INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Investigating Coumarin: A Potential scaffold in Anticancer Drug Design

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ARTICLE INFO

Published: 04 Aug 2025
Keywords:
Coumarin derivatives; Anticancer agents; Structure–Activity Relationship (SAR); Molecular docking; Tubulin polymerization; Kinase inhibitors; Hybrid compounds; Triazole; VEGFR-2; Carbonic anhydrase IX/XII
DOI:
10.5281/zenodo.16737654

ABSTRACT

The prevalence of cancer around the world emphasises how urgently novel treatments are needed. Because of their wide range of pharmacological characteristics, A class of benzopyrones found in nature called coumarins has become useful scaffolds in the development of anticancer drugs. Recent advancements in the synthesis, biological assessment, and structure–activity relationships (SAR) of coumarin derivatives and hybrids are thoroughly presented in this review. Triazoles, tetrazoles, glycosides, sulfonamides, and metal complexes have all been modified to produce strong cytotoxic agents that target leukaemia cell lines, breast, lung, and pancreatic cancers. These substances work via a variety of pathways, including DNA damage, kinase inhibition, cell cycle arrest, tubulin polymerisation inhibition, and apoptosis induction. Target specificity, selectivity, and pharmacokinetic behaviour are all improved by deliberate substitutions on the coumarin scaffold. These results are further supported by computational investigations such as QSAR modelling and molecular docking. As privileged scaffolds for logical anticancer drug development, coumarins have enormous potential.

INTRODUCTION

Novel, efficient, and selective anticancer therapies are desperately needed, as the worldwide burden of cancer keeps increasing. Natural products, both as therapeutic agents and as structural templates for synthetic modification, have been essential in the search for anticancer drugs in recent decades. Among these, coumarins, a class of heterocycles with oxygen and the benzopyran-2-one core, have become very useful scaffolds in medicinal chemistry. [31-32] Coumarins are naturally found in many different plant species and possess a variety of pharmacological properties, including anti-inflammatory, antimicrobial, antioxidant, and most notably, anticancer effects. [33]

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

A wide variety of coumarin derivatives, such as hybrids with triazoles, tetrazoles, glycosides, thiadiazoles, and metal complexes, have been made possible by recent developments in synthetic chemistry. [34-35] Because of these changes, coumarins' pharmacodynamic and pharmacokinetic profiles have been greatly improved, enabling them to be more selective and bioactive against cancer cells. [36] Key oncogenic targets and cellular functions, such as tubulin polymerisation, DNA topoisomerases, tyrosyl-DNA phosphodiesterase 1 (TDP1), carbonic anhydrases (particularly hCA IX and XII), cyclin-dependent kinases (CDKs), Vascular endothelial growth factor receptor (VEGFR-2), epidermal growth factor receptor (EGFR), and mitochondrial apoptosis pathways, have been demonstrated to be disrupted mechanistically by coumarin-based compounds. [37-38]

Furthermore, when combined with well-known chemotherapeutic agents like topotecan, doxorubicin, and cisplatin, coumarin derivatives have shown synergistic effects. [39] In photodynamic therapy (PDT), some have also shown promise as photosensitisers, providing a dual therapeutic (theranostic) and diagnostic benefit. [40] Crucially, research on the structure–activity relationship (SAR) has shed light on the functional group alterations that lead to improved target binding affinity, selectivity, and cytotoxicity.

Focussing on kinase inhibition assays apoptosis induction studies, in vitro and in vivo cytotoxicity profiles, and molecular docking insights, this review attempts to thoroughly present recent advancements in the design, synthesis, mechanistic assessment, and anticancer potential of coumarin derivatives. Highlighting coumarin's potential as a privileged scaffold in anticancer drug discovery and promoting additional translational efforts to fully realise its therapeutic potential are the objectives.

Structure–Activity Relationship (SAR)

The importance of different substitution sites on its core scaffold in connection to biological activity and pharmacokinetics, as demonstrated by the structure–activity relationship (SAR) of coumarin, a benzopyrone derivative. Positions 2 and 3 contain the α,β-unsaturated lactone moiety (C=C–C=O), which is critical for interactions with nucleophilic biological targets because it is a Michael acceptor and is necessary for electrophilic activity. Alkyl, aryl, or amino groups can be substituted at position 4 to increase lipophilicity, prevent metabolic breakdown, and possibly enhance interactions with particular target proteins. Substitutions at position 5, like OH, Cl, or NO_2, alter electrical characteristics and could improve membrane interactions.

Figure 1 :Showing the Physicochemical properties and SAR of Coumarin

OH, or OCH_3 substitution frequently occurs at position 6, which adds electron-donating groups, enhances the ability to scavenge radicals, and makes metal chelation easier. It is well known that substituents such as OH, OCH_3, or amino groups at position 7 improve fluorescence, enzyme binding, and bioavailability. In the meantime, changes at position 8,especially with CH_3, Cl, or Br, improve blood-brain barrier (BBB) permeability and boost lipophilicity, which is beneficial for medications that target the central nervous system. All things considered, this coumarin SAR map offers a framework for logical drug design, allowing for focused structural changes to maximise the pharmacological profile.

General Synthetic Approaches to Coumarin Derivatives

1. Pechmann Condensation

The Pechmann condensation, which involves reacting phenols with β-ketoesters or β-ketoacids under acid catalysis, is still one of the most popular techniques for creating 4-substituted coumarins. Mechanistically, the coumarin core is formed by intramolecular cyclisation, dehydration, and esterification of the phenolic hydroxyl group with the β-ketoester. Commonly used are homogeneous Lewis's acids (e.g., $ZnCl_2$, $FeCl_3$, $BiCl_3$, $TiCl_4$) and Brønsted acids (e.g., H_2SO_4, HCl, H_3PO_4, CF_3COOH). Green heterogeneous catalysts like Amberlyst-15, Al-MCM-41, sulfated zirconia, and functionalised ionic liquids have recently supplanted these, allowing for solvent-free, microwave-assisted, and recyclable processes with high yields and low environmental impact. For example, under microwave irradiation, Amberlyst-15 catalysed the solvent-free Pechmann synthesis of an 7-hydroxy-4-methylcoumarin in >90% yield.[41]

2. Knoevenagel Condensation

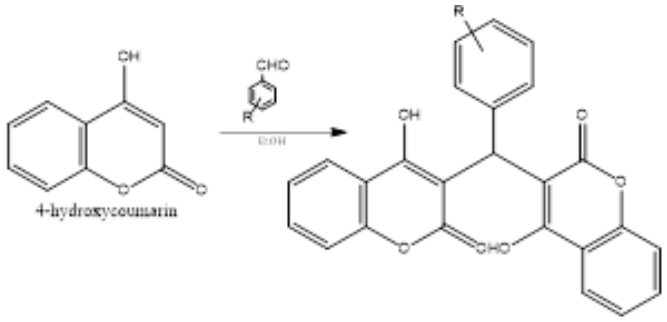
Another reliable method of producing coumarins is the Knoevenagel condensation, which usually involves the condensation of salicylaldehyde derivatives utilizing weak base catalysts (like piperidine and pyridine) and active methylene compounds (such ethyl acetoacetate, malonic acid, and Meldrum's acid), followed by cyclization.This approach allows for customised SAR studies by providing a great deal of flexibility in introducing substitutions at the 3-position and beyond. Deep eutectic solvents (DES) like choline chloride:urea are used in modern green protocols because they function as a solvent and a catalyst at moderate temperatures (about 80 °C), producing highly pure coumarins and recyclable materials. Conditions aided by microwaves or ultrasound further speed up reactions and increase yields.[42]

3. Auxiliary Methods

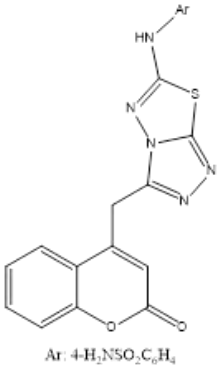
Other synthetic pathways include Wittig, Reformatsky, or flash vacuum pyrolysis methods for particular substitution patterns or complex coumarin systems, and the Perkin reaction, which condenses aromatic aldehydes with anhydrides to produce cinnamic acids that cyclize to coumarins. However, because of the harsher conditions or lower yields, these methods are not as widely used.[43]

Chen Y, Xu J, et al. "DBH2, a novel coumarin derivative, has demonstrated significant potential in inducing apoptosis and inhibiting the proliferation of chronic myeloid leukemia (CML) cells, highlighting its promise as a therapeutic candidate in targeted leukemia treatment. According to the study, DBH2, a novel coumarin derivative, may be used to treat chronic myelogenous leukaemia (CML), including variations that are resistant to TKIs. In K562 and resistant cells, DBH2 caused apoptosis and G2/M phase arrest while significantly inhibiting proliferation. Its efficacy was shown in transgenic

mice and bone marrow cells from CML patients. Indicating caspase-dependent apoptosis, DBH2 activated caspase-3, PARP1, and ROCK1 while inhibiting STAT3/5. Interestingly, DBH2 and imatinib greatly increased survival in CML model mice, suggesting that it can overcome TKI resistance. According to these findings, DBH2 is a promising adjuvant treatment for CML. To demonstrate its therapeutic potential and move it closer to clinical use, more studies on toxicity, pharmacokinetics, and clinical application are required.[1]

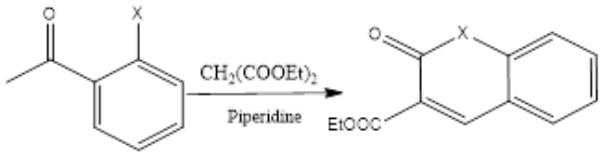


Rawat A, *et al*. Recent advancements in the study of coumarin derivatives have underscored their diverse and potent anticancer properties, with several novel analogs demonstrating significant efficacy across a range of malignancies, including hematological and solid tumors. This article highlights recent advancements in coumarin derivatives as potentially potent anticancer medications. Coumarins, which can be synthesised or derived from natural sources, have strong anticancer, antitumor, and anti-proliferative effects with minimal side effects. Furan, pyrazole, sulfonyl, and azoles are a few examples of these. The study demonstrates how different replacement patterns affect biological activity while improving selectivity and efficacy. It compiles tests against various cancer cell lines, both in vitro and in vivo, particularly using MTT assays. Research on the structure-activity relationship (SAR), which guides the rational creation of potent scaffolds based on coumarins, is also covered in the paper. These discoveries underscore the importance of coumarin derivatives in the development of anticancer drugs and encourage further research to optimise their therapeutic potential. The study offers a comprehensive road map for future drug discovery efforts.[2]



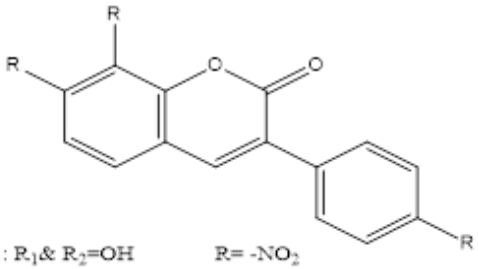
Bakare SB, *et al.* Showed that,The synthesis and biological evaluation of various coumarin and azacoumarin derivatives have revealed promising anticancer activities, with several compounds exhibiting potent cytotoxic effects and mechanistic potential against diverse cancer cell lines. The synthesis and biological assessment of hybrid substituted coumarin and azacoumarin-3-carboxylic acid derivatives (compounds 4–7) are the main focus of this work. The chemical integrity of the synthesised compounds was confirmed through structural characterisation through elemental and spectral analysis. Among these, in vitro cytotoxicity screening was performed on two cancer cell lines: HepG-2 (liver cancer) and MCF-7 (breast cancer) using substituted coumarin-3-carboxylic acids (4a, 5a) and azacoumarin-3-

carboxylic acids (4b, 5b, and 6). The findings support the therapeutic potential of coumarin and azacoumarin scaffolds in drug development by indicating that these derivatives have promising anticancer activity. The study also highlights how crucial molecular changes are to improving cytotoxic efficacy, opening the door for further structural refinement and mechanistic research on these hybrid compounds as potential new anticancer drugs.(3)



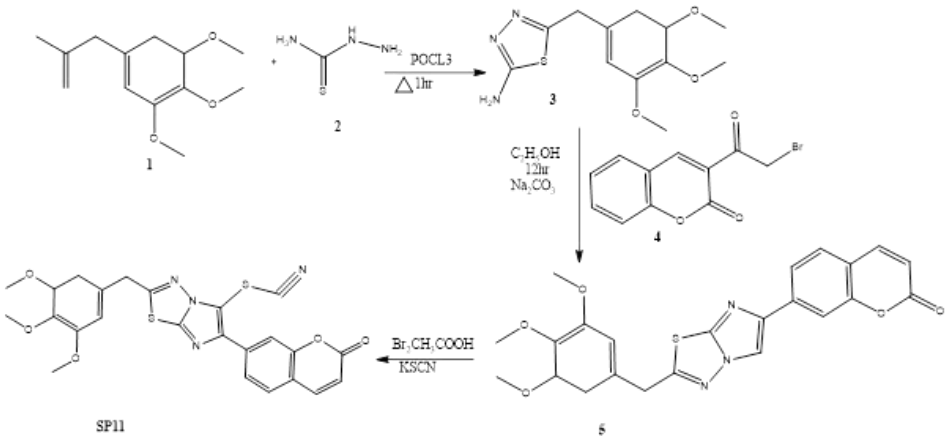
where a, X=O; b, X=NH

Musa MA, *et al*. Reported that, Methylsulfonyl phenyl-substituted 4-phenylcoumarin derivatives have been shown to induce reactive oxygen species (ROS)-mediated cell death in A549 human lung cancer cells, suggesting a potential mechanism of anticancer activity through oxidative stress pathways. This work compiles the cytotoxic potential of newly synthesized 3,4-diarylcoumarin derivatives (4a–i), paying particular emphasis to their activity against the prostate cancer cell line PC-3 and the lung cancer cell line A549; one of the compounds is 4f. 4-phenylcoumarin exhibited the maximum cytotoxicity in A549 cells (CC50 = 13.5 ± 0.15 µM). Mechanistic studies have shown that compound 4f increased ROS, induced cell cycle arrest, reduced mitochondrial membrane potential, and promoted apoptosis. N-acetylcysteine pretreatment was used to confirm ROS-dependence. These results suggest that the coumarin core's methylsulfonyl and diacetoxy substitutions are essential for its anticancer properties. The study supports the development of substituted diarylcoumarins as potential therapeutic agents, particularly for the treatment of lung cancer through ROS-mediated apoptosis, and identifies 4f as a promising lead compound.(4)



Where, 1: R_1& R_2=OH R= $-NO_2$
2: R_1& R_2=$OCOCH_3$ R= $-NO_2$
3: R_1& R_2=$OCOCH_3$ R= $-SO_2CH_3$

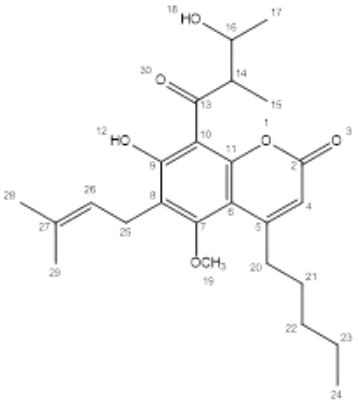
Nirgude S, *et al*. The coumarin–imidazothiadiazole hybrid compound SP11 has demonstrated notable antitumor efficacy by targeting HSP90 and its client proteins, effectively disrupting critical oncogenic signaling pathways and inhibiting tumor progression. The promising anticancer potential of SP11 , a novel HSP90 inhibitor assessed for blood cancers such as lymphoma and leukaemia, is highlighted in this study. SP11 showed selective cytotoxicity towards leukemic cells while sparing normal cells, in contrast to conventional HSP90 inhibitors that are highly toxic and cause heat shock reactions. In both allograft and xenograft mouse models , SP11 successfully decreased tumour burden without showing any signs of toxicity, suggesting favourable safety. Mechanistically, SP11 caused apoptosis by interfering with the function of the HSP90 client protein. It is noteworthy that SP11 binds both the N-terminal and C-terminal domains of HSP90; isothermal calorimetry and in silico studies have confirmed that the C-terminal binding is more effective. SP11 is a promising lead candidate for blood cancer therapy with a plasma half-life of \~2 hours and good bioavailability, deserving of additional clinical development.(5)



Synthesis scheme of SP11

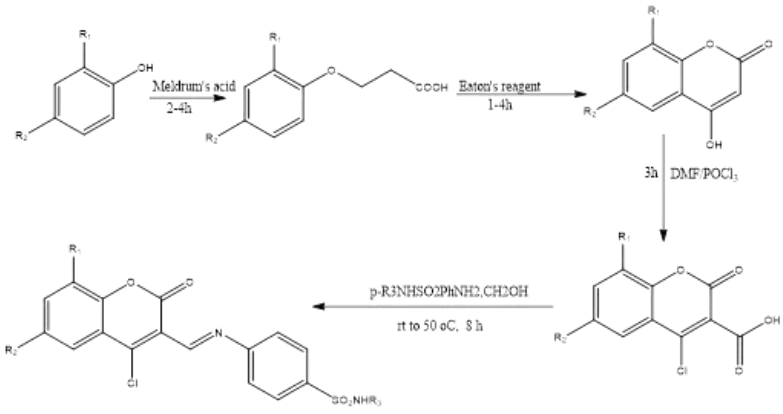
Wang H, *et al.* In cisplatin-resistant ovarian cancer cells, 7-hydroxycoumarin exerts its anticancer effects by inducing cell cycle arrest at the G2/M phase, activating caspases, and promoting apoptosis, highlighting its potential as a therapeutic agent in drug-resistant malignancies. This study provides strong evidence that 7-hydroxycoumarin has anticancer properties against ovarian cancer cells that are resistant to cisplatin. The study shows that 7-hydroxycoumarin preferentially inhibits cancer cell proliferation with negligible effects on normal cells using MTT assays, DAPI and AO/EB staining, flow cytometry, and western blotting. By downregulating important mitotic regulatory proteins, the substance results in cell cycle arrest at the G2/M phase and caspase-mediated apoptosis . According to these results, 7-hydroxycoumarin may have a dual mechanism of action by interfering with the survival and division pathways of resistant cancer cells. Its promise as a lead molecule in treating cisplatin-resistant ovarian cancer is highlighted by its selective cytotoxicity and capacity to overcome chemoresistance. To confirm its clinical applicability, more pharmacokinetic and in vivo research is advised.(6)

Mah SH, *et al.* Benjaminin, a coumarin-based compound, has exhibited notable antiproliferative activity across four human cancer cell lines; this study systematically investigates the cytotoxic potential of benjaminin (1), shedding light on its mechanism of action and therapeutic relevance ,a coumarin that was extracted from the roots of the medicinally used plant Calophyllum inophyllum . MS, IR, and NMR spectroscopy were used to characterise the compound's structure. Using the MTT assay, its anti-proliferative efficacy was assessed against four cancer cell lines: K562, SNU-1, Hep-G2, and NCI-H23. Benjaminin (1) exhibited broad-spectrum cytotoxicity , with SNU-1 stomach cancer cells showing the greatest impact (IC_{50} = 70.42 µM). The results highlight benjaminin's potential as a lead compound for the development of anticancer drugs. Even though the activity is moderate, more structure-activity relationship (SAR) studies are advised to increase potency. This study encourages further investigation of compounds derived from C. inophyllum and provides important new information on natural product-based cancer treatments.(7)



Chemical structure of Benjaminin

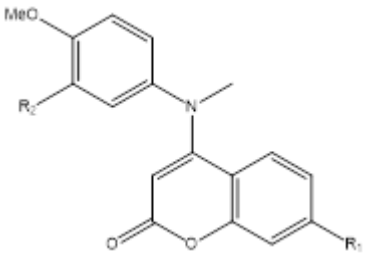
Irfan A, *et al.* Recent progress in the synthesis of coumarin–sulfonamide hybrids has highlighted their promising dual role as anticancer agents and enzyme inhibitors, offering valuable insights into their structure–activity relationships and therapeutic potential. This thorough investigation emphasises the broad biological range and significance of coumarin–sulfonamide hybrids in contemporary medicinal chemistry, as well as their substantial therapeutic potential. When combined with the sulfonamide moiety , the well-known pharmacophore coumarin shows improved anticancer, antibacterial, antifungal, antioxidant, and antiviral activities . Recent synthetic techniques, such as the use of catalysts, substrate modifications, and optimised reaction conditions to produce high-yield coumarin–sulfonamide derivatives, are methodically covered in the review. These hybrids are useful in drug development pipelines because of their use as carbonic anhydrase inhibitors and in oncology . With its insights into structure–activity relationships and synthetic innovations, this article is an essential resource for chemists and pharmacologists. It effectively highlights the coumarin–sulfonamide scaffolds' potential as multifunctional therapeutic agents with significant clinical utility in the future.(8)



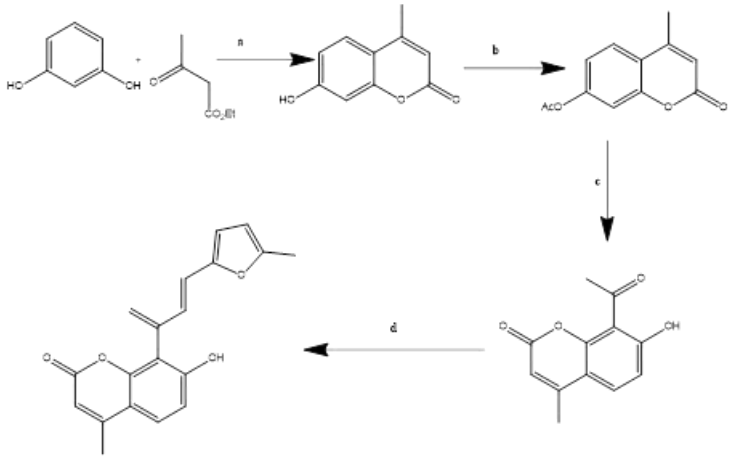
Synthesis of coumarin containing sulfonamide derivative

Dinparast L, *et al.* A QSAR analysis of 4-substituted coumarins has revealed their potent inhibitory activity against tubulin polymerization, providing critical insights into the structural features essential for enhanced anticancer efficacy. This study presents a well-structured computational investigation into the anticancer potential of coumarin derivatives , focusing on QSAR modeling to predict antiproliferative activity against HepG2 liver cancer cells. Using a dataset of 31 analogs and molecular descriptors generated via Dragon, HyperChem, and ACD/Labs, the authors employed genetic algorithm-based multiple linear regression (GA-MLR) to develop predictive models. The resulting QSAR models, with r^2 values of 0.670 and 0.692 , demonstrate acceptable accuracy and reliability, further supported by validation parameters. This work offers valuable insights for rational drug design and supports the continued

development of coumarin-based anticancer agents. The methodology is sound and replicable, making it a useful reference for researchers exploring computational drug discovery. Overall, this study contributes meaningfully to in silico anticancer drug development.(9)



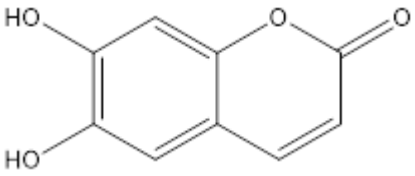
El-Telbany RFA, *et al*. Selected synthetic coumarin and benzofuran derivatives have demonstrated significant antitumor activity, attributed in part to their ability to inhibit multiple kinases involved in cancer progression and survival pathways. The design, synthesis, and biological assessment of novel coumarin and benzofuran derivatives as possible treatments for breast cancer are presented in this work. Compound 14 outperformed the reference medication lapatinib by demonstrating the strongest antiproliferative activity against MCF-7 cells among the compounds tested (IC_{50} = 0.07 µM). According to mechanistic studies, compound 14 inhibited multiple kinases (−39% to −97%), enhanced pre-G1 apoptosis , and caused G2/M cell cycle arrest , indicating broad-spectrum kinase inhibition . With caspase-3 activation, EGFR suppression, and elevated catalase levels, in vivo investigations validated its effectiveness in Ehrlich mammary adenocarcinoma models . Furthermore, its favourable pharmacokinetic and drug-likeness properties were confirmed by in silico analyses. Compound 14 is a strong lead candidate for additional research and development as a multitargeted anticancer agent for the treatment of breast cancer.(10)



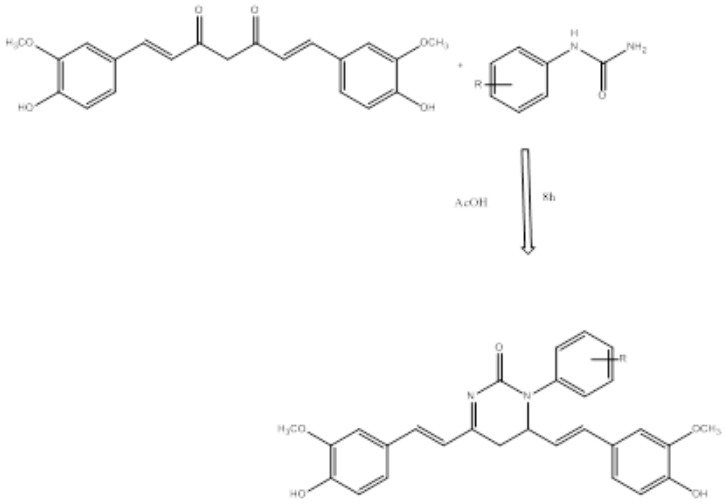
Synthesis of the target oxopyrimidine, thiopyrimidine, oxocarbonitrile, aminonicotinonitrile, and pyranoline chromenone derivatives Reagents and reaction conditions: (a) H_2SO_4, rt, 24h; (b) acetic anhydride, reflux, 2h; (c) $AlCl_3$, oil bath, 2h; (d) EtOH, 5-methylfurfural, NaOH, rt, overnight.

Faber KN, *et al*. Showed that, The bioactive coumarin derivative esculetin attenuates hepatic stellate cell activity by provoking cellular senescence through modulation of the PI3K–Akt–GSK3β signaling cascade.This study presents valuable insights into the antifibrotic potential of esculetin , a coumarin derivative, by demonstrating its ability to induce senescence in hepatic stellate cells (HSCs) —a critical step in mitigating hepatic fibrosis. Using primary rat HSCs, the authors effectively showed that esculetin reduces proliferation and activation markers (Acta2, Col1a1) while enhancing senescence markers (Cdkn1a/p21, P53) and

quiescence indicators (Pparg, Lrat). The induction of senescence was confirmed through SA-β-Gal staining and was shown to depend on the PI3K-Akt-GSK3β signaling pathway , as evidenced by increased phosphorylation of Akt and GSK3β. This mechanistic clarity strengthens the therapeutic relevance of esculetin. Overall, the findings support esculetin as a promising candidate for antifibrotic therapy , targeting HSC senescence as a novel strategy to halt or reverse liver fibrosis progression.(11)

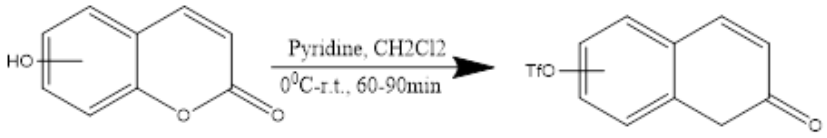


Ali A, *et al*. Curcumin's semi-synthetic analogs with the pyrimidine moiety are chemically modified to act as anticancer agents. Three semi-synthetic curcumin analogues bearing a pyrimidinone moiety are synthesised and evaluated in this work, with a particular emphasis on their potential as anticancer agents. In a single-dose NCI assay, compound C2 demonstrated the most promising activity among them, showing over 68% growth inhibition in 31 out of 59 cancer cell lines. Notably, C2 outperformed curcumin, gefitinib, and imatinib in its ability to combat leukaemia, breast, colon, and central nervous system cancer lines. C2 was non-selective in 5-dose assays but displayed low micromolar GI_{50} values (1.31–4.68 μM) . Favourable binding to EGFR was found by molecular docking, which was backed by π-cationic interactions and hydrogen bonds. As a strong and structurally optimised anticancer lead , C2 is highlighted in this work, promoting additional research and target-specific refinement for clinical use.(12)

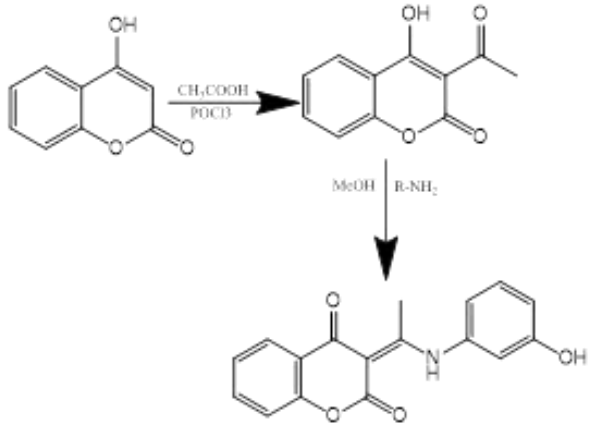


de Mélo NB, *et al.* Coumarin derivatives exhibit anti-lung cancer activity in A549 cells by inhibiting epithelial–mesenchymal transition (EMT) and suppressing cellular migration, thereby targeting key processes involved in tumor progression and metastasis. In this work, coumarin derivatives and isosteres are synthesised using palladium-catalyzed cross-coupling reactions, and their anticancer potential is assessed. compound 9f was the most effective of the compounds, exhibiting moderate toxicity towards normal NIH-3T3 cells and strong cytotoxicity against NSCLC cell lines A549 and H2170 (CC_{50} = 7.1 and 3.3 μM , respectively). Interestingly, 9f successfully inhibited IL-1-induced epithelial-to-mesenchymal transition (EMT) in A549 cells, which is a crucial stage in the development of cancer. The mesenchymal

phenotype was reversed, as evidenced by the disruption of F-actin organisation and the downregulation of vimentin expression. Additionally, 9f's anti-metastatic potential was supported by the significant reduction of cell migration observed in wound-healing assays. According to these results, 9f may be a promising therapeutic candidate for NSCLC , especially in cases where the progression of lung cancer is driven by EMT.(13)

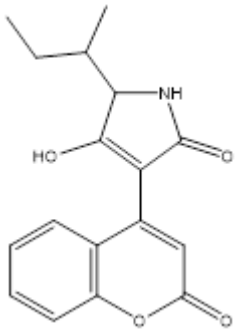


Krstic A, Pavic A, *et al.* When it comes to pancreatic cancer cells, the coumarin-palladium (II) complex is a strong and non-toxic anticancer agent. This study provides strong evidence for the anticancer efficacy of a coumarin–palladium (II) complex against pancreatic carcinoma. At micromolar concentrations (0.5 µM), the compound showed strong anti-proliferative, anti-colony formation, and anti-migratory effects on pancreatic cancer cells in vitro. Key genes linked to the progression of pancreatic ductal adenocarcinoma, apoptosis induction , an elevated BAX/BCL-2 ratio , and downregulation of SOX9 and SOX18 , were identified by mechanistic analysis. Crucially, substantial tumour mass reduction without detectable toxicity, including hepatotoxicity, was confirmed by in vivo validation using a zebrafish xenograft model . The compound's selectivity and therapeutic safety are highlighted by these findings. Given the limited effectiveness of existing treatments, the study presents a promising new direction in pancreatic cancer therapy . To fully explore its therapeutic potential, more clinical and pharmacological research is necessary. [14]

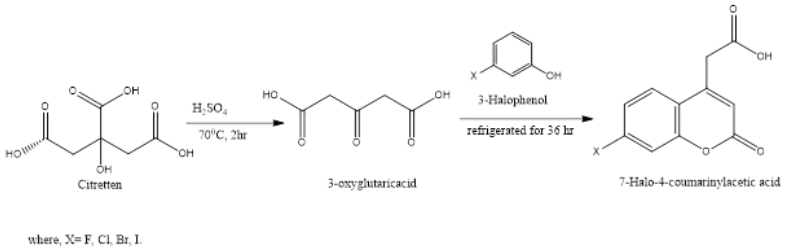


Niranjan V, *et al.* The creation of new coumarin derivatives that function as NUDT5 antagonists by limiting the synthesis of ATP in breast cancer cells. In order to treat breast cancer, this work investigates the logical, template-based design of a new coumarin derivative that targets ADP-sugar pyrophosphatase (NUDT5).The compound, (2R)-2-((S)-sec-butyl)-5-oxo-4-(2-oxochroman-4-yl)-2,5-dihydro-1H-pyrrol-3-olate , showed strong binding affinity in docking studies (−6.574 kcal/mol) and favorable MM-GBSA energy (−29.15 kcal/mol). Molecular dynamics (500 ns) confirmed binding stability (RMSD ≈ 2.4 Å), while metadynamics estimated a high unbinding energy (75.17 kcal/mol), reinforcing strong receptor interaction. In vitro validation using the

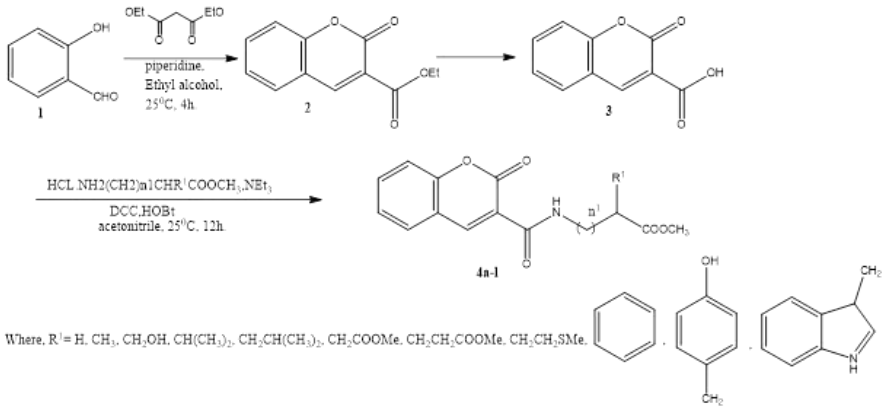
MCF-7 breast cancer cell line demonstrated an IC_{50} of 55.57 µg/mL, indicating promising anticancer potential. The use of quercetin as a positive control strengthens comparative insights. This integrated computational and experimental approach highlights the compound's therapeutic relevance and supports further investigation of phytoactive derivatives in combating chemoresistance in breast cancer. (15)



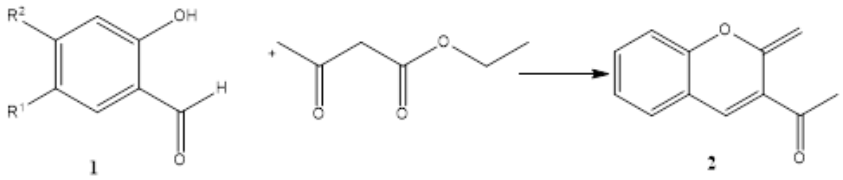
Mustafa YF, *et al.* Novel derivatives of 7-halocoumarin-4-acetic acid have been synthesized and evaluated for their antitumor properties, demonstrating promising cytotoxic activity and potential as lead structures for further anticancer drug development. Four derivatives of 7-halo-4-coumarinylacetic acid (RY1–RY4) are synthesised and evaluated in this work, with an emphasis on their potential as antitumor agents. Spectroscopic techniques verified the structures, and pre-ADMET was used for in silico pharmacokinetic profiling. Of the compounds that were synthesised, RY1 demonstrated the most promising antitumor activity. It significantly inhibited the MCF-7 (breast cancer) and HeLa (cervical cancer) cell lines, outperforming its analogues. All tested lines displayed consistent activity patterns, despite RY2–RY4 demonstrating comparatively lower efficacy when compared to 5-fluorouracil. The potential of RY1 as a lead compound is supported by its noteworthy cytotoxic activity and advantageous pharmacokinetic characteristics. The study is methodologically sound overall and points to RY1 and RY2 as useful scaffolds for the future development of broad-spectrum anticancer drugs. (16)



Fathalla W, *et al.* Simple Production of Certain Coumarin Derivatives and Their Cytotoxicity via Inhibition of VEGFR2 and Topoisomerase II.In this work, new semisynthetic coumarin derivatives that target VEGFR2 and topoisomerase II are synthesised and biologically evaluated with the goal of dual inhibition-induced apoptosis in cancer cells. Using DCC/HOBt-mediated synthesis, the compounds were created by coupling coumarin-3-carboxylic acid with amino acid methyl esters. In molecular docking studies, compounds 4k and 6c showed strong binding affinities that resembled co-crystallized ligand interactions. Notably, both substances demonstrated high apoptosis rates (>97%) and strong cytotoxicity against MCF-7 breast cancer cells, with IC50 values of 4.98 and 5.85 µM. Their potential as dual-target anticancer agents were highlighted by the fact that their inhibitory activity against VEGFR2 and topoisomerase II was on par with or better than that of conventional medications. The work is well-organised and offers insightful information about specific drug development tactics.(17)



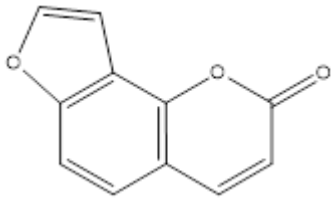
Lin J, *et al.* By combining network pharmacology and in vitro assay, 3-(coumarin-3-yl)-acrolein derivatives' design, synthesis, and anticancer activity studies were demonstrated. A thorough investigation into the synthesis and biological assessment of coumarin-acrolein hybrids as possible anticancer agents is presented in this manuscript. In order to create compounds with strong antiproliferative activity, particularly against A549 and KB cancer cell lines, and low cytotoxicity on healthy cells, the authors used a molecular hybridisation technique. The most promising lead was compound 6e, which successfully blocked the migration and invasion of cancer cells and triggered mitochondria-dependent apoptosis through the PI3K/AKT-Bcl-2 pathway. The mechanistic insight is strengthened by the combination of in vitro validation and network pharmacology. The work is thorough, contains pertinent biological assays, and has a clear structure. The results add significant knowledge to the field of coumarin-based anticancer drug design and provide encouraging leads for the future development of targeted chemotherapeutics.(18)



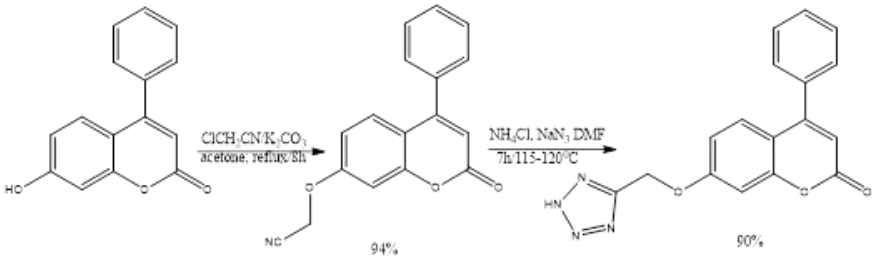
Synthesis of furanocoumarins

Ahmed S, *et al*. Furanocoumarins have emerged as promising anticancer agents, with recent studies elucidating their mechanistic roles in cell cycle regulation, apoptosis induction, and signaling pathway modulation, underscoring their therapeutic potential across various malignancies. This study thoroughly demonstrates the promising anticancer potential of furanocoumarins, highlighting their involvement in various cancers such as lung, breast, glioma, and leukaemia. The article effectively describes the different mechanisms through which these natural substances act, including the induction of apoptosis, autophagy, antioxidation, and metastasis inhibition. Notably, the ability of furanocoumarins to work synergistically with traditional chemotherapeutic agents adds translational value. The study offers valuable insights into the signalling pathways modulated by furanocoumarins and is well-structured. However, a more critical examination of the manuscript's pharmacokinetics, safety profiles, and challenges in clinical translation would be beneficial. Nevertheless, it persuasively advocates for the

value of natural substances in modern oncology and encourages further research into furanocoumarin-based therapies. It contributes a timely and insightful perspective to the literature on cancer drug discovery.(19)

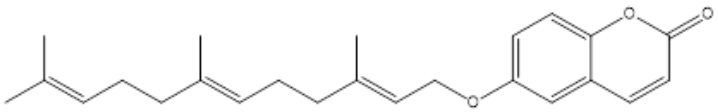


El-Sayed WA, *et al.* Study shows, A series of novel 1,2,3-triazole–coumarin–glycoside hybrids and their 1,2,4-triazolyl thioglycoside analogs have been synthesized and evaluated for anticancer activity, with docking simulations and biological assays indicating selective targeting of the mitochondrial apoptotic pathway. Recent triazole-coumarin-glycosyl hybrids and their tetrazole equivalents with different sugar moieties are thoroughly and methodically analyzed in this paper. A range of cancer cell lines were used to test the synthesised compounds' cytotoxic activities; derivatives 10, 13, and 15 showed notable efficacy, particularly against Paca-2, Mel-501, PC-3, and A-375. Of them, coumarin-tetrazole 10 was a particularly intriguing option because to its superior inhibitory efficacy against EGFR, VEGFR-2, and CDK-2/cyclin A2. Through the upregulation of caspase and cytochrome c and the downregulation of PD-1, mechanistic studies demonstrated its pro-apoptotic effect, offering significant therapeutic relevance. The high binding affinities were further confirmed by molecular docking. All things considered, this study makes important advances in the field of anticancer drug development and identifies coumarin-tetrazole 10 as a promising lead compound.(20)



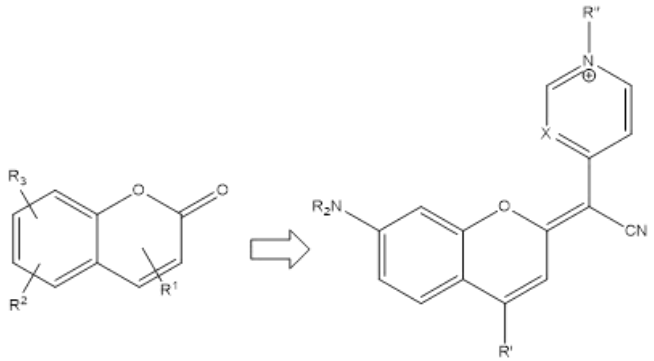
. Synthesis of tetrazolylmethyloxy (coumarine) derivative

Zhou R, *et al.* Indicates that Isoprenylated coumarin demonstrates significant antiproliferative effects in pancreatic cancer cells under nutrient-deprived conditions, primarily through the inhibition of autophagy, suggesting a promising strategy for targeting metabolically stressed tumor microenvironments.This work offers a promising exploration of the anticancer properties of the isoprenylated coumarin compound DCM-MJ-I-21 in pancreatic cancer cell lines when glucose is depleted. To clarify the mechanism of action, the well-structured study combines autophagic flux analysis by western blotting with cytotoxicity assays. The results demonstrate that when glycolysis is inhibited, DCM-MJ-I-21 specifically targets cancer cells, most likely by interfering with autophagy, a vital survival mechanism under metabolic stress. Strong mechanistic validation is provided by the observed rise in LC3-II levels and resemblance to well-known autophagy inhibitors (chloroquine, Spautin-1). The translational value is increased by using both 2D and 3D cultural models. The potential of DCM-MJ-I-21 as a selective therapeutic agent for pancreatic cancer is supported by this work, which also provides important insight into nutrient-dependent cancer vulnerabilities. (21)



Isoprenylated coumarin lead compound designated as DCM-MJ-I-21.

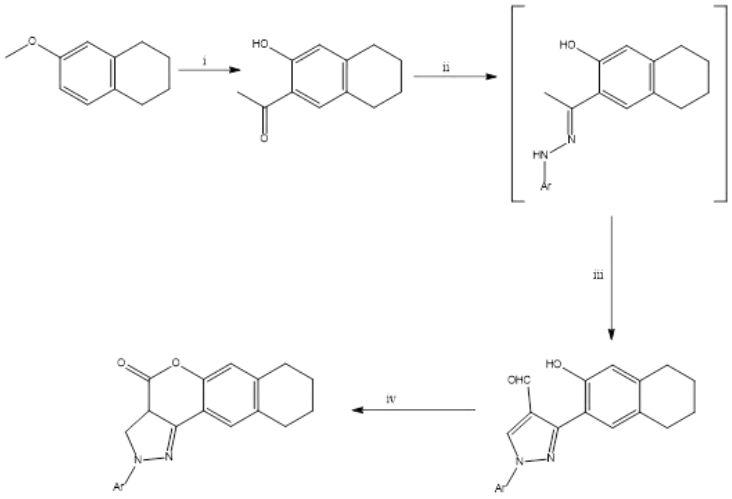
Ruiz J, *et al.* COUPY coumarins have emerged as a new class of mitochondria-targeted agents for photodynamic therapy, exhibiting potent anticancer activity through selective mitochondrial localization and light-induced cytotoxicity. This work offers a convincing investigation of new low-molecular-weight coumarins as potential photosensitisers for photodynamic therapy (PDT) in the treatment of cancer. Three lead candidates with high phototherapeutic indexes (up to 71) under both normoxic and hypoxic conditions were successfully identified by the authors after they carried out a systematic structure–activity relationship study across a library of 15 compounds. These coumarins showed strong light-induced cytotoxicity in cancer cells while sparing healthy cells, demonstrating exceptional selectivity. According to mechanistic research, these substances localise in mitochondria, produce reactive oxygen species (ROS), and, when activated by visible light, cause apoptosis and/or autophagy. Their clinical potential is further enhanced by their dual function as efficacious therapeutic and diagnostic (theranostic) agents. All things considered, this work offers solid candidates for additional preclinical development and makes a significant contribution to the design of effective, mitochondria-targeting PDT agents.(22)



General structureof theclassical coumarin scaffold and of coumarin-basedCOUPYderivatives.

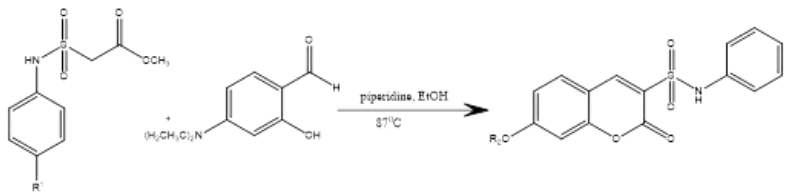
Molnár B, *et al.* A series of 2-pyrazolyl-estradiol derivatives, including pyrazolocoumarin–estradiol hybrids and related analogs, have been synthesized via a multistep approach and evaluated in vitro for their anticancer potential, revealing promising activity profiles and structure–activity relationships. This study presents a well-executed synthetic and pharmacological exploration of novel 2-heterocyclic estradiol derivatives, particularly focusing on 2-pyrazole and pyrazolocoumarin hybrids. The use of Friedel-Crafts acetylation, Vilsmeier-Haack cyclization, and subsequent oxidative and reductive modifications demonstrates an efficient and versatile synthetic strategy. The generation of both steroidal and non-steroidal analogs allows for comparative structure-activity relationship analysis. Notably, the application of microwave-assisted synthesis enhances reaction efficiency. The successful formation of A-ring-integrated pyrazolocoumarins is especially innovative. Biological evaluation reveals that several compounds exhibit significant overall and cancer cell-specific cytotoxicity, with IC_{50} values

reported for the most active derivatives. These findings suggest that 2-pyrazole modified estradiols could serve as promising hormone-independent anticancer agents. The study offers valuable insights for future development of estradiol-based therapeutics targeting cancer.(23)



(i) AcCl, AlCl3 (4 equivalents), DCM, N2 atm., 0 25 C, 4 hours,(ii) Ar-NHNH2HCl, NaOAc, EtOH, MW, 100 C, 20 min, (iii) POCl3, DMF, 0 C, 30 min, then 60 C, overnight, (iv) Jones reagent, acetone, reflux, 30 min

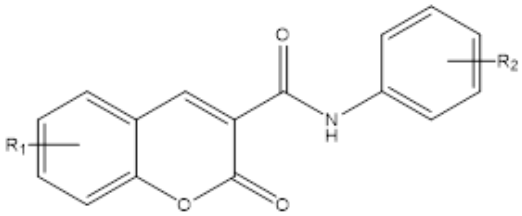
Wang Z, *et al.* showing that Coumarin-based sulfonamide and amide derivatives have been strategically designed and synthesized, with in vitro evaluations revealing noteworthy antitumor activity, highlighting their potential as promising scaffolds in anticancer drug development.This work highlights the antitumor potential of novel coumarin-based sulfonamide and amide derivatives by presenting their synthesis and biological evaluation. Compound 9c demonstrated significant cytotoxicity (IC_{50} = 9.33 μM), similar to 5-fluorouracil, when the compounds were screened against MDA-MB-231 and KB cell lines. Crucially, 9c demonstrated several anticancer mechanisms, such as apoptosis induction and inhibition of cell invasion and migration. Its pro-apoptotic effect was confirmed by the production of ROS and the upregulation of caspase-3. The study backs up the importance of coumarin scaffolds in the development of anticancer drugs by showing a strong structure–activity relationship. All things considered, compound 9c shows promise as a lead candidate for further research, and the study adds important information to the body of knowledge regarding coumarin-based anticancer medications. To confirm therapeutic potential, more in vivo research is encouraged.(24)



Coumarin Sulfonamides

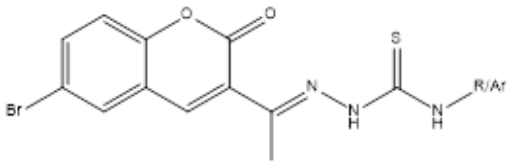
Phutdhawong W, *et al.* This study shows that Coumarin-3-carboxamide derivatives have been synthesized and subjected to comprehensive biological evaluation, revealing significant activity profiles that support their potential as versatile candidates in anticancer drug discovery.

The design, synthesis, and biological assessment of novel coumarin-3-carboxamide derivatives are presented in this work, with an emphasis on their potential as anticancer agents. The compounds' antibacterial activity was minimal, but some of their derivatives—specifically, 14b (4-fluorobenzamide) and 14e (2,5-difluorobenzamide)—showed significant cytotoxicity against HepG2 and HeLa cancer cell lines, with IC_{50} values that were comparable to those of doxorubicin. Interestingly, compound 14b showed selective anticancer activity with negligible toxicity to normal LLC-MK2 cells. Benzamide was identified as a crucial pharmacophore by molecular docking studies, which also confirmed their anticancer potential by demonstrating a strong interaction with the CK2 enzyme. This work supports additional preclinical investigation of these derivatives as selective CK2 inhibitors with decreased off-target toxicity and provides a promising path for the development of targeted cancer therapies based on coumarin scaffolds.(25)



R_1= H, R_2=4-COOH
R_1= 8-EtO, R_2= 4-Br
R_1= 6-Br, R_2= 4-I
R_1= 6-Cl, R_2= 3-NO_2, 4-Cl

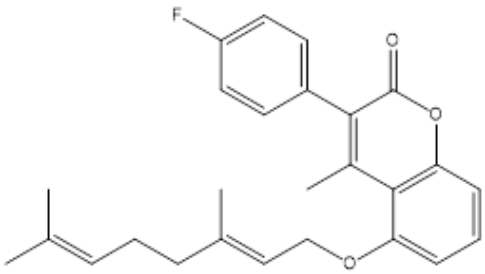
Sarhan MO, et *al.* Study explores the discovery of new coumarin-based lead with potential anticancer, cdk4 inhibition and selective radiotheranostic effect: Synthesis, 2d & 3d qsar, molecular dynamics, in vitro cytotoxicity, radioiodination, and biodistribution studies. Using both experimental and computational methods, this study describes the synthesis of new 6-bromo-coumarin derivatives and their potential as anticancer agents. Compound 2b emerged as the most promising candidate with a strong in vitro cytotoxicity against MCF-7, A-549, and CHO-K1 cell lines (IC_{50} = 0.0136–0.054 µM) and an excellent docking energy (ΔG = –15.34 kcal/mol) according to the QSAR model's strong predictive accuracy (r^2 = 0.92). Its mechanism of action was validated by CDK4 inhibition assays (IC_{50} = 0.036 µM), and molecular dynamics confirmed its stable binding. Moreover, radioiodination of 2b demonstrated its potential as a radiotheranostic agent by producing ^{131}I-2b with favourable tumour selectivity and biodistribution in mice. Compound 2b is a very promising candidate for targeted cancer diagnosis and treatment, according to this thorough investigation.(26)



Bromo derivative of substituted thiazolidine derivative of coumarin

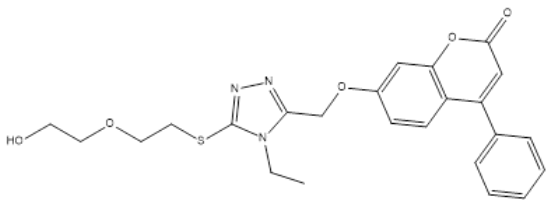
Artemova AO, *et al.* Reportedly, Novel 5-hydroxycoumarin-based inhibitors of tyrosyl-DNA phosphodiesterase I (TDP1) have been developed, demonstrating the ability to sensitize tumor cell lines to topotecan, thereby enhancing the chemotherapeutic efficacy through targeted DNA repair inhibition. The synthesis and biological assessment of new 5-hydroxycoumarin derivatives with monoterpene moieties as tyrosyl-DNA phosphodiesterase 1 (TDP1) inhibitors are presented in this work. Inhibiting TDP1, an essential enzyme for DNA repair, can make tumour cells more vulnerable to topoisomerase I toxins like topotecan. Geraniol conjugate 33a showed the strongest TDP1 inhibition of all the synthesised compounds (IC_{50} = 130 nM). Effective binding within the catalytic pocket was confirmed by molecular docking studies, which may have prevented enzymatic activity. Notably, these

conjugates showed selective sensitisation by increasing topotecan's cytotoxicity in HeLa cells while having no effect on normal HEK293A cells. A promising new class of TDP1 inhibitors is identified in this work, which may improve the effectiveness of currently available chemotherapeutics and be useful in the development of more potent combination therapies for the treatment of cancer.(27)



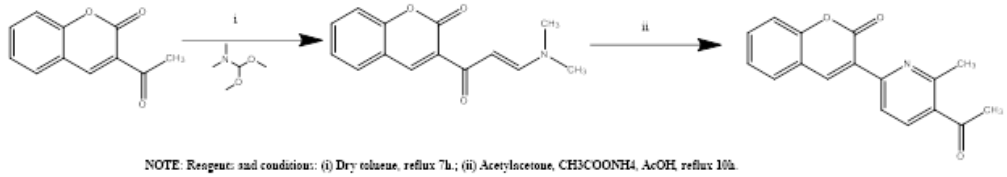
Fluorophenyl derivative of -4-methyl-2H-chromen-2-one

El-Sayed WA, *et al*. This paper explores on a novel series of 1,2,3-triazole–coumarin hybrid glycosides and their tetrazolyl analogues have been designed and evaluated for anticancer activity, with molecular docking studies indicating strong binding affinities toward key oncogenic targets including EGFR, VEGFR-2, and CDK-2.The continuous issue of drug resistance and toxicity in anticancer therapy is addressed in this study by creating novel 1,2,3-triazole-coumarin-glycosyl hybrids and their thioglycoside and acyclic counterparts. The synthesized compounds' derivatives 8, 10, 16, and 21 showed potent cytotoxicity against a variety of human cancer cell lines. Compound 10 triggered mitochondria-mediated apoptosis in MCF-7 cells by drastically changing the expression of Bcl-2, cytochrome c, caspase-7, and Bax.Compounds 8 and 10 outperformed common medications like erlotinib and sorafenib in their inhibitory activity against EGFR, VEGFR-2, and CDK-2/cyclin A2, according to kinase inhibition assays. Strong binding affinity to the target enzymes was confirmed by molecular docking, which also offered structural insights for upcoming optimisation. Overall, this study finds promising coumarin-triazole hybrids that have low toxicity and multi-target anticancer potential, which supports additional research for clinical use.(28)



1,2,4 triazole derivative of 2H-chromen-2-one

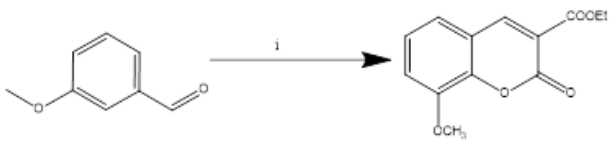
Al-Rashood ST, *et al.* Researched on a new series of 3-(6-methylpyridin-2-yl)coumarin-based chalcones has been developed, exhibiting potent antiproliferative activity through selective inhibition of cancer-associated carbonic anhydrase isoforms IX and XII, underscoring their potential as targeted anticancer agents. In contrast to the broadly dispersed hCA I and II, cancer-associated hCA IX and XII are preferentially targeted by isoform-selective carbonic anhydrase (CA) inhibitors developed in this work. With sub- to low-micromolar Ki values, the synthesized 3-(6-methylpyridin-2-yl)coumarin derivatives (3 and 5a–o) demonstrated robust and selective inhibition of hCA IX/XII and little activity against hCA I/II, suggesting their selectivity and lower danger of off-target effects. Importantly, these compounds also showed promising antitumor activity on the NCI-59 cancer cell panel, indicating that they may be used as a treatment. The structural design seems logical and well-supported by bioactivity data, and the study successfully connects CA inhibition and anticancer efficacy. According to these results, this coumarin-based series could be a useful platform for the future development of specific anticancer drugs with low systemic Toxicity. (29)



NOTE: Reagent and condition: (i) Dry toluene, reflux 7h.; (ii) Acetylacetone, CH3COONH4, AcOH, reflux 10h.

El-Baky AEA, *et al.* Study identifies novel Derivatives of 3-Substituted 8-Methoxycoumarin as Anti-Breast Cancer Medicines. This work uses ethyl 8-methoxycoumarin-3-carboxylate as the starting scaffold to synthesize and evaluate novel hybrid coumarin derivatives in an engaging manner.

Comprehensive spectral data (^{1}H NMR, ^{13}C NMR, elemental analysis, MS) supported the strong structural elucidation. Compound 6 is unique among the produced compounds because of its potent cytotoxic action on the breast cancer cell lines MCF-7 and MDA-MB-231. Its mechanism seems to be complex and includes inducing S-phase cell cycle arrest and apoptosis in addition to inhibiting tubulin polymerization, sulfatase, and aromatase.The inclusion of brominated derivatives adds structural diversity and potential for enhanced biological activity. Overall, the study is scientifically sound, and Compound 6 shows promising characteristics for further development as an anticancer agent. The findings contribute meaningfully to coumarin-based anticancer drug discovery.(30)



Synthesis of 8-methoxycoumarin

CONCLUSION

It has been demonstrated that coumarin and its structural derivatives are extremely versatile chemicals with significant anticancer potential. They are good candidates for both standalone and combination therapies because of their multitarget mechanism of action and scaffold modification-assisted physicochemical properties. Future studies should concentrate on pharmacodynamic optimisation, off-target toxicity reduction, and clinical efficacy validation. All of the data points to the importance of coumarin as a key framework for the upcoming generation of anticancer drug discovery.

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HOW TO CITE: Pavan Patil, Bhavesh Akbari, Pradeep Kumar M. R., Investigating Coumarin: A Potential scaffold in Anticancer Drug Design, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 8, 345-365. https://doi.org/10.5281/zenodo.16737654