LOCATIONS

B. 1. Plant-Derived Coumarins

Secondary metabolites, which enable plants to adapt to adverse environmental conditions, are produced through various pathways. Most of the secondary metabolites produced by the phenylpropanoid pathway are related to the defence mechanisms of plants. The secondary metabolite known as coumarins, synthesized by plants via the Phenylpropanoid pathway, can be classified as plant-derived coumarins [7], [10]. These coumarins, isolated from hundreds of plant species belonging to more than 40 different families, can be found in different parts of plants such as roots, leaves, flowers and fruits. They can also be found in the free form or in the form of glycosides. Plants belonging to the *Apiaceae* family are considered the main source of coumarins and have been reported to contain five different coumarin species [6]. Coumarins contained in plants are accepted as chemotaxonomic markers that will provide information about the evolution level of plants [6], [11]. Coumarins produced by plants protect plants against pathogens and also act as iron chelators [12].

B. 2. Microorganism-Derived Coumarins

Although coumarins are mostly synthesized in plants, they have been detected in some microorganisms. Examples include the new coumarin derivative isolated from two fungal species by J. Wang et al. in 2015 [13],

3 coumarin compounds obtained from *Alternaria* fungus by Umashankar et al. [14], and the new coumarin derivative isolated from *Aspergillus versicolor* fungus strain in 2020 [15].

B. 3. Animal-Derived Coumarins

Apart from plants and microorganisms, coumarins are also found in a small number of animal species [6]. In 2007, Simone et al. succeeded in isolating two coumarin derivatives, esculetin-4-carboxylic acid methyl ester and esculetin-4-carboxylic acid ethyl ester, from sea sponge of *Axinella corrugate* species for the first time [16]. Although research on this subject is limited, coumarin derivatives that may be found of animal origin in ongoing studies may be included in this class.

C. CLASSIFICATION OF COUMARINS BY SYNTHESIS METHODS

Perkin, Pechmann or Knoevenagel methods are mostly preferred for the synthesis of coumarins. However, the low yields of coumarin formed as a result of the Perkin reaction and the formation of by-products are the disadvantages of this method [17]. The Pechmann reaction has disadvantages such as the need for large amounts of acid, high temperatures and long reaction times [18]. The Knoevenagel reaction is an easy and highly efficient reaction. In addition, it provides high purity final products compared to other reactions. However, this reaction is limited as it can only be used for the synthesis of 3-substituted coumarins [19], [20]. Therefore, apart from these methods, researchers have also developed methods such as Wittig reaction, Reformatsky reaction, Kostanecki reaction, Claisen rearrangement for the synthesis of various coumarin derivatives with high efficiency. Chemical synthesis methods commonly used in the synthesis of coumarins are briefly explained below.

C. 1. Perkin Reaction

The Perkin reaction involves the formation of coumarin from aromatic 2-hydroxybenzaldehyde and acetic anhydride in a basic medium. Typically, this method yields 3- or 4-substituted coumarins (Figure 3) [21].

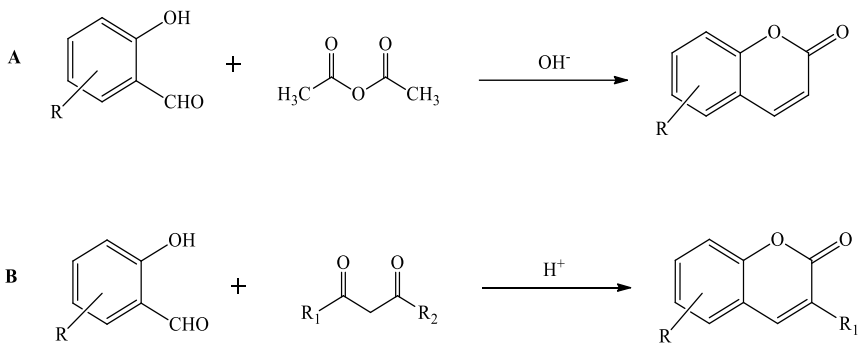


Figure 3. *(A) Perkin Reaction (B) Knoevenagel Reaction of Coumarins Synthesis.*

C. 2. Knoevenagel Reaction

Coumarin synthesis occurs through the interaction of salicylaldehyde derivatives and α, β-diketones in an acidic environment during the Knoevenagel reaction. This reaction method is commonly used to synthesize 3- or 4-substituted coumarins (Figure 3) [22].

C. 3. Pechmann Reaction

Phenol derivatives transform into coumarins when they react with β-ketoesters in an acidic environment in the Pechmann reaction. This method is preferred for the synthesis of 3- or 4-substituted coumarins (Figure 4) [20], [22]. Researchers have employed various catalysts to synthesize coumarins from substituted phenols and β-ketoester compounds. The Pechmann reaction has been successfully executed in the presence of various catalytic systems, including but not limited to Fe_3O_4@Boehmite-NH_2-CoII NP [23], Amberlyst-15 [24], $FeCl_3 \cdot 6H2O$ [24], $InCl_3$ [25], H_2SO_4 [26],

and SnO_2 nanoparticles [27]. These catalytic methodologies have demonstrated efficacy in facilitating the formation of coumarin derivatives under different reaction conditions.

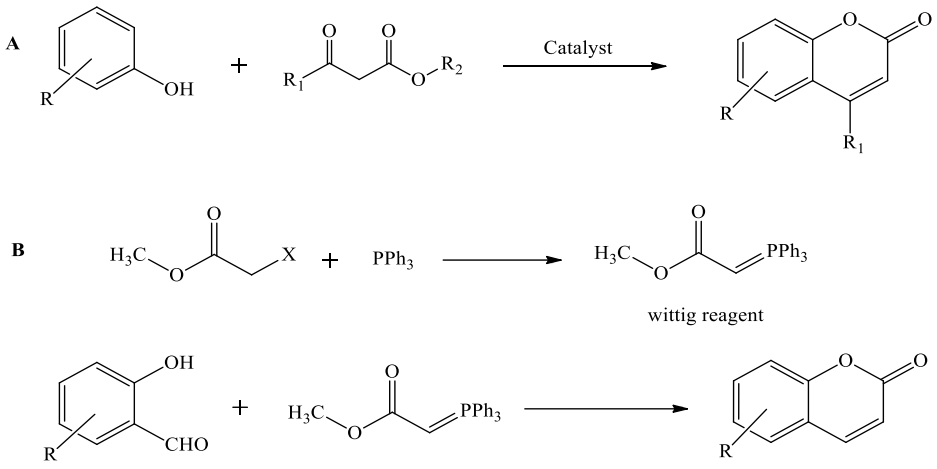


Figure 4. *(A) Pechmann Reaction (B) Wittig Reaction of Coumarins Synthesis.*

C. 4. Wittig Reaction

The Wittig reaction involves the synthesis of coumarins by the interaction of salicylaldehyde, methyl haloacetate, and phosphonium ylide. This method is commonly used to produce 3- or 4-substituted coumarins (Figure 4) [28], [29].

C. 5. Reformatsky Reaction

For the synthesis of coumarins, the Reformatsky reaction employs aldehyde or ketone derivatives with ethyl-α-haloacetate under Zn catalysis. This method is used primarily for the synthesis of 3,4-dialkylsubstituted coumarins (Figure 5) [22], [30].

C. 6. Kostanecki (acylation) Reaction

Known as the Kostanecki acylation, Kostanecki-Robinson or Allan-Robinson reaction involves the reaction of 2-hydroxyphenylalkylketone and its derivatives with aliphatic acetic anhydride in a basic medium to synthesize coumarin and chromone (Figure 5) [22]. The transformation of 2-hydroxyphenylalkylketone derivatives to chromone is represented by Allan-Robinson reaction, while the conversion to coumarin is reerred to as Kostanecki (acylation) reaction.

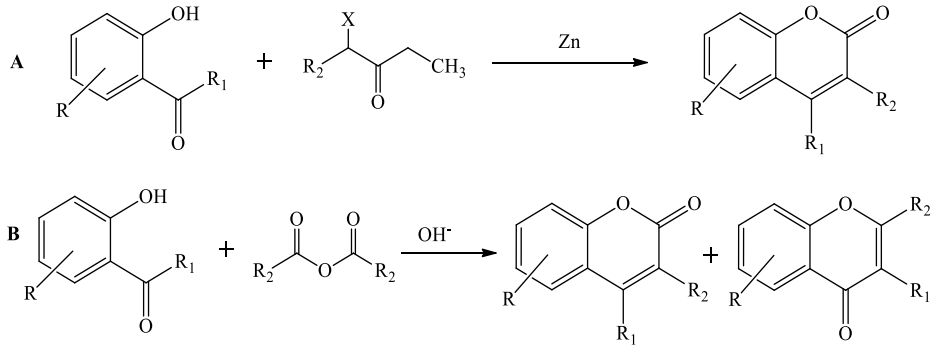


Figure 5. *(A) Reformatsky Reaction (B) Kostanecki Reaction of Coumarins Synthesis.*

C. 7. Claisen Rearrangement

Coumarin derivatives are obtained through the Claisen rearrangement by subjecting the claisen product, formed by heating the mixture of Methyl-2-((2-formylphenoxy) methyl)-3-phenylacrylate and 2,2'-disulfanediyldianiline, to an acidic environment (

Figure **6**) [31].

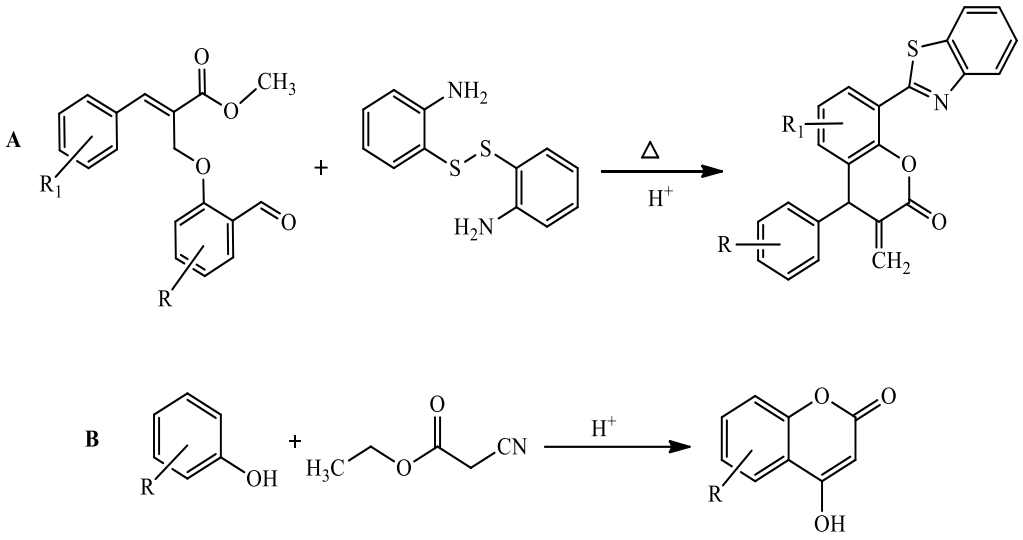


Figure 6. *(A) Claisen Rearrangement (B) Sonn Reaction of Coumarins Synthesis.*

C. 8. Sonn Reaction (Heuben-Hoesch Reaction)

Phenol derivatives react with ethyl cyanoacetate in an acidic medium to obtain coumarins during the Sonn Reaction (

Figure **6**) [20].

C. 9. Weiss-Merksammer Reaction

The Weiss-Merksammer Reaction involves the synthesis of coumarins resulting from the reaction of 2-hydroxyacetophenone with ethyl ethoxy methylene acetoacetate catalysed by NaOEt (Figure 7) [20].

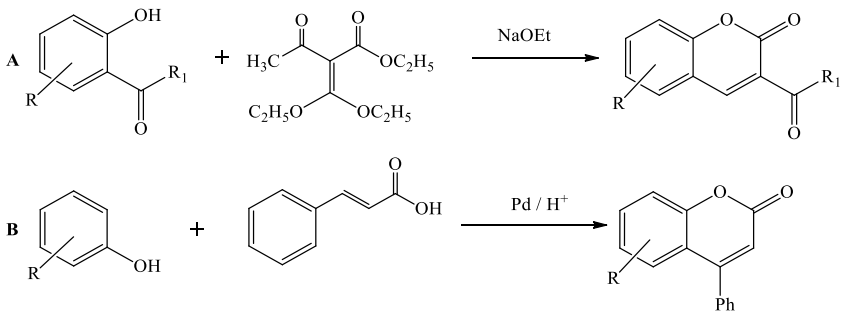


Figure 7. *(A) Weiss-Merksammer Reaction (B) Tsugio Kitamura Reaction of Coumarins Synthesis.*

C. 10. Tsugio Kitamura Reaction

Phenols react with cinnamic acid and trifluoroacetic acid, catalyzed by Pd and Pt, to form coumarin during the Tsugio Kitamura Reaction (Figure 7) [20], [32].

C. 11. Baker Reaction

3-phenylcoumarins are synthesized in the Baker Reaction through the reaction of phenols with 2-formylphenylacetonitrile in $POCl_3$ or HCl (Figure 8) [20].

C. 12. Smith-Dobrovolny Reaction

The Smith-Dobrovolny Reaction results in the synthesis of 3-carbethoxycoumarin derivatives by reacting Duroquinone and ethyl sodiummalonate (Figure 8) [20].

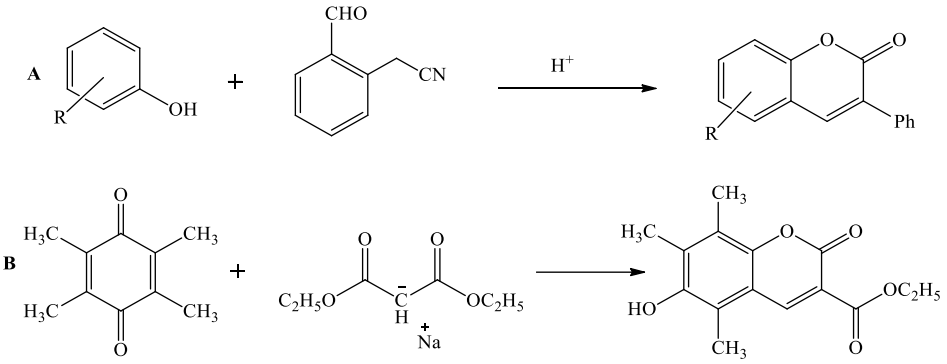


Figure 8. *(A) Baker Reaction (B) Smith-Dobrovolny Reaction of Coumarins Synthesis.*

C. 13. Chakravarti-Majumdar Reaction

The Chakravarti-Majumdar Reaction involves the synthesis of coumarins from 2-methoxyaryl alkyl ketone under Reformatsky reaction conditions (Figure 9) [20].

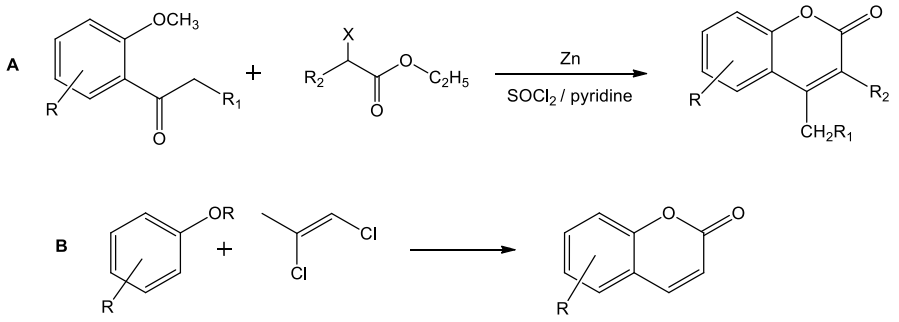


Figure 9. *(A) Chakravarti-Majumdar Reaction (B) Bert Reaction of Coumarins Synthesis.*

C. 14. Bert Reaction

The Bert Reaction converts phenolic ether and 1,2-dichloroprop-1-ene into coumarin in the presence of Zn or by the Friedel-Crafts reaction (Figure 9) [20].

C. 15. Baylis-Hillman Reaction

Salicylaldehyde reacts with methylacrylate in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO) to obtain coumarin and coumarone during the Baylis-Hillman Reaction (Figure 10) [33].

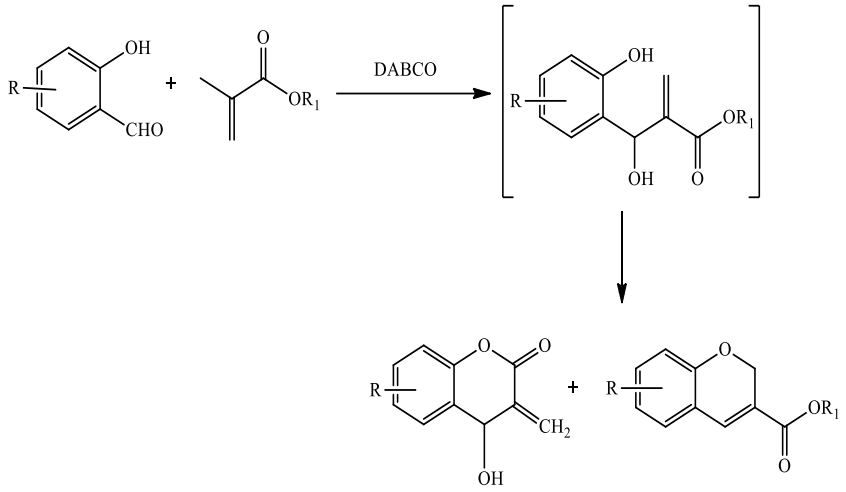


Figure 10. *Baylis-Hillman Reaction of Coumarins Synthesis.*

C. 16. Michael Addition Reaction

3-benzoylcoumarin derivatives can be synthesized with good yield using salicylaldehyde derivatives and 3,3-bis(methylsulfanyl)-1-phenylpropenone dithioacetate in the presence of piperidine during the Michael Addition Reaction (Figure 11) [33].

C. 17. Other Methods

In addition to the synthesis methods of coumarin and its derivatives above, some researchers have developed chemical synthesis methods based on different reactions. For example, Wang D. et al. synthesized a high-yield series of biscoumarins from $PhSO_3H$-catalyzed Bis(2-hydroxyphenyl) methanone derivatives and Meldrum's acid's reaction (Figure 11) [34].

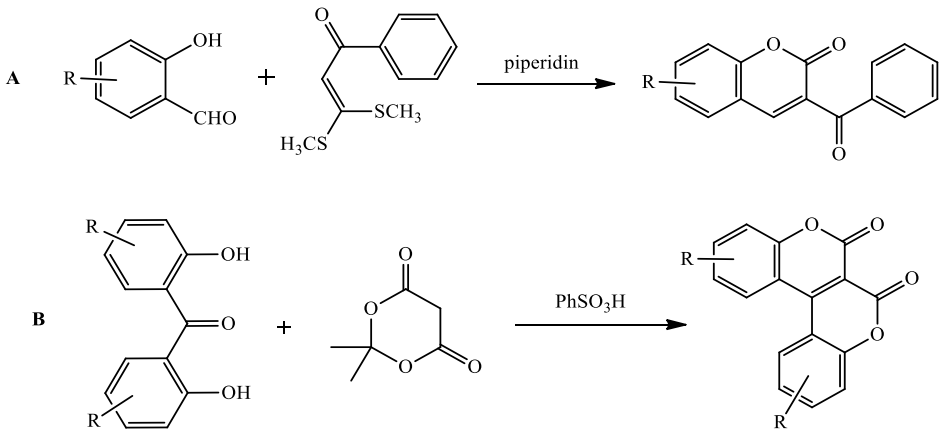


Figure 11. *(A) Michael Addition Reaction (B) Synthesis of Biscoumarins by Using Meldrum's Acid.*

Trost B. M. et al. used phenol derivatives and ethyl propiolates compounds in the presence of different catalysts in an acidic environment for the synthesis of substituted coumarins (Figure 12). In this study, as a result of the use of $Pd(OAc)_2$ or $Pd_2(dba)_3$ catalysts, an efficiency between 42-69% was obtained [35]. Kutubi S. et al., who made a similar study, obtained 60-93% efficiency by using the $FeCl_3$/AgOTf catalyst mixture [36]. Co_2Rh_2, which was used as a catalyst by Park K. H. et al., provided 79-89% efficiency [37]. Finally, $ZnCl_2$, which was used by Leao R. A. C. et al., achieved the best result with a yield of 70-95% [38].

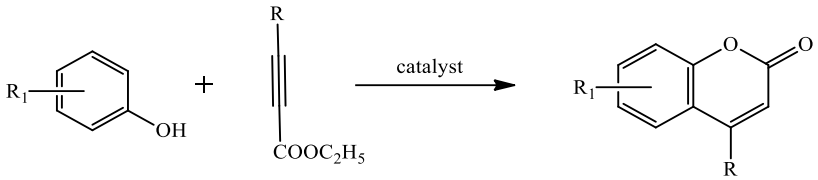


Figure 12. *Synthesis of Coumarin by Coupling of Phenol and Alkyne Derivatives.*

III. CHEMICAL SYNTHESIS OF COUMARINS

Coumarin was first synthesized in 1868 as a pharmaceutical agent (Dikumarol) [6]. Continued research on coumarin and its derivatives has given coumarin-based compounds a wide range of uses from medicine to industry [33]. Researchers have developed many strategies to find the most efficient and practical method for the synthesis of coumarin and its derivatives [39]. For the synthesis of coumarin and its derivatives; reflux, microwave and ultrasonic based methods have been developed. In these developed methods the research on increasing the yield of coumarin by changing the reaction conditions has made great progress [33].

In 2022, Sharma V. et al. synthesized compound 5-Amino-6-cyano-3-hydroxybenzo[c]coumarin by refluxing a homogeneous mixture of salicylaldehyde, ethyl acetoacetate and malononitrile in ethanol/water with Ni-Cu-Al-CO_3 hydrotalcite catalysis at 80 °C for 90 minutes. The obtained coumarin derivatives showed antimicrobial activity against human pathogenic bacteria such as *S. aureus*, *P. aeruginosa* and *P. bulgaria*. In this study, the effect of temperature, catalyst and solvent change was investigated. As a result, it was observed that increasing the reaction temperature up to 80 °C, increasing the amount of catalyst and using ethanol instead of acetone and acetonitrile increased the yield of coumarin [40]. In a study conducted by Rahayu et al. in 2022, 7-hydroxy-4-methyl coumarin was synthesized by microwave (800W) using resorcinol and ethyl acetoacetate under the catalysis of $SnCl_2.2H_2O$. It has been found that reducing or increasing the reaction time during synthesis does not increase the yield. A decrease in yield was reported when the ratio of reagents (resorcinol: ethyl acetoacetate) was changed from 1:1 mol to 1:1.25 mol. Performing the reactions without solvents resulted in better yields than performing them in the presence of ethanol (polar protic) and acetonitrile (polar aprotic) solvents. Finally, it has been reported that the highest efficiency was achieved when the $SnCl_2.H_2O$ catalyst used in this study was used as 10% mol [41].

Özdemir M. et al. (2022) synthesized the polymer containing sulfo-coumarin group in 4 steps. In the first step, 2,4-dihydroxybenzaldehyde, 4-methylsulfonyl) phenyl acetic acid and sodium acetate were dissolved in dry acetic anhydride. 7-acetyl-3-[4-(methylsulfonyl) phenyl] coumarin was then refluxed for 22 hours at 160 °C and under a nitrogen atmosphere. The product obtained in the second step was dissolved in methanol/THF and 7-Hydroxy-3-[4-(methylsulfonyl) phenyl] coumarin was synthesized by adding aqueous LiOH solution and refluxing for 3 hours. In the 3rd step, triethylamine and methacryloyl chloride were added to the product dissolved in THF, and sulfo-coumarin monomer was obtained by stirring for 12 hours. In the last step, the monomer was converted into polymer using the Radical Polymerization method [42]. Some studies based on chemical synthesis methods are summarized in Table 1.

Table 1. *Studies on Chemical Synthesis of Coumarins.*

Method	Reaction Conditions	Reagent	Catalyst	Solvent	Time *(h)*	Yield *(%)*	Number of compounds	Ref.
Microwave	800 W	resorcinol, ethyl acetoacetate	$SnCl_2.2H_2O$	-	0.07	55.25	1	[41]
	100 – 170 °C	salicylaldehyde derivatives, phenylacetic acid derivative	acetic anhydride, TEA	-	0.17 – 0.2	46 - 77	8	[43]
	Room temperature (RT) under argon atmosphere	2,3,4-Trimethoxybenzaldehyde, 4-methylphenylacetonitrile	NaOH	EtOH	0.5	88	1	[44]
	320 W	2-(2,3,4-trimethoxyphenyl)-1-(4-methyl phenyl)acrylonitrile, silicagel, pyridinium hydrochloride	-	-	0.42	74	1	
	250 °C	4-substitue salicylaldehyde, ethyl-2-(triphenylphosphoranylidene)acetate	-	N,N-dimethylanilin e	0.17 - 1	20 - 91	15	[45], [46]
	100 - 170 °C 100 - 200 W	salicylaldehyde derivatives, phenyl acetic acid derivatives	acetic anhydride, TEA	-	0.17 – 0.2	34 - 85	24	[47]
	-	2-hydroxy-4-propynyloxybenzaldehyde, 3-bromopropyne	K_2CO_3	DMF/H_2O	0.08 – 0.12	86 - 90	4	[48]
Reflux	80 °C	salicylaldehyde, ethylacetoacetateand malononitrile	Ni−Cu−Al−CO_3 hydrotalcite	EtOH/su	0.5 + 1	85	1	[40]
	160 °C under N_2 atmosphere	2,4-dihydroxy benzaldehyde, 4-methylsulfonyl)phenylacetic acid	sodium acetate	dry acetic anhydride	22	82	-	[42]

RT	hydroxycoumarin, alkyl halide	potassium carbonate	DMF	24	32 - 77	7	[49]
	4-hydroxycoumarin, acid chloride	TEA	THF	5	27	1	
	coumarin-3-carboxylic acid, Aromatic alcohol, dicyclohexylcarbodiimide (DCC)	4-(dimethylamino)pyridine	DCM	24	14 - 38	4	
	organic acid, amine, benzotriazol-1-yl oxytripyrrolidinophosphonium hexafluorophosphate (pyBOP)	TEA	DMF	24	41 - 73	7	
	2-hydroxy acetophenone, aldehyde	NaOH	MeOH	48	22.8	1	
	4-chromanon, aldehyde	pyrrolidine	MeOH	24	16 - 76	4	
60 °C	salicylaldehydes, β-keto ester	sulfated tungstate	-	TLC	81 - 98	20	[50]
110 °C	2-hydroxy benzaldehyde, phenyl/thiophenylacetic acid	N,N′-dicyclohexyl carbodiimide	dimethyl sulfoxide (DMSO)	24	-	20	[51]
Reflux	methoxy-3-arylcoumarin, acetic anhydride	hydriodic acid	Acetic acid	3	-	8	
55 °C	fluorescein, benzo-15-crown-5	NaOH	MeOH+ $CHCl_3$	6	-	3	[52]
Reflux	aldehyde, diethyl malonate	-	EtOH	6			
100 °C	ester derivatives	NaOH	MeOH	4			

Reflux	7-hydroxy-2*H*-chromen-2-one, benzyl chloride	K_2CO_3	acetonitrile	TLC	69 - 84	22	[53]
Reflux	benzylchlorides, 4-hydroxy benzylalcohol	K_2CO_3	ACN	TLC	-	1	
N_2 25 - 30 °C	4-(benzyloxy)phenyl)methanol, methane sulphonyl chloride	TEA	DCM	TLC	-	1	
Reflux	4-(benzyloxy)benzyl methanesulfonate, 7-hydroxy-2*H*-chromen-2-one	K_2CO_3	ACN	TLC	62 - 84	23	
Reflux or using backflow condenser	cyclopropane derivatives	glacial acetic acid	toluene	4 – 18	49 - 76	7	[54]
Reflux	cyclopropane derivatives	glacial acetic acid	chlorobenzene	16	67	1	
RT	cyclopropane derivatives	$DMF/POCl_3$	DMF	2	92	1	
RT	cyclopropane derivatives	$NaBH_4$	$MeOH/CHCl_3$	5	82	1	
boiling with backflow condenser	cyclopropane derivatives	glacial acetic acid	Toluene	6	48	1	
Reflux	cyclopropane derivatives	Zn powder, AcOH	MeOH	1	-	1	
Reflux; RT	7-diethylamino-3-formylcoumarin, sulfonamide; methyl trimethylsilyl dimethylketene acetal	pyridinium p-tolunesulfonate (PPTS); Y(OTf)	Toluene, DCM, THF	0.3 - 24	47 - 53	3	[55]
RT	8-formyl-7-hydroxy-4-Methylcoumarin, malononitrile	TEA	DCM	8	79.2	1	[56]

50 - 60 °C	4,4-dimethylpiperidine-2,6-dione, 4-bromomethyl coumarin	anhydrous K_2CO_3	dry acetone	10	73 - 84	10	[57]
RT °C	guanosine-6,8-dithione türevi + coumarin türevi	ammonium hydroxide	Water+ACN	1	70 - 86	18	[58]
RT	2-(2-(2-chloroethoxy)ethoxy) Ethanol, 4-toluenesulfonyl chloride	Et_3N, 4-dimethylaminopyridine (DMAP)	DCM	5	95	3	[59]
RT under argon atmosphere	2-(2-(2-chloroethoxy)ethoxy)ethyl 4-benzene sulfonate, 7-hydroxycoumarin	K_2CO_3, 18-crown-6	acetone	96	99		
70 °C	7-(2-(2-(2-chloroethoxy) ethoxy)ethoxy)-2H-cromen-2-one, NaI	-	acetone	120	87		
RT	N, N-diethylamino-3-acetyl coumarin, 2-hydrazino benzothiazole	H_2SO_4	EtOH	TLC	85	14	[60]
100 °C	5-isopropyl-2-methylphenol, $SnCl_4$, paraform aldehyde	Et_3N	toluene	8	63	2	[61]
110 °C	2-hydroxy-6-isopropyl-3-methyl benzaldehyde, acetic anhydride, 2-(3-methoxyphenyl)acetic acid	Et_3N	-	TLC	-		
Reflux	3-(bis(pyridin-2-ylmethyl)amino)phenols, ethyl acetoacetate	H_2SO_4	-	3	90 - 94	2	[62]
	7-(bis(pyridin-2-ylmethyl)amino)-4-methyl-coumarin, $Cu(NO_3)_2$	-	$MeOH/H_2O$	0.5	90 - 94	2	
Reflux	*o*-hydroxybenzaldehydes, pyridazinone ester	piperidine	2-propanol	5	73 - 87	6	[63]

	70 °C	phenol derivatives, malonic acid, $POCl_3$	$ZnCl_2$	-	20	-	4	[64]
	Reflux	naphthyl hydroxybenzaldehyde, methyl-2-(1,3,5-triazin-2-yl)acetate	Piperidin	EtOH	12 – 48	79 - 87	4	[65]
	112 °C MW, 80 °C reflux	2-phenylacetic acid derivatives, salicylaldehyde derivatives, HCl	TEA, acetic anhydride	EtOH	1.17 + 3	22 - 96	43	[66]
	80 °C MW 0 °C	salicylaldehyde derivatives, meldrum's acid, H_2SO_4	-	-	2 + 1,5	90	1	[48]
	Reflux under inert atmosphere	2-hydroxy-4-propynyloxybenzaldehyde, 3-bromopropyne	K_2CO_3	dry acetone	4 – 5,5	75 - 79	4	[67]
	0 - 5 °C	phenol derivatives, ethyl-4-bromo-3-oxobutanoate	H_2SO_4	-	-	-	2	[68]
Ultrasound	RT, 250 W, 40 kHz	aromatic aldehyde, malononitrile, phenylhidrazine, β-dicarbonyl compounds	L-proline	EtOH	0.83	78 - 90	20	[69]
	60 - 65 °C, 200 W, 35 kHz	aromatic aldehyde, aromatik amine, dimedone, 4-hydroxycoumarin	CTAB	H_2O	0.25	79 - 89	25	[70]
	130 W, 20 kHz	aromatic aldehyde, 4-hydroxycoumarin, 6-aminourasil or 6-aminothiourasil	sulfamic acid	EtOH/ H_2O	0.17 – 0.5	66 -98	26	[71]
	130 W, 20 kHz	aromatic aldehyde, 4-hydroxycoumarin, 2-aminopiridins	sulfamic acid	EtOH/ H_2O	0.07 – 0.63	70 - 97	30	[72]
	60 °C, 140 W, 50 - 60 Hz	isatin, malononitrile, dimedone or 4-hydroxycoumarin	S-alkyl O-hydrogen sulfothioate	EtOH/ H_2O or H_2O	1.75 – 4	76 - 94	12	[73]

		functionalized silica-coated magnetic nanoparticles (AHST-MNPs)					
45 °C	peracetylated glucose azide, coumarin alkyne	GO-Fe_3O_4@CuO	H_2O	1.33	85 - 96	6	[74]
80 °C	phenol derivatives, ethyl acetoacetate derivatives	Fe_3O_4@C@PrS-SO_3H NPs	-	0.25 – 0.67	58 - 98	14	[75]
70 °C	phenols, β-keto ester derivatives	$HFe(SO_4)_2$.4 H_2O-Ch NCs	-	0.17 – 6	59 - 99	28	[76]
50 – 60 °C, 100W, 36 kHz	2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) thiosemicarbazide, hydrazonoyl halide derivatives	Et_3N	dioxan	0.5	72 - 76	8	[77]
80 °C, 37 kHz	phenylhydrazone, vilsmeier reagent	-	-	0.33	91	1	[78]

IV. PROPERTIES OF COUMARINS

Coumarin (2*H*-chromen-2-one), which has a vanilla-like odor, has a volatile, colorless or yellow crystal structure. The molecular weight of coumarin is 146.15 g/mol and it sublimes at 100 °C. It melts between 68 - 70 °C and boils at 303 °C. While coumarin is soluble in diethyl ether, ethanol and chloroform, it is slightly soluble in water [79], [80].

Coumarins are compounds with fluorescent properties. These coumarins in solution or polymer form are generally located in the blue-green wavelength region. Synthesis of these fluorescent coumarin compounds is relatively easy. Therefore, various models have been reported and their photo-physical and spectroscopic properties have been extensively investigated. Recently, solid fluorescent dyes based on coumarin have received much attention [81]. Cocco A. et al. investigated the fluorescence properties of phenyl coumarins, which are coumarin derivatives. It was found that while the addition of Fe^{+3} to 6-(6-methoxynaphthalen-2-yl)-coumarin-3-carbonitrile (4e) and 6-(6-methoxynaphthalen-2-yl)-3-(methylsulfonyl)-coumarin (4f) compounds caused them to lose their fluorescent properties, the addition of Al^{+3} to the same compounds increased their fluorescent properties. It has been reported that ethyl 6-(6-methoxynaphthalen-2-yl)-coumarin-3-carboxylate (4c), 4e and 4f compounds, which were found to have low toxicity, may be candidates for bioimaging [82]. Sarih N. M. et al. synthesized a series of furocoumarin derivatives. Compound 2-(cyclohexyl amino)-3-phenyl-4*H*-furo[3,2-c] chromen-4-one (FH), which showed the strongest fluorescence of these compounds, was complexed with various metals. It was found that the fluorescence property of the obtained complexes was less compared to the FH compound and the complexes with Fe^{+3} lost their fluorescence property. Later, the FH-Fe^{+3} complex was formed into different complexes with 13 other metals, but it was observed that the FH-Fe^{+3}-metal compounds lost their fluorescence properties in general [83]. Hua C. J. et al. determined that coumarin-dihydropyridine derivatives have fluorescent properties. Among these compounds, 7-(p-tolyl)-9,10,11,12-tetrahydro-6*H*-chromeno[4,3-b] quinoline-6,8(7*H*)-dione (4e) showed the best fluorescence properties. Synthesized coumarin-dihydropyridine derivatives showed different fluorescence in acetic and basic environments, and it was noticed that the fluorescence color of these compounds changed from blue to yellow and then green when the pH value of these compounds was changed from acidic to basic [84]. Jarraya N. A. et al. compared 3-cyano-7-diethylamino-2-iminocoumarin with coumarin to search for compounds with the best fluorescence properties. It has been reported that the investigated compounds have very close fluorescence properties in solution, while in solid state, iminocoumarins are much more fluorescent than coumarins. As a result, it was found that coumarin derivatives behave very differently in liquid and solid state [81].

V. BIOLOGICAL ACTIVITY OF COUMARINS

Coumarin and its derivatives exhibit remarkable pharmacological properties. These compounds offer advantages such as high bioavailability, potent pharmacological activity, low potential for drug resistance, minimal side effect profiles, and optimized therapeutic efficacy. Numerous studies in the literature reveal the broad-spectrum bioactivity of coumarins. These studies report that coumarin derivatives possess antimicrobial, anti-tuberculosis, neuroprotective, anti-inflammatory, anticoagulant, antihypertensive, anti-hyperglycemic, antidiabetic, antioxidant, and antineoplastic properties [6], [12]. In light of this comprehensive bioactivity profile, the current review will focus specifically on the anticoagulant, antithrombotic, anti-neurodegenerative, and anticancer effects of coumarins. Analyzing the molecular mechanisms and potential therapeutic applications of these activities will contribute to a better understanding of the role of coumarins in drug discovery and development.

A. ANTICOAGULANT ACTIVITY

Coumarins are a class of heterocyclic compounds characterized by their anticoagulant properties. Anticoagulants are agents that modulate the hemostasis process and inhibit thrombus formation. This

pharmacological profile makes them valuable therapeutic tools in the prophylaxis and treatment of thromboembolic diseases. From a historical perspective, dicoumarol, the first synthesized coumarin derivative, played a critical role as a precursor compound in the development of anticoagulant drugs. Subsequent research has led to the synthesis and widespread clinical application of coumarin-based anticoagulants with various structural modifications [85].

The anticoagulant activity of coumarins is particularly evident in prototype molecules such as dicoumarol and warfarin, whose mechanism of action involves the inhibition of the enzyme vitamin K epoxide reductase. This enzymatic inhibition disrupts the biosynthesis of vitamin K-dependent coagulation factors, leading to the modulation of hemostasis and a consequent reduction in blood clotting capacity [86].

Coumarin derivatives hold a significant position in drug discovery and development due to their broad spectrum of biological activities. Coumarin analogs with anticoagulant efficacy are especially utilized as therapeutic agents in patients with a high risk of thrombosis during the perioperative period and in the primary and secondary prophylaxis of cardiovascular diseases. The optimization of these compounds' pharmacokinetics, pharmacodynamics, and safety profiles is a focal point of ongoing research aimed at enhancing the efficacy of anticoagulant therapy and minimizing potential side effects [85].

In a 2020 study by Bang et al., the synthesis of 7-hydroxycoumarin-salicylic acid derivatives was conducted. Among the compounds obtained, 1a-b derivatives were found to exhibit high anticoagulant activity. The chemical structures of these compounds are shown in figure 13. The analysis revealed that these derivatives were 1.5 times more active than warfarin [87].

B. ANTITHROMBOTIC ACTIVITY

Thrombosis poses a significant threat to human health worldwide as a major cause of mortality. Antithrombotic drugs play a critical role in the treatment of thrombotic diseases by preventing the onset and progression of these conditions. The need for new and safer antithrombotic drugs arises from the serious side effects and inadequate efficacy of existing medications. Coumarin derivatives have been demonstrated to exhibit antithrombotic properties, as well as anticoagulant and antiplatelet aggregation activities [88].

Coumarins prevent thrombosis due to their capacity to inhibit platelet aggregation, thus making them potential therapeutic agents in the treatment of cardiovascular diseases. This mechanism of action of coumarins is primarily attributed to their inhibition of the synthesis of coagulation factors through vitamin K antagonism, thereby regulating blood clotting. Additionally, some coumarin derivatives provide an extra benefit in reducing thrombosis risk by directly inhibiting platelet aggregation [89].

Recent studies on the antithrombotic effects of coumarin derivatives sheds light on their potential therapeutic applications. In a study conducted by Quezada et al. (2010), coumarin-resveratrol hybrid compounds were synthesized and their anti-platelet aggregatory activities were investigated. The researchers reported that compounds designated as 2a-c (Figure 13) exhibited higher anti-platelet aggregation activity than trans-resveratrol (t-RESV). Notably, compound 2b was found to demonstrate antiplatelet aggregatory activity thirty times more potent than t-RESV [90].

A study conducted by Lu et al. (2022) elucidated the mechanisms by which coumarin derivatives inhibit platelet aggregation. The research findings revealed that these compounds prevent platelet aggregation by inhibiting the glycoprotein GPIIb/IIIa complex on the platelet surface and adenosine diphosphate (ADP) receptor signaling pathways. Furthermore, intracellular mechanisms such as calcium release and regulation of platelet intracellular cyclic AMP (cAMP) were also found to play a role in this process [91].

In the same year, Mazreku et al. (2022) synthesized 4-hydroxycoumarin-pyridine derivatives and evaluated their *in vivo* anticoagulant effects in mouse models. The results demonstrated that compounds coded as 3a-b (Figure 13) exhibited higher Prothrombin Time values compared to the standard anticoagulant drug Warfarin. This finding indicates that these compounds more effectively modulate the blood coagulation process [92].

The study conducted by Hrubša et al. in 2022 provides significant contributions in terms of the synthesis of coumarin-indole hybrid compounds and the assessment of their antithrombotic potential. The researchers designed and synthesized a series of novel hybrid molecules by combining coumarin and indole structures using an innovative approach. The platelet antiaggregatory activities of these new compounds were systematically investigated through *in vitro* experiments. Among the obtained results, the high antiplatelet activity exhibited by compound 4 (Figure 13) is particularly noteworthy. This compound demonstrated stronger platelet aggregation inhibition when compared to the commonly used antithrombotic agent aspirin. This result suggests that compound 4 should be considered as a potential therapeutic candidate [93].

C. ANTI-NEURODEGENERATIVE ACTIVITY

Neurodegenerative diseases (ND) are a heterogeneous group of pathologies that affect the nervous system and are characterized by the progressive loss of neurons. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common types of these disorders, with increasing prevalence among the aging population. The etiology of NDs is complex and multifactorial, involving the interplay of aging, environmental, genetic, and epigenetic factors [63]. Protein aggregation and accumulation play a critical role in the pathogenesis, with cholinergic and dopaminergic system dysfunction being characteristic features of AD and PD, respectively. Current treatment strategies often focus on multi-target-directed ligands (MTDLs). In this context, the inhibition of enzymes such as monoamine oxidase (MAO), acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), and carbonic anhydrase (CA) isoforms has gained importance [94].

Coumarin derivatives have emerged as potential therapeutic agents in the treatment of neurodegenerative diseases (ND) due to their broad-spectrum biological activities and substitution potential at various positions in their molecular structure. Particularly, 3-aryl coumarin compounds exhibit high affinity and selectivity towards enzymes involved in neurodegeneration. The neuroprotective properties demonstrated by these compounds offer a promising approach for developing new therapeutic strategies in the treatment of NDs [95].

Berrino and colleagues (2023) synthesized coumarins with alkyl groups substituted at different positions to reduce oxidative stress and inflammation observed in neurodegenerative diseases (ND). These compounds were tested against enzymes like carbonic anhydrases (CA), monoamine oxidases (MAO), and cholinesterases (ChE), which play a role in neurodegeneration. The compounds 5a-b, shown in figure 13, stood out as the most promising due to their ability to inhibit multiple enzymes and exhibit *in vitro* neuroprotective activities. They demonstrated the capability to reduce oxidative stress-related neuroinflammation and inhibit the secretion of interleukin-6 [94].

The neuroprotective effects and mechanisms of action of coumarins have been better understood through recent studies. Specifically, coumarin derivatives like Osthole act by activating the Nrf2 signaling pathway and inhibiting the NF-κB pathway. Activation of the Nrf2 signaling pathway strengthens cellular defense mechanisms against oxidative stress by increasing the production of endogenous antioxidants such as HO-1 and NQO1. This effect has been demonstrated in both *in vitro* and *in vivo* studies, including in HT22 mouse hippocampal neuron cells and in mouse models of Alzheimer's disease [96], [97].

Inhibition of the NF-κB pathway reduces the production of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β). This effect has been observed in the reduction of LPS-induced inflammation in Caco-2 cells

and Caco-2/THP-1 macrophage co-cultures [98]. Additionally, simple coumarin derivatives like umbelliferon have been reported to exhibit similar effects through the Nrf2/ARE pathway [99].

The positive effects of coumarins on mitochondrial functions are primarily based on their ability to reduce oxidative stress and activate the Nrf2 signaling pathway. These mechanisms form the basis of the neuroprotective and anti-inflammatory effects of coumarins, making them potential therapeutic agents in the treatment of neurodegenerative diseases [100].

Despite the potential of coumarins in the treatment of NDs, there are some limitations. For instance, some coumarin derivatives have been reported to have limited ability to cross the blood-brain barrier (BBB), which could potentially limit their therapeutic efficacy. Additionally, some coumarin derivatives have been reported to cause hepatotoxicity at high doses [101]. These studies support the potential of coumarins in the treatment of NDs, while also highlighting the need for further research and optimization.

C.1. Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive loss of brain cells and is the most common form of dementia in the elderly population. Clinical symptoms include general and persistent memory loss, impairment of cognitive functions, emotional and behavioral changes, and loss of independent living skills [95]. While the pathogenesis of AD is not fully understood, the "cholinergic hypothesis" and "beta-amyloid cascade hypothesis" are among the most widely accepted theories. The cholinergic hypothesis suggests that the disease is caused by a reduction in acetylcholine synthesis, while the beta-amyloid cascade hypothesis emphasizes that the accumulation of β-amyloid peptide (Aβ) and the formation of neurofibrillary tangles (NFTs) from hyperphosphorylated tau protein are the hallmark pathological features of AD [95]. Mitochondrial dysfunction and dysregulation of the glycogen synthase kinase-3β (GSK-3β) enzyme play significant roles in the pathogenesis of AD. Increased GSK-3β activity has been observed in the brains of AD patients, and it has been suggested that this enzyme has a molecular relationship with Aβ and tau proteins. Experimental studies have shown that overexpression of GSK-3β leads to hyperphosphorylation of tau and its accumulation in hippocampal neurons [102].

Acetylcholinesterase (AChE) inhibitors and monoamine oxidase-B (MAO-B) inhibitors play a crucial role in the treatment of AD. These drugs are used to slow the progression of the disease and improve the cognitive functions of patients [95]. Coumarin derivatives hold promise as AChE and BuChE inhibitors. These compounds potentially improve cholinergic signaling and exhibit neuroprotective effects, offering potential in the treatment of AD [103]. Recent studies support the potential of coumarin derivatives in the treatment of AD. Hu et al. (2019) investigated the AChE and BuChE inhibitory activity of 3-substituted coumarin derivatives *in vitro* and *in vivo*. Compound 6c showed high AChE inhibitory activity, while compound 6a was found to be five times more potent than donepezil in inhibiting BuChE [104].

In another study, Huang et al. (2014) observed that derivatives synthesized by combining clioquinol and coumarin exhibited AChE/MAO-B inhibitory activity and inhibited beta-amyloid (Aβ1-24) aggregation. Particularly, compound 7 showed the highest effect in both MAO-B inhibition and inhibition of Aβ1–42 aggregation [105]. A study by Chiu et al. (2021) reported that new coumarin-chalcone hybrid compounds inhibited amyloid-β aggregation, reduced tau hyperphosphorylation, and improved cholinergic neurotransmission [106]. Finally, Babaei et al. (2022) investigated the anti-Alzheimer potential of a series of coumarin-pyridine hybrid compounds. Compound 8a was found to be seven times more effective against AChE than the standard drug, while compound 8b exhibited 305 times more inhibitory effect against BuChE [107].

C.2. Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive neurodegeneration and impaired motor control. The main pathological features of PD include the loss of dopaminergic neurons in the substantia nigra pars compacta and the aggregation of α-synuclein protein [108].

Monoamine oxidase (MAO) enzyme inhibitors play a crucial role in the treatment of central nervous system disorders such as depression and Parkinson's disease. Specifically, MAO-B inhibitors contribute to the control of motor symptoms by reducing the breakdown of dopamine. In this context, coumarin derivatives stand out as promising compounds in the treatment of PD due to their neuroprotective effects [109], [110].

The studies have shown that coumarin derivatives can influence PD pathogenesis through various mechanisms. These compounds inhibit MAO-B enzyme, reduce dopamine degradation, reduce oxidative stress with their strong antioxidant properties, inhibit α-synuclein protein aggregation, improve mitochondrial dysfunction, and suppress neuroinflammatory processes. These multifaceted mechanisms increase the potential of coumarins to be used as multi-target-directed ligands (MTDL) in the treatment of PD [110].

Various studies have investigated the potential therapeutic effects of different coumarin derivatives on PD. For instance, Sashidhara et al. (2014) synthesized a series of 3-aryl coumarin-tacrine derivatives, considering the complex etiology of PD. This study found that compounds 9a-b inhibited α-synuclein protein aggregation, increased dopamine levels, and exhibited strong antioxidant properties [111]. In another study by Kumar et al. (2018), scopoletin, found in the fruit of *Morinda citrifolia*, was investigated for its potential therapeutic effects on PD. Research has shown that scopoletin possesses strong neuroprotective properties. Specifically, scopoletin significantly reduced cell death by protecting SH-SY5Y cells from rotenone-induced apoptosis. The underlying mechanism of this protective effect was associated with the activation of the Nrf2/ARE pathway. Scopoletin enhanced the antioxidant response by increasing the phosphorylation and nuclear translocation of Nrf2 protein. Additionally, scopoletin supported the stabilization and activation of Nrf2 by raising DJ-1 protein levels. This effect played an important role in enhancing cellular defense against oxidative stress. As a result, scopoletin appears to have the potential to ameliorate the pathophysiological processes such as oxidative stress and protein aggregation underlying PD. These findings suggest that scopoletin could be used as a new therapeutic agent in the treatment of PD [112].

Tao et al. (2019) comprehensively evaluated the therapeutic potential of coumarin Mannich base (β-amino ketone) derivatives as a novel approach to PD treatment. Among the synthesized coumarin Mannich derivatives, compound 10 (Figure 13) showed particularly notable results. This compound demonstrated high selectivity in inhibiting the MAO-B enzyme and reducing neuroinflammatory processes in both *in vitro* and *in vivo* experiments. Additionally, compound 10 was observed to improve motor dysfunction, prevent dopaminergic neuron loss, and increase the number of tyrosine hydroxylase-positive neurons. It was also found to reduce neuroinflammatory response by inhibiting COX-2 and iNOS expression [113].

In another study, Ham et al. (2019) explored the therapeutic potential of a coumarin derivative called Peucedanocoumarin III in a PD model. Peucedanocoumarin III showed the ability to dissolve α-synuclein fibrils and prevent dopaminergic neuron loss [114]. Studies by Hannan et al. (2022) and Predhan et al. (2020) investigated the neuroprotective effects of a coumarin derivative named scopoletin in a PD model. Scopoletin was shown to reduce dopaminergic neuron loss associated with oxidative stress, improve mitochondrial function, and enhance dopamine efficacy [115], [116].
In a comprehensive study conducted by Sayed et al. (2022), the multifaceted effects of the furanocoumarin derivative xanthotoxin on PD have been examined. Researchers have revealed xanthotoxin's neuroprotective properties and its positive effects on various mechanisms involved in PD

pathogenesis. The findings indicate that xanthotoxin protects dopaminergic neurons, restores tyrosine hydroxylase-positive cells, reduces α-synuclein accumulation, and improves striatal dopamine levels. These effects have been clinically validated by the reduction of motor dysfunction in experimental animal models. Additionally, xanthotoxin has been found to reduce oxidative stress, strengthen antioxidant defenses, and suppress neuroinflammation. At the cellular level, it has been shown to act by preserving the MAPK signaling pathway and inhibiting apoptotic processes. These multifaceted effects have led to the consideration of xanthotoxin as a potential therapeutic agent in the treatment of Parkinson's disease [117].

Finally, Wang and colleagues (2024) synthesized coumarin-phenolic acid hybrid compounds targeting α-synuclein aggregation. Compounds 11a-c (Figure 13) demonstrated strong inhibitory effects. The candidate compounds showed the ability to prevent the formation of β-sheet aggregates by maintaining the proteostasis conformation of α-synuclein and to disassemble preformed α-synuclein oligomers and fibrils. In addition, the candidate compounds demonstrated impressive efficacy in inhibiting α-synuclein aggregation within neural cells, reducing the likelihood of inclusion formation [118].

D. ANTICANCER ACTIVITY

Coumarin and its derivatives are biologically active against various cancer cell lines and are considered potential anticancer agents in cancer treatment. These compounds can be effective against cancer cells through mechanisms such as cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, prevention of metastasis, and inhibition of telomerase and kinases. The anticancer effects of coumarins are primarily based on their ability to scavenge free radicals, which forms the basis of many of their biological activities. However, they may be associated with hepatotoxicity at high doses [118].

As antitumor agents, coumarins stand out for their ability to inhibit DNA-associated enzymes, trigger cell apoptosis, modulate estrogen receptors, and block the cell cycle. Additionally, they exhibit anticancer effects by inhibiting multi-drug resistance, human carbonic anhydrase, the PI3K/AKT/mTOR signaling pathway, microtubule polymerization, tumor angiogenesis, and proteins associated with apoptosis, as well as regulating reactive oxygen species. Due to this broad spectrum of biological activities and minimal side effects, coumarin derivatives are considered promising compounds in cancer therapy [119].

Shen and colleagues (2017) synthesized and evaluated new pyrazole-coumarin hybrid compounds as dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). The compound coded 1 (Figure 14) in the study showed strong inhibition against COX-2 and 5-LOX. It also exhibited antiproliferative effects and dose-dependent apoptosis induction against the lung cancer (A549) cell line. These findings suggest that compound 1 could be a potential lead molecule for the development of anticancer therapies [120].

In another study on coumarins, Muhamed et al. (2019) synthesized new pyrazole-thiazole-coumarin hybrid compounds (2a-d) (Figure 14). Their potential against five different cancer cell lines was examined. Specifically, compound 2d, shown in figure 14, exhibited significant VEGFR-2 inhibition and high cytotoxic effects against breast cancer MCF-7 cells. The mechanism of action of compound 2d was investigated in detail, revealing that it induced cell cycle arrest at the G2/M phase, increased apoptotic cell death, regulated p53 gene expression, and activated the apoptotic pathway by increasing the Bax/Bcl-2 ratio. Furthermore, it was found to enhance apoptotic induction by increasing caspase-7 and caspase-9 activation. These findings suggested that compound 2d could be considered an effective apoptosis modulator and a promising lead molecule for the development of future anti-breast cancer agents [121].

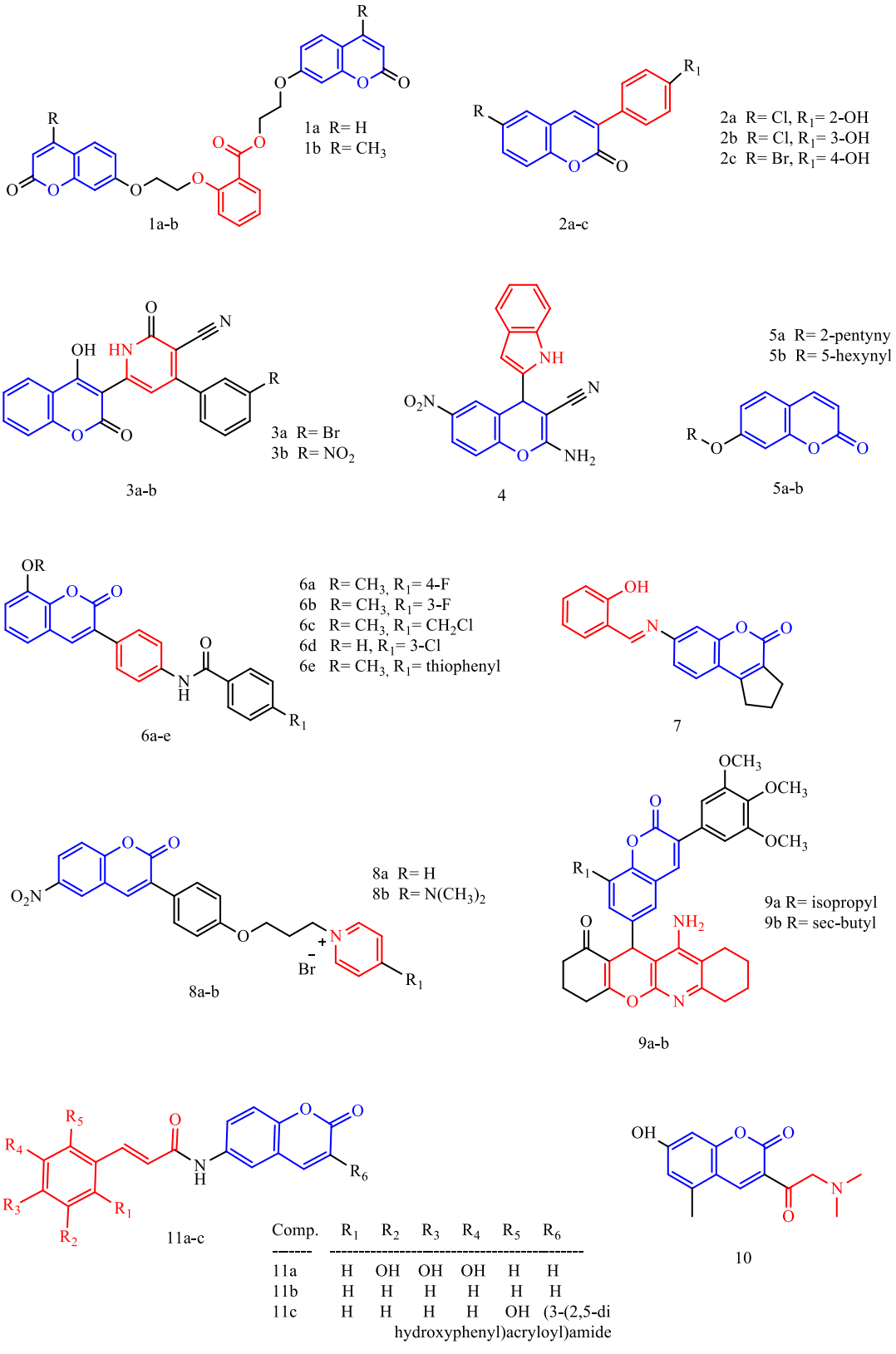


Figure 13. *Chemical Structures of Coumarin Hybrid Compounds with Diverse Biological Activities.*

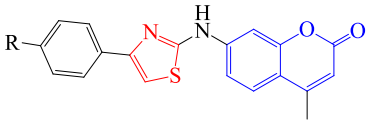
In this study, Durgapal and Soman (2019) synthesized coumarin-proline sulfonamide hybrid derivatives, which show promise for cancer treatment. The anticancer activities of all synthesized compounds were examined *in vitro* against lung cancer (A549) and breast cancer (MCF7) cell lines.

While all compounds exhibited moderate activity in the A549 cell line, they showed distinctly good activity in the MCF7 cancer cell line. Notably, compound 3 (Figure 14) demonstrated excellent activity against the MCF7 cell line [122].

Wang et al. (2020) developed new coumarin-chalcone hybrid compounds as thioredoxin reductase (TrxR) inhibitors and evaluated their anticancer potential. Compound 4 (Figure 14) showed strong antitumor activity against HCT-116 colorectal cancer cells. Due to its red fluorescent property, compound 4 allowed for intracellular imaging. It was observed to reduce TrxR expression, increase reactive oxygen species (ROS) accumulation, induce apoptosis, and inhibit the metastasis of cancer cells. These findings suggest that compound 4 could be a promising theranostic TrxR inhibitor for human cancer treatment [123].

Heris et al. (2020) conducted a study on the anticancer potential of aminothiazole-coumarin derivatives. The researchers identified a new class of aminothiazoles that function as energy-restricting mimetic agents (ERMA). These compounds exhibited strong anticancer activity, particularly against colorectal cancer (CRC) cell lines. Compounds 5a and 5b (Figure 14) showed the most promising results. Their mechanism of action involved inhibiting glucose uptake in cancer cells, increasing the production of reactive oxygen species (ROS), and decreasing the NADPH/NADP+ ratio. Additionally, these compounds demonstrated a synergistic effect with cisplatin. The study highlighted that thiazole-coumarin derivatives could be used as potential anticancer agents by targeting cellular energy mechanisms and showed promise in combination therapy with traditional chemotherapeutic agents. However, it was noted that further research is needed to evaluate their efficacy in different cancer types and in combination with other chemotherapeutic agents [124].

Ahmed and colleagues (2020) synthesized twenty-five new coumarin derivatives and evaluated their *in vitro* anticancer activities against breast cancer (MCF-7) and prostate cancer (PC-3) cell lines. Most of the synthesized compounds exhibited high anticancer activity against the MCF-7 cell line. In particular, compounds 6a and 6b (Figure 14) showed superior activity compared to the positive control, staurosporine. Additionally, compound 6a demonstrated VEGFR-2 kinase inhibitor activity, induced preG1 apoptosis, arrested cell growth in the G2/M phase, and activated caspase-9 [125].

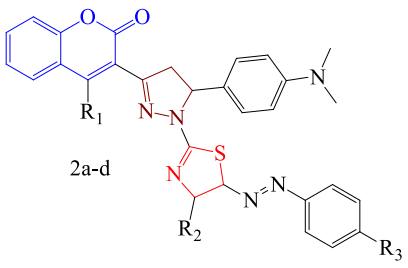


1a-b

1a R= Br
1b R= NO_2

($IC_{50\ M}$M)

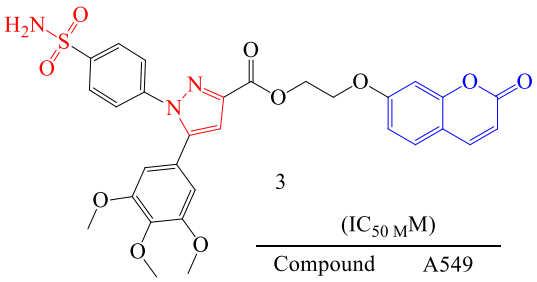
Compounds	HT-29	HCT-116
1a	0.38 ± 0.004	0.53 ± 0.077
1b	3.96 ± 0506	2.56 ± 0.553
OSU-OG5	10.14 + 0.373	2.85 + 0.111
OSU-OG12	10.82 + 1.259	3.4 + 0.581
4-Hydroxycoumarin	200>	200>



2a-d

($IC_{50\ M}$M)

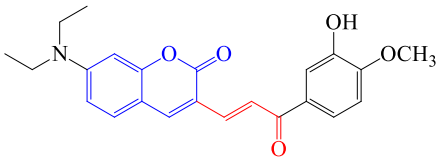
Compounds	MCF-7	R_1	R_2	R_3
2a	8.61	H	CH_3	Cl
2b	6.56	OH	Ph	CH_3
2c	6.51	H	Ph	Cl
2d	5.41	OH	Ph	Cl
Doxorubicin	6.73	--	--	--



3

($IC_{50\ M}$M)

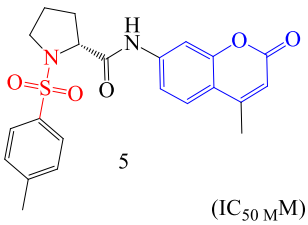
Compound	A549
3	4.48 ± 0.57
Celecoxib	7.68 ± 0.55



4

($IC_{50\ M}$M)

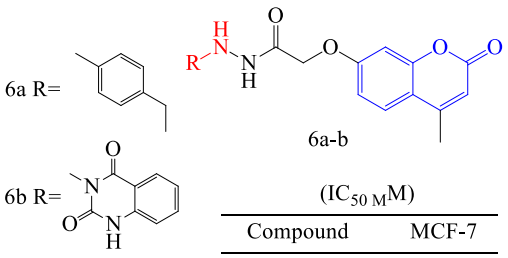
Compound	HCT-116
4	3.60 ± 0.06
Xanthohumol	27.60 ± 1.50



5

($IC_{50\ M}$M)

Compound	MCF-7
5	1.07
5-Fluorouracil	45.04



6a-b

($IC_{50\ M}$M)

Compound	MCF-7
6a	1.24 ±0.06
6b	1.65 ±0.07
Staurospiorine	8.81 ± 0.39

Figure 14. *Chemical Structures of Some Coumarin Hybrid Compounds with Anticancer Activity.*

Beyond their notable anticancer properties, coumarins have been explored for a range of other pharmacological activities. Some of these studies are compiled in in

Table **2** and

Table **3**, highlighting their antimicrobial, antioxidant, and other anti-inflammatory potentials. Furthermore, Table 4 summarizes the enzymatic activities of various coumarin derivatives, detailing the type of coumarin, concentration, and observed results.

Table 2. *Microbial Activity of Coumarins.*

Type of Coumarin	Compound Type	Concentration *(mg/mL)*	Microorganism Type	Microorganism	Test Method	Result *(mm)*	Ref.
Synthetic	Triazol	10 20	Bacteria	*S. Aureus* *B. Subtilis*	Disk diffusion	09- 26 17- 36 09- 27 18- 42	[48]
		10 20	Bacteria	*E. Coli* *K. Pneumonia*	Disk diffusion	08- 21 11- 29 04- 14 09- 22	
		50	Fungus	*Aspergillus niger* *Aspergillus flavus* *Fusariumoxy sporum*	Disk diffusion	08.2-18.8 06.4- 17.6 06.6- 19	
Synthetic	Coumarin-tethered (benz)imidazolium salts and their silver(I) N-heterocyclic carbene complexes	800	Bacteria	*S. Aureus* *B. Subtilis* *E. Coli* *P. Aeruginosa*	Disk diffusion	6-12 7-19 19-28 8-20	[126]
Synthetic	Coumarin-pyrazole hybrid	25000, 50000, 100000	Bacteria	*B. Subtilis* *S. Aureus* *E. Coli* *P. Aeruginosa*	Agar-Well Diffusion	6.25- 100 µg/mL 0.78- 50 µg/mL 3.125-100 µg/L 6.25- 100 µg/mL	[127]

Synthetic	Catechol-3-arylcoumarins	100 μM	Parasite	*Trypanosoma cruzi* *Vero cells*	MTT	7.4- 39.4 % 0.3- 30.4 %	[128]

Table 3. *Pharmacological Activity of Coumarins.*

Type of Coumarin	**Compound Type**	**Activity Type**	**Test Method**	**Result** *(μM/mL)*	**Ref.**
Synthetic	Triazol	Antioxidant	DPPH radical scavenging assay	0.061- 343.33	[48]
			H_2O_2 scavenging assay	0.061- 343.33	
		Anti-inflammatory	Egg-albumin	15.78- 238.13	
			Heat-induced hemolytic	12.06- 138.13	
Synthetic	3-arylcoumarin	Antioxidant	DPPH OH	1.33- 756.42 μM 244.02- 996.24 μM	[129, p. 3]
Synthetic	Trihybridized coumarin -1,3,4-oxadiazole derivatives	Antioxidant	DPPH	48.3- 113.89 μg/mL	[130]
Synthetic	Catechol- 3-arylcoumarins	Antioxidant	ORAC-FL	0.4-5.6 μM	[128]

Synthetic	Coumarin-pyrazole hybrid	Anti-inflammatory	Egg-albumin	3.78- 67.27 μg/mL	[127]

(DPPH): 1,1-diphenyl-2-picryl hydrazyl radical assay.
(ORAC-FL): Oxygen radical antioxidant Capacity-fluorescein

Table 4. *Biochemical (Enzymatic) Activity of Coumarins.*

Type of Coumarin	**Compound Type**	**Concentration** *(μM)*	**Enzyme**	**Result** *(μM)*	**Ref.**
Synthetic	3-arylcoumarin	100	α-glucosidase inhibitory	0.050- 280.38	[129]
		Less than 10.00	AGEs inhibitory	1.42- 298.83	
Synthetic	3-phenylcoumarin	100	monoamine oxidase A (MAO-A)	0- 24.57	[47]
		10	monoamine oxidase B (MAO-B)	75.75- 111.93	
		10	ER inhibition	0- 91.34	
		1	HSD1 inhibition	0- 54	
Synthetic	Trihybridized coumarin -1,3,4-oxadiazole derivatives	100, 50, 40, 30, 20, 10	Anticholinesterase AchE	28.68- 159.74	[130]
			Butyrylcholinesterase BuChE	23.97- 105.93	

VI. USAGES/APPLICATIONS

Coumaric compounds have a wide range of applications thanks to their electron-rich conjugate systems and their versatile and simple scaffold structure [6]. Coumarin and its derivatives, which can be used as fluorescent probe, ion-based receptor and biological dyes; It offers comprehensive application possibilities such as illuminating complex biological processes, monitoring enzyme activity and monitoring pharmacokinetic properties instantly [6].

Studies on coumarin and its derivatives have proven that the presence of different substituents in the coumarin ring gives it different biological properties [131]. It has become the focus of scientific research due to the antibacterial, antifungal, antiviral, anticoagulant, antimitotic, anticancer, anti-inflammatory, anti-allergic, antioxidant, antithrombotic anticonvulsant (antiepileptic) properties that coumarins offer [33], [132], [133], [134], [135], [136]. Coumarin-based compounds have been used in the pharmaceutical industry, especially due to their pharmacological properties such as antimicrobial (antibacterial, antiviral, antifungal and anti-parasitic), anticoagulant, anti-inflammatory, antioxidant and anticarcinogenic [137]. Studies have also reported that some coumarin derivatives have analgesic and hypothermic activity [138]. Some coumarin derivatives have been reported to increase the amount of acetylcholine in the brain by inhibiting acetylcholinesterase. These coumarinic compounds may be drug candidates for the treatment of Alzheimer's associated with learning and understanding memory functions [139].

Coumaric compounds are compounds with low toxicity, high fluorescence quantum yields and stokes shifts, giving absorption and emission spectra in the visible region. In addition, since coumarins can absorb UV light and are very sensitive to natural light, they offer the opportunity to be used in photochemotherapy and chemical sensors [6]. Due to the extraordinary properties of coumarins such as real-time detection, high selectivity and high efficiency, they can be used as fluorescent probes for intracellular bioimaging and can also be used to detect certain cancers. Today, medical imaging has made great advances in locating and distinguishing tumor lesions. Research continues to expand the use of coumarinic compounds as fluorescent probes [140].

Apart from the pharmaceutical industry, coumarin and its derivatives are also used in agriculture. It has been preferred in pesticides due to the herbicide properties of some coumarinic compounds [47]. It has been reported that coumarin derivatives are used as sweeteners and food additives in the food industry. Some coumarins have been used as flavor enhancers in alcoholic beverages and tobacco. It has also been used in perfumes since 1882 due to the nice smell of coumarins [6]. Coumarins are also used in the manufacture of soaps and cleaning products [141].

VII. CONCLUSION

Coumarins constitute a significant portion of the secondary metabolites produced by plants [142], [143]. While the complete synthesis pathway of natural coumarins remains not entirely elucidated, ongoing research has made substantial progress [144]. Studies have unveiled a myriad of pharmacological and biochemical activities associated with both natural and synthetic coumarins. Their exceptional properties have not only found applications in the pharmaceutical industry but have also extended to their use as additives in food, pesticides in agriculture, and fragrances in cosmetics. Notably, research has indicated that coumarin and its derivatives, which have undergone photophysical investigations, hold promise as biological probes owing to their fluorescence characteristics [145], [146]. In this review, we provided insights into the classification of coumarins, summarized various chemical synthesis methods, and elucidated the chemical-physical properties and biological activities of coumarin and its derivatives. Furthermore, we compiled their diverse application areas.

CONFLICT OF INTERESTS: The author has no competing interests to declare that are relevant to the content of this article.

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ETHICAL DISCLOSURES: Since this study is a data collection study (review), it does not have experimental data. Therefore, ethics committee approval was not obtained because it does not require ethics committee approval.

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