

Review Article

Pharmacological Significance of Coumarin-Linked Heterocycles: A Review

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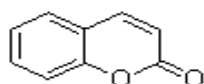
Abstract

Coumarins and its derivatives are an important group of heterocyclic compounds that exhibit a wide range of pharmacological properties such as anticancer, antimicrobial, anticoagulant, antiviral, antihypertensive, antioxidant. The biological potential of various heterocyclic scaffolds has drawn special attention of medicinal chemists and hence exhaustive efforts are being carried out in the search of lead molecules pertaining to it. These different biological applications of coumarin compounds have motivated new search for novel derivatives with improved biological activities and these are being extensively studied. Owing to the importance of this system, this review aims to highlight research reported on the biological potential of coumarin-linked heterocycles during past few decades.

Keywords: Coumarin, Anticancer, Antimicrobial, Antihypertensive, Antiviral.

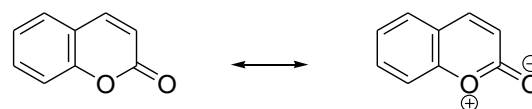
1. Introduction

Coumarins (benzopyran-2-ones) constitute an important class of naturally occurring compounds. Traditionally, it has been used to prevent over-grazing by animals, when present in plants due to their bitter taste. Coumarin is classified as a member of the 'benzopyrone' family of compounds all of which consist of a benzene ring joined to a pyrone ring. The benzopyrones can be subdivided into the benzo- α -pyrones to which coumarins belong and the benzo- γ -pyrones of which the flavonoids are principle members¹. Coumarin exists in two resonance structure, the oxygen containing ring has 6 π electrons, giving it aromatic character.



2H-chromen-2-one

Coumarin



Resonance Structures of Coumarin

Table 1: Physicochemical properties of coumarins.

Molecular Formula	C ₉ H ₆ O ₂
Molecular Weight	146.142
Refractivity	41.55
Log P Value	1.39
pKa	-6.9
Melting Point	71 °C
Density	0.935 g/cm ³
Solubility in water	1.7 mg/ml

The diverse biological activities of natural and synthetic coumarin derivatives as anticoagulants and antithrombotics are well known. Some of the coumarin derivatives are also reported as triplet sensitizers, anti-HIV agents, lipid-lowering agents, and antioxidants. They have also been found to inhibit lipid peroxidation and possess vasorelaxant, anti-inflammatory, and

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anticancer activity. Many coumarin derivatives are also known as free radical scavengers and two naturally occurring coumarins have been found to exhibit cytotoxicity against a panel of mammalian cancer cell lines. Coumarins form an important class of compounds, which have been found to occupy a special role in nature. Pharmacologically, they belong to flavonoid class of compounds, which have been found to exhibit a variety of biological activities, usually associated with low toxicity and have raised considerable interest because of their potential beneficial effects on human health. They have attracted intense interest in recent years because of their diverse pharmacological properties. Some of the important coumarin derivatives are discussed in this review.

Biological Activities

ACE Inhibitory Activity

A series of coumarin alkylamines matching the structural determinants of donepezil as acetylcholinesterase inhibitors (AChEIs) are currently the drugs of choice, although only symptomatic and palliative, for the treatment of Alzheimer's disease. For fairly good inhibition of AChE with high selectivity, 6,7-Dimethoxycoumarin derivatives carrying a protonatable benzylamino group, linked to position 3 by suitable linkers must be present. The inhibitory potency was strongly influenced by the length and shape of the spacer and by the methoxy substituents on the coumarin scaffold. Alzheimer's disease (AD) is a progressive, chronic, neurodegenerative disorder that is characterized by a loss of memory and cognition, severe behavioral abnormalities and ultimately death. It is the fourth leading cause of death in Western countries. As general health care improves and the proportion of the elderly increases, the number of AD patients is anticipated to increase dramatically². The loss of basal forebrain cholinergic cells results in sharp reduction in acetylcholine (ACh), which is believed to play an important role in the cognitive impairment associated with AD. On this basis, the cholinergic hypothesis has become the leading strategy for the development of anti-AD agents. Several anti-AChE agent such as ensaculin (Figure No.-1)

have shown to induce a modest improvement in memory and cognitive functions³.

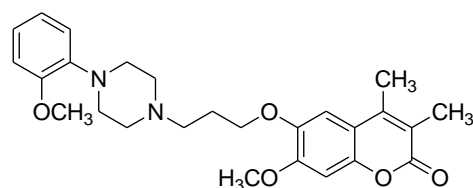


Figure No. 1

Recent study showed that AChE could also play a key role in accelerating amyloid β plaques deposition. It is likely that AChE interacts with amyloid β fibres and promotes amyloid fibril formation through a pool of amino acids located in proximity of the peripheral anionic binding site (PAS) of the enzyme. Moreover, it has been shown that molecules are able to interact either exclusively with PAS or with both catalytic and peripheral binding site, which can prevent the pro-aggregation of AChE toward amyloid β fibres. Compounds showing peripheral and dual binding with AChE are intriguing and could represent a new type of therapeutic agents through the prevention of amyloid β aggregation⁴.

Anticancer Activity

Advances in the field of cytotoxic properties of coumarins and their coordination complexes have been revealed. Variety of different coordination compounds and mechanism of cytotoxic action were studied before⁵. Coumarins are present in natural and synthetic compounds possessing different biological activities and with potential of acting at different stages of cancer formation. Some of them have cytostatic properties and the others have cytotoxic activity. Cytotoxicity against a panel of mammalian cancer cell lines have been exhibited by many naturally occurring coumarins. In recent years exhaustive studies are carried out on synthesis of coumarin compounds and their concern biological activities⁶. Coumarin-linked 3,4-dihydropyrazole (Figure No.-2) have shown several biological activities as tumor necrosis inhibitor. Currently, some of them are either being tested or clinically evaluated for new drug discovery. Novel precursor structure with

anti-gastric cancer activity and found some 2-chloro-pyridine derivatives containing phenylpropanoid (flavone, chome) or dihydropyrazole unit used as potential telomerase inhibitors. Compounds were evaluated for their cytotoxic activity against gastric SGC-7901, PC-3 (human prostate cancer), and A431 (human epidermoid carcinoma) cell lines⁷.

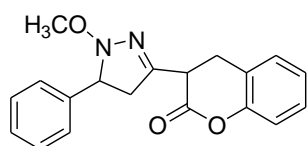


Figure No.-2

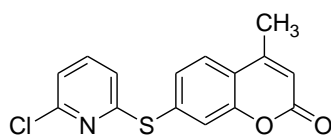


Figure No.-3

Thirty-five S- and O-substituted 7-mercaptocoumarin and 7-hydroxy- or 7-mercapto-chromone (Figure No.-3) analogs were designed, synthesized and evaluated in vitro against four human tumor cell lines [KB(nasopharyngeal), KB-vin (vincristine-resistant subline), A549 (lung) and DU145 (prostate)] with paclitaxel as the positive control. Many of the synthesized compounds exhibited potent cytotoxic activity⁸.

Antimicrobial Activity

The influence of the bioactive coumarin nucleus linked to thiazole (Figure No.-4) from a biological point of view, as a modulator of the biological activity (which show calculated log P value < 5) was studied by evaluating its antimicrobial potential. Organisms from routine clinical gram-positive (*S. aureus*, *S. epidermidis*, *S. hominis*, *Enterococcus sp.*, *E. faecalis*) and Gram-negative isolates (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, *P. aeruginosa*) can be isolated from respiratory tract. The isolates were subcultured on qualified medium to ensure purity. The in vitro antimicrobial activities of the compounds were determined with the broth micro dilution method using clotrimazole and metronidazole as standard antibacterial drugs⁹.

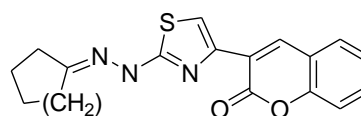


Figure No.-4

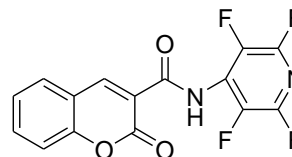


Figure No.-5

Compounds (Figure No.-5) were found to possess antibacterial activity targeting selectively towards metronidazole-resistant strains of *Helicobacter pylori*¹⁰. The newly synthesized coumarin-linked benzodiazepine compounds (Figure No.-6) have been screened for antimicrobial activity against *Staphylococcus typhi*, *Staphylococcus pyogenus*, and *Vibrio cholera* by broth dilution method. Ampicillin, chloramphenicol, were used as standards for comparison of antimicrobial activity. The result indicates that some of these compounds were active against all the four organisms¹¹.

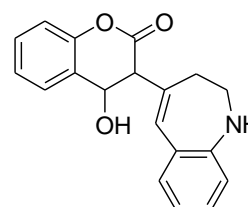


Figure No.-6

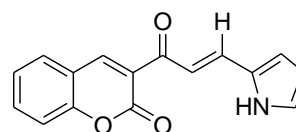


Figure No.-7

Compared with streptomycin, coumarin linked heteroaromatic moiety (Figure No.-7), these compounds revealed larger zones of inhibition against *Bacillus stearothermophilus* (i.e., >23 mm) and *Bacillus subtilis* (i.e., >27 mm), whereas compound showed the same zones of inhibition as streptomycin upon *Bacillus cereus* (23 mm)¹². However, high degree of

resistance as well as small zones of inhibition were observed upon the screening of synthesized compounds against *Bacillus cereus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, and *Shigella dysenteriae*¹³.

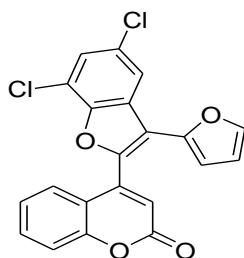


Figure No.-8

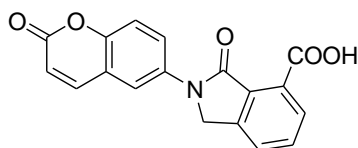


Figure No.-9

Coumarins when angularly linked with triheterocycles (Figure No.-8), have been shown to reveal good antimicrobial activity. These compounds have been tested in vitro for their anti-microbial activity against *Micrococcus aureus*, *Pseudomonas chinchori*, *Asperigillus fumigatus* and *Penicillium wortmanni* at 100, 50, and 25 $\mu\text{g ml}^{-1}$ concentrations. Coumarin linked to isoindolone (Figure No.-9) has been tested in vitro for their antimicrobial activity against gram-positive bacteria *Bacillus subtilis*, *Staphylococcus aureus*, one gram-negative bacteria, *Escherichia coli*¹⁴.

Antioxidant Activity

Coumarin-linked dihydropyrazole have been reported to affect the formation and scavenging of reactive substances derived from oxygen called as reactive oxygen species and influence processes involving free radical-mediated injury just as plant phenolics and flavonoids. There is also an evidence of naturally occurring prototypical compound (Figure No.-10), coumarin being significant in reducing tissue oedema¹⁵.

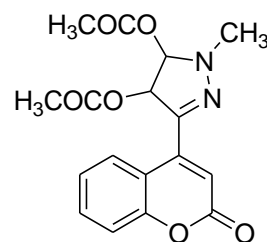


Figure No.-10

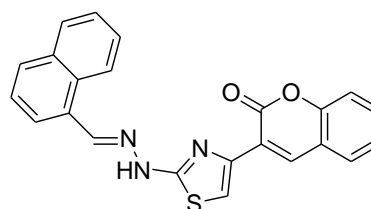


Figure No.-11

2,2-diphenyl-1-picryl-hydrazylhydrate (DPPH) free radical assay and 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) assay also indicate that almost all of the synthesized hydrazinyl thiazolyl coumarins (Figure No.-11) have significant radical scavenging activity that is comparable or better than the known antioxidants, quercetin and trolox. The coumarin linked thiazole, hydrazino, and phenolic moieties are the likely structural components contributing to free radical scavenging activity. However, the facile incorporation of the coumarin motif offers an opportunity to further optimize radical scavenging activity in the future for hit-to-lead development of new and improved synthetic antioxidants¹⁶.

Monoamine Oxidase Inhibitor Activity

Monoamine oxidase (MAO) inhibitors have been proved to be the most important drugs for the clinical management of depression and Alzheimer disease. Many studies have demonstrated potent MAO inhibitory activities of synthetic as well as natural coumarins. Coumarins linked with dihydrofuranyl (Figure No.-12) have been studied for this activity.

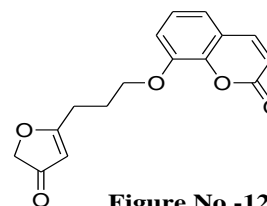


Figure No.-12

These findings have motivated the researchers to optimize pharmacological profile of this structural moiety as an important scaffold for the potential treatment of depression and Alzheimer disease. MAO inhibitory activity was found to be a function of drug concentration showing a specific IC_{50} value¹⁷.

Anti Malarial Activity

The main reason for recent dramatic increase in deaths as a result of malaria is attributed to the spread of *Plasmodium falciparum* strains resistant to the mainstay antimalarial chloroquine. To overcome the challenges of multi-drug resistance in this plasmodial species, many approaches are currently being adopted. These follow optimization of treatment with available drugs including combination therapy, developing analogs of the existing drugs and evaluation of drug resistance reversers such as chemo sensitizers as well as exploring new chemotherapeutic targets.

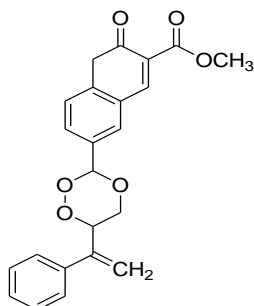


Figure No.-13

Recently the concept of hybrid antimalarials has attracted much attention for tackling the alarming problem of drug resistance, as these molecules often act on multiple therapeutic targets because of the presence of two different, covalently fused pharmacophores. Some hybrid molecules like trioxaquine and ferroquine are under clinical trials as hybrid antimalarial agents. This concept has been exploited to develop a new series of coumarin-linked trioxane (Figure No.-13) hybrids by using new methodology. These hybrids have been evaluated for their antimalarial activity against a sensitive strain of *P. falciparum* and some of which exhibited the moderate activity¹⁸.

Antifungal Activity

Macrocyclic molecules have attracted much attention because of their potential use in a variety of chemical processes, complexation ability, selective complexing agents for metal ions, and photo-induced electron transfer since its discovery by Pedersen. 4-aminomethyl coumarin crown ether derivatives have been studied for their antifungal activity. The complexation selectivity of coumarin fused crown ethers (Figure No.-14) has often been explained in terms of the size-fit concept which states that crown ether forms a more stable complex with the cation which is more suitable in size for the crown ether cavity¹⁹.

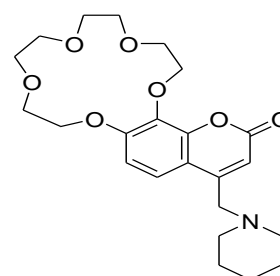


Figure No.-14

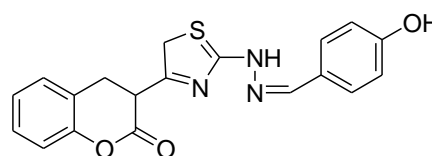


Figure No.-15

Also, antifungal activity of coumarins fused with thiazoles (Figure No.15) has been assessed against a fungal strain of *Candida albicans*. The minimum inhibition concentration (MIC) of the compounds was determined by broth micro-dilution method²⁰.

Anti-Inflammatory Activity

Coumarinyl ethers such as coumarin-linked to benzofuran (Figure No.-16) by ether linkages have also been investigated for their anti-inflammatory activity. This activity was studied using carrageenan-induced paw edema in rats. The inhibition of edema was evaluated by the comparison of paw volume measured with plethysmometer coupled to a peristaltic pump, immediately before and 3 hrs after the injection of carrageenan²¹.

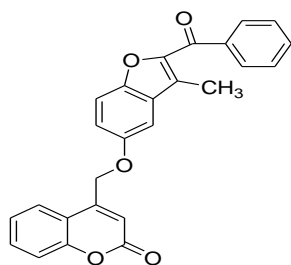


Figure No.-16

Studies have shown that coumarin nucleus can incorporate the styryl carbonyl moiety into a rigid framework as depicted in (Figure No.-17). It has been reported that styryl carbonyl derivatives possess appreciable anti-inflammatory activity. Moreover, coumarin and related derivatives have been used as inhibitors of lipoxygenase (LOX) and cyclooxygenase (COX) in arachidonic acid pathway²².

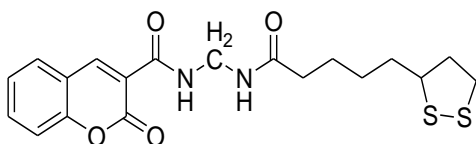


Figure No.-17

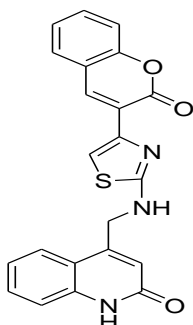


Figure No. 18

Inhibition of formalin-induced paw oedema in rats is one of the most acceptable test procedures to evaluate anti-inflammatory agents. This activity has been found to be exhibited by the coumarin-linked triheterocyclic thiazoles (Figure No.-18) and may be attributed to the inhibition of cyclo-oxygenase enzyme, which plays a vital role in inflammation process. The standard used for the present anti-inflammatory activity testing is phenyl butazone. The test compounds were found to be slow acting anti-inflammatory agents²³.

Antihepatitis Activity

Inhibitory activity against hepatitis virus RNA polymerase can be shown by coumarin-linked benzoxazole-5-carboxylic acids (Figure No.-19). Recently, it has been found that the benzoxazole moiety conjugated with a coumarin moiety with a methylene thio linker exhibited potent inhibitory effects on hepatitis virus.

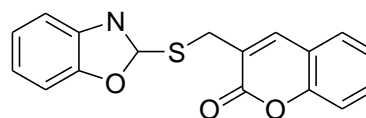


Figure No.-19

The thio methylene (-SCH₂-) linker has been used to connect a heterobicycle with various aromatic rings by synthetic methods to form hybrid compounds for antiviral bioassays. The coumarin can be linked with heterobicycles like benzimidazole, imidazopyridine, purine, benzoxazole, and benzothiazole to evaluate the activity²⁴.

Platelet Aggregation Inhibitor Activity

In vitro evaluation of coumarin-linked piperazine moiety for inhibitory activity on human platelet aggregation induced in platelet-rich plasma by adenosine diphosphate (ADP), collagen or the calcium ionophore. These compounds (Figure No.-20) show notably high activity towards all the platelet aggregation inducers used, and the most active one, 8-methyl-4-(1-piperazinyl)-7-(3-pyridylmethoxy)coumarin, proved to be a potent in vitro antiplatelet agent.

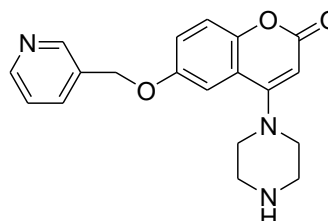


Figure No.-20

The screening of this compound can be carried out by conducting test in which human blood from healthy volunteers was added to a

130 mM trisodium citrate aqueous solution, then centrifuged to give platelet-rich plasma (PRP) which was diluted with platelet-poor plasma (PPP) and preincubated at 37°C with drug solution before the addition of the platelet aggregation agent. PRP aggregation was induced by inducers mentioned. The compound 8-methyl-4-(1-piperazinyl)-7-(3-pyridylmethoxy)-coumarin proved to be a potent in vitro inhibitor of human platelet aggregation towards all the platelet aggregation inducers used, suggesting proper heteroarylmethoxy groups as novel useful 7-alkoxy substituents²⁵.

TNF- α Inhibitory Activity

Tumor necrosis factor α (TNF- α) is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. It is a key cytokine in the inflammation cascade, causing the production and/or release of other cytokines and agents.

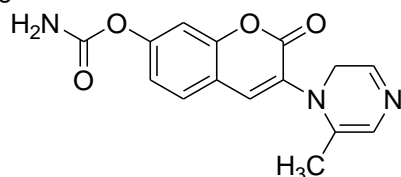


Figure No.-21

A coumarin-linked with piperidinylmethyl (Figure NO.-21), dimethyl-carbamic acid 3-benzyl-4-methyl-2-oxo-2H-chromen-7-yl ester has been found to be a moderate inhibitor of TNF- α . Representative compounds that possess excellent in vitro TNF- α inhibitory activity were tested in vivo by subcutaneous (sc) administration. TNF- α inhibitory activity was assessed by in vivo inhibition of serum TNF-production in the rats²⁶.

BASE-1 Inhibitory Activity

Alzheimer's disease (AD) is the biggest unmet medical need in neurology, with >12 million AD sufferers worldwide. Actually the 'amyloid cascade hypothesis' claims that amyloid b-42 (Ab42), a proteolytic derivative of the large transmembrane protein, plays an early and crucial role in all cases of AD. Ab42 forms aggregates that are thought to initiate a

pathogenic cascade that ultimately leads to neuronal loss and dementia.

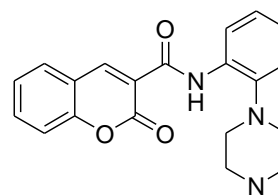


Figure No.-22

Two key enzymes β -secretase (BACE-1 and 2) and γ -secretase have been identified as ideal targets for therapeutic intervention. Coumarin-linked with substituted phenyl-piperazine (Figure No.22) have good β -secretase inhibitory activity like new nonpeptidomimetic derivatives which incorporate in their structure various heterocyclic moieties: coumarin, quinoline or chromene. These moieties have been linked through an amide bond to form phenyl-piperazine scaffold which have shown modified BACE inhibitory properties²⁷.

Lipid Lowering Activity

Atherosclerotic cardiovascular disease is the leading cause of death in developed countries. Epidemiological studies have identified a variety of independent risk factors that contribute to coronary artery disease (CAD); most notable are high low density lipoproteins (LDL)-cholesterol, triglyceride (TG) and low high density lipoproteins (HDL)-cholesterol.

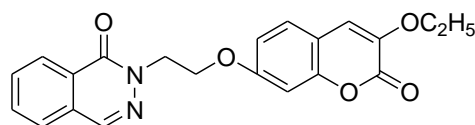


Figure No.-23

Current therapies mostly focus on lowering LDL-cholesterol and statins used for this purpose are very effective and also safe. Yet they are not effective in lowering TG and HDL. Plasma triglyceride lowering activity of coumarin-linked to heterocycle was determined. The compound (Figure No.-23) has shown maximum (45%) plasma triglycerides lowering activity and exhibits

significant reduction in TG at 3 mg/kg/day dose²⁸.

Casein Kinase-2 Inhibitory Activity

Casein kinase-2 (CK2) is probably the most pleiotropic protein kinase known, with more than 300 protein substrates already recognized, a feature which might, at least partly, account for its lack of strict control over catalytic activity. Its two catalytic subunits are in fact constitutively active either with or without the regulatory-subunits, which appear to play a role in targeting and substrate recruiting, rather than controlling catalytic activity.

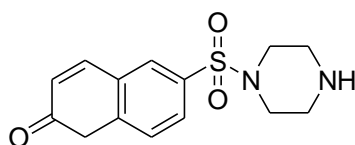


Figure No. 24

Although constitutively active CK2 is ubiquitous, essential, and implicated in a wide variety of important cell functions, evidence has been accumulating that its catalytic subunits may behave as oncogenes, consistent with the observation that they display an anti-apoptotic effect in prostate cancer cell lines. The most promising inhibitor, coumarin linked piperazine (Figure No.-24) has been also crystallized in complex with CK2, and the experimental binding mode has been used to derive a linear interaction energy (LIE) model. In the last few years, intensive screening program has been performed, using both conventional and *in silico* approaches, with the aim of discovering novel potent and selective CK2 inhibitors²⁹.

Cytochrome P450 Enzyme Inhibitory Activity

Cytochrome P450 (CYP) is a large family of hemoproteins present in most forms of life (plants, bacteria, and mammals). They are concerned with metabolism in vital processes and many of them with the ability to activate carcinogens have been implicated as risk factors for cancers.

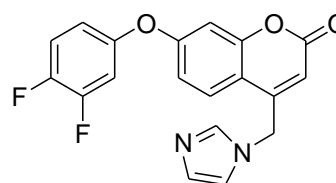


Figure No.-25

Coumarin-linked imidazoles (Figure No.-25) have been proved to be most promising compounds as CYP450 inhibitors. It has been shown to display stronger CYP19 inhibitory activity (IC₅₀ = 47 nM) than the standard drug fadrozole (IC₅₀=52 nM) with excellent selectivity over CYP11B1 and CYP11B2³⁰.

Conclusion

Coumarins are the least complex heterocyclic structures having lowest toxicities and can be obtained easily from nature as well as synthesized in laboratory. In the present review, emphasis is laid on search of coumarins linked with different heterocycles with respect to their diverse array of biological activities. Activities like antioxidant, anticancer, antimalarial, antimicrobial, enzyme inhibitory, anti-inflammatory of current interest are mentioned here. Coumarin-linked 3, 4-dihydropyrazoles exhibiting anticancer activity have been discussed. Anti inflammatory activity has been shown to be present in coumarin-based carbamates which have inhibitory activity for TNF- α making it pro inflammatory agent. Some coumarin-linked piperazines have also been studied for inhibitory activity on human platelet aggregation and also as potent and selective CK2 and BASE-1 inhibitors. Also, coumarin-linked benzoxazole-5-carboxylic acids have been found to endow potent inhibitory effects on hepatitis virus. Thus, it can be surmised that coumarins can serve as a good lead to treat several disorders such as AD, cancer, malaria, fungal infections, hepatitis, atherosclerosis, hyperlipidemia, some of which cannot be completely cured. Chemical modifications on this heterocycle could enhance the existing biological activities and develop promising new drug candidates in future.

Acknowledgement

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