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A current summary of coumarin-based compounds and their therapeutic applications

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Abstract

Because of their importance in pharmacy and medicine, compounds with coumarin backbones are a particularly significant category of chemicals. Because of their conjugated double ring system, coumarins are intriguing molecules for a variety of research fields. Coumarins are used in industry as cosmetics and perfume ingredients, food additives, and most notably in the pharmaceutical industry to synthesize a wide range of synthetic pharmaceutical products. Coumarin derivatives' properties and biological activities play an important role in drug development. Coumarins have received increased interest from the scientific community in recent years due to their vast spectrum of biological activities, mostly due to their capacity to interact with numerous enzymes and receptors in living organisms. Numerous research articles and reviews contain information on this important family of compounds. In this review article, we attempt to keep the reader up to date on recent advances in coumarin biological activity, which may serve as a step-in drug design.

Keywords: Coumarin, Cancer, Anti-inflammatory, Diabetic, Antioxidant, CA.

1. Introduction

Coumarin is a naturally occurring component of numerous plants and essential oils. It gets its name from the plant Coumarouna odorata[1]. Coumarin is a chemical that belongs to the benzopyrone family. The benzopyrones, which all include a fused benzene and pyrone ring (**Fig. 1**), based on the oxygen position within the pyrone ring, can be separated into two categories: the benzo-α-pyrones, which include coumarins, and the benzo-γ-pyrones, which include flavonoids[2].

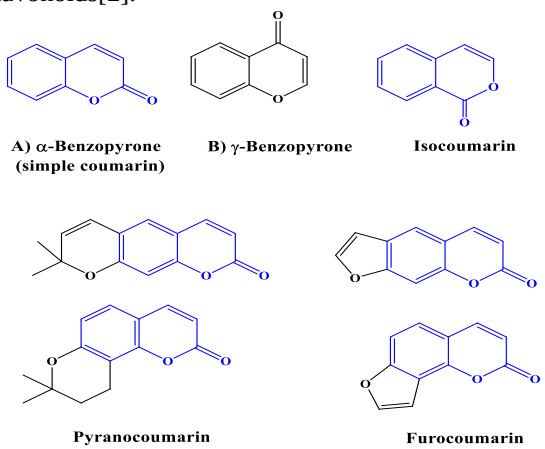

Fig. 1. The structure of the major coumarin classes

Compounds from both sub-classifications have been widely studied in both research and clinical contexts, and both groups have been revealed to have a wide range of beneficial pharmacological and physiological traits [3-6]. In addition to simple coumarins, there are various coumarin classes such as furocoumarins, pyranocoumarins, biscoumarins, and isocoumarin **(Fig. 1)**. Isocoumarins (1*H*-2-benzopyran-1-ones or isochromene derivatives) are coumarin isomers with a reversed lactone moiety[7] that are biosynthetically, structurally, and pharmacologically interesting natural products. Isocoumarins have been reported to have a variety of bioactivities, including antimicrobial, cytotoxic, antiallergic, immunomodulatory, antimalarial, and protease inhibitors[8-11]

Coumarins have several appealing properties, including low molecular weight, simple structure, high bioavailability, good solubility in most solvents, and low toxicity, which, combined with their multifaceted biological activities, ensures that they play an important role as lead compounds in drug research and development[3,4]. Coumarins have antimicrobial, anti-inflammatory, antidiabetic, antioxidant, and antiproliferative properties [12]. The following article highlights recent investigations on the pharmacological properties of coumarin derivatives.

2. Biological actions

Coumarins have a variety of pharmacological properties, including antibacterial, anticancer, anti-inflammatory, anti-diabetic, and antioxidant properties. Coumarins, in addition to their biological function, offer another important feature: luminescent properties. These compounds have a wide range of

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applications, such as photo-cleavable protection groups and fluorescent probes. However, the focus of this review will be on the most essential pharmacological features of coumarin derivatives.

a. Antimicrobial action

Despite tremendous advances in therapeutics and medical chemistry, bacterial and fungal infections, illnesses continue to be serious public health concerns. Even though many antimicrobial treatments are used and profitable in the clinic, they become less effective over time as microbes build resistance to them [13,14]. It is predicted that antibiotic-resistant infectious bacterial infections kill 700,000 people worldwide each year. In the absence of improved preventative or treatment methods, it is anticipated that by 2050, 10 million people will die each year from these deadly diseases over the world[15]. The development of new and more effective antimicrobial drugs is vital, and several studies have been carried out to broaden the scope of new agents. Coumarin rings are found in a variety of natural and synthetic compounds, and they have a wide range of activities, including antibacterial activity.

The ATPase domains of DNA gyrase and topoisomerase IV enzymes, both of which are required for bacterial DNA replication, have been identified as potential antibiotic targets [16-18]. A variety of coumarin conjugates with thiazolidinone (general structure **1**, **Fig. 2**) have recently been used as an advanced structural antibacterial modulator against fatal multidrug-resistant bacterial infections [19]. Bioactivity testing revealed that indole-incorporated coumarin thiazolidinone compound (R = indole) had low cytotoxicity to mammalian cells, a broad antibacterial spectrum, and strong inhibitory efficiency against the tested germs at low concentrations (0.25-2 mg/mL). Furthermore, Compounds **1**'s efficacy in removing bacterial biofilm proved advantageous in preventing medication resistance. Mechanistic studies demonstrated that compounds **1** were capable of destroying cell membranes, resulting in intracellular material leakage and metabolic inhibition. Excess reactive oxygen species (ROS) accumulation mediated by compounds **1** could impair glutathione (GSH) action and induce lipid peroxidation, hence suppressing bacterial growth. Furthermore, compounds **1** may not only intercalate into a DNA base pair but also engage non-covalently with DNA gyrase B, interfering with their biological activity.

Another two sets of coumarin-thiazole hybrids with remarkable bacteriostatic capability of general structure **2** and **3** (**Fig. 2**) have been developed[20]. Bioactivity testing revealed that hybrids with R = OCH_3 had a substantial inhibitory activity against MRSA (MIC = 0.004 µM), which was 6-fold more potent than the anti-MRSA activity of the reference norfloxacin (MIC =0.025 µM). According to molecular docking, these targets may bind to DNA gyrase by establishing stable hydrogen bonds. Furthermore, molecular electrostatic potential surfaces were constructed to explain the target compounds' remarkable antibacterial activity. Furthermore, preliminary mechanistic investigations revealed that these compounds could damage MRSA's bacterial barrier and insert themselves into MRSA DNA to inhibit replication, potentially becoming a viable antibacterial repressor against MRSA.

Recently[21], a new series of coumarin-6-sulfonamide derivatives **4a–n** (**Fig. 2**) was designed, synthesized and tested as potential antimicrobial agents. Compounds **4a** and **4b** exhibited significant antibacterial activity against all pathogenic strains of bacteria. Their MIC values were 4.88 µg/mL for *S. aureus* and 9.76 µg/mL for *C. albicans*, which is four times stronger than the neomycin control (MIC = 19.53 and 39.06 µg/mL, respectively), and their MIC value of 39.06 µg/mL against *E. coli* was the same as neomycin. Compound **4a** exhibited equivalent potency to neomycin against both *S. aureus* and *C. albicans*. Compound **4b** exhibited equivalent potency to neomycin against *S. aureus* and was twice as effective as neomycin against *C. albicans*. The results of the DNA gyrase inhibitory assay showed that compounds **4a** and **4b** significantly blocked DNA gyrase (IC_{50} = 2.50 and 1.80 µg/mL, respectively). Compound **4b** was about as effective as the standard drug novobiocin (IC_{50} = 1.40 µg/mL).

Furthermore, numerous studies have shown that coumarin metal complexes have antimicrobial action[22,23]. Recently, transition metal complexes formed from coumarin have been synthesized with bivalent metal ions, including manganese, cobalt, nickel, copper, and zinc. The antifungal efficacy of complex **6** (Fig. 2) was evaluated against Candida albicans and Aspergillus niger, which showed modest activity compared to the standard Clotrimazole. Moreover, the Minimum Inhibitory Concentration (MIC) was evaluated for antibacterial efficacy against *E. coli* and *S. aureus*, revealing that complex 6 exhibited remarkable antibacterial activity[24] . Another example is complexes of general structure **6** (**Fig. 2**), which are coumarin–quinoline hybrids coordinated with Cu (I) and show action against Flavobacterium psychrophilum, Gram-negative bacteria that causes severe septicemia in fish [25].

The development of new broad-spectrum medications to attack RNA viruses would be useful to humanity, but it would be difficult. A new family of quinazolin-4-amine-SCH_2-coumarin conjugated compounds with generic formula **7 (Fig. 3)** has been reported [26]. The virus-cell-based test data reveal that these candidates can inhibit chikungunya virus with EC_{50} values as low as 1.96 µM and hepatitis C virus with EC_{50} value of 16.6 µM.

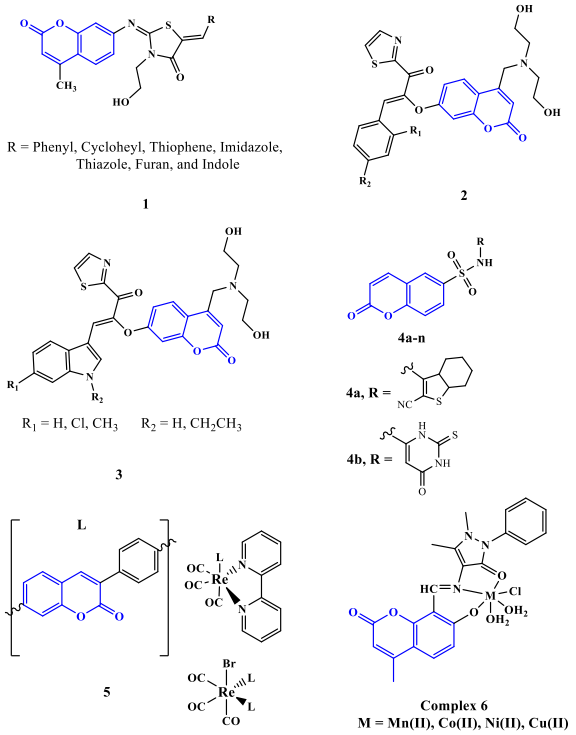


Fig. 2. Structure of coumarin-based antibacterials **1-6**.

Recently, the antiviral activity of two new coumarin series **8** and **9**, **Fig. 3**, was investigated utilizing Infectious hematopoietic necrosis virus (IHNV) [27]. Some of the novel compounds have an IC_{50} value of 2.96 µM against IHNV. The results showed that treatment with these compounds considerably reduced the virus-induced cytopathic effect (CPE) in EPC cells. The findings show that antiviral action may be achieved through interfering with IHNV adsorption. Furthermore, compound **8** was discovered to have an inhibitory effect on IHNV-induced apoptosis in EPC cells. As a result, these coumarin derivatives have the potential to be developed as antiviral medicines against rhabdoviruses.

Despite major breakthroughs in antiviral treatment, acquired immunodeficiency syndrome remains one of the leading causes of death around the world [28]. New antiretroviral therapies, as well as improved treatment approaches, are required to improve the suitability, tolerability, safety, and antiviral efficacy of existing drugs. In a recent study, a set of coumarin-based analogues (**10**, **Fig. 3**) has been synthesized and evaluated to identify a novel HIV-1 replication inhibitors[29]. Some of these new targets demonstrated enhanced potency against the wild-type HIV-1 strain (EC_{50} = 3.94 µM) and preserved action against a panel of mutant strains with EC_{50} values ranging from 5.62 µM to 202 µM. These compounds inhibited viral Ribonuclease H (RNase H) enzymes with an IC_{50} of 12.3 µM. Molecular docking experiments demonstrated that these targets could bind to HIV-1 RNase H active site.

Another two coumarin series [30,31] were developed, synthesised, and evaluated for antiviral activity. The compounds in the first series were designed as dual inhibitors of HIV-1 reverse transcriptase (HIV-1 RT) and protease (PR) via a hybridization approach between the coumarin portion responsible for RT action and the antiviral darunavir fragment active against HIV PR via various linkers (**Fig. 3**, general structure **11**)[30]. The second example documented the incorporation of a piperidine ring into the coumarins nucleus via a linker at position 7, resulting in hybrids with exceptional activity against filoviruses such as Marburg virus (MARV) or Ebolavirus (EBOV). Substitution of a trifluoromethoxy group in the para position results in compound **12** (**Fig. 3**) with IC_{50} values of 0.5 µM and 1.2 µM against EBOV and MARV, respectively [31].

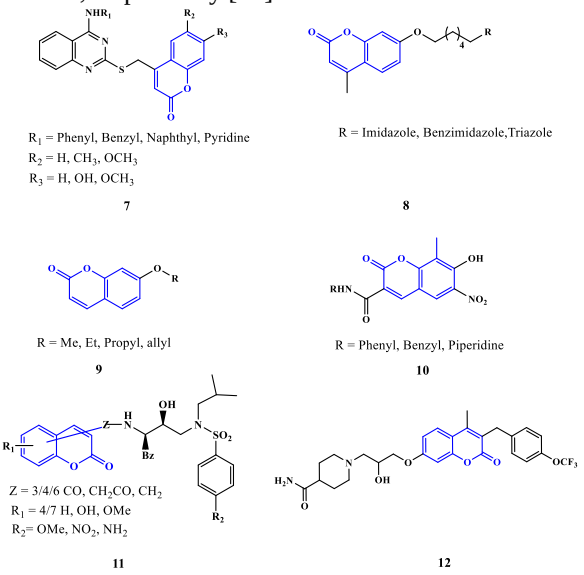


Fig. 3. Structure of coumarin-based antivirals **7-12**

Tuberculosis (TB) is one of the world's most resistant and fatal infectious diseases. According to the World Health Organization (WHO), tuberculosis infects more than one-third of the world's population and kills approximately 1.4 million people each year [32]. The advent of multidrug resistant (MDR-TB) and extensively drug resistant (XDR-TB) bacteria complicates the issue even further. As a result, novel medications with distinct modes of action and toxicity profiles are desperately needed for use in the global effort to treat and eradicate the illness [33]. A recent series of coumarin derivatives (**13**, **Fig. 4**) was tested for antimycobacterial action against Mycobacterium tuberculosis [34]. The novel compounds showed improved inhibitory actions, with MIC values ranging from 1.6 g/mL to 50 g/mL. The synthesised thioethers were also examined for hepatoprotective action, with the results revealing that the majority of the compounds emerged as an effective hepatoprotective agent, with cell viability greater than 90%, while some only exhibited modest protective activity.

A new set of coumarins conjugated with 1,2,3-triazole derivatives of overall structure **14** (**Fig. 4**) was designed, synthesised, and tested for antifungal activity[35]. The antifungal efficacy of the new derivatives was evaluated against Candida albicans, and their MIC values were examined and compared to two references namely miconazole and fluconazole. The derivatives investigated were found to be equipotent to miconazole and significantly more active than fluconazole.

The anti-Leishmania amazonensis activity of 7-hydroxy-4-phenylcoumarin derivatives of general structure **15**, as shown in **Fig. 4**, was investigated [36]. When R = OH, the compound's IC_{50} value against Leishmania amazonensis promastigote forms is 91 µM. Its precursor with a penta-*O*-acetyl-glucopyranosyl group, on the other hand, was shown to be the utmost active against the parasite's promastigote and amastigote forms, with IC_{50} values of 10 µM and 35 µM, respectively.

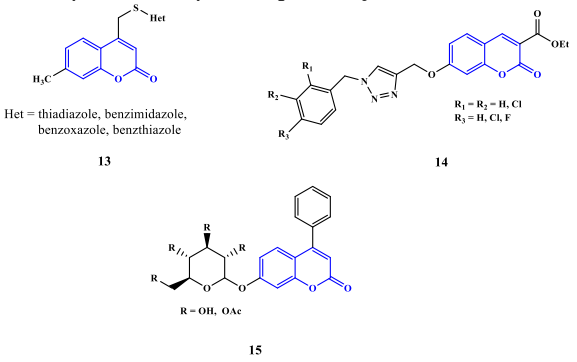


Fig. 4. Structure of coumarin-based antimicrobials **13-15**

b. Anticancer action

Cancer is one of the leading causes of death worldwide, and great efforts have been made to acquire novel chemotherapeutic drugs capable of working selectively on malignant cells while sparing healthy cells[37-42]. Several studies have emphasized the cytotoxic effects of coumarin-based analogues on various cancer cell lines, and some articles have disclosed the mechanisms underlying this influence.

Carbonic anhydrases (CAs) are enzymes that catalyze the reverse conversion of CO_2 into protons and bicarbonate which are engaged in many biological and biochemical processes. As a result, certain CA isoforms implicated in these processes are key therapeutic targets. These isoform inhibitors present a significant prospective for pharmaceutical intervention in a range of illnesses, including cancer [43,44].

Dmitry et al. [45] reported the synthesis of a collection of seventeen 3-sulfonamide substituted coumarin derivatives (**16**, **Fig. 5**). *In vitro* suppression of four isoforms of human carbonic anhydrase (hCA) was examined. Several coumarin sulfonamides inhibited clinically important hCA II, IX, and XII with low nanomolar KI values, but not hCA I. Some of these compounds inhibited the proliferation of RT4 human bladder cancer and, in particular, A431 human epidermoid carcinoma cell lines in a concentration-dependent manner. The compounds inhibited A431 cell growth profoundly and selectively with low nanomolar IC_{50} values, as well as apoptosis induction activities linked with caspase 3/7 activation in cancer cells. Because most of these compounds did not significantly inhibit the carbonic anhydrase isoforms in question, their antiproliferative effects are most likely due to other processes, such as DNA intercalation.

Another set of coumarin-linked 1,2,4-oxadiazoles **17** (**Fig. 5**) was developed and tested against the four important hCA isoforms, hCA I, II, IX, and XII[46]. Based on the findings, it was concluded that the coumarin-linked 1,2,4-oxadiazoles inhibited hCA IX and XII more selectively (low to medium nanomolar range) than hCA I and II (>10000 nM). Some of these new entities inhibited hCA XII with Ki values lower than the standard, Acetazolamide (AAZ). These compounds were docked within the hCA XII catalytic cleft to analyze their binding mechanisms with that isoform, which indicated significant binding interactions with hydrogen bond formation with the essential amino acids.

A recent work [47] details the design and synthesis of novel 3-substituted coumarin compounds and their inhibitory effects on multiple carbonic anhydrase isoforms. The findings indicated that the tertiary sulphonamide derivative **18** (**Fig. 5**) exhibited selective inhibition of CA IX with an IC_{50} of 4.1 µM. The binding mode was anticipated and confirmed using molecular docking and dynamic simulation.

Topoisomerase (Topo) inhibitors are a unique class of anticancer medications that cause cell death by interfering with DNA replication in cancer cells [48]. Zhao et al. [49] employed click chemistry to synthesize a new series of coumarin-podophyllotoxin hybrids (**19**, **Fig. 5**), which were tested *in vitro* for cytotoxicity against four human cancer cell lines. Some of the compounds tested showed significant inhibitory activity, with IC_{50} values ranging from 4.9 µM to 17.5 µM. Mechanistic studies demonstrated that Topo IIβ was selectively inhibited rather than Topo IIα, as well as a halted cell cycle in the G1 phase and disrupted microtubule organization. The molecular docking investigation within the Topo IIβ active site revealed the development of stable hydrogen bonds with DNA bases and Gln 778, as well as the accommodation of the coumarin moiety in a hydrophobic area, establishing a π-π stacking interaction with essential amino acids.

Halawa et al. developed and evaluated a novel series of 4-arylamino-3-nitrocoumarin derivatives against a human cervical cancer cell line [50]. These compounds were discovered to inhibit cell replication and cause cell death by targeting the DNA-Topo I

(human Topoisomerase I) complex. Thiazolidinylidene derivative **20** (**Fig. 5**) had the highest cytotoxic activity in this series, with an IC_{50} value of 21 µM.

Angiogenesis, mediated by Vascular Endothelial Growth Factor (VEGF), has a significant impact on the prognosis of ascites tumor. Inhibiting VEGF is one of the goals achieved in the therapy of ascites tumor [51]. A new series of 1, 3, 4-oxadiazole derivatives including coumarin-3-substituted aryl and heteroaryl moiety (**21**, **Fig. 5**) as a unique class of VEGF inhibitors for therapeutic involvement against ascites tumor malignancy was recently reported[52]. Cell-based screening of the newly synthesised hits against numerous cell lines produced compounds with significant IC_{50} values. The suppression of VEGF expression was demonstrated *in vitro*. Furthermore, the in-vivo ascites tumor model demonstrated that VEGF-mediated ascites malignancy was suppressed without causing any substantial toxicological side effects.

Govindaiah et al. [53] stated the synthesis of acryloylcyanohydrazones based on 4,7-dihydroxycoumarin (**22**, **Fig. 5**), which were tested for anti-proliferative efficacy against a panel of human cancer cell lines. The majority of the substances tested positive for anticancer activity, with IC_{50} values ranging from 3.42 to 6.09 µM. *In vitro* studies revealed that these compounds had high tubulin polymerization activity, which was superior to the reference colchicine in several circumstances. Furthermore, docking investigations revealed that the hydroxyl groups of the coumarin core and cyano group interacted with the tubulin colchicine binding site via five strong intermolecular hydrogen bonds. Furthermore, cell cycle analysis validated the G2/M phase arrest and apoptotic induction.

Cai and colleagues [54] synthesised fluorescent coumarin-benzo[b]thiophene 1, 1-dioxide conjugates. These conjugates influence STAT3, which regulates the mitochondrial apoptotic process[55]. Compound **23** (**Fig. 6**) induced cancer cell death and ROS generation while lowering STAT3 phosphorylation on Tyr705 and suppressing STAT3 DNA-binding activity. Furthermore, it suppressed the proliferation of 4T1 breast cancer cells transplanted *in vivo*.

For the treatment of prostate cancer, potent inhibitors of aldo–keto reductase (AKR) using an imino-coumarin scaffold **24** (**Fig. 6**) with activity ranging from 25 to 56 nM have been reported [56].

A limited collection of sulfamide 3-benzylcoumarin hybrids incorporating an oxadiazole ring **25**, illustrated in **Fig. 6**, was developed, and produced as multitarget mitogen-activated protein kinase (MEK) inhibitors and nitric oxide (NO) donors. The novel hybrids demonstrated effective antiproliferative activity[57]. A new class of cyclin-dependent kinase inhibitor hybrids, specifically CDK9 inhibitors, was designed, synthesized, and comprehensively reported [58]. Compound **26** (**Fig. 6**) displayed superior activity and selectivity for these receptors when compared to other kinases with enhanced antiproliferative activity. Histone deacetylases (HDACs) are another important cancer therapeutic target, particularly in lymphomas [59].

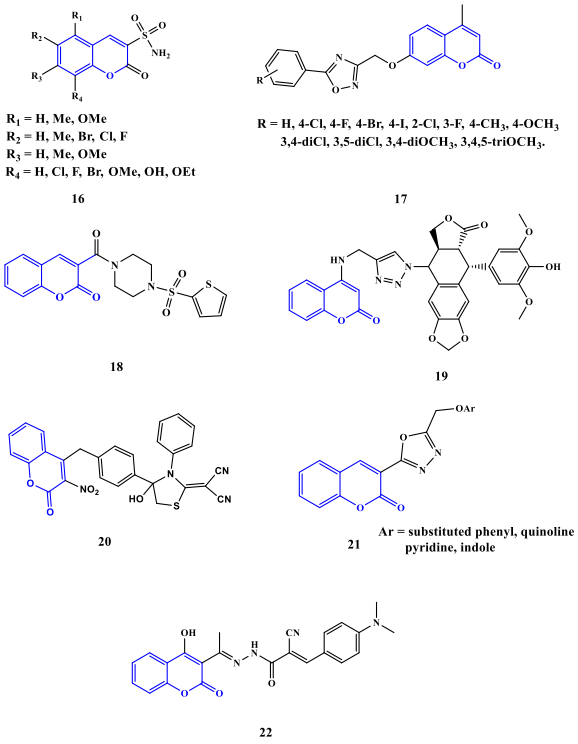


Fig. 5. Structures of coumarins-based anticancer **16-22**

A new series of coumarins (**27**, **Fig. 6**) with hydroxamate structures similar to HDACi vorinostat (SAHA) has been reported [60]. Nanomolar inhibitory action is demonstrated by these derivatives, which is improved by propyl or methoxy propyl derivatives.

Fayed et al. [61] reported the development of a novel family of coumarin derivatives (**28**, **Fig. 6**). The synthesised coumarins were tested for anticancer activity against various human cancer cell lines. The results revealed IC_{50} values ranging from 1.1 to 2.4 µM, with higher activity than the reference 5-FU (IC_{50} = 7.76 µM). Further mechanistic studies verified that the synthesised coumarins may trigger apoptosis in MCF-7 cells by halting the cell cycle in the G2/M phase and increasing caspase-3 and caspase-9 expression.

Recently, two series of coumarin-based Estrogen receptorα (ERα) antagonists, **29** and **30**, **Fig. 6**, were synthesised [62] and tested as selective ER antagonists. The tested compounds were shown to be selective estrogen receptor modulators with potent antiproliferative action against breast cancer cell lines, while demonstrating no agonistic impact in endometrial cell lines. Their method of action was investigated, and it was discovered that they work by inhibiting the Raf-1/MAPK/ERK signal transduction pathway and preventing MCF-7 cell proliferation at

the G0/G1 phase. Experiments *in vivo* demonstrating extraordinary effectiveness as tumor suppressors with optimal pharmacokinetic profiles but no notable histopathological characteristics. The data presented imply that the novel compounds are possible candidates for clinical trials for breast cancer therapy.
Herrera et al. developed a set of 3- and 7-styrylcoumarins, some of which shown antiproliferative action against human colon cancer cells [63]. Among these, compound **31** (**Fig. 6**) demonstrated the greatest efficacy (IC_{50} = 1.01 M) in triggering death in examined cells, most likely by altering the tumor-suppressor protein p53. *In vivo* testing revealed that compound **31** is capable of suppressing the early stages of colon cancer [64].

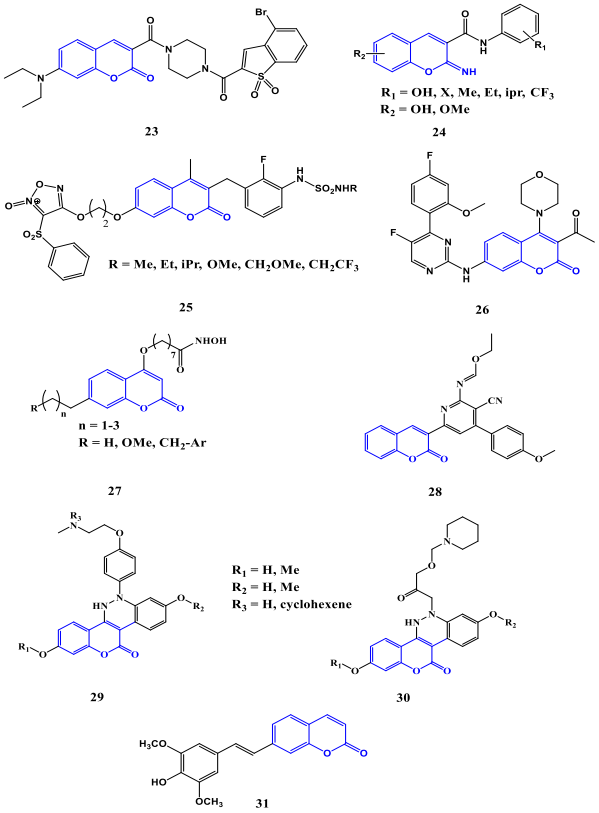


Fig. 6. Structures of coumarin-based anticancer agents **23-31**

c. Antioxidant action

The antioxidant capacity of the coumarin nucleus can be used to develop new hybrid compounds with improved antioxidant activity. A variety of novel hydroxytyrosol and coumarin conjugates (**32**, **Fig. 7**) were synthesized and tested in vitro for free radical scavenging, toxicity, and antioxidant mechanism[65]. The target hybrids have high radical scavenging activity, where the number and position of hydroxyl groups on the coumarin ring are important for antioxidant action. Furthermore, the most promising compounds had no harmful effects on WI-38 or GES normal cells and increased the viability of H_2O_2-induced HepG2 cells. Additionally, they inhibited ROS generation and LDH release while increasing GSH and SOD levels in H_2O_2-treated HepG2 cells. These findings suggest that hydroxytyrosol and coumarin conjugates have higher antioxidant capacity and are an effective approach for discovering new potential antioxidants[66].
Li and colleagues' synthesis a new series of chitosan derivatives (**33**, **Fig. 7**) including the coumarin nucleus [67]. The antioxidant potential of the novel hybrids was evaluated by measuring lipid peroxidation inhibition and free-radical scavenging activity. The results revealed that the novel compounds had more efficient scavenging action as well as suppression of lipid peroxidation products than chitosan alone, implying that the coumarin moiety significantly improves chitosan antioxidant capabilities.
Further hybrids of coumarin and phenolic fragments capable of acting as radical scavengers (**34**, **Fig. 7**) were designed and synthesized as Nitric Oxide Synthase inhibitors [68]. The newly developed hybrids showed promising antioxidant activity and were thus considered as a potential therapy for immunomodulatory disease.
Popova and colleagues [69] synthesised and characterize a set of 4-methylcoumarin derivatives (**35**, **36**, **37a-e**, **Fig. 7**). The antioxidant, membrane-protective (MPA), and radical-scavenging (RSA) properties of the produced compounds were tested *in vitro*. All of the substances examined showed good inhibitory action against the development of lipid peroxidation products (LPO). In the DPPH assay, the isobornyl derivatives demonstrated modest activity. In addition, the protective impact against cell membrane was assessed, as was the inhibitory efficacy against H_2O_2-induced hemolysis of red blood cells measured (RBCs). The greatest hopeful derivative in all of the trials was **XXXVc**, which had two isobornyl moieties. These investigations reveal that coumarin congeners have a high capability as antioxidants, membrane protectors, and radical scavengers, and that their action is mostly determined by the number and position of the hydroxy groups.

d. Anti-inflammatory action

Chronic inflammation is a key component of many diseases, including osteoarthritis, atherosclerosis, cancer, Alzheimer's disease, and others[70-75]. Anti-inflammatory drugs must be developed in order to prevent or treat these disorders in a synergistic manner. Recently, A series of chalcone derivatives were prepared as anti-inflammatory agents [76]. Coumarin-based chalcones **38** (**Fig. 8**) were developed and tested for their inhibitory action against COX-2 enzyme as well as suppression of nitric oxide generation. The results of the *in vitro* experiments showed that the tested compounds had good anti-inflammatory effect by selectively inhibiting the

COX-2 enzyme and suppressing nitric oxide levels in LPS-induced RAW264.7 macrophages.

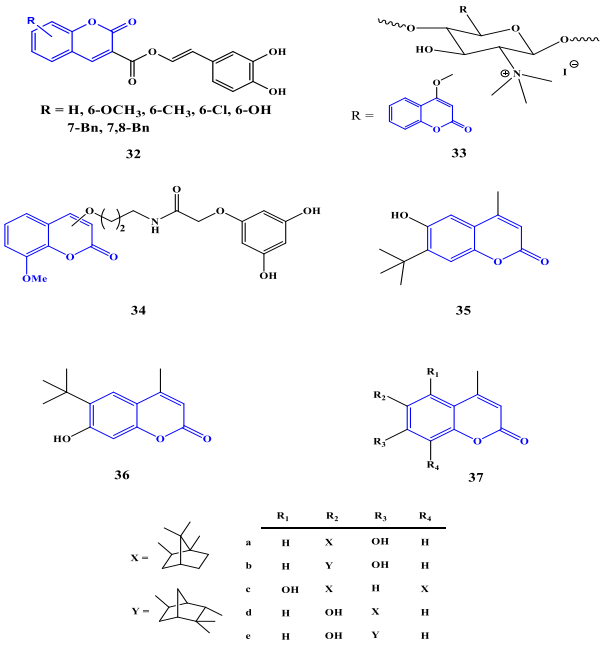


Fig. 7. Structure of coumarin-based antioxidant agents

The anti-inflammatory efficacy of coumarin-C3 benzimidazole hybrids was investigated by Krishan et al. The two most effective compounds **39 (X = Cl)** and **40 (X = Br)**, **Fig. 7** decreased paw edema by 47% and 45%, respectively, after 6 hours of rat paw injection. Their inhibition patterns were found to be comparable to that of indomethacin, indicating that these compounds work in the same way by blocking prostaglandin synthesis. According to the SAR analysis, coumarin-C6 substitution by electron-withdrawing groups such as chloro (**39**) and bromo (**40**) might improve the anti-inflammatory activity of these hybrids, however insertion of the amide linker (e.g., **41** and **42**, **Fig. 7**) decreased their anti-inflammatory activity [77].

Naganna et al. studied the anti-inflammatory activity of benzimidazole-coumarin hybrids with various linkers **43** and **44** (**Fig. 8**). *In vivo* anti-inflammatory experiments demonstrated that compounds **43** of the methylene hydrazine linker, and **44** of the thiazolidinone-NH linkers, are moderate anti-inflammatory agents. The presence of a thiazolidinone-NH linker with no substituent on coumarin-C4 produced the highest anti-inflammatory outcomes, comparable to that of the positive diclofenac sodium. Another important factor influencing the molecule's action is the presence of a methyl group on the coumarin-C4 site, which results in a significant decrease in the compound's activity [78].

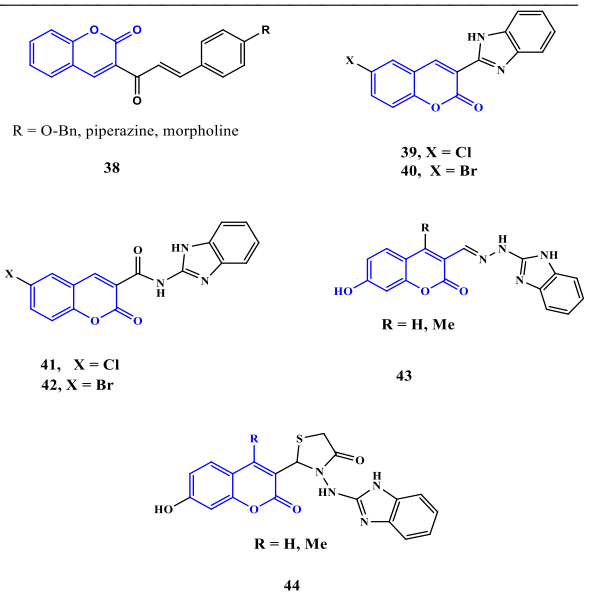


Fig. 8. Structure of coumarin-based anti-inflammatory agents.

3. Antidiabetic action

Diabetes is a long-term metabolic condition indicated by elevated blood sugar levels. It is mainly caused by a shortage of insulin synthesis by pancreatic cells or by the incapacity of the human body to utilize this hormone. Diabetes can lead to catastrophic complications such as blindness, kidney failure, and cardiovascular problems [79-81].

Menteşe et al. [82] synthesised a novel series of coumarin/1,2,4-triazole hybrids with general formula **45** (**Fig. 9**), combining the 1,2,4-triazole and coumarin moieties, both of which have a broad spectrum of biological activity and low toxicity profiles [83-88]. The action of these enzymes on α-glucosidases was then investigated. The results demonstrated that the majority of the tested compounds had substantial inhibitory activity when compared to the reference acarbose and that the investigated compounds inhibited α-glucosidases in a competitive manner.

Recently, Patagar et al.[89] reported a series of benzimidazole-tethered coumarin-3-carboxamide analogs as antidiabetic agents. *In vitro* tests to see which compounds were best at treating diabetes showed that all of them had a high level of α-amylase inhibition. The most potent compound was **46** (**Fig. 9**), which had an α-amylase inhibition IC50 of 67.52 µM compared to metformin's IC50 of 54.13 µM. The results of the molecular docking study involving the receptor protein alpha-amylase (PDB ID 4 × 9y) with the Autodock Vina tool were elucidated.

Insulin secretion stimulation could be an alternate therapy method. In this context, Ahmed and his colleagues extracted twenty-one coumarin compounds from natural sources, thirteen of which were reported for the first time [90]. The glucose-triggered insulin production of newly obtained murine islets was used to assess anti-diabetic efficacy. When compared to

glimepiride, compounds **47a**, **b**, and **c (Fig. 9**) were the most effective in stimulating glucose-prompted insulin release. More research is crucial to better identify structure-activity correlations in order to generate new active molecules.

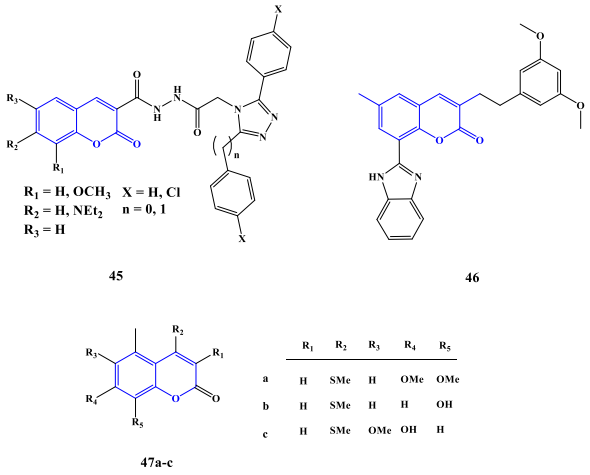


Fig. 9. Structure of coumarin-based antidiabetic agents

2.6. Anticoagulant Action

Coumarins' anticoagulant activity was discovered when seemingly healthy cattle in Canada and North America died of internal haemorrhages in the early 1900s. The primary cause of this annihilation was attributed to a mold infestation of damp hay, later dubbed "sweet clover disease." However, it was not until 1940 that Karl Link and his student Harold Campbell identified the responsible molecule: 3,3'-methylenebis(4-hydroxycoumarin), later known as dicoumarol [91,92]. Further research by Link's team resulted in the discovery of warfarin **(48)** in 1948, which was approved as a rodenticide in the United States in 1952 and for anticoagulation therapy in humans in 1954, under the brand name coumadin. Warfarin is currently one of the most widely used anticoagulation drugs, along with other coumarin derivatives such as acenocoumarol **(49)** and dicoumarol **(50)**, **Fig 10** [92-94].

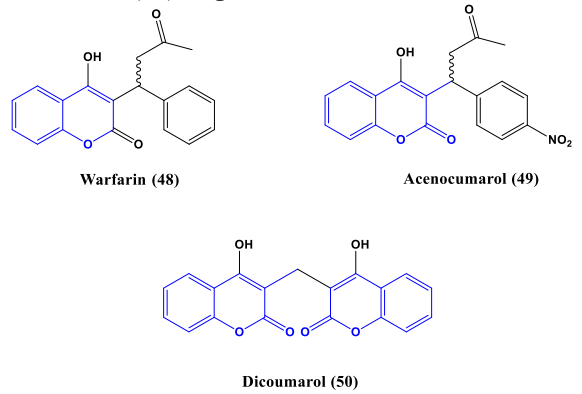


Fig. 10: Structure of anticoagulant coumarin derivative **48-50**

Warfarin and other anticoagulant coumarins are vitamin-K antagonists (VKAs). In fact, due to their structural similarity to vitamin-K, the compounds inhibit the vitamin-K dependent coagulation pathways, which involve a number of factors (II, VII, IX and X). Despite the effectiveness and benefits of oral therapy, warfarin has adverse effects, primarily related to bleeding, and problems, such as a limited therapeutic range and interindividual genetic variation in pharmacokinetics, which need ongoing patient monitoring [95,96].

As a result, a novel VKA called tecarfarin **(51)** (ATI-5923, **Fig. 11**), which is now under development[97], was discovered. Tecarfarin, unlike warfarin, is not metabolized by the cytochrome P450 system but rather by human carboxylesterase-2 (hCE-2) in hepatic microsomes. Tecarfarin is active after oral administration and functions as a vitamin-K epoxide reductase (VKOR) inhibitor. As a result, drug-drug or food-drug interactions are avoided, as is genetic variability in the CYP-450 system, resulting in a more stable anticoagulation effect than warfarin[79]. Albrecht et al. conducted a detailed study on the pharmacokinetics and pharmacodynamics of tecarfarin in healthy patients, as well as a recent phase I study on its tolerability in patients with severe kidney disease [98,99]. Tecarfarin has the potential to be a viable alternative to warfarin in the oral treatment of thromboembolic disease.

Bang et al reported the development of a new series of anticoagulant coumarins by chemical modification of the coumarin scaffold via conjugation of 7-hydroxylcoumarin and 7-hydroxy-4-methylcoumarin with salicylic acid derivatives. Among the compounds, derivatives **52** and **53** (**Fig. 11**) demonstrated strong anticoagulant activity, with prothrombin times (PT) increased to 10.88 ± 0.56 sec and 13.10 ± 3.56 sec, respectively. Both compounds were found to be 1.5 times more potent than warfarin (PT 7.97 ±1.93)[100].

Montagut-Romans et al. [101] used structural modifications of the 4-hydroxycoumarin core to investigate the potentiality provided by modifications performed on the C3 position by introducing a side chain (with one unsaturation) structurally related to vitamin-K cofactor. The underlying premise was Gebaur's SAR study from 2007, which revealed that structural modification for the C3 position by isoprenyl motifs increased the activity of 4-hydroxycoumarin[102].

In this competition, 14 new 4-hydroxycoumarins with various length alkyl chains, both linear and branched, were synthesised and their activity was assessed *in vitro* and *ex vivo*. *In vitro* inhibition of VKORC1 in rat liver microsomes was assessed, and with the exception of two compounds, the C3-alkyl derivatives demonstrated sub-micromolar activity (from 20 nM to

200 nM), outperforming the internal reference phenprocoumon. *Ex vivo* studies were conducted to assess the ability to increase prothrombin time (PT) *in vivo*, and compounds **54a** and **54b** (**Fig. 11**) demonstrated promising anticoagulant activity after 24 hours. The presence of the halogen atom may protect the drug from liver metabolism. Despite the intriguing anticoagulant activity, additional studies on liver metabolism are required to determine if these molecules are a substrate of CYP2C9, to which the variability in the dosage of oral vitamin-K antagonists is attributed due to its polymorphism[103] .

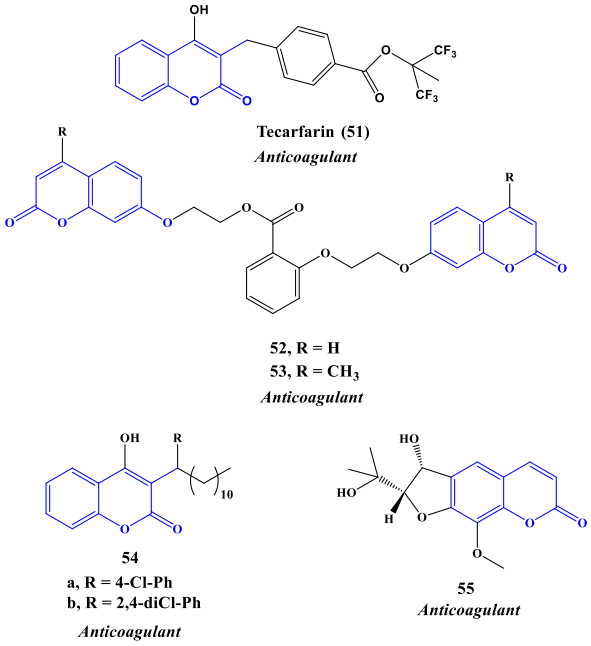


Fig. 11: Structures of some reported anticoagulant coumarins **51-55**

Gao et al. performed a phytochemical investigation on the Chinese herbal medicine Ainsliaea fragrans, resulting in the discovery of five new derivatives. *In vitro* and *in vivo* anticoagulant activity of all isolates was assessed using activated partial thromboplastin time (APTT), thrombin time (TT), and prothrombin time (PT) assays. When compared to warfarin (PT = 55.7s and TT 80.6s), compound **55** (**Fig. 11**) demonstrated remarkable anticoagulant activity (PT = 41.2s and TT 128.5s) with no significant hepatic or renal toxicity [104]. Although more research is needed to understand compound **55**'s mode of action, it appears to be a promising anticoagulant agent for preclinical studies.

2.7. Miscellaneous biological actions

2.7.1. Anticonvulsant action

Epilepsy is a common neurological disorder characterized by recurrent and unpredictable seizures and/or transient behavioral changes. Its pathogenesis is not fully understood; however, it is known that an imbalance between excitatory and inhibitory neurotransmission is involved [105-108]. Several recent studies on the use of coumarins as anticonvulsant agents have been reported here. Abd-Allah et al investigated the anticonvulsant activity of a series of coumarin derivatives developed by combining two or more pharmacophoric scaffolds to create new chemical entities with improved biological activity[109]. The compounds described have all essential elements required for anti-convulsant activity: a lipophilic aryl ring, a hydrogen-bonding domain, and an electron-donor moiety[110,111]. All of the compounds were initially screened (phase I) using two standard animal seizure models, subcutaneous pentylenetetrazole (scPTZ) and maximal electric shock (MES) seizure tests with ethosuximide as the reference drug. The rotarod test was also used to assess the potential neurotoxicity. Phase II involved determining the ED50 value for compounds that provided 100% protection in one or both tests. Finally, GABA levels were measured in the entire mouse brain for the most active compounds, with gabapentin serving as a control. Phase I tests revealed that all of the compounds tested had protective activity against scPTZ-induced absence epilepsy (variable results ranging from 17-100% protection). Among them, derivatives **56**, **57**, **58**, and **59** (**Fig. 12**) were the most active (100% protection) at 0.238, 0.239, and 0.283 mmol/kg, respectively, implying that the compounds are 1.49, 1.48, and 1.25 times more potent than ethosuximide. However, in the MES-induced seizures, none of the compounds completely protected the animals. The most active compound, compound **57**, was discovered to have an ED50 of 54.86 mg/kg (0.131 mmol/kg). As a result, it was chosen for further research to elucidate the mechanism of action, which was assessed through an assessment of GABA levels in mouse brain. As a result, the proposed mechanism for **57** is GABA-mediated, possibly through non-vesicular GABA release, GABAA receptor activation, or GABAB receptor inhibition, possibly through increased GABA synthesis or decreased GABA metabolism.

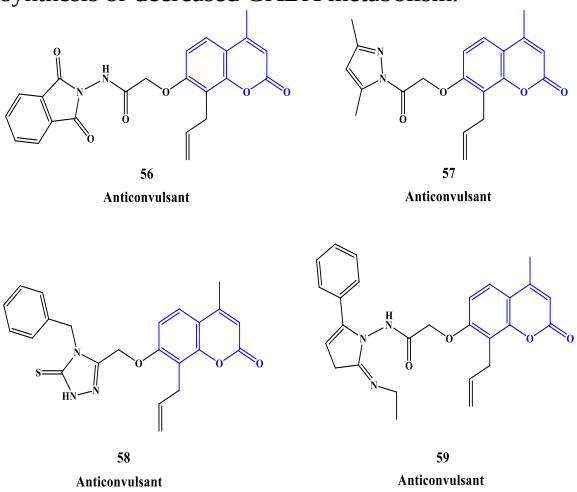


Fig. 12: Structure of anticonvulsant-based coumarins **56-59**

In order to produce a new chemical entity with a superior anticonvulsant profile than coumarin and oxadiazole alone, Mohammadi-Khanaposhtani and et al. used a similar pathway by synthesizing a series of coumarin-1,2,4-oxadiazole derivatives[112]. Several 5-member heterocyclic rings-containing compounds, including oxadiazoles, triazoles, and thiadiazoles, have been shown to have anticonvulsant activity [79,113,114] via the benzodiazepine (BDZ) receptor [115]. The new derivatives' activity was evaluated using PTZ- and MES-induced seizures in mice, with diazepam serving as a control. Except for three new compounds, **60**, **61**, and **62** (**Fig. 13**), none of the new compounds showed activity against PTZ-induced seizures. Compounds **63**, **64**, and **65** (**Fig. 13**) provided 100% protection against MES-induced seizures at doses of 7, 40, and 20 mg/kg, respectively (diazepam provides 100% protection at 2 mg/mL) [116]. The best activity was demonstrated by compound 152d, which had no substituents on position 4 of the coumarin ring and a 4-chloroaryl group connected to the 1, 2, 4-oxadiazole ring. To investigate the mechanism of action, the most active compounds, **63** and **64**, were used; the effect of flumazenil (a BDZ receptor antagonist) on their activity was evaluated. Flumazenil inhibited both **63** and **64**, indicating that both are BDZ receptor agonists. Finally, the *in vivo* neurotoxicity of compounds **63** and **64** was evaluated, and the tested compounds resulted in fewer neurological deficits than the reference drug diazepam.

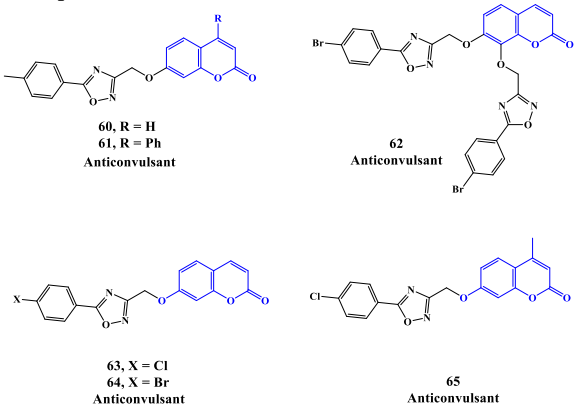


Fig. 13: Structures of compounds **60-65**

2.7.2. Anti-Alzheimer action

Alzheimer's disease (AD) is the most common type of dementia (AD causes 60-70% of dementia cases) and is a neurodegenerative disorder characterized by a slow, progressive, and irreversible loss of cognitive function and memory [117-119]. The current therapeutic approach, which is primarily based on the use of acetylcholinesterase (AChE) inhibitors, is symptomatic and does not slow the progression of degeneration. To cure cognition and motor dysfunctions, neurodegeneration, and depression, new innovative approaches, such as multi-targeted strategies, are urgently needed. Coumarins have been shown to inhibit some biological targets involved in Alzheimer's disease. Some recent studies examining the potential of coumarins in the treatment of Alzheimer's disease are discussed below.

Najafi et al. synthesised a series of tacrine-coumarin derivatives linked to a 1,2,3-triazole moiety and tested their activity in terms of AChE and BuChE inhibition, using donepezil and tacrine as reference drugs [120]. In addition, their beta-secretase 1 (BACE1) inhibitory activity and neuroprotective potential were assessed. Because tacrine is a well-known inhibitor of AChE's catalytic site, whereas coumarins showed affinity for the peripheral anionic site (PAS) [121], these new compounds may be potential dual—and thus more powerful—inhibitors of ChEs. The *in vitro* AChE and BuChE inhibitory activity was evaluated using the Ellman method[122]; among all the tested molecules, compound **66** performed the best in AChE inhibition (IC_{50} = 0.027 ± 0.009 µM; tacrine IC_{50} = 0.048 ± 0.011 µM, donepezil IC_{50} = 0.039 ± 0.097 µM) and compound **67** performed the best in BuChE inhibition (IC_{50} = 0.006 ± 0.002 µM; tacrine IC_{50} = 0.010 ± 0.004 µM) (**Fig. 14**).

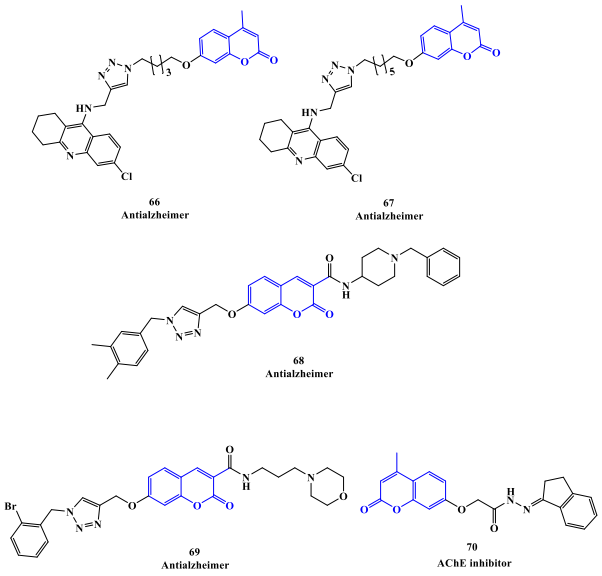


Fig. 14: Structure of some Anti-Alzheimer-based coumarins **66-70**

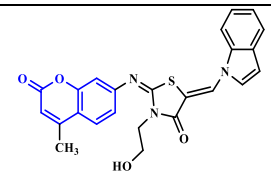
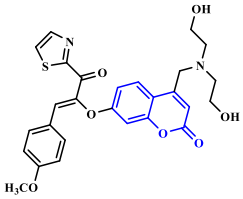
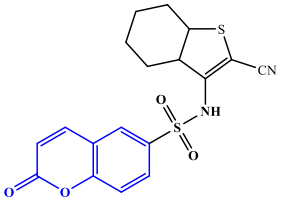
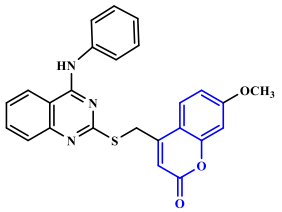
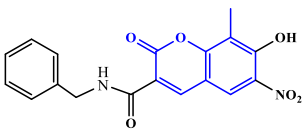
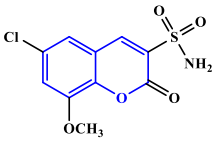
Structure-activity relationship studies on anti-BuChE activity revealed that the Cl and Me substituents, as well as the methylene linker, play a complex and poorly understood role in enzyme inhibition. The inhibitory activity of the synthesised compounds on BACE1 was evaluated, and compound **66** was found to have a moderate inhibitory activity (inhibition of 28.69% and 13.97% at 50 and 10 µM, respectively). The Morrison Water Maze method[123] was then used to evaluate compound **66** *in vivo*, and valuable results based on memory improvement in scopolamine-induced impairment were observed.

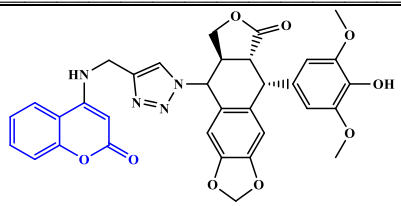
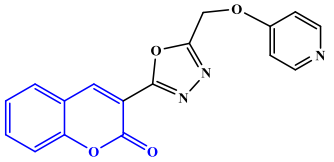
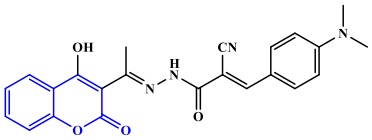
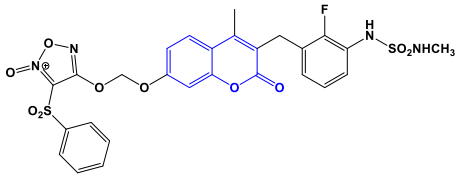
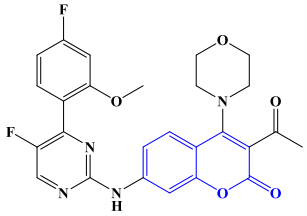
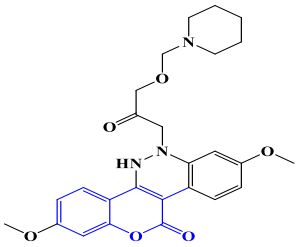
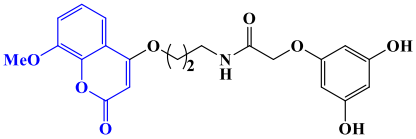
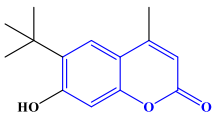
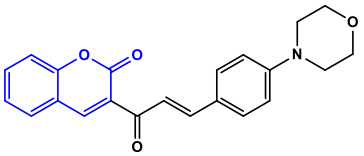
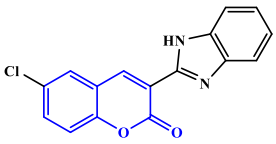
In another study, Rastegari and et al. synthesised a series of 1,2,3-triazole-chromenone carboxamide derivatives and investigated their potential as anti-Alzheimer's agent in terms of AChE, BuChE, and BACE1 inhibitory activity [124]. The new compounds' *in vitro* AChEI and BuChEI activities were assessed using donepezil as a control. Compound **68**, which contains a 3,4-dimethylbenzyl moiety linked to a 1,2,3-triazole moiety, and compound **69**, which contains 3-morpholinopropyl and 2-bromobenzyl moieties, demonstrated higher activities (**Fig. 14**), despite being much less active than donepezil (IC_{50} = 0.027 µM). Anti-BChE activity was also modest and was influenced by the type of amine connected to the amide moiety, morpholine or piperidine, as well as the position and electronic properties of substituents on the benzyl group connected to the 1,2,3-triazole ring.

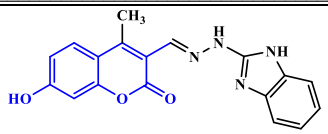
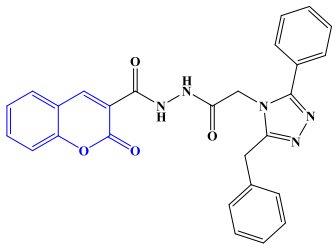
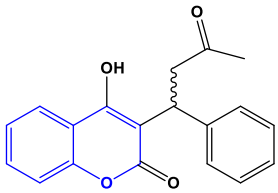
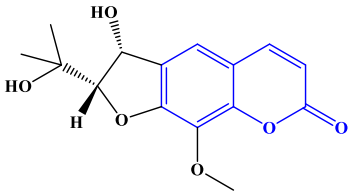
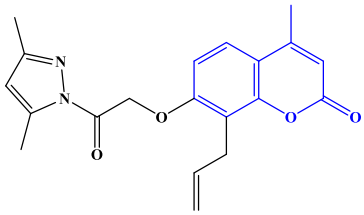
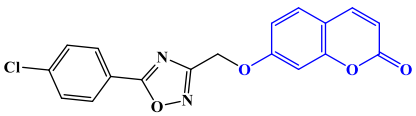
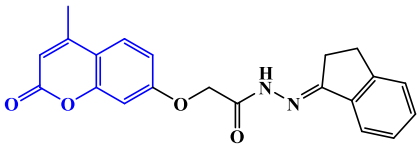
Kamel et al. recently published a paper[125] that report new 2-oxo-chromene-7-oxymethylene acetohydrazide derivatives that have a number of bioactive chemical parts. The newly synthesized compounds were assessed as acetylcholinesterase (AChE) inhibitors and antioxidant agents in comparison to donepezil and ascorbic acid, respectively. With an IC_{50} value of 0.802 µM and a DPPH scavenging activity of 57.14±2.77%, compound **70 (Figure 14)** had a strong inhibitory effect. Also, biochemical and hematological tests showed that compound **70** did not change the blood profile, liver enzyme levels (AST, ALT, and ALP), or total urea in rats that were given **70** compared to rats that were not given **70**. As part of an *in vivo* study, T-maze and beam balance tests were used to see how **70** improved cognitive performance in rats with Alzheimer's disease. In addition, **70** greatly raised MDA and GSH levels, achieving 90.64% for MDA and 27.17% for GSH compared to the standard treatment, which achieved 90.64% for MDA and 35.03% for GSH.

Table 1 summarizes the biological activity and molecular target of some of the coumarins mentioned above.

Table 1: Summary Table

Structure	Biological Activity	Molecular Target	Number	Ref.
	Antibacterial	-Antibiofilm -DNA gyrase inhibitor	**1**	[17]
	Antibacterial	DNA gyrase inhibitor	**2**	[18]
	Antibacterial	DNA gyrase inhibitor	**4a**	[19]
	Antiviral	Virus RNA	**7**	[24]
	Antiviral	Ribonuclease H (RNase H) inhibitors	**10**	[27]
	Anticancer	Carbonic anhydrase inhibitor	**16**	[41]

	Anticancer	Topo IIβ inhibitor	**19**	**[45]**
	Anticancer	VEGFR inhibitor	**21**	**[48]**
	Anticancer	Anti-tubulin activity	**22**	**[49]**
	Anticancer	MEK inhibitor	**25**	**[53]**
	Anticancer	HDAC inhibitor	**26**	**[55]**
	Anticancer	Estrogen receptorα (ERα) antagonists	**30**	**[58]**
	Antioxidant	Nitric Oxide Synthase inhibitor	**34**	**[63]**
	Antioxidant	Radical Scavenging	**36**	**[64]**
	Anti-inflammatory	COX-2 inhibitor	**38**	**[70]**
	Anti-inflammatory	Blocking prostaglandin synthesis	**39**	**[71]**

	Anti-inflammatory	COX-1/ COX-2	**43**	**[72]**
	Anti-diabetic	α-Glucosidases inhibitor	**45**	**[76]**
	Anticoagulant	Vitamin-K antagonists	**Warfarin (48)**	**[86]**
	Anticoagulant	Unidentified	**55**	**[99]**
	Anticonvulsant	GABA-mediated pathway	**57**	**[103]**
	Anticonvulsant	BDZ receptor antagonist	**63**	**[111]**
	Anti-Alzheimer	AChE inhibition	**70**	**[120]**

4. Toxicity of Coumarins

Coumarin has demonstrated the potential to induce hepatic damage at elevated dosages. The United States prohibited the use of synthetic coumarin as a food additive in 1954[126]. Extended exposure to high concentrations of coumarin in in vivo studies has been associated with hepatotoxicity, perhaps resulting in liver damage or failure over time[127]. Regulatory agencies, including the European Food Safety Authority (EFSA), have established maximum permissible limits for coumarin in specific food and beverage products. The Scientific Committee on Food of the European Commission proposed a maximum limit of 0.5 mg/kg of coumarin in food[127]. *In vivo* observations indicate carcinogenic and hepatotoxic effects. Researchers have documented hepatotoxicity in other mammalian species, not just rodents. Prolonged studies in rodents have demonstrated tumorigenicity, encompassing adenomas and malignancies of the liver and bile duct. Researchers only detected carcinomas at doses greater than 100 mg/body weight per day[128]. Laboratory animals have undergone a multitude of in vivo and in vitro investigations to examine the mechanisms of coumarin-related hepatotoxicity and elucidate coumarin metabolism. Coumarin's main metabolic processes are 7-hydroxylation, a detoxification process that all primates do, and changing the lactone ring to make coumarin-3,4-epoxide[129]. Humans metabolize coumarins by several mechanisms, notably coumarin 7-hydroxylation, a crucial detoxification process. It is crucial to acknowledge that the production of certain metabolites may be harmful. The work of Vassallo et al. shows that the CYP2A enzyme in the liver helps turn coumarins into 7-hydroxycoumarins[130]. Elevated dosages of

coumarin can impair blood coagulation and induce hepatic toxicity. Consequently, the consumption of coumarin is limited, and maximum permissible quantities are established for specific food items.

5. Conclusion

Coumarins therapeutic capabilities have been identified as a result of their existence in many medicinal plants. Coumarin isolation from such plants is time-consuming and costly, and only tiny quantities of required compounds can be obtained. As a result, synthesis of these derivatives is a faster and, in some situations, "greener" alternative to get the necessary chemicals. Coumarins have a variety of biological actions and have a good impact on human health. The goal of this review was to represent a number of recent studies that demonstrate the diverse spectrum of coumarin-related pharmacological actions (antioxidant, antimicrobial, anti-cancer, anti-inflammatory, antidiabetic, anticoagulant, and some miscellaneous activities). Despite the fact that the coumarin nucleus has an impressive number of biological activities, its presence in marketed drugs is not yet widespread. More work is needed to develop coumarin-based compounds with appreciable pharmacokinetic properties, as well as high efficacy and a low toxicity profile. However, more complete preclinical studies are needed to assess the effectiveness, safety, and pharmacokinetic properties of coumarins. We believe that this evaluation will help to further research and development into the potential of coumarins.

Conflicts of interest

The authors declare no conflict of interest.

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Abbreviation List

ATP: adenosine triphosphate
ROS: reactive oxygen species
GSH: glutathione
MRSA: Methicillin-resistant Staphylococcus aureus
MIC: minimum inhibitory concentration
S. aureus: Staphylococcus aureus
SAR: Structural Activity relationship
RNA: ribonucleic acid
EC_{50}: Half maximal effective concentration
IHNV: Infectious hematopoietic necrosis virus
CPE: cytopathic effect
HIV-1: human immunodeficiency virus-1
MARV: Marburg virus
EBOV: Ebolavirus
VEGF: Vascular Endothelial Growth Factor
G2 phase: second growth phase
M phase: mitosis phase
STAT3: signal transducer and activator of transcription 3
CDK9: Cyclin Dependent Kinase 9
HDACs: Histone deacetylases
ER: Estrogen receptor
Raf-1: Raf-1 gene
MAPK: Mitogen-activated protein kinase
DPPH assay: The 2,2-diphenylpicrylhydrazyl assay
COX-2: cyclooxygenase-2
VKAs: vitamin-K antagonists
VKOR: vitamin-K epoxide reductase inhibitor
scPTZ: subcutaneous pentylenetetrazole
AChE: acetylcholinesterase
BuChE: butyrylcholinesterase

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