COUMARINS: A UNIQUE SCAFFOLD WITH VERSATILE BIOLOGICAL BEHAVIOR

MANDEEP KUMAR GUPTA1, SUSHIL KUMAR2, SACHIN CHAUDHARY3

1Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, India. 2Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, IFTM University, Moradabad, Uttar Pradesh, India. 3Department of Medicinal Chemistry, College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates. Email: mandeepkrgupta@gmail.com

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Abstract

Benzopyrones are the club of compounds that can be coumarins or flavonoids. The hydroxyl derivatives of coumarins such as 4-hydroxycoumarins and 7-hydroxycoumarins have extensive biological activities which have employed for the synthesis of miscellaneous coumarin derivatives. These derivatives have exhibited impressive pharmacological and physiological activities such as anticoagulant, antibacterial, antiviral, antitumor, bactericidal, fungicidal, anti-inflammatory agents, and anti-HIV activity. This review comprised pharmacokinetic studies, including absorption, distribution, and metabolism of coumarin analogs along with toxicological studies. The studies of coumarins and their derivatives exhibiting immense pharmacological activity are also summarized in the current study.

Keywords: Benzopyrones, Coumarins, Anticoagulant, Antibacterial, Antiviral, Antitumor.

INTRODUCTION

Multitudinous, diverse and novel chemical analogs with the splendid potential to be used as drug have been obtained from natural sources. However, designing and synthesizing a novel drug analog using combinatorial chemistry along with high-throughput screening is still a challenging task for scientists. The word coumarins symbolize to “coumarou,” acknowledged as the Tonka bean (Dipteryx odorata wild, Fabaceae), from which coumarin itself was isolated in 1820 [1]. Coumarin is affiliated to benzopyrone, which consist of a benzene ring fused to a pyrone ring [2,3]. The benzopyrones can be sub-classified into the benzo-a-pyrones to which the coumarins belong and the benzo-y-pyrones to which the flavonoids belong [4-6] (Fig. 1).

CATEGORIZATION OF COUMARINS

Murray et al. [11] classified coumarins into four sub-classes as represented in Table 1.

PHARMACOKINETICS PORTRAIT OF COUMARINS

Absorption and distribution

Coumarin in humans, on oral administration is rapidly absorbed from the gastrointestinal tract and distributed throughout the body. Coumarin and 7-hydroxycoumarin both are less soluble in water (0.22 and 0.031% respectively) and it expressed of limited in vivo bioavailability. However, coumarin and 7-hydroxycoumarin have elevated partition coefficients in aqueous solution as 21.5 and 10.4% respectively, which is agreeable for the rapid absorption of compounds. It also conjugates the fact that being nonpolar in nature, it can cross lipid bilayers easily by passive diffusion [9-14].

Coumarin is metabolized by the liver in the first pass with only between 2% and 6% reaching the systemic circulation intact [9]. The low bioavailability of coumarin, in addition to its short half-life (1.02 h peroral vs. 0.8 h intravenous) has brought into question its importance in vivo and it is now acknowledged that coumarin is a prodrug with 7-hydroxycoumarin being the compound of main therapeutic importance [8]. Ritschel et al. [13] proclaimed that 35% of coumarin and 47% of 7-hydroxycoumarin binds to plasma proteins. Therefore, the bioavailability of the compounds should not be problematic since the proportions that bound were well below the accepted critical value of 80% binding. The pharmacokinetics profiles of coumarin have been studied in rats, dogs, gerbils, rhesus monkeys, and humans [9]. Recently, numerous immunoanalytical approaches including enzyme-linked immunosorbent assay-based methods have been employed for the detection of coumarin and 7-hydroxycoumarin in urine [16]. Antibody-based biosensors have also been utilized with either electrochemistry or surface plasmon resonance (BIAcore) to detect coumarin analogs in many matrices [17,18].

Metabolism

Multiple pharmacologists have accomplished their research in studying the metabolic fate of coumarins [9,19,20]. This study is essential to understand the possible coumarin-induced toxicity on metabolism [14]. Initially, coumarin is metabolized by cytochrome (CYP) P450-linked mono-oxygenase enzyme (CYP2A6) system in liver microsomes, leading to hydroxylation to form 7-hydroxycoumarin. Thereafter, phase II conjugation reaction resulting in a glucuronide conjugate is associated with 7-hydroxycoumarin. The 7-hydroxylase activity is remarkably high in human liver microsomes compared with its activity in the livers of other mammals. The activity of coumarin 3-hydroxylase is high in rodent microsomes but is absent in human microsomes. It is noteworthy that coumarin can be metabolized by hydroxylation at all six possible positions around the carbons. However, metabolic product in the form of 7-hydroxycoumarin has attained recognition since it is produced in humans and can be easily analyzed. The hydroxylation at carbon three results in further metabolism through mono-oxygenase enzyme (CYP2A6) system in liver microsomes, leading to hydroxylation to form 7-hydroxycoumarin. The 7-hydroxylase activity is remarkably high in human liver microsomes compared with its activity in the livers of other mammals. The activity of coumarin 3-hydroxylase is high in rodent microsomes but is absent in human microsomes.

It is imperative to mention that genetic and environmental factors result in changing the expression of CYP2A6 between humans, which causes interindividual variations in the metabolism of coumarins [21]. Metabolic studies in humans include the administration of drugs orally followed by urine collection and analysis with or without timed fractionation [7,22]. The measurement of urinary 7-hydroxycoumarin following an oral dose of coumarin is a vital biomarker of human hepatic CYP2A6, the CYP P-450 isozyme, which is responsible for the generation of 7-hydroxycoumarin in liver [14]. It is noticeable to mention that some
humans metabolize a significant proportion of coumarins in their body through 3,4-epoxidation pathway. CYP2A subfamily in humans has three genes, of which CYP2A6 is essential as the other two, namely CYP2A7 and CYP2A13 are either inactive or sometimes expressed improperly in the liver. CYP2A6 codes the enzyme, catalyzing the generation of 7-hydroxycoumarin (about 10% of total P450) [26]. Recently, CYP2A6 has been reported to be polymorphically expressed in the human liver and involved in the metabolism of nicotine and cotinine. Hence, the various studies proclaimed that some drugs, including various coumarin analogs are metabolized chiefly by CYP2A6. Many substrates and inhibitors currently known to be metabolized by or interfered with CYP2A6 in vitro and in vivo have been illustrated by Pelkonen et al. [26,27]. Nowadays, spectrofluorometry, high-performance liquid chromatography and capillary electrophoresis are employed for the analysis of many metabolic products [23-25]. Recent in vitro studies include tissue slices, hepatocytes, subcellular fractions, and purified, and cDNA-expressed enzymes [9]. The data for various coumarin dose levels and collection periods are tabulated in Table 2.

Toxicological studies
Since 1954, the Food and Drug Administration classified coumarins as toxic due to its possibility to produce liver tumor in rats [28] and banned foods containing coumarin [12]. National Institute for Occupational Safety and Health referred coumarins as a carcinogenic agent. However, caution must be taken in extrapolating this information to human situations. Various other tests (Ames, micronucleus) have reported that coumarin and its metabolites are non-mutagenic [6]. Preliminary examinations of early studies showed that coumarin was a toxin, but the fact that rat is a poor model compared to humans in metabolism [28,29]. Since now, multiple studies have been accomplished to understand the acute, chronic and carcinogenic effects of coumarin in the rat and mouse. In these studies, hepatic biochemical and morphological changes in rats have been analyzed for various periods of coumarin administration (1 week–2 years). Depending on the dose administered, coumarin treatment results in an increase in relative weight and changes in various hepatic biochemical parameters. Single oral doses of coumarin have been shown to produce liver necrosis and increase plasma transaminase activities in DBA/2 strain mice [9]. In contrast, studies involving baboons, Syrian hamsters and certain mice strains were resistant to acute coumarin-induced hepatotoxicity. Species differences in coumarin-induced toxicity in vitro have been analyzed in cultured
The relative resistance of human hepatocytes. These studies provide evidence for species differences in coumarin-induced toxicity in vitro. The relative resistance of human and cynomolgus monkey liver slices and/or hepatocytes to coumarin toxicity correlates with coumarin 7-hydroxylation, the major pathway of coumarin metabolism in these species. However, while coumarin-7-hydroxylation pathway is a detoxification pathway, this does not appear to be the only reason for the resistance of a species to coumarin-induced toxicity. This may result in enterohepatic circulation enhancing the exposure of liver cells to toxic coumarin metabolites. Species such as Syrian hamster, baboon, and humans excrete coumarin metabolites primarily in the urine. Low level coumarin from diet and fragrances used in cosmetic products would not be estimated to produce any hepatotoxicity even in individuals with lack of 7-hydroxylase activity [9,14].

COUMARINS AS ACTIVE BIOLOGICAL AGENTS

Antibacterial activity

Lin et al. [30] synthesized 4-hydroxy and 7-hydroxycoumarin derivatives by reaction with activated aziridines analog to produce a series of ring-opened products as represented in Fig. 2. 3-carbonyl coumarin amide dimer derivatives were also synthesized by reacting aliphatic alkyl amines and alkyl diamines with benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate and N,N-Diisopropylethylamine. Some of these compounds and dimer products exhibited antibacterial potential investigated by modified microplate antibacterial susceptibility test.

Hu et al. [31] synthesized imidazole bearing coumarin analogs in their structure and inspected for antibacterial activities against Escherichia coli, Staphylococcus aureus, Streptococcus agalactiae, and Flavobacterium commune. The results revealed that compound 13 and 18 were excellent antimicrobial agents. However, compounds 9, 14, and 19 were potent against S. aureus, S. agalactiae, and F. commune. The structure-activity relationship (SAR) study revealed that antibacterial efficacy was significantly affected by the length of linker and imidazole substituted group. Amin et al. [32] reported the synthesis of novel series of 7-hydroxy-4-methylcoumarin and 7-alkoxy-4-methylcoumarin derivatives following Pechmann condensation process. The derivatives were investigated for their antimicrobial activity against S. aureus, Bacillus subtilis, E. coli, Pseudomonas aeruginosa bacterial strains, and antifungal activity against Candida albicans. The author concluded that derivatives bearing 7-hydroxy group exhibited better antimicrobial activity than those bearing 7-alkoxy group in the structure. Astem et al. [33] synthesized 2,3-diyhdro-1,3,4-thiadiazoles, pyrazoles, and coumarin containing benzo[4-n]yl derivatives following the approach of green chemistry and investigated for their antibacterial activity. Hamid and Kubba [34] reported the synthesis and antibacterial activity of Schiff bases, chalcones, hydrazones, and hydrazinyl thiazoles derivatives incorporated in 8-formyl-7-hydroxy-4-methyl coumarin derivatives. The results revealed that novel chalcones having a phenyl group in the structure represented excellent activity against Gram-negative bacterial strains. However, hydrazone and cyclized hydrazinyl thiazole derivatives exhibited good activity against Gram-positive bacterial strains.

Antitubercular activity

Tandon et al. [35] explored the anti-tuberculosis (TB) potential of a series of amino and acyl aminocoumarins against H37Rv strain. The analogs were also tested for their MBCs, fractional inhibitory concentration index values, and cytotoxicity. The minimal inhibitory concentrations (MICs) for a susceptible and a multidrug-resistant clinical isolate of Mycobacterium tuberculosis were also evaluated. Electron and fluorescence microscopy of the test compound-treated mycobacterial samples was also analyzed to find out the target site. 7-Amino-4-methylcoumarin (7-amino-4-methyl-2H-chromen-2-one; NAS) showed the lowest MIC of 1 μg/L against H37Rv strain. Reddy et al. [36] synthesized a series of coumarin-oxime ether using the SN2 reaction of bromomethyl coumarins with butane-2,3-dione monoxime and the derivatives were tested for in vitro anti-TB activity against MTBH_Rv strain. The compound (1 h) was further used to explore the mode of interaction with a model serum protein, bovine serum albumin which displayed excellent interaction without influencing its normal functioning. Mangasuli et al. [37] synthesized a series of substituted C-4 bridged coumarin-theophylline hybrids and assayed for their anti-TB activity against M. tuberculosis H37Rv, antimicrobial activity against Gram-positive bacteria (S. aureus) and Gram-negative bacterial strains (E. coli, Salmonella typhi) as well as fungal strain (C. albicans). The compound (3a) represented remarkable

Fig. 2: List of 4-hydroxy and 7-hydroxy coumarin derivatives synthesized by treating with activated aziridines

Fig. 3: A series of novel 1,2,4-triazole (compounds 3-6), 4,5-dicyanoimidazole (compound 7) and Purine (compound 8-13) coumarin derivatives and their acyclic nucleoside analogs 14-18

Fig. 4: The structure of compound 22 and 67 exhibited potent inhibitory activity against tumor necrosis factor-α production

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anti-TB activity with MIC of 0.12 μg/ml. Compounds (3a, 3f) exhibited significant anti-microbial activity and 3a, 3b, and 3f revealed moderate antifungal activity. The structural analysis of synthesized compounds was accomplished using crystal X-ray diffraction technique, and molecular docking study against 4DQU enzyme of *M. tuberculosis* exhibited remarkable binding interactions.

Anticancer activity

Benci *et al*. [38] synthesized and investigated antitumoral potential of derivatives of novel 1,2,4-triazole (compounds 3–6), 4,5-dicyanoimidazole (Compound 7) and purine (compound 8–13) coumarin derivatives and their acyclic nucleoside analogs (14–18) (Fig. 3). The results of antitumoral assays conducted on human tumor cell lines, communicated that compound 6 had moderate anti-proliferative activity against the HeLa cell line (IC$_{50}$: 35 μM), whereas compound 10 was moderately active against the HeLa (IC$_{50}$: 33 μM), HepG2 (IC$_{50}$: 25 μM), and SW620 (IC$_{50}$: 35 μM) cell lines.

Cheng *et al*. [39] synthesized and explained SAR of various coumarin derivatives exhibiting tumor necrosis factor (TNF)-α inhibitory action. The compound 22 and 67 (Fig. 4) exhibited excellent TNF-α inhibitory action in human peripheral blood mononuclear cells triggered by bacterial lipopolysaccharide (LPS).

Lee *et al*. [40] synthesized a series of 7-diethylaminocoumarin derivatives and investigated for anti-proliferative action against human umbilical vein endothelial cell (HUVEC) and some other cancer cells. This research concluded that the cyanogroup at position-4 will elevate the biological efficacy. In particular, compounds 9 and 10 represented remarkable anti-proliferative activity against various cancer cell lines, and compounds 12 and 15 displayed commendable selectivity for HUVEC (Fig. 5). Hence, these analogs can be utilized as a prototype to develop novel non-toxic angiogenesis inhibitors and small molecular ligands to target HUVEC.

Chen *et al*. [41] isolated and characterized 2α,7β,20α-trihydroxy-3β,21-dimethoxy-5pregnene (1), 6,7,9α-trihydroxy-3,8,11α-trimethylcyclohexeno-[d, e]-coumarin (2), 3β-hydroxy-27-benzoyloxyp-20(29)-en-28-oic acid (3), and 3β-hydroxy-27-benzoyloxyp-20(29)-en-28-oic acid methyl ester (4), along with 24 known compounds from the roots and aerial parts of *Helicteres angustifolia* (Sterculiaceae). The two-cucurbitacin derivatives, cucurbitacin D and J exhibited excellent anti-proliferative activities against hepatocellular carcinoma BEL-7402 cells and malignant melanoma SK-MEL-28 cells.

Nofal *et al*. [42] synthesized and investigated a series of novel 3-bromo-4-methyl-7-methoxy-8-amino substituted coumarins and 2-substituted 7-bromo-6-methyl-8H-pyrano-benzimidazoles, benzoxazoles, and/or benzoxazine-8-ones against their cytotoxic potential. Out of the synthesized derivatives, the compound 15a (Fig. 6) represented remarkable antitumor activity against Ehrlich ascites carcinoma.

Lou *et al*. [43] reported for a novel coumarin, Juglans side C isolated from the bark of *Juglans mandshurica*. Juglans side C exhibited reasonable cytotoxicity against human hepatocellular carcinoma Hep3B cells (IC$_{50}$ value: 70.9 μM). In addition, Annexin V-FITC/PI staining assay technique specified that significantly induced apoptosis in Hep3B cells.

The study concluded that this plant could be an auspicious plant for the treatment of HCC and its findings could be explored in future research.

Tan *et al*. [44] synthesized and investigated a series of 8-ethoxy-3-nitro-2H-chromene based HDACIs against K562, A549, MCF-7, PC3, and HeLa cancer cell lines. The research revealed that o-amino anilide and D-Phe substituted α-amino amide derivatives (16a and 16b) were more effective toward HADC1 over HADC2 and were moderated to weak active over HADC6. However, the amide ZBG analogs (12a and 12b, 14 and 15) were only average HDAC6 inhibitors and were more active over HDAC1 and HDAC2. The o-aminoanilides 9b, 9c, 10b, 10c, 11b, and α-aminoamides, 16a and 16b were effective against HADC1. The phenyl substituted o-aminoanilides 10b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2. The α-aminoanilides 9b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2. The α-aminoanilides 9b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2. The α-aminoanilides 9b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2. The α-aminoanilides 9b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2. The α-aminoanilides 9b and 10c were more active than MS-275 as HADC1 inhibitors and more selective toward HADC2.

Lv *et al*. [45] designed and synthesized a series of 2-phenylpyrimidine derived coumarin analogs bearing telomerase-inhibiting activity. These analogs were investigated for cytotoxic action against CNE2, KB, and Cal27 cancer cell lines. The results displayed that most of the
compounds were effective in resisting tumor cell proliferation and concluded that compound 13 is a highly potent derivative that can inhibit CNE2 proliferation. The molecular docking studies revealed that compound 13 bonded through multiple interactions, including hydrogen bonding and hydrophobic interactions against telomerase reverse transcriptase. Yu et al. [46] designed and synthesized 34 new dibenzoxatriazol-2(3H)-benzoxopyran-4-one analogs and then analogs represented remarkable cytotoxic activities against HT-29 and MDA-MB-231 cell lines, especially under hypoxic condition. The SAR study and docking analysis had shown that carbonic anhydrase IX was the main target of the hybrids. The results had shown that these compounds noticeably exhibited antiproliferative activity against HT-29 cell lines, by arresting G0/G1 phase of HT-29 cells, blocked the movement of tumor cells, and induced a great reduction in mitochondrial membrane potential. Batran and Kassem et al. [47] reported the synthesis of a novel series of 4-phenylcoumarin derivatives, and explored these compounds for anticancer activity against MCF-7 cell lines. Compounds 3a, 3b, and 3f represented the excellent cytotoxic effect on MCF-7 cell lines without producing any cytotoxic effect on human normal skin cell line (B-1). In addition, tubulin polymerization assay was also accomplished for the most potent compounds, i.e. 3a, 3b, and 3f. The results revealed that the three derivatives represented significant inhibitory activity of TUBB polymerization in comparison with standard drug colchicine (IC50 = 9.37, 2.89 and 6.13 μM, respectively, vs. 6.93 μM for colchicine). Compound 3a was further exposed to cellular mechanistic studies on MCF-7 cells and showed induction of apoptosis and cell cycle arrest at G2/M phase, along with its significant activation of caspase-3. The combined studies of molecular docking, pharmacophore hypothesis, and MD studies exposed remarkably information on the structural features of the molecules, which are essential to explore drug interactions and designing of the novel drug molecule. Emami et al. [48] synthesized a new series of 3-(4-aminothiazole-5-carbonyl)-2H-chromen-2-ones, (3a-1) and (4a-c) with a cyclic amine, substituted cyclic amine, aniline or substituted aniline moieties, and investigated for cytotoxic potential employing MTT assay against MCF-7, HepG2, and SW400 cell lines. The thiomorpholine derivative (3k) was potent with (IC50 values: 7.5–16.9 μg/ml). The compound (3k), against MCF-7 cells represented apoptosis and ceased the cell proliferation at the G1-phase. The analogs had significant effects for free radical scavenging activity and ferric-reducing power as evaluated by 2,2-diphenylpicrylhydrazyl (DPPH) and ferric reducing antioxidant power assay method. Singh et al. [49] designed and synthesized 28 novel triazolebound isatin-coumarin hybrids, and investigated for antiproliferative potential against human cancer cell lines of THP-1, Colo-205, HCT-116, and PC-3 and compounds A1 to A6, B1 to B4, and C1 to C3 had prodigious inhibitory activity against THP-1, Colo-205, and HCT-116 cell lines. The SAR study expressed that the cytotoxic activity rely on substitution on isatin and the length of carbon-bridge linking isatin moiety with triazole moiety. Two carbon-bridge and unsubstituted isatin were found to be essential for cytotoxicity. Three most potent hybrids (A1, A2, and B1) were also evaluated for tubulin polymerization inhibition activity and compound (A1) was found to be most potent with IC50 value of 1.06 μM. Zhou et al. [50] designed and synthesized 5 new analogs of phenylmethylfuroxan joined with 3-benzyl coumarin and their sec-o-Ring derivatives (2–6). The compound 3 was highly active anti-cancer agent with IC50 values ranging from 0.5 nM to 143 nM against 9 drug-sensitive and 4 drug-resistant cancer cell lines. Compound 3 induced the early apoptosis and hardly affected the cell cycle of A2780. Xiang et al. [51] rationally optimized a series of 3-aryl-4-aniline/aryloxy-2H-chromen-2-one derivatives using structure-based modification of lead compound 1E18d to obtain a multifunctional effect against ERα and VEGFR-2. By means of bioisosteric replacement, F atom was incorporated to C4-position of 3-phenyl substituent while, O atom was substituted to the 4-position of coumarin moiety, for anticipated interactions with essential amino acid residues of targeted ERα receptor and VEGFR-2 enzyme. Among these derivatives, O-linked compounds represented potent ERα binding affinities and antiproliferative potential against cancer cells and angiogenesis-related cells. Further investigation exposed that (4zd) was able to inhibit MCF-7 cell migration and arrest cell cycle at G0/G1 phase in MCF-7 cells in a concentration-dependent manner. Furthermore, a significant anti-estrogenic property observed in RT-PCR, and (4zd), inhibited the activation of VEGFR-2 and the-signaling transduction of Raf-1/MAPK/ERK pathway in MCF-7 cells. Molecular docking analysis of (4zd) presented ER-α binding mode embodying three essential hydrogen-bonding interactions, which is the characteristic character of selective estrogen receptor modulator. Bu et al. [52] synthesized and characterized a chain of novel 5a, 8a-epidioxyanrost-3b-ol-17-(O-phenylacetamide) oxime derivatives (9a-o). These analogs were investigated for their anti-proliferative activities against human hepatocellular carcinoma cells (HepG2, Sk-Hep1) and human breast cancer cells (MCF-7, MDAMB231). The compounds 9d, 9h, 9j, and 9m exhibited significant anti-proliferative activity with IC50<20 μM). Moreover, coumarin-9d conjugate (12) localized in mitochondria, leading to higher anticancer activities over the lead moiety, which was confirmed by a fluorescence imaging technique.

Antimicrobial activity

López-Rojas et al. [54] synthesized a novel series of 26 compounds having coumarin-1,3-trirole conjugates with varied alkyl, phenyl, and heterocycle moieties at C-4 of the triazole nucleus using a copper(I)-catalyzed, Huisgen 1,3-dipolar cycloaddition reaction. Out of these analogs 6 compounds exhibited remarkable antibacterial activity against Enterococcus faecalis (MIC: 12.5-50μg/ml) based on their MICs against a selected microorganism. Furthermore, these compounds represented comparatively minimal toxicity against human erythrocytes. Twari et al. [55] synthesized 15 novel 3-(1-dicyclohexylaminocoumarin-3-one) (3a,3b) under solvent-free conditions.
condition using the ionic liquid [Et₃NH][HSO₄] as a catalyst which was further characterized by IR, ¹H-NMR, ¹³C-NMR, and mass spectral analysis. All the analogs were investigated for their antifungal and antibacterial efficacy, the results revealed that the compound (4k) was potent antifungal and the compound (4e) was potent antibacterial agent. The compound (4k) acts by inhibition of ergosterol biosynthesis in C. albicans that was confirmed using an ergosterol extraction and quantitation assay technique. The most active compounds 4e and 4k were non-cytotoxic against human cancer cell line HeLa.

Anti-HIV activity
Kostova et al. [56] presented the SAR of various synthetic coumarin derivatives used as an anti-HIV agent (Fig. 8). These were accomplished as reverse transcriptase inhibitors, protease inhibitor, and integrase inhibitors. Jashari et al. [57] developed an improved synthetic scheme in which 4-chlorocoumarin-3-sulfonyl chloride (4) was synthesized in excellent yield (Fig. 9). The synthesized compound 4-chlorocoumarin-3-sulfonyl chloride (4) was further reacted with 2-aminothiophenes and 2-aminothiazoles to yield substituted pyrido and thiazino-1,2,4-thiadiazino-benzopyranone dioxides (a potential anticancer and anti-HIV agents).

Antioxidant activity
Majumdar et al. [58] evaluated in vitro antioxidant potential and inhibition of α-amylase and α-glucosidase activities of methanolic extracts of leaves of few Indian medicinal plants. The antioxidant activities of the samples were measured by two different methods while the Folin–Ciocalteu reagent assay was used to estimate the phenolic contents of extracts. Methanolic extracts from dried leaves of Phyllanthus emblica, Cajanus cajan, Cannabis indica, andFormica pratensis were prepared. DPPH radical scavenging and iron chelating methods estimated antioxidant activities. The inhibitions of carbohydrate-hydrolyzing key enzymes, for example, α-amylase and α-glucosidase activities were assayed. Acarbose was used as a reference compound in both of assay procedures. Goudgaon et al. [59] developed that the reaction of synthon 3-acetyl-2H-chromen-2-one (1) with 3-substituted aryl-1-phenylpyrazol carboxaldehyde (2a–d) gave intermediate compounds 3-[3-(3-substituted aryl-1-phenylpyrazol-4-
Singh et al. [61] studied and described the kinetics and the transient absorption spectra from the reactions of OH, O:\(•\) and SO\(_4\):\(•\) radicals with coumarin, 4-methyl-7-hydroxycoumarin, 7-methoxycoumarin, and 6,7-dimethoxycoumarin in aqueous solutions by pulse radiolysis with optical detection (Fig. 11).

Beillerot et al. [62] synthesized and evaluated the protective effects of coumarin derivatives against oxidative stress induced by doxorubicin (DOX). 4-Methyl-7,8-dihydroxycoumarin represented excellent antioxidant potential, less cytotoxicity and could decrease reactive oxygen species (ROS) production generated by DOX without affecting DOX toxicity in MCF7 cells.

Anti-inflammatory activity
Nicolaides et al. [63] synthesized 3-hydroxy-β-lapachone (4) with ylide (5) gave the coumarin derivative (7a), which was transformed to compounds (10–14). Compound 14 was then converted to benzof][n]seselin (15) as well as to benzo][ll]benzyl lactones 16, 18 from which the targeted compounds 17, 19I, 19II, 20, 21I, and 21II were synthesized (Fig. 12). All the compounds were interacted with DPPH in a concentration and time-dependent manner: All the compounds were highly active against the soybean lipoxygenase, whereas compounds 12, 17, and 19I significantly compete with dimethylsulfoxide (DMSO) for •OH. Compounds 7a, 7b, 12, and 17 showed 48.7–58.9% anti-inflammatory activity against carrageenan-induced rat paw edema.

Sreeja et al. [64] reported the in silico molecular modifications of proposed derivatives using different software. The five analogs were shortlisted for the synthesis with the help of selection parameters and were synthesized by conventional and microwave assisted synthetic methods. The synthesized compounds were subjected to pharmaco logical screening such as acute toxicity study, analgesic activity, and anti-inflammatory activity by carrageenan-induced rat paw edema method. Gummudavede et al. [65] synthesized a new series of 7–methoxy-4-methyl-8-[5-(substituted aryl)isoxazol-3-yl]-2H-benzopyran-2-ones by cyclization of chalcones, 9–(2-substituted prop-2-ene)-7-methoxy-4-methyl-2H-benzopyran-2-ones with hydroxylamine hydrochloride (Fig. 13). The synthesized compounds were investigated for their antimicrobial and anti-inflammatory activities and some of them exhibited significant activity.

Nicolaides et al. [66] synthesized a novel coumarin derivatives with a 7-azomethine linkage starting from 7-formylcoumarin (Fig. 14). The compounds were tested in vivo for their anti-inflammatory and in vitro for antioxidant potential. Compounds (3a) and (3e) displayed significant anti-inflammatory action against carrageenan-induced rat paw edema.

Chen et al. [67] designed and synthesized a series of new phenyl-pyrazoline-coumarin derivatives (4a-4m). All of the compounds had been assayed for their anti-inflammatory activity using carrageenan-induced paw edema technique for evaluating their inhibition against LPS-induced IL-6 release. The compound (4m) was potent anti-inflammatory agent resulted in inhibiting IL-6, TNF-α, and nitric oxide (NO) production. In addition, the compound (4m) significantly suppressed the expressions of nitric oxide synthase, cyclooxygenase-2 and the productions of IL-6, TNF-α, NO through NF-κB/MAPK signaling pathway. Moreover, in vivo studies revealed that compound (4m) could inhibit AA-induced rat ankle joints. Yong Jiang et al. [68] isolated three new prenylated phenylpropenols, exotiacetals A–C (1–3), 10 new coumarin derivatives, exoimarmars A–E (4–13), and 35 known analogs (14–48) from the roots of Murraya exotica. The absolute configurations of the new compounds were characterized through comparison of their specific rotations, single-crystal X-ray diffraction data, Mosher’s method, the ECD exciton coupling method, comparison of experimental and calculated ECD data, and the ECD data of the in situ formed transition metal complexes.

Antipyretic activity and analgesic activity
Keri et al. [69] synthesized a series of 4-[6-(phenyl-pyrimidin-4-yl)-phenoxymethyl]-chromen-2-ones [5-7(a-e)] from various 4-bromomethyl coumarins 1(a-e) (Fig. 15). The synthesized compounds were screened for analgesic and antipyretic activities at a dose of 25 and 100 mg/kg, body weight, respectively. The compounds 5 (d), 6 (c), and 7 (d) represented significant analgesic activity comparable with standard drug Analgin using Tail-flick model. Compounds 5 (a) and 7 (a–d) exhibited significant antipyretic activities comparable with standard drug aspirin using yeast induced pyrexia model. QSAR
Fig. 17: The structure of 3,3′-(4-chlorophenylmethylene)bis-(4-hydroxy-2H-1-benzopyran-2-one) (12).

Fig. 18: The structure of the series of coumarin-3-acyl derivatives.

Fig. 19: The structure of 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-butene)-coumarin

Studies concluded that compounds with 2-amino group of pyrimidine ring increase analgesic and antipretctive activities and compounds with 2-hydroxy and 2-hio group of the pyrimidine ring improves DNA cleavage activities.

Anti-Alzheimer’s activity

Zhou et al. [70] designed and synthesized three series (A-C) of coumarin analogs by substitution with phenyl piperazine and investigated against Alzheimer’s disease (AD) (Fig. 16). The anticholinesterase activities of these compounds were also evaluated according to Elman’s method against freshly prepared acetylcholinesterase (AChE) using donepezil as the standard drug.

Costas-Lago et al. [71] synthesized a novel series of hybrid structure pyridazine-coumarin through a multistep approach based on Knoevenagel reaction using as key intermediate pyridazine-16 as potent, selective, and reversible inhibitors of monoamine oxidase (B (MAO-B)). Compounds 9b and 9d are the most potent compounds with IC_{50} values of 0.75±0.17 μM and 0.56±0.04 μM, respectively, and lack of cytotoxic effects. Liang et al. [72] designed and synthesized a novel series of coumarin-dithiocarbamate hybrids for the treatment of AD. The compound 4n was found to inhibit AChE (IC_{50} 0.027 μM for hAChE) and good inhibition of Ab aggregation (40.19% at 25 μM). The compound (4n) could interact with the catalytic active site and peripheral anionic site of AChE determined by kinetic and molecular modeling studies. However, compound 4n exhibited remarkable blood-brain barrier permeability, specific metal-chelating property, and low toxicity in SH-SYSY neuroblastoma cells. Furthermore, compound 4n could reverse the cognitive dysfunction of scopolamine-induced AD mice and did not exhibit any acute toxicity in mice at doses up to 1000 mg/kg. Its excellent in vitro and in vivo profiles proclaimed it as a potential lead molecule to treat AD. Xie et al. [73] designed and synthesized novel hybrids by combining N-benzyl pyridinium moiety and coumarin, with ChE and MAO-B inhibitory activities. Most of the compounds exhibited excellent inhibitory activity for ChE and Aβ (1-42) self-aggregation and selectively inhibition to MAO-B over MAO-A. The compound 7l showed excellent inhibitory action against hMAO-B, and balanced inhibitory action for ChEs and hMAO-B (2.32 μM for eBuchE; 1.57 μM for hMAO-B; 0.0373 μM for eeAChE). The compound 7l was found to be a mixed-type inhibitor, which interacts simultaneously to CAS and PAS of AChE, determined by molecular modeling and kinetic studies and it was a competitive inhibitor for the active site of MAO-B. Furthermore, compound 7l with lack of toxicity on PC12 neuroblastoma cells exhibited good ability to inhibit Aβ (1-42) self-aggregation and cross the blood-brain barrier. Kong et al. [74] designed and synthesized a series of coumarin-pargyline hybrids (4a-x) and screened as novel dual inhibitors of AD. Most of the compounds revealed an excellent ability to inhibit amyloid-β (Aβ) aggregation and monoamine oxidases. Especially, compound (+) exhibited significant inhibitory actions against monoamine oxidases (IC_{50} 3.275±0.04 μM for MAO-A, 0.0275±0.004 μM for MAO-B) and Aβ1-42 aggregation (54.0±1.1%, 25 μM). Furthermore, compound (8+) showed low toxicity estimated by in vitro cell toxicity test and good blood-brain barrier permeability. These results revealed that compound (8+) was an effective and an auspicious candidate for Alzheimer’s. Khoobi et al. [75] synthesized a novel series of coumarin-lipoic acid hybrids through cycloaddition click reaction and evaluated them for the treatment of AD. All the compounds were investigated for their neuroprotective and cholinesterase inhibitory activities. Among them, compound (11) which was found to be the most potent AChE inhibitor, exhibited the excellent inhibitory effect on intracellular ROS formation, and β-aggregation, as well as the ability of selective bimetal chelation and neuroprotection against H_{2}O_{2} and β1-42-induced cytotoxicity. Collectively, this result indicated that the compound (11) was a promising lead compound with desired multifunctional properties, in the treatment of AD. Baraah et al. [76] evaluated the inhibitory efficacy of two substituted coumarin derivatives on neuroprotective and cholinesterase inhibitory activities in the presence of human SA. The experimental results indicated the inhibition to be of noncompetitive type with both the systems showing substantial inhibitory activity on AChE. The compound (9+4) potently inhibited (IC_{50} 48.9±5.6 μM). These results revealed that the compound was an effective and auspicious candidate for AD. Akbarzadeh et al. [77] designed and synthesized a new series of coumarin-pyridinium hybrids as novel dual inhibitors of Aβ. The synthesized compounds were evaluated for anti-butyrylcholinesterase and anti-acetylcholinesterase using Ellman’s method, among synthesized derivatives, the compounds (7l) were found to be the most active compound toward AChE (IC_{50} 10.14 nM), 7g and 7h exhibited highest BChE inhibitory activity (IC_{50} 0.32 and 0.43 μM, respectively). Among them, the compound 7g selectively bound to BChE with SI of 101.18. The kinetic study of the compounds 7g and 7l revealed that they were mixed type inhibitor for both AChE and BChE. In addition, they showed low inhibitory activity against β-secretase.

Anticoagulant activity

Manolov et al. [78] synthesized 4-hydroxy coumarin derivatives. The X-ray crystallography analysis of 3,3′-(2,3,4-trimethoxyphenylmethylene) bis-(4-hydroxy-2H-1-benzopyran-2-one) (7) and 3,3′-(3,5-imethoxy-
4-hydroxyphenylmethylene) bis-(4-hydroxy-2H-1-benzopyran-2-one) (9) confirmed the structure of these compounds and a comparative pharmacological study of the anticoagulant effect with respect to warfarin showed that the synthesized compounds have good anticoagulant activities. The most active compound is 3,3’-(4-chlorophenylmethylene) bis-(4-hydroxy-2H-1-benzopyran-2-one) (12) with low toxicity, very good index of absorption and dose-dependent anticoagulant potential (Fig 17).

Antiparkinsonism activity
Chimenti et al [79] synthesized a series of coumarin-3-acyl derivatives and screened for their selective inhibitory potential against monoamine oxidases (Fig 18). The coumarin-3-carboxylic acids (2a-e) showed selective, reversible inhibitory activity against MAO-B isoform. The compound (2a) exhibited pIC₅₀ 7.76, and a selectivity index (pS.I.) 2.94 and the compound (2b) represented pIC₅₀ 7.72 and a pS.I. of 2.80. The compounds (3a-e) exhibited high pIC₅₀ values against both MAO-A and MAO-B isoforms; however, compound (3d) represented excellent potential against MAO-B with a pIC₅₀ value of 8.00.

Antimalarial activity
Oketch-Rabah et al [80] isolated a new antiplasmodial coumarin, 5,7-dimethoxy-8-(4-fluorophenyl-1-butenyl)-coumarin from the roots of Toddalia asiatica (Fig 19), revealing its traditional use to treat malaria.

Himangini et al [81] synthesized coumarin-pyrazoline hybrids and investigated them as an anti-malarial agent against chloroquine-sensitive (MRC-02) and chloroquine-resistant (RKL-2) strain of Plasmodium falciparum and Plasmodium berghei malaria. The most active antimalarial compound was 3-[1-benzoyl-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-7-(diethyamino)-2H-chromen-2-one (IC₅₀: 4.21 mg/ml) and it provided complete protection to the infected mice at 24 mg/kg for 4 days. Awasthi et al [82] synthesized 22 coumarin-triazole derivatives by alklylation of 7-hydroxy-4-methyl coumarin followed by click chemistry at seventh-position. The synthesized compounds were investigated for antiplasmodial activity against chloroquine sensitive strain of E. falciparum (3D7) and compound 9 was found to be the most potent molecule with IC₅₀ value of 0.763 ±0.0124 μg/ml.

Anticonvulsant activity
Siddiqui et al [83] synthesized multiple coumarin derivatives of heteroaryl semicarbazones by the reaction of heteroaryl hydrazine carboxamide with aryl aldehydes or ketones (Fig 20). The analogs were tested for their anticonvulsant activity employing pentylenetetrazole-induced seizure, and maximal electroshock seizure tests at 30, 100, and 300 mg/kg dose levels along with the study of neurotoxicological indications. Three compounds having 3,4-Cl₂C₆H₄ 2-OCH₃C₆H₄ and 4-BrC₆H₄ represented highest anticonvulsant activity at a dose of 30 mg/kg, as compared with phenytoin.

Anti-hyperlipidemic activity
Sashidhara et al [84] designed and synthesized derivatives bearing both coumarin and indole moieties in a single molecule (Fig 21) by the Duff reaction on naphthalene-1-ol which was engaged in a Knoevenagel type reaction with appropriate active methylene compounds and tested them for hypolipidemic activity. These coumarin aldehyde derivatives were further electrophilically substituted with suitable indoles using iodine in acetonitrile to produce coumarin bis-indole analogs. Similarly, another series of coumarin bis-indole analogs were also synthesized starting from 2-sec-butylphenol to synthesize another set of coumarin bis-indole analogs. These derivatives were investigated for hypolipidemic activity in the hyperlipidemic hamster model. In both the series of compounds, as far as coumarin, a pharmacophore is focused, the derivatives bearing substitution at position three plays a key role, and the presence of ethyl ester over methyl is preferred for profound activity. However, it was noticed that unsubstituted indoles have a good activity profile compared to substituted indoles. Among 12 tested compounds, the one bearing R=-C₆H₄ and R₆=H exhibited lower plasma triglyceride levels by 55%, total cholesterol (TC) by 20%, accompanied by an elevation in HDL-C/TC ratio by 42% in hyperlipidemic rats to a maximum extent than some of the reference statins.

Tyrosinase inhibitor activity
Fais et al [85] resynthesized coumarin-resveratrol hybrids by a traditional Perkin reaction carried out in refluxing DMSO between o-hydroxybenzaldehydes (or their methoxy substituted derivatives) and the corresponding aryl acetic acids, using dicyclohexylcarbodimide as dehydrating agent to investigate the SAR (Fig 22). Tyrosinase activity assays were accomplished with L-DOPA as substrate with little modifications and activity of mushroom tyrosinase was evaluated by spectrophotometric technique. IC₅₀ values represented that these analogs...
exhibited tyrosinase inhibitory activity. 3-(3,4,5-trihydroxyphenyl)-6,8-dihydroxy-7-coumarin was the most potent compound (IC\textsubscript{50}: 0.27 mM) than umbelliferone (IC\textsubscript{50}: 0.42 mM). The kinetic studies disclosed that the compound resulted in non-competitive inhibition of tyrosinase and the number and position of free hydroxyl groups play a key role in the biological activity.

**Antiobesity activity**
Singh et al. [86] synthesized novel coumarin-dihydro quinazolinone analogs and investigated for agonist activity at GPR109a receptor. A compound 10c exhibited robust agonist activity at GPR109a with EC\textsubscript{50} < 11 nM. The homology model of human GPR109a protein was assayed to explore the binding capacity of the active molecule with the active site of GPR109a. Further, it was discovered that compound 10c resulted in minimization of body weight in diet-induced obese mice model and reduced leptin in blood plasma and total serum cholesterol.

**Antidiabetic activity**
Lu et al. [87] synthesized 4flavonoid-coumarin analogs using natural 8-(6'-umbelliferyl)-apigenin as a lead moiety and screened for their α-glucosidase inhibitory and glucose consumption promoting activity.

The SAR studies revealed that C5/C7-C6" and C6/C5-C6" analogs improved α-glucosidase inhibition as compared with their flavone and coumarin lead structures. Compounds (5a) and (14a) were recognized as new α-glucosidase and α-amylase dual inhibitors similar to acarbose. Furthermore, compounds (5a) and (14a) exhibited glucose consumption-promoting activity in insulin-resistant and non-insulin resistant HepG2 cells models. Therefore, compounds (5a) and (14a) could be potential drug candidates for drug design to treat diabetes mellitus. Saeed et al. [88] designed and synthesized three series of diamine-bridged bis-coumarin oxadiazole hybrids by one-pot multi-component technique. The synthesized conjugates (4a-j, 5a-j, and 6a-j) were screened for potential inhibitory activity on α-glucosidase enzyme. Compound (6f) was used as the lead molecule that selectively inhibits the α-glucosidase enzyme (IC\textsubscript{50} value: 6f of 0.07 ± 0.001 μM). This inhibition value was approximately 545-fold higher compared to the standard drug. Compound 6f was also appeared as the lead molecule with good inhibition strength (IC\textsubscript{50}: 0.04±0.02 μM) against intestinal maltase-glucosamylase. Against β-glucosidase enzyme, compound (6g) was emerged as the lead inhibitor with an IC\textsubscript{50} value of 0.08±0.002 μM. Michaels-Menten kinetic experiments were performed to explore the mechanism of inhibition. Molecular docking studies of the synthesized compounds were accomplished against glucosidase enzyme to explore ligand-protein interactions at the molecular level.

**CONCLUSION**
Coumarins and its analogs obtained from either natural or synthetic sources exhibited vital biological potential. The key role of coumarin derivatives in plants and animal biology has not been explored until now. The study of novel approaches employed to design and synthesize coumarin analogs bearing essential biological activities along with the study of SAR in addition to the proposed mechanism of action is incorporated in this review. Therefore, this review will help the researchers to design novel coumarin analogs by careful understanding of SAR studies incorporated in this review.

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Mandeep Kumar Gupta initiated the idea of designing the review article and downloaded relevant publications from SciFinder, PubMed, ScienceDirect, and Google Scholar, and Research Gate database. Sachin Chaudhary and Sushil Kumar assisted in designing the manuscript.

**CONFLICTS OF INTEREST**
The authors declare that they have no conflicts of interest.

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