

Recent findings on the anticancer potential of coumarin hybrid derivatives

Mohd Akil¹, Chandra Shekhar Yadav^{1,2}, Atul Krishna³, Vijay Kumar Verma², Iqbal Azad^{*1},
Tridev Katiyar⁴, Amar Chandra Sharma⁵, Mirza Masroor Ali Beg⁶

¹Department of Chemistry, Integral University, Lucknow, Uttar Pradesh, India

²Department of Laboratory Animal Facility, CSIR-CDRI, Lucknow, Uttar Pradesh, India

³Division of Molecular Microbiology and Immunology, CSIR-CDRI, Lucknow, Uttar Pradesh, India

⁴Department of Trauma Surgery, King George Medical University, Lucknow, Uttar Pradesh, India

⁵Department of Trauma Surgery, King George Medical University, Lucknow, Uttar Pradesh, India.

⁶Faculty of Medicine, Alatau International University, Bishkek, Kyrgyzstan

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ABSTRACT

Coumarin derivatives have attracted substantial scientific interest due to their broad therapeutic potential in the field of oncology research due to their anticancer potential. Both naturally occurring and synthetically modified coumarins possess diverse pharmacological activities, and evidence highlights their strong anticancer properties. Studies emphasize the importance of understanding molecular mechanisms and structural interactions that govern the biological actions of coumarin hybrids, as these insights are crucial for optimizing their therapeutic efficacy in terms of treatment. Coumarin-based hybrid compounds demonstrate the ability to modulate multiple cellular signalling pathways critical for cancer progression, including those regulating apoptosis, angiogenesis, oxidative stress, and uncontrolled cell division. Mechanistic studies show that many coumarin hybrids effectively induce apoptosis through mitochondrial disruption, caspase activation, and modulation of pro and anti-apoptotic proteins. Additionally, several derivatives exhibit potent anti-angiogenic activity by inhibiting VEGF-mediated signaling, thereby limiting tumor vascularization and growth. Their capacity to interfere with cell cycle regulators, such as cyclins and CDKs, further contributes to their antiproliferative effects. The multitargeted nature of these molecular interactions highlights the therapeutic versatility of coumarin hybrids. Overall, the emerging preclinical evidence positions coumarin derivatives as promising lead compounds for anticancer drug development, warranting further investigation through advanced pharmacological, structural, and clinical studies.

*Corresponding author: Iqbal Azad ✉ Iqbal.azad11@outlook.com

INTRODUCTION

The unchecked proliferation of aberrant cells within the body is known as cancer (Williams and Stoeber, 2012). When the body develops cancer, aged cells do not die. Instead, they proliferate uncontrollably to give rise to aberrant new cells (Sriharikrishnaa *et al.*, 2023). The fast DNA replication caused by these aberrant cells also prevents regular cells from secreting proteins (Budzowska and Kanaar, 2009). Certain malignancies, like those that spread most frequently throughout the world among people, include lung, breast, cervical, and prostate cancers (Mattiuzzi and Lippi, 2019). Millions of people worldwide lose their lives to cancer each year. In 2020, there were 10 million cancer-related deaths worldwide and 19.3 million cases, according to the most recent IARC reports (Ghufran *et al.*, 2023). Furthermore, the WHO's main sheet said that, in 2018, cancer claimed around 9.6 million lives worldwide, accounting for one in every six deaths (Zafar *et al.*, 2019). According to a recent assessment, lung cancer is responsible for 1.8 million deaths worldwide, while breast cancer accounts for 0.6 million (Tiwari, 2023). Out of all cancer types, female breast cancer is the most common cause of death for women, with one in four of them afflicted by this fatal illness (Akram *et al.*, 2017). According to depressing cancer statistics, during the next 20 years, there is a projected rise in the global cancer burden from 19.3 to 28.4 million yearly instances (Bizuyehu *et al.*, 2024). Although they may cause harm to normal cells, conventional therapies, including surgery, chemotherapy, and radiation therapy, are mostly available for treating cancer (Bizuyehu *et al.*, 2024). Conventional cancer therapies, including immunotherapy, radiation, chemotherapy, and surgery, are the most widely used therapeutic techniques (Yagawa *et al.*, 2017).

Conventional chemotherapeutic drugs randomly disperse throughout the body, impacting both nearby normal cells and malignant ones (Kaur *et al.*, 2023).

In the kingdom of plants, oxygenated heterocyclic polyphenolic compounds, or coumarins, are

extensively distributed (Matos *et al.*, 2017). As secondary metabolites in bacteria, fungi, and plants, about 1300 chemotypes have been identified (Stadler and Hellwig, 2004). Plants' roots (*Ferulago campestris*), leaves (*Murraya paniculata*), fruits (*Aegle marmelos*), and seeds (tonka beans) all contain its derivatives (Awaad, 2018). The fused aromatic oxygen-heterocyclic nucleus can change how it interacts with receptors, which alters its electron density and affects its chemical, physical, and biological properties (Venkatachalam and Kumaravel, 2019). This flexibility makes it an important tool for pharmacological screening of pharmaceuticals (Cozzini *et al.*, 2008). These scaffolds are intriguing in the way that cancer treatments work. On various cancer cells, the coumarin derivatives can cause carbonic anhydrase inhibition, telomerase suppression, angiogenesis inhibition, and cell cycle arrest (Berrino, 2020). The substitution patterns inside their nucleus determine the medicinal uses and pharmacological characteristics of coumarins (Hussain *et al.*, 2019) (Fig. 1).

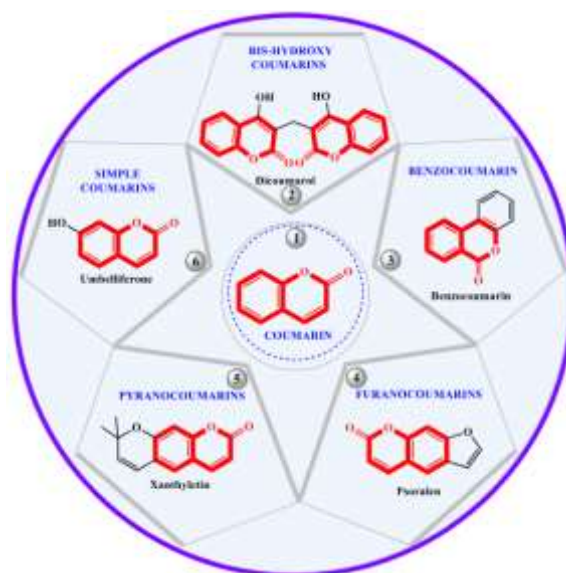


Fig. 1. Classification of coumarins and its structures

Recent years have seen reports on the finding of new anticancer compounds and their thorough structure-activity relationship (SAR) investigations (Keri *et al.*, 2015). In addition, several studies provided the most recent details regarding the formation of efficacious medication equivalents. The most recent promising

anticancer compounds' mode of action and SAR are extensively studied (Kontogiorgis *et al.*, 2020). On the other hand, the current work aims to provide updated information on several coumarin-based anticancer scaffolds that have been reported in the recent five years (Stefanachi *et al.*, 2018). A variety of studies on natural and synthetic coumarin derivatives that may help fight cancer, along with their structure-activity relationship (SAR) related to the coumarin core, was also discussed in detail (Kostova, 2011).

Various synthesis reactions of the coumarin and its derivatives

The French term "coumarou" for the Tonka bean is where the word "coumarin" originates, and it was first isolated as a natural product in 1820 (Vogel, 1820). Plants widely distribute it and its derivatives in their fruits, seeds, roots, and stems (Venugopala *et al.*, 2013). In medicinal chemistry, benzopyran, a bicyclic heterocyclic system, is a privileged structure (Murray *et al.*, 1982). Several natural compounds include benzopyran units (Borges *et al.*, 2005). Because of their polar nature, coumarins typically reside in a free state in plants where they absorb UV radiation and glow blue. Coumarin derivatives are frequently utilised in the cosmetic industry to enhance scent in addition to having an excellent pharmacological profile (Venugopala *et al.*, 2013). Extended coupling in coumarin rings with electron-rich and charge-transfer properties makes this scaffold capable of interacting with molecules and ions (Stefanachi *et al.*, 2018). Its chemical structure is formed by the fusion of the benzene ring and pyran-2-one (Kontogiorgis *et al.*, 2020). Thus, it has a dual fuse ring system, where oxygen occupies position 1 and carbonyl carbon takes position 2. Therefore, its scientific name is 2H-1-benzopyran-2-one (Kostova, 2011). Using established reaction methods with different types of catalysts, both those without metals and those with metals including (Sashidhara *et al.*, 2010): Baylis-Hillman reaction, Claisen condensation, Heck-lactonization, Knoevenagel condensation, Kostanecki-Robinson coupling, Michael addition, Pechmann condensation, Perkin reaction, Reformatsky reaction, and Wittig reaction (Rohini *et al.*, 2015) Fig. 2.

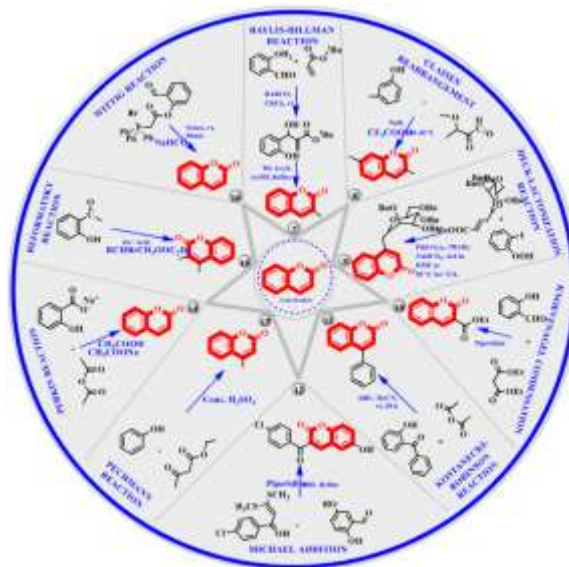


Fig. 2. Various name reactions for the synthesis of coumarin

Here, we explain various reaction and mechanism of several coumarin derivatives synthesized through various known reaction techniques including: A carbon-carbon bond is formed when an activated alkene and an electrophile, like an aldehyde, combine to generate highly functionalized adducts. This reaction is called the Baylis-Hillman (BH) reaction or the Morita-Baylis-Hillman (MBH) reaction. A Michael addition, quenching of the zwitterionic intermediate, and an elimination step to renew the catalyst are all part of the reaction, which is aided by a nucleophilic catalyst, usually a tertiary amine (such as ABCO) or a phosphine (Basavaiah *et al.*, 2012). A powerful base catalyzes the creation of a new carbon-carbon bond between two ester molecules (or an ester and another carbonyl chemical) in an organic process known as the Claisen condensation, which results in the production of a beta-keto ester or a beta-diketone. A leaving group is expelled after an ester enolate attacks the carbonyl carbon of another ester. Since the beta-keto ester product is highly acidic and is deprotonated by the strong base, the reaction is forced to completion overall, making the final step irreversible (Carey and Sundberg, 2007). The Heck reaction, also known as the Mizoroki-Heck reaction, is a cross-coupling reaction that is catalyzed by palladium and creates a carbon-carbon bond between

an alkene and an aryl or vinyl halide (or triflate). A substituted alkene is produced by this reaction, which also involves oxidative addition, alkene insertion, beta-hydride elimination, and reductive elimination steps in a palladium catalytic cycle. Richard F. Heck was awarded the 2010 Nobel Prize in Chemistry for his work on the Heck reaction, which is an essential technique in organic synthesis for producing complicated compounds (Heck, 1982). An active methylene molecule condenses with an aldehyde or ketone in the presence of a weak base to create an α , β -unsaturated compound in the Knoevenagel reaction, an organic chemical process. Similar to an aldol condensation, it is a process that forms carbon-carbon bonds but makes use of active methylene molecules such as cyanoacetates or malonic esters. The reaction is useful for creating compounds with a variety of uses, such as medications, polymers, and fragrances (Jones, 2014) (Fig. 3).

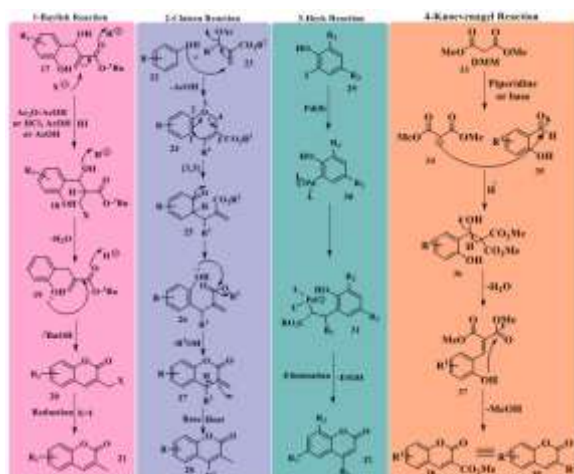


Fig. 3. Mechanism of Bayliss, Claisen, Heck and Knoevengel rection

Through a multi-step mechanism that includes O-acylation of the phenolic group, intramolecular aldol condensation of the resultant enol ester to form a hydroxydihydrochromone intermediate, and subsequent dehydration to yield the final chromone or coumarin product, the Kostanecki–Robinson reaction converts o-hydroxyaryl ketones, aliphatic acid anhydrides, and the corresponding acid salt into coumarins or chromones (Kostanecki and Robinson, 1904). A base deprotonates a Michael donor to create

a nucleophilic carbanion in the Michael addition process. Through 1,4-conjugate addition, this carbanion then attacks the electrophilic beta-carbon of a Michael acceptor (an α , β -unsaturated carbonyl molecule), creating a new enolate intermediate and a new carbon-carbon bond. The final product is obtained by protonating the new enolate, usually with water during workup, to complete the reaction (Michael, 1887). In the Pechmann reaction, a β -keto ester is transesterified with a phenol by an acid catalyst, then the ring is formed by electrophilic aromatic substitution, and the coumarin product is obtained by dehydration. The general process leads to the creation of the distinctive benzopyrone structure of coumarins, even if the precise order of the transesterification and electrophilic aromatic substitution stages might change based on the particular chemicals and catalyst utilized (Pechmann and Duisberg, 1884) (Fig. 4).

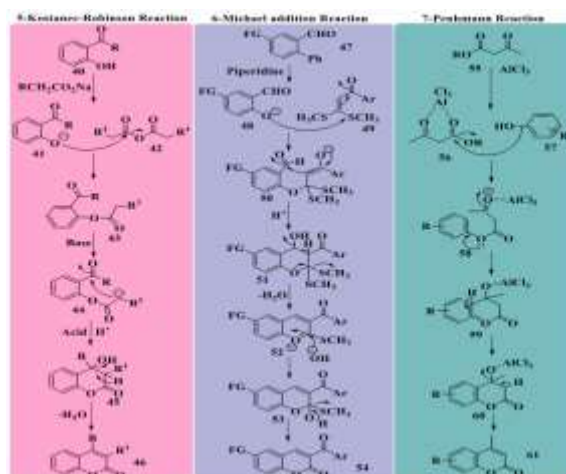


Fig. 4. Mechanism of Kostanec-Robinson, Michael addition and Penhmann rection

A weak base abstracts an alpha-hydrogen from an acid anhydride to create a nucleophilic carbanion, which is the first step in the Perkin reaction process. In a condensation that resembles an aldol, this carbanion then targets the electrophilic carbonyl carbon of an aromatic aldehyde. An acetyl group transfer is facilitated by a cyclic intermediate, resulting in a more stable intermediate that eliminates a carboxylate ion. Ultimately, an α , β -unsaturated aromatic acid is produced upon

acidification (Perkin, 1868). Three crucial phases are involved in the Reformatsky response mechanism: The first is oxidative addition, in which an organozinc intermediate (Reformatsky enolate) is created when activated zinc metal enters the C-halogen link of an α -haloester. Second, this intermediate is nucleophilically added to the carbonyl carbon of a ketone or aldehyde to generate a zinc alkoxide and a six-membered ring transition state. Ultimately, the alkoxide is protonated by an acid workup, producing the β -hydroxy ester product (Reformatsky, 1887). A phosphorus ylide (Wittig reagent) attacks a carbonyl molecule (aldehyde or ketone) via the Wittig reaction process, forming an oxaphosphetane, a four-membered ring intermediate. The strong P=O connection that forms is what propels this unstable ring's quick breakdown, which produces an alkene and triphenylphosphine oxide.

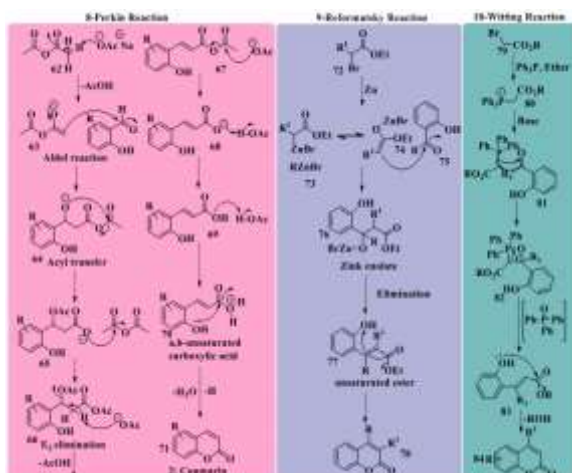


Fig. 5. Mechanism of Perkin, Reformatsky, Wittig reaction

The oxaphosphetane can be formed immediately by a concerted [2+2] cycloaddition or by a two-step process that involves a charge-separated intermediate known as a betaine (Wittig and Geissler, 1953) (Fig. 5).

The anticancer properties of coumarin

Coumarin-triazole hybrids

Sinha Sohini *et al.* (2016), Because they are frequently used as scaffolds for anticancer treatments, coumarins with the triazole moiety have recently drawn the interest of researchers (Fig. 6). The triazole moiety increases

enhanced solubility and boosts the enzyme and receptor binding affinities. The cytotoxic efficacy against HeLa and MCF-7 cancer cell lines was evaluated using fluorescent probes based on triazolyl-coumarin, which showed promising biological activity. Compounds 85 and 86 were determined to be the most promising scaffolds (MTT cytotoxicity). Both diagnosis and treatment relied on these unique scaffolds (Sinha *et al.*, 2016). Zengin *et al.* (2019) IR, NMR, and mass spectra were used to synthesize and analyze novel twenty-seven compounds in three series, coumarin-based aldehydes substance 87, and coumarin-sulfonamide-based target molecules 14. The capacity of each chemical to inhibit the CA I, CA II, CA IX, and CA XII isoforms was examined. 4-(((2-((1-(3-((2-oxo-2H-chromen-7-yl)oxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)amino)methyl)benzenesulfonamide, compound 88, with a K_i of 45.5 nM, showed the highest hCA IX inhibition.

Furthermore, it was shown that 88 was effective in selectively preventing the growth of cancer cells (IC_{50} 17.01 \pm 1.35 mM for HT-29, IC_{50} 118.73 \pm 1.19 mM for HEK293T) (Zengint *et al.*, 2019).

Zengin *et al.* (2019) A series of novel bis-coumarin derivatives containing triazole moiety as a linker between the alkyl chains was synthesized and their inhibitory activity against the human carbonic anhydrase (hCA) isoforms I, II, IX and XII were evaluated. In addition, cytotoxic effects of the synthesized compounds on renal adenocarcinoma (769P), hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MDA-MB-231) cell lines were examined. In contrast to the tumor-associated isoforms hCA IX and XII, which were inhibited in the high nanomolar range, the hCA I and II isoforms were inhibited in the micromolar range. 4-methyl-7-((1-(12-((2-oxo-2H-chromen-7-yl)oxy)dodecyl)-1H-1,2,3-triazol-4-yl)methoxy)-2H-chromen-2-one 90 exhibited the most potent inhibitory effect against hCA IX, with a K_i of 144.6 nM, and 4-methyl-7-((1-(10-((2-oxo-2H-chromen-7-yl)oxy)decyl)(4-yl)methoxy)-1H-1,2,3-triazol- With a K_i of 71.5 nM, 2H-chromen-2-one 89 showed the highest hCA XII. In accordance with multiple studies, triazole

nucleobases have synergistic effects and improve solubility (Zengin *et al.*, 2019).

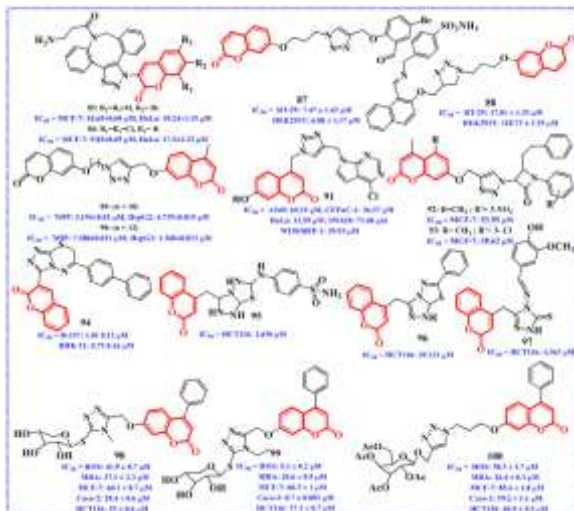


Fig. 6. Structure of important coumarin-triazole hybrids

Bistrović *et al.* (2018) synthesized new halogenated purines and pseudopurines with various aryl-substituted 1,2,3-triazoles. While 3-deazapurine and N-9 alkylated purine required p-(trifluoromethyl)-substituted 1,2,3-triazole for significant but non-specific action on pancreatic cancer cells (CFPAC), the p-fluorophenyl-substituted derivative of 7-deazapurine demonstrated selective cytostatic activity against metastatic colon cancer cells SW620. The most pronounced inhibitory effect against non-small-cell lung cancer A549 was observed with 1-(p-chlorophenyl)-1,2,3-triazole-tagged benzimidazole, which acted in the nanomolar range. This compound targeted extracellular and plasma membrane-associated molecular pathways regulated by GPLD1 and growth-factor receptors PDGFR and IGF-1R, resulting in inhibition of cell proliferation and induction of apoptosis mediated by NF- κ B and p38 MAP kinase. Further optimization may lead to a novel drug candidate effective against lung cancer. Compared with the positive control cisplatin, compound 91 showed significant cytotoxicity by selectively targeting apoptosis through Gal-1 protein regulation. Additionally, coumarin-tagged β -lactam-triazole hybrids enhanced DNA replication and reduced DNA damage (Bistrović *et al.*, 2018).

Dhawan *et al.* (2019) developed several coumarin-tagged β -lactam-triazole hybrids and evaluated their cytotoxic potential against HEK-293 (normal cells), MDA-MB-231, MCF-7, and A549 cancer cell lines. Compounds 92 and 93 showed strong cytotoxic activity against MCF-7 cells, with IC₅₀ values of 53.55 μ M and 58.62 μ M, respectively, while showing negligible toxicity toward HEK-293 normal cells. Structure-activity relationship (SAR) studies revealed that nitro and chloro substituents at the C-3 position of the phenyl ring significantly enhanced anticancer activity (Dhawan *et al.*, 2019).

Aliya *et al.* (2016) designed and synthesized a series of coumarin-triazolothiadiazine hybrid molecules using the molecular hybridization strategy. Cyclocondensation reactions involving bromoacetophenones and coumarinyl-4-amino-1,2,4-triazole yielded the target compounds in good yields. Structural characterization was performed using spectroscopic techniques. The compounds were evaluated against lung carcinoma (H-157) and kidney fibroblast (BHK-21) cell lines. Compound 94 exhibited the strongest cytotoxic activity against H-157 cells (IC₅₀ = 1.01 \pm 0.12 mM) and also acted as a promising ALP inhibitor, showing better cytotoxic and apoptotic effects compared with cisplatin (Aliya *et al.*, 2016).

Al-Wahaibi *et al.* (2018) performed docking studies on triazole-coumarin hybrids, suggesting a potential interaction with CDK2 and a measurable cytotoxicity profile. Compounds 95, 96, and 97 showed the highest cytotoxic activity comparable to the reference drug, attributed to strong hydrogen bonding and favorable electrostatic interactions (Al-Wahaibi *et al.*, 2018).

El-Sayed *et al.* (2022) reported newly synthesized 1,2,3-triazole-coumarin glycosyl conjugates and 1,2,4-triazole-thioglycosidic analogues. Biological evaluation against HOS, MDA-MB-231, MCF-7, Caco-2, and HCT-116 cancer cell lines demonstrated that coumarin-triazole-glycoside hybrids 98, 99, and 100 exhibited strong anticancer activity particularly

against MCF-7, while compound 16 showed significant potency against HOS and MDA human cancer cells (El-Sayed *et al.*, 2022).

Mentese *et al.* (2020) this study involved the design and synthesis of a new series of unique coumarin derivatives with a triazole ring. The newly created compounds were tested for their *in vitro* anticancer activity against the cancer cell lines CRL5807, CRL5826, MDA-MB231, HTB177, PC-3, PANC-1, and CCD34Lu, as well as a healthy cell line.

Compounds 101 and 102 demonstrated notable cytotoxicity against all cancer cell lines and their most impacted cells, MDA-MB231 and CRL5807, respectively, out of all the chemicals that were evaluated. Compared to the common doxorubicin medication, compounds 101 and 102 demonstrated stronger antitumor inhibitory actions against the CCD34Lu cell line (Mentese *et al.*, 2020).

Vagish *et al.* (2021) Using microwave irradiation, this study synthesized a series of α,β -saturated carbonyl linked coumarin–triazole hybrids. The target compounds were created in four stages, beginning with substituted aromatic primary amines and 4-hydroxycoumarin. The anticancer potential of these coumarin–triazole hybrids was evaluated *in vitro* against PC-3 and DU-145 prostate cancer cell lines.

The results demonstrated that compound 103 exhibited the strongest activity against both PC-3 and DU-145 cell lines (Vagish *et al.*, 2021).

Pavić *et al.* (2021) synthesized harmirins using Cu(I)-catalyzed azide–alkyne cycloaddition, forming a 1H-1,2,3-triazole ring from the corresponding alkynes and azides under mild conditions. The antiproliferative activities were tested *in vitro* against four human cancer cell lines (MCF-7, HCT116, SW620, HepG2) and one normal human cell line (HEK293T).

Compounds 104 and 105, substituted at C-3 and O-7 of the β -carboline core and carrying a methyl group at

position 6 of the coumarin ring ($SI > 7.2$), showed the highest selectivity. The most significant cytotoxic effects were observed against MCF-7 and HCT116 cell lines with IC_{50} values in the single-digit micromolar range. Further investigation revealed that harmirin 105 localizes primarily in the cytoplasm (Pavić *et al.*, 2021).

Mallikarjun *et al.* (2023) synthesized hybrid heterocyclic systems via 1,3-dipolar cycloaddition and aldol condensation, combining two or more pharmacophores in a single structure. The compounds were evaluated *in vitro* against several cancer cell lines, including HT1080 (fibrosarcoma), HeLa (cervical carcinoma), PANC-1 (pancreatic cancer), A549 (lung cancer), and HEK293 (human embryonic kidney cells).

Among the synthesized derivatives, para-nitrile chalcone compound 106 exhibited notable IC_{50} values ranging from 3.1 to 7.02 $\mu\text{g/ml}$ (Mallikarjun *et al.*, 2023).

Augsten *et al.* (2023) investigated the cytotoxicity of coumarin–triazole hybrids against various cancer cell lines including A549 (lung), HepG2 (liver), J774A1 (mouse sarcoma macrophage), MCF7 (breast), OVACAR (ovarian), RAW (murine leukemia macrophage), and SiHa (uterine carcinoma). Toxicity was also assessed in 3T3 normal fibroblast cells.

Four hybrids from the in-house library showed promising pharmacokinetic predictions. All demonstrated cytotoxicity against MCF7 breast cancer cells with IC_{50} values ranging from 2.66 to 10.08 μM , which were significantly lower than that of cisplatin (45.33 μM). The most active molecule was compound 107 (Augsten *et al.*, 2023).

Arvas *et al.* (2024) designed and synthesized six novel coumarin–triazole hybrids. The anticancer activity of the most promising compound was tested against HeLa (human cervical adenocarcinoma) and MCF-7 breast cancer cell lines. Among the synthesized derivatives, compound 108, a phenyl-substituted

coumarin derivative, showed the lowest IC₅₀ value and the highest cytotoxic activity. To enhance drug delivery, poly (lactic-co-glycolic acid) nanoparticles (PLGA NPs) containing compound 108 were developed using the emulsifying solvent evaporation method.

The nanoparticles had an average size of 225.90 ± 2.96 nm, zeta potential of 16.90 ± 0.85 mV, and drug loading capacity of 4.12 ± 0.90%. Characterization was performed using FT-IR, UV-Vis spectroscopy, Raman spectroscopy, X-ray diffraction, thermogravimetric analysis, and scanning electron microscopy. The nanoparticles exhibited an initial burst release within the first 6 hours, followed by a controlled release over approximately one month, achieving total drug release of 50% at pH 7.4 and 85% at pH 5.5 (Arvas *et al.*, 2024).

The primary synthesis technique was the copper-catalyzed cycloaddition of 3-propynyl modified 2-oxo-2H-chromene-3-carboxylate with several azides and diazide. The traditional MTT assay was used to assess the novel series of 1,2,3-triazolyl-modified coumarins' *in vitro* anticancer efficacy against human cancer cell lines. Normal epithelial VERO cells were not harmed by any of the substances. Coumarin derivatives with a 4-carboxyphenyl substituent at the N1-position of the triazole ring 109 demonstrated superior activity in the series on cervical cancer cells (C33 A, CaSki, and HeLa); breast carcinoma cells MCF-7; and prostate cancer cells DU-145, out of all the 3-(1,2,3-triazolylmethoxycarbonyl) coumarins that were synthesized (Kishkentayeva *et al.*, 2025). In Rukhsana Kausar *et al.* (2024), we synthesized a wide range of coumarin–triazole hybrids, and we used appropriate analytical methods to describe these compounds. Our research goes beyond the synthetic endeavor to investigate these chemicals' potential for medicinal use. After carefully evaluating the produced compounds against the tyrosinase enzyme *in vitro*, these coumarin derivatives showed good IC₅₀ values between 0.339 ± 0.25 μM and 14.06 ± 0.92 μM. With IC₅₀ values of 0.339 ± 0.25 μM and 3.148 ± 0.23 μM, respectively, the most active of the six compounds in

the synthesized chemical library had exceptional anti-tyrosinase potential.

These compounds were also shown to be more potent than normal ascorbic acid (IC₅₀ = 11.5 ± 1.00). Additionally, to validate our experimental results, an *in silico* modeling investigation was conducted to identify the primary interactions of these chemicals with the tyrosinase protein (PDB ID: 2Y9X). The produced coumarin derivatives and their anti-tyrosinase activity showed a strong association in the quantitative SAR investigations. The experimental findings were confirmed by the docking studies, and ligand 110 demonstrated a strong contact with the tyrosinase core residues (Kausar *et al.*, 2024) (Fig. 7).

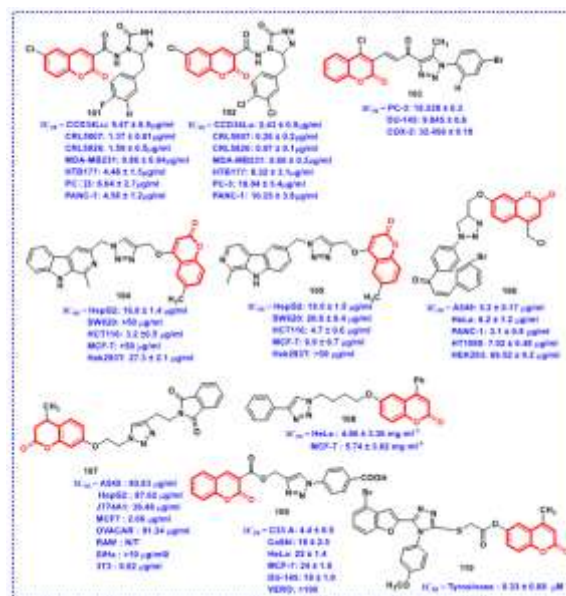


Fig. 7. Structure of coumarin-triazole hybrids

Oxazoles/Thiazoles coumarin

In 2019, Vaarla and colleagues designed and developed effective anti-cancer medicines. They conducted molecular docking studies, synthesis, and anti-cancer activity of new 3-(2-(5-amino-3-aryl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-ones. Evaluated against five human cancer cell lines [L1210, CEM, DU-145, HeLa, and MCF-7] to determine their anti-cancer potential. While 6,8-Di tert butyl substituted compound 112 had encouraging activity against DU-145 and MCF-7 cancer cell lines with IC₅₀ values of 7 ± 1 and 9 ± 6 μM, 6-diethylamino

substituted compound 111 demonstrated exceptional potency against tested cancer cell lines. To determine the most likely binding site interactions of the drugs with the human epidermal growth factor receptor (EGFR), a molecular docking analysis was conducted (Vaarla *et al.*, 2019).

Gabr *et al.* (2017) A brand-new class of derivatives of thiazolylcoumarins was created. A molecular hybridization technique, which combines the thiazole and coumarin pharmacophores, was adopted in the planned strategy. The anticancer efficacy of the novel hybrid compounds against kidney fibroblast (COS 7) and cervical (Hela) cancer cells was evaluated in vitro. With regard to the Hela cell line, compounds 113, 114, 115, and 116 showed encouraging activity. Furthermore, it was shown that the most active candidates for the COS-7 cell line were 114 and 116. The four active analogs—113, 114, 115, and 116—were tested for both in vitro cytotoxicity toward W138 normal cells and in vivo anticancer activity over EAC cells in mice. To determine which pharmacophoric characteristics of the synthesized compounds matched those of trichostatin A, 3D pharmacophore analysis was used in this investigation. According to computer silico studies, the substances under investigation satisfy the requirements for optimal oral absorption without any anticipated toxicity risks (Gabr *et al.*, 2017).

In 2018, Ayati and colleagues synthesized a compound based on the chalcone-type 4-amino-5-cinnamoylthiazole scaffold and evaluated its antioxidant and anticancer properties in vitro. Specifically, the 2-thiomorpholinthiazole derivative 117 showed good cytotoxic effects against the investigated cell lines MCF-7, HepG2, and SW480, with IC₅₀ values ranging from 7.5 to 16.9 mg/ml. This chemical causes G₁-phase arrest in the cell cycle and apoptotic cell death in MCF-7 cells, according to additional research using flow cytometric analysis. Furthermore, as determined by the DPPH and FRAP tests, the majority of compounds possessed inherent potential for ferric-reducing power and radical scavenging activity (Ayati *et al.*, 2018).

Hersi *et al.*, 2020 The prevalence of diseases linked to obesity, such as diabetes, heart disease, and various malignancies, highlights the need of dietary regulation in both prevention and treatment. However, most people find it difficult to maintain long-term nutritional management. An alternate strategy to influence the energy machinery of cancer cells is the use of energy restriction mimetic agents (ERMAs), which has shown promise as a cancer treatment method. Since the survival rate of rapidly proliferating tumor cells is highly dependent on the robust availability of energy, ERMAs reduce the high energy requirement of these cells. The discovered chemotypes were able to raise the amount of ROS in cancer cells and prevent glucose uptake. The half-maximal inhibitory concentration (IC₅₀) of HT-29 and HCT116 ranges from 0.25 to 0.38 μ M. The capacity of these lead therapeutic candidates to cause cancer cell death through, at least partially, energy restriction was demonstrated by additional biological analyses of 118 and 119 employing Western blotting, caspase activity, glucose uptake, ROS generation, and NADPH/NADP ratios. Additionally, the evaluation of 118 and 119 synergistic action with cisplatin produced encouraging results. By focusing on the cellular energy mechanism in cancer cells, the lead compounds 118 and 119 demonstrate the substantial potential of these compounds as possible anticancer medicines (Hersi *et al.*, 2020).

In 2018, Lingaraju *et al.* Human melanoma cancer cell line (UACC 903) and fibroblast normal cell line (FF2441) were used to test the cytotoxic potential of a number of novel coumarin-tethered isoxazolines. With IC₅₀ values of 10.5 μ M, respectively, preliminary findings showed that several of these coumarin-tethered isoxazolines 120 shown a substantial antiproliferative action against human melanoma carcinoma (UACC 903). However, at the studied concentration, chemical 120 did not harm healthy human cells. Additionally, we have selected compound 120 to test its anticancer and antiangiogenic qualities in an in vivo Ehrlich Ascites Carcinoma animal model. Cell viability, body weight, ascites volume, and the development of neovasculature, including tumor volume reduction, were all markedly

decreased by our lead chemical. The current investigation shows the potential for becoming a powerful anticancer medication in the near future (Lingaraju *et al.*, 2018).

Kakkar *et al.* (2018) Compounds 121 and 122 demonstrated encouraging efficacy against specific bacteria species, according to the conducted antimicrobial activity. molecule 122 was the most effective molecule against HCT116 ($IC_{50} = 71.8 \mu M$) according to antiproliferative screening, while compound 121 was the most effective compound against MCF7 ($IC_{50} = 74.1 \mu M$).

Additionally, a molecular docking study was conducted to determine how active oxazole compounds interacted with the CDK8 (HCT116) and ER- α (MCF7) proteins. The results showed that compounds 121 and 122 had a good dock score, were more potent within the ATP binding pocket, and could serve as a guide for logical anticancer drug design (Kakkar *et al.*, 2018).

In 2018, Dhawan *et al.* A new collection of 1,3,4-oxadiazole conjugates with coumarin tags was created, and its antiproliferative properties against the MDA-MB-231 and MCF-7 breast cancer cell lines were assessed. Compound 123 was the most effective chemical against the MCF-7 cell line, according to the assessment experiments, with an IC_{50} value of less than $5 \mu M$. Remarkably, compounds 123 exhibited a similar pattern in ER-negative (ER-negative) cells compared to ER-positive (ER+) cells, with a lower inhibitory dose ($IC_{50} = 7.07 \mu M$). Studies of the structure-activity relationship (SAR) showed that conjugates with benzyl moieties 123 exhibited higher activities than their alkyl counterparts.

Tamoxifen was 1.4 times less effective against the MCF-7 cell line than the most potent chemical, 123. Docking investigations corroborated these findings, showing that the sulfone unit linked to the substituted benzyl moiety in the produced conjugates' pharmacophores is what gives them a higher binding affinity (Dhawan *et al.*, 2018).

Batran *et al.* (2023) A number of 4-hydroxycoumarin derivatives based on thiazolines and thiazolidinones were created utilizing both traditional synthesis methods and microwave-assisted approaches. The cytotoxic effect of the novel compounds was assessed against three human cancer cell lines MCF-7, HCT-116, and HepG2—as well as one normal human cell line (BJ-1). The ability of the potential anti-proliferative drugs 124 to inhibit PI3K/mTOR and EGFR was evaluated. The compound with the strongest inhibitory activity against the signalling pathway was 124. We looked studied derivative 6a's cell cycle arrest potential and apoptotic effect. Additionally, the prospective compound's physicochemical characteristics, pharmacokinetic parameters, and molecular docking were examined (Batran *et al.*, 2023) (Fig. 8).

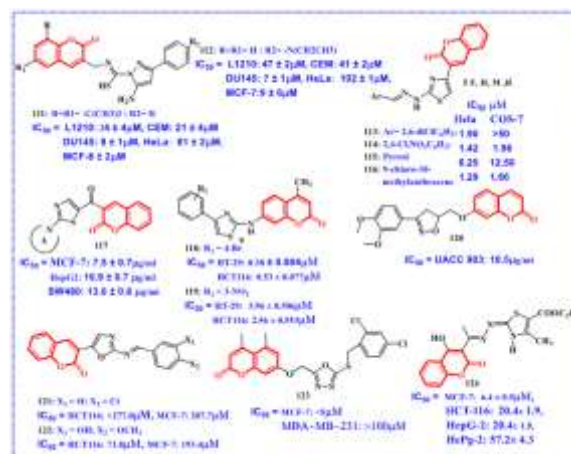


Fig. 8. Structures of important coumarin-thiazole/oxazole Hybrids-I

Coumarin pyrazoles/Furans

Mohamed *et al.* 2019 *in vitro* tests were conducted to evaluate the anticancer potential of newly synthesized thiazolylpyrazolyl coumarin derivatives against five distinct human cell lines: breast MCF-7, lung A549, prostate PC3, liver HepG2, and normal melanocyte HFB4. Compared to the reference medication doxorubicin ($IC_{50} = 6.73 \mu M$), breast cancer showed increased sensitivity to compounds 125, 126, 127, 128 and 129, with IC_{50} values ranging from 5.41 to $10.75 \mu M$. Furthermore, no discernible toxicity was shown to HFB4 in normal cells. Furthermore, *in vitro* tests of the promising cytotoxic compounds' ability to

inhibit VEGFR-2 in the human breast cancer MCF-7 cell line revealed that compounds 125, 126, 127, 128 and 129 were strong inhibitors at low micromolar concentrations ($IC_{50} = 0.034\text{--}0.582\mu\text{M}$) in comparison to the reference medication, sorafenib ($IC_{50} = 0.019\mu\text{M}$). To identify the molecular processes governing the metastasis of breast cancer, numerous theoretical and experimental investigations were conducted. Because of its strong VEGFR-2 inhibition and outstanding cytotoxic activity against MCF-7, the promising chemical 129 was evaluated for its mechanistic efficacy in cell cycle progression, apoptotic induction, and gene regulation. Compound 129 promoted cell growth halt at G2/M phase and raised the percentage of cells at pre-G1 phase that stimulate MCF-7 cell apoptosis, according to flow cytometric study. Additionally, the real-time PCR assay demonstrated that compound 129 increased the expression of the p53 gene and the Bax/Bcl-2 ratio, confirming the compound's mechanism of action. Furthermore, compound 129 efficiently. Compound 129 may be regarded as a potent apoptosis modulator and a good starting point for the creation of novel anti-breast cancer drugs in the future (Mohamed *et al.*, 2019).

Tangella *et al.* (2017) A one-pot, three-component, high-yielding procedure has been established for the selective synthesis of trans-2,3-dihydrofuro[3,2-c]coumarins and trans-1,2-dihydrobenzo[h]furo[3,2-c]quinolinones. This procedure involves intramolecular SN_2 cyclization, a Michael addition, and a domino Knoevenagel condensation. The in vitro cytotoxic efficacy of each produced chemical against specific human cancer cell lines has been assessed. It's interesting to note that in all examined cell lines, the majority of the compounds showed significant cytotoxicity with IC_{50} values less than $10\mu\text{M}$. Furthermore, in comparison to other evaluated cell lines, these compounds showed greater effectiveness against MCF-7 (breast cancer) cell lines. All four of the investigated cell lines were significantly cytotoxically affected by compounds 130 and 131. According to cytotoxicity experiments, the produced chemicals' toxicity was significantly greater in tumor

cells than in healthy cells. According to research on the structure–activity connection, these compounds' activating groups tended to increase activity more than their deactivating groups. We conducted binding assays using calf thymus DNA (CT-DNA) to gain a better understanding of these drugs' mechanisms of action. These chemicals may have an affinity for binding DNA through intercalation, according to both molecular docking and biophysical investigations. They have the capacity to cleave pBR322 plasmid DNA strands in a dose and time dependent manner, as demonstrated by photocleavage investigations. Furthermore, chemicals 130 and 131 demonstrated notable inhibitory effects on topoisomerase II (Tangella *et al.*, 2017) (Fig. 9).



Fig. 9. Structures of important coumarin pyrazole/furan hybrids

Coumarin benzamides and Sulfonamides

Bondock *et al.* (2023) in order to create potent and innovative anticancer drugs, new thiadiazole sulphonamide compounds were created as human carbonic anhydrase inhibitors (hCAIs). The target compounds were designed using the tail modification strategy, and they were synthesized using a two-step process that began with 5-acetyl-3-N-(4-sulfamoylphenyl)-2-imino-1,3,4-thiadiazoline. The diazene derivative 2 was found to be cytotoxic, with IC_{50} values of $1.18\mu\text{M}$, $5.28\mu\text{M}$, and $7.15\mu\text{M}$ against MCF-7, Caco 2, and HepG-2, respectively (Fig. 10).

Furthermore, against Caco2, HepG-2, and MCF-7, the dihydroxyphenyl triazene derivative 5 showed IC_{50} values of $3.03\mu\text{M}$, $5.66\mu\text{M}$, and $12.50\mu\text{M}$, respectively. Similarly, the IC_{50} values for the carbohydrazide coumarin 132 against Caco 2 and HepG2 were $2.00\mu\text{M}$ and $12.30\mu\text{M}$, respectively.

Using their insilico ADME evaluation, molecular docking with hCAIX and hCAXII was used to explain the achieved cytotoxicity at the molecular level (Bondock *et al.*, 2023).

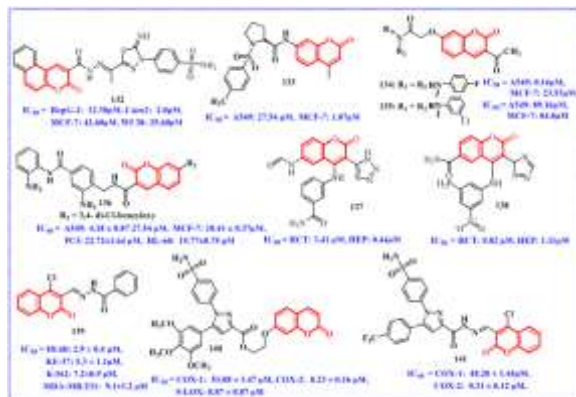


Fig. 10. Chemical structures of important coumarin sulphonamide/benzamide hybrids

In 2019, Durgapal *et al.* Diabetes and cancer are regarded as two main illnesses that have an impact on people's health globally. Peptide linkage containing proline sulfonamide may be a viable treatment for both diabetes and cancer. There are several medicines available to treat diabetes and cancer separately. Here, we describe the synthesis and design of new coumarin-proline sulfonamide compounds that have anti-cancer and antidiabetic properties. The anticancer activity of all produced compounds was tested using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and the DPP-IV inhibition assay against the lung cancer cell line (A549) and breast cancer cell line (MCF7). Compound 133 had outstanding efficacy against the MCF7 breast cancer cell line, with an IC₅₀ value of 1.07 mM. DPP-IV inhibition was moderate for all medications (Durgapal *et al.*, 2019).

Durgapal *et al.* (2017) Using the MTT assay, we created and synthesized new 7-substituted-3 acetylbenzopyrones and ethyl 7-substituted-3-carboxylatebenzopyrones and tested them for anticancer properties. Comparing 5-fluorouracil to the A549 lung cancer cell line and the MCF7 breast cancer cell line, most of the evaluated compounds demonstrated very good efficacy. Excellent 84.8 nM activity against the MCF7 cell line was demonstrated by compounds 134

and 135 respectively. At very low concentrations, compounds 134 and 135 demonstrated remarkable anticancer action, falling well inside the nanomolar range. In a UV-based DNA titration, compounds 134 and 135 demonstrated a very good binding constant for DNA binding through intercalation. This was further validated by a fluorescence-based EtBr displacement experiment in the DNA-EtBr complex. anticancer activity, exhibiting corresponding IC₅₀ of 84.8 nM against the MCF7 cell line and 0.16 nM against the A549 cell line. Excellent anticancer action was demonstrated by compounds 134 and 135 at very low concentrations, much within the nanomolar range. In a UV-based DNA titration, compounds 134 and 135 demonstrated a very good binding constant for DNA binding through intercalation. This was further validated by a fluorescence-based EtBr displacement experiment in the DNA-EtBr complex (Durgapal *et al.*, 2017).

Histone deacetylases (HDACs) are appealing therapeutic targets for the treatment of cancer and other illnesses (Abdizadeh *et al.*, 2017). Its four classes include class I isozymes, which are particularly important for encouraging the growth, angiogenesis, differentiation, invasion, and metastasis of tumor cells. They are also good targets for cancer treatments.

Their inhibitory properties against the pan HDAC and HDAC1 isoforms were assessed. In addition to having strong pan-HDAC inhibitory activity (which includes HDAC isoenzymes) (IC₅₀ ¼ 0.80 e14.81 mM) and HDAC1 inhibitory activity (IC₅₀ ¼ 0.47 e0.87 mM), four compounds 136 demonstrated significant cytotoxicity with IC₅₀ in the range of 0.53e57.59 mMon cancer cells and no effect on the viability of Huvec (human normal cell line) (IC₅₀ > 100 mM). With an IC₅₀ value of 0.47 ± 0.02 mM, which was almost identical to that of the reference medication Entinostat (IC₅₀ ¼ 0.41 ± 0.06 mM), 136 of them showed a greater potency for HDAC1 inhibition. Compound 136 potential method of interaction with the HDAC1 enzyme was revealed by molecular docking investigations and molecular dynamics simulation (Abdizadeh *et al.*, 2017).

Daratu *et al.* (2022) The anticancer activity recently created substituted 4-anilino coumarin derivatives was predicted using our two QSAR models. The QSAR predictions showed that compounds 137 and 138 had the best expected anti-colon cancer and anti-hepatoma effects, respectively. The results demonstrated that this approach can aid in the search for novel anticancer medications. Moreover, the retrosynthesis analysis of both compounds in a logical reversal of organic synthetic routes is described by the Knoevenagel and Perkin reactions (Daratu *et al.*, 2022).

Angelova *et al.* (2016) Nuclear magnetic resonance, mass spectrometry, elemental analysis, and Fourier transform-infrared spectroscopy were used to create and describe a number of novel hybrid molecules containing a hydrazone fragment. The hydrazones nuclear magnetic resonance spectra revealed the exchange of syn and antiperiplanar conformers surrounding the amide bond, with the antiperiplanar conformer being more stable. The E configuration surrounding the C=N bond is confirmed by the nuclear Overhauser effect spectroscopy (NOESY) spectra. A micromolar range of concentration-dependent cytotoxic effects were demonstrated by the investigated substances against human tumor cell lines using the MTT (3-(4,5-dimethylthiazol 2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay. The series' strongest antiproliferative agent turned out to be hydrazone 139.

In the antioxidant screening, 139 showed the biggest rate constant for the reaction with 2,2-diphenyl-1-picrylhydrazyl and the highest radical scavenging activity (% RSA max) (Angelova *et al.*, 2016).

In 2017, Shen *et al.* As new COX-2 inhibitors, we created a number of pyrazole compounds in our earlier work. We designed and synthesized compounds by hybridizing pyrazole with substituted coumarin, which was reported to exhibit 5-LOX inhibition, in order to obtain novel dual inhibitors of COX-2 and 5-LOX. We then used sufficient biological trials, sequentially, including

selective inhibition of COX-2 and 5-LOX, anti-proliferation in vitro, cell apoptosis, and cell cycle, to select potent compounds. Comparing them to the positive controls Celecoxib (IC₅₀ = 0.41 ± 0.28 μM for COX-2, IC₅₀ = 7.68 ± 0.55 μM against A549) and Zileuton (IC₅₀ = 1.35 ± 0.24 μM for 5-LOX), the most potent compound, 140 (IC₅₀ = 0.23 ± 0.16 μM for COX-2, 0.87 ± 0.07 μM for 5-LOX, and 4.48 ± 0.57 μM against A549), demonstrated initial superiority. Subsequent research verified that 140 may, in a dose-dependent manner, prevent the cell cycle at the G₂ phase and cause apoptosis in human non-small cell lung cancer A549 cells. Our research may help develop COX-2, 5-LOX dual inhibitors, which could lead to the exploitation of exciting new cancer prevention drugs (Shen *et al.*, 2017).

Malignant tumors often overexpress cyclooxygenase-2, and the resulting PGE₂ facilitates the growth and spread of cancer cells. To enhance the biological activities of COX-2 inhibition and anticancer, we created a new series of coumarin sulfonamide derivatives. In comparison to the control positive compound Celecoxib (0.31 μM, 43.37 μM, 7.79 μM), compound 141 exhibited the strongest selective inhibitory and antiproliferative action among them (IC₅₀ = 0.09 μM for COX-2, IC₅₀ = 48.20 μM for COX-1, and IC₅₀ = 0.36 μM against HeLa cells). The findings of an experiment for cancer cell apoptosis showed that compound 141 efficiently stimulates HeLa cell apoptosis in a dose- and time-dependent manner. Furthermore, 141 has the ability to dramatically inhibit the adhesion, migration, and invasion of cancer cells—all of which are critical processes in the spread of cancer. A realistic design of a selective COX-2 inhibitor with anticancer properties in the future was guided by the results of docking simulations, which also showed that compound 141 might bind well to the COX-2 active site (Shen *et al.*, 2017).

Chalcones/Furoxans coumarin

Zaki and Elshemya in the year 2017 Three sets of coumarin-based hybrids were created using the molecular hybridization technique by combining 8-methoxy coumarin with substituted chalcones,

acrylohydrazides, and pyridine moieties. The hybrids had limited activity against the normal cell line WI-38, suggesting selectivity toward the tumor cells, and considerable cytotoxic activity against the liver cancer Hep G2 and Leukemia K562 cell lines, with IC₅₀ values 0.49–3.96 μ M, equivalent to the positive controls (Fig. 11).

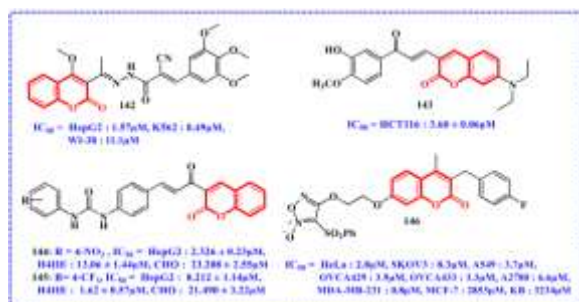


Fig. 11. Structures of important coumarin chalcone/furoxan hybrids

With IC₅₀ values ranging from 0.65 to 2.02 μ M, coumarin-chalcone hybrids have shown the most promising action against both cancer cell lines. Interestingly, with an IC₅₀ value of 0.49 μ M, the acrylohydrazide hybrid 142 exhibited the maximum cytotoxic effect against the leukemia cell line (K562). In comparison to the untreated cells, all of the coumarin hybrids under investigation were able to raise the expression levels of the caspase-3 and caspase-9 proteins, indicating that the activation of caspases 3 and 9 was partially responsible for the apoptosis caused by coumarin hybrids. The down-regulation of Bcl-2 and the up-regulation of Bax protein expression level further supported apoptosis. Additionally, 142's cell cycle analysis revealed the activation of apoptotic signals as a result of G2/M phase arrest. Our study's findings can provide insight into coumarin-based hybrids as potentially effective anticancer agents (Zaki and Elshemya, 2017).

Many studies have been conducted on the selenoprotein thioredoxin reductases (TrxRs) as a possible target for anticancer medication development. Here, we created, produced, and assessed a number of coumarin-chalcone hybrids that function as TrxR inhibitors. Compared to xanthohumol (Xn), the majority of them showed

enhanced anticancer activity. Red fluorescence imaging makes it easy to track drug uptake in living cells, and the representative 143 (IC₅₀ = 3.6 μ M) was a fluorescent agent. 143 significantly increased ROS generation to trigger the mitochondrial apoptotic pathway and down-regulated TrxR expression. Moreover, 143 eliminated the capacity of cancer cells to form colonies and prevented cancer cell metastases. When considered collectively, these findings suggest that compound 143 could be a promising theranostic TrxR inhibitor for the treatment of human cancer (Wang *et al.*, 2020).

Zengin *et al.*, 2020 since medications do not sufficiently improve survival against the rising number of cancer cases worldwide, there is a steady increase in interest in the development of novel treatments. The current study focused on the design and synthesis of coumarin derivatives with various substituted chalcone-urea moieties, in light of the documented anticancer activity of coumarin, chalcone, and urea derivatives. Novel coumarin chalcone derivatives with a urea moiety were synthesized using a structure-based molecular hybridization technique, and their invitro antiproliferative properties against the cancer cell lines (H4IIE and HepG2) were evaluated. Furthermore, the synthetic chemicals were tested on a non-cancerous Edona cell line (CHO) to assess the potential harm they could do to healthy cells. showed superior H4IIE inhibition among the synthesized drugs in comparison to sorafenib. Additionally, 144 demonstrated superior inhibition against HepG2 compared to Sorafenib. Specifically, 144 stopped the cell cycle at the S Phase and caused H4IIE apoptosis. As a result, 144 and 145 might be strong antitumor agents and a good starting point for additional optimization (Zengin *et al.*, 2020).

In 2018, Guo *et al.*, five novel phenyl sulfonylfuroxan hybrids combining 3-benzyl coumarin were created in this work. In contrast to compound 146 clearly caused early apoptosis and had little effect on the cell cycle of A2780. When compared to their drug-sensitive counterparts, MCF-7 and KB, it demonstrated 559- and 294-fold selectivity antiproliferation activity in P-

gp overexpressed drug-resistant cancer cell lines, MCF-7/ADR and KB-V, suggesting that compounds 2–6 may have an additional mechanism of anti-MDR-cancer with P-gp overexpression (Guo *et al.*, 2018).

Dihydroxycoumarins

In 2019, Govindaiah *et al.*, four distinct cancer cell lines (A549, HeLa, SKNSH, and MCF7) were used to test the antiproliferative potential of a series of new acryloylcyanothiazone derivatives based on 4,7-dihydroxycoumarin. Against every examined cancer cell line, the majority of the compounds showed strong cytotoxicity, with IC₅₀ values ranging from 3.42 to 31.28 μM. For pharmacological mechanistic investigations on tubulin polymerization inhibition assay and cell cycle progression, the most active drug, 8h, was assessed. With an IC₅₀ of 6.19 μM, the results showed that compound 147 hindered tubulin polymerization and caused cell cycle arrest at the G₂/M phase. The molecular docking technique was used to evaluate the experimental data of the tubulin polymerization inhibition assay, and the results showed significant hydrogen bonding interactions with tubulin's amino acids (ASN-101, TYR-224, ASN-228, LYS-254) (Govindaiah *et al.*, 2019) (Fig. 12).

Han *et al.* (2018) A number of shikonin derivatives were created for the current investigation, and their anticancer properties were assessed. The antiproliferation activity of 148 was the highest, with an IC₅₀ value of 3.25 ± 0.35 μM. Furthermore, a dose-dependent event characterized by apoptosis was observed when HeLa cells were treated with different doses of the target medication. Furthermore, the apoptosis finding agreed with the mitochondrial potential study. Furthermore, the progression of apoptosis as shown by western blotting involved PARP. We looked at the expression of E-cadherin and HIF-1α in HeLa cells to determine the precise function and mechanism of 148 in the development of human cervical cancer. The findings indicated that E cadherin protein was increased and HIF-1α expression was downregulated. In the meantime, HeLa cells showed a reduction in the glycolysis-related protein PDK1. On the other hand, PDH-E1α

expression was elevated. The results of the docking simulation also show that 148 might be well coupled to HIF-1α. All things considered, our findings suggest that compound 148 may be created as a possible anticancer drug (Han *et al.*, 2018).

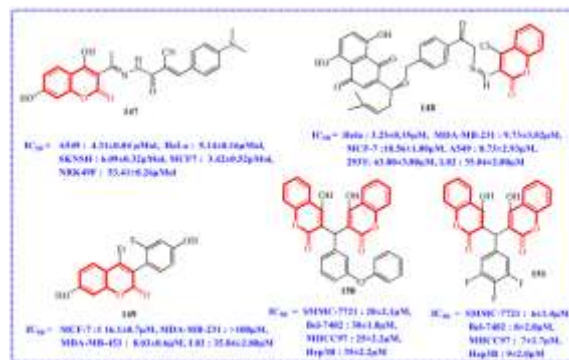


Fig. 12. Structures of important dihydroxycoumarins

Lu *et al.* (2017) Understanding drug action throughout preclinical and clinical studies can be enhanced by incorporating biological imaging into the early phases of the drug discovery process. For drug-target binding imaging, we created and synthesized coumarin-based nonsteroidal type fluorescent ligands in this research. The synthetic compounds demonstrated strong ER binding affinity, antiproliferative potency in breast cancer MCF-7 cells is comparable to that of the licensed medication tamoxifen. When combined with ERα or ERβ *in vitro*, compounds 149's fluorescence changed significantly and was dependent on the solvent's characteristics. Additionally, target molecule 149 did not require cell washing in order to cross the cell membrane, localize, and image drug-target interaction in real time. With both diagnostic and therapeutic benefits, the coumarin-based technology thus represents a potentially novel ER-targeted delivery vehicle (Lu *et al.*, 2017).

The anti-tumor activity of 4-hydroxycoumarin derivatives with various aromatic rings was produced and assessed by Han *et al.* in 2019. The results of the biological experiments showed that compound 151 had better anti-cancer activity than compound 150. This is further supported by molecular docking studies that indicate compound has a stronger contact

with proteins. These findings suggested that chemical might be developed further as an anticancer agent (Han *et al.*, 2019).

Pyrimidine, pyridine, and piperidine derivatives of coumarin

In 2019, Kumar *et al.*, this work reports a linear method for manufacturing the chromeno-thio/furo pyridine system as possible analogues of the anticancer drug lamellarin D. The FeCl₃ catalyzed modified Pictet-Spengler reaction was the essential last step that produced the target compounds in modest to good yields. The total yield of compounds with furan rings was higher than that of their thiophene counterparts. Three distinct cancer cell lines were used to screen for anticancer activity in the final compounds. Compounds 152 with fused furan rings had superior activity; when tested against MCF-7 (breast cancer) cell lines, the best IC₅₀ value was 6.83 μM (Kumar *et al.*, 2019) (Fig. 13).

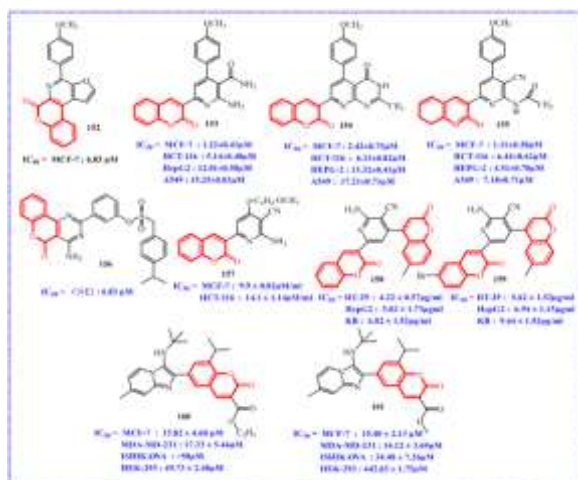


Fig. 13. Structures of coumarin-pyridine/pyrimidine derivatives

Fayed *et al.* (2019) They devised and synthesized a new family of coumarin-pyridine/fused pyridine hybrids. The human cancer cell lines MCF-7, HCT-116, HepG-2, and A549 were used to test their anticancer efficacy.

With IC₅₀ values ranging from 1.1 to 2.4 μM, compounds 153, 154, and 155 demonstrated the most growth inhibitory effects against the MCF-7 cell line.

These substances caused cell cycle arrest in the G₂/M phase, which was followed by apoptotic cell death, according to flow cytometry examination. The activity of caspase-3 in MCF-7 cells was examined in accordance with these findings. Comparing chemicals 153, 154, and 155 to the control group, the results showed a significant increase in caspase 3 activity. Furthermore, a docking investigation verified their binding affinity for caspase-3. The combination of these results points to the possibility that these coumarin derivatives could be antiproliferative agents (Fayed *et al.*, 2019).

Lv *et al.* (2017) We developed and synthesized a series of 2-phenylpyrimidine coumarin compounds that may have telomerase-inhibiting properties. The antiproliferative properties of each chemical were tested in vitro against the CNE2, KB, and Cal27 cell lines. The findings demonstrated that most of the derivatives were effective in preventing the growth of tumor cells; the molecule with the highest activity was compound 13, 3-(4-amino-5-oxo-5H-chromeno[4,3-d] pyrimidin-2-yl) phenyl 4-(dimethyl amino)benzenesulfonate. Although the compounds' in vitro anticancer efficacy and telomerase inhibition were consistent, compound 156 exhibited the best telomerase-inhibiting activity and the capacity to prevent telomere extension. According to the results of molecular docking, compound 156 formed a bind with telomerase reverse transcriptase (TERT) via a variety of interactions, including hydrophobic and hydrogen bonding. The study's findings broaden the range of telomerase inhibitors that can be used as parent structures by revealing more details about two phenyl pyrimidine coumarins (Lv *et al.*, 2017).

El-Naggar *et al.* (2017) By reacting 3-(3-(4-methoxyphenyl)acryloyl)-2H-chromen-2-one (3) with various carbon nucleophiles, including ethyl acetoacetate, ethyl cyanoacetate, malononitrile, and ethyl benzoylacetate, under conventional heating and microwave irradiation conditions, coumarin derivatives were synthesized efficiently and quickly. These coumarin derivatives were then utilized as a source of pyran and pyridine derivatives. Elements and spectroscopic evidence were used to characterize

each of the newly created substances. The cytotoxicity of each produced molecule was examined *in vitro*. The majority of the compounds exhibited moderate cytotoxic activity against HCT-116 and MCF-7 cell lines, according to the preliminary screening results. However, compound 157 had strong action against the two cell lines, on par with the common medication 5-fluorouracil (El-Naggar *et al.*, 2017).

Chougala *et al.* (2017) New bioactive 2-amino-4-(2-oxo-2H-chromen-4-yl) catalyst free Using a one-pot, four-component coupling reaction and a simple microwave approach, 6-arylpyridine-3-carbonitrile molecular entities were created from 4-formylcoumarins using malononitrile, various ketones, and ammonium acetate. Every chemical has been thoroughly characterized, and the synthetic compounds' anticancer qualities have been documented. At modest concentrations (105M), Three cancer cell lines, including HT-29, Hep-G2, and KB, are also included. The strongest anticancer molecules, 158 and 159, were evaluated for their CT-DNA cleavage and fluorescence quenching research using transport protein BSA. Of the eight compounds, 158 and 159 are showed the most promising activity. Using the podophyllotoxin-tubulin stathmin-like domain complex (PDB 1SA1), a molecular docking analysis was conducted for the produced drugs with the tubulin binding site, and the results are excellent. The most powerful substances' IC₅₀ values were determined (Chougala *et al.*, 2017).

Sashidhara *et al.* (2016) A number of physiologically significant 6-(imidazo[1,2-a]pyridin-2-yl)-2H chromen-2-one derivatives were created using the Groebke–Blackburn–Bienayme multicomponent synthesis, which was catalyzed by silver(I). The potential osteoprotective qualities of the synthesized compounds were examined in primary calvarial osteoblast cells using the alizarin red-S staining assay and the alkaline phosphatase assay. Additionally, qPCR was used to assess the impact of active in the expression of the osteogenic genes BMP2, RUNX2, COL1, and OCN. Using mitochondrial depolarization, 160 and 161 two of the three promising compounds—

significantly increased apoptosis in MDA-MB-231 cancer cells while having no effect on healthy cells. In a bone metastasis *in vitro* co-culture paradigm, we examined whether coumarin–imidazo[1,2-a]pyridine hybrids could counteract the detrimental effect of MDA-MB-231 cancer cells on osteoblast development. These findings demonstrate how engineered hybrids can help restore bone homeostasis. These results highlight the importance of recently created hybrids as lead compounds with anti-osteoporotic and anti-cancer characteristics that can be turned into novel therapeutic medicines to treat osteoporosis and bone metastases (Sashidhara *et al.*, 2016).

Diversions of anilincoumarins

Mohamed *et al.* (2018). Our primary goal was to create and examine the cytotoxic properties of recently synthesized coumarin derivatives. The newly synthesized compounds 162 and 163 were classified as chemotherapeutically relevant due to their substantial cytotoxic activity against HepG-2 malignancy and their strong cytotoxic action against MCF-7 (Mohamed *et al.*, 2018).

Ahmed *et al.* 2020 the *in vitro* anticancer activity of 25 newly synthesized coumarin scaffold-based derivatives was evaluated against the MCF-7 breast and PC-3 prostate cancer cell lines. Additionally, there *in vitro* VEGFR-2 kinase inhibitory activity was evaluated. Most of the synthesized compounds showed highly promising cytotoxicity against MCF-7, according to the *in vitro* cytotoxic experiments. Compounds 164 (IC₅₀= 1.24 μM) had remarkable activities that were superior to the positive control staurosporine (IC₅₀= 8.81 μM). With IC₅₀ values ranging from 2.07 to 8.68 μM, most of the compounds also demonstrated stronger antiproliferative effects when compared to the reference standard. To assess their inhibitory potencies against VEGFR-2 kinase, the two cytotoxic derivatives 164 were chosen. Interestingly, compound 164 showed a noteworthy IC₅₀ of 0.36 μM, which is similar to staurosporine's (IC₅₀: 0.33 μM). Additionally, it could activate caspase-9, cause cell growth stop at the G₂/M phase and induce preG₁

death. However, all of the compounds showed considerable cytotoxic action against the PC-3 cell line (Ahmed *et al.*, 2020).

In 2017, Soni *et al.*, many substituted amino methyl benzocoumarin compounds have been created, described, and A549 (lung carcinoma cell line), MCF7 (breast cancer cell line), and A375 (melanoma cell line) were used to assess the anticancer activity of all the produced compounds. Good growth inhibitory activity was demonstrated by compounds 165, 166, and 167 against each of the three cell lines. Additionally, compounds 165 and 166 showed great promise as anticancer agents against MCF7 and A549 cell lines at extremely low concentrations (Soni *et al.*, 2017).

Luo *et al.* (2017) Numerous derivatives of 3-substituted 4-anilino-coumarin have been created, produced, and their anti-proliferative qualities examined. Using the MTT assay, the *in vitro* cytotoxicity screening was carried out against the cancer cell lines MCF-7, HepG2, HCT116, and Panc-1. Against these four evaluated cancer cell lines, the majority of the synthesized compounds had anti-proliferative activity that was comparable to that of the positive control 5-fluorouracil. The 3-trifluoroacetyl group was the most promising of the several substituents at the C-3 position of the coumarin scaffold.

Compounds 168 and 169, in particular, shown outstanding anti-proliferative properties on MCF-7, HepG2, HCT116, and Panc-1 cell lines, respectively (IC₅₀ = 16.57, 5.45, 4.42, and 5.16 μ M and 20.14, 6.71, 4.62, and 5.62 μ M). Compounds 168 and 169 showed low toxicity to human umbilical vein endothelial cells (HUVECs), indicating that their safety profiles in normal cells are acceptable. Additionally, the outcomes of *in silico* ADME investigations showed that 168 and 169 both had favorable pharmacokinetic characteristics (Luo *et al.*, 2017).

Cao *et al.* (2016) Several new 4-substituted coumarin derivatives were created and presented in this

research. At subnanomolar IC₅₀ values, 170 of these compounds demonstrated strong antiproliferative activity against a panel of tumor cell lines. Compound 170 maintained full activity in multidrug-resistant cancer cells and had strong antiproliferative abilities (IC₅₀ values of 7–47 nM). Microtubule dynamics experiments, competition assays with N,N'-ethylene bis(iodoacetamide), and immune-fluorescence staining all demonstrated that compound 170 interacted with the tubulin's colchicine-binding site and produced G₂/M phase arrest. In HUVEC cells, compound 170 inhibited cell migration and interfered with the development of capillary-like tubes. In four xenograft models, including paclitaxel-sensitive and resistant ovarian tumors (A2780s and A2780/T) and adrmicycin-sensitive and resistant breast tumors (MCF 7 and MCF-7/ADR), compound 170 significantly and dose-dependently decreased tumor growth. This suggests that compound 170 is a promising novel antimetabolic compound for the possible treatment of cancer (Cao *et al.*, 2016).

Lipeeva *et al.*, 2019, an easy-to-follow procedure is shown for the quick and effective synthesis of 3-bromopeuruthenicin 2 from plant coumarin peuruthenicin 1. Under reflux in chloroform, coumarin 2 has been effectively combined with N-methylpiperazine or 5-aminoisoquinoline to generate 3-(N-substituted) aminoumbelliferons. The presence of tautomerization processes in 3-bromo-7-hydroxycoumarin 2 under reaction conditions explains the ease of production of the compounds. The palladium-catalyzed C–N coupling reaction was investigated to obtain large yields of 3-(arylamino) coumarins in the reaction of 3-bromocoumarin 2 with substituted anilines. When the Pd(OAc)₂-Xantphos catalytic system was present, the reaction proceeded without incident and the relevant coupling products were formed. 3-(N-(aryl-hetaryl)) aminocoumarins 171 and 172 were formed in good yields by the Suzuki cross-coupling reaction of 3-(3-bromophenylamino) coumarin with aryl- and (hetaryl) boronic acids 11, 13, and 14 using PdCl₂(dppf) as the catalyst. The traditional MTT tests were used to assess the cytotoxicity of novel umbelliferone derivatives against

human cancer cells. Aminocoumarins 171 and 172 shown selectivity for the breast cancer cells MCF-7, and the data showed that these compounds had the most promising cytotoxic potential. On these cell lines, the cytotoxicity of 3-(N-substituted) aminocoumarins 171 and 172 was equivalent to that of the common medication doxorubicin (Lipeeva *et al.*, 2019) (Fig. 14).

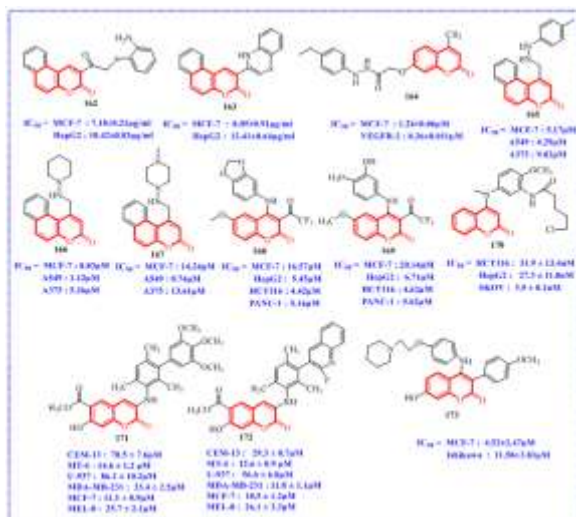


Fig. 14. Structures of important anilino-coumarins

Luo *et al.* (2017) The genesis and progression of breast cancer have been significantly influenced by the estrogen receptor (ER), which is also a key target for the development of anticancer drugs. Based on previously published lead compounds, we developed and synthesized novel 3-aryl-4-anilino-2H-chromen-2-one derivatives to create novel selective ERα modulators (SERMs). The biological results showed that, in comparison to the positive control tamoxifen, the majority of the compounds had strong ERα binding affinity and superior anti-proliferative actions against MCF-7 and Ishikawa cell lines. With an IC₅₀ value of $4.52 \pm 2.47 \mu\text{M}$, compound 173 had the strongest anti-proliferative action against MCF-7 cells. Additional molecular docking studies were conducted to examine the newly synthesized drugs' binding pattern with ERα. These 3-aryl-4-anilino-2H-chromen-2-one derivatives with a basic side chain may be attractive candidates for additional optimization as novel SERMs, according to all of these findings along with the structure–activity relationships (SARs) (Luo *et al.*, 2017).

Unclassified coumarins

El-Agrody and colleagues, 2020 A series of 2-amino-4-aryl-5-oxo-4,5-dihydropyrano[3,2-c] chromene-3-carbonitrile with good to excellent yields was produced by a one-pot three-component condensation reaction between 4-hydroxy-2H-chromen-2-one, various aryl aldehydes, and malononitrile using piperidine as a catalyst in ethanol under microwave irradiation conditions. The *in vitro* anticancer activity of the targeted compounds was assessed using the sulphorhodamine B test (SRB) method against the human colon cancer (HCT-116), liver cancer (HepG-2), and mammary gland breast cancer cell line (MCF-7). As the standard reference drug, doxorubicin was utilized. The cancer cells were given different dosages of the generated chemicals, and the cells' viability was evaluated. Against all cancer cell lines, compounds 174, 175, and 176 showed exceptional anticancer effectiveness, with IC₅₀ values ranging from 0.2 to 1.7 μM. The properties of cell cycle arrest in compounds 174, 175, and 176 were investigated (El-Agrody *et al.*, 2020).

In 2019, Junjie *et al.*, a series of coumarin derivatives with a 2-methylbiphenyl moiety were designed and synthesized using a hybrid pharmacophore technique. These compounds were then tested for their *in vitro* anticancer and PD-1/PD-L1 inhibitory properties against four cancer cell lines (MCF-7, A549, H460, and HT29). With IC₅₀ values of 6.45, 8.65, 6.57, and 8.13 μmol/L, respectively, the most promising molecule 177 demonstrated the highest anticancer activity against the four tested cancer cell lines. Additionally, screening for PD-1/PD-L1 inhibitory activity showed that compound 177 could effectively block PD-1/PD-L1 binding, and molecular docking was used to investigate compound 177's binding interactions with PD-L1 protein (Junjie *et al.*, 2019).

In 2019, Patel and Patel, by reacting different 3-coumarinoyl methyl pyridinium bromide salts with a specific set of acetyl naphthalene in the presence of sodium acetate in refluxing glacial acetic acid, novel congeners of naphthalene substituted benzo[c]coumarins were created. Tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

bromide (MTT) cell viability assay was used to screen synthesized compounds for antibacterial activity and cytotoxicity against various human cancer cell lines, including cervix cancer (HeLa), breast cancer (MCF-7), and lung cancer (A549). All three cancer cell lines showed notable growth inhibitory and cytotoxic effects, albeit at differing degrees. Compounds 178 and 179 demonstrated notable cytotoxicity and growth inhibition against the cancer cell lines indicated above (Patel and Patel, 2019).

Saisuree *et al.* (2018) Allylation, Claisen rearrangement, allylation, and ring-closing metathesis (RCM) were employed to create a sequence of fused dihydrooxepino[h]- and dihydrooxepino[g]coumarins, respectively. Using tamoxifen (TAM) as the positive control, the synthesized chemical was tested against human colon cancer (Caco-2), liver cancer (HepG2), and breast cancer (SKBR-3) cell lines. Comparing compound 180 to all other coumarin derivatives, it demonstrated strong anti-proliferative action against resistant Caco-2 and SKBR-3 cell lines. Curiously, compound 181 proved more effective against the sensitive HepG2 cell line than TAM (Saisuree *et al.*, 2018).

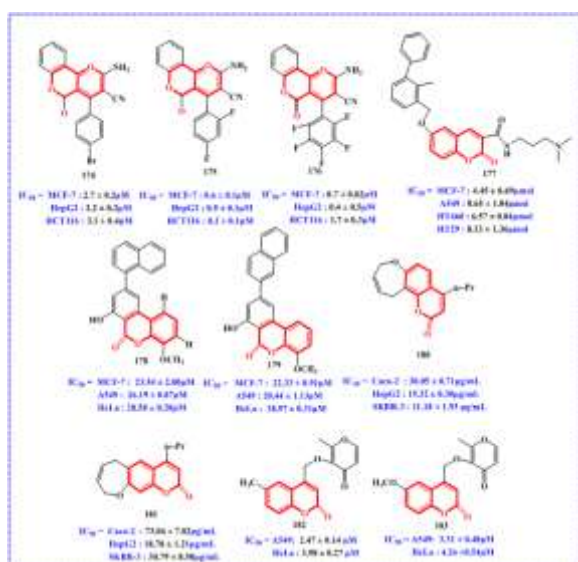


Fig. 15. Structures of important unclassified coumarin hybrids

Koparde *et al.* (2018) used microwave irradiation to selectively prepare several novel coumarin-

maltol hybrids in high yields. The produced compounds' *in-vitro* anticancer efficacy against two human cancer cell lines HeLa (human cervical cancer) and A-549 (human lung carcinoma) was assessed. Compounds 182 and 183 exhibited strong cytotoxicity against A-549 and HeLa cancer cells, with IC₅₀ values ranging from 2.47 to 4.26 μM. Compounds 182 and 183 were shown to completely break the DNA, since no traces of DNA were detected in the DNA cleavage assay conducted using the gel electrophoresis method (Koparde *et al.*, 2018) (Fig. 15).

Future perspectives

Because there are few choices for prevention, ineffective cancer treatment approaches, and inadequate diagnosis, the rate of death from cancer is concerning. Because coumarin is widely found in many naturally occurring chemicals, coumarin-privileged scaffolds have an exceptional anticancer profile. Consequently, a variety of coumarin derivative classes have been thoroughly studied for their potential to combat cancer via a range of modes of action.

But the novel substances that have been extracted from organic sources, such plants and animals, and the potential mixing of these substances with traditional chemotherapeutic medicines appear to be crucial for enhancing the quality of life, particularly for cancer patients. Further optimisation can be achieved by investigating the potential integration of steroids into the coumarin structure. Preclinical trials involve pharmacological interaction, toxicity, specificity, and in vivo evaluation. For this reason, many lead candidates are not financially viable for non-profit organisation researchers. Drug repositioning has changed this, and as a result, additional human illnesses have emerged. We have emphasised the potency of coumarin, but more work needs to be done to find therapeutic medications with great specificity. In terms of biological efficacy, positions 3 and 4 have been deemed more prominent.

The dihydroxy group's redox characteristics linked to simple coumarin may not be advantageous for *in vivo* conditions and result in adverse effects. To

combat adverse effects, pyrone rings must also be modified. Modern synthetic techniques like microwave irradiation and MCR have produced molecules with numerous bioactivities in addition to high yields.

According to the research, ligand-ligand azole derivatives bind directly to DNA, potentially improving oxidative stress even more. To acquire the more potent anticancer drugs, potential structural alterations will need to be clarified through further mechanistic and kinetic studies including the HDACs inhibitory activity of thiazolyl attached coumarins.

CONCLUSION

Biologically active compounds have drawn the attention of several scientists towards coumarins. These compounds have several pharmacological effects, which are antioxidant activity, prevention of diseases, and maintenance of cellular growth processes. Coumarins significant antitumor potential by its action as an immune modulator, inhibitor of cell proliferation process and a cellular differentiator. The hepatotoxicity of certain natural coumarins limits the therapeutic use of these natural coumarin derivatives, but the structural adaptation of these moieties has led to the creation of harmless and more potent analogues and showed that the addition of various substituents to distinct sites of the coumarin core may substantially increase anticancer effects. Some coumarin derivatives and hybrid molecules have been demonstrated in recent years to have promising anticancer effects, making them worthy of consideration as obstacles to the production of novel anticancer agents.

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REFERENCES

- Altemimi A.** 2018. Secondary metabolites: Secondary metabolic products consisting of C and H; C, H, and O; N, S, and P elements; and O/N heterocycles. In *Atlas of medicinal plants and their extracts* **2**(74), 165–309. https://doi.org/10.1007/978-3-319-92387-1_3
- Abdizadeh T, Kalantari M, Ezzatzadeh E, Mahdavi M, Foroumadi A, Shafiee A.** 2017. Design, synthesis and biological evaluation of novel coumarin-based benzamides as potent histone deacetylase inhibitors and anticancer agents. *European Journal of Medicinal Chemistry* **132**, 42–62. <https://doi.org/10.1016/J.EJMECH.2017.03.024>
- Ahmed EY, Abdel Latif NA, El-Mansy MF, Elserwy WS, Abdelhafez OM.** 2020. VEGFR-2 inhibiting effect and molecular modeling of newly synthesized coumarin derivatives as anti-breast cancer agents. *Bioorganic and Medicinal Chemistry* **28**(5), 115328. <https://doi.org/10.1016/J.BMC.2020.115328>
- Akram M, Iqbal M, Daniyal M, Khan AU.** 2017. Awareness and current knowledge of breast cancer. *Biological Research* **50**(1), 33. <https://doi.org/10.1186/S40659-017-0140-9>
- Al-Wahaibi LH, Abu-Melha HM, Ibrahim DA.** 2018. Synthesis of novel 1,2,4-triazolyl coumarin derivatives as potential anticancer agents. *Journal of Chemistry* **2018**(1), 5201374. <https://doi.org/10.1155/2018/5201374>
- Angelova VT, Vassilev NG, Vasileva-Tonkova E, Momekov G, Ivanov IC.** 2016. Antiproliferative and antioxidative effects of novel hydrazone derivatives bearing coumarin and chromene moiety. *Medicinal Chemistry Research* **25**(9), 2082–2092. <https://doi.org/10.1007/S00044-016-1661-4>
- Arvas B, Yilmaz B, Korkmaz N, Çelik M, Şahin E.** 2024. Synthesis of novel coumarin-triazole hybrids and first evaluation of the 4-phenyl substituted hybrid loaded PLGA nanoparticles delivery system to the anticancer activity. *Nanotechnology* **35**(30), 305602.

Augsten LV, Tavares MT, de Souza MVN, Ferreira VF, Cunha AC. 2023. Antiproliferative activity and toxicity evaluation of 1,2,3-triazole and 4-methyl coumarin hybrids in the MCF7 breast cancer cell line. *RSC Medicinal Chemistry* **14**(5), 869–879.

<https://doi.org/10.1039/D3MD00031A>

Awaad AS. 2018. Biological activities and medicinal applications of coumarins and their derivatives. *Pharmacognosy Reviews* **12**(24), 123–132.

https://doi.org/10.4103/phrev.phrev_22_18

Ayati A, Emami S, Asadipour A, Shafiee A, Foroumadi A. 2018. Synthesis and biological evaluation of new coumarins bearing 2,4-diaminothiazole-5-carbonyl moiety. *European Journal of Medicinal Chemistry* **155**, 483–491.

<https://doi.org/10.1016/J.EJMECH.2018.06.015>

Basavaiah D, Veeraraghavaiah G. 2012. The Baylis–Hillman reaction: A novel concept for creativity in chemistry. *Chemical Society Reviews* **41**, 68–78.

<https://doi.org/10.1039/c1cs15174f>

Batran RZ, Ahmed EY, Awad HM, Ali KA, Abdel Latif NA. 2023. EGFR and PI3K/m-TOR inhibitors: Design, microwave assisted synthesis and anticancer activity of thiazole–coumarin hybrids. *RSC Advances* **13**(42), 29070–29085.

<https://doi.org/10.1039/D3RA03483F>

Berrino E. 2020. Carbonic anhydrase inhibitors: Versatile agents for the treatment of human diseases. PhD thesis.

Bistrović A, Krstulović L, Harej A, Grbčić P, Sedić M, Pavelić SK. 2018. Small molecule purine and pseudopurine derivatives: Synthesis, cytostatic evaluations and investigation of growth inhibitory effect in non-small cell lung cancer A549. *Journal of Enzyme Inhibition and Medicinal Chemistry* **33**(1), 271–285.

<https://doi.org/10.1080/14756366.2017.1414807>

Bizuayehu HM, Bray F, Ferlay J, Laversanne M, Soerjomataram I. Global burden of 34 cancers among women in 2020 and projections to 2040: Population-based data from 185 countries/territories. *International Journal of Cancer* **154**(8), 1377–1393.

<https://doi.org/10.1002/IJC.34809>

Bondock S, Fadaly W, Metwally MA. 2023. Design, synthesis, cytotoxic evaluation and molecular docking of novel 1,3,4-thiadiazole sulfonamides with azene and coumarin moieties as carbonic anhydrase inhibitors. *Arabian Journal of Chemistry* **16**(8), 104956.

<https://doi.org/10.1016/J.ARABJC.2023.104956>

Borges F, Roleira F, Milhazes N, Santana L, Uriarte E. 2005. Simple coumarins and analogues in medicinal chemistry: Occurrence, synthesis and biological activity. *Current Medicinal Chemistry* **12**(8), 887–916.

Budzowska M, Kanaar R. 2009. Mechanisms of dealing with DNA damage-induced replication problems. *Cellular and Molecular Biology Letters* **53**(1), 17–31. <https://doi.org/10.1007/S12013-008-9039-Y>

Cao D, Liu Y, Yan W, Wang Y, Zhao Y, Liu J. 2016. Design, synthesis, and evaluation of in vitro and in vivo anticancer activity of 4-substituted coumarins: A novel class of potent tubulin polymerization inhibitors. *Journal of Medicinal Chemistry* **59**(12), 5721–5739.

<https://doi.org/10.1021/ACS.JMEDCHEM.6B00158>

Cao D, Liu Y, Wang Y, Zhao Y, Liu J. 2019. Design and synthesis of 3-(N-substituted)aminocoumarins as anticancer agents from 3-bromopuruthenicin. *ChemistrySelect* **4**(34), 10197–10201.

<https://doi.org/10.1002/SLCT.201901377>

Carey FA, Sundberg RJ. 2007. *Advanced organic chemistry: Part B – reactions and synthesis.* Springer.

- Chougala BM, Samundeeswari S, Holiyachi M, Shastri LA, Dodamani S, Jalalpure S.** 2017. Microwave synthesis of coumarinyl substituted pyridine derivatives as potent anticancer agents and molecular docking studies. *ChemistrySelect* **2**(18), 5234–5242. <https://doi.org/10.1002/SLCT.201700358>
- Cozzini P, Kellogg GE, Spyrakis F, Abraham DJ, Costantino G, Emerson A, Fanelli F, Gohlke H, Kuhn LA, Morris GM, Orozco M, Pertusi DA, Rizzi A, Sottriffer CA, Vallone B.** 2008. Target flexibility: An emerging consideration in drug discovery and design. *Journal of Medicinal Chemistry* **51**(20), 6237–6255. <https://doi.org/10.1021/JM800562D>
- De Araújo RS, Guerra FQ, De Queiroz AC.** 2013. Synthesis, structure-activity relationships (SAR) and in silico studies of coumarin derivatives with antifungal activity. *International Journal of Molecular Sciences* **14**(1), 1293–1309.
- Dhawan S, Kumar S, Sharma PK, Kumar V, Narasimhan B.** 2018. Synthesis, computational studies and antiproliferative activities of coumarin-tagged 1,3,4-oxadiazole conjugates against MDA-MB-231 and MCF-7 human breast cancer cells. *Bioorganic and Medicinal Chemistry* **26**(21), 5612–5623. <https://doi.org/10.1016/J.BMC.2018.10.006>
- Dhawan S, Kumar S, Sharma PK, Narasimhan B.** 2020. Synthesis, cytotoxicity and antimicrobial evaluation of new coumarin-tagged β -lactam triazole hybrid. *Chemistry and Biodiversity* **17**(1), e1900462. <https://doi.org/10.1002/CBDV.201900462>
- Durgapal SDz, Soman SS.** 2019. Evaluation of novel coumarin-proline sulfonamide hybrids as anticancer and antidiabetic agents. *Synthetic Communications* **49**(21), 2869–2883. <https://doi.org/10.1080/00397911.2019.1647439>
- Durgapal SD, Soni R, Umar S, Suresh B, Soman SS.** 2017. Anticancer activity and DNA binding studies of novel 3,7-disubstituted benzopyrones. *ChemistrySelect* **2**(1), 147–153.
- El-Agrody AM, Al-Omar MA, Amr AE, Abdalla MM, Alsharif MA.** 2020. *In vitro* anticancer activity of pyrano[3,2-c]chromene derivatives with both cell cycle arrest and apoptosis induction. *Medicinal Chemistry Research* **29**(4), 617–629. <https://doi.org/10.1007/S00044-019-02494-3>
- El-Naggar AM, Hemdan MM, Atta-Allah SR.** 2017. An efficient one-pot synthesis of new coumarin derivatives as potent anticancer agents under microwave irradiation. *Journal of Heterocyclic Chemistry* **54**(6), 3519–3526. <https://doi.org/10.1002/JHET.2975>
- El-Sayed WA, Alminderej FM, Mounier MM, Nossier ES, Saleh SM, Kassem AF.** 2022. New 1,2,3-triazole-coumarin-glycoside hybrids and their 1,2,4-triazolyl thioglycoside analogs targeting mitochondria apoptotic pathway: Synthesis, anticancer activity and docking simulation. *Molecules* **27**(17), 5688. <https://doi.org/10.3390/MOLECULES27175688>
- Elshehy HAH, Zaki MA.** 2017. Design and synthesis of new coumarin hybrids and insight into their mode of antiproliferative action. *Bioorganic and Medicinal Chemistry* **25**(3), 1066–1075. <https://doi.org/10.1016/J.BMC.2016.12.019>
- Fayed EA, Sabour R, Harras MF, Mehany ABM.** 2019. Design, synthesis, biological evaluation and molecular modeling of new coumarin derivatives as potent anticancer agents. *Medicinal Chemistry Research* **28**(8), 1284–1297. <https://doi.org/10.1007/S00044-019-02373-X>
- Gabr MT, El-Gohary NS, El-Bendary ER, El-Kerdawy MM.** 2017. Design, synthesis and biological evaluation of novel thiazolylcoumarin derivatives as anticancer agents. *European Journal of Medicinal Chemistry* **128**, 36–44.
- Ghufran MS, Soni P, Duddukuri GR.** 2023. The global concern for cancer emergence and its prevention: A systematic unveiling of the present scenario. In *Bioprospecting of tropical medicinal plants*, pp. 1429–1455. https://doi.org/10.1007/978-3-031-28780-0_60

- Giraldo C, Gómez S, Weinhold F, Restrepo A.** 2016. Insight into the mechanism of the Michael reaction. *ChemPhysChem*, 2022–2034. <https://doi.org/10.1002/CPHC.201600166>
- Govindaiah P, Dumala N, Grover P, Jaya Prakash M.** 2019. Synthesis and biological evaluation of novel 4,7-dihydroxycoumarin derivatives as anticancer agents. *Bioorganic and Medicinal Chemistry Letters* **29**(14), 1819–1824. <https://doi.org/10.1016/J.BMCL.2019.05.008>
- Guo Y, Zhang X, Li J, Wang Z, Chen Y, Liu H.** 2018. Novel nitric oxide donors of phenylsulfonylfuroxan and 3-benzyl coumarin derivatives as potent antitumor agents. *ACS Medicinal Chemistry Letters* **9**(5), 502–506. <https://doi.org/10.1021/ACSMEDCHEMLETT.8B00125>
- Han H, Li C, Zhang ZF, An GF.** 2019. RETRACTED: Synthesis, biological evaluation and docking studies of 4-hydroxycoumarin derivatives as anti-liver cancer agents. *Main Group Chemistry* **18**(3), 193–201. <https://doi.org/10.3233/MGC-180717>
- Han HW, Kim HJ, Kim SY, Lee JH, Lee SJ, Kim KW.** 2018. The evaluation of potent antitumor activities of shikonin coumarin-carboxylic acid, PMMB232 through HIF-1 α -mediated apoptosis. *Biomedicine and Pharmacotherapy* **97**, 656–666. <https://doi.org/10.1016/J.BIOPHA.2017.10.159>
- Hersi F, Alkahtani HM, Alanazi AM, Aleanizy FS, Alqahtani FY, Alhoshani AR.** 2020. Design and synthesis of new energy restriction mimetic agents: Potent anti-tumor activities of hybrid motifs of aminothiazoles and coumarins. *Scientific Reports* **10**(1), 1–17. <https://doi.org/10.1038/S41598-020-59685-X>
- Hussain MI, Syed QA, Khattak MNK, Hafez B, Reigosa MJ, El-Keblawy A.** 2019. Natural product coumarins: Biological and pharmacological perspectives. *Chemicke Zvesti* **74**(7), 863–888.
- Ibrar A, Zaib S, Jabeen F, Iqbal J, Saeed A.** 2016. Unraveling the alkaline phosphatase inhibition, anticancer, and antileishmanial potential of coumarin–triazolothiadiazine hybrids: Design, synthesis, and molecular docking analysis. *Archiv der Pharmazie* **349**(7), 553–565. <https://doi.org/10.1002/ARDP.201500392>
- Javahershenas R, Han J, Kazemi M, Jervis PJ.** 2024. Recent advances in the multicomponent synthesis of heterocycles using thiosemicarbazide. *ChemistrySelect* **9**(30). <https://doi.org/10.1002/SLCT.202401496>
- Jones G.** 2014. The Knoevenagel condensation. *Organic Reactions* **15**, 204–599.
- Kakkar S, Narasimhan B, Sharma PK, Kumar S, Kumar V.** 2018. Design, synthesis and biological evaluation of 3-(2-aminoxazol-5-yl)-2H-chromen-2-one derivatives. *Chemistry Central Journal* **12**(1), 1–13. <https://doi.org/10.1186/S13065-018-0499-X>
- Kaur R, Bhardwaj A, Gupta S.** 2023. Cancer treatment therapies: Traditional to modern approaches to combat cancers. *Molecular Biology Reports* **50**(11), 9663–9676. <https://doi.org/10.1007/S11033-023-08809-3>
- Kausar R, Zahoor AF, Tabassum H, Kamal S, Ahmad Bhat M.** 2024. Synergistic biomedical potential and molecular docking analyses of coumarin–triazole hybrids as tyrosinase inhibitors: Design, synthesis, *in vitro* profiling, and *in silico* studies. *Pharmaceuticals* **17**(4), 532. <https://doi.org/10.3390/PH17040532>
- Keri RS, Sasidhar BS, Nagaraja BM, Santos MA.** 2015. Recent progress in the drug development of coumarin derivatives as potent anticancer agents. *European Journal of Medicinal Chemistry* **100**, 257–269. <https://doi.org/10.1016/j.ejmech.2015.06.017>

- Kishkentayeva AS, Zhumagalieva AB, Abdullin KA, Nurmaganbetova ZS, Tashenova RK.** 2025. Synthesis and biological evaluation of some coumarin-triazole conjugates as potential anticancer agents. *Scientia Pharmaceutica* **93**(2), 16. <https://doi.org/10.3390/SCIPHARM93020016>
- Koley M, Han J, Soloshonok VA, Mojumder S, Javahershenas R, Makarem A.** 2024. Latest developments in coumarin-based anticancer agents: Mechanism of action and structure-activity relationship studies. *RSC Medicinal Chemistry* **15**, 10. <https://doi.org/10.1039/d3md00511a>
- Kontogiorgis CA, Hadjipavlou-Litina DJ.** 2020. Biological evaluation of coumarin derivatives as multifunctional agents: A review. *Current Medicinal Chemistry* **27**(7), 1090-1123.
- Koparde S, Hosamani KM, Barretto DA, Joshi SD.** 2018. Microwave synthesis of coumarin-maltol hybrids as potent antitumor and anti-microbial drugs: An approach to molecular docking and DNA cleavage studies. *Chemical Data Collections* **15-16**, 41-53. <https://doi.org/10.1016/J.CDC.2018.03.004>
- Kostova I.** 2011. Synthetic and natural coumarins as cytotoxic agents. *Current Medicinal Chemistry* **18**(24), 3929-3951.
- Kumar TU, Bobde Y, Pulya S, Rangan K, Ghosh B, Bhattacharya A.** 2019. Fused chromeno-thieno/furo-pyridines as potential analogs of lamellarin D and their anticancer activity evaluation. *ChemistrySelect* **4**(36), 10726-10730. <https://doi.org/10.1002/SLCT.201902946>
- Kurt BZ, Gazioglu I, Sonmez F, Kaplancikli ZA, Turan-Zitouni G.** 2019. Synthesis, biological activity and multiscale molecular modeling studies of bis-coumarins as selective carbonic anhydrase IX and XII inhibitors with effective cytotoxicity against hepatocellular carcinoma. *Bioorganic Chemistry* **87**, 838-850. <https://doi.org/10.1016/J.BIOORG.2019.03.003>
- Kurt BZ, Ozten Kandas N, Dag A, Sonmez F, Kucukislamoglu M.** 2020. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. *Arabian Journal of Chemistry* **13**(1), 1120-1129. <https://doi.org/10.1016/J.ARABJC.2017.10.001>
- Lingaraju GS, Balaji KS, Jayarama S, Anil SM, Kiran KR, Sadashiva MP.** 2018. Synthesis of new coumarin tethered isoxazolines as potential anticancer agents. *Bioorganic and Medicinal Chemistry Letters* **28**(23-24), 3606-3612. <https://doi.org/10.1016/J.BMCL.2018.10.046>
- Looker JH, McMechan JH, Mader JW.** 1978. An amine solvent modification of the Kostanecki-Robinson reaction. Application to the synthesis of flavonols. *Journal of Organic Chemistry* **43**(12), 2344-2347. <https://doi.org/10.1021/JO00406A008>
- Lu XY, Wang ZC, Ren SZ, Shen FQ, Man RJC, Zhu HL.** 2016. Coumarin sulfonamides derivatives as potent and selective COX-2 inhibitors with efficacy in suppressing cancer proliferation and metastasis. *Bioorganic and Medicinal Chemistry Letters* **26**(15), 3491-3498.
- Luo G, Zhang X, Wang Y, Li J, Liu H.** 2017. Design, synthesis and biological evaluation of novel 3-substituted 4-anilino-coumarin derivatives as antitumor agents. *Bioorganic and Medicinal Chemistry Letters* **27**(4), 867-874.
- Lv N, Sun M, Liu C, Li J.** 2017. Design and synthesis of 2-phenylpyrimidine coumarin derivatives as anticancer agents. *Bioorganic and Medicinal Chemistry Letters* **27**(19), 4578-4581. <https://doi.org/10.1016/J.BMCL.2017.08.044>
- Ma J, Huang K, Ni X, Chen R, Xu B, Wang C.** 2019. Design, synthesis, biological activity and molecular docking study of coumarin derivatives bearing 2-methylbiphenyl moiety. *Chemical Research in Chinese Universities* **35**(3), 410-417. <https://doi.org/10.1007/S40242-019-8310-7>

- Makarov YA.** 2025. Bioactive coumarins: Bioorganic strategies for targeting enzymes, receptors, and DNA. *Russian Journal of Bioorganic Chemistry* **51**(5), 2304–2335.
<https://doi.org/10.1134/S1068162025601788>
- Mallikarjun E, Shastri LA, Holiyachi M, Samundeeswari S, Jalalpure S.** 2023. Synthesis of novel anticancer coumarin-triazole-chalcone hybrids as potential AKT inhibitor. *Indian Journal of Chemistry* **62**(11), 1162–1170.
<https://doi.org/10.56042/IJC.V62I11.2610>
- Matos MJ, Santana L, Uriarte E, Abreu OA, Molina E, Yordi EG.** 2015. Coumarins—An important class of phytochemicals. In: *Studies in Natural Products Chemistry*, Elsevier **42**, 97–140.
<https://doi.org/10.1016/B978-0-444-63424-5.00003-0>
- Matos MJ, Vazquez-Rodriguez S, Fonseca A, Uriarte E, Santana L, Borges F.** 2017. Heterocyclic antioxidants in nature: Coumarins. *Current Topics in Medicinal Chemistry* **21**(4), 311–324.
<https://doi.org/10.2174/1385272820666161017170652>
- Mattiuzzi C, Lippi G.** 2019. Current cancer epidemiology. *Journal of Epidemiology and Global Health* **9**(4), 217–222.
<https://doi.org/10.2991/JEGH.K.191008.001>
- Menteşe E, Güner A, Polath E, Emirik M, Bektaş H, Kahveci B.** 2021. Synthesis and anticancer activities of some new coumarin derivatives including the triazole ring and their in silico molecular docking studies. *Archiv der Pharmazie* **354**(3), 2000284.
<https://doi.org/10.1002/ARDP.202000284>
- Mohamed KS, Elbially EE.** 2018. Synthesis, characterization, and cytotoxicity evaluation of some new benzo[f]coumarin derivatives. *Journal of Heterocyclic Chemistry* **55**(4), 893–898.
<https://doi.org/10.1002/JHET.3115>
- Mohamed TK, Batran RZ, Elseginy SA, Ali MM, Mahmoud AE.** 2019. Synthesis, anticancer effect and molecular modeling of new thiazolylpyrazolyl coumarin derivatives targeting VEGFR-2 kinase and inducing cell cycle arrest and apoptosis. *Bioorganic Chemistry* **85**, 253–273.
<https://doi.org/10.1016/J.BIOORG.2018.12.040>
- Murray RDH, Mendez J, Brown SA.** 1982. *The natural coumarins: Occurrence, chemistry and biochemistry.* Wiley.
- Patel M, Patel K.** 2019. Naphthalene substituted benzo[c]coumarins: Synthesis, characterization and evaluation of antibacterial activity and cytotoxicity. *Heterocyclic Communications* **25**(1), 146–151.
<https://doi.org/10.1515/HC-2019-0024>
- Pavić K, Beus M, Poje G, Uzelac L, Kralj M, Rajić Z.** 2021. Synthesis and biological evaluation of harmirins, novel harmine–coumarin hybrids as potential anticancer agents. *Molecules* **26**(21), 6490.
<https://doi.org/10.3390/MOLECULES26216490>
- Prateptongkum S, Mahavorasirikul W, Duangdee N.** 2018. Synthesis and anti-proliferative activity of novel oxepin-annulated coumarins. *Arkivoc* **2018**(7), 73–85.
<https://doi.org/10.24820/ARK.5550190.P010.547>
- Putri DEK, Wahyuni FS, Dachriyanus, Zaini MA, Arbain D.** 2022. The predicted models of anti-colon cancer and anti-hepatoma activities of substituted 4-anilino coumarin derivatives using quantitative structure-activity relationship (QSAR). *Journal of King Saud University - Science* **34**(3), 101837.
<https://doi.org/10.1016/J.JKSUS.2022.101837>
- Rohini R, Reddy PM, Shanker K, Hu A, Ravinder V.** 2015. Antimicrobial and anticancer activities of coumarin derivatives: A review. *European Journal of Medicinal Chemistry* **101**, 1–14.

- Sashidhara KV, Kumar M, Khedkar SA, Kumar A, Singh P, Saxena AK.** 2016. Design, synthesis and in vitro evaluation of coumarin–imidazo[1,2-a]pyridine derivatives against cancer induced osteoporosis. *RSC Advances* **6**(83), 80037–80048.
<https://doi.org/10.1039/C6RA15674F>
- Sharma D, Kumar S, Narasimhan B.** 2023. Recent methods for synthesis of coumarin derivatives and their biological activities. *Current Organic Chemistry* **27**(5), 452–470.
<https://doi.org/10.2174/1385272826666220914123456>
- Shen FQ, Wang J, Wang Y, Liu H, Zhang X.** 2017. Synthesis of novel hybrids of pyrazole and coumarin as dual inhibitors of COX-2 and 5-LOX. *Bioorganic and Medicinal Chemistry Letters* **27**(16), 3653–3660.
<https://doi.org/10.1016/J.BMCL.2017.07.020>
- Sinha S, Kumaran AP, Mishra D, Paira P.** 2016. Synthesis and cytotoxicity study of novel 3-(triazolyl)coumarins based fluorescent scaffolds. *Bioorganic and Medicinal Chemistry Letters* **26**(22), 5557–5561.
<https://doi.org/10.1016/J.BMCL.2016.09.078>
- Soni R, Umar S, Shah NN, Balkrishnan S, Soman SS.** 2017. Design, synthesis, and anticancer activity of 3H-benzof[chromen-3-one derivatives. *Journal of Heterocyclic Chemistry* **54**(4), 2501–2510.
<https://doi.org/10.1002/JHET.2853>
- Sriharikrishnaa S, Suresh PS, Prasada KS.** 2023. An introduction to fundamentals of cancer biology. In: *Cancer Biology and Advances in Treatment*, Springer, 307–330.
https://doi.org/10.1007/978-3-031-31852-8_11
- Stadler M, Hellwig V.** 2004. PCR-based data and secondary metabolites as chemotaxonomic markers in high-throughput screening for bioactive compounds from fungi. In *Handbook of industrial mycology*, pp. 288–327.
<https://doi.org/10.1201/9780203970553-13>
- Stefanachi A, Leonetti F, Pisani L, Catto M, Carotti A.** 2018. Coumarin: A natural privileged scaffold for medicinal chemistry. *Molecules* **23**(2), 250.
- Talhi O, Silva AMS, Cavaleiro JAS.** 2000. Natural product-like combinatorial libraries based on privileged structures. 1. General principles and solid-phase synthesis of benzopyrans. *Journal of the American Chemical Society* **122**(41), 9939–9953.
- Tangella Y, Singh SP, Vishwakarma RA, Bharate SB.** 2017. An efficient one-pot approach for the regio- and diastereoselective synthesis of trans-dihydrofuran derivatives: Cytotoxicity and DNA-binding studies. *Organic and Biomolecular Chemistry* **15**, 6837.
<https://doi.org/10.1039/c7ob01456b>
- Thakur A, Singla R, Jaitak V.** 2015. Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *European Journal of Medicinal Chemistry*.
- Tiwari AK, Singh MV.** 2023. Insights into the origin and therapeutic implications of benzopyran and its derivatives. *ChemistrySelect* **8**(20).
<https://doi.org/10.1002/SLCT.202300220>
- Torre D.** 2023. Causes of cancer and mechanisms of carcinogenesis. In *Understanding cancer: From mechanisms to therapeutics*, pp. 229–279.
- Vaarla K, Reddy YT, Reddy PN, Reddy VM.** 2019. 3-(2-(5-Amino-3-aryl-1H-pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-ones as potential anticancer agents: Synthesis, anticancer activity evaluation and molecular docking studies. *ChemistrySelect* **4**(7), 2193–2200.
- Vagish CB, Kumara K, Vivek HK, Bharath S, Lokanath NK, Ajay Kumar K.** 2021. Coumarin-triazole hybrids: Design, microwave-assisted synthesis, crystal and molecular structure, theoretical and computational studies and screening for their anticancer potentials against PC-3 and DU-145. *Journal of Molecular Structure* **1230**, 129899.
<https://doi.org/10.1016/J.MOLSTRUC.2021.129899>

- Venkatachalam H, Kumaravel S.** 2019. The oxygen-containing fused heterocyclic compounds. In: *Heterocyclic Chemistry*, IntechOpen. <https://doi.org/10.5772/intechopen.84666>
- Venugopala KN, Rashmi V, Odhav B.** 2013. Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Research International* **2013**, 963248. <https://doi.org/10.1155/2013/963248>
- Wang Y, Zhang W, Dong J, Gao J.** 2020. Design, synthesis and bioactivity evaluation of coumarin-chalcone hybrids as potential anticancer agents. *Bioorganic Chemistry* **95**, 103530. <https://doi.org/10.1016/J.BIOORG.2019.103530>
- Watson HB.** 1941. Mechanism of the addition and condensation reactions of carbonyl compounds. *Transactions of the Faraday Society* **37**, 707–713. <https://doi.org/10.1039/TF9413700707>
- Williams GH, Stoerber K.** 2012. The cell cycle and cancer. *Journal of Pathology* **226**(2), 352–364. <https://doi.org/10.1002/path.3022>
- Yagawa Y, Tanigawa K, Kobayashi Y, Yamamoto T, Okajima K.** 2017. Cancer immunity and therapy using hyperthermia with immunotherapy, radiotherapy, chemotherapy, and surgery. *Journal of Cancer Metastasis and Treatment* **3**, 218–248.
- Yang L, Wang Y, Li J, Zhang X, Liu H.** 2017. Dual functional small molecule fluorescent probes for image-guided estrogen receptor-specific targeting coupled potent antiproliferative potency for breast cancer therapy. *Bioorganic and Medicinal Chemistry* **25**(13), 3531–3539.
- Zafar SN, Shah AA, Hashmi ZG, Haider AH, Zogg CK, Schneider EB.** 2019. Patient care management of cancer. *World Journal of Surgery* **43**(9), 2203–2210.
- Zengin Kurt B, Sonmez F, Ozturk D, Akdemir A, Angeli A, Supuran CT.** 2019. Synthesis of coumarin-sulfonamide derivatives and determination of their cytotoxicity, carbonic anhydrase inhibitory and molecular docking studies. *European Journal of Medicinal Chemistry* **183**, 111702.