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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Recent advances on biologically active coumarin-based hybrid compounds

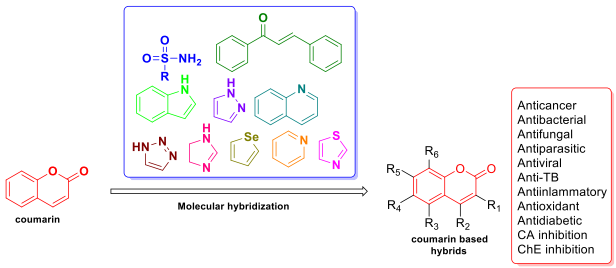
Metin Yildirim[1] · Samet Poyraz[2] · Mehmet Ersatir[3]

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Abstract

Coumarin hybrids have been designed and synthesized as an important new strategy in the field of medicinal chemistry. Coumarin core has been shown to form various compounds to combat several diseases including microbial, cancer, inflammatory, and neurodegenerative disorders. Recently, a number of coumarin-based drugs (e.g., coumadin, acenocoumarol, dicoumarol, phenprocoumon, and novobiocin) have been FDA-approved and are in the clinic, and several coumarin-containing compounds are in clinical trials. Our group classified coumarin-based hybrid compounds into groups showing shared biological activities and discussed their potential therapeutic targets.

Graphical Abstract



Keywords Coumarin hybrids · Coumarin sulfonamide hybrids · Coumarin-triazole hybrids · Coumarin thiazole hybrids · Coumarin-chalcone hybrids · Coumarin-imidazole hybrids

Introduction

The drug resistance of disease-causing bacteria makes even curable infections dangerous. Antimicrobial resistance is recognized as one of the greatest future health risks [1]. In recent years, the World Health Organization (WHO) has compiled a list of priority multi-drug-resistant pathogens and published a report to raise awareness of the problem and propose solutions [2]. According to the WHO's 2020 report, tuberculosis is one of the top ten causes of death worldwide [3]. Multidrug-resistant *Mycobacterium tuberculosis* (TB), the causative agent of tuberculosis, has been reported to be contagious and responsible for numerous fatalities throughout the years [4]. Resistance to drugs used in the long-term treatment of tuberculosis and side effects make this treatment difficult [5]. Pathogens such as *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* have been shown to acquire substantial resistance to carbapenems, which are currently utilized in treatment [1]. Neurodegenerative disorders, such as Alzheimer's (AD) and Parkinson's disease (PD), often start

✉ Metin Yildirim
metinyildirim4@gmail.com

[1] Department of Pharmacy Services Tarsus University Vocational School of Health Services, Tarsus, Mersin, Turkey

[2] Department of Analytical Chemistry, Harran University Faculty of Pharmacy, Haliliye, Sanliurfa, Turkey

[3] Department of Chemistry, Cukurova University Arts and Science Faculty, Seyhan, Adana, Turkey

slowly and worsen over time, and are among the leading causes of death and disability worldwide. Currently, all available drugs for AD and PD are only for symptomatic relief and cannot prevent or cure the disease [6]. Existing sulfonamide-based CA inhibitors have side effects such as anorexia, depression, nausea, exhaustion, and weight loss [7]. Due to their structural resemblance to CA IX, non-target isoenzymes CA I and CA II may have adverse effects and decrease the bioavailability of non-selective CA IX inhibitors [8]. Therefore, it is essential to develop new, highly selective, and potent CA IX inhibitors that are devoid of adverse effects. Cancer is widely recognized as the most serious disease, with its severity and lethality caused by a discrepancy between cell growth and proliferation [9, 10]. Many attempts have been made to find effective cancer treatment methods, and numerous strategies have been developed and tested. Chemotherapy is the cornerstone method for treating cancer, using both natural and synthetic agents to destroy cancer cells [11]. The treatment of cancers continues to be a significant problem despite the rapid advancements in drug research and chemotherapeutic agents, mostly because of the toxicity, resistance, and lack of selectivity of available anticancer drugs [12]. Despite advances in technology and science, licensing of new pharmaceuticals for the treatment of new diseases or diseases with mostly infectious and high socio-economic impacts, such as cancer, neurodegenerative and microbial diseases, is progressing slowly [13].

Molecular hybridization is a novel technique that integrates two or more pharmacophores within a structure to create new hybrid compounds. The resultant hybrids could have a broad spectrum of biological activities, great selectivity, numerous mechanisms of action, and negligible side effects [14]. The physicochemical characteristics that determine the efficacy of a medicine, including absorption, distribution, metabolism, excretion, and toxicity, can be adjusted by modifying and redesigning these structures [15].

Coumarins are oxygen-containing heterocyclic compounds that are extracted from plants, particularly green plants, and also called 2*H*-chromen-2-one or benzopyran-2-one, with a history of about 200 years, were isolated from melilot or sweet clover flowers and tonka bean in 1820 [16]. The generic name coumarin comes from the French word for tonka bean, "*coumarou*" [17]. Approximately 1300 coumarin compounds derived from nature are known [18]. Many plants, including tonka bean, acacia, lavender, deer tongue, apricot, strawberry, cherry, and cinnamon, contain them naturally in their fruit, bark, stem, and leaves [19]. Besides natural coumarins isolated from plants, synthetic and semi-synthetic coumarin derivatives are also available [20, 21]. Coumarins were first synthesized by W. H. Perkin by heating the sodium salt of salicylaldehyde with acetic acid [22]. In general, coumarins are obtained using one of the Pechmann, Perkin, Knoevenagel, Reformatsky, and Witting reactions employing a variety of catalysts [23]. The Pechmann reaction, which enables the synthesis of coumarin derivatives with high yields from simple starting materials, is the most commonly used method. [24]. Coumarin could be substituted at six different points, and its substituents can be tethered at different positions, allowing it to have a wide range of pharmacological activities [25]. Moreover, in the clinic, coumarin-based drugs such as warfarin, acenocoumarol, dicumarol, novobiocin, calanolide A, and hymecromone are utilized (Fig. 1) [26]. Therefore, there has been a steady rise in recent research into coumarin derivatives [27–30]. Coumarin derivatives have a wide range of activities, including antibacterial [31–34], antifungal [35–38], antituberculosis [39, 40], antiviral [41–44], anticancer [45–48], anticonvulsant [49–51], antileishmanial [52–54], antioxidant [47, 52–57], anti-inflammatory [58–61], anticoagulant [62–64], and central nervous system (CNS) stimulant [49, 65] properties, in addition to enzyme inhibition properties such as acetylcholinesterase [66, 67], butyrylcholinesterase [68, 69], a glucosidase [42, 70, 71], and monoamine oxidase [72–74]inhibition.

Combining coumarins, which have privileged structure and diverse pharmacological activities, by molecular hybridization with pharmacophores such as thiazole, triazole, indole, chalcone, sulfonamide, quinoline, selenophene, pyridine, pyrazole, and benzimidazole/imidazole, which have important biological properties, may be promising for the treatment of aforementioned disorders and diseases.

In this review, we attempted to cover the biological and pharmacological properties of coumarin hybrid compounds synthesized in recent years (from 2015 to 2023). This study is expected to encourage scientists about the need for new potential bioactive coumarin hybrids to overcome challenging health disorders.

Coumarin hybrids

Coumarin sulfonamide hybrids

In addition to being a class of compounds containing a sulfur-containing group, sulfonamides are a privileged group in medicinal chemistry, similar to coumarins, as they exhibit a number of biological properties, such as antitumor [75], antioxidant [76], antibacterial [77], anticarbonic anhydrase [8, 78, 79], monoamine oxidase inhibitor [80], cholinesterase [78] antidiabetic [81], anti-inflammatory [82], anticonvulsant [83], and analgesic [84], and are intensively studied due to these prominent properties. The incorporation of significant pharmacophore groups into a novel compound, such as coumarin and sulfonamide, may have a positive effect on biological activity. The anticancer

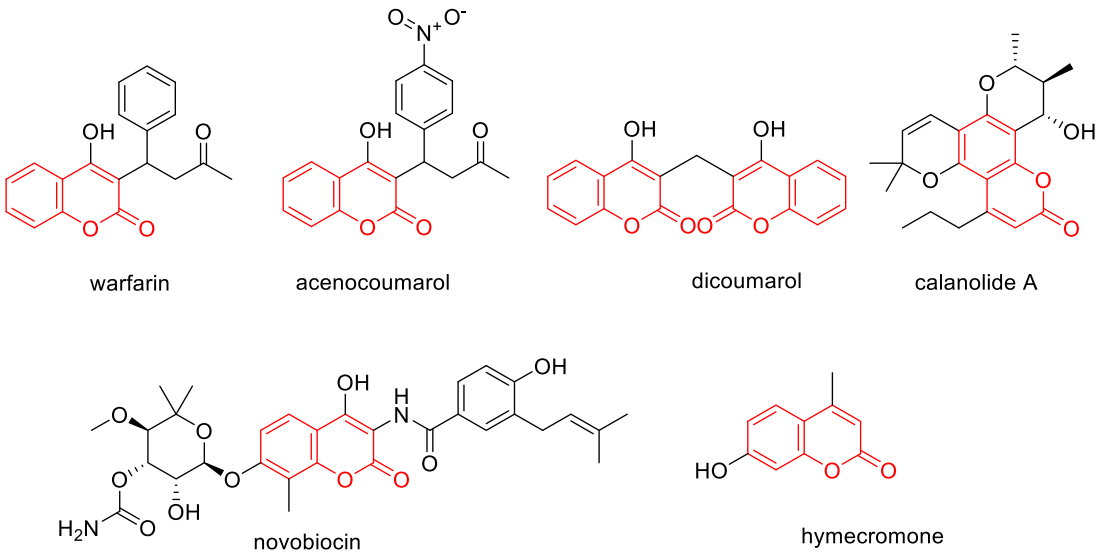


Fig. 1 Coumarin-based marketed drugs

[85–87], antibacterial [88, 89], antifungal [90, 91], antiviral [44, 92], anticarbonic anhydrase [93, 94], and anti-inflammatory [95] activities of coumarin sulfonamide derivatives were densely researched. Furthermore, many sulfonamide-based drugs (sulfisoxazole, chlorthalidone, benzthiazide, diclofenamide, sulfadoxine, celecoxib, glymidine, sulfasalazine) are currently being used in clinics to treat a wide range of disorders [96].

Zhang et al. described the synthesis of coumarin sulfonamides to identify potential anticancer agents (Fig. 2). Compound **1** was the most effective molecule against breast cancer (MDA-MB-231) cells, with an IC_{50} value of 9.33 µM, comparable to reference anticancer drug 5-fluorouracil. The majority of these derivatives exhibited good cytotoxic activity against MDA-MB-231 and human epithelial carcinoma (KB) cells. In further analysis, it was found that **9c** inhibited cell migration and invasion in addition to triggering apoptosis, both of which were effective against malignancies. Moreover, compound **1** was found to increase cancer cell death by increasing reactive oxygen species (ROS) levels and upregulating the production of caspase-3 in MDA-MB-231 cells, according to ROS assay and western blot analysis. Based on these findings, compound **1** shows promise as a lead molecule for additional research into anticancer drugs [87].

Ahmed et al. synthesized new coumarin-based derivatives **2** with various functional groups and assessed their antiproliferative potential against human breast cancer (MCF-7) and human prostate cancer (PC-3) cell lines (Fig. 2). Compounds **2a-d** in the series of sulfonamide-based coumarin derivatives bearing piperidine, benzimidazole, benzodioxol, and 2,4,6-trimethoxybenzyl moieties respectively exhibited remarkable cytotoxicity, with IC_{50} values ranging from 2.07 to 7.79 µM, compared to the standard staurosporine ($IC_{50} = 8.8$ µM). Most of the sulfonamides were found to have potent cytotoxic activity, which is consistent with the published general SAR of coumarins, which acknowledges the importance of substitution at the 6th position for anticancer activity. In general, the results indicate that many of the newly synthesized compounds are interesting candidates that could be used as lead compounds to optimize new breast cancer-targeting anticancer agents [85].

Eldehna et al. synthesized different coumarin-6-sulfonamide derivatives **3** (Fig. 2) to develop potent anticancer agents. The newly synthesized coumarins were tested for their antiproliferative effects on three different human tumor cancer cell lines using a sulforhodamine B (SRB) colorimetric assay: hepatocellular carcinoma (HepG2), MCF-7, and colon cancer (Caco-2). Compared to the reference drug doxorubicin ($IC_{50} = 46.9 \pm 2.05$ µM), compounds **3b** and **3c** bearing phenyl thiazole and dihydrothiazole rings respectively emerged as the most active derivatives against HepG2 cells ($IC_{50} = 43.48 \pm 0.28$ and 5.03 ± 0.39 µM, respectively). Moreover, compound **3a** bearing phenyl hydrazine moiety had the most potent growth inhibitory activity towards Caco-2 cells ($IC_{50} = 48.53 \pm 0.72$ µM), with the activity that was 2 times lower than that of doxorubicin ($IC_{50} = 44.10 \pm 1.37$ µM). The increased Bax and decreased Bcl-2 expression, as well as the increased caspase-3 levels, confirmed that compounds **3b** and **3c** were able to cause apoptosis in HepG2 cells [86].

Durgapal et al. reported the synthesis and anticancer evaluation of a series of novel coumarin-proline sulfonamide hybrids (Fig. 2) towards lung cancer (A549) and MCF-7 cell lines by using an MTT assay. Corresponding hybrids were synthesized from 7-amino-4-methyl coumarin and 3-amino

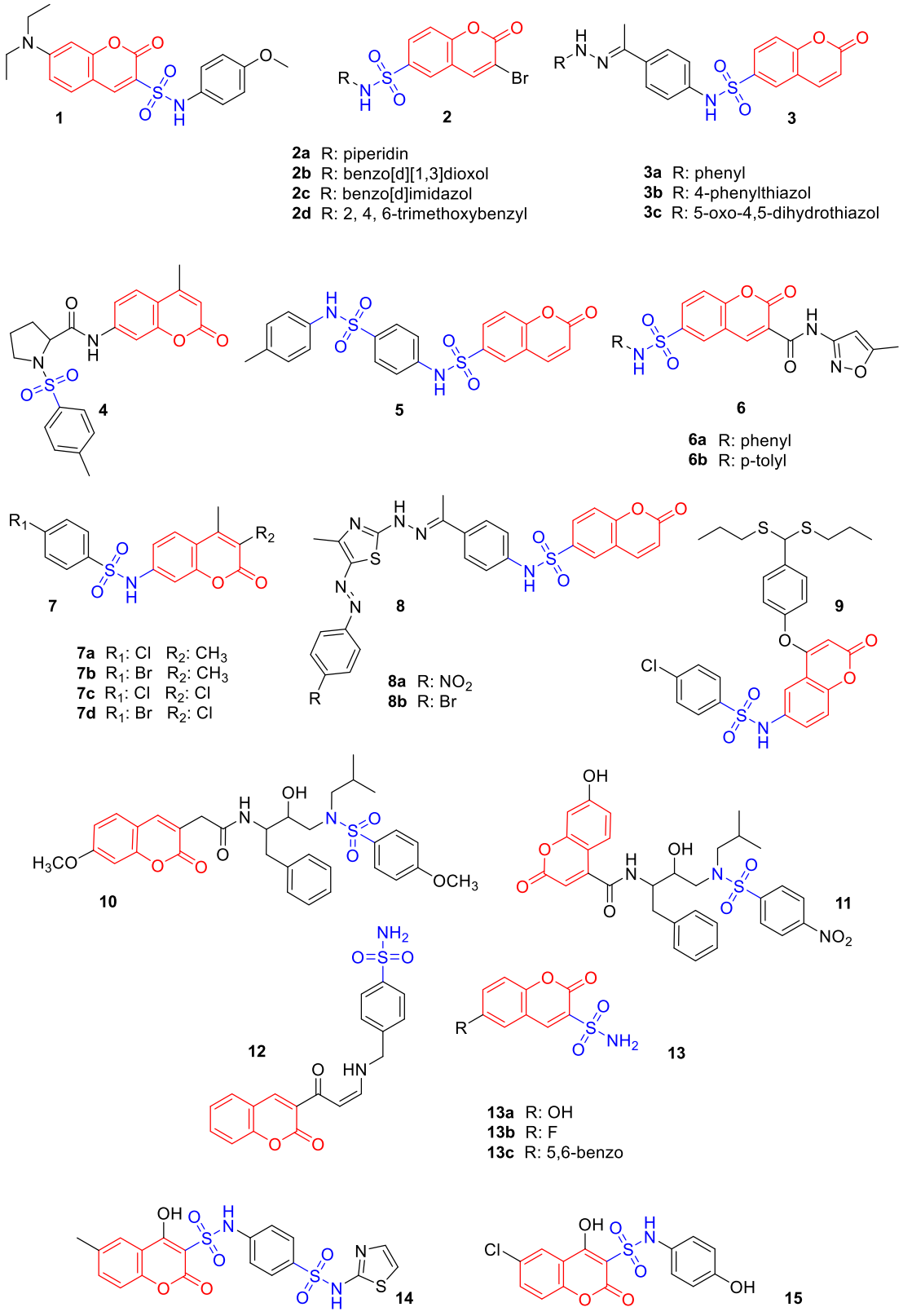


Fig. 2 Coumarin-sulfonamide hybrids

coumarin in good to excellent yield to get more potent derivatives compared to their previous significant results [97–99]. The compound **4** bearing methyl-substituted phenyl ring was found to be the most active compound against the MCF-7 cell line with the $IC_{50} = 1.07$ µM (approx 45 times higher than the reference) with respect to reference 5-fluorouracil ($IC_{50} = 45.04$ µM) [100].

Aminarshad et al. designed and synthesized different series of coumarin sulfonamide hybrids (Fig. 2) from coumarin chloride derivatives as an entry in solvent-free conditions. In addition, the antibacterial activities of the synthesized compounds were screened against *S. aureus* and *E. coli* standard strains by using the agar dilution method by comparing them with the reference antibacterial agents ampicillin and chloramphenicol. All of the novel compounds showed moderate to good activity against bacterial strains. The compound **5** bearing disulfonamide group was found to be the most active compound against *S. aureus* compared to reference agents [88].

Esfahani et al. synthesized several coumarin sulfonamide hybrids bearing isoxazole moiety (Fig. 2) and evaluated the compatibility of the experimental antibacterial activity results with the 3D-QSAR study. Using the agar dilution and disk diffusion methods, the synthesized molecules were tested for their antibacterial activity against *E. coli* and *S. aureus*. The results showed that the most effective compounds against *E. coli* and *S. aureus* strains were aromatic amines without a substituent **6a** and aromatic amines with a methyl substituent at the para position **6b** of the phenyl ring. The predicted activity of the compounds was close to the Minimal inhibitory concentration (MIC) activity and in accordance with the expectation [89].

Zhang et al. have synthesized a series of novel benzenesulfonamide substituted coumarin derivatives (Fig. 2) and investigated whether they have promising antifungal activities against six phytopathogenic fungi including *B. cinerea*, *A. solani*, *G. zeae*, *R. solani*, *C. anthrax*, and *Alternaria* leaf spot by mycelium growth rate method. Particularly, the antifungal activity values of the compounds **7a–d** against *Botrytis cinerea* ($EC_{50} = 27.34$, 27.76, 27.78, and 20.52 µg/mL) were higher than those of the standard fungicide Osthole ($EC_{50} = 33.67$ µg/mL). Compound **7d** could be the most promising candidate for additional research [91].

Sabt et al. synthesized coumarin-6-sulfonamide thiazole and thiadiazole hybrids (Fig. 2) and investigated the potential for a novel mucorales fungicide. The ability of all synthesized compounds to inhibit the proliferation of *M. racemosus*, and *S.racemosum* was screened in vitro by broth microdilution method. Compounds **8a** (MIC: 40 µg/mL) and **8b** (MIC: 40 µg/mL) showed the same anti-mucormycosis activity as the standard antifungal agent Posaconazole (MIC: 40 µg/mL) against *S. racemosum* strain [90].

Zhao et al. designed and synthesized a new series of coumarin derivatives containing sulfonamide and dithioacetal (Fig. 2) structures to develop new antiviral drugs against the Cucumber mosaic virus (CMV), known as the noxious plant virus, and their anti-CMV activities were determined by the half-leaf dead spot method. Ningnanmycin and chitosan oligosaccharide (COS) were used as standard reference drugs. Based on the results of the biological activity analysis, compound **9** ($EC_{50} = 128$ µg /mL) exhibited a much stronger anti-CMV activity than either ningnanmycin ($EC_{50} = 436$ µg /mL) or COS ($EC_{50} = 781$ µg /mL). There was a correlation between the anti-CMV activity of compound **9** and an increase in the amount of chlorophyll and defense enzymes [44].

Zhu et al. described the novel HIV-1 protease (PR) and HIV-1 reverse transcriptase (RT) inhibitors with coumarin-sulfonamide pharmacophores (Fig. 2), which play a crucial role in the treatment of AIDS. All the compounds exhibited excellent potency against PR and weak inhibition of RT. Among them, compounds **10** and **11** inhibited PR with IC_{50} values of 15.5 and 62.1 nM, respectively, and also weakly affected RT with IC_{50} values of 241.8 and 188.7 mM, respectively, which in future dual HIV-1 PR/RT indicates the possibility of developing inhibitors [92].

Ibrahim et al. designed the synthesis of novel coumarins containing the pharmacophore zinc-binding sulfonamide (Fig. 2) and examined its effect on four HCA isoforms I, II, IX, and XII inhibitor potency and selectivity. Coumarin sulfonamides inhibited both tumor-associated hCA IX (K_Is: 8.9–133.5 nM) and hCA XII (K_Is: 3.4–42.9 nM) isoforms. The most effective inhibiting coumarin sulfonamide derivative is compound **12** (K_Is; hCA = 111.7 nM, hCAII = 44.4 nM, hCAIX = 8.9 nM, and hCA XII = 15.6 nM) compared to reference CA inhibitor acetazolamide (AAZ) [94].

Darin et al. synthesized a series of compounds consisting of 3-sulfonamide-substituted coumarin derivatives (Fig. 2) and tested their in vitro carbonic anhydrase inhibitory activities against hCA I, II, IX, and XII. Coumarin sulfonamides therapeutically exhibited low K_i activity against hCA II, IX, and XII but did not inhibit hCA I. Among the compounds, **13c** showed the best inhibitory activity for hCA I (K_i: 75.1 nM), **13a** for hCA II (K_i: 53.9 nM) and hCA VII (K_i: 26.5 nM), and **13b** for hCA IX (K_i: 32.6 nM) [93].

Alshibl et al. designed and synthesized a novel series of coumarin-sulfonamide (Fig. 2) starting with chromene-3-sulfonyl chloride intermediates and evaluated their different biological activities including anti-inflammatory activity. In vitro anti-inflammatory activities of newly synthesized compounds were tested against proteinase enzyme in rats using the formaldehyde-induced paw edema method. Compounds **14** and **15**, which are the most active compounds, were also tested in vivo for their acute anti-inflammatory activities [95].

Coumarin thiazole hybrids

In 1887, Hantzsch and Weber were the first to describe thiazole, one of the five-membered heterocyclic compounds containing sulfur and nitrogen heteroatoms [101]. The thiazole structure has received a great deal of attention from researchers in organic and medicinal chemistry [102–106]. Many naturally occurring, medically and biologically active compounds, including commercially marketed drugs such as thiamine, ritonavir, clomethiazole, thiazofurine, febuxostat, and pramipexole, contain this structure [107]. Thiazole derivatives are of great importance since they have diverse biological activities such as antibacterial [108, 109], antifungal [110], antiviral [111], anti-inflammatory [112], anticancer [113], and antituberculosis [108, 114]. A rational approach to drug design is the incorporation of two bioactive moieties into a single molecule *via* a hybrid pharmacophore. The coumarin-thiazole hybrids obtained using this approach have been shown to possess antibacterial [21, 115–117], antifungal [21, 117, 118], antiviral [116], cholinesterase [119], DNA gyrase [115], urease [120], anticancer [45, 121], and antituberculosis [116] properties.

Nuha et al. have designed and synthesized a series of new coumarin-thiazole hybrids (Fig. 3) and reported molecular docking, molecular dynamics simulation, and DFT studies in addition to evaluating their antimicrobial properties. The novel compounds are prepared from the reaction of synthesized intermediates with various phenacyl bromides in good yields. Standard CLSI procedure was used to test the antibacterial activities of the newly synthesized compounds against *E. coli*, *S. marcescens*, *K. pneumoniae*, *P. aeruginosa*, *E. faecalis*, *B. subtilis*, *S aureus*, and *S. epidermidis* strains. The newly synthesized compounds showed moderate antibacterial activity (1.95–250 µg/mL) compared to the reference antibacterial agent Azithromycin (< 0.97 µg/mL). The most potent compound was found **16c** against *E. coli* with the MIC value of 3.90 µg/mL and **16a** against *E. Faecalis* with the MIC value of 1.95 µg/mL. The antifungal activity of the compounds was tested against *C. albicans, C. krusei*, and *C. parapsilopsis* strains. Compound **16b** (MIC: 0.97 µg /mL against *C. parapsilopsis*) was shown to be twofold and fourfold more active than reference antifungal agents voriconazole (MIC: 1.95 µg/mL) and fluconazole (MIC: 3.90 µg/mL) respectively [21].

Yang et al. synthesized a series of multitargeted coumarin-thiazole hybrid (Fig. 3) compounds by cyclization, nucleophilic substitution, and condensation reactions using resorcin as the starting material. The antibacterial activity of all compounds was tested against methicillin-resistant *S. aureus* (MRSA), *E. faecalis*, *S. aureus*, *K. pneumonia*, *E. coli*, *P. aeruginosa*, *A. baumannii*, *P. aeruginosa*, and antifungal activity was tested against *C. albicans*, *C. tropicalis*, *A. fumigatus*, *C. parapsilosis* strains. The compounds were also evaluated for their time-kill kinetics, cytotoxicity, hemolytic activities, and ability to eradicate biofilm. Specifically, the methyl oxime-substituted coumarin-thiazole compound **17** exhibited a broad antimicrobial spectrum against nearly all strains and was effective against Gram-positive bacteria MRSA (MIC = 1 µg/mL) and Gram-negative bacteria *A. baumanii* (MIC = 2 µg/mL), exhibiting even better inhibitory activity than the reference (Norfloxacin, Ciprofloxacin) drugs. Furthermore, compound **17** demonstrated superior antifungal activity to fluconazole, which is currently used in therapy. Further research revealed that the active molecule **17** causes membrane destruction, cytoplasmic leakage, insertion into DNA, and intracellular oxidative stress. Compound **17** was also discovered to have good anti-biofilm activity, a lower risk of drug resistance, and less toxicity to mammalian cell lines [117].

Osman et al. synthesized a series of coumarin thiazole derivatives (Fig. 3) from *N*-substituted thioureas by Hantzsch cyclization reaction and investigated whether the compounds have antibacterial, antituberculosis, and antiviral effects. The antibacterial activity of the compounds was tested against *E.coli, E.aerogenes, S.typhi, S.pneumoniae*, and *S.aureus* standard strains by broth microdilution method and compared with reference drugs streptomycin, kanamycin, and vancomycin. The compounds **18b** (MIC: 79 µg) and **18d** (MIC: 73 µg) bearing 2-bromo phenyl substituted thiazole moiety have the strongest antibacterial activity against all the bacterial strains. The antituberculosis activity of the compounds was tested against *Mycobacterium tuberculosis* H37Rv strain using Microbial Cell Viability assay and compared with the reference drug isoniazid. 2,4-dichlorophenyl substituted coumarin thiazole compound **18c** had the highest activity (MIC: 60 µg) among all the compounds compared to isoniazid. Based on cytopathic effect protection (CPE) experiments in Madin-Darby canine kidney (MDCK) cells, compound **18a** significantly reduced H1N1 influenza A virus replication (IC_{50} value 4.84 µg) [116].

Yang et al. designed and prepared coumarin thiazoles containing trifluoro methyl group (Fig. 3) as a series of potential antifungal agents by one-pot reaction under solvent-free conditions. The antifungal activity of the newly synthesized compounds was screened towards *F. moniliforme*, *F. graminearum*, and *C. Lunata strains*. Compound **19a** had the highest inhibitor rate of 74% at 0.5 mg/mL against *F. moniliforme*, whilst compound **19b** demonstrated the highest inhibitor rates of 89% and 93.4% at 0.5 mg/mL against *F. graminearum* and *C. lunata*, respectively. The trifluoromethyl group contributed to an increase in the antifungal activity of the compound structures [118].

Alshabanah et al. synthesized a series of coumarin thiazole (Fig. 3) derivatives by ultrasonic irradiation and tested their in vitro anticancer properties against HEPG2-1 cell

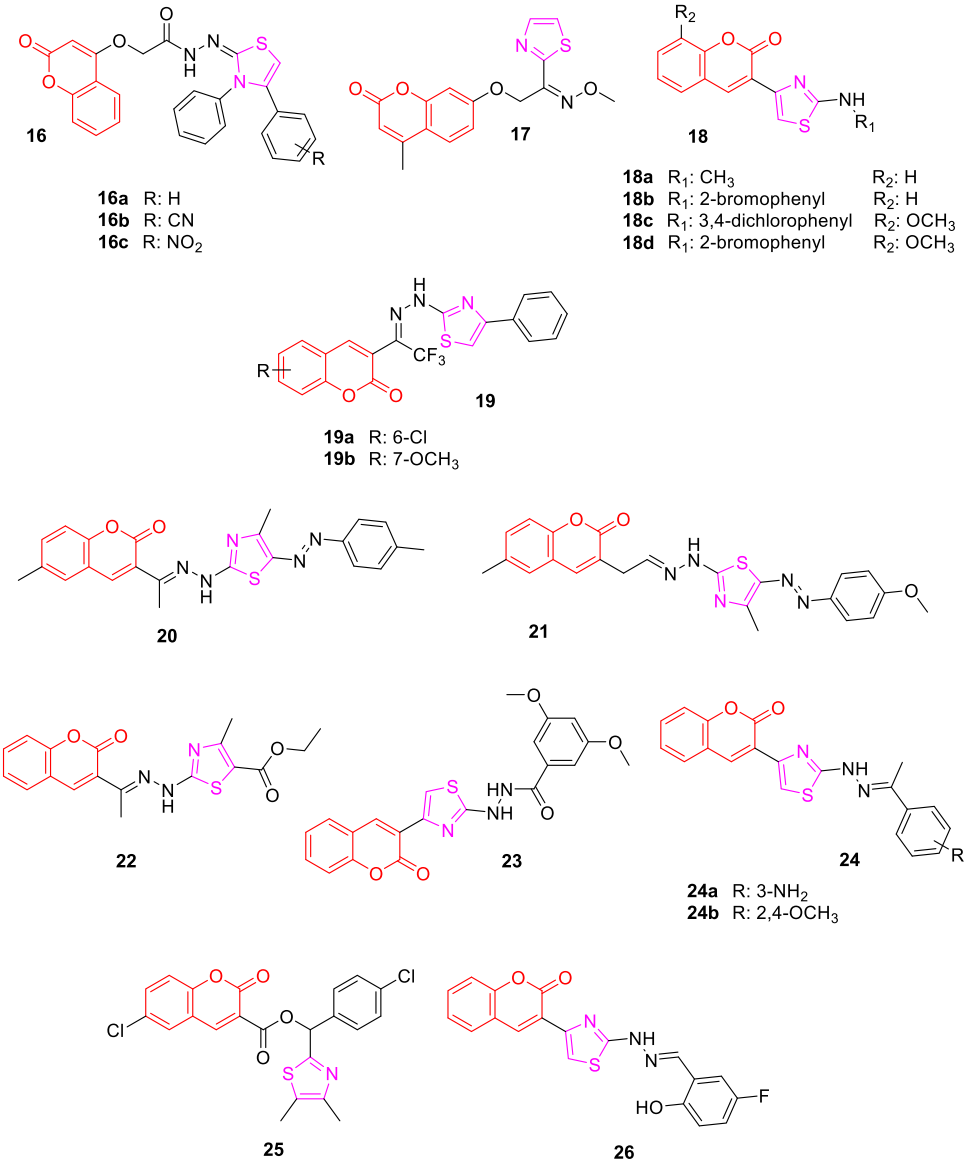


Fig. 3 Coumarin-thiazole hybrids

line with MTT assay. Among the tested compounds, **20** ($IC_{50} = 0.43 \pm 0.66$ µg) and **21** ($IC_{50} = 0.29 \pm 0.45$ µg) could be evaluated as promising anticancer agents for further investigations compared to the reference anticancer agent doxorubicin ($IC_{50} = 0.31 \pm 0.48$ µg) [45].

El-Kerim et al. synthesized efficiently novel coumarin thiazole analogs in combination with coumarin and 2-aminothiazole pharmacophores (Fig. 3) to get novel molecules with potential cytotoxic activity by MTT assay against human cervical cancer cell lines (HeLa cells). According to the results of the cell cycle research, compound **22** caused an arrest in the G0/G1 phase of the cell cycle. This result suggests that the CDK2/E1 complex, which involves a critical cellular process, maybe a possible biological target for these newly prepared compounds. Biological testing showed that the compounds have potent CDK2 inhibitory effects with an IC_{50} of 0.022–1.629 nM [121].

Thacker et al. obtained a series of coumarin thiazole compounds (Fig. 3) by reacting different thiosemicarbazides with 3-bromo acetyl coumarin as inhibitor candidates against cancer-related human carbonic anhydrases (hCAs) IX and XII. The designed compounds showed stronger inhibition for hCA IX compared to hCA XII. Compound **23** could be considered as a promising hCA XII inhibitor with a *Ki* value of 91.1 nM [122].

Ibrar et al. designed the synthesis of new coumarin-thiazole hybrid (Fig. 3) compounds and assessed their activities against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) to determine the potential of each compound to prevent Alzheimer's disease (AD). In comparison to the reference drugs neostigmine (IC_{50}: 28.2 ± 2.01 µM) and

donepezil (IC_{50}: 7.23 ± 0.13 µM), compound **24a** (3-NH_2-Ph substituted) exhibited the highest inhibitory activity against AChE, with an IC_{50} of 0.87 ± 0.09 µM, while compound **24b** (2-OH-4-OMe-Ph substituted) exhibited the highest inhibitory activity against BuChE, with an IC_{50} of 11.01 ± 3.37 µM [119].

New coumarin-thiazolyl ester derivatives (Fig. 3) were synthesized by Liu et al. and their antibacterial activities against *S. aureus*, *L. monocytogenes*, *E. coli*, *Salmonella* strains were compared with Ciprofloxacin, Novobiocin, Gatifloxacin, and Levofloxacin references by agar dilution method. Compound **25** exhibited excellent antibacterial activity against four bacterial strains with respective MIC values of 0.05, 0.05, 8, and 0.05 µg/mL. In addition, the DNA gyrase inhibition effect of **25**, the most active compound, was investigated and found 0.13 µM. The SAR and molecular docking studies showed the potential antibacterial activity could be related to chlorine substitution on benzene and alteration of the coumarin core [115].

Salar et al. synthesized aryl hydrazone derivative compounds carrying thiazolyl coumarin hybrids (Fig. 3) by reaction of thiosemicarbazones with 3-bromoacetyl coumarins under basic conditions and investigated their urease inhibition activities. The compounds exhibited good to moderate inhibitory potential in the range of IC_{50} = 16.29 ± 1.1–256.30 ± 1.4 µM towards urease enzyme. Compound **26** was discovered to have the highest activity (IC_{50} = 16.29 ± 1.1 µM), acting as a more effective urease inhibitor than reference acetohydroxamic acid (IC_{50} = 27.0 ± 0.5 µM) [120].

Coumarin-triazole hybrids

Triazoles are heterocyclic compounds containing a five-membered ring of two carbon atoms and three nitrogen atoms with the molecular formula $C_2H_3N_3$. Triazoles are core scaffolds of various pharmaceuticals including albaconazole, fluconazole, voriconazole, sitagliptin, letrozole, anastrozole, itraconazole, deferasirox, and maraviroc [123]. Triazole derivatives exhibit antimicrobial [124, 125], anticancer [126–128], antioxidant [129, 130], antiparasitic [131, 132], anti-diabetic [133], analgesic [134, 135], and anti-inflammatory [136, 137] activities.

Basappa et al. designed and synthesized 8 novel coumarin-triazole hybrids (Fig. 4) to treat diabetes **27a** and **27b** showed maximum α-amylase enzyme inhibition with values ranging from 5.43 µM and 5.98 µM respectively [138].

In another study, 8 coumarin-4-yl-1,2,3-triazol-4-yl-methyl-thiazolidine-2,4-diones compounds (Fig. 4) were synthesized and evaluated for their in vitro glucose uptake and cytotoxic activities. Compounds **28**, **29a**, **29b**, and **29c** showed notable activity with 93.25%, 91.01%, 92.84%, and 91.55% glucose uptake at 200 µg/ml concentrations respectively compared with Pioglitazone (94.0% of glucose uptake at 200 µg/ml) [139].

Novel 1,2,3-triazole-coumarin-glycoside hybrids (Fig. 4) were synthesized as targets to treat breast cancer. Moreover, their potential EGFR, VEGFR-2, and CDK-2/cyclin A2 kinases enzyme inhibition was evaluated. Compounds **30a** and **30b** exhibited excellent broad inhibitory activity for each enzyme, ranging between IC_{50} = 0.12–0.22, 0.79–0.93, and 0.15–0.24 ± 0.20 µM, respectively [46].

Recently, Sanduja et al. synthesized novel 28 pyrimidine-coumarin-triazole hybrids (Fig. 4). All of the compounds exhibited antiproliferative activity against MCF-7 with IC_{50} between 1.55 and 19.55 mM [140]. Compound **31** with fluorine substituent was found to be the most active compound with IC_{50} value of 1.55 mM.

Kaushik et al synthesized coumarin-1,4-disubstituted 1,2,3-triazoles (Fig. 4). The antioxidant and antimalarial activity of all synthesized compounds were measured. **32a**, **32d**, **32e**, and **32 f** have shown antimalarial activity with IC_{50} values of 0.53, 0.38, 0.49, and 0.54 µg/mL, respectively. **32b** and **32c** have showed promising antioxidant activity (IC_{50} = 3.33 and 3.86 µg/mL, respectively) [141].

A new series of coumarin-1,2,3-triazole hybrids (Fig. 4) were synthesized by Rojas et al. The antibacterial activity of twenty-six compounds was measured and their MIC value was calculated. Twenty compounds showed significant antibacterial activity against *E. faecalis* with MIC value between 12.5–50 µg/mL. The compound **33** bearing methoxyphenyl substituent showed the highest bacterial activity against *E. faecalis* strain [142].

Similar to this study, 1,2,3-triazole-substituted coumarins (Fig. 4) were prepared and evaluated their antibacterial activity against *S. aureus*, *B. subtilis*, *A. viscosus*, and *E. coli* bacterial strains. **34** exhibited excellent activity against *S. aureus* strains, and **35** was showed against *B. subtilis* and *E. coli* species [143].

Najafi et al. designed Novel tacrine-coumarin hybrids (Fig. 4) linked to 1,2,3-triazole as the target for Alzheimer's disease. While tested **36a** exhibited the best activity with IC_{50} = 27 nM, tested **36b** showed the most potent anti-BChE activity (IC_{50} = 6 nM). The enzyme inhibition activity of these two compounds was better than standard compounds such as tacrine and donepezil [144].

Coumarin-indole hybrids

Indole is an aromatic heterocyclic compound, also called benzopyrrole, in which benzene and pyrrole rings are fused together [145]. Indoles and some compounds containing indole rings are aromatic heterocyclic organic compounds that are widely used as useful intermediates in drug synthesis [146]. The broad-spectrum activity of indole and its derivatives makes them suitable candidates to combat the

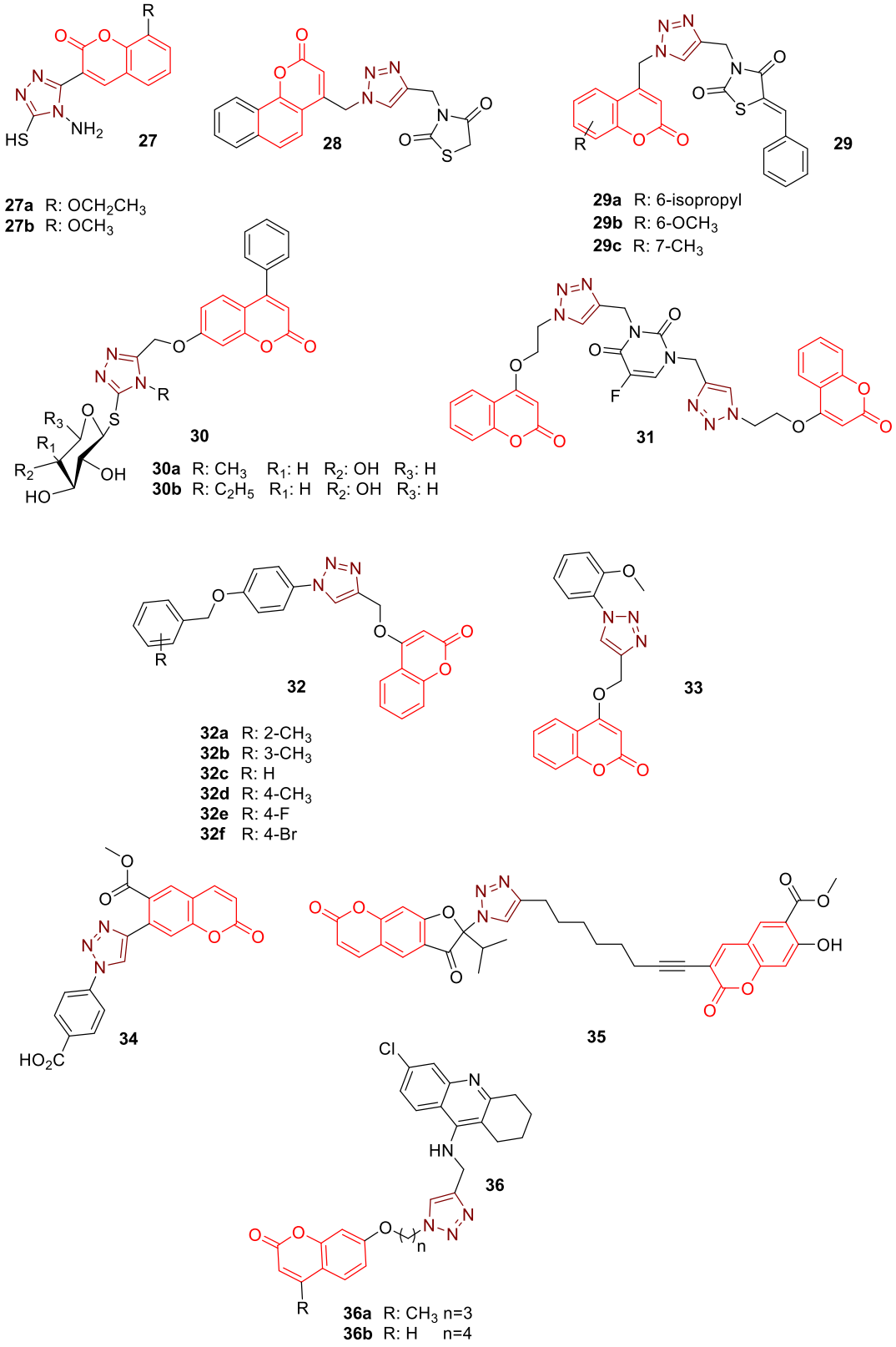


Fig. 4 Coumarin-triazole hybrids

current problem of multidrug resistance [147]. Indole-derived compounds are known to have antiviral [148], anti-inflammatory [149], anticancer [150], anti-HIV [151], antioxidant [152], antibacterial [153], antifungal [154], and antituberculosis [155–157] properties. Furthermore, the indole structure is present in currently commercially available drugs including indomethacin, fluvastatin, vilazodone, tropisetron, and sumatriptan. [158]. Coumarin indole hybrids possess antibacterial [159], antifungal [159], antioxidant [159, 160], antileishmanial [160], anticancer [161–163], α-glucosidase [28], cholinesterase [164] activity.

Basha et al. synthesized a series of coumarin indole derivatives (Fig. 5) and examined their in vitro antimicrobial and antioxidant activities. The radical scavenging abilities of compounds **37d**, **38a**, and **38b** against the DPPH free radical were all impressive. Compounds **37c** and **37e** have potent antibacterial activity against *methicillin-resistant S. aureus* (MRSA), and compounds **37b**, **38a**, and **38b** are effective against *Bacillus sp*. Compounds **37f** and **39** exhibited notable antifungal activity against *C. albicans*, and compounds **37a** and **37d** showed good antibacterial activity against *E. coli*, *K. pneumoniae* [159].

Sangshetti et al. synthesized a series of coumarin indole hybrids (Fig. 5) to test their antileishmanial and antioxidant activities. In comparison to reference sodium stibogluconate ($IC_{50} = 490.00$ µg/mL), the compounds **40a**, **40b**, and **40d** were found to have significant anti-leishmanial effect (IC_{50} values = 95.50, 95.00, and 99.00 µg /mL). The compounds **40a** ($IC_{50} = 12.40$ µg /mL), **40b** ($IC_{50} = 13.49$ µg/mL), **40c** ($IC_{50} = 13.24$ µg/mL), and **40e** ($IC_{50} = 13.74$ µg/mL) showed remarkable antioxidant activity compared to the references [160].

Song et al. synthesized novel coumarin-indole derivatives (Fig. 5) with a fragment-based design strategy and investigated their in vitro antiproliferative activities towards MGC-803, Kyse450, and HCT-116 cells. **41** had the highest activities against MGC-803, Kyse450, and HCT-116 cells, with IC_{50} values of 0.011, 0.021, and 0.037 µM, respectively, stronger than colchicine. According to the findings, **41** is a promising lead molecule that should be investigated further as a potential anti-gastric cancer treatment agent [163].

Pathoor et al. reported the synthesis of indole-triazole-coumarin hybrids (Fig. 5) *via* multicomponent coupling reaction as a potential inhibitor of the protein kinase CDK 2, which is responsible for many different types of cancer, including breast cancer in humans. The anticancer activity of the compounds was compared both in vitro and theoretically. According to docking analyses found that the 2-Cl-substituted molecule **42** binds to CDK2 with the highest affinity. Compound **42** exhibited the lowest IC_{50} (17.5 µM) against MCF-7 in the in vitro cytotoxicity experiments, demonstrating that the theoretical and experimental results were consistent [162].

Kamath et al. synthesized three different series of coumarin-indole derivatives (Fig. 5) and evaluated their dose-dependent cytotoxic effect on MCF-7 cell line and normal cell lines with the MTT test by comparing them with the reference drug Vincristine. In addition, docking studies were conducted on the synthesized molecules and the apoptosis-related gene Bcl-2. Compound **43** was found to be the most potent cytotoxic molecule with an IC_{50} value of 7.40 µM. Due to cell cycle arrest in the G2/M phase, **43** was found to exhibit apoptotic cell death mode by flow cytometric cell cycle analysis [161].

Niri et al. obtained coumarin-indole hybrids (Fig. 5) that could be α-glucosidase inhibitors from 4-hydroxycoumarin and 1*H*-indole in a single step and assessed their in vitro and in silico α-glucosidase activity. Even while the majority of the compounds showed significant α-glucosidase activity in comparison to the standard compound acarbose, the 3-phenoxyphenyl substituted molecule **44**, in particular, showed more inhibition than acarbose (MIC: 750.0 ± 5.0) with a MIC of 116.0 ± 0.7 µM [28].

Nasab et al. prepared coumarin-indole carboxamides derivatives (Fig. 5) from the reaction of coumarin acyl chlorides with tryptamine as new cholinesterase inhibitor candidates. The highest activity among the compounds was found to be **45** with a 4-fluorobenzyloxy substituent in its structure, with an IC_{50} value of 0.16 µM [164].

Coumarin-imidazole/benzimidazole hybrids

Imidazole is a five-membered heterocyclic aromatic compound with two nitrogen atoms, one of which is pyrrole-type nitrogen and the other pyridine-type nitrogen. Benzimidazole, 2*H*- and 4*H*-imidazole, imidazolines, imidazolidines, imidazo-2-yldiene, and imidazolidin-2-yllidene are examples of compounds that resemble imidazoles [165]. Many essential drugs contain imidazole derivatives in their structure (bifonazol, tetrahyrozoline, tolazoline, antrazoline, carbimazole, sulconazole) [166]. Due to their diverse biological activities, coumarin-imidazole/benzimidazole hybrid molecules have contributed significantly to numerous studies in the field of medicinal chemistry [167]. Depending on the substitution site, coumarin-imidazole derivatives can display a variety of activities. Anticancer [168, 169], antibacterial [165], antioxidant [170, 171], antiviral [172, 173], anthelmintic [174], antitubercular [175, 176], anticonvulsant [177, 178], and anti-inflammatory [179] are some of its most well-known properties.

Yang et al. synthesized various coumarin-imidazole hybrids (Fig. 6) and examined their antibacterial activities against *S. aureus*. Among the 5 different imidazole derivatives synthesized, compounds **46a** and **46b** showed better antibacterial activity than the others against the gram-positive bacteria *S. aureus* with the MIC: 16 µg/mL [180].

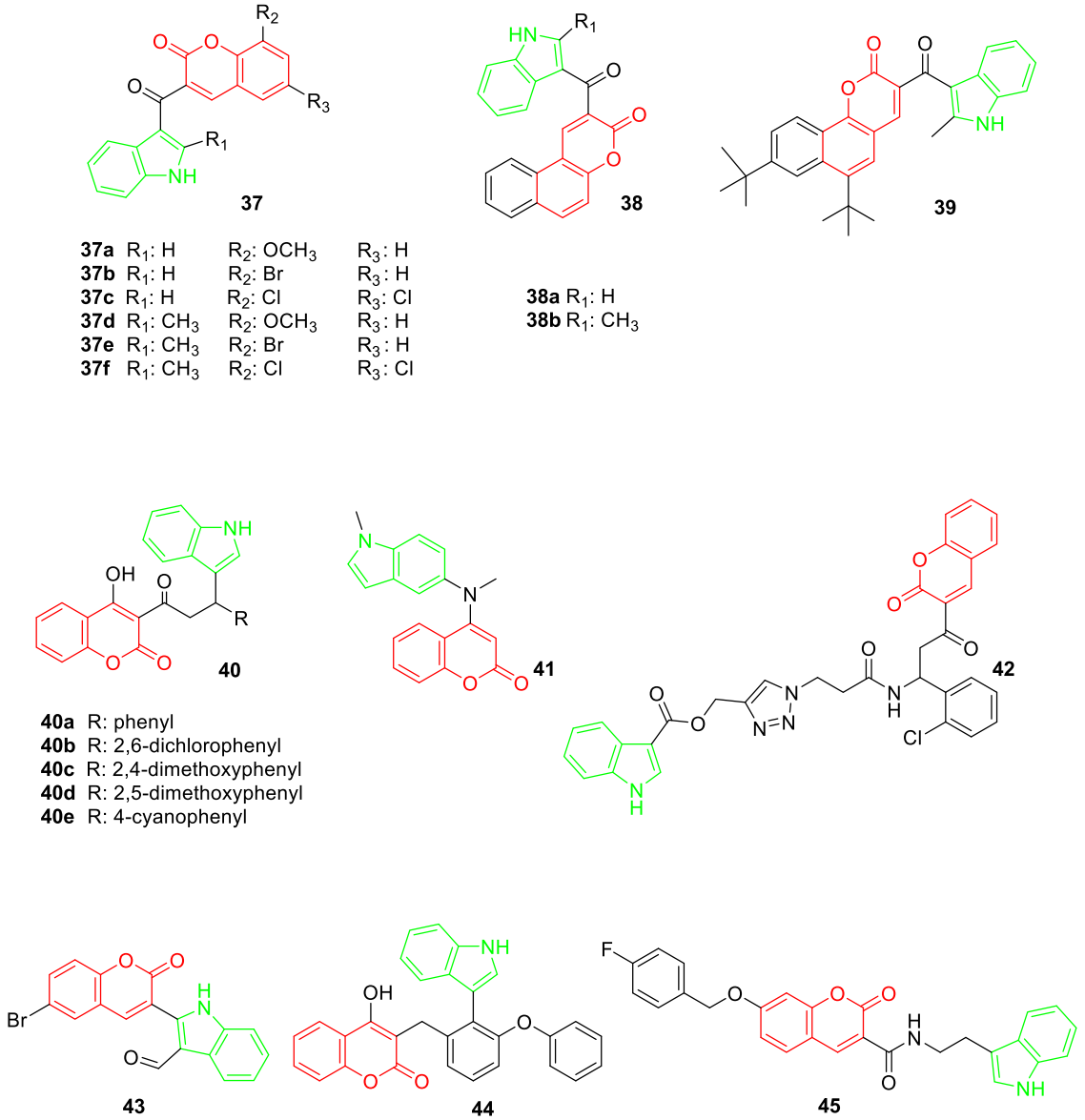


Fig. 5 Coumarin-indole hybrids

Liu et al. synthesized a series of coumarin-imidazole hybrids (Fig. 6) and evaluated the antiparasitic effect of these compounds against *D. intermedius* in goldfish. Especially, compounds **47a**, **47b**, and **48** showed better antiparasitic activity than the others with EC_{50} values in the range of 0.18-0.26 mg/L [181].

Obaiah et al. synthesized 4-hydroxycoumarin-benzimidazole hybrids (Fig. 6) and investigated their antibacterial, antifungal, and antioxidant activities. Compounds **49a** and **49b** were shown to be the most active compounds against a wide range of pathogens when their minimum inhibitory concentration values (MIC) were compared to those of the reference drugs streptomycin and fluconazole (Scheme 14). Compound **49b** showed better antioxidant activity with an IC_{50} value of 9.82 ± 1.79 mg/mL and an inhibition rate of 74% than butylated hydroxytoluene (BHT) used as reference (IC_{50}: 10.5 ± 1.06 mg/mL, inhibition rate: 78%) [182].

Mohareb et al. synthesized coumarin-benzimidazole derivatives (Fig. 6) and examined their cytotoxic activity against glioma cell line (U87MG), human lung carcinoma (A549), cellosaurus cell line (SMMC-7721) and toxicity study against shrimp larvae. Compound **50a** exhibited better anti-cancer activity against U87MG, A549, and SMMC-7721 cells with an IC_{50} of 0.29, 0.25, and 0.22 µM respectively compared to foretinib. (Scheme 15). According to obtained data from toxicity studies, compounds **50a** and **50b** were nontoxic [183].

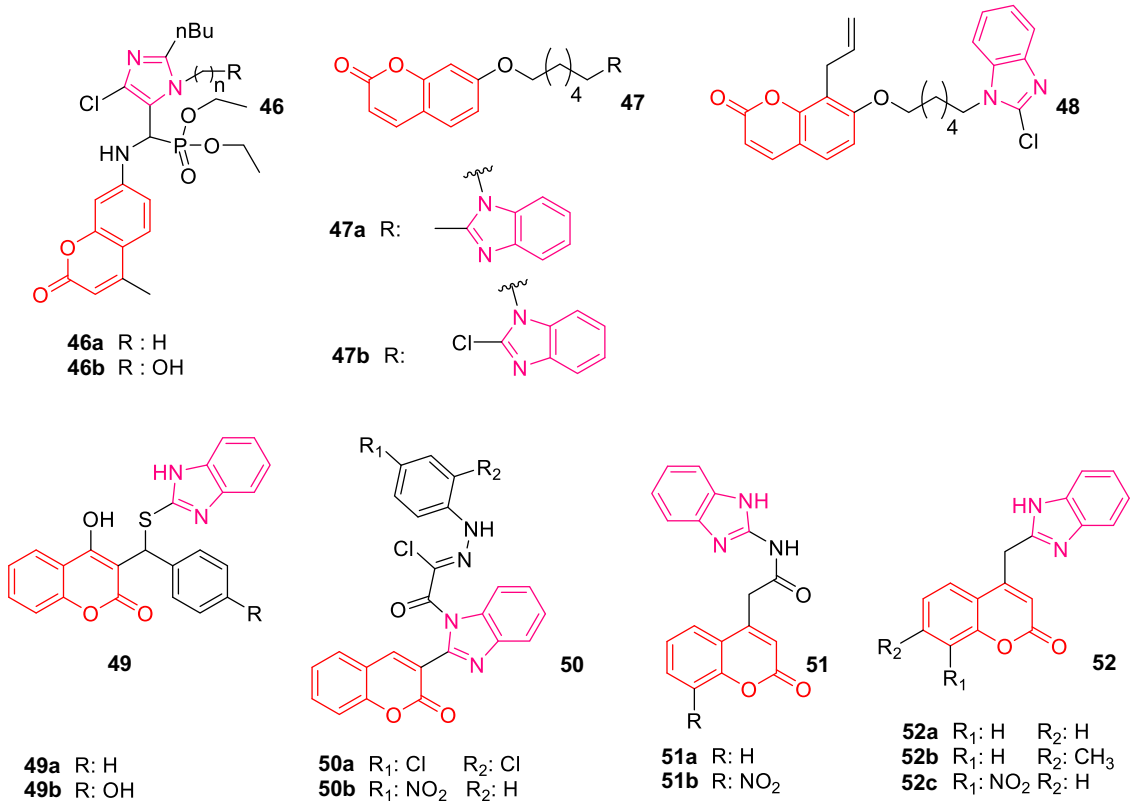


Fig. 6 Coumarin-imidazole/benzimidazole hybrids

Sethi [184] et al. investigated the anthelmintic, anti-inflammatory, and antioxidant activities of compounds synthesized by substituting the C-4 position of the coumarin ring with benzimidazole (Fig. 6). According to the anthelmintic activity results, the most active compound **51a** is the one without substituent in the coumarin ring. Compound **51a** showed paralytic activity and mortality at 0.1% w/v concentration compared to reference albendazole, while no significant activity was observed in compounds containing hydroxy, methyl, and nitro groups in the coumarin ring. After 3 h of treatment, when the anti-inflammatory effects of the compounds were evaluated, the percent inhibition values compared to indomethacin ranged from 36 to 45 percent. The most active compounds were nonsubstituted coumarin **52a** and its methyl analog **52b**. Comparing the antioxidant activities of these compounds with the reference butylated hydroxytoluene ($EC_{50} = 23.4$ mM), compounds **52c** ($EC_{50} = 0.17$ mM) and **51b** ($EC_{50} = 0.08$ mM) containing nitro groups in the coumarin C-8 ring showed excellent activity.

Coumarin-quinoline hybrid compounds

Quinoline, a heterocyclic aromatic organic compound with the chemical formula C_9H_7N, was first extracted from coal in 1834 by the German chemist F. F. Runge [185]. Quinolines are known to exhibit tyrosinase enzyme activity [186] as well as anti-Alzheimer's [187, 188], and anticancer activities [189, 190]. In addition, these compounds are used in food, medicine, agriculture, etc. due to their fluorescent properties [191]. Quinoline-based drugs such as imiquimod, oxyquinoline, diiodohydroxyquinoline, grepafloxacin, and pitapat are widely used in clinics [192].

Hirbod et al. synthesized a novel series of coumarin-quinoline hybrids (Fig. 7) as novel cholinesterase inhibitors. Among all the compounds, **53a** and **53b** exhibited the most potent BuChE inhibitor activity with an IC_{50} value of less than 30 µM. Moreover, these compounds showed AChE inhibitor activity with an IC_{50} value 35 µM, 8 µM respectively [193]

Gardelly et al. synthesized the hybrid compounds (Fig. 7) with quinoline units substituted at the coumarin ring's C-3 carbon. The synthesized compounds exhibited BuChE enzyme inhibitory activity. Compounds were reported to show moderate inhibition of the BuChE enzyme ($IC_{50} = 40$–112 µM) compared to reference galantamine ($IC_{50} = 0.38$ µM). The 6-methoxyquinoline **54b** compound showed the highest activity ($IC_{50} = 40$ µM). In addition, in the same study, the research group also examined the tyrosinase enzyme inhibition activities of these compounds.

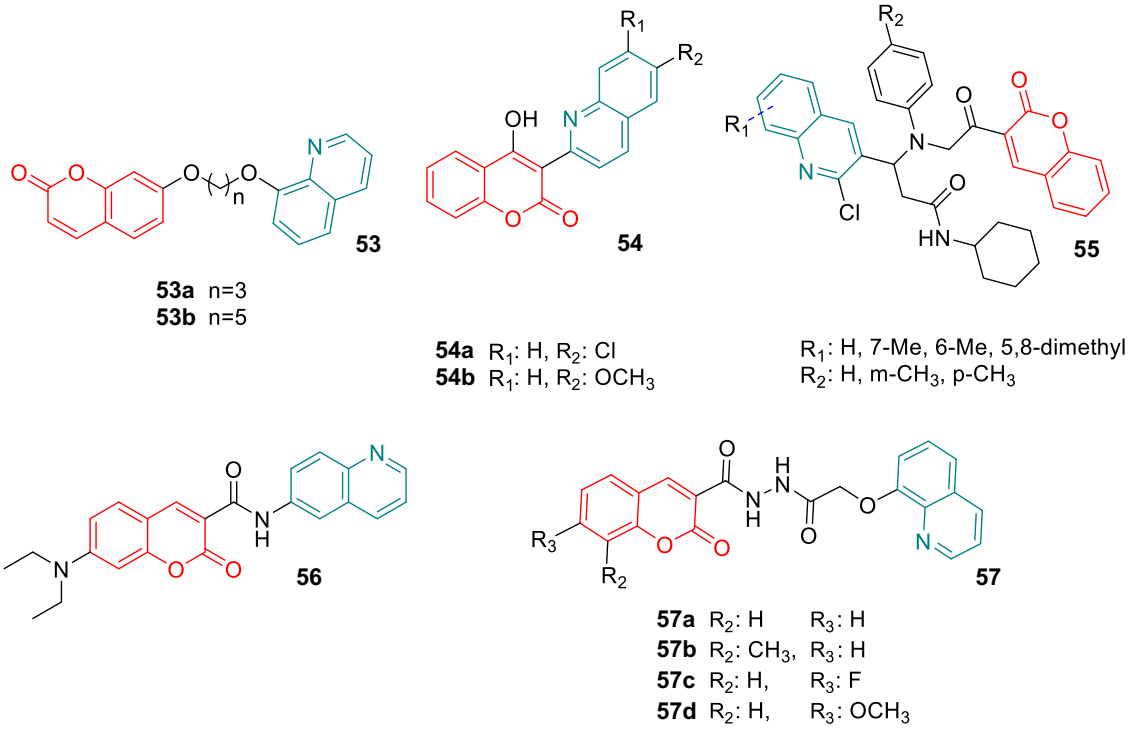


Fig. 7 Coumarin-quinoline hybrids

The compounds showed promising tyrosinase enzyme activity in contrast to the results of BuChE enzyme inhibition. In particular, four compounds showed significant activity (in the range of 15.1–18.3 µM). Among these compounds, 6-chloroquinoline substituted **54a** was the most active compound with an IC_{50} value of 15.1 µM. The compounds showed lower activity than reference kojic acid ($IC_{50} = 12.1$ µM) [186].

Taheri et al. synthesized coumarin-quinoline hybrids **55** (Fig. 7) and investigated their antiapoptotic activities. The anticancer activity of the compounds was evaluated against ovarian cancer (A2780) cells. The IC_{50} values of the two compounds containing –H and $–CH_3$ substituents were determined as 25 and 62 µg/ml, respectively. However, these compounds did not show any cytotoxicity against PC12 cells. The compound containing a -H substituent was found to be cytotoxic at a concentration of 25 µg /ml when caspase 3 and caspase 9 were activated on A2780 cells. This compound induced ROS [194].

Duarte et al. synthesized a series of coumarin-quinoline hybrids (Fig. 7) and examined the iron-chelating effect and cytotoxicity of these compounds. AChE and BuChE enzyme inhibition effects of these compounds were also tested. In addition to exhibiting an outstanding iron chelating agent effect (chelating iron at 100 µM = 72.87%), compound **56** exhibited better acetylcholine enzyme inhibition ($IC_{50} = 159.53 \pm 0.01$ µM) than the other compounds [195].

Prashanth et al. synthesized four new coumarin-quinoline compounds (Fig. 7) and investigated the apoptogenic role of these compounds against murine ascitic carcinoma. Compound **57b** exhibited vigorous activity against EAC and DLA cells [196].

Coumarin pyrazole/pyrazoline/pyrazolone hybrids

Pyrazoles are five-membered heterocyclic scaffolds with two nitrogens. The reaction methods and synthesis of pyrazole hybrids have always fascinated researchers to investigate its structural unit to effects on biological activities against several diseases [197]. Pyrazole-based drugs are commercially available such as entrectinib, fomepizole, epirizole, antipyrine, and metamizole [198]. Pyrazole derivatives have a broad spectrum of biological activities including anticancer [199, 200], anti-inflammatory [199, 201], antimicrobial [202, 203], antifungal [204–206], and antitubercular [207, 208].

Given the above findings in 2022, Patel et al. reported a series of novel pyrazoline scaffolds from coumarin–carbazole chalcones as anticancer agents (Fig. 8). In vitro cytotoxic activity of all tested compounds was studied against HeLa and squamous cell carcinoma (NCI-H520). The compounds **58a** and **58b** were found the most active compounds against HeLa and NCI-H520 cell lines. [209].

Coumarin-pyrazoline derivatives have drawn great attention due to their anti-cancer activity. Therefore,

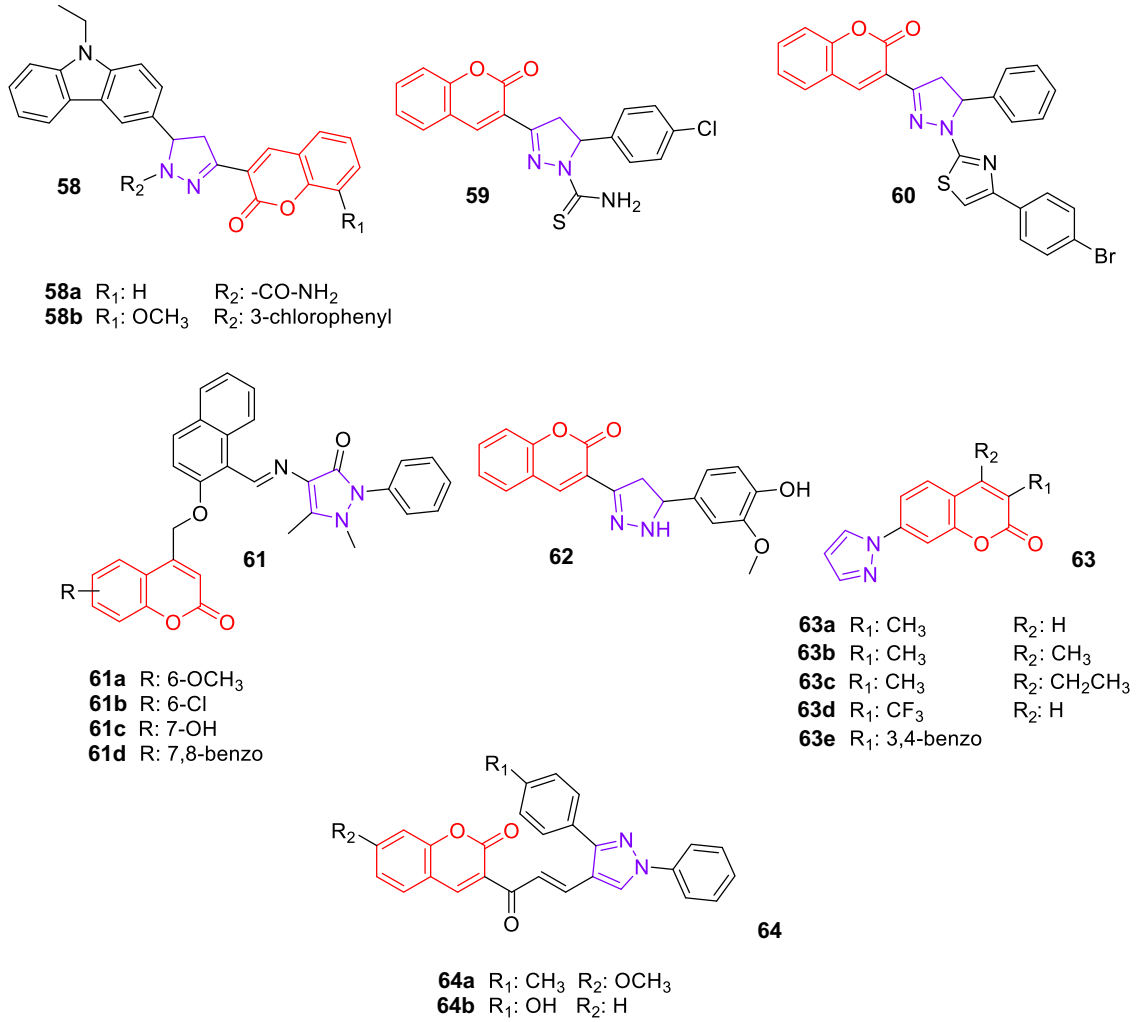


Fig. 8 Coumarin-pyrazole hybrids

Ragab et al. prepared a novel series of coumarin–pyrazoline hybrids (Fig. 8) and tested their anti-proliferative activity on HCT-116, HepG2, A549, and SGC-7901 cancer cells. Most of the tested compounds exhibited potent cytotoxic activity to the MCF-7 cells. All the compounds demonstrated better cytotoxic activity than the reference chemotherapeutics including doxorubicin and erlotinib towards all the cancer cell lines. Furthermore, compounds **59** and **60** increased in the cells in the pre-G1 phase of 14 and 22 fold and reduced EGFR levels [210].

Chavan et al. reported a series of coumarin-pyrazole hybrids (Fig. 8) as antibacterial and anti-inflammatory agents in 2018. Agar-well diffusion method was used to determine the antibacterial activity of prepared compounds **61**. Moreover, the egg albumin denaturation method was used for inflammatory activity. Tested **61b** and **61d** showed antibacterial activity with MIC 0.78 µg /ml and MIC 1.562 µg /ml against Gram-positive *S. aureus* bacterial strain, respectively. Moreover, tested **61a** and **61c** compounds have inhibited heat-induced protein denaturation more efficiently than standard aceclofenac [211].

Chate et al. synthesized a series of novel coumarin-linked pyrazoline inhibitors (Fig. 8) of D-alanine ligase and investigated them as inhibitors of *E. coli* DdlB ligase. Compound **62** was found most active, and the enzyme inhibition study reveals substitution (–OH, $–CH_3$, and $–OCH_3$ groups) at the 4- and 3-position of the coumarins linked to the pyrazolines scaffold enhances enzymatic inhibition. [212].

Zhang et al. reported a series of pyrrole- and pyrazole-substituted coumarin derivatives (Fig. 8) as potent anti-fungal agents. The five tested compounds **63a-e** showed better antifungal activity towards *A. leaf spot* and *C. anthrax* than the control osthole [213].

Kumar et al. have synthesized 22 pyrazole-coumarin chalcones (Fig. 8) as anti-tubercular agents. The anti-TB activity of the compounds was determined by Alamar Blue assay against *M. tuberculosis* H37Rv strain and

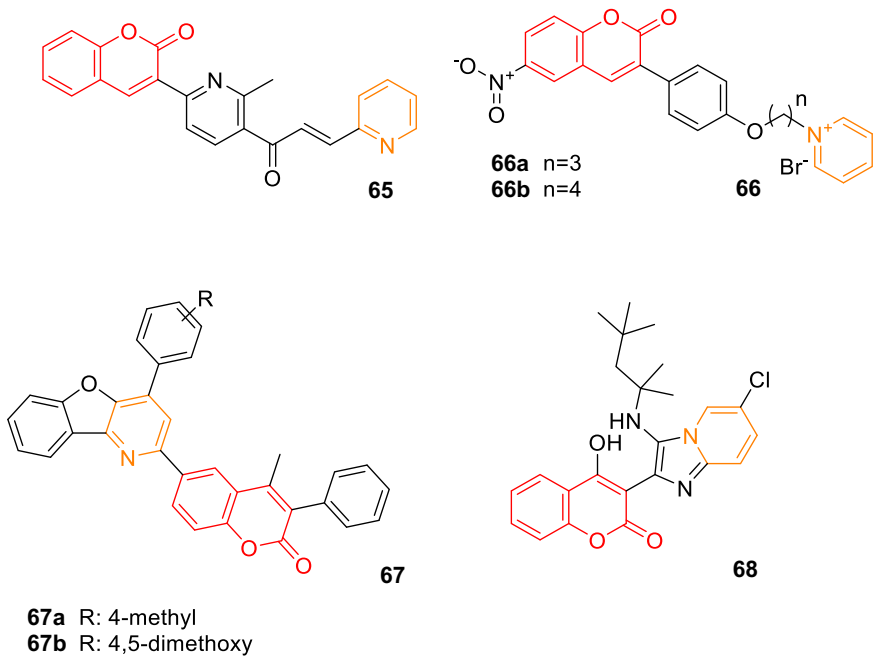


Fig. 9 Coumarin-pyrdine hybrids

compared with positive controls isoniazid, rifampicin, and ethambutol. Among all the tested compounds, **64a** and **64b** showed promising anti-TB activity the MIC values with 3.125 µg/ml [214].

Coumarin pyridine hybrids

Pyridine, a six-membered heterocycle with the molecular formula C_5H_5N, is also present in the structures of several drugs, including pyridoxal phosphate, pyridoxine, pantoprazole, indinavir, nevirapine, disopyramide, and omeprazole. [215]. Hybridization of coumarin derivatives with pyridine ring has formed novel molecular scaffolds with potent biological activities including anticancer [216], antitubercular [217], antiviral [217], antibacterial [217], antifungal [217], antiAlzheimer [218], and anticarbonic anhydrase [216].

Tawfik et al. synthesized a new series of 3-(6-methylpyridin-2-yl)coumarin derivatives (Fig. 9). Carbonic anhydrase (CA) inhibition and anti-tumoral activity of coumarin pyridine hybrids were evaluated. Coumarins with inhibition constants ranging from sub- to low-micromolar range inhibited *hCA* IX/XII. According to results, compound **65** showed anti-proliferative activity against leukemia (K-562), NSC Lung cancer (HOP-92), colon cancer (HCT-116, SW-620), U251, melanoma (LOX IMVI), and MCF-7, with GI_{50} values ranging from 3.20 to 8.49 mM [216].

Babaei et al. synthesized and evaluated coumarin-based scaffolds linked to pyridine compounds (Fig. 9) as anti-Alzheimer's Disease agents. To evaluate their anti-AD activity, AChE, and BuChE enzyme activities were measured by Ellman's method. According to obtained data, all compounds inhibited the cholinesterase enzymes more effectively than reference donepezil. The nitro group on the 6-position of the coumarin ring increased the inhibitor activity of the compounds. Among all the tested compounds, **66a** and **66b** were found the most potent hybrids [218].

Giri et al. designed coumarin-pyridine hybrids (Fig. 9) and evaluated their anti-microbial activity against *S. aureus, B. subtilis, E. coli, S. typhi, C. albicans, and A. niger*, and anti-TB activity against *M. tuberculosis* H37Rv strain. Among all compounds, **67a** and **67b** exhibited most promising activity against both anti-TB and anti-microbial [217].

Manvar et al. synthesized coumarin-pyridine compounds (Fig. 9) by Groebke–Blackburn–Bienaymé multicomponent reaction as potential NS5B inhibitors, determined as a promising target for the development of selective anti-HCV drugs inhibitors. The results obtained from the docking studies compound **68** showed better XP scores than the reference ligand [219]

Coumarin-chalcone hybrid compounds

Chalcones, which are biologically active and naturally isolated compounds with an, α, β-unsaturated carbonyl group between two aromatic rings, could also be synthesized by a variety of reactions. Some important chalcone derivatives (flavokawin B, ferulic acid, butein, isobavachalcone, and licochalcone A) isolated from plants are used as active pharmaceutical ingredients [220]. If at least one of these

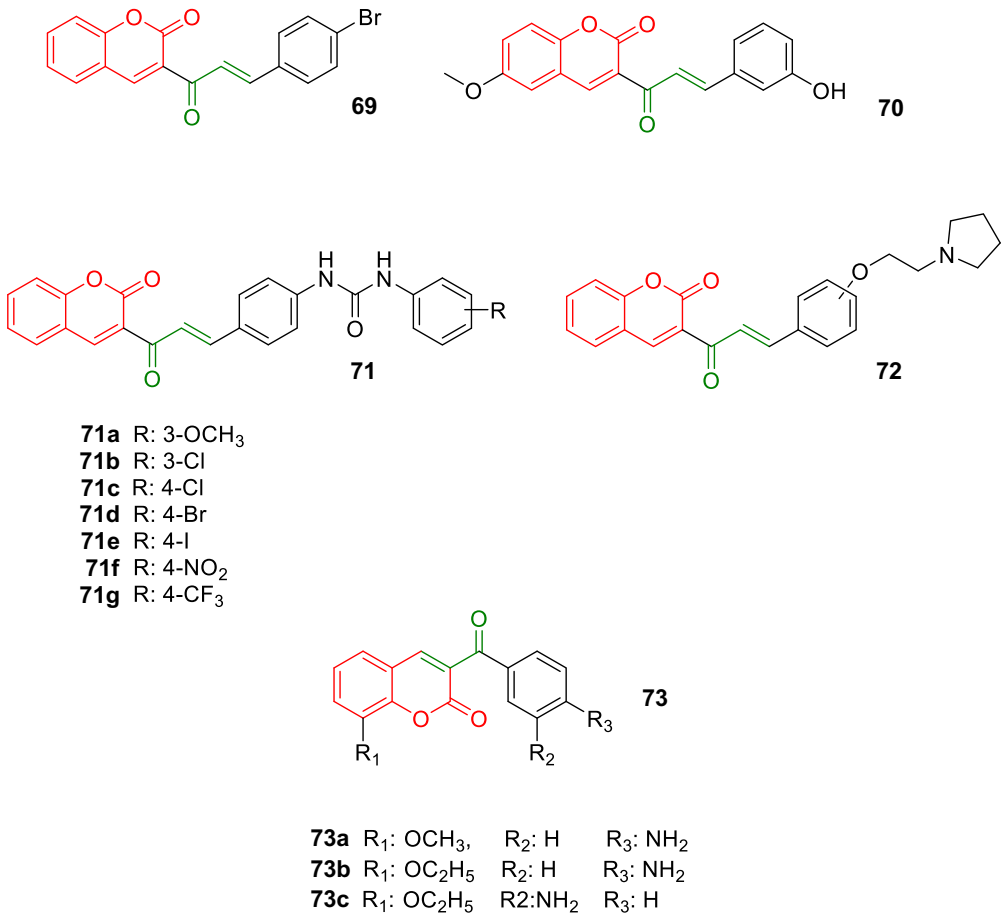


Fig. 10 Coumarin-chalcone hybrids

aromatic rings is coumarin, it is possible to synthesize highly active and broad-spectrum molecules, especially in drug discovery research [42, 221–223].

Hu et al. synthesized a series of coumarin-chalcone hybrids (Fig. 10) and tested the α-glucosidase enzyme inhibition activities of these compounds. All the synthesized compounds (IC_{50}: 24.09 ± 2.36 to 125.26 ± 1.18 μM) showed better α-glucosidase enzyme inhibitory activity than starting compound 3-acetylcoumarin (IC_{50}: 1.5 $\times 10^5$ μM). Compound **69** (IC_{50}: 24.09 ± 2.36 μM) was found to have 10 times higher activity than reference acarbose (IC_{50}: 259.90 ± 1.06 μM) [42].

Moya-Alvarado et al. synthesized 14 new C-3 substituted coumarin-chalcone hybrid compounds (Fig. 10) and investigated their monoamine oxidase B (MAO-B) inhibitory activities. While all the compounds inhibited the enzyme, molecule **70** demonstrated the highest activity, with an IC_{50} value of 0.76 ± 0.08 μM [223].

Kurt et al. synthesized a series of coumarin-chalcone hybrid compounds (Fig. 10) and investigated their anti-tumor activities against H4IIE (rat hepatoma), and CHO (Chinese hamster ovary) cell lines. Five compounds (**71b–e** and **71g)** showed better activity than Sorafenib against the H4IIE cell line. Similarly, compounds **71a, 71c**, and **71f** showed better activity than Sorafenib against the HepG2 cell line [222].

Kang et al. synthesized 36 new coumarin-chalcone derivatives (Fig. 10) and tested the AChE and BuChE enzyme inhibition activities of these compounds. Compound **72** showed the best inhibitory effect against AChE, with an $IC_{50} = 0.15 \pm 0.01$ μmol/L (Scheme 20). The selectivity of the compound in AChE inhibition is 27.4 times better than BuChE [221].

Vazquez-Rodriguez et al synthesized coumarin-chalcone hybrids (Fig. 10) with antibacterial activity against the pathogen causing tenacibaculosis in fish. Three hybrid compounds **73a–c** showed significant activity against 14 strains of *Tenacibaculosis maritimus*. Compound **73c** showed 20-fold better activity than standard enrofloxacin against *Tenacibaculosis maritimus* strains LL01 8.3.1 and LL018.3.8. Antibacterial activity was found to be better when hybrid compounds have benzoyl moiety and contain amino groups at ortho and para positions [224].

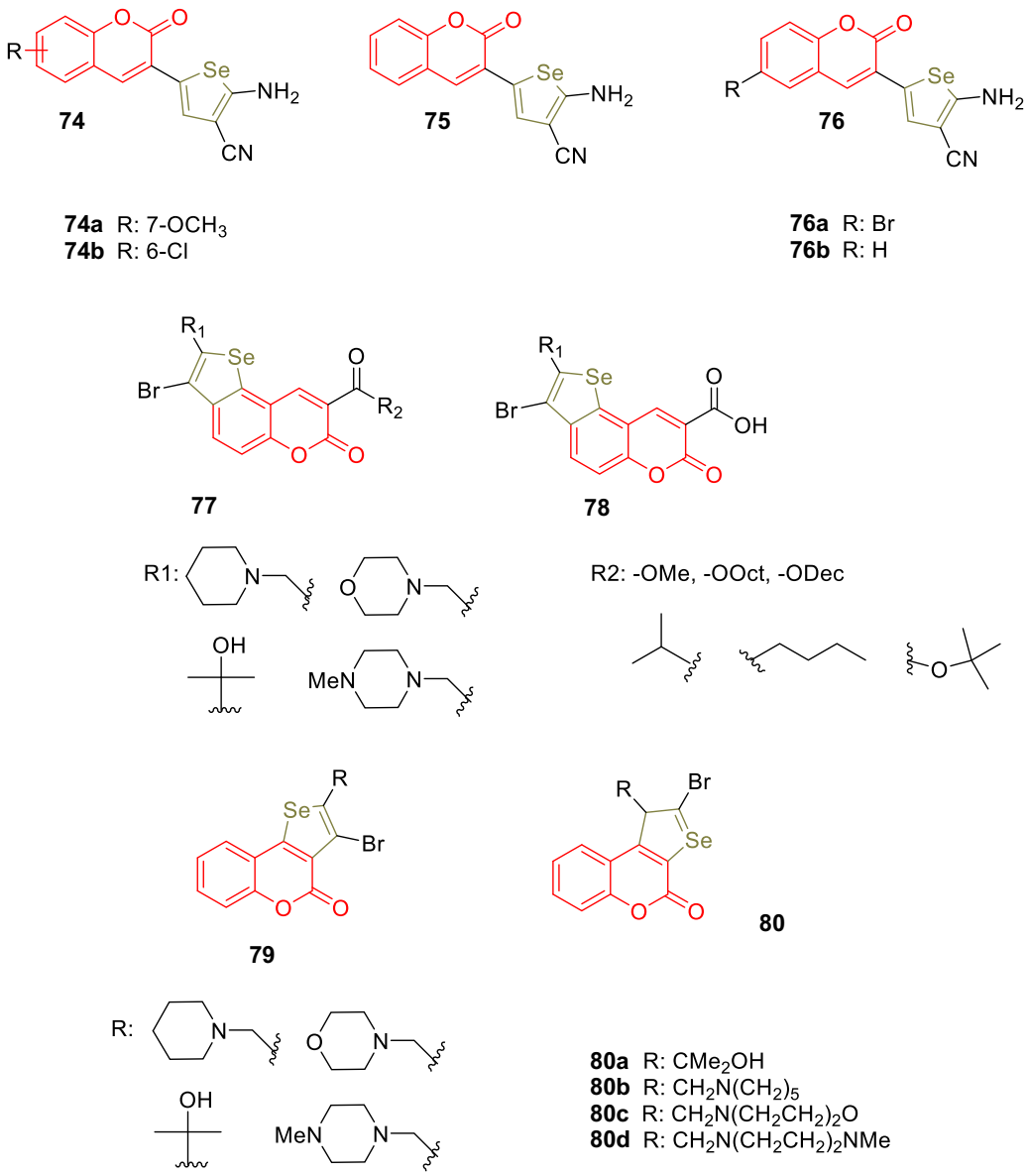


Fig. 11 Cytotoxic selenofeno [2,3-*c*]coumarin compounds

Coumarin-selenophene hybrids

Selenophene, a five-membered aromatic heterocyclic compound containing selenium, was first synthesized by Paal in 1885 [225]. Selenophene compounds have a variety of biological activities, including anticancer [226–228], anti-HIV [229], antioxidant [230], and antifungal [231] properties. Although selenium is a vital element for the body, taking more than a specific amount of it can be hazardous. The synthesis of coumarin-selenophene hybrid compounds has emerged with the studies that have been brought to the literature in the last ten years.

Yıldırım [232] et al. investigated the anti-inflammatory effect of 7 different coumarin-selenophene hybrid compounds (Fig. 11) in LPS-induced-RAW 264.7 macrophage cells. They investigated the inhibitory effects of hybrid compounds on NO, PGE2, IL-6, and TNF-α production in LPS-induced RAW 264.7 macrophage cells. The presence of a 6-substituted chlorine group or a 7-substituted methoxy group on the coumarin ring was found to increase the anti-inflammatory effect. The measurements revealed that **74a** and **74b** compounds are the most active hybrids.

Yıldırım et al. also investigated the cytotoxic and apoptotic effects of some coumarin-selenophene hybrid compounds (Fig. 11) in the DU145 prostate cancer cell line in their study in 2021. The antiproliferative effect of 4 different hybrids was evaluated. The results are found in the range of $IC_{50} = 20.0–44.0\ \mu M$. Compound **75**, which has no

substituents in the coumarin ring, has the highest potency. To elucidate the mechanism involved in the induction of apoptosis, Caspase 3, Caspase 8, and Caspase 9 levels were measured in DU145 cells that interacted with these compounds. The increase in the expression level of Caspase 3 and Caspase 9 were statistically significant after interaction with compound **75**. The increase in caspase 8 level was not statistically significant [233].

In another study reported by Erşatır et al., 8 different coumarin-selenophene hybrid compounds (Fig. 11) were synthesized from 3-acetylcoumarin derivatives and the antioxidant activities of these compounds and their antiproliferative effects on the MCF-7 cell line were investigated. Compound **76a** with –Br substituent at the C-6 position of the coumarin moiety showed the highest antiproliferative effect ($IC_{50} = 10.84\ \mu M$). The highest antioxidant activity was found in compound **76b** with 91.28% inhibition [234].

Arsenyan et al. synthesized 2*H*-selenofeno[3,2-*f*]coumarin derivatives **77**, **78** (Fig. 11) and investigated the antimetastatic effects of these compounds on melanoma and carcinoma. The compounds inhibited breast and melanoma cancer metastasis in vivo, with no side effects [235].

Domracheva et al. determined the antitumor efficacy of selenophenocoumarin **79** compounds (Fig. 11) they synthesized through the mechanism of cancer cell apoptosis. In vitro cancer cell proliferation was tested on HepG2, hepatocellular carcinoma of the mouse (MH-22A), and MCF-7 cell lines. Among the selenophenocoumarins **79**, regioisomer-bearing methylpiperazine substituent exhibited a relatively strong effect. The percentage of apoptotic cells reached 41% after 4 h, and all the cells were dead within 24 h. In addition, the antioxidant activities of the compounds were calculated and the relationship between antioxidant level and caspase 7 activity was explained [236].

Arsenyan et al. synthesized a series of novel selenofeno[2,3-*c*]coumarin compounds **80** (Fig. 11) and examined the cytotoxic and antioxidant activities of these compounds. They also determined that the compounds showed lower acute toxicity than sodium selenide against most tumor cells by performing matrix metalloproteinase enzyme inhibition tests [237].

Conclusion

This review highlighted the current advances of these coumarin derivatives showing multiple biological activities and exhibiting their functionality in the treatment of several diseases. Attractively, coumarin-based therapeutics are currently used for treating several diseases. Coumarin core can be incorporated with other bioactive compounds to give potent hybrids displaying higher therapeutic effects. We believe more coumarin-based hybrids with potent activity will emerge in the future and assist in the discovery and development of more effective therapeutic agents.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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