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Review paper

Coumarin Based Analogues, a Vivid Terrace for Developing Oncology Medications

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KEYWORDS

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Topoisomerase
Triazole
Halo coumarin
Quinone
Aromatase

ABSTRACT

Coumarins are found in higher plants like Rutaceae and Umbelliferae and essential oils of cinnamon bark, cassia leaf, and lavender oil. It shows different biological properties, viz antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-HIV, antihypertension, anticoagulant, anticancer, antiviral, anti-inflammatory, analgesics, antidiabetic, anti-depressive, and other bioactive properties. Despite numerous effects of coumarins in the search for bioactive compounds, they remain as one of the most versatile class of compounds for anticancer drug design and discovery. Coumarin and its derivatives possess anticancer activity against different types of cancers such as prostate, renal, breast, laryngeal, lung, colon, CNS, leukemia, malignant melanoma. In this review, current developments of coumarin-based anticancer agents viz simple coumarin, furanocoumarin, pyranocoumarin, pyrone-substituted coumarin, and their important derivatives have been discussed. The coumarin-triazole, coumarin-chalcone, coumarin-thiosemicarbazone derivatives, and coumarin-metal complexes have been found more potent than coumarin. Hence, further study and structural improvement on coumarin and its derivatives may lead to the design and development of more potent anticancer agents.

1. Introduction

Cancer is a lethal disease, and it is responsible for the millions of deaths across the globe every year. According to the latest IARC reports, in 2022, there were an estimated 20 million new cancer cases and 9.7 million deaths. The estimated number of people who were alive within 5 years following a cancer diagnosis was 53.5 million. About 1 in 5 people develop cancer in their lifetime, approximately 1 in 9 men and 1 in 12 women die from the disease. In addition, the key sheet of WHO reported that cancer is responsible for about 14 million global demises in 2022, and one out of every sixth death is related to this [1,2].

It contains a wide class of natural and synthetic compounds that showed versatile pharmacological effects. Despite numerous effects of coumarins in the search for bioactive compounds, they still remain as one of the

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most versatile class of compounds for anticancer drug design and discovery. Coumarin and its derivatives possess anticancer activity against different types of cancers such as prostate, renal, breast, laryngeal, lung, colon, CNS, leukemia, malignant melanoma. The study of coumarin dates to 1820, when Vogel first extracted coumarin from the tonka bean (Dipteryxodorata). Chemically, coumarin (2H-1-benzopyran-2-one) belongs to the subgroup of lactones. These are benzo-α-pyrone 1 usually known as coumarin and benzo-γ-pyrone 1a as chromone, (Fig. 1), differing in a carbonyl group at position 1 of the pyrone ring [3].

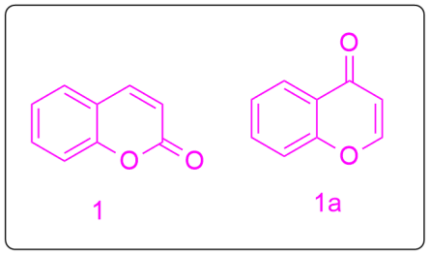


Fig. 1 Chromone

It is extensively available in various parts of the plant kingdom, and its derivatives occur alternatively in the roots, stems, fruits, and seeds of plants. Usually, coumarin exist as free state in plants owing to their polar structure, and they exhibit blue fluorescence on UV-light absorption [4]. It has been largely studied since its skeleton is present in many biologically active agents. Coumarin and some of its derivatives have become drugs, as the anticoagulants warfarin 3, acenocoumarin 4, and phenprocoumon 5, all acting as vitamin K antagonists, the choleretics armillarisin A 6 and hymecromone (umbelliferon) 7, and the antibiotic novobiocin 8 (Fig. 2), which is a potent inhibitor of bacterial DNA gyrase (GyrB) [5].

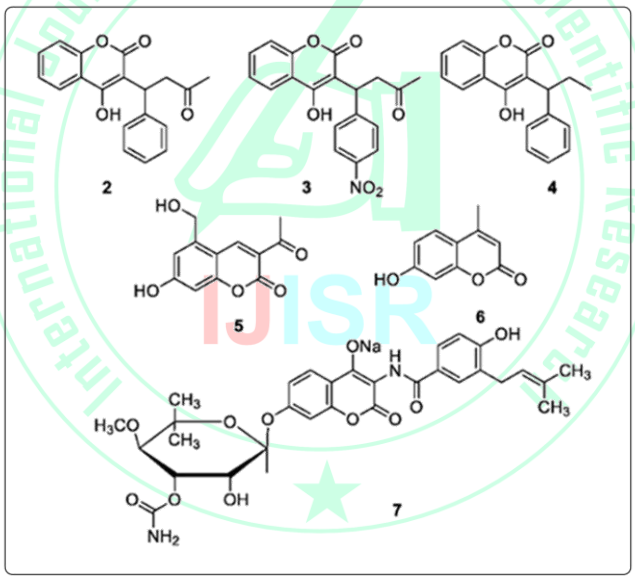


Fig. 2 Structures of some coumarin drugs: the anticoagulants warfarin 2, acenocoumarin 3, and phenprocoumon 4, the choleretics armillarisin A 5 and hymechromone 6, and the antibiotic novobiocin 7.

Biological investigations of coumarins revealed the engrossment of innumerable pathways by which coumarins act as anticancer agents. Coumarins target several pathways in cancer such as kinase inhibition, cell cycle arrest, angiogenesis inhibition, heat shock protein (HSP90) inhibition, telomerase inhibition, antimitotic activity, carbonic anhydrase inhibition, monocarboxylate transporters inhibition, aromatase inhibition and sulfatase inhibition. Furthermore, such research helped in derivation of structure activity relationship studies (SARs) which led to the discovery of diverse substitution of coumarin nucleus, thereby enhancement/ broadening of activity continuum [6-8].

2. Synthetic Strategies of Coumarines

The synthesis of coumarins and their derivatives has attracted considerable attention in research and development to both organic and medicinal chemists. Keeping in view the importance of coumarins, we have compiled numerous synthetic strategies for the preparation of substituted Coumarines, in recent years as shown in Fig. 3. The Pechmann Condensation (3a) allows the synthesis of coumarins by reaction of phenols with β-keto esters. The reaction is conducted with a strong Bronsted acid such as methanesulfonic acid or a

Lewis acid such as $AlCl_3$ [9] An efficient annulation (3b) of phenolic acetates with acrylates in the presence of $[Rh_2(OAc)_4]$ as catalyst and formic acid as reducing agent provides high yield of coumarin derivatives via C-H bond activation. The addition of NaOAc as a base increased the yield of the products. The reaction is quite successful for both electron-rich as well as electron-deficient phenolic acetates, affording coumarins with excellent regioselectivity (Fig. 3) [10].

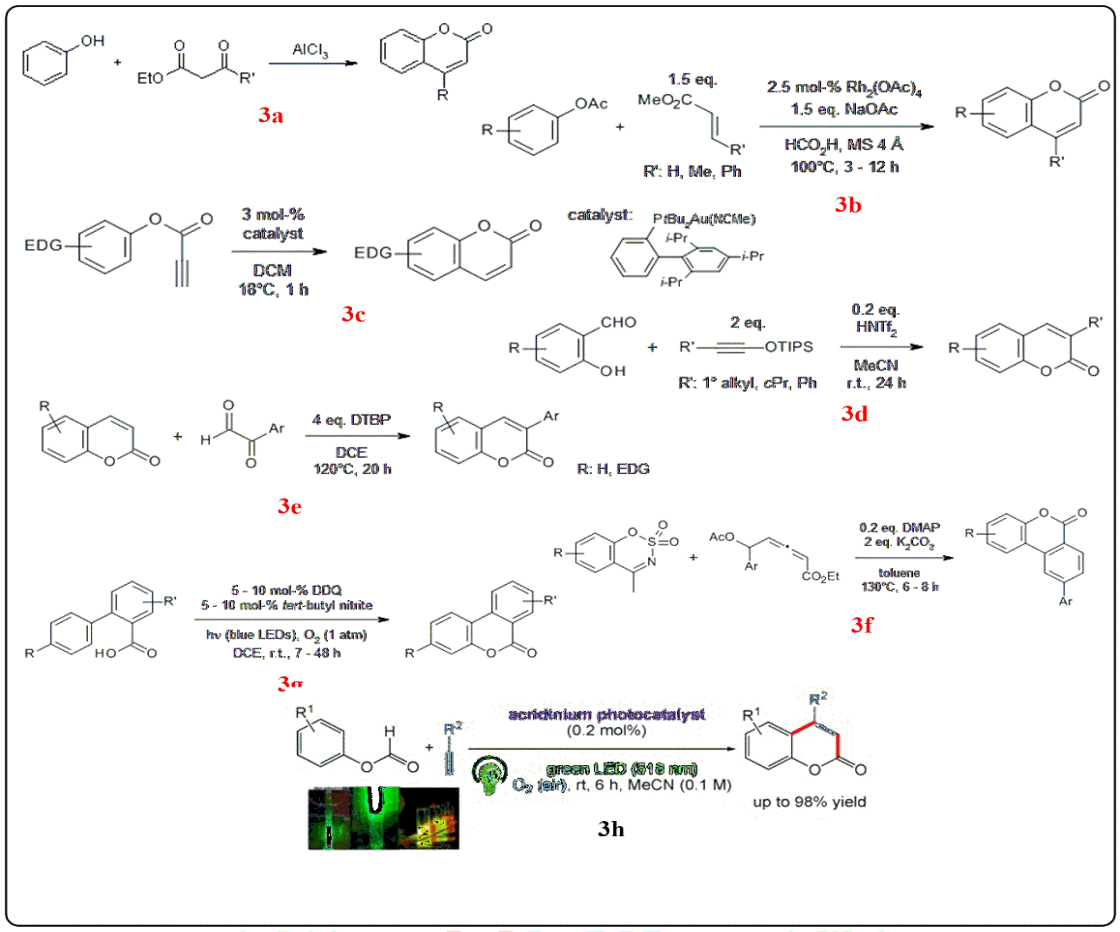


Fig. 3 Synthetic Strategies of Coumarines

Methods are reported for the efficient assembly of a series of phenol-derived propiolates, and their Au(I)-catalyzed cyclization (intramolecular hydroarylation) to give the corresponding coumarins (3c). A related process is described for the conversion of propargyl ethers such into the isomeric 2*H*-chromene precocene, a naturally occurring inhibitor of juvenile hormone biosynthesis [11] (Fig. 3). A new approach for the synthesis of coumarins (3d) from alkynes and salicylaldehydes is disclosed. Unlike the previous benzannulation reactions of siloxy alkynes that all proceed by electron-inversed Diels–Alder mechanism, this process represents a new [4+2] cyclization. In the presence of the superior $HNTf_2$ catalyst, a wide range of coumarins were efficiently synthesized. This process was also extended to the synthesis of 2-quinolones. The polarized electron-rich triple bond might react sequentially with the aldehyde and hydroxy group by polarity switching in the stepwise formation of the C–C and C–O bonds. Control experiments provided insights into the mechanistic understanding [12]. A facile and efficient synthetic approach (3e) to various valuable 3-aryl- and 3-aroylcoumarins by the direct arylation and aroylation of coumarins with glyoxals in a metal-free manner is presented. The aryl glyoxal is for the first time recognized to serve as an aryl surrogate in addition to its role as an aroyl transfer reagent via a simple switch in reaction conditions. The approach accommodates a broad substrate scope and high yields of the two types of cross-coupling reactions starting from identical starting materials [13]. A DMAP-catalyzed sequential benzannulation and lactonization strategy in which δ-acetoxy allenoate functions as a *5C-synthon* in its reaction with cyclic sulfamidate imines is reported (3f). This platform delivers π-extended coumarin frameworks under metal-free conditions via allylic elimination followed by Mannich coupling, proton shifts, C–N bond cleavage, and lactonization as key steps. The driving force for this domino reaction is the formation of the diene-ammonium intermediate and O–S bond cleavage. ESI-HRMS has been useful in gaining insights into the reaction pathway [14]. A visible-light photocatalytic aerobic oxidative lactonization of arene C(sp^2)–H bonds proceed in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *tert*-butyl nitrite (TBN) (3g). Under the optimized conditions, a range of 2-arylbenzoic acids is

converted into the corresponding benzocoumarin derivatives in moderate to excellent yields. This method is characterized by its atom economy, mild reaction conditions, the use of a green oxidant and metal-free catalysis [15] (Fig. 3). A straightforward, environmentally friendly, and highly efficient, metal-free, visible light mediated organophotocatalysed method (3h) has been devised for synthesizing potentially biologically active substituted coumarin scaffolds. This method involves the reaction between substituted ethynylbenzene and substituted phenyl formate under visible light photoredox catalysed conditions at room temperature using acridinium as photocatalyst [16] (Fig. 3).

3. Anti-cancer Potential of Coumarines

coumarin is characterized by a simple structure, benzopyrone, on which there are multiple substitution sites. According to the different substituents, coumarins can be divided into five classes: simple coumarins, pyranocoumarins, furocoumarins, dicoumarin, and isocoumarin (Fig. 4). By modifying the structure of coumarin and introducing functional groups, researchers have synthesized more complex and diverse coumarin derivatives with more application value and more performance. In recent years, coumarin and its derivatives have shown an extremely wide and inestimable potential in the field of anti-tumor therapy. Their anti-tumor mechanisms are very diverse, including inhibiting carbonic anhydrase (CA), targeting PI3K/Akt/mTOR signaling pathway, inhibiting aromatase and sulphatase, targeting HSP90, telomerase, inhibiting multiple drug resistance (MDR), and inducing apoptosis, etc. In this review, the anti-tumor activity, and the research progress of coumarins have been emphasized in recent years [17].

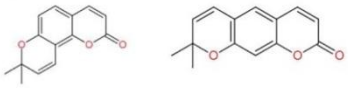
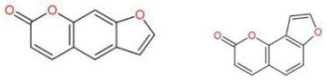
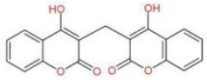
Species	Chemical formula	Introduction
Simple coumarins		Only have substituents on the benzene ring of coumarin
Pyranocoumarins		The C-6/ C-8 on the benzene ring is replaced by the pyran group
Furocoumarins		The C-6/ C-8 on the benzene ring is replaced by the furan group
Dicoumarin		The dimer of coumarins
Isocoumarin		The isomer of coumarin

Fig. 4 Structure of simple coumarins, pyranocoumarins, furocoumarins, dicoumarin, and isocoumarin.

Moreas et al. developed a new series of compounds (Fig. 5) by molecular hybridization of the nucleobases uracil and thymine, or the xanthine theobromine, with coumarins, and linked through 1,2,3-triazole heterocycles, and evaluated for their in vitro anticancer activity colon carcinoma (HCT116), laryngeal tumor cells (Hep-2), and lung carcinoma cells (A549). The hybrid compound 4 exhibited better activity in the series, showing an IC50 of 24.19 ± 1.39 μM against the HCT116 cells, with a selectivity index (SI) of 6. The in-silico search for pharmacological targets was achieved through molecular docking studies on all active compounds, which suggested that the synthesized compounds possess a high affinity to the Topoisomerase 1–DNA complex, supporting their antitumor activity. These findings indicate that molecular hybridization from natural derivative molecules is an interesting approach to seek new antitumor candidates [18].

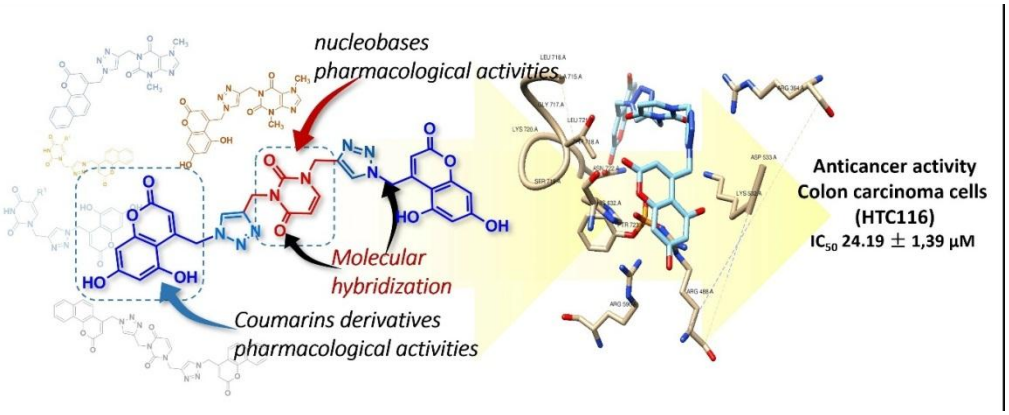


Fig. 5 Hybrid Compound **4**

Mustafa et al. aimed to synthesize four novel skipped diene-3-halocoumarin (Fig. 6) conjugates coded SDC1-SDC4 5 and explored their anticancer activity. On the other hand, the anticancer and cytotoxicity of these conjugates were investigated against eight cancer and three healthy cell lines, respectively, using an MTT-probing technique. These findings projected the influence of a 3-position substitute of the coumarin backbone on the biological activities under research. From these, it is concluded that the chemical structures of SDC1-SDC4 may represent potent anticancer compatible scaffolds [19].

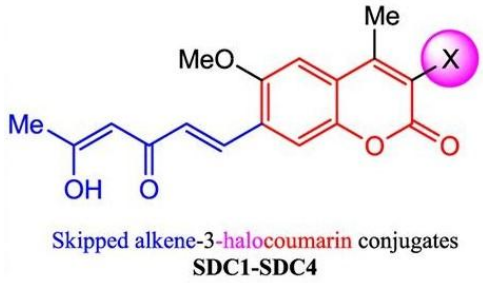


Fig. 6 Structure of Compound **5**

Wang and coworkers designed a solvent-free green methodology to synthesize substituted coumarin containing sulphonamides derivatives, and screened for carbonic anhydrase inhibitory activities for their in vitro anticancer activity against mouse melanoma cells (B16–F10) and breast carcinoma cell lines (MCF-7), and two human carbonic anhydrases against hCAs II (cytosolic off target isoform) and hCAs IX (trans-membrane tumor-associated isoform). In this study, the most active derivative was substituted dimethyl pyrimidine-based coumarin benzene sulfonamide 6 (Fig. 7), which displayed the highest and remarkable significant anticancer potential against MCF-7 cell lines with IC_{50} 0.0088 µM when compared with the reference drugs doxorubicin IC_{50} 0.072 µM and semaxanib IC_{50} 0.012 µM.

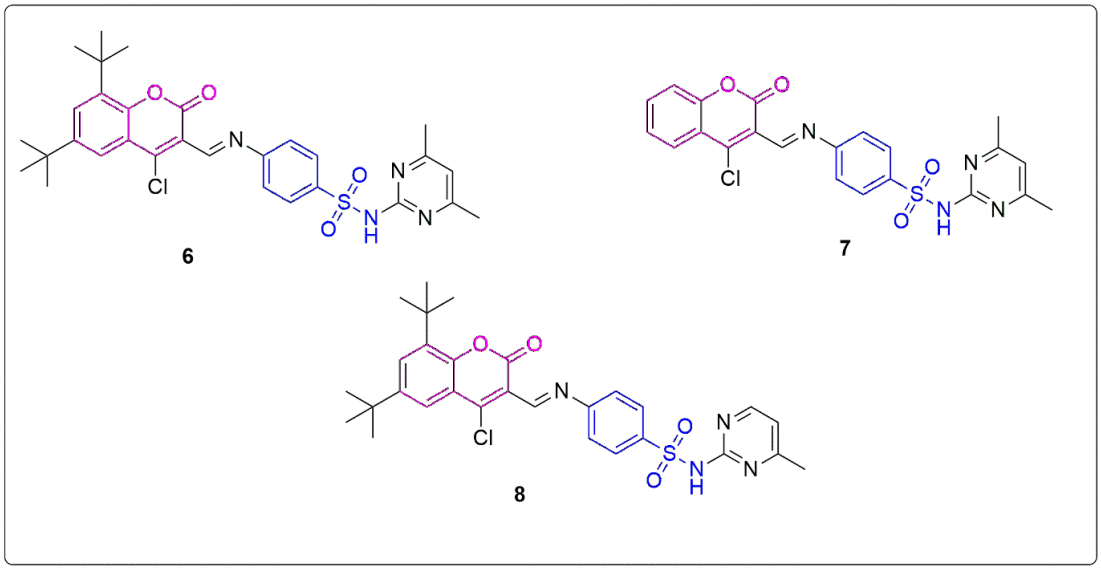


Fig. 7 Structures of coumarin containing sulphonamides derivatives (**6-8**)

Both the virtual screening and anticancer activity results for MCF-7 showed that the over-expressed CA might be the most active therapeutic candidate that coumarin sulfonamides interacted with. The substituted pyrimidine-based coumarin benzene sulfonamide 7 (Fig. 7) and di-*tert*-butyl substituted coumarin benzenesulfonamide containing pyrimidine 8 (Fig. 7) displayed strong inhibition against hCAs II and hCAs IX isoforms with IC_{50} values of 0.063 µM and 0.124 µM respectively, when compared with standard drugs acetazolamide (AAZ) and sulfanilamide (SA). The SAR studies investigated that the introduction of thiazole and methyl pyrimidine substitutions in the benzenesulfonyl ring of the coumarin enhanced the anticancer and carbonic anhydrase inhibition activities of the below-mentioned coumarin derivatives [20].

Coumarin carrying triazole moiety has gained wide attention from the researchers and is largely used as anticancer scaffold. Triazole moiety favours improvement in solubility and enhances binding affinity to the receptors and enzymes. The chemical structures of various triazole based coumarin derivatives are presented excellent biological activity, triazolyl-coumarin based fluorescent probes were designed to evaluate cytotoxic activity against MCF-7 and HeLa cancer cell lines. The compounds 9 and 10 (MTT cytotoxicity) were turned

out to be the most potent. Notably, compound 5 (MTT assay) presented significant cytotoxicity by targeting Gal-1 protein apoptosis in cell treatment as compared to the positive control cisplatin. In addition to this, coumarin tagged β-lactum triazole hybrids aided in DNA replication and controlled DNA damaging. SAR studies proposed that the presence of nitro and chloro group on phenyl at C-3 position favoured the anticancer activity as a result 11, 12 exhibited substantial activity (Fig. 8) [21-22].

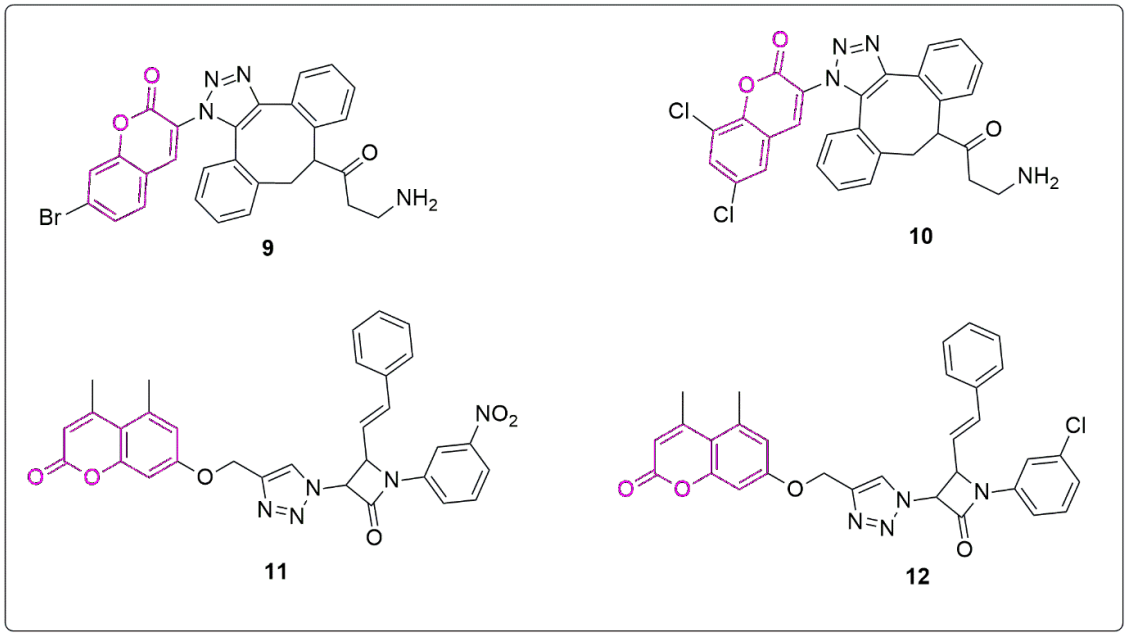


Fig. 8 Coumarin-triazole Hybrid Compounds (**9-12**)

Three-component reaction for the synthesis of novel 3-heteroaryl-coumarin utilizing acetyl coumarin synthon under ultrasonic irradiation was developed using chitosan-grafted poly(vinylpyridine) as an eco-friendly catalyst. The process is a simple, facile, efficient procedure for the preparation of compounds displaying a thiazole ring linked to coumarin moiety. The cytotoxic activity of the newly prepared compounds was determined against liver carcinoma cell line (HEPG2-1) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Compounds 13, 14, and 15 have promising activities (IC_{50} value of 0.43 ± 0.66, 0.29 ± 0.45, and 0.49 ± 0.38 µM, respectively), compared with doxorubicin standard drug (IC_{50} value of 0.31 ± 0.48 µM) (Fig. 9) [23].

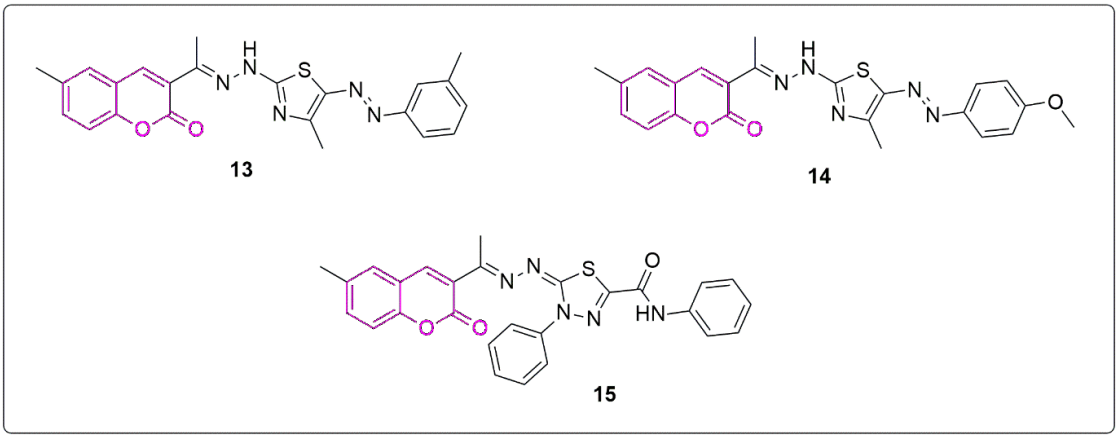


Fig. 9 Coumarin-thiazole hybrid Compounds (**13-15**)

Chen et al. in 2004 synthesized a series of coumarin derivatives as potent competitive inhibitors of aromatase, and was observed that compounds (16-19) (Figure 10) showed maximum activity against aromatase as compared to Naringenin. Coumarin inhibitors was investigated for selectivity towards aromatase through receptor transfection assays and compounds (16-19) were found to have no effect on other enzymes and hormone receptor including steroid 5α-reductase, ERα, ERβ, ERRα, ERRβ and ERRγ, this assessment suggested that compounds are potent and selective inhibitor of aromatase (Figure 10). Three functional group chlorophenyl, benzyl, and methoxy were necessary for the activity. Upon comparing study of the most potent compound and androstenedione, it was found that coumarin nucleus and chlorophenyl group mimics A, B and D-ring of the substrate respectively. The methyl group of the substrate is pointed towards the heme group

present at the binding site of aromatase, which is the site of hydroxylation and the 4-benzyl group of the compound is found to be in close alignment of the substrate. Phenyl group was unable to accommodate in between C-19 and heme group due to its bulky sized. On the other hand, benzyl group due to its flexibility fits in space between C-19 and heme. 7-methoxy group of coumarin acts as hydrogen bond donor due to close structural alignment with C-3-keto oxygen of the substrate. 3-(4-chlorophenyl) is electron withdrawing group due to its alignment near the C-17 keto oxygen suggests that electron pulling group in this vicinity may be preferred [24].

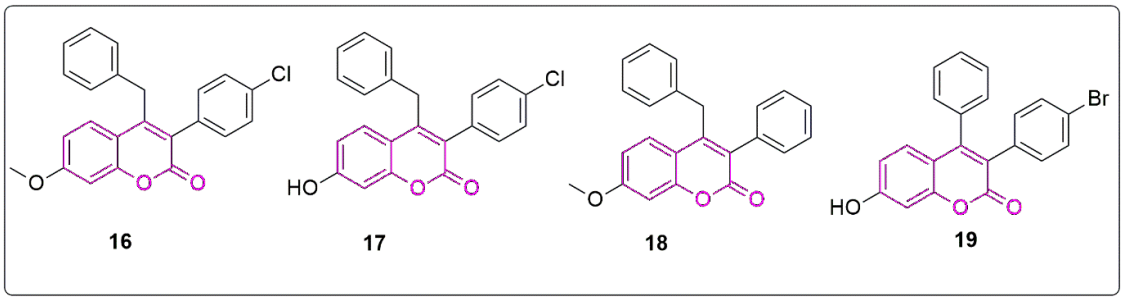


Fig. 10 Structure of coumarin derivatives (**16-19**) as aromatase inhibitors.

Leonetti et al. designed, synthesized, and evaluated a series of new aromatase inhibitors bearing a coumarin scaffold (C) are reported. Properly substituted coumarin derivatives displayed the highest aromatase inhibitory potency and selectivity over 17-alpha-hydroxylase. The modeling of the aromatase inhibition data by Comparative Molecular Field Analysis (CoMFA/GOLPE 3D QSAR approach. The relationship between aromatase inhibition and the steric and electrostatic fields generated by the examined Coumarine inhibitors enables a clear understanding of the nature and spatial location of the main interactions modulating the aromatase inhibitory potency. Among the tested inhibitors, the two coumarin derivatives 20 and 21 (Figure 11) can be considered promising leads for further structural modifications guided by the valuable information derivable from our detailed analysis of the SAFIR and from the close examination of the is contour maps developed from the very informative and statistically significant two-field PLS model ES [25].

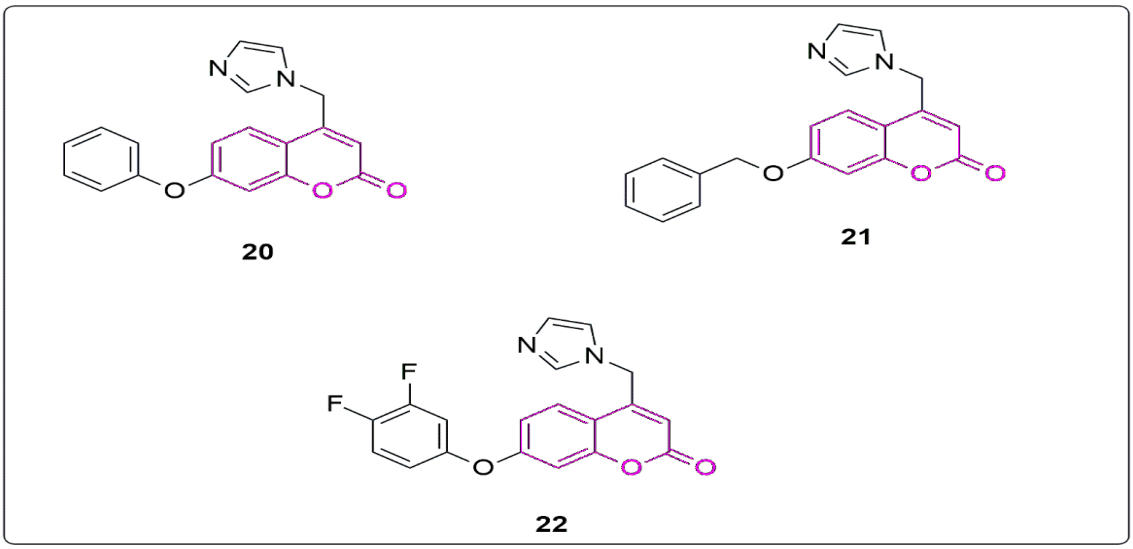


Fig. 11 Structure of coumarin derivatives (**20-22**)

Stefanachi et al. synthesized and evaluated of a series of new aromatase (AR, CYP19) inhibitors bearing an imidazole ring linked to a 7-substituted coumarin scaffold at position 4 (or 3) are reported. Many compounds exhibited an aromatase inhibitory potency in the nanomolar range along with a high selectivity over 17-α-hydroxylase/C17-20 lyase (CYP17). The most potent AR inhibitor was the 7-(3,4-difluorophenoxy)-4-imidazolylmethyl coumarin 22 (Figure 11) endowed with an IC_{50} = 47 nM. Docking simulations on a selected number of coumarin derivatives allowed the identification of the most important interactions driving the binding and clearly indicated the allowed and disallowed regions for appropriate structural modifications of coumarins and closely related heterocyclic molecular scaffolds [26].

Several new coumarin prototype derivatives have been synthesised and evaluated for their Erα and ERβ selective activity. Coumarin prototype compounds 23 & 24 (Fig. 12) were found to be ERα selective and the most active, exhibiting potential antiproliferative activity against both ER +ve & ER -ve breast cancer cell lines. In addition, both the compounds were also devoid of any estrogenic activity, which correlates to their

antiestrogenic behaviour in the two breast cancer cell lines. Assessment of selectivity using specific SiRNAs for ERα and ERβ revealed that most of the compounds showed ERα and ERβ-mediated action. Computational docking analysis of active compounds 23 and 25 (Fig. 12) was conducted to correlate the interaction with the two receptors and it was found that the docked conformations of the coumarin prototype, compound 23 at ERα and ERβ active sites were superimposable on each other. However, the unique orientation of the aminoalkoxy side chain of novel chromene (prototype III) compound 25 in the ERβ binding cavity may be responsible for its potential biological response [27].

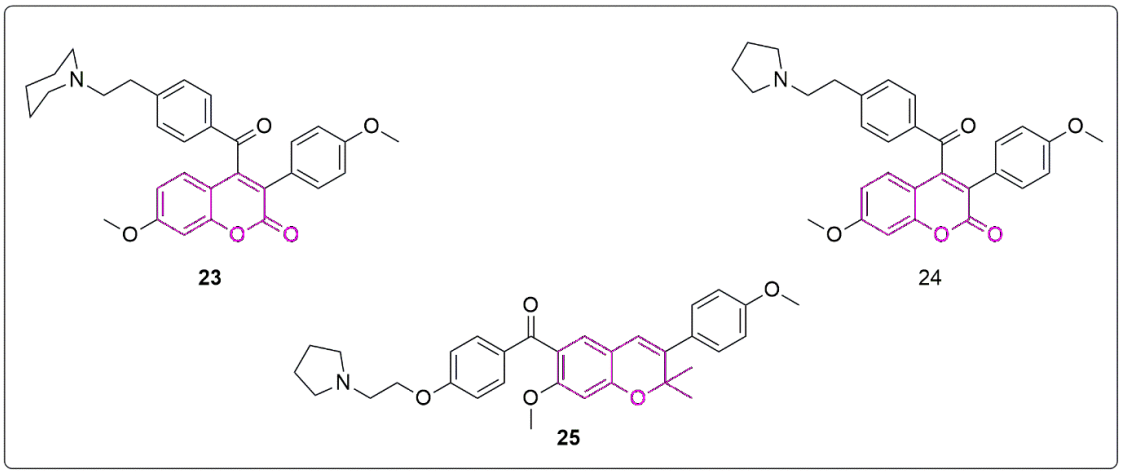


Fig. 12 Structure of coumarin derivatives (**23-25**)

The cell division cycle 25 (Cdc25) family of proteins are dual specificity phosphatases that activate cyclin dependent kinase (CDK) complexes, which in turn regulate progression through the cell division cycle. Overexpression of Cdc25 proteins has been reported in a wide variety of cancers; their inhibition may thus represent a novel approach for the development of anticancer therapeutics. Herein we report new coumarin-based scaffolds endowed with a selective inhibition against Cdc25A and Cdc25C, being 26 and 27 (Fig. 13) the most efficient inhibitors and worthy of further investigation as anticancer agents [28].

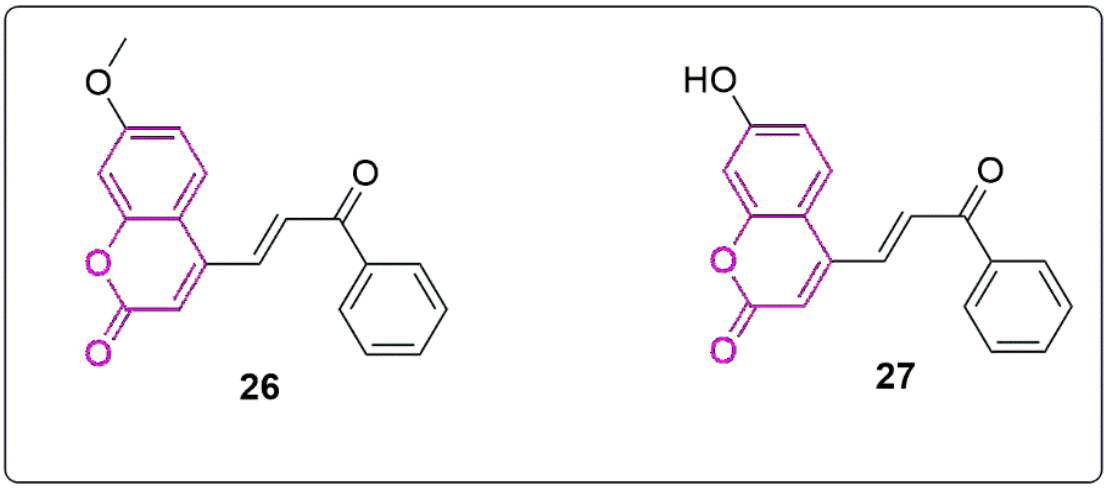


Fig. 13 Structure of coumarin derivatives (**26-27**)

Coumarin derivatives as well as diallyl polysulfides are well known as anticancer drugs. To find new drugs with anticancer activities, Bennett et al. combined coumarins with polysulfides in the form of di-coumarin polysulfides. These novel compounds were tested in the HCT116 colorectal cancer cell line. It turned out that they reduced cell viability of cancer cells in a time and concentration dependent manner. Cells tested with these coumarin polysulfides accumulate in the G2/M phase of the cell cycle and finally they go into apoptosis. A decrease in bcl-2 level, and increase in the level of bax, cytochrome c release into the cytosol, cleavage of caspase 3/7and PARP suggested that coumarin polysulfides induced the intrinsic pathway of apoptosis. The activities of the coumarin tetrasulfides and the corresponding diallyl tetrasulfides are similar. The novel coumarin compounds (28, 29, 30) (Fig. 14) regulated the phosphatase activity of the cell cycle regulating cdc25 family members, indicating that these phosphatases are implicated in the induction of cell cycle arrest and possibly in apoptosis induction as well. In addition, coumarin polysulfides also down-regulated the level of cdc25C, which also contributed to the arrest in the G2-phase of the cell cycle [29].

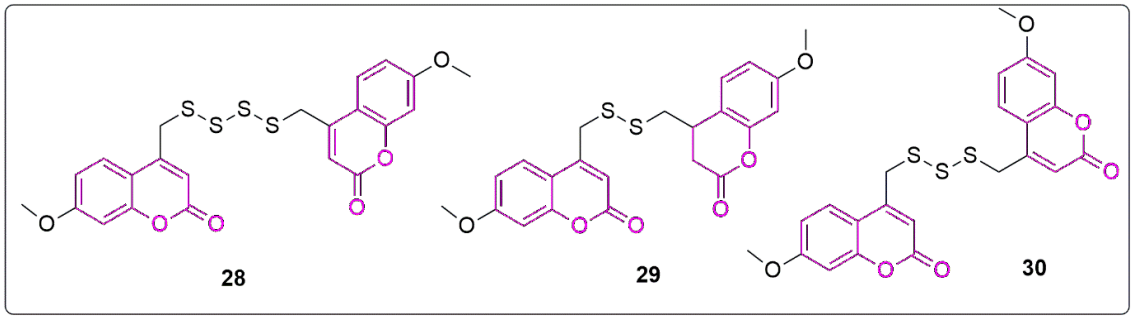


Fig. 14 Structure of coumarin derivatives as cdc25 inhibitors (**28-30**)

A series of 4-(1,2,3-triazol-1-yl) coumarin conjugates were synthesized and their anticancer activities were evaluated in vitro against three human cancer cell lines, including human breast carcinoma MCF-7 cell, colon carcinoma SW480 cell and lung carcinoma A549 cell. To increase the biological potency, structural optimization campaign was conducted focusing on the C-4 position of 1,2,3-triazole and the C-6, C-7 positions of coumarin. In addition, to further evaluate the role of 1,2,3-triazole and coumarin for antiproliferative activity, compounds possessing 4-(piperazin-1-yl) coumarin framework and three derivatives baring quinoline core were also synthesized. By MTT assay in vitro, most of the compounds display attractive antitumor activities, especially 31. Further flow cytometry assays demonstrate that compound 31 (Fig. 15) exerts the antiproliferative role through arresting G2/M cell-cycle and inducing apoptosis [30].

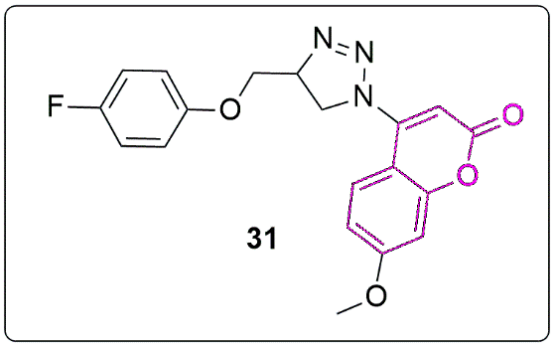


Fig. 15 Structure of coumarine-triazole hybrid **31**

Targeting CDC25 by compounds, able to inhibit their activity, appears a good therapeutic approach. Here, we describe the synthesis of a new inhibitor (32) (Fig. 16) whose structure is based on both coumarin and quinone moieties. An analytical in vitro approach shows that this compound efficiently inhibits all three purified human CDC25 isoforms (IC50 1–9mM) in a mixed-type mode. Moreover, SV37 inhibits growth of breast cancer cell lines. In MDAMB-231 cells, reactive oxygen species generation is followed by pCDK accumulation, a mark of CDC25 dysfunction. Eventually, SV37 treatment leads to activation of apoptosis and DNA cleavage, underlining the potential of this new type of coumarin–quinone structure. They described coumarin–quinone hybrid structure as a potent CDC25 inhibitor. The newly designed compound showed improved differential toxicity compared to its natural counterparts. 32 triggers cell growth inhibition in breast cancer cell lines, accompanied by generation of ROS, accumulation of pCDK and apoptosis in the triple negative MDA-MB-231 cells. Accordingly, this coumarin–quinone structure may serve as a starting point for further optimization and development of derivatives with yet improved inhibitory activity against CDC25 [31].

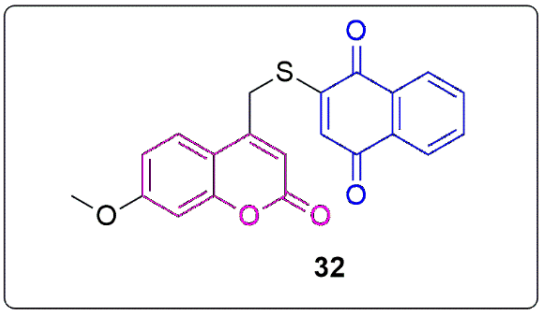


Fig. 16 Coumarin–quinone hybrid **32**

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide, and is the third most common cause of cancer related death. Constitutive activation of NF-κB is the underlying mechanism behind

tumorigenesis and this protein regulates the expression of genes involved in proliferation, survival, drug resistance, angiogenesis, and metastasis. The design of inhibitors which suppress NF-κB activation is therefore of great therapeutic importance in the treatment of HCC. In this study, we investigated the effect of newly synthesized coumarin derivatives against HCC cells, and identified (7-Carbethoxyamino-2-oxo-2H-chromen-4-yl) methylpyrrolidine-1 carbodithioate (CPP) as lead compound. Further, we evaluated the effect of CPP on the DNA binding ability of NF-κB, CXCL12-induced cell migration and invasion, and the regulated gene products in HCC cells. We found that CPP induced cytotoxicity in three HCC cells in a time and dose dependent manner, and suppressed the DNA binding ability of NF-κB. CPP significantly decreased the CXCL12-induced cell migration and invasion. More evidently, CPP inhibits the expression of NF-κB targeted genes such as cyclin D1, Bcl-2, survivin, MMP12 and C-Myc. Furthermore, the molecular docking analysis suggested that CPP interacts with the p50 binding domain of the p65 subunit, scoring best among the 26 docked coumarin derivatives of this study. Thus, they have introduced CPP as a potent inhibitor of the pro-inflammatory pathway in Hepatocellular carcinoma [32].

A novel series of coumarin-pyridine/fused pyridine hybrids were designed and synthesized by Fayed et al. Their anticancer activity was evaluated against human cancer cell lines MCF-7, HCT-116, HepG-2, and A549. Compounds 33, 34, and 35 (Fig. 17) showed the most potent growth inhibitory activities with IC_{50} values ranging from 1.1 to 2.4 µM, against MCF-7 cell line. Flow cytometric analysis revealed that these compounds induced cell cycle arrest in the G2/M phase followed by apoptotic cell death. Consistent with these results, the activity of caspase-3 in MCF-7 cells was tested. The results indicated that compounds 33, 34, and 35 increased caspase-3 activity significantly compared to control group. Moreover, their binding affinity for caspase-3 was confirmed by docking study. Taking all these data together, it is suggested that these coumarin derivatives may be potential antiproliferative agents [33].

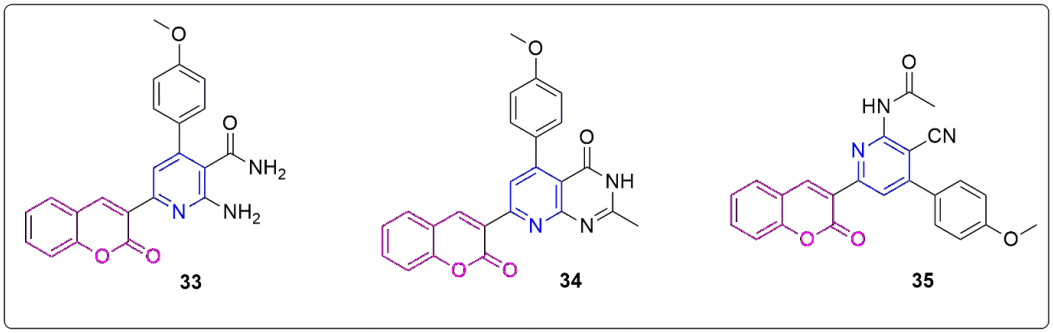


Fig. 17 coumarin–pyridine of fused pyridine hybrid (**33-35**)

Based on the X-ray crystal structure of complexes of inhibitors containing coumarin nucleus with human NAD(P)H: quinone oxidoreductase-1 and human phosphodiesterase 4B enzymes, some novel coumarin derivatives have been designed as probable inhibitors specifically for pancreatic cancer. These two enzymes are overexpressed in various tumors, the former specifically in pancreatic cancer. The computational analysis by e-pharmacophore and docking studies suggested that specific groups at position 8 of 4-methyl-7-hydroxycoumarin have anticancer activity against skin cancer in mice and can enhance the anti-tumor activity. The chemical syntheses of 4-methyl-7-hydroxycoumarin and its 8-formyl derivative were carried out using Pechmann's condensation followed by Duffs reaction. Treatment of the 8-formyl derivative with nine different N, N-di substituted cyanoacetamides in the presence of piperidine afforded the corresponding nine new 8-substituted-4-methyl-7-hydroxycoumarin derivatives. From the docking simulation study, it was concluded that the derived coumarin derivatives (36, 37, 38) (Fig. 18) are active against more than one protein and most importantly addition of substituents at the 8th position of 4-methyl-7- hydroxycoumarin support the possibility of new coumarin derivatives having comparatively higher binding affinity and therefore more potent inhibitors [34].

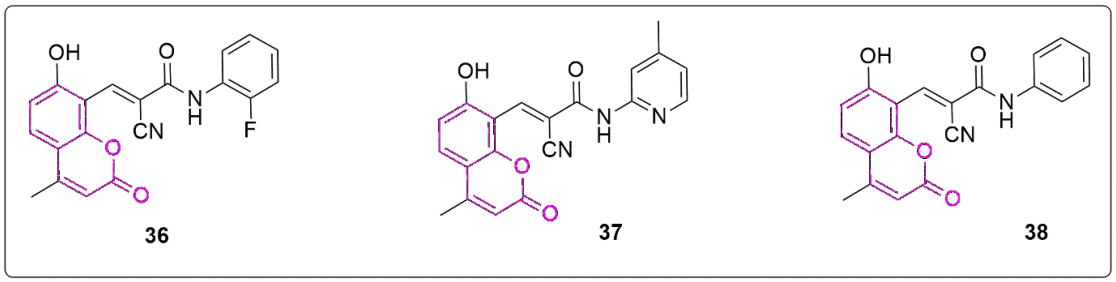


Fig. 18 Coumarin – cyanoacetamides hybrid (**36-38**)

A novel series of triazolyl coumarin derivatives was developed by Al-Wahaibi et al., which was biologically assessed as antitumor agents against human colorectal cancer HCT-116cell line. Based on the obtained results from the cellular assay, compounds 39 and 40 (Fig. 19) possessed the most potent anticancer activity with the values of IC_{50} equal 4.363 and 2.656 µM, respectively compared to the reference drug doxorubicin (IC_{50} = 2.601 µM) [35]. The preparation of 3-(2-(5-amino-3-aryl-1H-pyrazol-1-yl) thiazol-4- yl)–2H-chromen-2-ones was described by Vaarla et al. in 2019. The anticancer effect of the target coumarins was evaluated towards five human cancer cell lines (DU-145, L1210, HeLa, CEM and MCF-7) using MTT assay. All the synthesized coumarins revealed moderate to good action toward the tested cell lines. Among all, compound 41 showed significant potency against the tested cancer cell lines, whereas compound 42 (Fig. 19) had excellent activity against MCF-7 and DU-145 cells with IC50 values of 9 ± 6 and 7 ± 1 µM, respectively (Table 2). Moreover, SAR examination suggested that grafting of electron-donating functionalities on coumarin motif improved the potency toward MCF-7 and DU-145 cell lines [36].

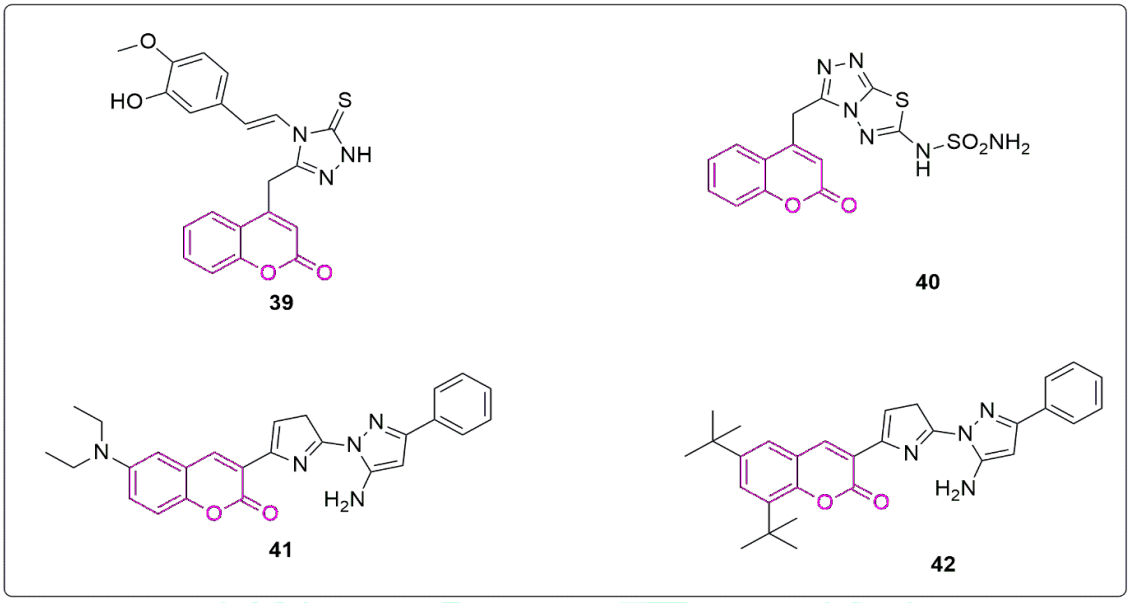


Fig. 19 Structure of Coumarin derivatives (**39-42**)

4. Future Perspective

Coumarins are a wide class of natural and synthetic compounds that showed versatile pharmacological effects. Despite numerous effects of coumarins in the search for bioactive compounds, they remain as one of the most versatile class of compounds for anticancer drug design and discovery. Several studies have investigated the possible use of simple coumarins such as 7- hydroxycoumarin, 6-nitro-7-hydroxycoumarin, scopoletin and esculetin in the treatment of cancer cells. Coumarins exhibited antitumor activities at different stages of cancer formation through various mechanisms, for example blocking cell cycle, inducing cell apoptosis, modulating estrogen receptor (ER), or inhibiting the DNA-associated enzymes, such as topoisomerase. Due to the potential applications of coumarins in the cancer chemotherapy, extensive efforts have been made on the design and synthesis of coumarin derivatives with improved anticancer activity. In this review, we have tried to give a general overview of the most recent reports in this area. In this article we reviewed current developments of coumarin-based anticancer agents and discusses the structure activity relationship of the most potent compounds. Numerous attempts were made for modifying the different position of coumarin nucleus to improve their anticancer activities against various cell lines. Modifications on the coumarin nucleus have resulted in many compounds having diverse mechanism of actions. In the present study, we have tried to classify coumarin-based anticancer agents according to the type and position of the main pharmacophoric substituent on the coumarin core structure. Lots of efforts have focused on the modifications of positions 3, 4 and 7. The most attractive compounds were coumarins containing amide, hydrazide or (hetero) aryl moieties at C-3, 4-substituted coumarins with methylene linker, O-substituted 7-hydroxycoumarins, 3,4-fused coumarins and coumarin hybrids. It is believed that, this review is helpful for medicinal chemists to rational design and development of more active and less toxic anticancer drugs possessing coumarin scaffold.

Due to the urgent necessity for developing novel effective agents for treatment of the human malignancies, a plenty of coumarin-bearing compounds were developed and screened as anticancer agents. Significant progress in this field has been achieved by the rational design of coumarin-containing molecules, targeting mechanism of action for a specific receptor/enzyme/protein. In this regard, many coumarin derivatives have

been reported as intercalating agents, alkylating agents, topoisomerases inhibitors, hormone antagonists, angiogenesis inhibitors, antimitotic agents, apoptosis inducers, carbonic anhydrase inhibitors. Many of these compounds revealed significant anticancer activity and selectivity with lower toxicity and side effects. Several coumarin drug candidates with good efficacy and suitable pharmacological profile are under clinical evaluation. Therefore, we expect that the present review may be helpful for medicinal chemists and the drug discovery community as it will help the design and development of new and effective coumarin molecules that target different human malignancies.

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