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Coumarin: A Novel Tool for Multidisciplinary Activities

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Coumarin 2H-1-benzopyran-2-one core has been a field of attention due to its exclusive propensity to accept variable classes of replacements which proves it as the origin for multi-disciplinary activities. Many researchers replicates that coumarin derivatives synthesized by structural modifications & alterations that exhibits diverse pharmacological activities like Anticancer, Carbonic Anhydrase Inhibition, Anti-bacterial, Antifungal, Antiviral, Anticoagulant, Anti Alzheimer activity, Anticonvulsant Activity, Anti-inflammatory etc.The motive of this study is to review, various substituted coumarin derivatives and provide the opportunity of designing & synthesizing novel coumarin based drugs and exploring their possible derivatives in the cure of numerous disorders. This review summerizes the recent development in synthesis of Coumarin based derivatives with various biological activities.

Keywords: Coumarin derivatives; anti-cancer; anti-bacterial; anti- fungal; carbonic anhydrase inhibition; toxicity.

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1. INTRODUCTION

Coumarin belongs to their group term toward Coumarou, obtained from tonka beans; contain attached benzene (C6H6) as well as alpha-pyrone groups [1]. This denotes huge species of derivative that biologically originated from plants. Four chief Coumarin sub-classes contain (a) Simple Coumarins, (b) Furano-coumarins, (c) pyrano coumarins, as well as(d) Pyrone substituted Coumarins [2]. Some basic coumarins were the hydroxylated, alkoxylated, also alkylated products of parental drug. It includes derivatives of coumarin like 7-hydroxyl coumarin, also 6, 7- dihydroxy coumarin. Furano coumarins cover five membered furan rings committed to the coumarin core, separated into rectilinear or angular categories by replacement at single or both of the residual benzoid sites. [3] Pyrano coumarin parts are similar to furano coumarins however comprise a 6 membered ring. It includes units like Seselin as well as Xanthyletin coumarins replaced in the pyrone group contain 4-Hydroxycoumarin. [4] Coumarin exhibit antiviral as well as antibacterial activities. [5] Along with several anti-inflammatory capabilities [6] several coumarins have antioxidant activity rummaging super-oxide anion radicals [7,8], decrease oedema in rat appendage carrageenan assessment as well as extra inflammatory sand rat representations [9]. Coumarin was initialy segregated in 1820 by scintist Vogel [10] as of tonka beans [Dipteryx odoranta Wild, Fabaceae family] also termed as Coumarou, a dialect French term. Afterward segregation, structural categorization (fig.1), synthesis, and genetical action of thousands of natural coumarins from plants, bacteria, fungi [11-13] , as well as chemical synthesis [14] was done.

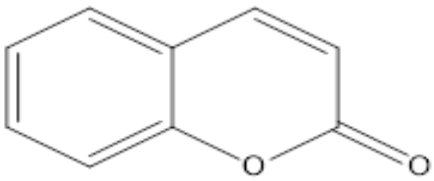
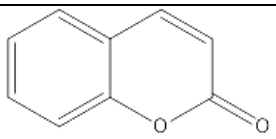
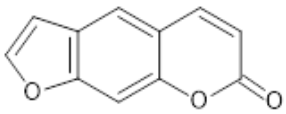
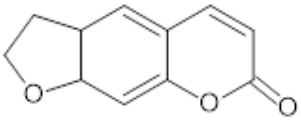
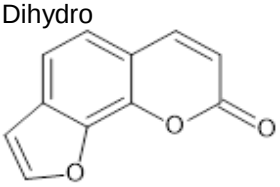
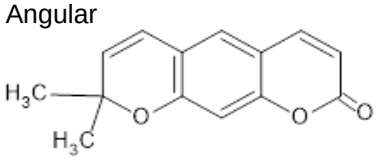
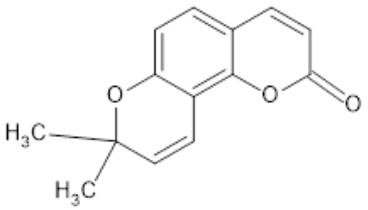
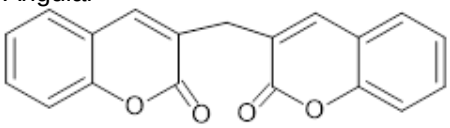
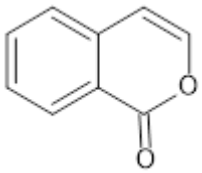
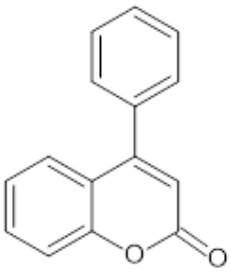


Fig. 1. Structure of coumarin nucleus

Following Table 1 describes the classification of coumarin according the structure and examples relates with the significant pharmacological actions.

Table 1. Classification of coumarins

Class	General Structure	Example
Simple Coumarins		Osthole (neuroprotective, osteogenic, immunomodulatory, anti-cancer, hepatoprotective, cardiovascular protective and antimicrobial)
Furanocoumarins	 Linear  Dihydro  Angular	Psoralen (antifungal) Antoghenol (antibacterial) Columbianedin (anti-inflammatory)
Pyranocoumarins		Grandivittin (antibacterial) Inophyllum A, B, C, E, P, G_1, G_2 (antiviral)

Class	General Structure	Example
	Linear 	
Biscoumarins	Angular 	Dicoumarol (anticoagulant)
Isocoumarin		Thunberginols (antidiabetic)
Phenylcoumarins		Isodispar B (Anti-inflammatory)

2. PHARMACOLOGICAL ACTIVITIES OF COUMARIN

2.1 Anti-Alzheimer Activity

Alzheimer's disease is a deteriorating disorder of the central nervous system (CNS) that is primarily known by advanced remembrance damage [15-17]. Nowadays about 47 million individuals existing along with dementia globally. By 2050, this figure will have amplified overhead 135 million. Dementia distresses4 people out of 1000 at the age ranging from 60 to 64 years [18]. Triazolyl-tacrine-coumarin derivatives as acetyl cholinesterase inhibitors used in the treatment of Alzheimer disease [19].

The present therapy approach, which mostly involves the use of acetylcholinesterase (AChE) inhibitors (rivastigmine, donepezil, galantamine) or N-methyl-D-aspartic acid (NMDA) receptor inhibitors (memantine), is symptomatic and does not prevent degeneration from progressing.

The antioxidant and AChE/BuChE inhibitory activities of aerial parts, fruits, flowers, and root extracts from Ferulago cassia Boiss was examined by Karakaya and associates in 2019. In the TBA experiment, root and fruit dichloromethane extracts had the best antioxidant potential. The Ellman's method was used to assess anticholinesterase activity: dichloromethane extracts showed significant inhibition against BuChE (96.56 percent 2.98 and 82.33 percent 2.69, respectively) at 20 g/mL, as well as appreciable inhibition against AChE (53.24 1.22 and 31.38 5.41 percent, respectively) at 20 g/mL. Peucedanol, suberosin, grandivitinol, and umbelliferone were discovered in Ferulago cassia. As a result, F. cassia can serve as a starting point for the production of new antioxidant and anticholinesterase chemicals.

2.2 Anti-bacterial Activity

Multi-drug resistant bacteria are non-susceptible strains to more than one bacterial strain and are classified as enormously drug resistant strains. [20, 21] In 2005, more than 50 naturals as well as synthetic compounds were assisted and then estimated for structural activity relationship analysis. The antibacterial power of approximately 50 coumarin products, natural as

well as synthetic, was assessed and then connected by a SAR analysis. Amongst the dynamic drugs, osthenole, exhibit maximum activity against S.aureus as well as B.cereus exhibited the maximum effective action with a MIC against S. areus as well as B. cereus [22]. In 2015, Nagamallu and colleagues demoralized the Vilsmeier-Haack reaction to get a sequence of novel pyrazole-holding coumarins as well as estimated their antioxidant along with antibacterial actions [23]. In the middle of the series, two compounds (Y-R=CONH2 and Z-R=CSNH2) exhibited pharmacological activity.

In2018, Chavan and Hosamani projected a superficial process for the microwave assisted coumarin pyrazol derivatives and estimated their pharmacological action [24]. The investigators estimated in vitro antibacterial activity by agar plate diffusion method [25].

2.3 Anti-cancer Activity

The word “cancer” describes a varied series of disorders produced by the accretion of alterations and categorized by a multistep procedure, including numerous diverse features which may not openly be the reason for cancer themselves nonetheless can rise the probabilities of genomic transformations. [26,27] Lately, Maleki et al. require manufactured 18 O-prenylated coumarin products also verified this upon Hela Cervical Cancer also HDF usual cell units via MTT Assay [28].

Halawa et al. produced as well as categorized an innovative sequence of 4-arylamino-3-nitrocoumarin equivalents from 4-Hydroxycoumarin besides verified upon the individual cervix cancerous cellular space [29]. That compounds remained got towards the aim of human Topoisomerase-I compound, thus delaying in unit duplication besides leads toward cell demise.

Herrera et al. manufactured a sequence of 3 as well as7-styrylcoumarins, closely of which revealed anti-proliferative action upon SW-480 individual colon adeno-carcinoma cell units [30]. Between those,7-(4-Hydroxy-3, 5-dimethoxystyryl)-2H-chromen-2-one (Fig. 4) exhibited the maximum action, also this leads to cell-apoptosis in SW-480 cell units, possibly via moderating the tumour-suppressor protein (P-53). The novel derivatives were verified *in-vivo*, few compounds capable to suppress initial development for Colon Adeno-carcinoma [31].

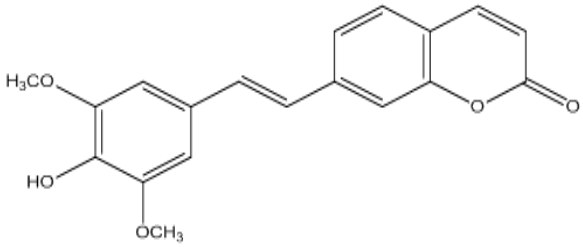


Fig. 2. Chemical structure of Styryl coumarin

Cai et al. created luminous coumarin-benzo[b]thiophene 1, 1-dioxide conjugates. STAT3, a protein involved in the control of the mitochondrial apoptotic pathway, is influenced by these chemicals. They speculated that inhibiting Tyr705 and Ser727 phosphorylation would hinder STAT3 activation. To test the biological activity of the newly synthesised chemicals, researchers used four STAT3 over-activated human cancer cell lines (human breast carcinoma MDA-MB-231 and MCF-7 cells, human colonic carcinoma HCT-116 cells, and human hepatocellular carcinoma HepG2 cells). Some coumarin conjugates induced cancer cell death and ROS production by suppressing STAT3 phosphorylation on Tyr705, altering mitochondrial membrane potential, and blocking STAT3 DNA-binding activity.

2.4 Anticoagulant Activity

The anticoagulant action of coumarins was recognized in 1920.Karl Link and Harold Campbell synthesized 3,3’-methylenebis (4-hydroxycoumarin), after some time, identified as to dicoumarol. [32-36].

In spite of efficiency in addition with the benefits of an oral treatment, warfarin is not lacking of side-effects used as effective anti-coagulant agent. [37-38].

Therefore, the study of new harmless and well-organized compounds of a novel Vit -K Antagonist (VKA), tecarfarin (ATI-5923), presently under advancement [39]. Subsequently, drug-drug or food-drug connections remain evaded, along with genetic changeability of CYP-450 scheme, provided that a steadier anticoagulation action associated to warfarin [40]. Albrecht et al., organized with the new stage one study of patients among serious Kidney disorders [41-42]. Tecarfarin is a suitable replacement of Warfarin for oral treatment for thrombo-embolic disorder.

Montagut-Romans et al., in 2017 discovered substituted derivatives with substitution on C-3 site by incorporating an unsaturated series.[43]. The fundamental evidence existed the SAR report accomplished by Gebaur in 2007, show that the action of 4-hydroxycoumarin was improved only by structural alteration at C-3 site via isoprenyl substitution.

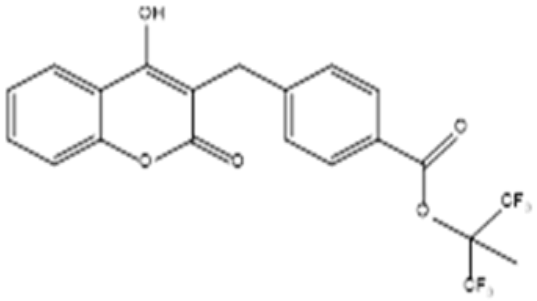


Fig. 3. Structure of Tecarfin

2.5 Anticonvulsant Activity

Epilepsy is a common neurological disease, categorized by episodic also random attacks, including convulsions or temporary behavioural fluctuations. Its pathogenesis has not been totally explained yet. [44-48]. At this point, we report some current developments in the usage of coumarins by way of anticonvulsant drugs. Abd-Allah and colleagues freshly calculated the anticonvulsant action of a sequence of coumarin products, attained by integration two or extra pharmacophoric supports in series to produce novel biochemical units using an enhanced biotic action [49].

The compounds now defined have all the essential fundamentals to use antiepileptic/ Anticonvulsant action: a lipotropic aryl group, the H-bonding field in addition with an electron-donor group. [50-51] A like divalent medication method was tracked by Mohammadi-Khanaposhtani and colleagues, who manufactured a succession of coumarin-1,2,4-oxadiazole offshoots in order to make an innovative biochemical unit with better anticonvulsant outline than coumarin.

2.6 Antifungal Activity

Fungal disorders are a familiar wave for animal as well as for human being also. Above 90% of all stated fungal related infections fit into one of the 4types: Cryptococcus, Candida, Aspergillus and Pneumocystis [52-54]. Coumarin products are able with antifungal action, possibly valuable in together pharmaceutical and food industry. Here insection, we will pay attention on the current developments in the advancement of new antifungal drugs aimed for human use. In spite of several classes of Candida can be a source of syndrome, [55,57,58]. In 2016, Shaik and co-workers planned an innovative sequence of coumarin derivatives coupled with other compounds, on the basis of a former effort by Shi and Zhou and of the communal usage of azoles as antifungal medicines. The anti-fungal strength of the new compounds existed verified counter to Candida albicans and additional fungous microorganisms [59]. Additionally, molecular docking studies exposed that these complexes have a high attraction in the direction of the active position of enzyme P450 cytochrome lanosterol 14α-demethylase . Coumarin based anti-fungal azoles have been further more examined by Elias and colleagues, in 2019, established a chain of 11 coumarins coupled by 1, 2, 4-triazole as well as imidazole [60-62].

2.7 Anti-inflammatory Activity

Inflammation is a chief self-protective action of existing tissue to several injury causes, such as biotic pathogens, noxious chemicals, irritations as well as other injurious provocations. [63-64] As a complicated biological in addition physiological procedure, inflammation is branded by 5 chief sign and indications, together with puffiness, soreness, warmth, discomfort and local disfunction.[65] Infection, it is a defensive immune reply and is generally valuable. Though, insistent and overblown inflammation will help tissue injury and be the reason for diseases, for example, Arthritis, Sepsis, Athero-sclerosis, and also even sarcoma. [66-68]. approximately some coumarins with diverse pharmacophores at C3 site must estimate for Anti-inflammatory actions. [69-72] Sulfone along with sulfoxide products covering heterocyclic fractions fit in to a significant type of energetic compounds having various biotic activities. [73-74]. It has been stated that the mixture of different pharmacophores in the equivalent structure is very possible to gain compounds with noteworthy action. Therefore, so as to advance innovative anti-inflammatory mediators, benzyl sulfone/sulfoxide groups was presented at C3 site of coumarin basic skeleton then aim complexes, 3-replaced coumarin products was constructed also produced.

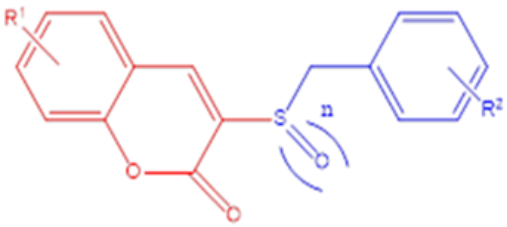


Fig. 4. The proposal of 3-substituted coumarin spinoffs

Srivastava and colleagues investigated the anti-inflammatory and analgesic effects of a series of manufactured 7-substituted coumarins in 2016, and the most active compounds were then tested for 5-LOX inhibition in vitro. When compared to acetylsalicylic acid, In vitro kinetic studies of (IC50 = 2.09 nM) revealed that it inhibits 5-LOX in a mixed or non-competitive manner. The presence of a substituent on the benzothiazole ring's C6 position was discovered to be crucial for enhancing activity.

2.8 Antiviral Activity

Human past is aggrieved by the cyclical string of pandemic conditions and the study of novel antivirals is still enduring, because of the skill of viruses to alter their structure [75-76]. Numerous compounds which show antiviral activity [77-80]. Coumarins, similarly other poly-phenolic compounds, show an extra ordinary antiviral action [81-82]. The antiviral activity of coumarins explains by means of different way which disturbs the lifecycle of viruses and their genetic actions might be altered dependent upon the mixture of several substituents with conjugates [83-84]. Coumarins seem to be more effective on many viruses. Liu and colleagues synthesized prenylated coumarins [85] checked for their anti-inflammatory as well as anti-HIV activity. Cytopathic action of HIV-1 (EC50) and cytostatic action of C8166 cell line conferring to MTT assay [86-87]. Three novel coumarin derivatives exhibited the greatest prohibition action of 0.29, 0.68 and 0.17 μM, individually.

Some of the probable benefits of oxidized coumarins might be their method of action in contradiction of viruses. Due to antioxidant action, coumarin derivatives might disturb intracellular redox-sensitive paths valuable for viral duplication [88]. As previously stated, coumarins used as anti-hepatitis agents. Tsay and colleagues examined the action in contrast to Hepatitis C Virus (HCV) of certain unusual imidazole-coumarin compounds [89]. Huang and colleagues attentive on the investigation of the potency stated by esculetin or dihydroxycoumarin) against Hepatitis B Virus (HBV) [90] . Here we concluded that esculetin proficiently obstructs Hepatitis B Virus (HBV) repetition equally in vitro also in vivo, which delivers a chance for more advancement of the drug by means of anti-viral drug.

2.9 Carbonic Anhydrase Inhibition

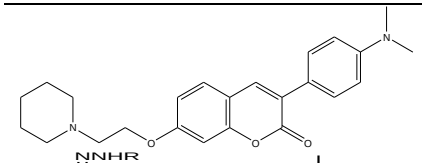
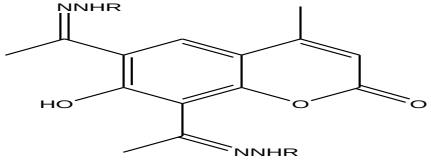
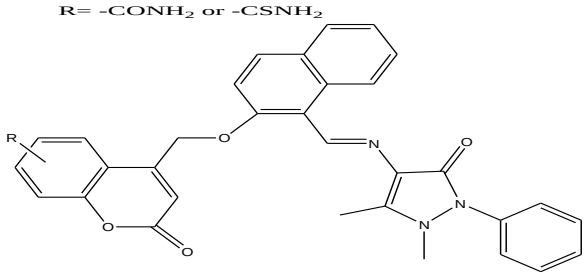
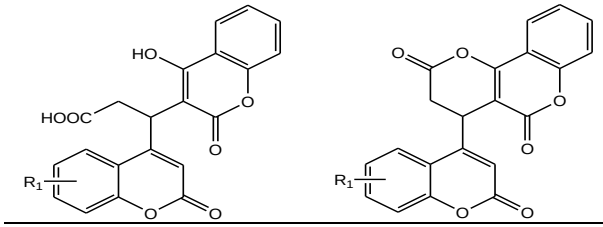
Carbonic anhydrase is universal metallo-enzymes which catalyse alterable hydration of CO2 into Bicarbonate buffer system. This enzyme was included within an extensive variety for biological also immunological procedures [91] and derestricting by means of carbonic anhydrases inhibitors might exists valuable action for various diseases [92-95]. The model Carbonic anhydrase inhibitor might specifically show activity contrary to following Iso-forms hCA IX, XII, for occurrence associated to some disorders [96--97].

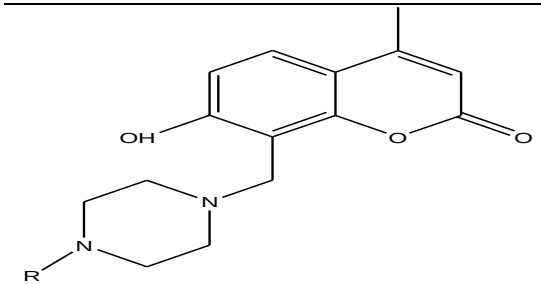
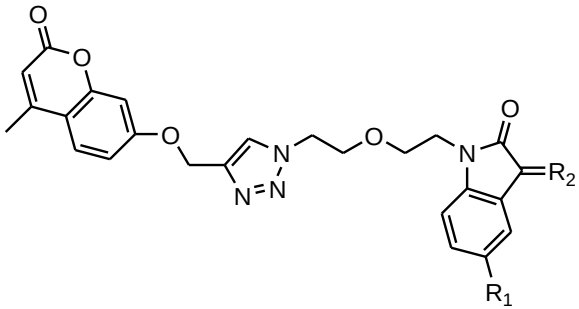
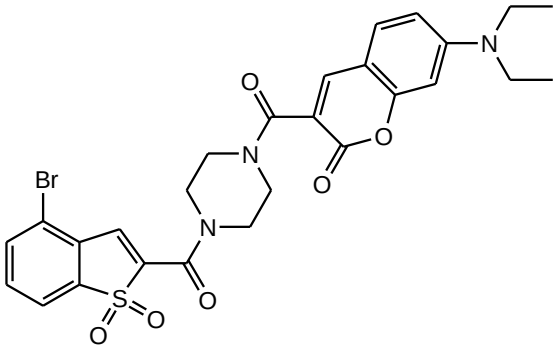
In 2019, 4-methylumbelliferone, Buran with colleagues manufactured, a sequel of eight substituted Coumarin dependent compounds having alkyl piperazine as well as aryl piperazine, and estimated their repressive action counter to isoforms hCA I, II, IX and XII. [98] Altogether verified drug which was capable for suppress isoform.

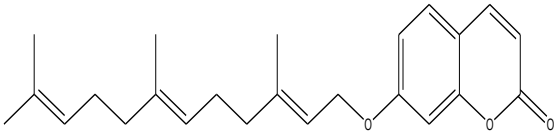
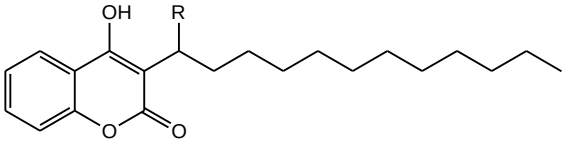
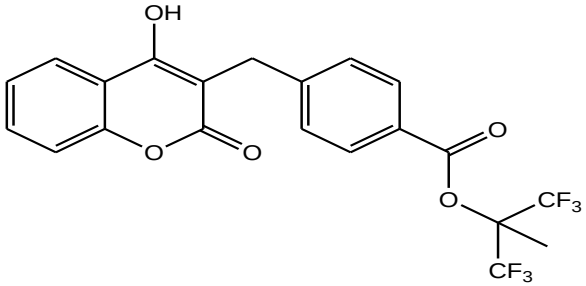
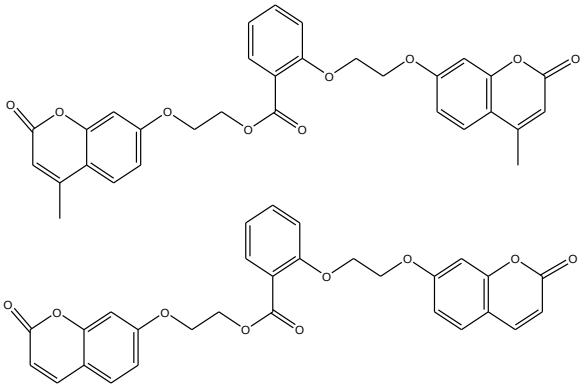
Compound with substitution at C-8 site for 4-Methylumbelliferone doesn’t have any effect happening on suppression. But substitution within the side chains of compounds shows increased activity. An analogous outcome was gone through numerous additional units which possess newly produced coumarin-depended mixtures as well as estimate disoforms. Sulpho-cumarins, Bis-Coumarins along with coumarins 1, 3, 4-Oxadiazole spinoffs were certain samples [99-102].

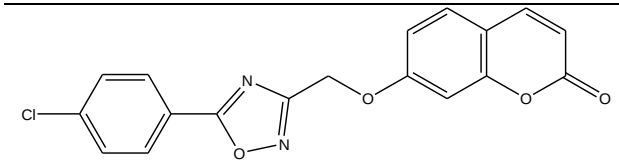
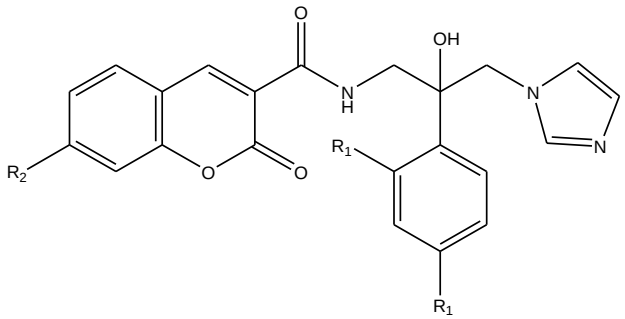
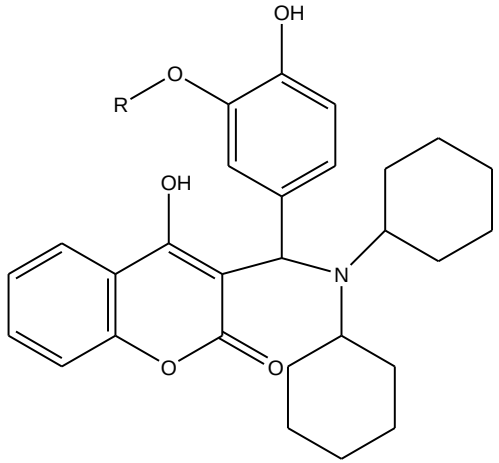
Following Table 2. summarises derivatives of coumarin with their pharmacological activities, molecular targets and mechanism of action.The mechanism of action of some coumarin derivatives are not known or they are still under investigation.

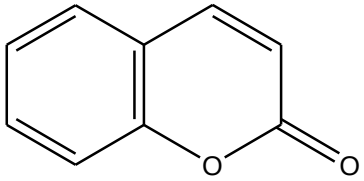
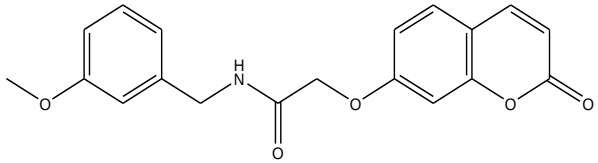
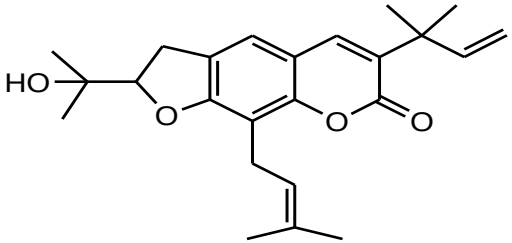
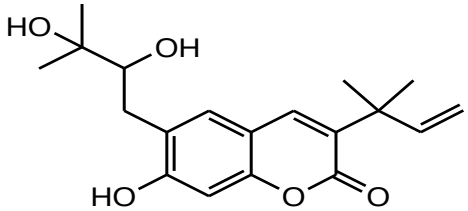
Table 2. Various coumarin derivatives with biological activity, molecular target and mechanism of action

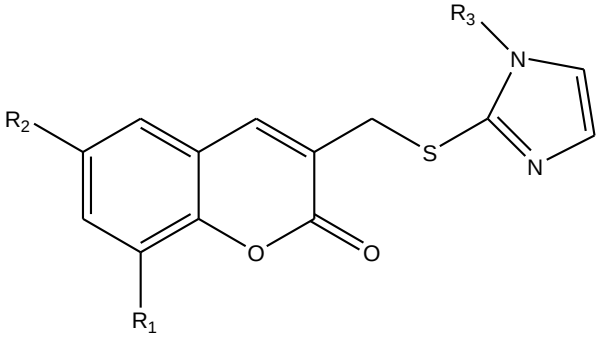
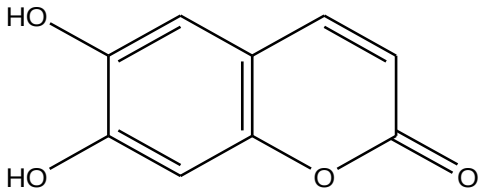
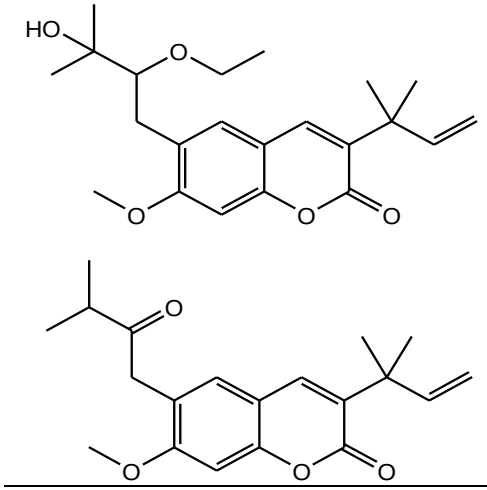
Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Anti-Alzheimer	AChE, BuChE	Interacts with Trp286 causing AChE, BuChE inhibition	Synthetic	[123]
	Antibacterial/ Antifungal	S. aureus, E. coli, P. aeruginosa, A. Niger, A. flavus, C. albicans	-	Synthetic	[23]
	Antibacterial	S. aureus	Binds to active site of the DHPS causes its inhibition	Synthetic	[24]
	Antibacterial	S. Aureus, E. faecalis, E. coli	-	Synthetic	[116]

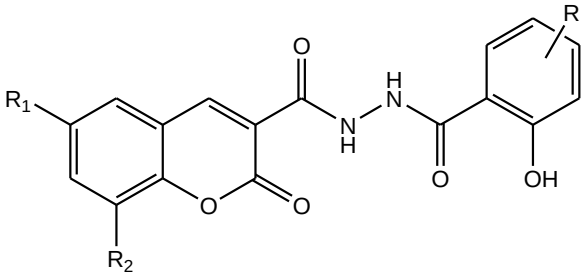
Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Anticancer	Carbonic Anhydrase IX and XII	Inhibit Carbonic Anhydrase IX, XII thus inhibit activation of gene CA9 via HIF-1 α	Synthetic	[70]
	Anticancer	-	-	Synthetic	[106]
	Anticancer	STAT3	inhibit STAT3 phosphorylation on Tyr705, affecting mitochondrial membrane potential and preventing STAT3 DNA-binding activity.	Synthetic	[114]

Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Anticancer	Carbonic Anhydrase IX and XII	Inhibits Carbonic Anhydrase IX and XII and the growth, metastasis and angiogenesis of tumor cells	Natural	[115]
	Anticoagulant	murine VKORC1 inhibitor	inhibition of the activity of murine VKORC1 regulating biosynthesis of biologically active vitamin K	Synthetic	[43]
	Anticoagulant	VKOR inhibitor	Effects on coagulation factor VII & X & reversal of anticoagulant by vit K-1, together with VKOR inhibition	Synthetic	[121]
	Anticoagulant	n.g.	-	Synthetic	[122]

Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Anticonvulsant	BZD receptor	BZD binding site of GABAA receptor giving anticonvulsant activity	Synthetic	[62]
	Antifungal	Several Candida strains-mode of action involving CYP51 and additional unidentified mechanism	-	Synthetic	[59]
	Antifungal	C. albicans	inhibition ergosterol biosynthesis by binding lanosterol 14a-demethylase	Synthetic	[117]

Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Antifungal	C.albicans-antibiofilm	inhibits bacterial biofilm as a quorum-sensing inhibitor	Natural	[118]
	Anti-inflammatory	NF-kB signalling pathways	inhibiton of NF-κB signaling inhibiting the pro-inflammaory agents activity	synthetic	[125]
	Antiviral	HIV	Anti-HIV reverse transcriptase	Natural	[85]
					

Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Antiviral	Hepatitis C virus	-	Synthetic	[89]
	Antiviral	Hepatitis B virus	inhibits the expression of HBx protein causing apoptosis, inhibiting the repair of damaged DNA	Natural	[112]
	Antiviral	HIV reverse transcriptase	-	Natural	[119]

Structure	Biological activity	Molecular target	Mechanism	Origin	Reference
	Antiviral	HIV1-IN	Inhibition of cell proliferation by forming hydrophobic interaction with proteins	Synthetic	[120]

2.10 Toxicity of Coumarins

For human lives, coumarin part takes a minor poisonous outcome. The primary dose, to the amount of four grams, shows the sign and symptoms of sickness also weakness. It has no fixed harmful outcome taking place in the heart; it slows the sense of the sympathetic nerves as well as paralyses the smooth muscles. Dihydrocoumarin, o-hydroxylphenyl propyl alcohol, as well as chroman have a sedative property. It is projected that the normal Western food may comprise about 1gm/day of benzopyrones, mainly coumarins in addition with flavonoids [103]. Therefore, wide-ranging study going on the genetical, pharmacological, as well as toxicological assets of coumarins has been passed out. Metabolic rate as well as toxicity analyses has been revised [104] . Since inspections on the security used for human beings of coumarins current in foods, as well as in perfumes for beautifying usage. On the other hand, other documents theme out several important poisonousness of coumarin as well as certain coumarin derivatives. Actually, hepatotoxic properties have been seen in hepatocytes of various types, together with human being [104-106]. In another exciting document [107], it has been showed that cytotoxic properties of coumarins are metabolism along with species-dependent, and as importance, rat models can't be used to estimate a probable toxicity of coumarin in human beings. Certainly, an in-vitro dynamic study of o-HPA development, and in specific, the large amounts of coumarin essential for o-HPA manufacture in humanoid liver microsomes, recommended that human beings are not likely to show toxicologically applicable concentrations percentage of this metabolite, coming from the verysensitive 3, 4-coumarin epoxide in addition with 3-hydroxycoumarin, for the reason that of the comparatively small dose of coumarin contacts [107]. Recent studies in zebrafish embryos advised for coumarin also warfarin teratogen have lethal effects, but then at higher doses [108]. Developing harmfulness was appealed for coumarin and hydroxycoumarins. Remarkably, current studies established human being data showed a Tolerable Dose Intake (TDI) of coumarin equivalent to 0.1 mg/kg of body. This amount necessity not be crossed to evade toxic action. Undeniably, through Christmas time of year in Germany, the eating of cassia cinnamon has led to in a higher dosage that the TDI of coumarin was regularly touched, therefore raising the danger for hepatotoxic as well as carcinogenic properties [109s].

3. CONCLUSION

In recent years increased number of publications in many journals proves the importance of therapeutic & diagnostic use of substituted coumarin derivatives. Various Coumarin-based complexes have also attracted attention due to their broad spectrum of biological activities. In above mini-review we summarized the recent development in the substituted coumarin derivatives which shows various activities like anticancer, antimicrobial, antifungal, or antioxidants, anti-inflammatory, anticoagulant, anticonvulsant, antiviral etc. Despite of showing multiple biological activities increased toxicity, resistance and cost along with decreased efficacy of present coumarin based heterocyclic drugs necessities the need of the synthesis of new molecules. Therefore, it is essential to do the literature review which will be beneficial for the further development of the new substituted coumarin derivatives. Coumarin derivatives have acknowledged growing consideration for their varied pharmacological actions. In this review, we tried to cover work associated with structural modifications that gives significant pharmacological actions related to coumarins. This review is of great importance for the proposal and enhancement of the coumarin derivatives as novel principal molecules for various disease therapies. It is our expectancy that this review will help for future synthesis and development of coumarin possible activities.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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