A REVIEW OF COUMARIN DERIVATIVES HAVING DIFFERENT BIOLOGICAL ACTIVITIES

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ABSTRACT: Coumarin (2H-Chromen-2-one) is a heterocyclic compound having molecular formula $C_9H_6O_2$ and contains oxygen in its structure. Coumarin belongs to the lactones family having a benzopyrene system. Many coumarinnucleiplay an important role in medicinal chemistry to synthesize a series of various biologicalactive derivatives as anti-inflammatory, antipyretic, antioxidant, bronchodilator, vasodilator, antiamoebic, antibacterial, and antifungal activities. Apart from this, coumarinsalso act as lipid-lowering agents having mild triglyceride-lowering activity.Many chemical reactions have been established that can be used to synthesize coumarinslike the Knoevenagel condensation reaction, Perkin, Pechmann reaction, and Reformat sky and Wittig reactions. All the coumarin derivatives are mentioned in the article,these derivatives of coumarin are tested for various pharmacological activities. The main motive of this review article isto describe their pharmacological action and activities against different types of bacteria by using different types of models(*invitro* assay, *in vivo* assay,etc). This review article aims to review the various biological activities of coumarin derivatives.

KEYWORDS:coumarin, chroman, chrome, heterocyclic compounds, Spiro [chromane-2, 4'-piperidine]-4(3*H*) one, Chroman-4-one.

INTRODUCTION:2H-Chromen-2-one or 2H-1-benzopyran-2-one (coumarin)is a naturally occurring heterocyclic compound containing oxygen in their structure abundantly present in the different kingdoms of the plant; it was first found in Tonka bean trees (Dipteryxodorata Wild). The history of these natural products started 200 years ago the name of the class derived from the plant Coumarin moderate (Dipteryxodorata) from which coumarin itself (Figure 1) is the simplest member of this family, which was isolated by Vogel in 1820. Chemically, coumarins are organic heterocyclic compounds and their nucleus is represented by benzo-α-pyrone (2H-1-benzopyran-2-one), whose systematic nomenclature was established by the International Union of Pure and Applied Chemistry (IUPAC) [1].

Fig.1. Structure of coumarin nucleus.

Coumarin and its derivatives are reported to have a wide spectrum of biological activity [2–5]. Many of these compounds have been proven to be active as antibacterial [6–8], antifungal [9], anti-inflammatory [10], anticoagulant [11], anti-HIV [12], and antitumor agents [13]. Coumarins are extensively used as food additives, perfumes, cosmetics [14], pharmaceuticals, and optical brighteners [15] and would dispersed fluorescent and laser dyes [16].The first time coumarin is reported in 1884 by Pechmann *et al.*which was first synthesized via the Perkin reaction in 1868 and many simple coumarins are still prepared through this method. In the early 1900s, the Knoevenagel reaction exploits as an important synthetic method to synthesize coumarin derivatives with a carboxylic acid at the 3-position. To date, many other synthetic methods were reported for coumarins, like the Pechmann, Reformat sky, and Wittig reactions[17].

Chromens is a benzopyran ring-containing compound. Benzopyran is a heterocyclic organic compound popular as chromenes that are obtained by the fusion of the pyran ring, which containsan oxygen hetero atom with the benzene ring. A sufficient amount of chromeis found in the bark oil of cinnamon, essential oil, oil of cassia leaf and lavender oil, etc. In the IUPAC

system, it is named chromenes. Saturated chromene is called chroman (3, 4-dihydro-2*H*-chromene). The structure of 2*H*-chromene is shown below-

Chroman is a bicyclic aromatic compound having the chemical formula $C_9H_{10}O$ and a molecular weight of about 134.18.Chromeconsistsof a pyran ring and a benzene ring which is ortho-fused at positions C_2 and C_3.

PHARMACOLOGICAL ACTIVITIES:

Antiprotozoal activities:

The analogous of chalcone having a double bond in the side chain between the carbonyl moiety and the phenyl residue was nearly as active as the natural product [18]. The synthetic tricyclic chromene 2 which has the exocyclic benzylidene moiety also showed strong antileishmanialactivity[19]. The medicinal plant Ageratum conyzoides L. (Asteraceae) is used in traditional medicine against numerous diseases including protozoan infections [20]. Recently, it was reported that the dichloromethane extract of A. conyzoides L. shows significant activity against T. b. rhodesiense[21]. In a search for the active constituents, when tested after total synthesis the chromeneencecalolangelate 3[22] was noticed in the extract but depicted only low anti-trypanosome activity [23]. The stability of the 3 compounds was found to be ultra-low so the weak bioactivity may be related to its rapid degradation when tested as a pure compound. The instability of the 3 compounds begins from the superficial dissociation of the angelate anion since the rest of the benzylic cation is stabilized by two substituents. Thus, when storing the angelate 3 in a methanolic solution a rapid formation of the corresponding methyl ether was detected[23](Figure 2).

Figure 2. Chromenes with antiprotozoal activity.

Various heterocyclic compounds possessing favorable biological activity consist of Aryl triazoles and are found as a potent antimicrobial agent [24, 25] and adenosine A2A receptor antagonist [26]. According to the green chemistry approach, there are several solvent-free reactions of 1, 2, and 4-aryl triazoles have been reported [27, 28].

4-Thiazolidinones have been broadly examined for their utilization in the field of medicine and agriculture [29]. They are also used as promising antimicrobial [30], anti-inflammatory [31, 32], antimalarial [33], anticancer [34], tuberculostatic [35], and antiviral agents [36]. Several one-pot multiphase syntheses of 4-thiazolidinedione have been reported [37–38].

1,2,4 -Triazole 4-Thiazolidine

Spiro [chromane-2, 4'-piperidine]-4(3H)-one (Fig. 3) belongs to the six-membered oxygen and nitrogen-containing tricyclic compound whereas bicyclic chroman-4-one (2, 3-dihydro-1-benzopyran-4-one) moiety is fused at C2 position with piperidine ring. The introduction of Spiro junction at the C2 position makes a big difference in its structure than that of standard chroman-4-one and resulted in favorable alteration in their chemical structure and medicinal properties.Spiro [chromane-2, 4'-piperidine]-4(3H)-one is one of the important pharmacophores. It is a structural component in many drugs, drug candidates (or lead compounds), and various biochemical reagents. The synthesis of Spiro heterocyclic compounds with various chemotherapeutic applications was performed by several researchers [39].

Fig.3. Structure of Spiro [chromane-2, 4'-piperidine]-4(3*H*) one

Conformational structure(s)

Spiro[chromane-2,4'-piperidine]-4(3H)-one-functionalized compounds aregreat attention due to their interesting conformationalproperties of the spirocyclic ring[40] and playing a vital role in developing bioactive properties. The existence of two conformational forms (Fig. 4 compound 3 and 4) with modulated spirocyclic piperidine ring system allows pharmacological potentials in the entire variety of protein interactions. The piperidine pattern was structurally defined under the chair conformer whereas the strength of substituents is aligned equatorially.

Fig.4. Most stable conformational form of Spiro [chromane-2, 4'-piperidine]-4(3*H*) one

The Spiro[chromene-2,4'-piperidin]-4(3H)-one functionalized compounds are an important intermediate and interesting building block in organic compounds synthesis and design of new lead compounds in drug design and discovery. It's become a booming skeleton given its broad and inspiring activities in various therapeutic areas such as growth hormone secretagogues[42], anti-arrhythmic[43], anti-cancer[44,45], anti-tubercular[41,46], antimicrobials[47], histamine-3 antagonists[48], acetyl-CoA carboxylase (ACC) inhibitors[49-50], stearoyl-CoA desaturase-1 (SCD)-1 inhibitors[51], histone deacetylase (HDAC) inhibitors[52], anti-malarial[53] and δ opioid receptor agonists[54].New series of spirochromanes tested its activity against HDAC as a well-established antineoplastic target reported by Thaler et al. reported very recently [55]

Anticancer and anti-TB activity:

Spiro compounds are investigated for their potential anticancer and anti-TB activity. Some clinically used spiro drugs as potent anticancer and anti-TB agents are shown in (Fig 5)

Fig.5. Clinically used Spiro drugs as potent anticancer and anti-TB agents.

Spiro chromanones as Acetyl-CoA carboxylase (ACC) inhibitors:

Acetyl-CoA carboxylase (ACC) is examined as an important research area in medicinal chemistry and it is currently a 'trending' research topic. It is one of the biotin-dependent homo-oligomericproteins, responsible for the synthesis of malonyl-CoA from acetyl-CoA in an ATP-dependent manner and consists of a biotin carboxyl carrier protein, a carboxyl transferase (CT) and biotin carboxylase (BC) domains.

Many companies Merck-Banyu [56a, 57], Takeda [56b], and Pfizer [56c] possess multifaceted Spiro chromanones 25, 26, and, 6 respectively. (Fig. 6)

Fig.6. Spiro [chromane-2, 4'-piperidine]-4(3H)-one derived ACC inhibitors

Followed to this, there was a notable structural improvement in the basic constituent of Spiro [chroman-2, 4'-piperidin]-4-one exhibit for ACC inhibitors. In the year 2007, the group of Takeru *et al.* [57] developed Spiro chromanone derivatives 7 and 27, containing a bicyclic naphthalene ring incorporated hydrophobic core and assessed as potent ACC inhibitors. (Fig.7)

Fig.7. ACC inhibitors with modification at C6 position of chromanone.

Chroman-4-one is a six-membered heterocyclic compoundconsisting of a benzene ring fused to a 2, 3-dihydro-γ-pyranone ring [58]. The structure of chroman-4-one is differ from chromone by the reduction of C2–C3 double bond saturated compound forms (Fig. 8). These small changes in the structure of chroman-4-ones and chromones resulted in big differences in their chemical structure and biological activity.

Fig.8. Structures of chroman-4-one and chromone

The chroman-4-one scaffold is a privileged structure in the development of drug and drug discovery. Chroman-4-one derivatives such as (2S)-5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-2,3-dihydro-4Hchromen-4-one, 4'-hydroxy flavanone, 5-deoxy flavanone, 5,4'-dideoxy flavanone, and (2S,3S)- trans-dihydro quercetin are under experiment or clinical trial, and hesperidin has been foundas a cholesterol-lowering agent [59].(Fig.9)

Fig.9. Structures of some 4-chromanone-derived drugs under development.

Anticancer activity:

A series of 3-benzylidine-4-chromanones 17 were synthesized by Perjési*et al.* as cytotoxic agents(Fig. 10). These compounds were examined as oxygen analogs of 2-benzylidene-1-tetralones 16 and tested against Molt 4/C8 and CEM T-lymphocytes as well as murine L1210 lymphoid leukemia cells. In general, 3-benzylidene-4-chromanones 17 were more potent than the corresponding 2-benzylidene-1-tetralones 16. Also, the 3-benzylidene-4-chromanones 17 was reported to have selective toxicity for cancer cells concerning that of normal cells and has been tolerated in mice [60].

Fig.10. Cytotoxic 3-benzylidene-4-chromanones as Isoesters of 2-benzylidene-1-tetralones

Antitubercular activity:

Roy and colleagues prepared a series of (E)-7-hydroxy-3-benzylidene-chroman-4-one analogs as efflux pump inhibitors against Mycobacterium smegmatis mc2 155.

The SAR study demonstrated that the (E)-7- hydroxy-3-benzylidene-chroman-4-one structure is required for efflux pump inhibitory activity. The substation of the hydroxy group at C-5 or C-8 and methoxy group at the C-8 position of the chromanone ring diminish the efflux pump inhibitory activity [61].

Yempala *et al.* reported a series of dibenzofuran-incorporated 3-benzylidene-4-chromanones 27 as antimycobacterial agents. Their design was based on the molecular hybridization of plant-origin dibenzofuran derivative 26 (Fig. 12) with natural homoisoflavonoids in one molecular scaffold. A distinct path involving base catalyzed Baylis–Hillmann reaction of 2-dibenzofuran carboxaldehyde and methyl acrylate was used for the synthesis of (E)-3-(dibenzo[b,d]furan-2-yl-methylene)-chroman-4-one derivatives.

Fig.12. Design of dibenzofuran-incorporated 3-benzylidene-4-chromanones as antimycobacterial agents

Monoamine oxidase (MAO) inhibitory activity:

MAO inhibitors were implemented in the treatment of many psychiatric and neurological disorders. Desideri and colleagues reported a series of homoisoflavonoids as inhibitors of human monoamine oxidase isoforms A and B (hMAO-A and hMAO-B). The evaluation of compounds using the AmplexRedMAO assay kit foundthat compounds 32 and 33 (Fig. 14) were the most potent and demanding hMAO-B inhibitors (IC50 values 8.61 and 8.51 nM, respectively). Their potency was more than that of selegiline (standard drug). The hMAO-B selectivity of both compounds can be related to the different hydrogen bond interactions in hMAO-B active site. [62]

Fig.14. 3-Benzylidene-4-chromanones with MAO inhibitory activity

Antibacterial activity:

Jogi et al. have reported the antibacterial activity of novel coumarin-based azo compounds as shown in (Fig.17), synthesized by using hymecromone as a starting material, and exhibited promising antibacterial activity against the test bacteria. Compounds have been found to show an antibacterial activity comparable with ampicillin and streptomycin (63).

Fig.17. Coumarin-based azo compounds having an antibacterial activity developed by Jogi et al.

Antioxidant activity:

Šarkanj*et al.*have reported the synthesis of two series, as shown in (Fig.18), of new five hybrid coumarins, herein termed N18-N22, starting from hymecromone. In the first series, hymecromone was incorporated with thiosemicarbazides, while in the second series, it was incorporated with 4- thiazolidinediones. The chain-breaking ability of these new coumarins was tested versus 2, 2- diphenyl-1-picrylhydrazyl (DPPH) and galvinoxyl free radicals. The authors concluded that the incorporated coumarins of the first series showed better antioxidant activity than that of the second one. Also, the best activity was contributed to compounds N20 and N21. (64)

N18: R=Methyl
N19: R=Ethyl
N20: R=phenyl
N21: R=*p*-Tolyl
N22: R=*p*-Methyl

Fig.18.coumarins having antioxidant activities prepared by Šarkanj *et al.*

Molnar *et al.*have prepared 26 new coumarin-Schiff bases, as shown in (Fig.19), using hymecromone as a starting material. These products, herein termed N23-N48, were examined for their antioxidant potential against galvinoxyl and DPPH free radicals. The authors concluded that coumarin derivatives N30-N34 having dihydroxy phenyl moiety in their chemical structures showed the best antioxidant activity among the others. (65)

RR			
N23	H	N36	3-phenoxy
N24	2-OH	N37	2-OH-5NO_2
N25	3-OH	N38	3,4,5-$(OCH_3)_3$
N26	4-OH	N39	2-Cl
N27	2-OCH_3	N40	3-Cl
N28	3-OCH_3	N41	2-Br
N29	4-OCH_3	N42	3-Br
N30	2,3-$(OH)_2$	N43	4-Br
N31	2,4-$(OH)_2$	N44	2-F
N32	2,5-$(OH)_2$	N45	3-F
N33	3,4-$(OH)_2$	N46	4-F
N34	3,5-$(OH)_2$	N47	styryl
N35	3-OCH_3-4-OH	N48	4-$N(CH_3)_2$

Fig.19.New coumarins prepared by Molnar et al. have antioxidant activity.

Anti-inflammatory potential:

Naik et al. has reported the synthesis of 13 hymecromone-based derivatives. The anti-inflammatory impact of the resulting derivatives (Fig.20) was screened by a protein denaturation technique and also studied their QSAR (quantitative structure-activity relationship). The conclusions exhibit that these derivatives have a prominent anti-inflammatory activity. Also, the authors concluded that various changes in the aromatic ring have a minor impact on this type of activity. (66)

Fig.20. Chemical structures of hymecromone-based derivatives as depicted by Naik et al. having anti-inflammatory activity.

Antiviral potential:

Bishnoi et al. have reported the synthesis of five hymecromone-based derivatives, herein termed N49- N53 (Fig.21), and their antiviral activity was tested versus the RNA virus named Japanese encephalitis virus. The results exhibited that compounds N49 and N52 showed excellent antiviral activity with an inhibition percent of 100. Compounds N50 and N53 have shown a good inhibition percentage of about 75. Only compound N51 has shown poor activity that may be assigned to having weak interactions with the target. [67]

Fig.21. Chemical structures of hymecromone-based derivatives as depicted by Bishnoi et al. having antiviral activity.

A large number of natural 2, 2-dimethyl chromene (2, 2-dimethyl-2H-l-benzopyran, 1) derivatives are found in the literature. This moiety is implanted in various natural products [68] including coumarins (2). In these coumarins, the fusion of the 2, 2- dimethyl pyran ring to the benzene ring of parent coumarin is involved. These are called furanocoumarins. 2, 2-Dimethylpyranocoumarins are found in various plants and these coumarins exhibit a wide range of pharmacological activities. They act cytostatically, antiheroically, and as a spasmolytic ally on coronary vesicles [69]

Depending on which manner the pyran ring is fused to coumarin these compounds are classified into angular and linear furanocoumarins. These possibilities are shown by structures 3-8.

Hepatoprotective Activity:

The liver plays a vital role in various body functions from protein production and blood clotting to cholesterol, glucose, and iron metabolism. Many diseases and drugs can damage liver cells and disrupt their function. Hence a study of the hepatoprotective activity of linear furanocoumarins is of major importance. Xia et al. in their study reported the isolation of new linear furanocoumarins (9-11) from Clausenaemarginata Huang (Rutaceae). It is a medicinal plant that has been used to treat coughs, headaches, rheumatic arthritis, gastrointestinal diseases, and other sickness and is broadly spread in southern China.The authors reported the anti-hepatotoxicity of these coumarins against DL-galactosamine-induced toxicity in WB-F344 cells. Authors determined that linear furanocoumarins 9, 10 & 11 revealed the hepatoprotective effects at the concentration of 10μM, emphasizing their potential utility for further research.

CONCLUSION:

Coumarin (2H-Chromen-2-one) is a heterocyclic compound having oxygen in its structure.Based on various literature surveys Coumarin is reported to have many biological activities such as anti-inflammatory, antipyretic, antioxidant, bronchodilator, vasodilator, antiamoebic, antibacterial, and antifungal activities. This paper includes the various coumarin derivatives such as Spiro [chromane-2, 4'-piperidine]-4(3H)-one with anti-cancer and anti-TB, Acetyl-CoA carboxylase (ACC) inhibitors activity. 3-benzylidene-4-chromanones with anticancer, antitubercular, antioxidant,monoamine oxidase inhibitors, and diagnostic imaging activities. The SAR study exhibited that for accumulation and efflux pump inhibitory activity,(E)-7- hydroxy-3-benzylidene-chroman-4-one structure is essential. The substitution of the hydroxy group at C-5 or C-8 and the methoxy group at the C-8 position of the chromanone ring diminished the efflux pump inhibitory activity. The coumarin-based azo compound hasantibacterial activity. The design of a 3-benzylidene-7-methoxy-4-chromanones-basedstructure isa well-known cytotoxic agent, dibenzofuran-incorporated 3-benzylidene-4-chromanones as antimycobacterial agents. The overall conclusion is that benzopyran has been one of the prosperous heterocycles shown a wide range of biological activities.

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