Research Article

Current Developments of C3-Substituted Coumarin Hybrids as Anti-Cancer Agents

Anees A. Pangal*, Javed A. Shaikh, Ejazuddin M. Khan
Dept. of Chemistry & Post Graduate Research Centre, Abeda Inamdar Sr. College of Arts, Science & Commerce, Camp, Pune, Affiliated to Savitribai Phule Pune University, Pune, India.
***Corresponding author's E-mail:** aagpan@gmail.com

Received: 30-10-2016; **Revised:** 24-12-2016; **Accepted:** 10-01-2017.

ABSTRACT

Coumarin (benzopyran-2-one or chromen-2-one) is a fused benzene and pyrone ring system which prompt biological investigation to assess their potential therapeutic significance. It possesses immeasurable anticancer potential with minimum side effects depending on the substitutions on the basic nucleus. These analogs are the small molecules that act as anticancer agents by targeting abundant mechanisms that appear to be involved in a variety of cancers. Conjugation of coumarin with varied pharmacophores responsible for different biological activities has yielded many novel hybrid molecules, which have improved pharmacokinetics. Researchers have explored for their inhibitory activity towards kinases, cell cycle arrest, angiogenesis, heat shock protein (HSP90), telomerase, mitosis, carbonic anhydrase, monocarboxylate transporters, aromatase and sulfatase, blocking cell cycle, inducing cell apoptosis, modulating estrogen receptor (ER), or inhibiting the DNA-associated enzymes such as topoisomerase. Many of these agents are hybrid molecules designed through concept of molecular hybridization and have shown multiple pharmacological activities. The present review compiles research reports on development of different C3-coumarin hybrids. It covers the current developments of C3- substituted Coumarin-based anticancer agents and will provide a wide outlook for medicinal chemists on the research and developments of more active and less toxic anticancer drugs possessing coumarin hybrids.

Keywords: Coumarin; benzopyran-2-one; chromen-2-one; C3-coumarin hybrids; anticancer.

INTRODUCTION

Coumarins have been established as a well known naturally occurring heterocyclic compounds isolated from various plants. Coumarins comprise a very large class of compounds found throughout the plant kingdom. They are found at high levels in some essential oils, particularly *cinnamon* bark oil (7,000 ppm), *cassia* leaf oil (up to 87,300 ppm) and *lavender* oil. Coumarin is also found in fruits (e.g. *bilberry, cloudberry*), green tea and other foods such as *chicory*. Most of the coumarins occur in higher plants, with the richest sources being *Rutaceae* and *Umbelliferone*[1]. They belong to the family of lactones having 1-benzopyran-2-one system that can be isolated from plants as well as can be carried out in the laboratory[2]. Coumarins occupy a special role in nature. They belongs to the flavonoid class of plant secondary metabolite, which exhibit a variety of biological activities, associated with low toxicity and have achieved considerable interest due to their beneficial potential effects on human health[3]. It possesses immeasurable anticancer potential with minimum side effects depending on the substitutions on the basic nucleus. Coumarins have a tremendous ability to regulate diverse range of cellular pathways that can be explored for selective anticancer activity[4]. Cancer being the second leading cause of death worldwide[5], a number of experiments is going on to develop compounds with minor or no side effects and coumarins were reported to exhibit negligible or mild side effects[6]. Naturally occurring coumarins, having wide spectrum of activities such as antioxidant[7], anti-inflammatory[8], anticancer[9], MAO-B inhibitory[10], antinociceptive[11], hepatoprotective[12], antithrombotic[13], antiviral[14], antimicrobial[15], antituberculosis[16], anti-carcinogenic[17], antidepressant[18], antihyperlipidemic[19] and anticholinesterase[20-23] activities are frequently used by the researchers to develop novel synthetic and semi synthetic coumarin based therapeutic agents. Many of these agents are hybrid molecules designed through concept of molecular hybridization with multiple pharmacological activities[24]. This multifunctional attribute of these hybrid compounds makes them potential drug candidates for the treatment of multi factorial diseases such as cancer, Alzheimer's disease, metabolic syndromes, AIDS, malaria and cardiovascular diseases[25].

In recent years, molecular hybridization strategy has emerged as a novel approach that involves conglomeration of two or more pharmacophores in one molecular scaffold to develop hybrid multifunctional molecules[26]. The latter have multiple biological activities, modified selectivity profile, different or dual modes of action with reduced undesired side effects due to mixing of pharmacophores in one molecule. Such molecules may be further modified to exhibit favorable pharmacokinetics and oral bioavailability[27-28]. Using this approach, several research groups have designed and synthesized many hybrid molecules. Some prominent examples of such molecules include ziprasidone, duloxetine and ladostigil for multi factorial CNS diseases, and sunitinib and lapatinib for treatment of cancers[29]. Many more hybrid

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

molecules for treatment of other multi factorial diseases that are highly variable and heterogeneous involving multiple organ systems and targets such as metabolic disorders, malaria, inflammation, organophosphorous poisoning and ischaemia have been reported[30].

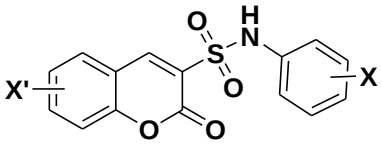
Hybridization or coupling of different coumarin derivatives with varied bioactive molecules such as resveratrol, maleimide sulfonamides, pyrazoline, chalcone, triazoles and a lipoic acid has produced novel hybrid molecules, which are endowed with vasorelaxant[31], platelet anti-aggregating[32], anticancer[33], mono amineoxidase-B (MAO-B) inhibitory[34], antimicrobial, antioxidant and anti-inflammatory properties[35]. Therefore, molecular hybridization approach is playing an important role in development of novel molecules for treatment of numerous multi factorial diseases.

Anti-cancer drugs are cytotoxic and exhibit severe side effects particularly on normal proliferating tissues such as hematopoietic system[36]. Often combination therapies, wherein several cytotoxic agents are combined in anticancer treatment regime, offer better results with fewer side effects[37]. Currently, combination of chemotherapy, radiotherapy and surgery offers the best outcomes for cancer patients. Such combinations have been successfully used in treatment of particular cancer types, for example, Hodgkin's lymphoma, testicular cancer and various leukemias[38]. Researchers are now exploiting natural products having anticancer profile to develop drugs with fewer side effects. Among various phytochemicals, coumarins have attracted considerable interest in the past few years[39]. Coumarins have the potential not only to treat cancer but also to counter the side effects associated with radiotherapy. Hybridizing the coumarin nucleus with other moieties leads to new molecules with improved anticancer activity profile[40].

In the present study, we have made an attempt to elaborate C3 substituted coumarin-based anticancer agents. This review will provide a wide outlook for medicinal chemists on the research and developments of more active and less toxic anticancer drugs possessing coumarin hybrids.

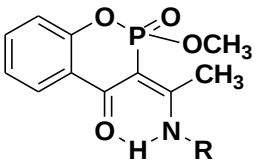
Anticancer Activity of C3-Substitued Coumarins

Reddy NS et al. synthesized coumarin 3-(N-aryl) sulphonamides **1**. The effect of all the compounds on the growth of human tumor cells in culture was evaluated using androgen receptor negative prostate (DU145), colorectal (DLD-1), non-small cell lung carcinoma (H157), estrogen receptor negative breast (BT20), and chronic myeloid leukemia (K562) cell lines. The dose response of each cell line was established by determining the number of viable cells after 96 hours of continuous treatment against five different concentrations (1-100 µM range) of each compound. The activation of JNK1 by these compounds as shown in immune complex kinase assay clearly showed that they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway[41].

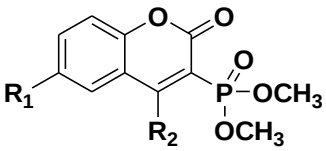


1

Budzisz E et al. determined the cytotoxic effects and alkylating activity of a series of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione,2-methoxy-3-[1-(alkylamino)-ethylidene-2,3-dihydro-2,4-dioxo-2λ5- benzo [e] [1,2] oxa phosphinane **2** and [2-oxo-4- phenyl(alkyl)-2H-chromen-3-yl]-phosphonic acids dimethyl ester 3 on the two leukemia cell lines HL-60 and NALM-6. These compounds were highly toxic to NALM-6 cells than to HL-60 cells. IC50 data are about nine times lower for the NALM-6 than for the HL-60 cell lines. Their cytotoxic effect increased with an increase of the hydrophobic parameters in the region of the substituents at the 2-, 3- and 4-positions of the benzopyrone skeleton of these compounds[42].

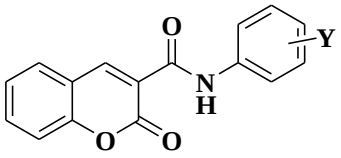


2



3

A series of coumarin-3-(N-aryl) carboxamides **4** were prepared and evaluated as cytotoxic agents against SKBr3 and BT474 breast cancer cell lines as well as normal HFLs (human lung fibroblasts. Among the synthesized compounds, 6-chlorocoumarin derivative (X = 6-Cl and Y= 3-NO_2-4-Cl) showed the highest inhibitory activity against ErbB-2 kinase (IC50 = 0.166 mM). Some derivatives including the latter compound were found to have respectable cytotoxic activity against SKBr3 and BT474 cells (IC50 values = 16.3-94 mM). The SAR study showed that the substitutions on the coumarin ring and also on the N-phenyl moiety can strongly affect the cytotoxic profile of the compounds[43].

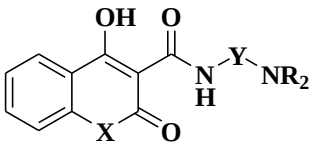


4

Matiadis et al. studied a series of coumarin and quinolinone-3-carboxamide derivatives **5** and **6** were synthesized and examined for their anticancer activities against several cancer cell lines including prostate cancer cells DU145 and PC3, colon cancer HCT15, breast cancer MCF7, ovarian cancer IGROV1, liver cancer SKHep1, and leukemia cancer HL60 (TB). Cell viability assay by the trypan blue dye exclusion method demonstrated that

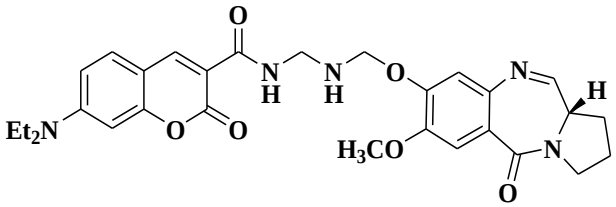
© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

coumarin derivative containing N-(8-aminooctyl) side chain [X= O, Y= $(CH_2)_8$, and R= H] had the highest inhibitory effects against DU145 prostate cancer cells (GI50 < 10 mM)[44].



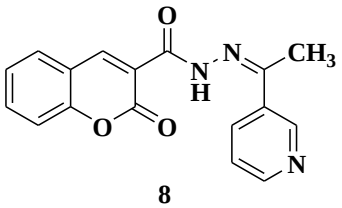
5 : X = O
6 : X = N

The C-3 position of coumarin ring is an attractive position for preparing conjugate analogs via amidic linker. The pyrrolo [2, 1-c] [1,4] benzodiazepines (PBD) are a class of the sequence selective DNA-targeting agents that interact covalently with guanine bases at the DNA minor groove, preferably at purine-guanine-purine sites. DNA interaction, cytotoxicity and differential cellular localization of a series of fluorescent 7-diethylamino coumarinepyrrolo benzodiazepine conjugates **7** is investigated by Wells et al. The cytotoxicity assay showed that the synthetic intermediate ethyl 7-(diethyl amino)-2-oxo-2H-chromene-3-carboxylate was inactive against both tested cell lines (OVCAR5 ovarian carcinoma and LOX IMVI melanoma). In contrast, the Coumarin-PBD conjugate bearing a propylene linker (X= CH_2) was the most potent compound (IC50 values ≤ 3.2 mM). The biological assessments revealed that the linker structure within these Coumarin-PBD conjugates had significant influence on the extent and time course of DNA binding, in vitro cytotoxic potency and cellular distribution[45].



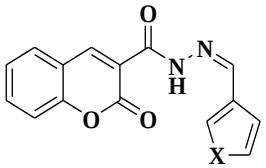
7

Mohareb et al. have synthesized a series of hydrazide-hydrazone derivatives including coumarin **8**. The effect of compound **8** on the in vitro growth of three human tumor cell lines namely breast adenocarcinoma (MCF7), non-small cell lung cancer (NCIH460) and CNS cancer (SF268) indicated that the best inhibitory activity was against NCIH460 with IC50 value of 10 mM[46].

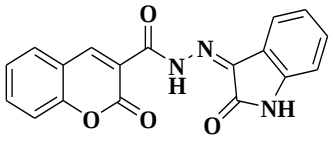


8

Naser et al. have reported the synthesis and antitumor activity of coumarin-3-hydrazide-hydrazone hybrids **9-12**. The compounds were assessed against human drug-resistant pancreatic carcinoma (PANC1) cells and drug-sensitive (hepatic carcinoma; HepG2 and leukemia; CCRF) cell lines. The 6-bromocoumarins (R = 6-Br) containing furan, thiophene and isatin moieties were more potent than doxorubicin against resistant PANC1 cells. Furthermore, 6-bromo analog of **9** showed promising cytotoxicity against all cell lines. The obtained biological data revealed that these compounds can induce apoptosis in drug resistant PANC1 and sensitive HepG2 cell lines[47].

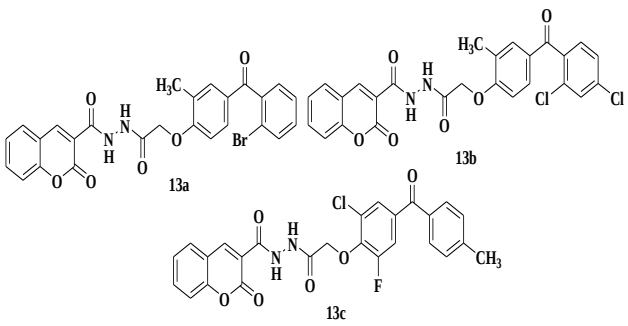


9 : X = S
10 : X = O
11 : X = NH



12

The investigations on the generation and development of cancer cells have demonstrated that promotion of angiogenesis and resistant to apoptosis are the two important hallmarks of cancer[48]. Thus, the development of multi-target therapy is an interest approach to overcome cancer. Hence, many efforts have been carried out to designing compounds with potential of anti angiogenesis and apoptosis inducing activities. Benzophenones are noteworthy scaffold for versatile biological profiles such as antitumor effect. In order to development of novel antiangiogenic as well as anticancer agents, Khanum et al. designed and evaluated the inhibitory effects of synthesized benzophenone-conjugated coumarin-3-carbohydrazides **13** series on cell proliferation of MCF7, Trypan blue and MTT assays were performed. Among the tested derivatives, compounds **13a-c** exhibited potent anticancer properties (IC50 values < 10 mM). The inhibition of neo vessel formation in choriallanotoic membrane (CAM) model, which is angiogenesis dependent, was observed following the treatment with compounds **13a-c**. The effects of compounds **13a-c** on homogeneous caspase and PI3-kinase in MCF-7 cells indicate that the homogeneous caspase activity was increased in MCF-7 cells by these compounds. Also, these compounds showed significant inhibition against PI3K and apoptosis induction[49].

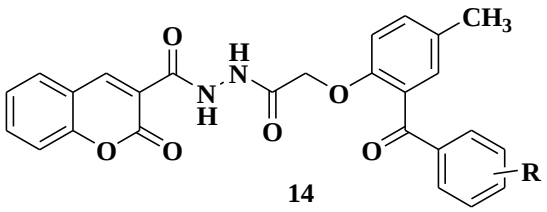


13a **13b** **13c**

Khanum and co-workers synthesized new series of coumarin-conjugated benzophenone **14** with anti angiogenic and proapoptotic properties as regional isomers of compounds **13**. For screening these

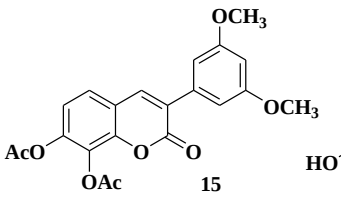
© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

compounds against Ehrlich ascites carcinoma (EAC) and Daltons lymphoma ascites (DLA) cell lines, Trypan blue, MTT and LDH release assays were carried out. The obtained results from Trypan blue and MTT assays showed that 2-bromobenzophenone derivative (R = 2-Br) exhibited potent IC50 valuesof less than 10 mM against cancer. Effect of 2-bromobenzophenone derivative on cellular integrity as verified by LDH release assay indicated a concentration dependent increase in the LDH release with the IC50 values less than 10.6 mM in EAC and DLA cell lines. The latter compound was considered as a lead compound with potent cytotoxic and antitumor efficacy by inhibiting the neovascularization and promoting apoptosis[50].

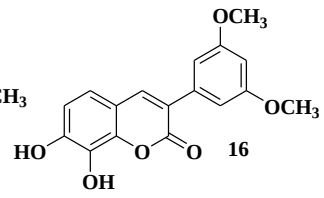


14

Trans-Stilbenes are attractive for broad-range of biological activities such as, protection properties against cancer, heart diseases, stroke, Alzheimer's disease, inflammations and infections. Resveratrol, pterostilbene and piceatannol are examples of compounds containing trans-stilbene backbone[51-53]. Based on trans-stilbene structure, some Coumarin-stilbenes hybrids called 3-arylcoumarins were designed, prepared and screened for antitumor properties against nasopharyngeal (KB), KV, MCF7, MCF7/ADR cancer cell lines by Céline Rivièrea et al. Among them, compounds **15**, and **16** showed significant anticancer properties. Especially, compound **15** with IC50 value of 5.18 mM exhibited the highest activity against KB cell line. The obtained results showed that 7,8-dihydroxy or 7,8-diacetoxy substituent on 3-arylcoumarin had positive effects on cytotoxic potency[54].

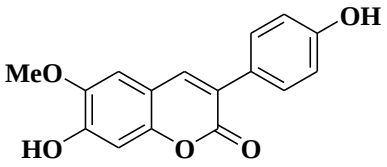


15



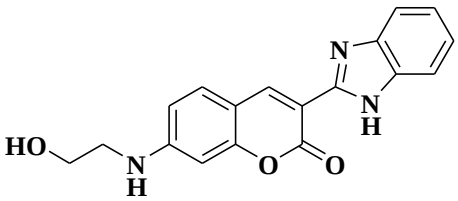
16

In another experiment, Yang et al. reported the synthesis of some hydroxylated analogs of 3-phenylcoumarins. The antioxidant activity against 2,20-azobis(2-amidinopropane) hydrochloride. (AAPH)-induced pBR322 DNA strand breakage, and anti proliferative effects of compounds on human promyelocytic leukemia HL-60 and human lung adenocarcinoma epithelial A549 cells were evaluated in vitro. The obtained results from MTT assay demonstrated that compound **17** bearing 6-methoxy-7-hydroxy substituent on the coumarin ring and 4-hydroxy on phenyl group was the most potent compound (IC50 values ≤ 7.5 mM). Although compound **17** exhibited poor antioxidant activity but appeared to be the most potent compound, and this activity was mediated by deregulation in cell cycle and induction of apoptosis[55].



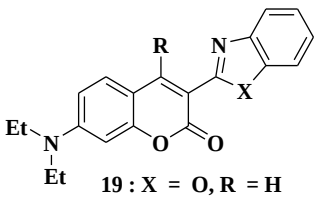
17

The benzimidazole moiety is a well-known motif for clinical values toward tumor cells and in particular, 2-arylbenzimidazoles possess potent anticancer activites[56]. A family of Coumarin-benzimidazole hybrids were synthesized and assessed for in vitro anticancer activity against preliminary 60 tumor cell lines. Among them, Coumarin-benzimidazole hybrid **18** with a 7-(2-hydroxyethyl amino) moiety demonstrated stronger growth inhibitory effect against most of the cancer cell lines and higher selectivity on leukemia cancer cells (CCRF-CEM, HL60(TB), K562, RPMI8226), HCT116, HCT15, melanoma cancer cells (LOX IMVI, UACC257) and breast cancer cells (MCF7, T47D)[57].

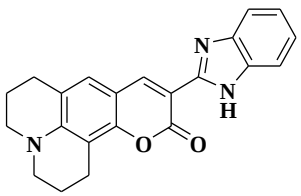


18

A series of 7-aminocoumarins **19-21** bearing heteroaryl moiety at C-3 position were synthesized and screened for cytotoxic activity against human umbilical vein endothelial cell (HUVEC) and several cancer cells by Paul et al. Benzoxazole derivatives **19** and **20** showed significant inhibitory effect on various cancer cell lines and **21** and **22** exhibited high selectivity for HUVEC. It was found that the introduction of benzothiazolyl group at C-3 position of Coumarin ring had positive effect on inhibitory profile and presence of a cyano group at the fourth position offered the selectivity towards HUVEC[58].



19 : X = O, R = H
20 : X = O, R = CN
21 : X = S, R = CN

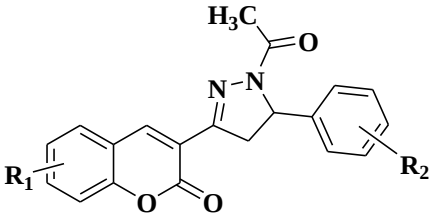


22

Pyrazole and pyrazoline are prominent structural motifs found in numerous antitumor agents[59]. Liu et al. have reported the design and synthesis of coumarin derivatives possessing pyrazoline moiety as potential telomerase inhibitors with enhanced anticancer activities. Telomerase plays a critical role in cancer makes it an important target for the development of cancer

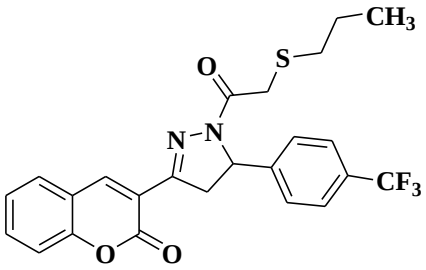
© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

chemotherapy. In particular, telomerase is closely related to the occurrence and development of human gastric cancer[60]. The biological evaluation of compounds **23** for their cytotoxic activity against human gastric cancer (SGC7901), human prostate cancer (PC3), and human epidermoid carcinoma (A431) cell lines revealed that unsubstituted derivative (R1 = R2 = H) with IC50 value of 2.69 mg/mL was the most potent compound against SGC7901, being superior to 5-fluorouracil. Furthermore, modified TRAP assay for telomerase inhibition showed that the latter compound can strongly inhibit telomerase (IC50 value = 2.0 ± 0.07 mM)[61].



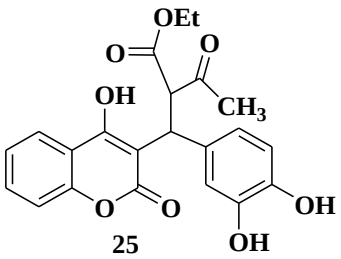
23

In a study by Liu et al., a series of Coumarin-pyrazoline derivatives bearing a thio acetyl moiety were designed and synthesized to find out affective lead compound with anti proliferative activity. The in vitro anticancer activity of compounds were assessed in comparison to 5-fluorouracil against SGC7901, MGC803, Bcap37 and HepG2 cell lines. Some compounds showed significant antiproliferative activity superior to standard drug 5-fluorouracil. In particular, the n-butylthio derivatice **24** showed the most potent inhibitory activity (IC50 value = 0.92 ± 0.09 mM) against telomerase in TRAP assay. The biological assays indicated that compound 38 could suppress cell proliferation through inducing cell cycle arrest in G0/G1 phase[62].



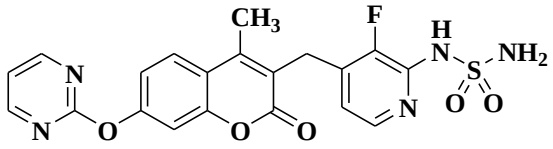
24

Stanchev et al synthesized some 3-benzyl-4-hydroxycoumarin derivatives and tested them for cytotoxic activity against two tumor cell lines, urinary bladder carcinoma cells (EJ-60) and leukemia-derived HL-60 cells in comparison to melphalan as reference drug. The best cytotoxic activity was obtained with 3,4-dihydroxy derivative **25**[63].



25

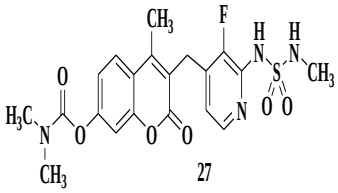
In a study by Aoki et al. synthesized some 3-benzylcoumarins bearing sulfamide moiety with strong Raf/MEK inhibitory activity and acceptable pharmacokinetics profile. Among the title compounds, 6-fluorocoumarin sulfamide derivative **26** exhibited potent in vitro cytotoxic activity against HCT116 cells (IC50 = 8 nM) and high in vivo antitumor efficacy against HCT116 xenograft (ED50 = 4.8 mg/kg). Compound **26** had potent Raf/MEK inhibitory activity, good pharmacokinetics profile and relatively weak CYP inhibitory or CYP induction activities[64].



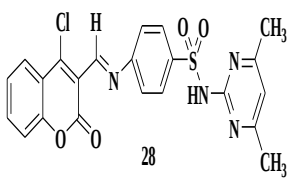
26

Several coumarins containing imine bond at C-3 have been reported as anti-cancer agents, possessing diverse mechanisms of actions. Carbonic anhydrases, specifically isozyme IX (CA IX) are highly over expressed gene in response to hypoxia in cancer cells[65]. Thus, CA IX inhibition may be a new approach for the management of hypoxic tumors[66]. Coumarin derivatives were recently shown to be inhibitors of the CA enzymes[67]. For example, Maresca et al. reported a series of CA inhibitors with coumarin and thio coumarin structures[68].

Wang and coworkers designed and synthesized some imine-linked sulfonamide-coumarin analogs with high affinity and selectivity on tumor-associated CA IX and assessed their potential to inhibit mouse melanoma B16eF10 and MCF7 cells and hCAs II (cytosolic, off target isoform) and hCAs IX (trans membrane, tumor-associated enzyme). Among them, compounds **27** and **28** more strongly inhibited the hCA II (IC50 = 23 nM) and hCA IX (IC50 = 24 nM), respectively. The IC50 values of the latter compounds against B16eF10 and MCF7 cells were ≤ 0.19 mM[69].



27



28

CONCLUSION

Coumarins are the small molecules that act as anticancer agents by targeting abundant mechanisms that appear to be involved in a variety of cancers. Conjugation of

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

coumarin with varied pharmacophores responsible for different biological activities has yielded many novel hybrid molecules, which have improved pharmacokinetics. Researchers have explored for their inhibitory activity towards kinases, cell cycle arrest, angiogenesis, heat shock protein (HSP90), telomerase, mitosis, carbonic anhydrase, monocarboxylate transporters, aromatase and sulfatase, blocking cell cycle, inducing cell apoptosis, modulating estrogen receptor (ER), or inhibiting the DNA-associated enzymes, such as topoisomerase. There is still a lot to explore about the coumarin analogs.

Currently existing data shows that all coumarins derivatives covered in this manuscript are reported to exhibit a tremendous anticancer potential. Despite numerous effects of coumarins in the search for bioactive compounds, they still remain as one of the most versatile class of compounds for anticancer drug design and discovery. Molecular hybridization is an attractive strategy, through which coumarin pharmacophores can be coupled or fused with other pharmacophores to develop novel therapeutic drugs that can be used for treatment of even complex multi factorial diseases.

In the present study, we have made an attempt to elaborate C3 substituted coumarin-based anticancer agents as main pharmacophoric substituent on the coumarin core structure. Lots of efforts have focused on the modifications of positions 3. The most attractive compounds were coumarins containing amide, hydrazide or (hetero)aryl moieties at C-3, 3,4-fused coumarins and coumarin hybrids. It is believed that, this review will provide a wide outlook for medicinal chemists on the research and developments of more active and less toxic anticancer drugs possessing coumarin hybrids. Thus, such similar derivatives can be explored which may lead to the development of a potent anticancer pharmacophore.

Recently, new derivatives of coumarins possessing a broad spectrum of pharmacological activities have been synthesized, however to discuss these in detail will lead to finalization of a new review on this topic by itself.

REFERENCES

1. Anees Pangal, Muiz Gazge, Vijay Mane, Javed A. Shaikh, Various Pharmacological Aspects of Coumarin Derivatives: A Review, *IJPRBS*, 2(6), 2013, 168-194.
2. Batra Nikhil, Batra Shikha, Pareek Anil, Nagori Badri Prakash, Diverse Pharmacological Activities of 3-Substituted Coumarins: A Review, *Int. Res. J. of Pharma*, 3(7), 2012, 24-29.
3. Gummudavelly Sandeep, Y Sri Ranganath, S Bhasker and N Rajkumar, Synthesis and Biological Screening of Some Novel Coumarin Derivatives, *Asian J. Research Chem,* 2(1), 2009, 46-48.
4. Jyoti Dandriyal, Ramit Singla, Manvendra Kumar, Vikas Jaitak, Recent developments of C-4 substituted coumarin derivatives as anticancer agents, *Eur. J. Med. Chem* 119, 2016, 141–168.
5. Yena Jin, Younghwan Kim , Yu-Jin Lee , Dong Cho Han and Byoung-Mog Kwon, Natural products targeting STAT3 signaling pathways in cancer cells, *Biodesign*, 4(1l), 2016, 1-17.
6. Anuradha Thakur, Ramit Singla, Vikas Jaitak, Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies, *Eur. J. Med. Chem,* 101, 2015, 476-495.
7. Kostova, S. Bhatia, P. Grigorov, S. Balkansky, V. S. Parmar, A. K. Prasad and L. Saso, Coumarins as Antioxidants, *Curr. Med. Chem.* 18, 2011, 3929-3951.
8. Konstantina C. Fylaktakidou, Dimitra J. Hadjipavlou-Litina, Konstantinos E. Litinas and Demetrios N. Nicolaides, Natural and Synthetic Coumarin Derivatives with Anti-Inflammatory / Antioxidant Activities, *Curr. Pharm. Des.* 10, 2004, 3813-3833.
9. Masoumeh Alipour, Mehdi Khoobi, Saeed Emami, Saeed Fallah-Benakohal, Seyedeh Farnaz Ghasemi-Niri, Mohammad Abdollahi, Alireza Foroumadi and Abbas Shafiee, Antinociceptive properties of new coumarin derivatives bearing substituted 3,4-dihydro-2H-benzothiazines, *DARU Journal of Pharmaceutical Sciences*, 22(9), 2014, 1-8.
10. Mukadder Atmaca, Hakkı Murat Bilgin , Basra Deniz Obay, H üda Diken, Mustafa Kelle, Ebru Kale, The hepatoprotective effect of coumarin and coumarin derivates on carbon tetrachloride-induced hepatic injury by antioxidative activities in rats, *J. Physiol. Biochem.,* 67, 2011, 569-576.
11. Xin-Mei Peng, Guri L.V. Damu and Cheng- He Zhou, Current Developments of Coumarin Compounds in Medicinal Chemistry, *Curr. Pharm. Des.* 19, 2013, 3884-3930.
12. Massimo Curini, Francesco Epifano, Federica Maltese, Maria Carla Marcotullio, Sylvia Prieto Gonzales and Juan Carlos Rodriguez , Synthesis of Collinin, an Antiviral Coumarin, *Aust. J. Chem*. 56, 2003, 59-60.
13. David A. Ostrov, José A. Hernández Prada, Patrick E. Corsino, Kathryn A. Finton, Nhan Le and Thomas C. Rowe, Discovery of Novel DNA Gyrase Inhibitors by High-Throughput Virtual Screening, *Antimicrob. Agents Chemother.,* 51, 2007, 3688-3698.
14. Saeed Emami, Alireza Foroumadi, Mohammad A. Faramarzi and Nasrin Samadi, Synthesis and Antibacterial Activity of Quinolone-Based Compounds Containing a Coumarin Moiety, *Arch. Pharm. Chem. Life Sci*., 341(1), 2008, 42-48.
15. Niall A. Gormley , George Orphanides, Andrew Meyer, Paul M. Cullis, and Anthony Maxwell, The Interaction of Coumarin Antibiotics with Fragments of the DNA Gyrase B Protein, *Biochemistry*, 35(15), 1996, 5083-5092.
16. Manvar, A. Bavishi, A. Radadiya, J. Patel, V. Vora, N. Dodia, K. Rawal, A. Shah, Diversity oriented design of various hydrazides and their in vitro evaluation against Mycobacterium tuberculosis $H37_{Rv}$ strains, *Bioorg. Med. Chem. Lett*. 21(16), 2011, 4728-4731.
17. R.V. Nair, E.P. Fisher, S.H. Safe, C. Cortez, R.G. Harvey, J. Digiovanni, Novel coumarins as potential anti carcinogenic agents, *Carcinogenesis,* 12(1), 1991, 65-69.
18. K.V. Sashidhara, A. Kumar, M. Chatterjee, K.B. Rao, S. Singh, A.K. Verma, G. Palit, Discovery and synthesis of novel 3-

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

phenylcoumarin derivatives as antidepressant agents, *Bioorg. Med. Chem. Lett.* 21(7), 2011, 1937-1941.

19. B. Yuce, O. Danis, A. Ogan, G. Sener, M. Bulut, A. Yarat, Antioxidative and lipid lowering effects of 7,8-dihydroxy-3-(4- methylphenyl) coumarin in hyper lipidemic rats, *Arzneim., Forsch. Drug Res.* 59(3), 2009, 129-134.
20. S.F. Razavi, M. Khoobi, H. Nadri, A. Sakhteman, A. Moradi, S. Emami, A. Foroumadi, A. Shafiee, Synthesis and evaluation of 4-substituted coumarins as novel acetylcholinesterase inhibitors, *Eur. J. Med. Chem*. 64, 2013, 252-259.
21. Asadipour, M. Alipour, M. Jafari, M. Khoobi, S. Emami, H. Nadri, A. Sakhteman, A. Moradi, V. Sheibani, F. Homayouni Moghadam, A. Shafiee, A. Foroumadi, Novel coumarin-3-carboxamides bearing N-benzylpiperidine moiety as potent acetyl cholinesterase inhibitors, *Eur. J. Med. Chem*. 70, 2013, 623-630.
22. M. Alipour, M. Khoobi, A. Moradi, H. Nadri, F. Homayouni Moghadam, S. Emami, Z. Hasanpour, A. Foroumadi, A. Shafiee, Synthesis and anti-cholinesterase activity of new 7-hydroxycoumarin derivatives, *Eur. J. Med. Chem*. 82, 2014, 536-544.
23. S. Mohammad Bagheri, M. Khoobi, H. Nadri, A. Moradi, S. Emami, L. Jalili-Baleh, F. Jafarpour, F. Homayouni Moghadam, A. Foroumadi, A. Shafiee, Synthesis and Anticholinergic Activity of 4-hydroxycoumarin Derivatives Containing Substituted Benzyl-1, 2, 3-triazole Moiety, *Chem. Biol. Drug Des*. 86(5), 2015, 1215–1220.
24. Priscila Longhin Bosquesi, Thais Regina Ferreira Melo, Ednir Oliveira Vizioli, Jean Leandro dos Santos and Man Chin Chung, Anti-Inflammatory Drug Design Using a Molecular Hybridization Approach, *Pharmaceuticals*, 4, 2011, 1450-1474.
25. Saeed Emami, Sakineh Dadashpour, Current developments of coumarin-based anti-cancer agents in medicinal chemistry, *Eur. J. Med. Chem,* 102, 2015, 611-630.
26. Adriano D. Andricopulo, Lívia B. Salum and Donald J. Abraham, Structure-Based Drug Design Strategies in Medicina Chemistry, *Curr. Top Med Chem*, 9(9), 2009, 771-790.
27. Bansal, Y.; Silakari, O., Multifunctional compounds: Smart molecules for multifactorial diseases, *Eur. J. Med. Chem*., 76, 2014, 31-42.
28. Werner J. Geldenhuys, Moussa B.H. Youdim, Richard T. Carroll, Cornelis J. Van der Schyf, The emergence of designed multiple ligands for neurodegenerative disorders, *Prog. Neurobiology*, 94(4), 2011, 347-359.
29. Song, H. Y.; Ngai, M. H.; Song, Z. Y.; MacAry, P. A.; Hobley, J.; Lear, M. J., Practical synthesis of maleimides and Coumarin – linked probes for protein and antibody labeling *via* reduction of native disulfides, *Org. Biomol. Chem.*, 7, 2009, 3400-3406.
30. Georgia Melagraki, Antreas Afantitis, Olga Igglessi-Markopoulou, Anastasia Detsi, Maria Koufaki, Christos Kontogiorgis, Dimitra J. Hadjipavlou-Litina, Synthesis and evaluation of the antioxidant and anti-inflammatory activity of novel coumarin-3-aminoamides and their alpha-lipoic acid adducts, *Eur. J. Med. Chem*., 44, 2009, 3020-3026.
31. Manuel Campos-Toimil, Francisco Orallo, Lourdes Santana, Eugenio Uriarte, Synthesis and Vasorelaxant Activity of New Coumarin and Furocoumarin Derivatives, *Bioorg. Med. Chem. Lett.* 12(5), 2002, 783-786.
32. Divya Singh, Dharam Pal Pathak And Anjali, Coumarins: An Overview of Medicinal Chemistry. Potential for New Drug Molecules, *IJPSR*, 7(2), 2016, 482-504.
33. Jelena Klenkar and Maja Molnar, Natural and synthetic coumarins as potential anticancer agents, *J. Chem. Pharm. Res*., 7(7), 2015, 1223-1238.
34. Santiago Vilar, Elías Quezada, Lourdes Santana, Eugenio Uriarte, Matilde Yánez, Nuria Fraiz, Carlos Alcaide, Ernesto Cano, Francisco Orallo, Design, synthesis, and vaso relaxant and platelet antiaggregatory activities of coumarin–resveratrol hybrids, *Bioorg. Med. Chem. Lett.* 16(2), 2006, 257-261.
35. Sonali Sandhu, Yogita Bansal, Om Silakari, Gulshan Bansal, Coumarin hybrids as novel therapeutic agents, *Bioorganic & Medicinal Chemistry,* 22, 2014, 3806–3814.
36. P. K. Jain and Himanshu Joshi, Coumarin: Chemical and Pharmacological Profile, *Journal of Applied Pharmaceutical Science*, 2(6), 2012, 236-240.
37. Douglas Hanahan, Gabriele Bergers and Emily Bergsland, Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice, *J Clin Invest*. 105(8), 2000, 1045–1047.
38. Aoife Lacy and Richard O'Kennedy, Studies on Coumarins and Coumarin-Related Compounds to Determine their Therapeutic Role in the Treatment of Cancer, *Current Pharmaceutical Design*, 10, 2004, 3797-3811.
39. Chamandeep Kaur Bhinder, Amandeep Kaur, Synthesis and Spectral Studies of Novel 3-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-2H-chromen-2-one Derivatives as Anticancer Agents, *Int. J. Chem, Pharm, Sci.,* 3(10), 2015, 2006-2023.
40. Sonali Sandhu, Yogita Bansal, Om Silakari, Gulshan Bansal, Coumarin hybrids as novel therapeutic agents, *Bioorganic & Medicinal Chemistry,* 22, 2014, 3806–3814.
41. Agarwal, R., Synthesis & biological screening of some novel Coumarin derivatives, *Biochem. Pharmacol*. 6, 2000,1042-1051.
42. Reddy NS, Mallireddigari MR, Cosenza S, Gumireddy K, Bell SC, Reddy EP et al, Synthesis of new coumarin 3-(N-aryl)sulfonamides and their anticancer activity, *Bioorg Medicinal Chem Lett*, 14, 2004, 4093-4097.
43. Budzisz E, Brzezinska E, Krajewska U, Rozalski M, Cytotoxic effects, alkylating properties and molecular modelling of coumarin derivatives and their phosphonic analogues, *Eur J Med Chem*, 38, 2003, 597-603.
44. N.S. Reddy, K. Gumireddy, M.R. Mallireddigari, S.C. Cosenza, P. Venkatapuram, S.C. Bell, E.P. Reddy, M.V.R. Reddy, Novel Coumarin-3-(N-ary)carboxamides arresr breast cancer cell growth by inhibiting ErbB-2 and ERK1, *Bioorg. Med. Chem*. 13(9), 2005, 3141-3147.
45. D. Matiadis, V. Stefanou, G. Athanasellis, S. Hamilakis, V. McKee, O. Igglessi-Markopoulou, J. Markopoulos, Synthesis, X-ray crystallographic study, and biological evaluation of coumarin and quinolinone carboxamides as anticancer agents, *Monatsh. Chem*. 144(7), 2013, 1063-1069.

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.

46. G. Wells, M. Suggitt, M. Coffils, M.A.H. Baig, P.W. Howard, P.M. Loadman, J.A. Hartley, T.C. Jenkinsd, D.E. Thurstona, Fluorescent 7-diethylaminocoumarin pyrrolobenzodiazepine conjugates: Synthesis, DNA interaction, cytotoxicity and differential cellular localization, *Bioorg. Med. Chem. Lett*. 18(6), 2008, 2147-2151.

47. R.M. Mohareb, D.H. Fleita, O.K. Sakka, Novel Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor Activity, *Molecules* 16(1), 2011, 16-27.

48. T. Nasr, S. Bondock, M. Youns, Anticancer activity of new coumarin substituted hydrazide-hydrazone derivatives, *Eur. J. Med. Chem*. 76, 2014, 539-548.

49. H. Douglas, R.A. Weinberg, Hallmarks of Cancer: The Next Generation, *Cell* , 144(5), 2011 646-674.

50. V.L. Ranganatha, F. Zameer, S. Meghashri, N.D. Rekha, V. Girish, H.D. Gurupadaswamy, S.A. Khanum, Design, Synthesis, and Anticancer Properties of Novel Benzophenone-Conjugated Coumarin Analogs, *Arch. Pharm. Chem. Life Sci.* 346(12), 2013, 901-911.

51. B.R. Vijay Avin, P. Thirusangu, V. Lakshmi Ranganatha, A. Firdouse, B.T. Prabhakar, S.A. Khanum, Synthesis and tumor inhibitory activity of novel coumarin analogs targeting angiogenesis and apoptosis, *Eur. J. Med. Chem*. 75(21), 2014, 211-221.

52. M. Tolomeo, S. Grimaudo, A. Di Cristina, M. Roberti, D. Pizzirani, M. Meli, L. Dusonchet, N. Gebbia, V. Abbadessa, L. Crosta, R. Barucchello, G. Grisolia, F. Invidiata, D. Simoni, Pterostilbene and 3-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells, *Int. J. Biochem. Cell Biol*. 37(8), 2005, 1709-1726.

53. Roupe KA, Remsberg CM, Yáñez JA, Davies NM., Pharmacometrics of stilbenes: seguing towards the clinic, *Curr. Clin. Pharm*. 1(1), 2006, 81-101.

54. Céline Rivièrea, Tristan Richarda, Lysiane Quentina, Stéphanie Krisab, Jean-Michel Mérillonb, Jean-Pierre Montia, Inhibitory activity of stilbenes on Alzheimer's β-amyloid fibrils in vitro, *Bioorg. Med. Chem*. 15, 2007, 1160-1167.

55. C.F. Xiao, L.Y. Tao, H.Y. Sun, W. Wei, Y. Chen, L.W. Fu, Y. Zou, Design, synthesis and antitumor activity of a series of novel coumarin-stilbenes hybrids, the 3-arylcoumarins, *Chin. Chem. Lett.*, 21(11), 2010, 1295-1298.

56. J. Yang, G.Y. Liu, F. Dai, X.Y. Cao, Y.F. Kang, L.M. Hu, J.J. Tang, X.Z. Li, Y. Li, X.L. Jin, B. Zhou, Synthesis and biological evaluation of hydroxylated 3-phenylcoumarins as antioxidants and antiproliferative agents, *Bioorg. Med. Chem. Lett*. 21(21), 2011, 6420-6425.

57. R.S. Keri, A. Hiremathad, S. Budagumpi, B.M. Nagaraja, Comprehensive review in current developments of benzimidazole-based medicinal chemistry, *Chem. Biol. Drug Des*., 86(1), 2015, 799-845.

58. K. Paul, S. Bindal, V. Luxami, Synthesis of new conjugated coumarin–benzimidazole hybrids and their anticancer activity, *Bioorg. Med. Chem. Lett*. 23(12), 2013, 3667-3672.

59. S. Lee, K. Sivakumar, W.S. Shin, F. Xie, Q. Wang, Synthesis and anti-angiogenesis activity of coumarin derivatives, *Bioorg. Med. Chem. Lett*. 16(17), 2006, 4596-4599.

60. H. Kumar, D. Saini, S. Jain, N. Jain, Pyrazole scaffold: A remarkable tool in the development of anticancer agents, *Eur. J. Med. Chem*. 70 (2013) 248-258

61. W.E. Wright, J.W. Shay, Cellular senescence as a tumor-protection mechanism: the essential role of counting, *Curr. Opin. Genet. Dev.* 11(1), 2001, 98-103.

62. X.H. Liu, H.F. Liu, J. Chen, Y. Yang, B.A. Song, L.S. Bai, J.X. Liu, H.L. Zhu, X.B. Qi, Synthesis and molecular docking study of novel coumarin derivatives containing 4,5-dihydropyrazole moiety as potential antitumor agents, *Bioorg. Med. Chem. Lett*. 20(19), 2010, 5705-5708.

63. X.Q. Wu, C. Huang, Y.M. Jia, B.A. Song, J. Li, X.H. Liu, Novel coumarin-dihydropyrazole thio-ethanone derivatives: Design, synthesis and anticancer activity, *Eur. J. Med. Chem*. 74, 2014, 717-725.

64. S. Stanchev, G. Momekov, F. Jensen, I. Manolov, Synthesis, computational study and cytotoxic activity of new 4-hydroxycoumarin derivatives, *Eur. J. Med. Chem.* 43, 2008, 694-706.

65. T. Aoki, I. Hyohdoh, N. Furuichi, S. Ozawa, F. Watanabe, M. Matsushita, M. Sakaitani, K. Ori, K. Takanashi, N. Harada, Y. Tomii, M. Tabo, K. Yoshinari, Y. Aoki, N. Shimma, H. Iikura, The sulfamide moiety affords higher inhibitory activity and oral bioavailability to a series of coumarin dual selective RAF/MEK inhibitors, *Bioorg. Med. Chem. Lett.* 23(23), 2013, 6223-6227.

66. M. Lopez, L.F. Bornaghi, A. Innocenti, D. Vullo, S.A. Charman, C.T. Supuran, S.A. Poulsen, Sulfonamide linked neoglycoconjugates-A new class of inhibitors for cancer-associated carbonic anhydrases, *J. Med. Chem.* 53(7), 2010, 2913-2926.

67. C.P.S. Potter, A.L. Harris, Diagnostic, prognostic and therapeutic implications of carbonic anhydrases in cancer, *Br. J. Cancer*, 89, 2003, 2-7.

68. Maresca, C. Temperini, L. Pochet, B. Masereel, A. Scozzafava, C.T. Supuran, Deciphering the Mechanism of Carbonic Anhydrase Inhibition with Coumarins and Thiocoumarins, *J. Med. Chem.*, 53(1), 2010, 335-344.

69. Z.C. Wang, Y.J. Qin, P.F. Wang, Y.A. Yang, Q. Wen, X. Zhang, H.Y. Qiu, Y.T. Duan, Y.T. Wang, Y.L. Sang, H.L. Zhu, Sulfonamides containing coumarin moieties selectively and potently inhibit carbonic anhydrases II and IX: design, synthesis, inhibitory activity and 3D-QSAR analysis, *Eur. J. Med. Chem.*, 66, 2013, 1-11.

Source of Support: Nil, **Conflict of Interest:** None.

© Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.