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Natural and synthetic coumarins as potential anticancer agents

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ABSTRACT

Coumarins, natural or synthetic, due to their wide range of biological activities, have become an interesting subject of investigation for many researchers. Coumarin scaffold has proven to have an important role in anticancer drug development due to a fact that many of its derivatives have shown an anticancer activity on various cell lines. Action of coumarins on tumour cells is carried out via different mechanisms and some of them show very good selectivity toward the cancer cells. In this work a brief literature review (2010-2015) on coumarins as potential anticancer drugs is given, which can serve as an excellent tool for future investigations on design and synthesis of such derivatives.

Key words: Coumarin, Anticancer drugs, Anticancer activity

INTRODUCTION

Coumarins (Fig.1) belong to benzopyrone chemical class, more precisely benzo-*α*-pyrones, where benzene ring is fused to pyrone ring [1]. In nature, coumarins are found in higher plants like *Rutaceae* and *Umbelliferae* and some essential oils like cinnamon bark oil, cassia leaf oil and lavender oil are also rich in coumarins. Except from higher plants, coumarins were found in microorganisms as well, like novobiocin and coumermycin from *Streptomyces* and aflatoxins from *Aspergillus* species [1, 2].

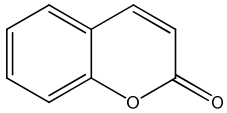


Fig. 1 Chemical structure of coumarin

Coumarins are proven to possess a wide range of biological activities, anti-inflammatory [3], antimicrobial [4], antiviral [5], antioxidant [6], antinociceptive [7], anti–tumor [8], antiasthmatic [9], antidepressant [10], anti-HIV [11], antituberculosis [12], anti- Alzheimer [7], anti–influenza [13], antihyperlipidemic [14] - being only some of them.

Anticancer activity of coumarins

Cancer is a fatal disease, which accounts 7, 6 million deaths (around 13 % of all deaths) worldwide in 2008. The number of deaths from cancer will continue to rise, with an estimated 13.1 million people dying in 2030 [15].

There are many different mechanisms how anticancer drugs can inhibit the division of cancer cells, some of them working as DNA intercalating agents, DNA cross-linking agents, topoisomerase inhibitors, cytoskeleton-disrupting agents and antimetabolites [16]. Most of the anticancer drugs kill cancer cells by triggering apoptosis in the cancer cells [17]. Apoptosis, which is the result of complex interaction between pro- and anti- apoptotic molecules, regulates the homeostasis and eliminates the damaged cells [18].

As antitumor activity of natural and synthetic coumarin derivatives have been extensively explored by many researchers [19, 20, 21, 22, 23, 24] and it has been proven that coumarins, depending on their structure, can act on various tumour cells by different mechanisms; they inhibit the telomerase enzyme, protein kinase activity and down regulating oncogene expression or induce the caspase-9-mediated apoptosis, suppress cancer cell proliferation by arresting cell cycle in G0/G1 phase, G2/M phase and affecting the p-gp of the cancer cell [15, 25].

Coumarin derivatives can possess not only cytostatic, but cytotoxic properties as well [26]. Marshall M. E. et al.(1994) showed that coumarin and 7-hydroxycoumarin can inhibited growth in human cancer cell lines [27], such as A549 (lung), ACHN (renal), H727 (lung), MCF7 (breast) and HL-60 (leukaemia) and in some clinical trials they exhibited anti-proliferative activity in prostate cancer [28], malignant melanoma [29] and renal cell carcinoma [30]. Coumarin, itself also exhibited the cytotoxic effect against Hep2 cells (human epithelial type 2) in dose dependent manner and showed some typical characteristics of apoptosis with loss of membrane microvilli, cytoplasmic hyper-vacualization and nuclear fragmentation [31].

Coumarins were also found to be excellent agents for treating side effects caused by radiotherapy which was demonstrated by Mahler et.al (1992) who applied a combinational therapy of coumarin/troxerutin in a protection of salivary glands and mucosa in patients undergoing radiotherapy [32].

2.1. Ovarian cancer

Ovarian cancer, as a very common cause of death in women worldwide, is often diagnosed in its late stages and the major obstacle in its treatment is multi-drug resistance (MDR) where most of the patients develop a resistance to platinum based drugs or paclitaxel, chemotherapy drug used for treating ovarian cancer, breast cancer, lung cancer and Kaposi´s sarcoma [33, 34, 35].

Coumarin derivative RKS262 as an analogue of Nifurtimox, a drug that induces the cytotoxic and antitumor effects in neuroblastoma *in vivo* and *in vitro*, showed very potent activity in ovarian cancer (OVCAR-3 cells, human ovarian epithelial adenocarcinoma cell line) chemoresistant to platinum-based drugs [19].

Its structure is shown on Fig. 2 where it is visible that nitrofuran ring of Nifurtimox is replaced by 6-bromo-4-chlorocoumarin group. Lipophilic properties of modified coumarin group and hydrophilic character of 1-aminotetrahydrothiazine ring ensure that this potential drug could have good bioavailability [19]. The anticancer activity of this compound towards ovarian cancer cell lines (OVCAR-3) was exhibited by reducing the mitochondria-transmembrane-depolarization potential, regulating the mitochondrial Bcl-2 family pathway, increasing the pro-apoptotic factors Bid, Bad and Box expression and decreasing the expression of Bcl-xl and Mcl-1 [36].

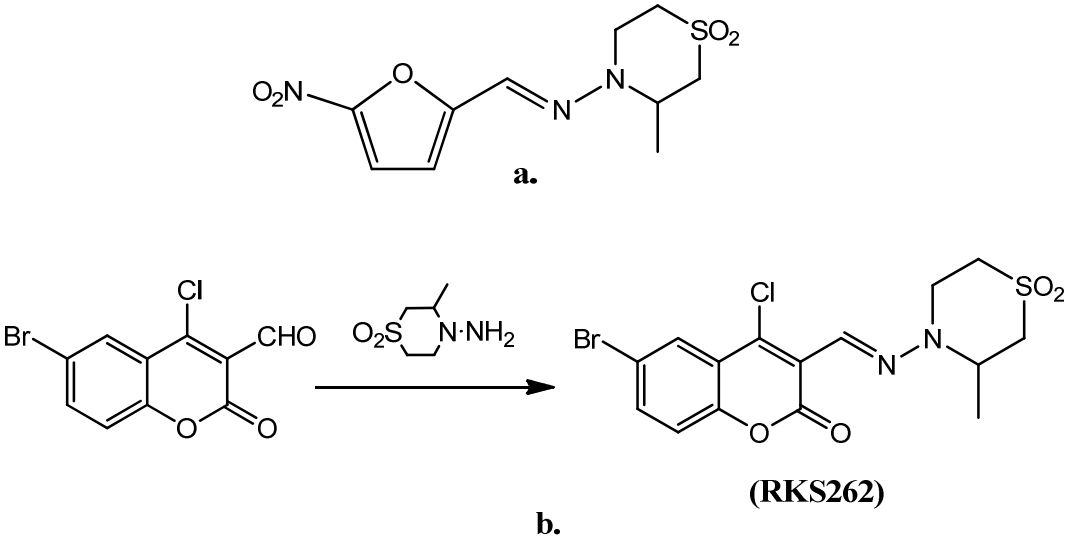


Fig. 2 a. Structure of Nifurtimox; b. Synthetic pathway for RKS262 (4) from 6-brom-4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde and 1-aminotetrahydrothiazane [19]

Jamier et al. (2014) synthesized chalcone-coumarin derivatives and evaluated them for anticancer activity against different cancer cell lines, where compound on Fig.3 had the highest cytotoxic activity against ovarian cancer (OVCAR) [37].

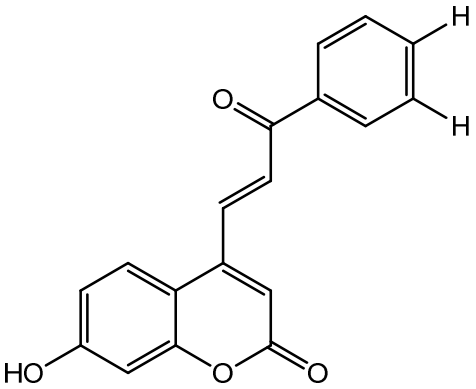


Fig. 3 Chemical structure of the most potent chalcone-coumarin derivative against ovarian cancer cell lines (OVCAR) - 7-hydroxy-4-[(1*E*)-3-oxo-3-phenylprop-1-en-yl]-2*H*-chromen-2-one [37]

2.2. Lung cancer

Lung cancer is characterized by two main types: small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), respectively [38].

Treatment for NSCLC often fails because of drugs insusceptibility to advanced lung cancer stages [38]. Many coumarin derivatives, natural and synthetic have proven to be excellent anticancer agents on this type of cancer. Osthole (7-methoxy-8-(3- methyl-2-butenyl)coumarin) (Fig. 4), which was extracted from many therapeutic plants such as *Cnidium monnieri* [39] and *Prangos ferulacea* (L.) [40] inhibited the growth of human lung cancer (A- 549 cancer cells) by inducing G2/M arrest and apoptosis [41]. Umbelliprenin, (Fig. 4) which was isolated from *Ferula* plant species, induced the apoptosis in QU-DB (large cell lung cancer) and A549 adenocarcinoma cell line, at different doses [20].

Wang et al. (2013) demonstrated that naturally extracted 7,8 –dihydroxycoumarin (daphnetin) (Fig. 4) inhibits the proliferation of A549 human lung adenocarcinoma cells and by suppression of Akt/NF-κ B signalling pathways induces the apoptosis in concentration dependent manner [17].

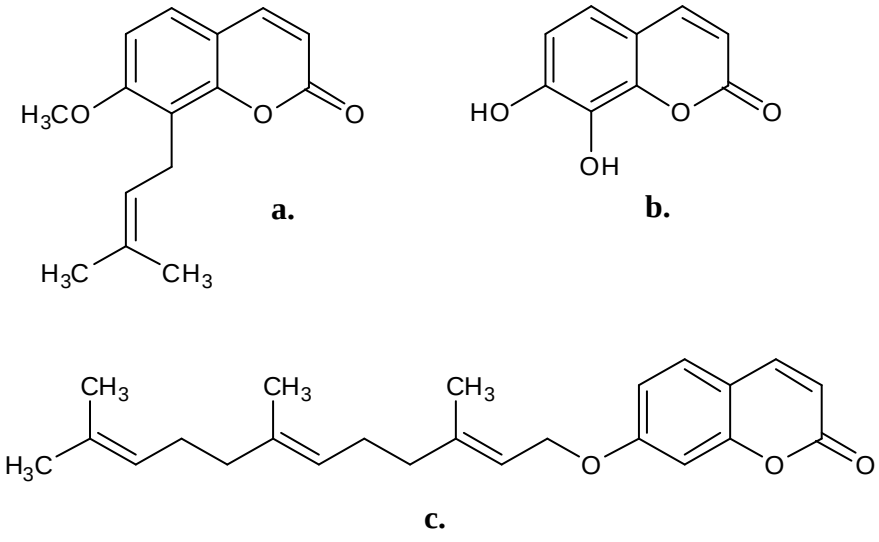


Fig. 4 Structure of the most active natural coumarins against lung cancer: a. osthole (7-methoxy-8-(3-methyl-2-butenyl)coumarin) [41]; b. 7,8–dihydroxycoumarin (daphnetin) [17]; c. umbelliprenin [20]

Musa et al. (2012) found that some of the coumarin-based benzopyranone derivatives induced apoptosis in human lung cancer (A549) by a different mechanisms. Coumarin derivative on Fig. 5a. induces the apoptosis by increasing the expression of pro-apoptotic Bax and decreasing anti-apoptotic Bcl-2 expression. However, coumarin-benzopyranone derivative on Fig. 5b. decreased an expression of both Bax and Bcl-2 proteins [38].

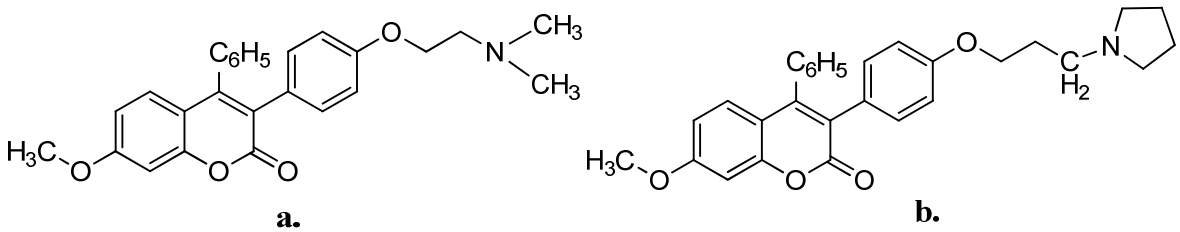


Fig. 5 Structure of the potent anticancer coumarin-benzopyranone derivatives against lung cancer: a. 3-(4-(2-(dimethylamino)ethoxy)phenyl)-7-methoxy-4-phenyl-2*H*-chromen-2-one; b. 7-methoxy-4-phenyl-3-(4-(3-(pyrrolidin-1-yl)propoxy)phenyl)-2*H*-chromen-2-one [38]

Musa et al. (2015) also investigated *in vitro* antitumor activity of some 3-arylcoumarin derivatives in A549 cancer cell lines (lung cancer). The most active compound was 8–(acetyloxy)-3-(4-methanesulfonyl phenyl)-2-oxo-2*H*-chromen-7-yl acetate (Fig. 6), a compound which showed selective cytotoxicity, causing cell arrest in S phase of the cell cycle which is the indication of inhibiting DNA synthesis in cells, loss of MMP (matrix metalloproteinase) and increase of ROS (reactive oxygen species) production in A549 cancer cell lines [21].

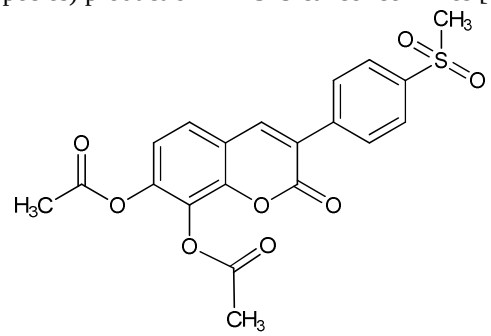


Fig. 6 Structure of 8–(acetyloxy)-3-(4-methanesulfonyl phenyl)-2-oxo-2*H*-chromen-7-yl acetate [21]

Among synthesized iodinated-4-aryloxymethylcoumarins improved anti-cancer activity against A-549 (human lung cancer) was observed in compounds having clorine at position 6 and 7 and bromine at position 6 of coumarin ring (Fig. 7) [42].

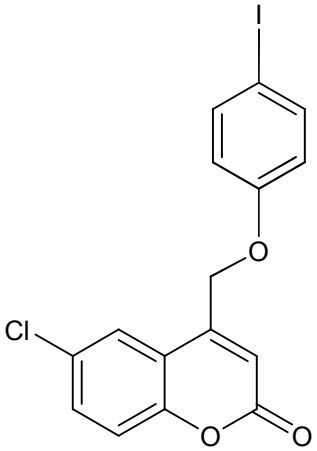


Fig. 7 Structure of 6-chloro-4-[(4-iodophenoxy)methyl]-2*H*-chromen-2-one [42]

Hybrid molecules which consist of substituted trans-vinylbenzene moiety on coumarin scaffold were synthesized by Belluti et al. (2010) [43]. The most promising results, with an excellent antiproliferative and proapoptotic activities were 7-methoxycoumarin nucleus with 3,5- disubstitution pattern of the trans-vinylbenzene moiety. Compound on Fig. 8a. 4-[(*E*)-2-(2,4-dimethoxyphenyl)ethenyl]-7-methoxy-2*H*-chromen-2-one administered orally at dose of 10-20 mg/kg in patients with lung carcinoma (H460) inhibited growth of cancer cells, without a toxic effects [43].

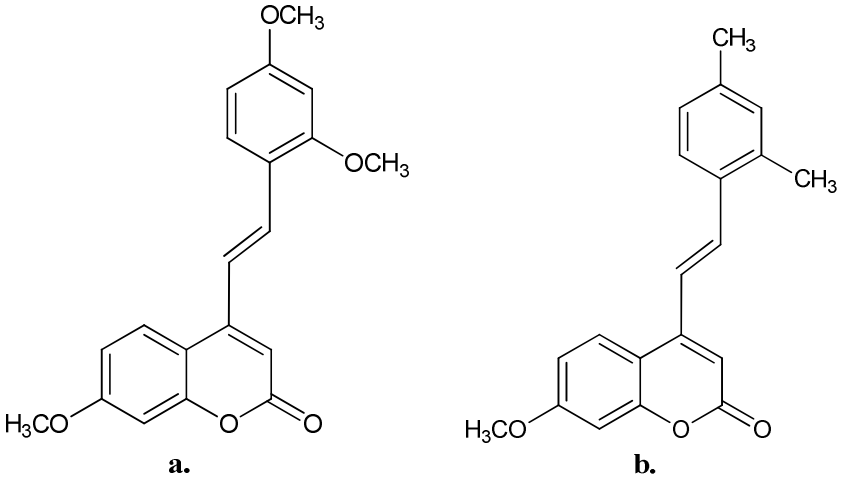


Fig. 8 Structure of: a. 4-[(*E*)-2-(2, 4-dimethoxyphenyl)ethenyl]-7-methoxy-2*H*-chromen-2-one; b. 4-[(E)-2-(2,4-dimethylphenyl)ethenyl]-7-methoxy-2*H*-chromen-2-one [43]

Among S- and O-substituted 7-mercaptocoumarin derivatives synthesized by Chen at al. (2012), compound on Fig. 9 significantly increased cellular apoptosis in concentration dependent manner and also caused cell cycle arrest at G2/M phase in A549 cell line [44].

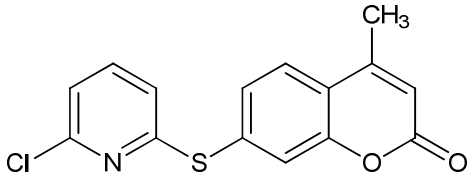


Fig. 9 Chemical structure of 7-[(6-chloropyridin-2-yl)sulfanyl]-4-methyl-2*H*-chromen-2-one [44]

When lung cancer is treated with combination of coumarin-3-carboxylic acid and valproic acid (Fig. 10) a significant inhibition of proliferation and migration of lung cancer cells was observed [45].

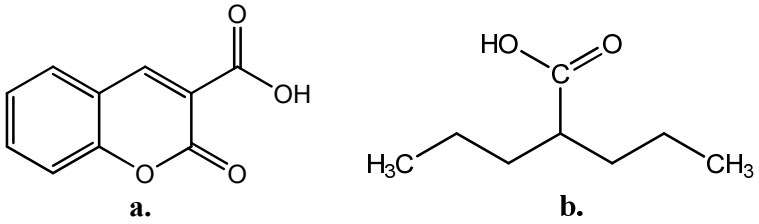


Fig. 10 Structure of potential combinational therapy in lung cancer: a. coumarin-3-carboxylic acid; b. valproic acid [45]

2.3. Breast cancer

Hormone oestrogen has the crucial role in development of the breast cancer, the most frequent malignant disease in women, therefore many therapies are designed to block his activity [46]. Cinnamoyl-coumarin derivatives were especially effective in oestrogen-dependent cancers, such as breast (MCF7) and ovarian (OVCAR) cancer cell lines, the most potent is on the Fig. 11. These compounds are selective nonsteroidal inhibitors of 14 β-hydroxysteroid dehydrogenase type 1, an enzyme that catalyses NADPH-dependent reduction of the weak oestrogen, oestrone, into the most potent oestrogen, oestradiol [37].

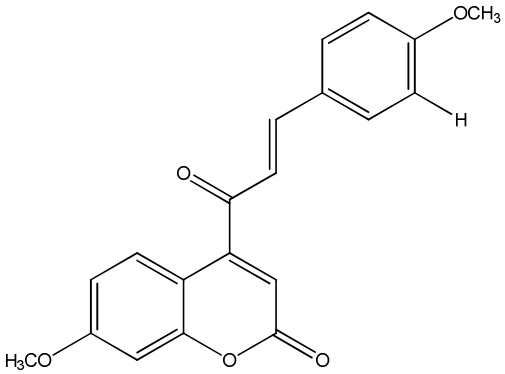


Fig. 11 Chemical structure of the most potent cinnamoyl-coumarin derivative against breast cancer (MCF-7) - 7-methoxy-4-[(2*E*)-3-(4-methoxyphenyl)prop-2-enoyl-2*H*-chromen-2-one [37]

A new group of coumarin-oestrogen conjugates were synthesized by attaching the β-oestradiol (Fig. 12) to a coumarin ring with most of the compounds showing antiproliferative activity against panel of breast cancer cell lines [47].

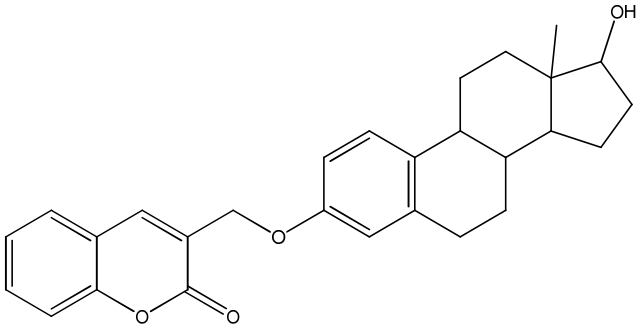


Fig. 12 Structure of the conjugate of coumarin with β-oestradiol [47]

Tamoxifen (TAM) (Fig13.) as non-steroidal triphenylethylene derivative is the most widely used selective oestrogen receptor modulator (SERM), [48] but usually a drug resistance develops through couple of years of treatment in patients [46]. Therefore, Sashidhara et.al. (2013) developed a new hybrid molecules coumarin – monastrol, where compound on the Fig. 13. showed the most potent selective activity against breast cancer cell lines MCF-7 and MDA–MB-231. This compound induced caspase-3 activation and apoptosis and caused arrest of MCF-7 cell cycle at G1 phase [46].

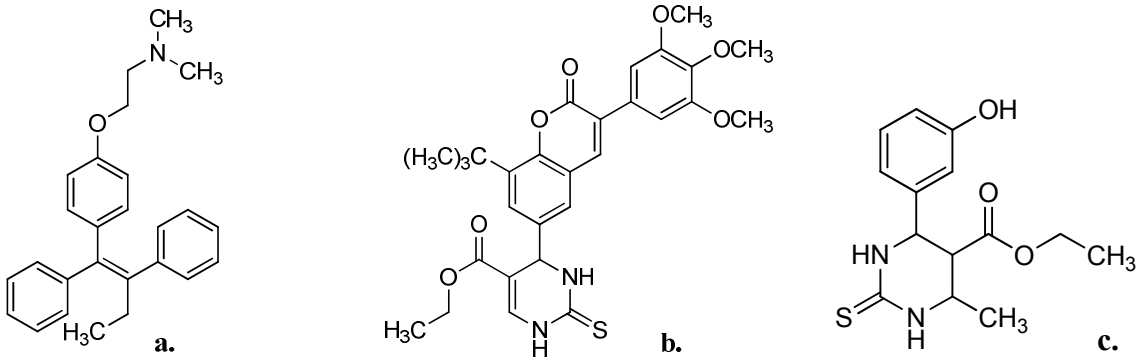


Fig. 13 Structure of a. Tamoxifen; b. monastrol; c. coumarin–monastrol hybrid [46]

Mustafa et al. (2011) synthesized series of new N1-(coumarin-7-yl)amidrazones incorporating N-piperazines and related congeners where 7-{2-[1-(4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)piperazin-1-yl)-2-oxopropylidene]hyrazinyl}-4-methyl-2*H*-chromen-2-one (Fig. 14), showed the most potent activity against MCF-7 cell line (breast cancer) [49]. Among a series of coumarin substituted benzothiazoles synthesized by Kini et al. (2012), the most potent compound against breast cancer (MCF-7) was SC20 (Fig14.) with 79.40 % at the dose of 250 µM/ ml [50].

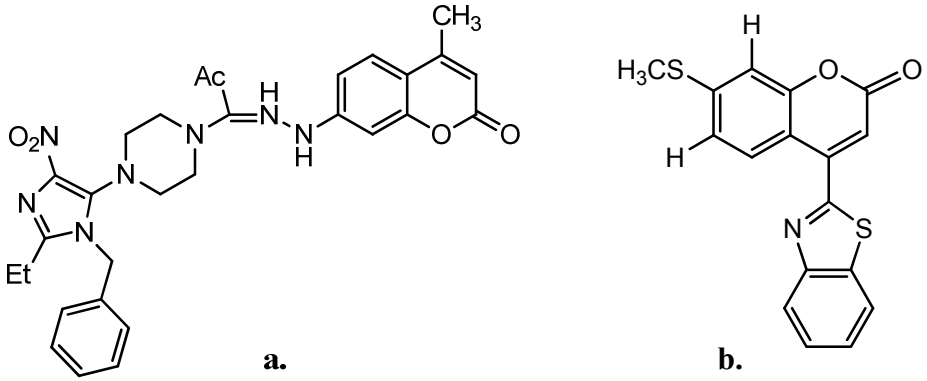
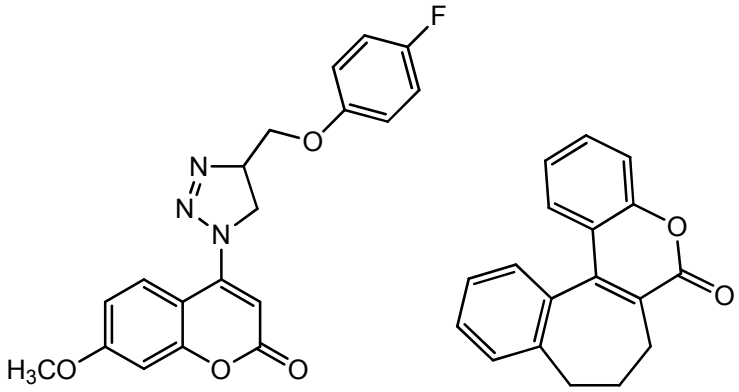


Fig. 14 Chemical structure of; a. *N*1-(coumarin-7-yl)amidrazone [49]; b. coumarin substituted benzothiazol [50]

One of the 4-(1,2,3-triazol-1-yl)coumarin derivatives, 4-(4-((4-fluorophenoxy)methyl)-1,2,3-triazol-1-yl)-7-methoxycoumarin showed excellent anticancer activity against MCF-7 (breast cancer) and also SW480 (colon cancer) and A549 (lung cancer). This compound (Fig. 15a.) inhibited proliferation of cells by inducing apoptosis and causing cell cycle arrest at G2/M phase [23]. Yadagiri et al. (2014) synthesized benzosuberone bearing coumarin moieties where compound on Fig. 15b. showed the most potent activity against all tested cell lines A549

(human alveoral adenocarcinoma cell line), HeLa (human cervical cancer) and also two human breast cancer cell line MDA-MB-231 and MCF-7, respectively [51].



a. **b.**

Fig. 15 Structure of a. 4-(4-((4-fluorophenoxy)methyl)-1,2,3-triazol-1-yl)-7-methoxycoumarin [23]; b. 8, 9-dihydrobenzo[3,4]cyclohepta[1,2-c]chromen-6(7*H*)-one [51]

2.4. Prostate cancer

Li. et. al. (2015) demonstrated that scopoletin (6-methoxy-7-hydroxycoumarin) (Fig. 16), a natural coumarin found in plants such as *Erycibe obtusifolia*, *Aster tataricus* and *Foeniculum vulgare*, exhibited anticancer activity against prostate cancer cells (LNCaP) by inhibition of expression of cyclin D_1 which caused cell cycle arrest at G2/M phase and induced early and late apoptosis in LNCaP cancer cell lines [52].

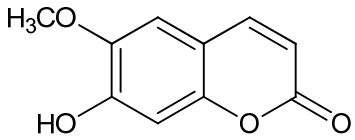


Fig. 16 Structure of scopoletin [52]

Since the importance of amide bond on C-3 position of coumarin for cytotoxic activity was proven by Reddy et al. (2005) [53], Matiadis et al. (2013) synthesized the series of coumarins and quinolinone-3-aminoamide derivatives, with coumarin aminoamide derivative (Fig. 17) possessing the highest activity against DV 145 prostate cancer cell lines [54].

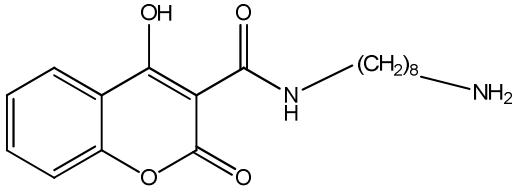
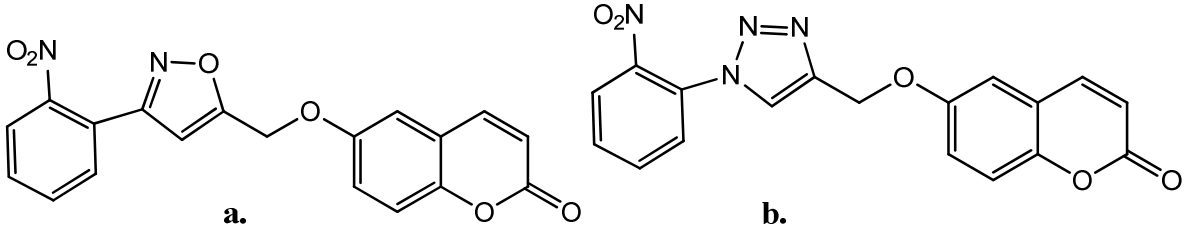


Fig. 17 Structure of *N*-(8-aminooctyl)-4-hydroxy-2-oxo-2*H*-chromene-3-carboxamide [54]

In their attempt to synthesize biological active compounds Rehman et al (2014) designed 6-hydroxy coumarin derivatives with triazole and isoxazole ring. The best anticancer activity against prostate cancer cell line (PC-3) was obtained with compound on Fig. 18 carrying isoxazole ring, while compound carrying triazole ring (Fig. 18) was the most potent against lung cancer cell line (A-549) [24].



a. **b.**

Fig. 18 Chemical structure of: a. 6-((3-(2-nitrophenyl)isoxazol-5-yl)methoxy)-*2H*-chromen-2-one potent against prostate cancer cell line (PC-3); b. 6-((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-*2H*-chromen-2-one potent against lung cancer cell line (A-549) [24]

Szliska et al. (2011) demonstrated that neobavaisoflavone and psoralidin (Fig. 19) isolated from *Psoralea corylifolia* in combination of TRAIL (tumor necrosis factor related apoptosis inducing ligand) enhanced the potential of TRAIL for inducing apoptosis in sensitized TRAIL-resistant LNCaP (prostate cancer cells). TRAIL molecules expressed on

the cell surface of T-lymphocytes, natural killer cells, dendritic cells, neutrophils, monocytes or macrophages, induces apoptosis in cancer cells with no effect on normal cells [55].

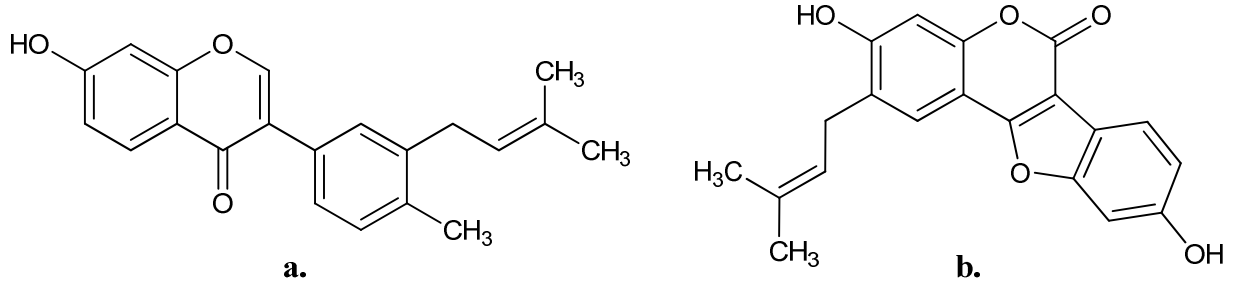


Fig. 19 Chemical structure of: a. neobavaisoflavone; b. psoralidin [55]

2.5. Bladder carcinoma

Transitional cell carcinoma (TCC), one of the most common bladder cancers, is difficult to treat due to its resistance to a wide range of chemotherapeutic agents [56].

Cytotoxic activity on bladder cancer cells was investigated by Haghighi et al. (2014) on 7-isopentenyloxycoumarin (7-IP) (Fig. 20a), compound that can be synthesized both naturally and chemically and it exhibited selective cytotoxic effect on 5637 cells (bladder cancer) in comparison to normal HDF-1 cells (human dermal fibroblast) [56].

Diversin, terpenoid coumarin (Fig. 20b), isolated from *Ferula diversivittata* by Haghighitalab et al. (2014) was found to have cytotoxic effect in 5637 cells (bladder cancer) causing arrest of the cells in the G2/M phase [57].

From Korean *Angelica gigas* root Kim et al. (2010) isolated pyranocoumarin decursin (Fig. 20c), which inhibited proliferation in bladder cancer 235J cells and also in colon cancer HCT-1116 cells. Decursin induced apoptosis in both cancer cell lines through expression of Bax protein and reduced Bcl-2 protein levels [58].

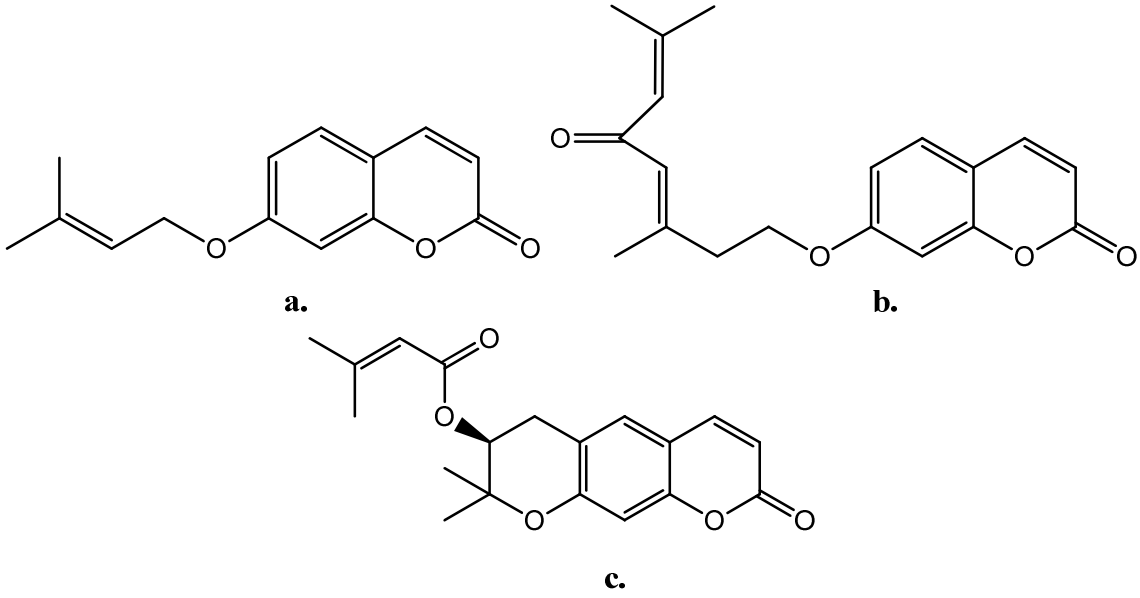


Fig. 20 Chemical structure of: a. 7-isopentenyloxycoumarin (7-IP) [56]; b. diversin [57]; c. decursin [58]

Citotoxicity of cisplatin (Fig. 21a) (platinum based drug), used in treating different kind of cancers including bladder cancer, was significantly enhanced in combination with herniarin (Fig. 21b). In herniarin, hydrogen atom on position 7 of umbelliferone is replaced by methyl group, so the compound is also called methyl umbelliferone [59].

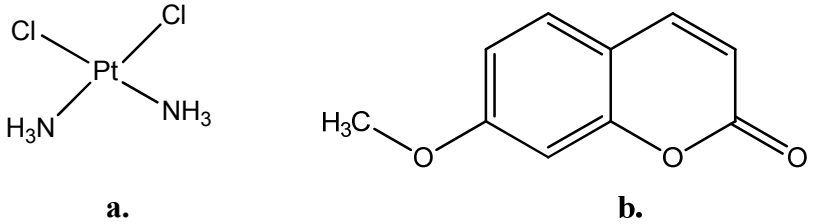


Fig. 21 Structure of: a. cisplatin and b. herniarin [59]

2.6. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is very aggressive type of cancer and also immune to standard therapies (chemotherapy and radiotherapy), so there is an enormous need for new anticancer agents for treating HCC [60].
Osthole (7-methoxy-8-(3-methyl-2-butenyl)coumarin) (Fig. 4), a natural coumarin derivative found in, seeds of the dried ripe fruit of *Cnidium monieri* (*L) Cuss* (Common Cnidium) and *Angelica pubescens* [61] can inhibit growth of HCC tumor cells (SMMC-7721) *in vivo* and *in vitro*, through inhibiting Akt/NF-κ B signaling pathway, which induces G2/M arrest and apoptosis [60].

Esculetin (Fig. 22), coumarin presented in several plants such as *Fraxinus rhynchophylla* and *Artemisia capillaris*, significantly inhibited proliferation of HCC cells (SMMC-7721 cancer cell lines) by causing cell cycle arrest at S phase and inducing apoptosis[22].

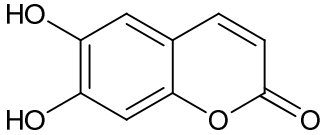


Fig. 22 Chemical structure of esculetin [22]

Prasad et al. (2010) isolated 8-hydroxypsoralen (Fig. 23) from peels of wampee (*Clausena lansium (Lour.)* Skeels), which belongs to *Rutaceae* family widely distributed in India, southern China, Thailand and Vietnam. 8-Hydroxypsoralen showed high anti-proliferative activity against HepG2 (human hepatocellular liver carcinoma), A549 (human lung adenocarcinoma epithelial cell line) and HELA(human cervical carcinoma cell line) [62].

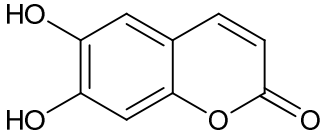


Fig. 23 Chemical structure of 8-hydroxypsoralen [62]

Zhao et al. (2014) modified the structure of scopoletin, main active component of *E. obtusifolia* Benth stems, and got a new compound, named SC-III3 (Fig. 24). SC-III3 was effective in inhibiting the growth of HEpG2 (hepatocellular carcinoma) by inducing generation of intracellular ROS, DNA damage and arrest in S phase. This inhibitory effect of SC-III3 was very low on normal liver cell lines [63].

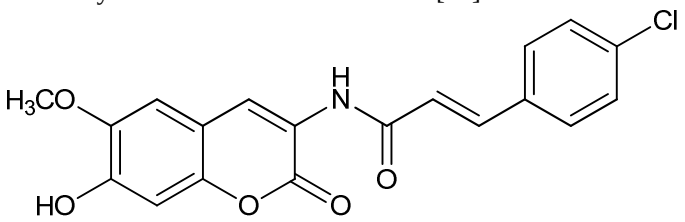


Fig. 24 Chemical structure of SC-III3 (modified scopoletin) [63]

Coumarins with attached pyrazoline ring were synthesized from 8-acetyl-7-methoxycoumarin and evaluated for anticancer activity against HepG2 cell line. The most potent coumarin pyrazoline hybrid was the one on the Fig. 25 [64].

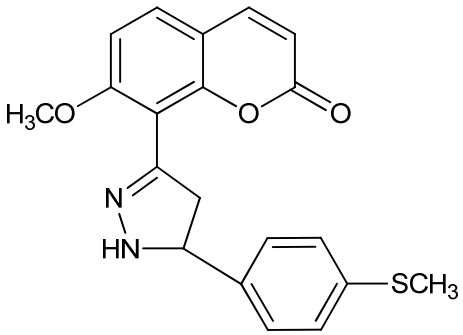


Fig. 25 Chemical structure of the most potent coumarin-pyrazole hybrid against HepG2 cell line (7-methoxy-8-{5-[4-(methylsulfanyl)phenyl]-4,5-dihydro-1*H*-pyrazol-3-yl}-2*H*-chromen-2-one) [64]

Nasr et al. (2014) synthesized coumarin hydrazide-hydrazone derivatives (CHHDs) with the one shown on Fig. 26 being the most potent antiproliferative agent against resistant Hep-G2 cell line (HCC) [25].

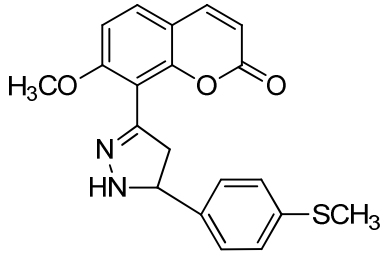


Fig. 26 Structure of the most potent CHHD against Hep-G2 cell line (6-bromo-2-oxo-*N*'-[(*E*)-thiophen-2-ylmethylidene]-2*H*-chromene-3-carbohydrazide) [25]

Studies have shown that chloropurine derivatives exhibited cytostatic activity against many cancer cell lines. Coumarin derivative containing 2-amino-6-chloropurine ligand had the best cytostatic activity on hepatic carcinoma (Hep-G2) (Fig. 27) and also against colon cancer (SW620) [26].

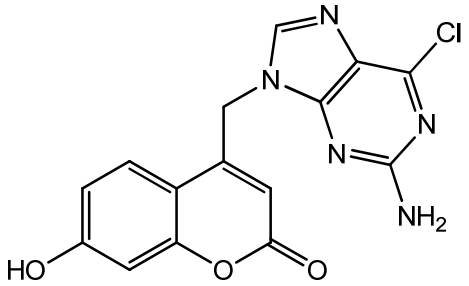


Fig. 27 Structure of 4-[(2-amino-6-chloro-9H-purin-9-yl)methyl]-7-hydroxy-2*H*-chromen-2-one [26]

Synthetic coumarin, 7-carbethoxyamino-2-oxo-2*H*-chromen-4-yl)methylpyrrolidine-1 carbodithioate (CPP) (Fig. 28) synthesized by Neelgundmath et al. (2015) targeted the nuclear factor kappa (NF-κB) in hepatocellular carcinoma, which is an inducible transcription factor playing an important role in cell proliferation and survival, also found in the cytoplasm of almost all mammalian cells. CPP induced cytotoxicity in three HCC cells: HepG2, PLC/PRF5 and Huh7 in dose and time dependent manner, by suppression DNA binding ability of NF-κB, decreasing the CXCL12-induced cell migration and invasion and inhibition of expression NF-κB targeted genes such as cyclin D1, Bcl-2, survivirin, MMP12 and C-Myc [65].

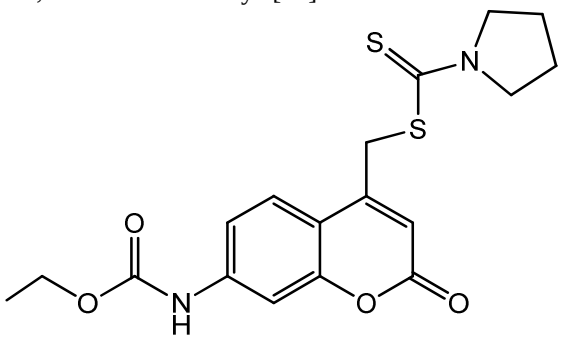


Fig. 28 Structure of (7-carbethoxylamino-2-oxo-2*H*-chromen-4-yl)methylpyrrolidine-1 carbodithioate (CPP) [65]

2.7. Colon cancer

The most common chemotherapeutic agent used in treating of colorectal cancer is 5-fluoruracil (5-FU), but patients often develop resistance on 5 -FU with high recurrence rate, so research for the new drugs for treating this type of cancer is crucial [66].

Furocoumarins, coumarin derivatives fused with furan ring, showed a wide range of biological activities such as anti- HIV [67], anticancer [68], anti-influenza [13], anti- inflammatory [69]. Furo[3,2-c] coumarin derivatives (Fig. 29), which Rajabi et al. (2015) synthesized showed a very good anticancer activity by cell growth inhibition of HCT–15 cell line (colon cancer) [70], while di-coumarin polysulfides synthesized by Saidu et al. (2012) caused arrest in HCT 116 colorectal cancer cell in G2/M phase of the cell cycle and also induced apoptosis [71].

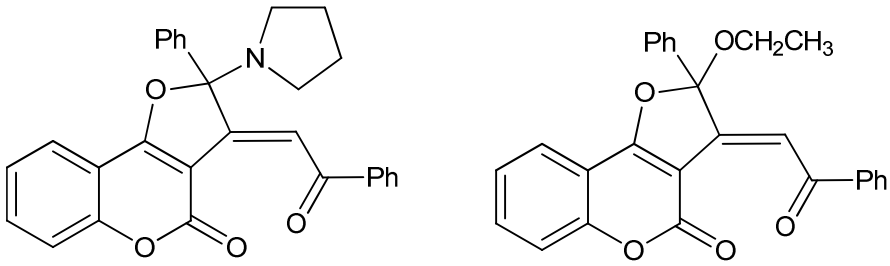


Fig. 29 Chemical structure of the most potent furo[3,2-c]coumarin analogs against HCT-15 cell line (colon cancer): a. (*E*)-3-(2-oxo-2-phenylethylidene)-2-phenyl-2-(pyrrolidin-1-yl)-2H-furo[3,2-c]chromen-4(3*H*)-one; b. (*E*)-2-ethoxy-3-(2-oxo-2-phenylethylidene)-2-phenyl-2*H*-furo[3,2-c]chromen-4(3H)-one [70]

Di-coumarin polysulfide SV25 (Fig. 30) caused arrest in HCT 116 colorectal cancer cell in G2/M phase of the cell cycle and also induced apoptosis [71].

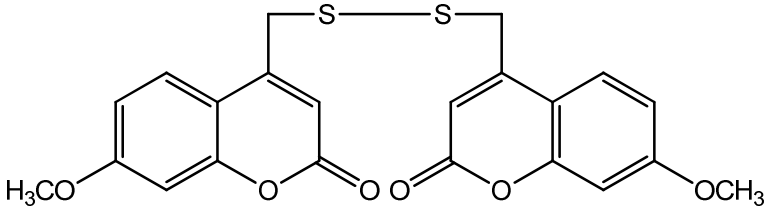


Fig. 30 Chemical structure of di-coumarin polysulfide SV25 [71]

Lin et al. (2014) showed that alkylation on position 6 of coumarin induces apoptosis in colon cancer cells. DMAC (5,7-dihydroxy-4-methyl-6-(3-methylbutanoyl)-coumarin) (Fig. 31) induced apoptosis in two human colon cancer cells: HCT-116 and LoVo. Also in combination with conventional anticolon cancer drugs, such as 5-FU and CPT-11, DMAC increased effectiveness of this drugs [72].

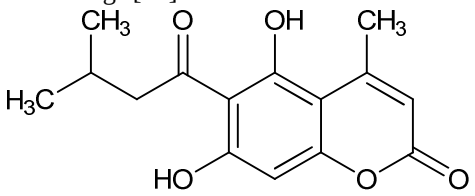


Fig. 31 Chemical structure of DMAC (5, 7-dihydroxy-4-methyl-6-(3-methylbutanoyl)-coumarin) [72]

Umbelliprenin (Fig. 4) showed moderate activity against invasive SW48 and noninvasive SW1116 colon cancer cell lines when used in at higher concentrations, but also showed significant proliferation of noninvasive cancer cell line when used in lower concentrations, so when treating colon cancer patients with this compound it be used with care [73]. Patil et al. (2012) isolated 5-geranyloxy-7-methoxycoumarin (Fig. 32) from *Citrus aurantifolia* L. Osbeck (*Rutaceae*), commonly known as Mexican lime. This coumarin inhibited proliferation of SW-480 cells (human colon cancer) by induction of apoptosis through the activation of tumour suppressor gene p53, caspase 8/3, regulation of Bcl2 and inhibition of p38 MAPK phosphorylation [74].

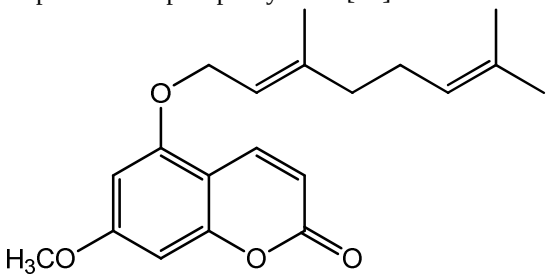


Fig. 32 Structure of 5-geranyloxy-7-methoxycoumarin [74]

Shi et al. (2011) synthesized 3-aminohexahydrocoumarin derivatives, among which seven compounds showed stronger citotoxicity than powerful anti-cancer drug doxorubicin hydrochloride against SW1116 (colon cancer) with lower viability rates at the same dose (10 g/ml). One of this compounds is shown on the Fig. 33 [75].

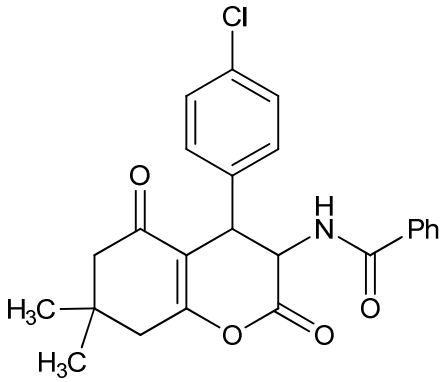


Fig. 33 Chemical structure of *N*-(4-(4-chlorophenyl)-3,4,5,6,7,8-hexahydro-7,7-dimethyl-2,5-dioxo-2*H*-chromen-3-yl)benzamide [75]

2.8. Gastric cancer

Prognosis for the patients with gastric cancer is very poor compared to the other solid malignancies and the only available treatment that could cure this type of cancer is complete resection of the tumour. The most widely used chemotherapeutics such as fluoropyrimidine and/or platinum based drugs have not been able to attain satisfactory survival [76].

Telomere and telomerase are closely associated to the development and occurrence of human gastric cancer. In early stages of life telomerase mantains telomere lenght and chromosomal integrity of frequently dividing cells. In most somatic cells during adulthood telomerase keeps dormant, while in cancer cells becomes reactivated keeping the short length of telomers of rapidly dividing cells. This leads to the immortality of cancer cells [77].

Coumarin derivative containing 4,5-dyhidropyrazole moiety (Fig. 34) exhibited high activity against human gastric cancer cell SGC-7901, acting as telomerase inhibitor in molecular docking study [77]. Wu et al. (2013) synthesized a series of 1-(3-substituted-5-phenyl-4,5-dihydropyrazol--yl)-2-thio-ethanone derivatives as potential telomerase inhibitors. Coumarin derivative on Fig 34. showed the most potent telomerase inhibitory activity and showed the highest antiproliferative activity against MGC-803 (human gastric cancer), Bcap-37 (human breast cancer cell line), SGC-790 (human gastric cancer) and HEPG-2 (human hepatocellular liver carcinoma) [78].

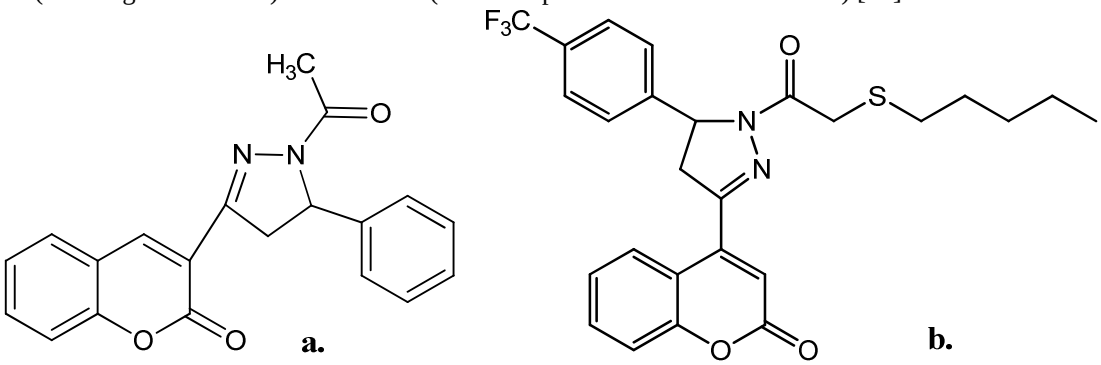


Fig. 34 Structure of potent telomerase inhibitors: a. 3-(1-acetyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one [77]; b. 3-(1-(2-(penthylthio)acetyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one [78]

Studies showed that xanthoxyletin (Fig. 35), isolated from *Erythrina variegata* has antiproliferative activity against SGC-7901 cells (gastric cancer), which is the result of DNA damage, apoptosis and cell cycle arrest in S phase in dose-dependent manner [79].

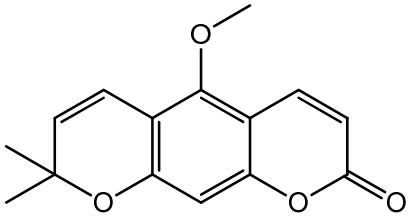


Fig. 35 Structure of xanthoxyletin [79]

2.9. Leukaemia

Leukaemia is a type of cancer that typically begins in the bone marrow and causes the high number of abnormal white blood cells [80].

It was showed that benzofuran-coumarin derivative (Fig. 36) can cause cell cycle arrest in G1, S or G2 phase and induce apoptosis in K562 cell lines (chronic myeloid leukaemia) [81]. Seidel et.al (2014) synthesized a series of coumarin derivatives which carry α, β-(mono- or bis)-unsaturated ketone at the C3 or C4 position. (*E*)-7-methoxy-4-(3-(4-methoxyphenyl)acryloyl)-*2H*-chromen-2-one (Fig. 36) strongly inhibited proliferation in chronic myeloid leukaemia K-562 and histiocytic lymphoma U-937 cell lines. This compound also inhibited histone deacetylase (HDAC) activity; enzyme crucial in cancer development [82].

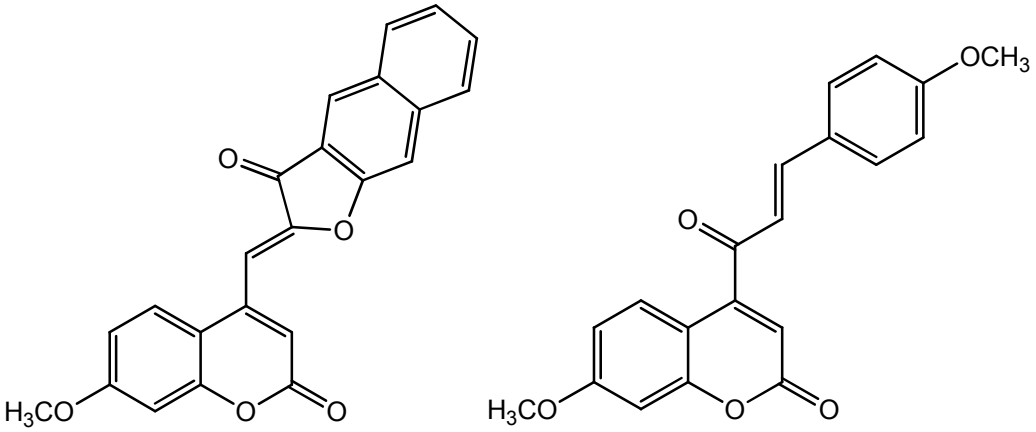


Fig. 36 Structure of: a. benzofuran-coumarin derivative (*Z*)-2-((7-methoxy-2-oxo-2*H*-chromen-4-yl)methylene)naphtho[2,3-*b*]furan-3(2*H*)-one [81]; b. (*E*)-7-methoxy-4-(3-(4-methoxyphenyl)acryloyl)-*2H*-chromen-2-one [82]

Among series of hybrids of chalcone-coumarin derivatives synthesized by Pingaew et al. (2014) the one on Fig. 37 showed the most potent citotoxic activity against MOLT-3 cells (human acute T-lymphoblastic leukaemia) with an IC_{50} at the dose of 0.53 µm [83].

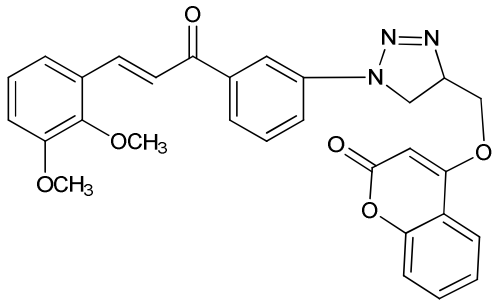


Fig. 37 Structure of potent chalcone-coumarin derivatives linked by 1,2,3-triazole ring ((*E*)-4-((1-(3-(3-(2,3-dimethoxyphenyl)acryloyl)phenyl-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one) [83]

Ethanolamine at position 7 of coumarin-benzimidazole hybrid was responsable for the higher selectivity against leukaemia cancer cells (CCRF-CEM, HL-60 (TB), K-562, RPMI-8226) and also colon cancer cells (HCT-116, HCT-15), melanoma cancer cells (LOX IMVI, UACC-257) and breast cancer cells (MCF7, T-47D). Compound on the Fig 38. inhibited more than 50% cancer cells in this cancer cell lines [84].

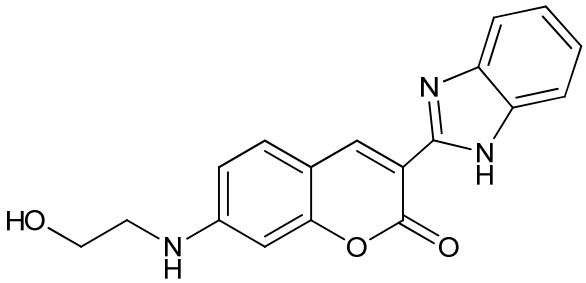


Fig. 38 Structure of 3-(1*H*-benzimidazol-2-yl)-7-[(2-hydroxyethyl)amino]-2*H*-chromen-2-one [84]

Hejchman et al. (2014) synthesized a series of gallic acid esters and 7-hydroxycoumarins and investigated their anticancer activity. Acetylated esters showed significant cytostatic and cytotoxic activity, they reduced 70% cell viability at dose 100 µm. Among non acetylated derivatives compound on the Fig. 39 at the lowest concentration (50µm) showed 50% of cell growth inhibition in HL-60 myeloid leukeamia cells [85].

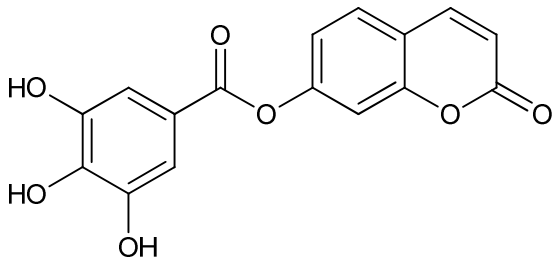
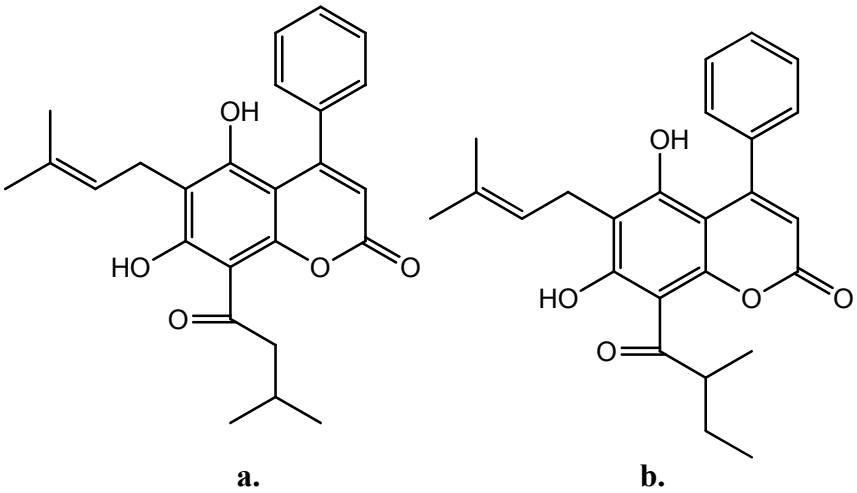


Fig. 39 Chemical structure of 7- hydroxycoumarinylgallate [85]

The mixture of the coumarins mammea A/BA and A/BB (Fig40.) which were isolated from the leaves of *Calophyllum brasiliense* (tropical rainforest tree of the American continent) showed the significant cytotoxic activity against K562 leukaemia cells [86].



a. **b.**

Fig. 40 Chemical structures of mammea coumarins: a. mammea A/BA; b. mammea A/BB [86]

2.10. Pancreas cancer

A geranylgeranylated hydroxycoumarin based compound (Fig. 41) exhibited 100% cytotoxicity against PANC-1 cells (human pancreas cancer) under nutrient-deprived medium at doses of only 6.25 µm, which makes this compound potential in developing new anti-austerity agents [87].

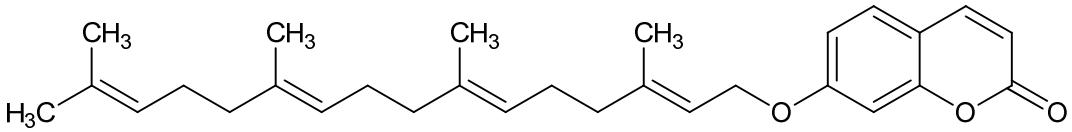


Fig. 41 Structure of 7-(((2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)oxy)-2*H*-chromen-2-one [87]

CONCLUSION

This article showed some of the potent natural and synthetic coumarins against different cancer cell lines. Coumarins exhibited anticancer activity against various types of cancer such as breast cancer, prostate cancer, gastric cancer, bladder cancer, leukaemia etc. Due to their low toxicity and good selectivity, they are of great interest to many medicinal chemists for developing even more biologically active derivatives. Since much work has already been done on their biological activity, and some reviews are already written, this review was focused on the literature survey published between 2010 - 2015.

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