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Research Article

Underlying mechanisms of Anticancer Coumarins: An overview

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Abstract

Coumarin derivatives either natural or synthetic have become an interesting subject of investigation for many researchers due to their wide range of biological activities. Coumarin scaffold has been reported to have inhibitory effect on number of cell lines serving as a pharmacophore of utmost importance for anticancer drug development. Action of coumarins on tumour cells is being exhibited *via* different mechanisms and some of them have been reported to possess high selectivity towards the cancer cell lines. In present work, the role of coumarins as potential anticancer drugs has been briefly reviewed which can serve as an excellent tool for future investigations on design and synthesis of such derivatives.

Keywords: Coumarin, benzopyrones, anticancer

Introduction

Cancer is a major public health burden both in the developed and developing countries. About one in four persons is suffering from cancer during his or her lifetime and at present about one in five of all deaths is due to cancer[1].From the literature survey, researchers reported that coumarin play an important role in the anticancer activity.Coumarins are wide class of natural and synthetic compounds exhibiting versatile pharmacological actions[2].Coumarin is classified as a member of the benzopyrone family of compound, all of which consist of a benzene ring joined to a pyrone ring. The benzopyrones (Figure 1) can be subdivided into the benzo-α-pyrone (1a) benzo-γ-pyrone (1b). They differ from each other only in the position of carbonyl group in heterocyclic ring. The benzo-α-pyrone is also known as coumarins.It has sweet odor, readily recognized as the scent newly-mown hay, and has been used in perfumes since 1882. Coumarin was first synthesised in 1868 [3]. Coumarin can be synthesized by pechmann condensation, Perkin, knoevengel, witting.Several studies have investigated the possible use of simple coumarin such as Scopoletin (Figure 2), 7-hydroxycoumarin (Figure 3)and Esculetin (Figure 4) in treatment of cancer cells [4]. Coumarin exhibited antitumor activity at different stage of cancer formation through various mechanisms.

Mechanism of action

Depending upon the structure of Coumarins, they can act on various tumour cells by different mechanisms *viz.* inhibition of the tolemerase enzyme, inhibition of protein kinases and down regulation of oncogenes expression or induce the caspase-9-mediated apoptosis which suppress cancer cell proliferation by arresting cell cycle in G0/G1 phase, G2 /M phase and affecting the cancer cells [5].

Anticancer activity of coumarin

T.Abdizadeh*et al.* (2017) designed and synthesis a novel series of coumarin based benzamides as HDAC inhibitors. Histone deacetylase (HDACs) are attractive therapeutic target for the treatment of cancer and other diseases. It has four classes among them class 1isozyme are involved in promoting tumor cells proliferation, angiogenesis, differentiation, invasion and metastasis and also viable targets for cancer therapy. The cytotoxicity activity of the all the synthesized compounds (Figure 5) was evaluated against six human cancer cell lines including HCT116, A2780, MCF-7, PC_3, HL60, A549 and a single normal cell lines. In the investigation done by the researchers the four

compounds (2a, 2b, 2c, 2d) (Figure 5) exhibited cytotoxic with IC_{50} [6]. Among all of them compound 2u show a higher potency for $HDAC_1$ inhibition with IC_{50} value.

J.XUE *et al. (*2017) designed and synthesis a series of NO-donating Scutellarin derivatives and the antiproliferative activity against MCF-7, HCT-116, PC-3 and HepG2 cancer cell lines. Amongst all, the compounds 3a-c (Figure 6) exhibited antiproliferative activity. The compound 3c was the most active and displayed low toxicity against normal human liver L-O_2 cells with an IC_{50}. They show good selectivity between normal and malignant liver cell [7].The compound 3bacted anticancer by inducing apoptosis and cell cycle arrest at S-phase and led to mitochondrial dysfunction in the HepG2 and PC-3 cell lines further human apoptosis protein array kit could induce apoptosis through down –regulating the level of procaspse-3 and inhibiting the expression of surviving, C-1AP1, HSP27, HSP60, HSP70, in HepG2 cell lines.

A.Bisi*et al. (*2017) designed and synthesized a small library of coumarins carrying butynyl- amino chains in the field of MDR reverting agents and in order to obtained multipotent agent to combat malignancies. By the investigation done by the researchers the reported anticancer and chemo preventive natural product 7-isopentenyloxy coumarin was linked to different terminals amines .the anticancer behavior and MDR reverting ability of new compounds were evaluated on human colon cancer cell, particularly prone to develop the MDR phenotype. Amongst all, the compounds 4a-e (Figure 7), the compound 4e emerged as the most interesting of series showing a multipotent biological profile and conjugation of an appropriate coumarin with a properly selected butynyl-amino chain allowed to obtain novel hybrid molecules with improved *in vitro* antitumor activity [8].

G. Zoidis*et al. (*2017) designed and synthesized a series of indeno (1, 2c) cinnoline-11-one (Figure 8) derivatives DNA intercalating agents are consolidated therapeutic option in treatment of tumor diseases. By the investigation of the researchers the inhibition of human topoisomerase and antiproliferative assay on HELA and MCF-7 tumor cell lines [9].

G. Keller *et al. (*2016) designed and synthesis a series of novalisocoumarin derivatives by using castro-stephens cross coupling. A novel 3, 4 dihydroisocoumarin derivatives were obtained by catalytic hydrogenation of corresponding isocoumarin precursors. The antiproliferative activity of all compounds 5a-h (Figure 9) was evaluated *in vitro* in different tumor cell. The 3,4 –dihydroisocoumarin derivatives of compound forms hydrogen bond with Ser190 and Gln 192 residues of Kallikrein5 (KLK5) [10]. The compound 5b is the most active compound in the series with potent antiproliferative activity and high selectivity index against breast cancer cell.

G.Wang *et al. (*2016) designed and synthesis a new series of coumarin thiazole derivatives and evaluated for their α-glucosidase inhibitory activity. The majority of the screened compounds displayed potent inhibitory activities with IC_{50} values [11]. Among all of the tested molecules from 6a-e (Figure 10), compound 6e was found to be most active compound in the library of coumarin thiazole derivatives. The binding interaction of compound 6e with the active site of α-glucosidase was confirmed through molecular.

K. Vaarla*et al. (*2015) designed and synthesis a novel series of coumarin substituted thiazolyl -3-aryl pyrazole-4-carbaldehyde (Figure 11)*via* an efficient one-pot multicomponent approach involving 3(2-bromoacetyl) coumarin and substituted acetophenones utilizing Vielsmeir-haack reaction condition. By the investigation done by the researchers all the synthesized compounds were screened for the *in vitro* cytotoxic activity against MCF-7, DU-145, and Hela-cell lines [12]. The compound 6 exhibited significant cytotoxic activity with IC_{50} values against Hela-cell lines.

M. Rajabi*et al. (*2015) designed and synthesis a series of furo (3, 2-c) coumarin derivatives of compound 7a-d (Figure 12) and evaluated for their antiproliferative activity against MCF-7 breast and HCT-15 colon cancer cell lines using sulforhodamine B assay [13]. Compound 7b and 7d showed higher antiproliferative activity. U.V-Vis spectroscopy was used for DNA and BSA binding affinity of compound 7b and 7d gave over all affinity constant.

Z.Lung *et al. (*2014) designed and synthesis a series of 4-(1, 2, 3-triazol-1-yl) (Figure 13) coumarin con-

jugates and their anticancer activities were evaluated in vitro against three human cancer cell lines, including human breast carcinoma, colon carcinoma and lung carcinoma 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 and C-7 position of coumarin. The role of 1, 2, 3 triazole and coumarin for antiproliferative activity possessing 4-coumarin is also addressed [14]. The compound 4 exert the antiproliferative role through arresting G_2/M cell-cycle and inducing apoptosis.

J. Moyer *et al. (*2014) designed and synthesis a series of isoprenylatedcoumarin and evaluated against human pancreatic adenocarcinoma cell lines PAN-1 under nutrient rich and nutrient – deprived condition [15]. The compound described the effect of isoprenyl chain length and positioning on cell growth inhibition. After the investigation done by researcher they displayed that majority of compounds8a-f (Figure 14)show cytotoxicity against PAN-1 cells selectivity in the absence of essential amino acids, glucose and serum and showed no cytotoxicity under nutrient rich condition.The compound 8f exhibited the highest cytotoxic activity with an LC_{50} values and induced apoptosis like morphological changes in PAN-1 cells after a24h incubation.

K. M. Amin *et al. (*2014) designed and synthesis anticancer activity of coumarin and pyrazoline derivatives, bearing substituted moieties. By the investigation of the researchers the target compounds were synthesized from the 8 acetyl-7-methoxy-coumarin (Figure 15) by claisen Schmidt condensation with various aldehyde to give the chalcones, they show potent activity by reaction with hydrazine hydrate, phenyl hydrazine or semicarbazide under appropriate condition. Cytotoxicity of the compound was evaluated in vitro against liver HepG2 cell lines [16].

Conclusion

The present work gives an overview of the anticancer activity of diverse coumarin derivatives. The coumarin moiety has been an indispensable pharmacophore for various bioactive molecules. During last five years, coumarin have occupied a significant position in anticancer research by exhibiting variety of mechanism of action and possessing *in vitro* activity against various cancer cell lines.Coumarins have been demonstrated to possess several biological activities such as anti-inflammatory, antimicrobial, antiviral, antioxidant, antinociceptive, anti–tumor, antiasthmatic, antidepressant, anti-HIV, antituberculosis, anti-Alzheimer, anti–influenza, antihyperlipidemich. This paper gives an overview of mechanism ofthe anticancer activities of various coumarinderivatives. Therefore, this paper is a guideline for the development of coumarin asanti cancer agents, which can be a lead nucleus for future developments to get safer and effective compounds.

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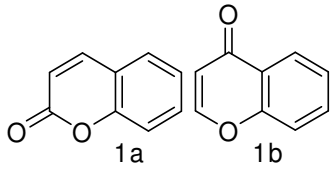


Figure.1: Types of coumarin

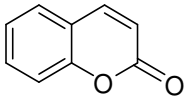


Figure.2: Scopoletin

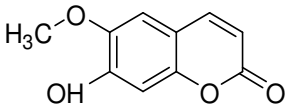


Figure. 3: 7-Hydroxycoumarin

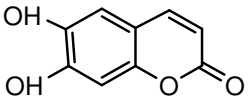
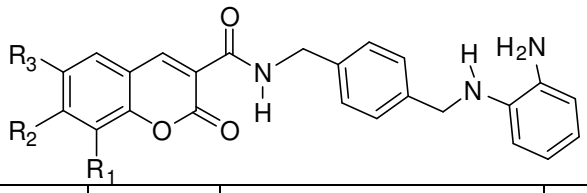
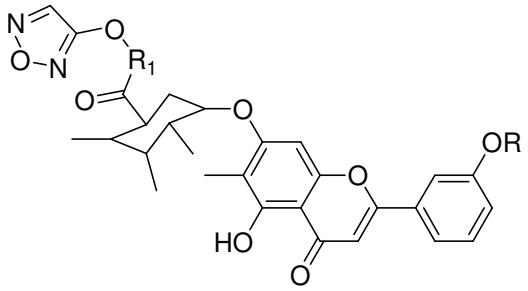


Figure.4: Esculetin



S.NO.	R_1	R_2	R_3
2a	H	OCH_2CH_3	H
2b	H	4-Br-Benzyloxy	H
2c	H	4-OCH_3-Benzyloxy	H
2d	H	3,4Di-D-Benzyloxy	H

Figure .5: Coumarin based benzamides derivatives [above]



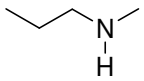
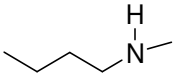
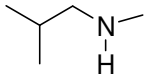
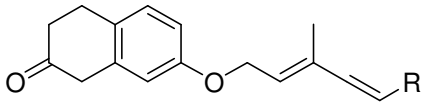
S. NO.	R	R_1
3a	Bn	
3b	Bn	
3c	Bn	

Figure.6: Scutellarin derivatives



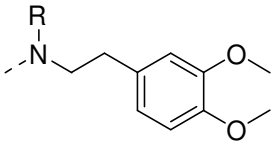
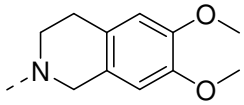
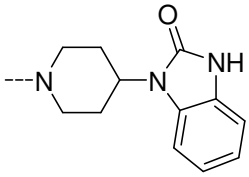
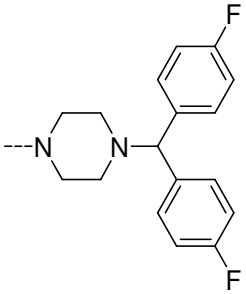
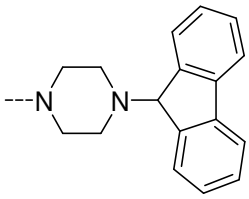
S.NO	R
4a	
4b	
4c	
4d	
4e	

Figure.7: 7-Isopentenyloxy coumarin derivatives

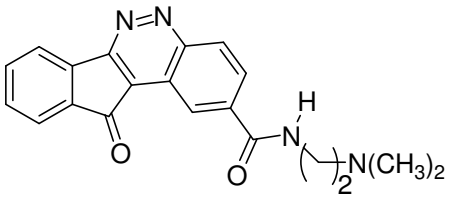
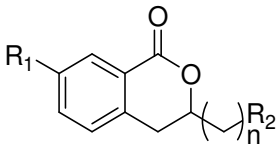
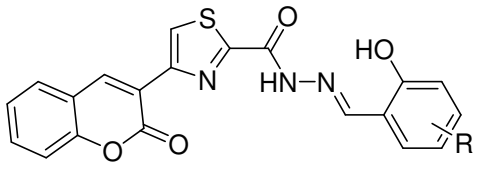


Figure.8: Indeno [1, 2-C]Cinnoline-11-one



S.NO	n	R_1	R_2
5a	1	H	OH
5b	1	OCH_3	OH
5c	3	OCH_3	OH
5d	3	OCH_3	O-*n*-pentyl
5g	3	OCH_3	1-phenyl-1*H*-tetrazole-5-thiol
5h	3	OCH_3	5-phenyl-1*H*-tetrazole

Figure. 9: 3, 4 –Dihydroisocoumarin derivatives



S.NO	R
6a	4-OCH_3
6b	2-OH
6c	4-OH
6d	3, 5-tBu_2, 2-OH
6e	3, 5-Cl_2

Figure.10: 3-Thiazole substituted Coumarin derivatives

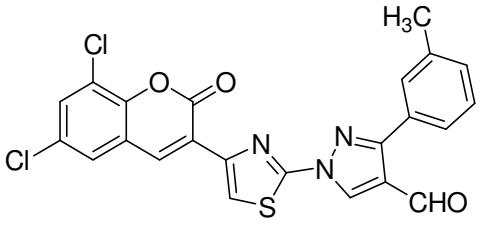
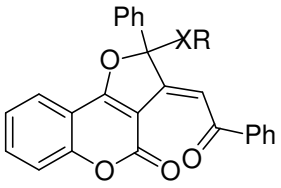


Figure. 11:Coumarin substitutedThiazolyl -3-aryl pyrazole-4-carbaldehyde



S.NO	X	R
7a	O	CH_3
7b	O	CH_2CH_3
7c	N	CH_3CH_2
7d	N	$CH_2CH_2CH_2CH_2$

Figure. 12: Furo [3, 2-C]Coumarin derivatives

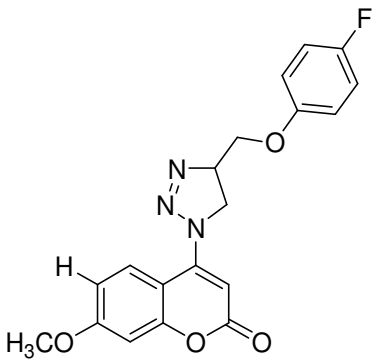
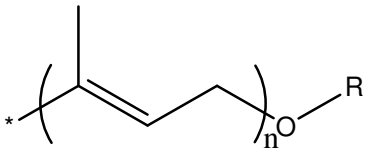


Figure.13: 4-(1, 2, 3-Triazol-1-yl)coumarin conjugate



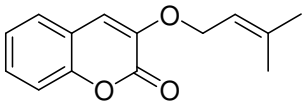
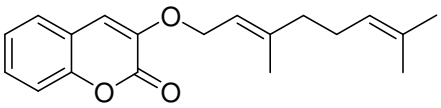
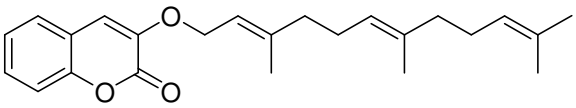
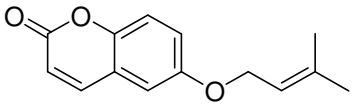
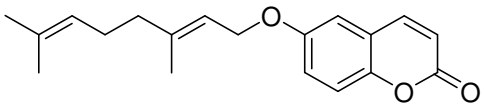
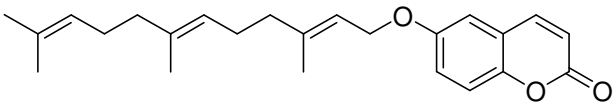
S.NO.	R
8a	
8b	
8c	
8d	
8e	
8f	

Figure.14: Isoprenylatedcoumarin derivatives

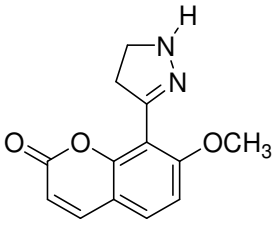


Figure.15: 8-Pyrazolyl-7-methoxy-coumarin