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COUMARIN RING: A BIOLOGICALLY ACTIVE SCAFOLD

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ABSTRACT: Coumarin, natural or synthetic, has become an interesting subject of investigation for many researchers due to its wide range of biological activities. Coumarin scaffold has an important role in anticancer drug development because many of its derivatives have shown anticancer activity on various cell lines. The action of coumarins on tumour cells is carried out via different mechanisms and some of them show very good selectivity toward the cancer cells. A brief literature review (2010-2015) on coumarins as potential anticancer drugs is given in this work, which can serve as an excellent tool for future investigations on the design and synthesis of such derivatives. Coumarin is available naturally and synthetically from various methods; due to its wide range of biological activities has become an interesting subject of research from many researchers. Coumarin forms a scaffold with different heterocyclic rings and shows different biological activities like anticancer, anti-tubulin, anti-inflammatory, anti-virus, *etc*. The coumarin nucleus is now used to develop novel compounds for various life-threatening diseases.

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

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The name comes from a French term for the tonka bean, coumarou, one of the sources from which coumarin was first isolated as a natural product in 1820. It has a sweet odour, readily recognized as the scent of newly mown hay and has been used in perfumes since 1882. Sweet woodruff, meadowsweet, sweet grass, and sweet-clover in particular are named for their sweet (*i.e.*, pleasant) smell, which in except where otherwise noted, data are given for materials in their standard state turn is related to their high coumarin content.

Coumarin is a somewhat bitter-tasting appetite suppressant when it occurs in high concentrations in forage plants. It is presumed to be produced by plants as a defense chemical to discourage predition. Coumarin is used in certain perfumes and fabric conditioners [1].

Coumarins are important naturally occurring compounds, which play a key role in nature and interest in its chemistry continues unabated because of their usefulness as therapeutically active agents. Coumarins exist as secondary plant metabolites and exhibit numerous interesting pharmacological activities. Till now, 1800 different natural coumarins have been investigated. Most of these coumarins are mono or deoxygenated in the aromatic ring. The well-known natural compound containing coumarin nucleus is 7-hydroxycoumarin (umbelliferone) and is found in carrots, coriander, and garden angelica. It has been used as a sunscreen, fluorescence indicator, and dye indicator. Warfarin is also a naturally occurring compound containing the 4-hydroxy coumarin moiety. It has been isolated from woodruff and from lavender and is used to prevent clotting of blood in the veins, lungs, or heart [1].

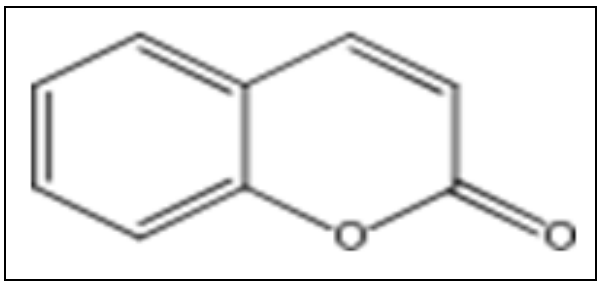

FIG. 1: CHEMICAL STRUCTURE OF COUMARIN

Coumarin Scaffold as Anti-Cancer Activity: Coumarin enjoys an important place in the drug discovery process due to its presence in the diversity of biologically active compounds. Many compounds of plant origin are derivatives of coumarin. Taking these natural products like lead, research groups across the globe have designed and synthesized numerous coumarin analogues for the treatment of varied diseases [2]. Cancer is a leading cause of death worldwide. Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. The number of cancer cases in India is increasing every year. According to WHO's Cancer Report, lung, oral, lip, throat and neck cancers are the most common among men while women suffer more from cervix, breast and ovarian cancers in India. In the elderly, the most commonly occurring cancers are kidney, intestine, and prostate cancer. The commonly used cancer treatments in India include Surgery, Chemotherapy, Radiation therapy, Immunotherapy, Hormone Therapy, Stem cell transplant, targeted therapy and precision medicine. Chemotherapy is one of the most common treatments for cancer. It uses certain drugs to kill cancer cells or stop them from growing and spreading to other parts of your body. Depending on the type of cancer they get, the oncologist may choose one or a combination of treatment options used to cure cancer. Cancer is one of the dreadful chronic diseases, and many drugs are available for its treatment. Various natural, semi-synthetic, and synthetic coumarin derivatives are developed to treat various types of cancer. Coumarin scaffold act as a promising scaffold for anticancer activity [2]. T. G. kralijevic *et al* was synthesized to introduce the *in-vitro* anticancer and antibacterial activities and *in-silico* studies of new 4-substituted 1, 2, 3-triazole– coumarin hybrids.

The 4-substituted 1, 2, 3-triazole core in designed coumarin hybrids with diverse physicochemical properties was introduced by eco-friendly copper (I)-catalyzed Huisgen 1,3-dipolar cycloaddition under microwave irradiation. Coumarin–1,2,3-triazole–benzofused heterocycle hybrids emerged as the class of compounds exhibiting the highest antiproliferative activity [3].

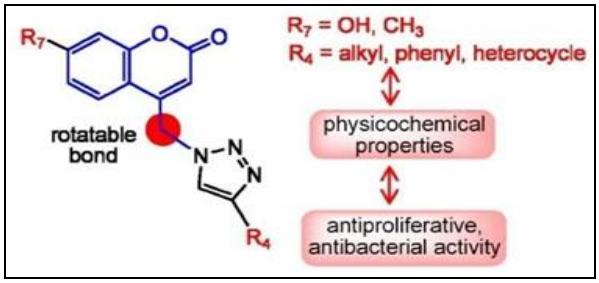

FIG. 2: 4-SUBSTITUTED 1, 2, 3-TRIAZOLE COUMARIN HYBRIDS

Vyshnavi Yechury *et al.* has synthesized the Novel fatty substituted 4-methyl - 2H chromen-2-one, by employing cross-metathesis, a key step in the synthesis. The antioxidant activities of the title compounds were compared with the commercial antioxidants, namely butylated hydroxytoluene (BHT) and α-tocopherol, glycosidic and other substituted 4-methyl-2H-chromen-2-ones. Among the different 4-methyl- 2H-chromen-2-ones, the glycosidic substituted 4-methyl-2H-chromen-2-ones was excellent, while those with aliphatic fatty acid chain and hydroxyl substituents were good. Among the substituted 4-methyl-2H-chromen-2-ones, glycosidic, hydroxyl, and cyano containing 4-

methyl-2H-chromen-2-ones exhibited good, while fatty substituted exhibited moderate anticancer activities against the four different cancer cell lines tested, namely DU145 (Prostate carcinoma cancer cell), HepG2 (Hepatocellular carcinoma cancer cell), SKOV3 (Ovarian cancer cell) and MDA-MB 231 (Human breast cancer cell) [4].

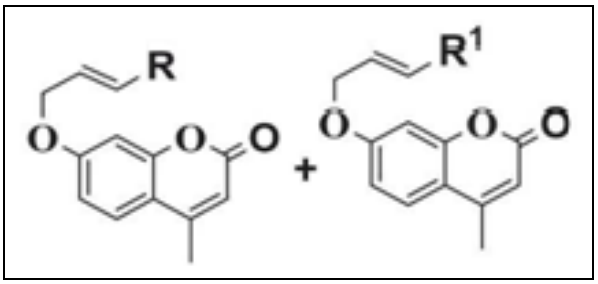

FIG. 3: 2-METHYL-2H-CHROMEN-2-ONE VIA CROSS-METATHESIS

Sahar M. Abou-seri *et al'* synthesis &biological evaluation of coumarinpyrazoline hybrids endowed with phenylsulfonyl moiety as antitumor agent. Two groups of coumarin-pyrazoline hybrids were synthesized. The target compounds were obtained by cyclization of the coumarin chalcones with various substituted hydrazines to produce the corresponding pyrazolines through 1, 4-addition on α,β-unsaturated carbonyl system.

Selected compounds were investigated for their anticancer activity towards 60 cancer cell lines according to US NCI protocol where breast cancer MCF7 and colon cancer HCT-116 were the most susceptible to the influence of compounds 7d, 8c, and 9c. Encouraged by this, all final compounds were screened against colorectal cell line HCT-116.

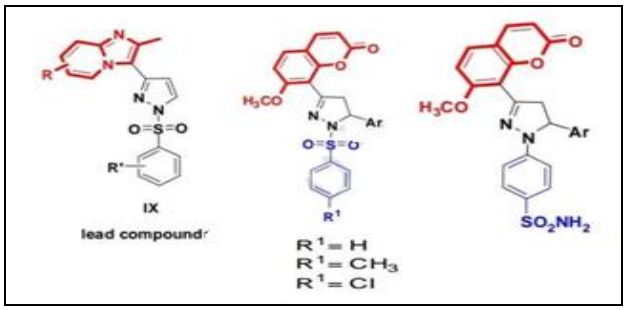

FIG. 4: DESIGN OF THE NEW COUMARIN-PYRAZOLINE HYBRIDS BASED ON THE LEAD COMPOUNDS IX

The tested compounds exhibited high potency with IC_{50} ranging from 0.01 µM to 2.8 µM. Moreover, compound 9c, which possessed the highest cytotoxicity, proved to have weak enzyme inhibitory activity against PI3K (P110α/p85α) [5]. A series of new coumarin-containing compounds 3 and 4 were designed and synthesized based on the chalcone-type 4 - amino – 5 - cinnamoylthiazole scaffold 2 and screened for their *in-vitro* anticancer and antioxidant activities. Representatively, the 2-thiomorpholinothiazole derivative 3k with IC50 values of 7.5e16.9 mg/ml demonstrated good cytotoxic effects against tested cell lines MCF-7, Hep G2, and SW480. Further investigation by flow cytometric analysis confirmed that the compound induces apoptotic cell death in MCF-7 cells and causes G1-phase arrest in the cell cycle. Moreover, most compounds had the intrinsic potential for radical scavenging activity and ferric reducing power as investigated by DPPH and FRAP assay. The antiproliferative activity of compounds 3 and 4 was investigated against breast carcinoma (MCF-7), human colon adenocarcinoma (SW480) and human liver cancer (HepG2) cell lines using MTT assay [6].

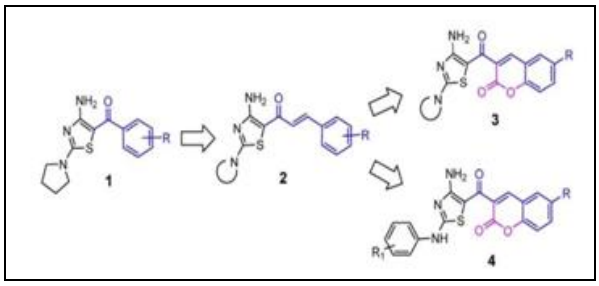

FIG. 5: DESIGN OF COMPOUNDS 3 AND 4 BASED ON THE THIAZOLE-DERIVED LEAD 1, AS NEW ANTICANCER AGENTS

T. Devji *et al.* synthesized the hydroxycoumarin derivatives and evaluated them against human pancreatic PANC-1 cancer cells under nutrient-deprived conditions. Several compounds exhibited 100% preferential cytotoxicity at low micromolar concentrations under malnutrition starvation and showed no cytotoxicity under nutrient-rich conditions.

In this study, a novel geranylgeranylated ether coumarin derivative 9 was found to exhibit the highest cytotoxic activity of 6.251M within 24 h. The preferential anti-tumour activity exhibited by compound 9 against PANC-1 under low oxygen and nutrient environment illustrate its great potential as a promising lead structure for the development of novel agents to combat pancreatic cancer [7].

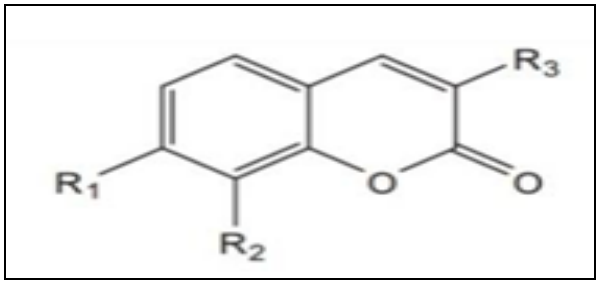

FIG. 6: HYDROCOUMARIN DERIVATIVES

Mohmed Ibrahim *et al.* was synthesized the series of fused tricyclic coumarin sulfonate derivatives. Their *in-vitro* antiproliferative activities against a panel of 57 human cancer cell lines of nine different cancer types were tested at the NCI. Compounds 1e, 1f, 1h, 1i, and 1o showed the highest mean percentage of inhibition values over the 57 cell line panel at 10μM, and they were further tested in 5-dose testing mode to determine their IC_{50} values. Compounds 1e, 1f, and 1o were more selective against leukemia and colon cancer subpanels, while compounds 1h and 1i showed broad-spectrum anticancer activities.

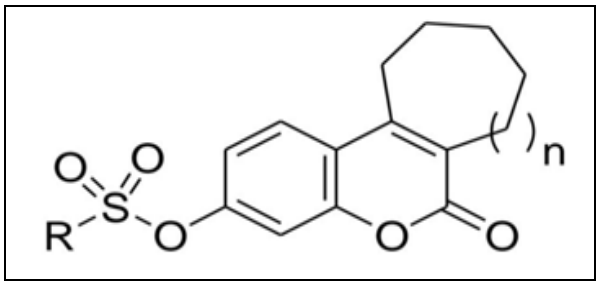

FIG. 7: STRUCTURES OF THE TARGET COMPOUNDS

Compounds 1e, 1f, 1h, 1i, and 1o demonstrated high selectivity towards cancer cell lines than RAW 264.7 macrophages. Compound 1h exerted lethal effect over NCI- H522 NSCLC, SK-MEL-5 melanoma and A498 renal cancer cell lines with the percentage of inhibition values of 114.10%, 103.23% and 100.52% at 10 μM, respectively. Moreover, the IC_{50} value of compound 1o against HT29 colon cancer cell line was 53nM. Compounds 1e, 1f, 1h, 1i and 1o were tested for inhibitory effect over cyclooxygenase-2 (COX-2) enzyme as a possible mechanism of action. Furthermore, *in-silico* studies were conducted to check the compliance of those five compounds with Lipinski's rule of five and hence estimate their oral bioavailability [8]. All compounds were screened for antiproliferative activity against CNE2, KB and Cal27 cell lines *in-vitro*.

The results showed that most of the derivatives had a favorable effect on resisting tumor cell proliferation; compound. 3-(4-amino-5-oxo-5H-chromeno [4,3-d] pyrimidine-2-yl) phenyl 4-(dimethyl amino)benzene sulfonate, exhibited the best activity. Flow cytometry revealed that compound can inhibit CNE2 proliferation. Telomerase inhibition and *in-vitro* antitumor activity were consistent among the compounds, but the compound showed the best telomerase-inhibiting activity and could inhibit telomere extension. Molecular docking results indicated that the compound bonded with telomerase reverse transcriptase (TERT) through multiple hydrogen bonding and hydrophobic interactions. The study results provide further information on 2- phenyl pyrimidine coumarins, expanding the types of telomerase inhibitors as the parent structures [9].

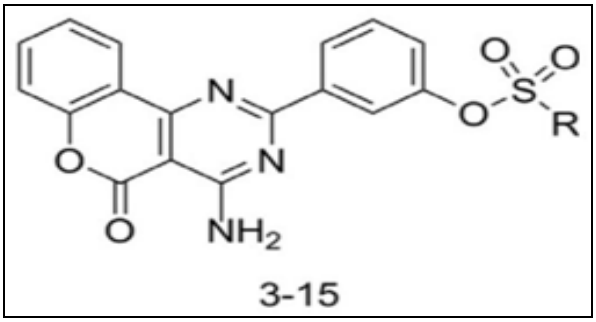

FIG. 8: SULFONATE-SUBSTITUTED 2-PHENYL-BENZOPYRANOPYRIMIDINE DERIVATIVES

Ran An *et al.* was; designed and synthesized fifteen new compounds containing coumarin, 1,2,3-triazole and benzoyl substituted arylamine moieties and tested *in-vitro* for their anticancer activity. The results showed that all tested compounds had moderate antiproliferative activity against MDA-MB-231, a human breast cancer cell line, under both toxic and hypoxic conditions. Furthermore, the 4-substituted coumarin linked with benzoyl 3,4-dimethoxyaniline through 1,2,3- triazole displayed the most prominent antiproliferative activities with an IC_{50} valueof0.03 μM, about 5000 times stronger than 4-hydroxycoumarin (IC_{50} > 100 μM) and 20 times stronger than doxorubicin (IC_{50} = 0.60 μM). Meanwhile, almost all compounds revealed general enhancement of proliferation-inhibiting activity under hypoxia, contrasted with nor toxic. A docking analysis showed that compound 5e had the potential to inhibit carbonic anhydrase IX (CA IX) [10].

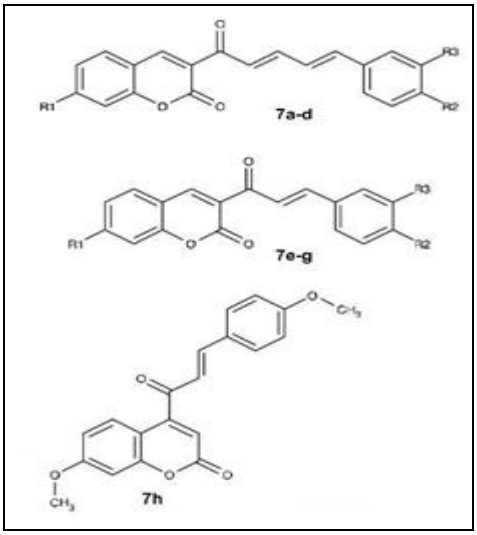

FIG. 9: COMPOUND AGAINST MDA-MB-231 CELL

Carole Scidel *et al* was; designed & synthesized the 3-alkenoyl coumarins & the Histone deacetylases (HDACs) are well-established, promising targets for anticancer therapy due to their critical role in cancer development. Accordingly, an increasing number of HDAC inhibitors displaying cytotoxic effects against cancer cells have been reported. Among them, a large panel of chemical structures was described, including coumarin-containing molecules. This study described the synthesis and biological activity of new coumarin-based derivatives as HDAC inhibitors. Among eight derivatives, three compounds showed HDAC inhibitory activities and antitumor activities against leukemia cell lines without affecting the viability of peripheral blood mononuclear cells from healthy donors [11].

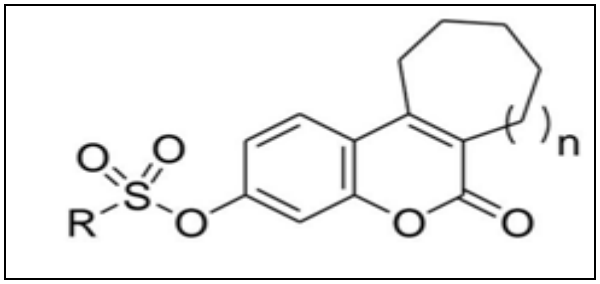

FIG. 10: STRUCTURES OF DESIGNED AND SYNTHESIZED COMPOUNDS

Yubin Wang *et al* was; designed & synthesized the Twenty-seven 3, 7- disubstituted coumarin derivatives, and they were evaluated *in-vitro* as anticancer agents. Most of the compounds showed moderate to potent anti-proliferative activity against K562 cells. Compounds 7b and 7d were chosen to evaluate the concentration of 50% growth inhibition (GI50) against SN12C, OVCAR, BxPC-3, KATO- III, T24, SNU-1, WiDr, HeLa, K562, and AGS cell lines. The most potent compound 7d was selected for further cell cycle arrest assay in the AGS cell line. The *in-vitro* data indicated that methylation of benzimidazole moiety at the 3-position of coumarin exhibited a significant enhancement of anticancer activity [12].

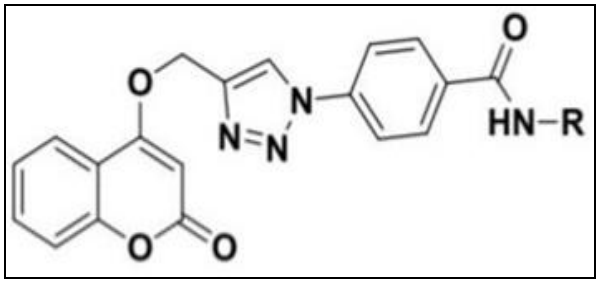

FIG. 11: STRUCTURE OF 3.7 DISUBSTITUTED COMPOUND

Coumarin Scaffold as Anti-Tubulin: Tubulin in molecular biology can refer either to the tubulin protein superfamily of globular proteins or one of the member proteins of that superfamily. α- and β-tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton. Microtubules function in many essential cellular processes, including mitosis. Tubulin-binding drugs kill cancerous cells by inhibiting microtubule dynamics required for DNA segregation and cell division. Tubulin is in contrast to those drugs acting on DNA for cancer chemotherapy inhibitors are drugs that interfere directly with the tubulin system, which. Microtubules play an important role in eukaryotic cells. Alpha- and beta-tubulin, the main components of microtubules, have gained considerable interest because of their function and biophysical properties and has become the subject of intense study. These compounds inhibit cell mitosis by binding to the protein tubulin in the mitotic spindle and preventing polymerization or depolymerization into the microtubules. This mode of action is also shared with another natural agentcalled colchicine. Molecular diversity of trimethoxyphenyl-1,2,3-triazole hybrids as novel colchicine site tubulin polymerization inhibitors.

Recently, a variety of colchicine site tubulin inhibitors containing a trimethoxy phenyl (TMP) moiety were designed to treat cancer. Cis-restricted pyrazole disrupted microtubule assembly, inhibited migration and suppressed tumour growth of the

SK-OV-3 xenograft model. β-Lactam-azide derivative 2 as colchicine site tubulin inhibitors from our group displayed potent anticancer activity against MGC-803 cells with an IC50 value of 1 by induction of arrest and apoptosis. 3-(3′,4′,5′-Trimethoxy anilino) benzol furan 3 bound to the colchicine site of tubulin and exhibited potent vascular disrupting properties both *in-vitro* and *in-vivo.* 2-Amino-4- (3′,4′,5′-trimethoxyphenyl)-5-aryl thiazole 4 as microtubule targeting agent showed potent inhibitory activity in multidrug-resistant cancer cells and induced cell death by apoptotic pathway. Alkyne intermediates used in this work were synthesized firstly in the high yields, and structures of alkyne intermediates were described in Scheme 1. Hydroxy, sulfhydryl, and amino derivatives reacted with propargyl bromide in the presence of sodium hydroxide to obtain alkyne intermediates. In addition, benzene sulfonyl chloride derivatives were reacted with propargylamine to form alkyne intermediates in the presence of triethylamine [13].

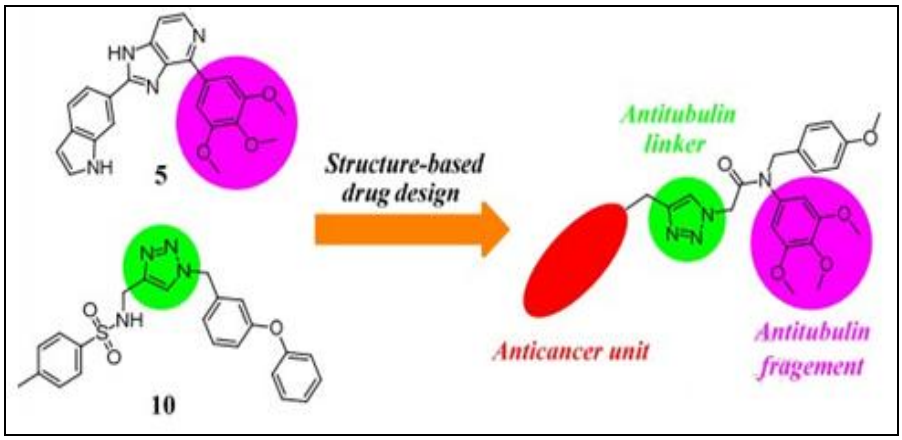

FIG. 12: ANTI TUBULIN ACTIVITY

Many of the currently available antitumor drugs cannot differentiate between normal and neoplastic cells or overcome primary or secondary resistance mechanisms evolved in the tumor cells. Thus, there is a pressing need for new antitumor agents with high potency, less toxicity in non-cancerous cells, and unique action targets. Currently, tumor therapy has been successfully utilized to interfere with a single biological molecule or pathway. However, therefore a general belief that agents modulating more than one target or multiple sites on solitary target could have superior efficacy than solo target drugs.

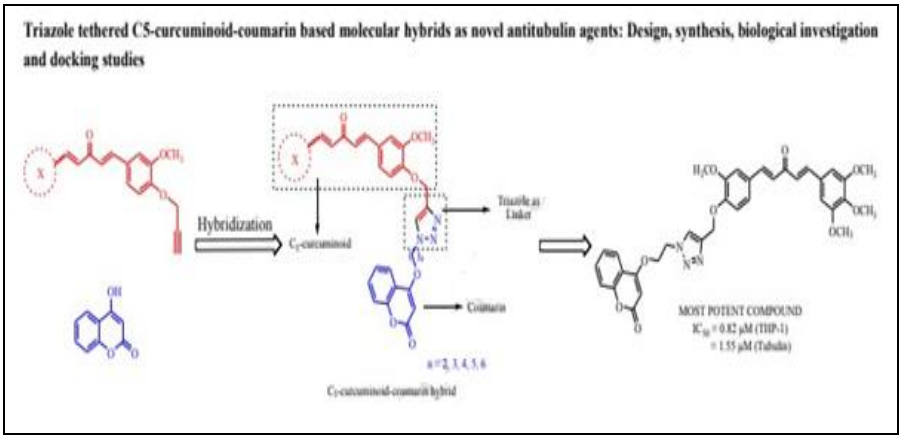

FIG. 13: TRIAZOLE TETHERED C5-CURCUMINOID-COUMARIN

Sulfur investigated all the synthetics for *in-vitro* cytotoxicity against four human cancer cell lines. The cells were allowed to proliferate in the presence of test material. All the synthesized hybrids were screened against the cell lines. The hybrids showing percentage inhibition of greater than 70% at least against one cell line were only evaluated at different concentrations and IC_{50}

values were calculated. In contrary to our previous report, among the four-cancer cell. The most active compounds among the series were evaluated for their inhibitory effects on tubulin polymerization, using a cytoskeleton tubulin polymerization assay. Compound A-2 with a trimethoxy phenyl ring also displayed the most potent anti-tubulin activity and exhibited significant tubulin polymerization inhibition. A-7 with naphthyl ring was endowed with the weak inhibitory potential for tubulin polymerization. The in-vitro tubulin polymerization assay results indicate that both A-2 and A-3 exert their cytotoxic effects through tubulin inhibition [14].

Cancer is the uncontrolled, rapid, pathological proliferation of abnormal cells, a major problematic affliction worldwide, causing 2-3% annual deaths. Based on the recognition of pharmacophoric sub-units in the molecular skeleton of two or more known biologically active derivatives.

The revived interest among the researchers in the discovery of hybrids that can concomitantly address more than one biological target is increasing day by day. Molecules thus give new dimensions by lowering the risk of drug-drug interactions and minimizing drug resistance as well; hence are highly beneficial for the society fighting this dreadful disease. Tubulin is one of the most useful strategic molecular targets for antitumor drugs as it is involved in several cellular processes [15].

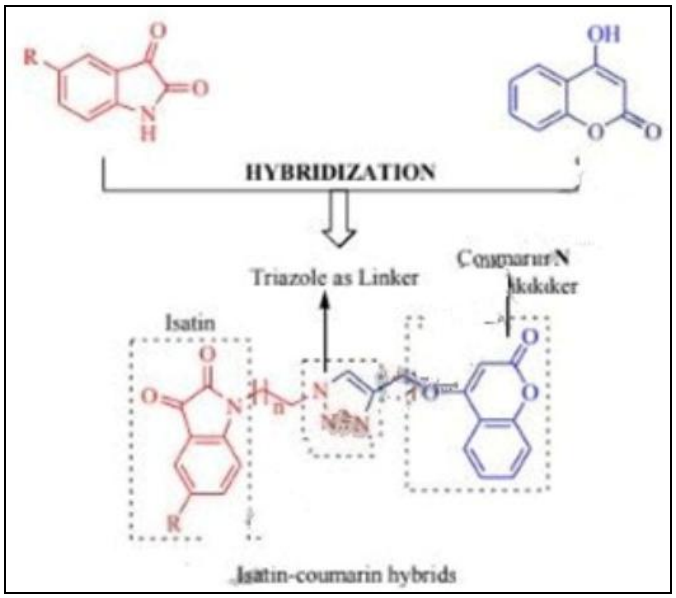

FIG. 14: DESIGN STRATEGY TARGET HYBRIDS WERE SYNTHESIZED *VIA* A SEQUENCE OF REACTIONS

Tubulin an αβ-heterodimer, assembles into microtubules in a head-to-tail manner and these can polymerize and depolymerize to regulate normal cell physiological activities. Tubulin participates in numerous cellular processes, including maintaining cell shape and cell division. In mitosis, which is an important cellular event during cancer cell proliferation, tubulin is needed to form spindles, making it an attractive target in the design of anti-cancerdrugs. Structural biology Porcine brain tubulin from Cytoskeleton Inc. was used for a structural biology study.

The preparation of the crystals is described in our previous study. To soak the compounds into the crystals, of the compound solution was added to the crystal-containing drops. Beamlines at the Shanghai Synchrotron Radiation Facility were used to obtain. X-ray diffraction data. Determination of the structure and the refinement protocols were the same as those in our previous study. PYMOL and Discovery Studio Client were used to generate the data and refinement statistics and evaluated their anti-tubulin activities against eight cancer cell lines by assay. Showed strong activity in this cancer cell. The effect was comparable width. Drug resistance has become a severe problem to first-line chemotherapy. The common mechanisms of resistance identified in preclinical or clinical studies include the overexpression of a cellular membrane protein called P-glycoprotein (P-g p) or changes in the expression levels of different β-tubulin isotypes [16].

Hybridization of different pharmacophores from various bioactive substances into a single molecule may provide new leads with complementary activities and/or multiple pharmacological targets and/or one part can counterbalance the side effects caused by another part, so hybridization is emerged as an encouraging strategy in the discovery of new drugs with the potential therapeutic application. Therefore, great efforts have been placed on seeking novel hybrids and significant achievements have been obtained in the last 30 years. The most emblematic examples are which exhibited excellent *in-vitro* and *in-vivo* biological activities are under different stages of a clinical trial and maybe introduced into clinical practice to fight against various diseases in the near future. Coumarin-1,2,3-triazole hybrids.

A set of novel coumarin hybrid decorated with 1,2,3- triazole moiety was assessed for their *in-vitro* antimicrobial activities against fungi, Gram-positive and Gram-negative pathogens and acute toxicity. The preliminary results showed that all hybrids displayed considerable activity against all tested strains. SAR studies revealed that substituent and length and position of alkyl spacer have a profound effect on antimicrobial potency. Including promising activity against microbial strains that was as potent as the references Miconazole and Ciprofloxacin (CPFX); low toxicity risks in *in-silico* analysis, with LD50 in a range of 43 to 1,100 mg/kg on mouse and rat that was comparable with Miconazole god oral bioavailability; and better drug-likeness and drug-score values, nearly similar or better than Moxifloxacin, CPFX, Miconazole and Fluconazole. Thus, both hybrids 1a and 1b could act as leads for further investigations [17].

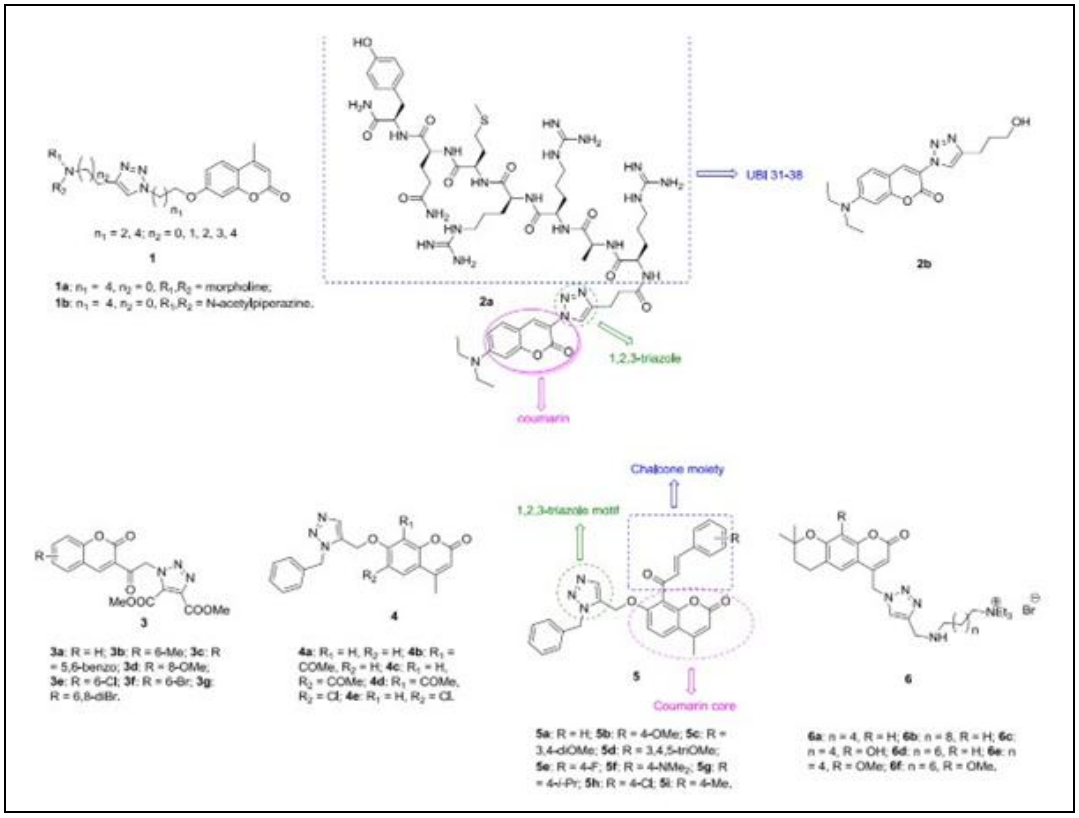

FIG. 15: CHEMICAL STRUCTURE OF COUMARIN-1,2,3-TRIAZOLE HYBRID

Microtubules, polymers of a-and b-tubulin heterodimers are part of a structural cytoskeleton network within the cytoplasm. In addition to structural support, microtubules take part in many other, including intracellular transport, mitotic spindle formation, as well as other cellular processes. They are capable of growing and shortening in order to generate force, and there are also motor proteins that allow organelles and other cellular factors to move along the microtubule. The most important structure involving microtubules is the mitotic spindle, which is essential for correct chromosomal segregation during the mitotic division of eukaryotic cells. Microtubules are highly dynamic between polymerization and depolymerization during mitotic spindle formation and chromosomal segregation. They investigated the possible link between DBC-induced phase arrest and G2/M regulatory protein expression changes. It has been well demonstrated that activation of cdc2 kinase is indispensable for the G2/M transition of the cell cycle, which requires accumulation of cyclin B protein and dephosphorylation of cdc2. We first examined the level of cyclin B1, and phosphorylation level DBC treatment caused an increase in cyclin expression, which was accompanied by a decrease in the phosphorylation level level in both cells. These results further support that DBC treatment can induce cell cycle arrest at the mitotic stage, resulting from activation in MDR cancer cells. A critical role of Aurora kinases has been

demonstrated for cell cycle regulation and high-fidelity mitosis. Because specific inhibition of Aurora kinases can lead to errors in chromosome alignment and segregation, resulting in mitotic arrest, Aurora kinases are appreciated as promising targets for the development of antitumor drugs [18].

Oumarin Scaffold as Antituberculer Activity: Tuberculosis (TB) is a life-threatening chronic deadliest infectious disease caused predominantly by Mycobacterium tuberculosis (MTB) which primarily affects the lungs (pulmonary TB) apart from other vital organs.

The emergence of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and the recent cases of totally drug-resistant (TDR) towards currently accessible standard drugs was increased up to the alarming level in the recent decades.

Numerous derivatives have been synthesized and screened for their anti-TB activity in pursuit of new anti-TB agents. Coumarins are one of the most important classes of natural products that exhibit various biological activities. Their derivatives are regarded as a new class of effective anti-TB candidates owing to their potential anti-TB activity. Thus, the coumarin skeleton has attracted great interest in the development of new anti-TB agents. This review outlines the advances in the application of coumarin-containing derivatives as anti-TB agents and the critical aspects of these derivatives' design and structure-activity relationship [19].

Silvia H. Cardoso1, *et al.* present article describes a series of 21 benzylidene-2-oxo- 2H-chromene-3-carbohydrazides 4a–4v, which were synthesized and evaluated for their cell viabilities in non-infected and Mycobacterium bovis Bacillus Calmette Guerin-infected macrophages.

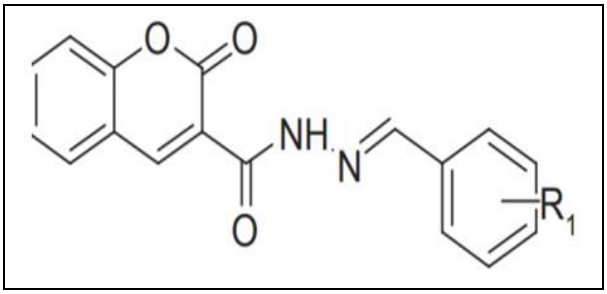

FIG. 16: BENZYLIDENE-2-OXO-2-H-CHROMENE-3-CARBOHYDRAZIDES

These results could be considered a good starting point for further studies to develop new lead compounds to treat multidrug-resistant tuberculosis [20]. V. T. Angelova1 *et al* presents article describes the evaluation of the *in-vitro* activity against M. tuberculosis H37Rv of eight coumarin-derived amino alcohols and amidoamine. This work is a continuation of our efforts on the development of molecular templates as novel anti-mycobacterial agents [21].

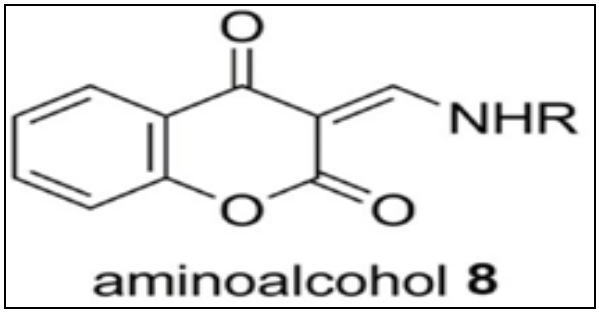

FIG. 17: EIGHT COUMARIN-DERIVED AMINO ALCOHOL

Chao Fanga *et al.* established a coumarin scaffold as a starting point for inhibiting Mycobacterium tuberculosis (Mtb) FadD32 enzymatic activity.

After further profiling of the coumarin inhibitor 4 revealed chemical stability, we discovered that a quinoline ring circumvented this instability and offered additional substitution vectors to optimize further. Ensuing SAR studies gave rise to quinoline-2-carboxamides with potent anti-tubercular activity [22].

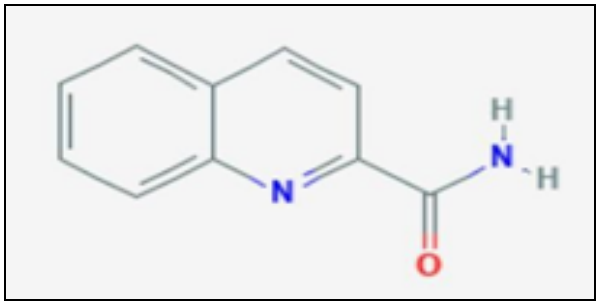

FIG. 18: QUINOLINE-2-CARBOXAMIDES

Jyoti M. Madar1 *et al.* their recent research target was to design biological active coumarin-4-thiazolidinone derivatives using coumarin Schiff base, which is a pharmacologically and medicinally important scaffold. Synthesized novel coumarin-4-thiazolidinone derivatives were evaluated for their *in-vitro* anti-tuberculosis activity against Mycobacterium tuberculosis [23].

FIG. 19: COUMARIN-4-THIAZOLIDINONE

Carprofen and coumarins are biologically promising potent heterocyclic compounds as they possess very good anti-tubercular, antimicrobial, anti-inflammatory, and anticancer activities. In the present study, the condensation of substituted 4-bromomethyl coumarin and carprofen in anhydrous potassium carbonate gives exclusively coumarin-carprofen hybrid [24].

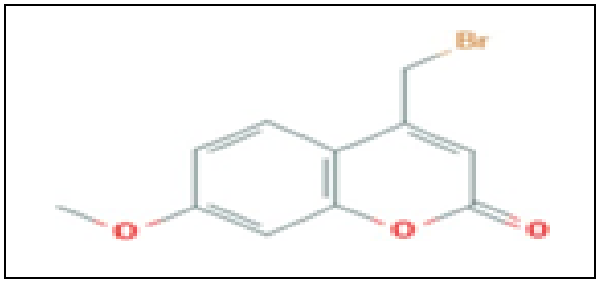

FIG. 20: BROMOMETHYL COUMARIN

Coumarin Scaffold on Antihiv Activity: HIV/AIDS pandemics is a serious threat to the health and development of mankind, and searching for effective anti-HIV agents remains actual. Considerable progress has been made in recent years in the field of drug development against HIV. A lot of structurally different coumarins were found to display potent anti-HIV activity. The current review demonstrates the variety of synthetic coumarins having a unique mechanism of action referring to the different stages of HIV replication. Recent studies based on various synthetic coumarins seem to indicate that some of them serve as potent non-nucleoside RT-inhibitors, others as inhibitors of HIV-integrase or HIV-protease. The merits of selecting potential anti-HIV agents to be used in rational combination drugs design and structure-activity relationships are discussed. The scientific community is looking actively for new drugs and combinations for the treatment of HIV infection effective for first-line treatment and against resistant mutants. The investigation of chemical anti-HIV agents gives hope and optimism about it.

This review article describes recent progress in discovering, structure modification, and structure-activity relationship studies of potent anti-HIV coumarin derivatives [25]. Li Huangpu *et al.* Numerous plant-derived compounds have been evaluated for inhibitory effects against HIV replication. Some coumarins have been found to inhibit different stages in the HIV replication cycle. This review article describes recent progress in discovering, structure modification, and structure-activity relationship studies of potent anti-HIV coumarin derivatives. A dicamphanoyl- khellactone (DCK) analogy, which was discovered and developed in our laboratory, and calanolide a are currently in preclinical studies and clinical trials, respectively [26].

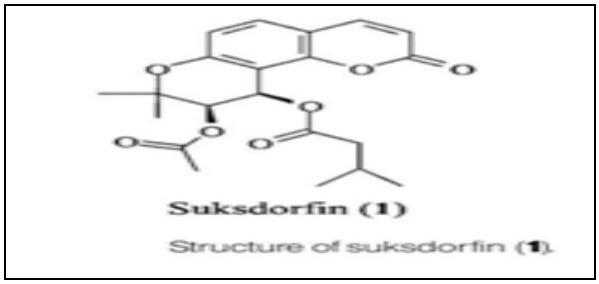

FIG. 21: DICAMPHANOYL-KHELLACTONE (DCK)

P. Pramitha, D. Bahulayan *et al* an efficient synthesis of ester-triazole-amide amphiphiles of coumarin derivatives by triazole randomization based on click approach is described. Twenty-five small peptide azides were synthesized using Ugi or alternate Mannich -type multi-component reactions. The new azides were then used for the triazole randomization of alkyne functionalized coumarin ester under CuAAC conditions. Sixty-five new peptide bio-hybrids are obtained in nearly quantitative yield with the high region and stereo selectivity [27].

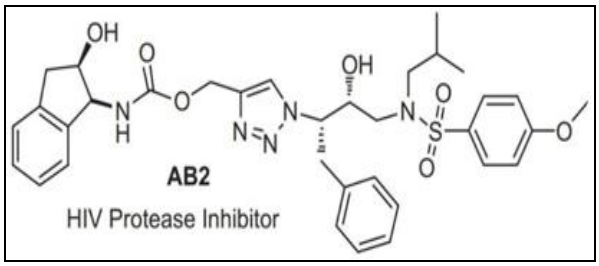

FIG. 22: ESTER-TRIAZOLE-AMIDE AMPHIPHILES

V. K. Srivastav, M. Tiwari *et al.* series of 6-acetyl-coumarin derivatives (2a-n) were synthesized and evaluated for antiretroviral activity in C8166 T-cell

line infected with HxBru-Gluc strain of human immunodeficiency virus-1. It was found that electron-withdrawing group at phenyl ring, attached to the coumarin nucleus, was crucial for activity against the human immunodeficiency virus.

The present study may be helpful in the development of some potent antiretroviral agents. Fig no.5.3) 6-Acetyl-coumarin Derivatives against HIV-1 Infection [28].

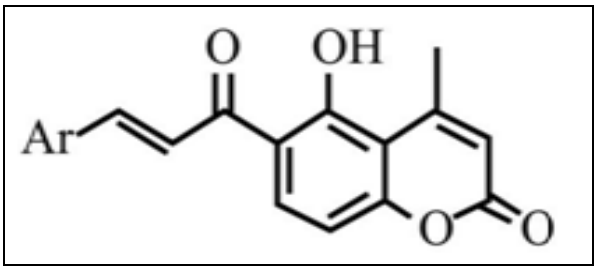

FIG. 23: ACETYL-COUMARIN DERIVATIVES AGAINST HIV-1 INFECTION

Richa Minhas *et al.* many naturally existing antioxidants contain coumarin nucleus as a common pharmacophore, whereas benzoxazole is identified as pharmacophore for anti-inflammatory activity from benzoxaprofen, a potent anti-inflammatory drug.

These two therapeutically important nuclei were coupled to generate two series of benzoxazole-coumarin derivatives (4a-4e and 5a-5e) to develop novel compounds with potent anti-inflammatory and antioxidant activities with insignificant amounts or no ulcerogenic potential [29].

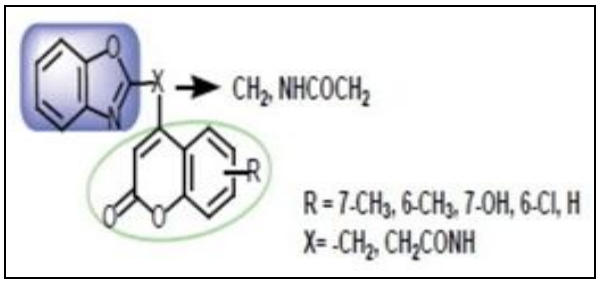

FIG. 24: BENZOXAZOLE-COUMARIN DERIVATIVES

Venugopal Rao Narayana *et al.* synthesized C3- and O-alkylated 4-hydroxycoumarin derivatives from reusable solid superacid catalyst, compounds were evaluated for anticoagulant activity.

Among the compounds tested for anticoagulant activity, compound 3b, 3c, 3d, and 3g showed significant activity compared to that of standard [30].

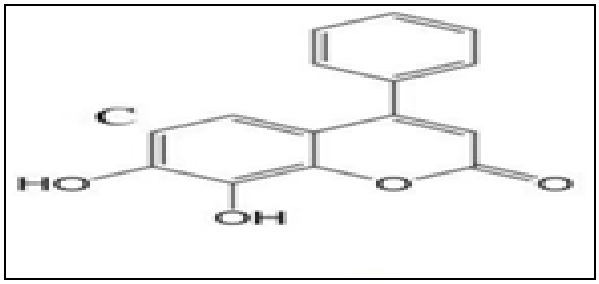

FIG. 25: C3- AND O-ALKYLATED 4-HYDROXYCOUMARIN DERIVATIVE

Microwave *et al.* an easy efficient microwave-assisted protocol, has been developed to synthesize coumarin-purine hybrids (3a-3j). The newly constructed 1,3-dimethyl- 7-((substituted)-2-oxo - 2H – chromen – 4 - yl) methyl)-1H-purine-2,6(3H,7H)-dione derivatives were evaluated for their *in-vitro* antioxidant activity by DPPH free radical scavenging ability assay and DNA cleavage by using calf thymus. Compound 3i shows the most excellent DPPH scavenging activity with an e OH substitution at C7 of coumarin ring. In addition, the structure of the compound has been elucidated using a single-crystal X-ray diffractiontechnique [31].

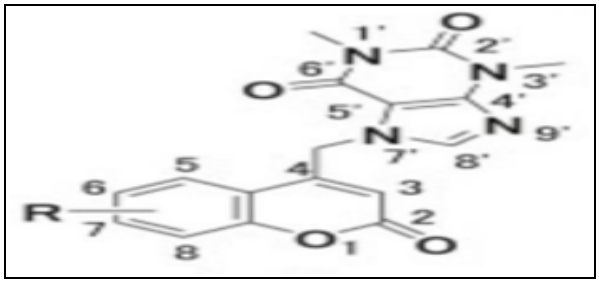

FIG. 26: COUMARIN-PURINE DERIVATIVES

Ahead Jayshree *et al.* an improved synthetic method is affording 4-chlorocoumarin-3- sulfonyl chloride (4) in very good yield (ca. 85 %) is reported. This compound was reacted with various bidentate nucleophiles such as 2-aminopyridines and 2- aminothiazoles in order to obtain substituted pyrido- and thiazino-1,2,4-thiadiazino-benzopyranone dioxides (potential anticancer and anti-HIV agents).

These reactions occurred rapidly at room temperature giving yellowish precipitates, which are insoluble in common organic solvents, making the purification process challenging. Further investigation has shown that these fused heterocycles are not stable and decompose with the opening of the 1,2,4-thiadiazine ring [32].

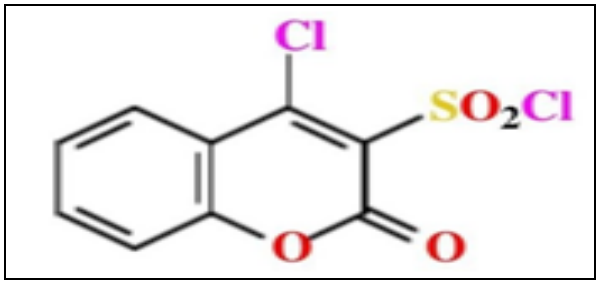

FIG. 27: 4-CHLOROCOUMARIN-3-SULFONYL CHLORIDE

CONCLUSION: In the present review, an attempt has been made to present the pharmaceutical applications of coumarins. A wide range of natural sources and new coumarin analogues are being discovered or synthesized regularly. The coumarins are of great attention due to their therapeutic property. Their physiological, anti-cancer, Ant tubulin, anti-HIV and other pharmaceutical properties make the coumarins a novel class for therapeutic applications. Clinical applications of coumarins for the treatment of several diseases were critically discussed.

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