Review Article

A Meticulous Review on Coumarin Derivatives as a Marvel Medication for Thousands of Ailments

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ABSTRACT

Coumarin derivatives have progressively enticed medicinal chemists because of their potential role in preventing and treating ailments. They epitomize a key motif nucleus in heterocyclic chemistry and a privileged structure in medicinal chemistry because of its extensive-range pharmacological activity. Regardless of the advancement in medicine over the past century, cancer is still remain the prominent source of death in the world and it makes indispensible needs to synthesize the compounds with coumarin as the core nucleus. Synthesis of various coumarin derivatives and evaluation of their pharmacological effects can perceive a solution to certain enigmatic demands in health sector. This review article is fixated on different synthetic routes of coumarin nucleus containing compounds. The review article also highlights different biological activities such as anticancer, antibacterial, anti- inflammatory, anti-hyperlipidemic and enzyme inhibition activities.

Keywords: Coumarins, Pyridine, Indole, Alzheimer'sdisease, Osteoporosis, Hypo-lipidemic agents, Anti- bacterial, Anti-inflammatory, Periodontal disease.

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INTRODUCTION

Physico-chemical features along with its versatile and stress-free synthetic strategies. They are phytochemicals that holds numerous biological and pharmacological properties like anti- cancer[1],anti-viral[2],antibacterial[3],anti-coagulant[4],anti-thrombotic[5],anti-inflammatory[6]etc.

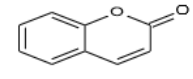
Coumarins naturally occur in many plants, primarily in angiosperm, including Umbelliferae, Rutaceae, Leguminosae, Compositae, and Thymelaeceae. For instance, linear furanocoumarins are found primarily in the Umbelliferae, Moraceae, Rutaceae and Leguminosae families.Isolation, identification and applications of these compounds are useful in scientific, technical and pharmaceutical industrial growth.[7]

Coumarin are colorless crystalline solid with a sweet odour analogous to the scent of vanilla and a bitter taste. They are also known as 1,2-benzopyrone or o-hydroxycinnamic acid-8-lactone, which constitute a vivacious and large class of oxygen heterocycles, often found as plant secondary metabolites in the plant kingdom. They have low molecular weight, simple structure, high bioavailability, high solubility in most of the organic solvents and low toxicity, which, together with their polygonal biological activities, ensure them a prominent role as lead compounds in drug research and development[8,9].

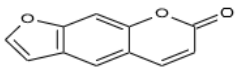
Coumarins comprises of a benzene molecule with two adjacent hydrogen atoms replaced by a lactone-like chain forming a second six-membered heterocycle that parts two carbons with the benzenering. It can be placed in the benzopyrone chemical class and considered as a lactone. Many of the coumarins are oxygenated at position C-7, which become 7-hydroxycoumarin, generally known as umbelliferone, often regarded as the biogenetic predecessor of more complex coumarins. Because of their varied pharmacological properties, coumarins have engrossed increasing research interest in recent years[10].

Types of Coumarin

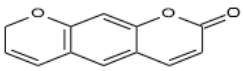
The coumarins can be coarsely categorized as follows: simple coumarins, furano-coumarins, pyrano-coumarins, dicoumarins, and others like phenyl-coumarins[11].



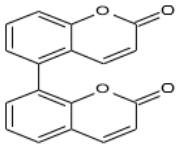
simplecoumarins



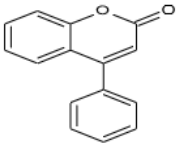
furanocoumarins



pyranocoumarins

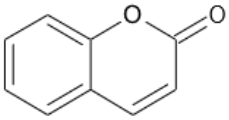


dicoumarins



phenylcoumarin

Chemistry of Coumarins



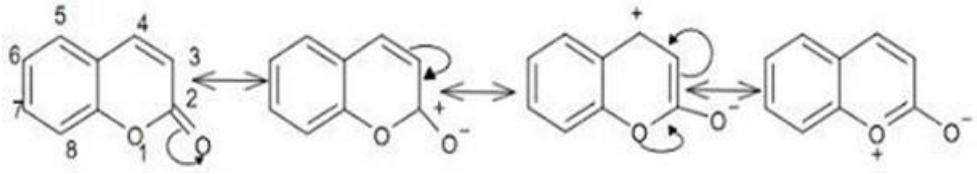
- Coumarin is an aromatic compound that possess a bicyclic structurewith lactone carbonyl groups.
- The existence of an electronegative atom is effective for hydrogen bond formation and for solubility to some level .
- Aromatic ring is accountable for having hydrophobicity.
- The coumarin ring system, which embraces a benzenoid part and the heterocyclic - pyrone part, can give several derivatives with substituents in either component of the ring system.
- Several halogen, nitro, amino, and sulfonic acid derivatives have been obtained[12].
- The oxygen atom of the carbonyl group accepts electron density both by the enone chromophore from the internal resonance of the lactone group .
- Nucleophilic addition takes place typically at the carbon atom of the carbonyl group causing ring opening.
- Similarly, electrophilic reagents encircling an element capable of making a strong bond to oxygen (oxophiles) bind to the oxygen atom of the carbonyl group.
- The other less oxophilic electrophiles provide C-6 substituted Coumarins, however it is undefined whether the substrate for these reactions is the free coumarin or a cation made up by protonation or bonded via a Lewis acid at the carbonyl oxygen[13].
- Benzene nucleus of the coumarin ring system is not so reactive as that of a simple benzene derivative[14].
- Pyrone ring of coumarin nucleus offers radical scavenging ability, lipid peroxidation activity and increase inhibitory effect on enzymes.
- The double bond between carbon atoms 3 and 4 in the coumarin nucleus is highly reactive; it adds bromine , hydrogen cyanide, and sodium bisulfite with countless facility.
- The preliminary action of alkali on a coumarin opens the pyrone ring, with the formation of a salt of coumarinic acid which on acidification restores the original coumarin.
- These coumarinic or m-o-hydroxycinnamic acids are unstable, thus there are a few exclusions of formation of moderately stable coumarinic acids, such as those derived from 8-nitrocoumarin[15], 3-acetyl-4,5,7-trimethylcoumarin-6,8-dicarboxylic ester[16] , 6-nitro-αβ-l, 2-naphthopyrone, and 6-nitro-αβ-l, 2-naphthopyrone-4-acetic acid [17]and a few others.
- In all these cases, the coumarinic acid is stabilized by the entrance of acidic groups, the effect more ostensible when the acidic radical is in position 8 of the coumarin ring system.
- The ingress of alkyl groups, on the other hand, is found to produce the opposite effect.
- Some αβ -1,2-naphthopyrone derivatives which give stable coumarinic acids, notwithstanding the presence of alkyl groups and the absence of any acidic substituent in the coumarin ring.
- If the action of alkali is extended under suitable conditions, the stable coumaric acid is formed [18,19]. Sometimes the action of alkali results in the complete exclusion of thepyrone ring, leading to the formation of a phenol [20,21] or a styrene derivative[22].
- Thus coumarins on hydrolysis produce coumarinic acid. Nevertheless some exceptions are also seen.
- 7-hydroxy-4,5-dimethylcoumarin[23] and 4-isopropyl-l,2-a-naphthopyrone[24] have been found to form orcacetophenone and 1-hydroxy-2- naphthoic acid, correspondingly, on hydrolysis.
- Hydrolyzing the coumarin and averting the closure of the lactone ring by subsequent methylation by dimethyl

sulfate will give an o-methoxycinnamic acid derivative.

- When a glacial acetic acid solution of bromine is added to a solution of coumarin,it provides soluble 3-bromo derivative.
- The coumarin ring system, which involves a benzenoid part and the heterocyclic - pyrone part, can give numerous derivatives with substituents in either component ofthe ring system.
- Several halogen, nitro, amino, and sulfonic acid derivatives have been achieved. There are, however, many complications in the preparation of alcohols, aldehydes, ketones, and carboxylic acids of the coumarin chain as the benzene nucleus of the coumarin ring system is not so reactive as that of a simple benzene derivative.

Molecular Geometry Figures For Coumarin

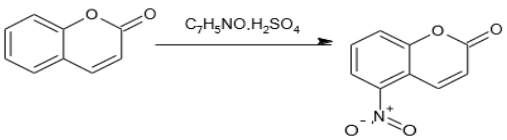
The canonical forms of coumarin are given below:



Chemical Reactivity of CoumarinNitration

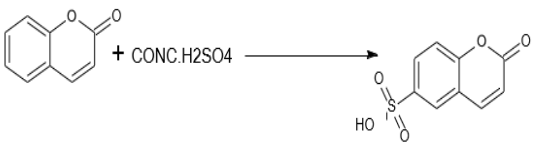
Nitration is the class of chemical process that introduces the nitro group into an organic chemical compound.coumarin was found to repel strongly the introduction of more than one nitro group, but this resistance weakens very appreciably with the introduction of alkyl groups in the molecule. when 8-nitrocoumarin is nitrated, the second nitro group goes to the 6-position, and that when 6-nitrocoumarin is nitrated, 3,6-dinitrocoumarin is attained.

The presence of a nitro group in the 3-position is exposed by the reaction with alkali. When the substance is boiled with alkali, preferably concentrated ammonia solution, it dissolves and on subsequent acidification forms the corresponding salicylaldehyde derivative. This bizarrely easy rupture of the lactone ring is found to be a property of all 3-nitrocoumarins. The strain of obtaining higher nitration products of coumarin is due to the general acidity conferred on the molecule by the lactone ring; the introduction of methyl groups progressively weakens this acidity and makes the molecule more vulnerable to the action of nitric acid[25].



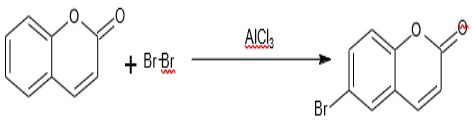
Sulfonation

Aromatic sulfonation is an organic reaction in which a hydrogen atom on an arene isreplaced by a sulfonic acid functional group in an electrophilic aromatic substitution.



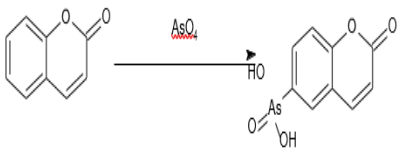
Halogenation

Halogenation is a reaction that occurs when one or more halogens are added to a substance.In the halogenation of coumarins, the halogen atom enters the pyrone ring firstly in the 3-position and then enters the benzene nucleus. The bromination of 4- methylcoumarin forms the 3-bromo-4-methylcoumarin. By the action of bromine in carbon disulfide solution in a sealed tube, 3,6-dibromo-4-methylcoumarin was attained, and when the reaction was carried out under pressure 3,6,8-tribromo-4-methylcoumarin was formed[26,27].,Bromination is not restricted to the pyrone ring alone but proceeds to the benzene ring as well In the case of hydroxycoumarins [28]. This trouble is overcome by protecting the hydroxyl group by acetylation ,methylation, or carbethoxylation[29] . The presence of an acyl group in the benzene ring in the position ortho to the hydroxyl group appears to have a similar effect. For example, the bromination of 6-acetyl-5-hydroxy-4- methylcoumarin produces the monobromo derivative mixed with the dibromo derivative. To get a good yield of the 3-bromo derivative only, the bromination of the acetyl derivative was performed, the deacetylation taking place during the reaction. The halogenation of 8- methoxycoumarin, in contrast to the typical rule of halogen entering the pyrone ring first, halogenation proceeds with substitution in the benzene ring[30].



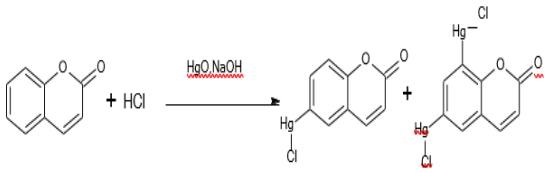
Arsonation

Arsonate is the arsenic oxoanion formed by loss of a single proton from arsonic acid. It is a conjugate base of an arsonic acid.Addition of an arsonate group to a compound is meant by arsonation reactions[14].



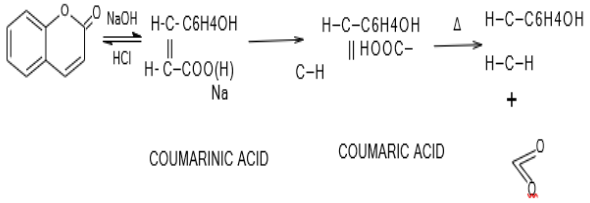
Mercuration

Introduction of mercury into an organic compound is termed as mercuration. Usual reagents effectively employed in the mercuration of organic compounds botched to mercurate coumarin in aqueous, alcoholic, or acetic acid solution. When, the lactone ring was open and the masked hydroxyl group brought to prominence, mercuration readily took place with mercuric oxide or with mercuric acetate. By boiling the dilute solution of coumarin in alkali with yellow mercuric oxide, monochloro- and dichloro-mercuricoumarins were attained. If the 6-position was occupied, no mercury compound was formed but geometrical inversion to o-coumaric acid derivatives occured. The coumarins from -naphthol did not undertake mercuration. Mercuric acetate in methyl alcoholic solution reacts with the double bond of the coumarin and further mercurates the benzene ring if the 6- and 8- positions are free, forming 3,6,8-triacetoxymercuro-4-methoxymelilotic anhydride. Mercuric chloride adds also to the double bond of coumarin and of 7-methylcoumarin[31].



Geometrical Inversions in Acids Derived From Coumarins

Coumarins, being the lactones of o-hydroxycinnamic acids treatment with alkali produce the salts of the corresponding coumarinic acids, which on acidification instantly revert to the coumarins; therefore the coumarinic acids are cis compounds. They are unable of free existence, though some stable cis acids are known. If the action of alkali is prolonged under suitable conditions, cis-to-trans inversion occurs.

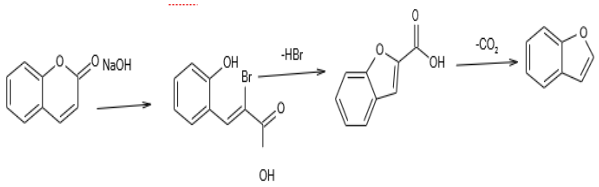


In this reaction, the primary formation of the alkali salt of coumarinic acid takes place, which then undertakes inversion under the influence of the reagent. This change is significantly facilitated by the addition of some reagent which acts as an addendum at the double bondof the pyrone ring.

The trans coumaric acids are capable of free existence and on heating they decompose into carbon dioxide and hydroxystyrenes[32,33]. They undertake inversion to the cis forms under the influence of sunlight and are then readily changed into coumarins, the esters inverting even more readily than the free acids. Amid other methods of producing the trans-to-cis change, concentrated sulfuric acid at 100°C has been sometimes used but it was found that this process gives only a poor yield; a saturated solution of hydrogen chloride in alcohol was higher to sulfuric acid in some cases. They have exposed that a satisfactory method of trans-to-cis inversion is to boil the trans isomer with mercuric chloride solution.

Fittig and Ebert's Reaction

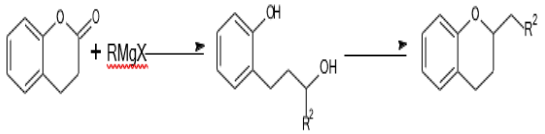
3-Halogenated coumarins are converted into the resultant coumarilic acids by treatment with alkali. The pyrone ring opens and misses a molecule of halogen acid, with the successive formation of coumarilic acid, which on heating breaks down into carbon dioxide and produce coumarones .This known as Fittig and Ebert's reaction[14].



This method, which works sound with simple coumarins, is not directly applicable to hydroxycoumarins, as bromination of these coumarins is not restricted to the pyrone ring but proceeds to the benzene ring.Hence, bromo-free coumarones are not obtained. This difficulty is stunned by protecting the hydroxyl group and carrying out the bromination to get the monobromo derivative. Thus, coumarone is a degradation product of coumarin in which the five membered ring is attained from the pyrone ring. Several coumarones have been synthesized from coumarins in this way. Coumarones are employed in industry for themanufacture of coumarone resins.

Action On Grignard Reagen

When Grignard reagents react with dihydrocoumarins, carbinols are acquired which on ring closure give 2,2-dialkylchromans[34].

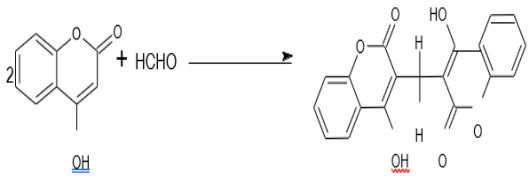


The action of Grignard reagents on coumarins, however, is much more complex because of the occurrence of the conjugated double bonds, and a variety of products is obtained based on the conditions of the reaction. The interaction of coumarin and Grignard reagents under cautiously specified conditions leads to the synthesis of monoalkyl pyrylium salts[35]. A meticulous investigation of 3- and 4- substituted coumarins led to the judgement that the production of either Δ2- or Δ3-chromene is influenced merely by the position of the substituent in the pyran ring. When dilute solutions are used with 3-methyl-, 3-phenyl-, and 3-methoxycoumarins, the reaction continues

smoothly and provides sufficient yields of the resultant 2-phenylbenzopyrylium salts, but that when more concentrated solutions are hired,Δ3 chromenes are obtained.

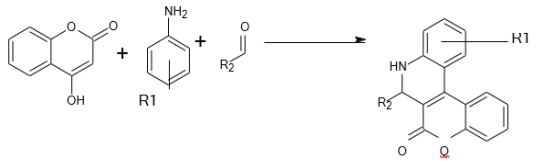
Condensation Reaction

Two molecular equivalents of 4-hydroxycoumarin condense with formaldehyde, giving 3,3 '- methylenebis (4-hydroxycoumarin), which is the causative agent of the hemorrhagic sweet clover disease of cattle. The reaction has been stretched to other aliphatic and aromatic aldehydes, the products attained have been dehydrated to form the substituted 1,4-pyran derivatives, 3,3'-alkylidene- or 3,3'-arylidene-4,4'-epoxydicoumarins, by means of acetic anhydride in pyridine[14].



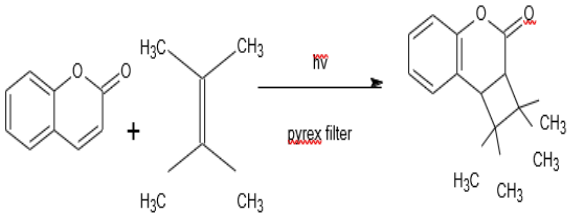
Skraup Doebner-Von-Miller Reaction

3-Hydroxycoumarin is one of the most broadly reconnoitred and readily available substratesin organic synthesis. 4-hydroxycoumarin along with aromatic amines as a 1,3-binucleophile to form a CFDQ moiety by reaction with aldehydes[36].



Photochemical Cycloaddition Reaction

A solution of coumarin ,tetremethylethylene, benzophenone and dioxane was Irradiated through pyrex glass with a 500-watt mercury arc lamp leading to the formation of the coumarin-tetramethylethylene 1:1 adduct[37].



Properties

By the studies on the chemical reactivity's and the spectral features of coumarin we canencapsulate their properties as below.

- The absorption spectra of several coumarin derivatives in 0.001 M alcoholic solution for wave numbers (-1 in centimeters) from 2000 to 5000 displays two absorption maxima in this region, at 3200 A^0. and 3600 A^0. When hydroxyl groups are hosted, the substance shows only one absorption maximum.
- The fluorescence and absorption spectra of 7-hydroxycoumarin-3-carboxylic acid andmethyl 7-hydroxy- and 7,8-dihydroxy-coumarin-3-acetates have been inspected and the fluorescence maxima are at 4596, 4727, and 4679 A. and the absorption maxima are at 3300, 4314, and 4517 A^0, correspondingly.
- The Raman spectra of coumarin in the solid state as well as in solution in different solvents with reference to (1) the C=C and {2) the C=0 frequencies. Of the three frequencies belonging to (1), which are honestly constant throughout, the two lower ones signify the aromatic double bonds of the benzene ring and the third represents the ethylene double bond of the pyrone ring. The C=0 frequency is noticeably low in the solid state as well as in the solutions with certain polar solvents, possibly due to the waning of the C=0 bond by the formation of hydrogen bonds through coordination.
- The dipole moment of coumarin at 20°C. (4.51 X 10^{-19}e.s.u.) has been measured and specifies a state of resonance between the normal and excited states.
- The occurrence of carbethoxyl, carbonyl, or acetyl in the 3-position of 7-hydroxy- and 7-methoxy-coumarins boosts the fluorescent property of the compounds to such an extent that they exhibit bright fluorescence even in neutral alcoholic solutions, while the same groups in the 4-position yield no such effect. 7- Hydroxycoumarins produce bright fluorescence in neutral or alkaline media, but the intensity is significantly diminished in acid media. The fluorescence of 7- hydroxycoumarins is blue, whereas their methoxy derivatives display fluorescence more on the violet side. 3-Benzoyl compounds are yellow in the solid state as well as in solution and unveil no visible fluorescence under any conditions.
- 5-Hydroxycoumarins dissolve in alkali giving a deep yellow non-fluorescent color[14].

Synthetic Methodology

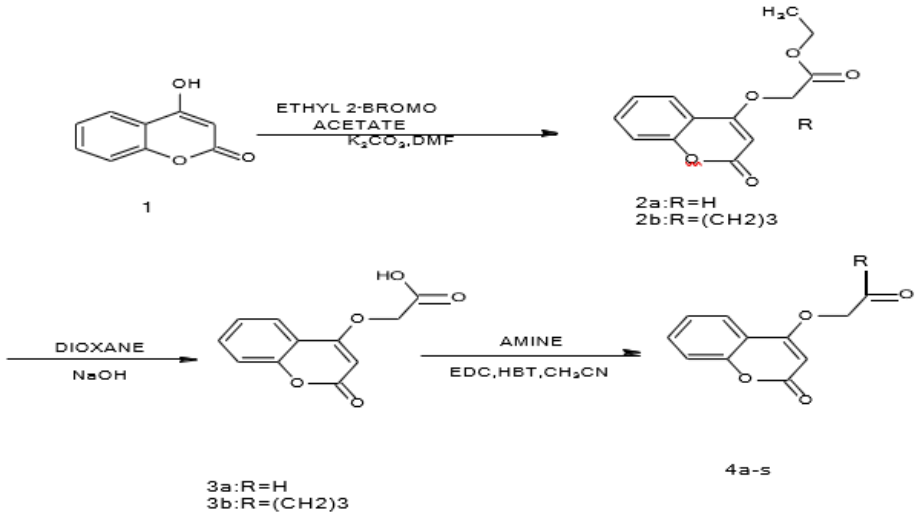
The different types of schematic representations were used to synthesis thederivatives of coumarins[38,39,40,41].

Scheme1

Synthesis of 4-Substituted Coumarins as Novel Acetyl Choline EsteraseInhibitors

The synthetic route to target compounds starts from commercially available 4-hydroxy coumarin.O-alkylation of 4-hydroxy coumarin with ethyl 2-bromoacetate along with potassium carbonate in DMF produce ester derivatives.These esters were hydrolysed with aqueous sodium hydroxide solution in dioxane to yield the corresponding acids .The condensation of the carboxylic acids with appropriate amines were attempted by various reagents and conditions such as carbonyldiimidazole (CDI)

and dicyclohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N[1]-ethylcarbodiimide hydrochloride (EDC) and hydroxybenzotriazole (HBT) in different solvents, but the best result was obtained by EDC/HBT in acetonitrile[38].



The resulted compounds were screened for In vitro inhibition studies of choline-esterases using Electrophorus electricus acetylcholinesterase (eelAChE) and horse serum butyryl cholinesterase (eqBChE) by modified Ellman's method and also for Ferric reducing/antioxidant power (FRAP) using FRAP assay.

Scheme2

Synthesis of new coumarin-pyridine hybrids as promising anti-osteoporoptcagents

The Duff reaction on ortho-substituted phenols along with hexamethylenetetraamine (HMTA) and TFA at 120°C generates aromatic di-carbaldehydes. These di-carbaldehyde intermediates were subjected to Knoevenagel-type reaction with different active methylene compounds form coumarinic compounds. Further,these coumarinic aldehyde compounds were used for Hantzsch di-hydropyridine synthesis via a multi-component reaction, using coumarinic aldehydes, active methylene compounds and ammonium acetate (nitrogen donor) . For symmetrical Hantzsch di-hydropyrimidines (5a-c), two equivalents of ethyl/methyl acetoacetate were employed while for un-symmetrical Hantzsch polyhydroquinolines (5d-m), uniequivalent of ethyl/methyl acetoacetate and different 1,3-cyclohexadiones were taken. Finally, aromatisation by means of the 2,3-Dichloro-5,6- dicyano-1,4-benzoquinone (DDQ) in the presence of tetrahydrofuran (THF) as a solvent at room temperature provides the preferred coumarin pyridine hybrids (6a-m).All the synthesized compounds were characterized using 1 H NMR, 13C NMR, IR spectroscopy and ES[39].

a:ethyl/methylacetoacetate, different 1,3cyclohexadiones, NH4OAc,AcOH, EtOH,reflux, 5h.b:DDQ, THF, room temperature, 1h.

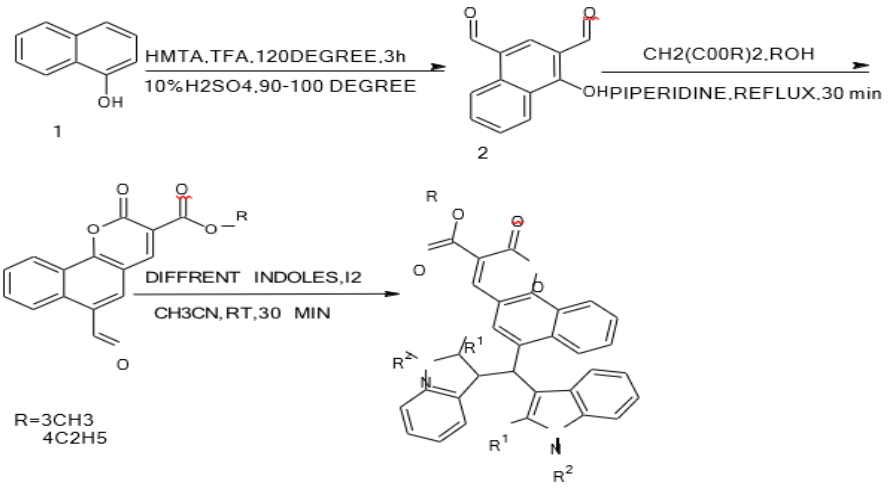
These compounds are subjected to Alkaline phosphatase assay , Mineralized nodule formation assay and Cytotoxicity assay.

Scheme 3

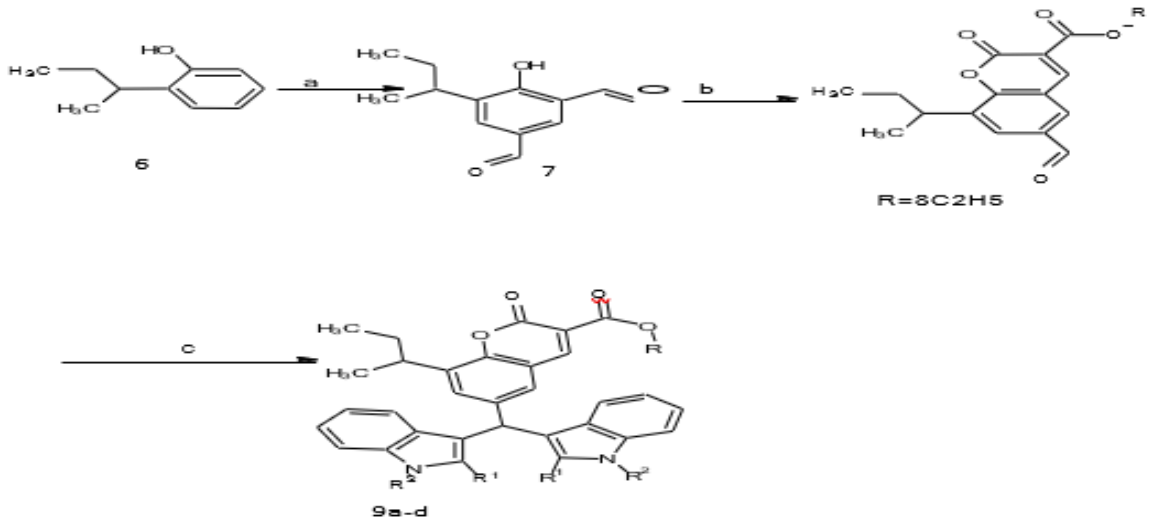
Synthesis of novel coumarin-bisindole hybrids as anti-hyperlipidemic agents

The Duff reaction on naphthalen-1-ol gave a compound, which was subjected to Knoevenagel type reaction with appropriate active methylene compounds,resulting in the production of coumarinic compounds. Besides, an efficient electrophilic substitution of suitable indoles with these coumarin aldehydes derivatives using iodine in acetonitrile supplied coumarin bisindole hybrids (Step 1). Correspondingly, another series of coumarin bisindole hybrids were synthesised using 2-sec-butylphenol as starting compound which wassubjected to same series of above-mentioned transformations that results in the formation of another set of coumarin bisindole hybrids (Step 2). The structures of the compounds were authenticated by 1 H NMR, 13C NMR, mass spectrometry, and IR spectroscopy. The purity of these compounds was established by TLC and spectral analysis[40].

Step 1



Step 2



All the synthesized compounds are screened for anti-dyslipidemic activity of coumarin bisindole hybrids in the high fat diet (HFD) fed dyslipidemic hamster model, which is reported as an ideal in vivo model for gauging anti-dyslipidemic drugs.

Scheme 4

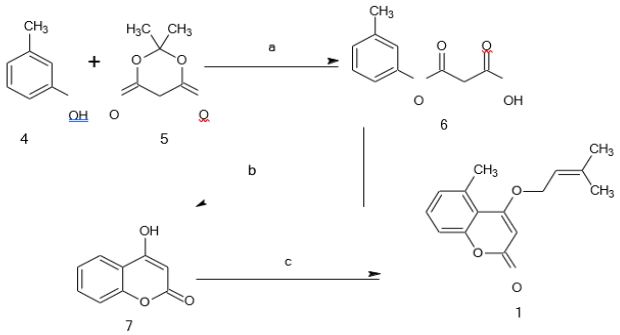
Synthesis of novel coumarin hybrids as anti-bacterial and anti- inflammatory agents

The three O-prenylcoumarins have been manufactured using renowned schemes leading to the formation of chromen-2-one nucleus. In general, compound (1) has been synthesized from commercially available m-cresol (4) as starting compound and Meldrum's acid (5). They react under solvent-free conditions for 24 h at 120 °C, yielding the monoester (6), which was cyclised in the presence of a catalytic amount of conc. H2SO4 at 120 °C for 5 h to provide the coumarin (7). The synthesis of (1) was then completed by alkylation of the OH group using 3,3-dimethylallyl bromide in acetone (80 °C for 1 h) in the presence of K2CO3 (base) (Step 1). Compound (2) has

been synthesised by a two-step procedure from commercially available 2-methoxyhydroquinone (8) and 3,3-diethoxyethyl propionate (9) that react in the presence of H_3PO4 (85% for 2 h at 100 ℃) followed by crystallization to form pure 6-hydroxy-7-methoxycoumarin (10). This latter was then prenylated by the usual way (Step 2). Compound (3) has been synthesized from commercially available 3-methoxycatechol (11) that has been subjected to a Pechmann reaction with propiolic acid

(12) in the presence of catalytic amounts of conc. H2SO4 at 120 ℃. The so obtained 8- hydroxy-7-methoxycoumarin (13) was then prenylated in the usual way as described above (Step 3)[41].

Step 1

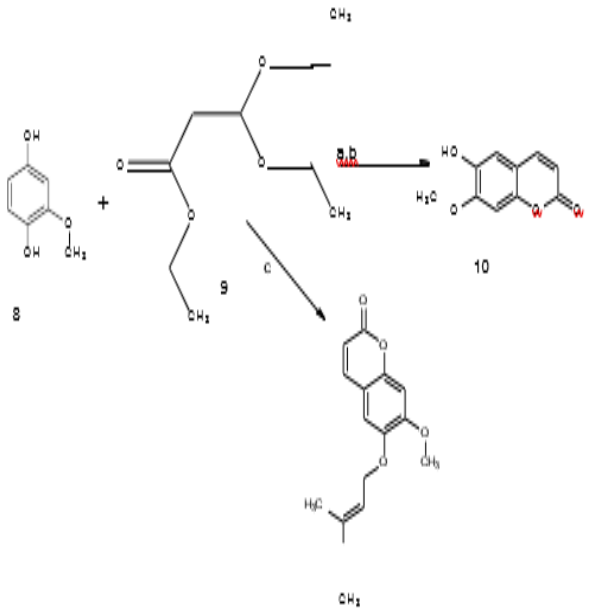


a:120 ℃,24h.

b:conc.H2SO4

c:3,3-dimethylallyl bromide,acetone,K2CO3,80℃,1h.

Step 2

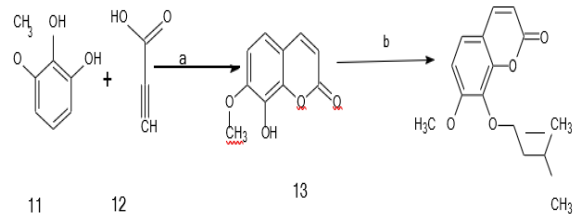


a:H3PO4,100℃,2h.

b:crystallisation.

c: 3,3-dimethylallyl bromide,acetone,K2CO3,80℃,1h

Step 3



a:conc.H2SO4,120℃,2h.

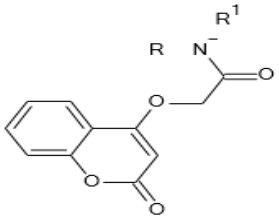
b: 3,3-dimethylallyl bromide, acetone,K2CO3,80℃,1h

The synthesized compounds are screened for Broth microdilution assay for determination of minimal inhibitory concentrations and minimal bactericidal concentrations, Membrane permeabilization assay and Determination of NF-kB activation.

Biological Activities 1.Anti-Alzheimer's Activity

Alzheimer's disease is a prolonged and progressive neurodegenerative disorder of the central nervous system, affiliated with memory loss, cognitive impairment and debility in language[42]. Neuro-pathological substantiation shown that the decrease levels of acetylcholine, b-amyloid senile plaques and neurofibrillary tangles formation within the brain of suffering individuals play a decisive role in the pathogenesis of Alzheimer's disease[4]. Since acetylcholinesterase (AChE) plays a pro-aggregating role in hastening b-amyloid peptide aggregation and deposition into the fibrils [5], thus inhibition of AChE is still the most successful therapeutic strategy for the symptomatic treatment of Alzheimer's disease and its progression[43] .

Abbas Shafiee et.al.,reported the synthesis of 4-(2-Oxo-2-(4-phenylpiperazin-1-yl)ethoxy)- 2H-chromen2-one substituted compounds. Ferric reducing/antioxidant power (FRAP) and In vitro inhibition studies of cholinesterases were measured for synthesized compounds.Most of the componds shown good ANTI-ALZHEIMER'S ACTIVITY.

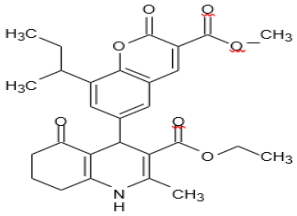


Anti-Osteoporotic Activity

Osteoporosis is a progressive skeletal disorder, due to the uneven coupling between osteoclast mediated bone resorption and osteoblast mediated bone formation[44]. It is a widespread ailment in the geriatric population and effects up to 50% of females[45]. It is characterized by diminution in bone mineral density and consequent increase in bone fragility, causing great risk of fractures[46].

Coumarins are an important class of plant secondary metabolites which owns varied range of biological activities[47] .Furthermore bone anabolic effects of coumarin was also reported[48]. Current report recommends that the pyridine ring comprising compounds may curb anti-osteoporotic activity. Furthermore, substituted thieno-pyridine derivatives were reported as as bone anabolic agents. This urged to create new coumarin containing pyridine hybrids as potential anti-osteoporotic agents.

Koneni V et.al., reported the synthesis of diethyl 4-(3-(methoxycarbonyl)-8-methyl-2-oxo- 2H-chromen-6-yl)-2,6- dimethylpyridine-3,5-dicarboxylate derivatives. Cytotoxicity assay, Mineralized nodule formation assay, Alkaline phosphatase assay was performed for the synthesized compounds and shown potent ANTI-OSTEOPOROTIC ACTIVITY.

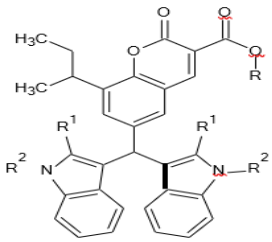


Anti-Hyperlipidemic Activity

Cholesterol plays a captain role in the association of membranes and performs other important biological functions in human heart health. Though, when plasma cholesterol exceeds the level required for these functions, it results in aathe progress of athero-sclerotic cardiovascular disease such as coronary heart disease and stroke.[49]Indole and their derivatives are recognized as antihypertensive, antitubercular, anticancer , antiviral, Alzheimer disease & antioxidant properties, and free radical induced lipid peroxidation. Additionally, fluvastatin, which is a synthetic member of the statin class contains indole moiety in its molecular structure. Countless coumarins and their derivatives endured widespread studies aimed to judge their potential beneficial effects on human health[3],such

as anti-HIV, anticancer, anticoagulan, and antimicrobial. Additionally many coumarin products have the special talent to scavenge reactive oxygen species (ROS) and to effect processes including free radical injury[50]. Likewise, coumarins like umbelliferone and its derivatives are exposed to possess lipid lowering potential. The acknowledgment of vital structural features within coumarin family is essential for the design and improvement of new analogs with advanced activity and for the depiction of their mechanism of action and potential side effects.

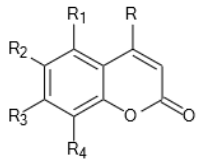
Koneni V et.al., reported the synthesis of coumarin indole derivatives that shows potent anti-hyperlipidemic activity than reference drug lovastatin and atorvastatin.



Anti-Bacterial And Anti-Inflammatory Activity

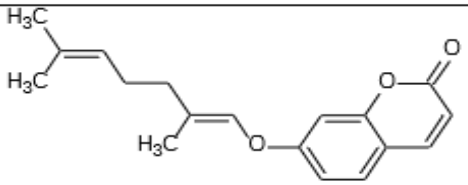
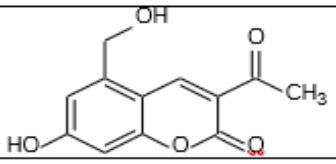
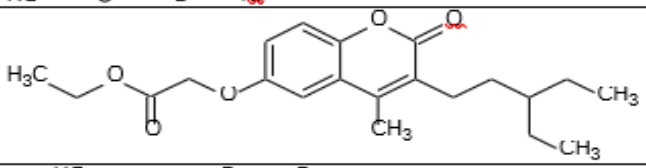
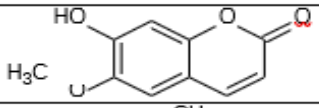
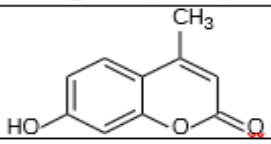
Periodontal ailments are common chronic inflammatory disorders in grown-ups. More explicitly, approximately 5–15% of the population is affected by severe forms of the disease[51]. Specific Gram-negative anaerobic bacteria, including *Porphyromonas gingivalis*, that colonize the periodontal pocket are the major causative element of periodontal diseases[52]. Nonetheless, the continuous and too much host inflammatory response to these pathogens results in the discharge of cytokines and matrix metalloproteinases that kerbs periodontal tissue destruction. From this intricate etiopathogenesis, the custom of therapeutic drugs with dual antibacterial and anti-inflammatory properties represents a treasured adjunctive therapy to govern this ailment. Coumarins are a group of heterocyclic compounds in a large variety of plant families. Plentiful biological activities, including antimicrobial, anti-inflammatory, anti-cancer and antioxidant properties, have been shown by coumarins and their derivatives[53]. Conversely, they have been recently re-considered as valuable and auspicious biologically active phytochemicals.

Daniel Grenier et.al., reported the synthesis of (5-methyl-4-[(3-methylbut-2-enyl) oxy]- 2Hchromen-2-one, (6-[(3-methylbut-2-enyl)oxy]-7-methoxy-2Hchromen-2-one) and (7- methoxy-8-[(3-methylbut-2-enyl) oxy]-2Hchromen-2-one) compounds and found that theyhave potent ANTI-BACTERIAL AND ANTI-INFLAMMATORY ACTIVITY.



Marketed Formulations

Some of coumarin containing clinically used drugs or drug candidates[54]

NAME	STRUCTURE	INDICATION
Auraptene		Chemopreventive agent.
Armillarisin A		Antibiotic.
Carbochromen		Coronary disease.
Scopoletin		Anti-coagulant
Hymecromone		Chloretic,Anti-spasmodic

Future Scope of The Study

Synthesized compounds should have substantial anti-alzheimer's activity in FRAP assay and choline esterase inhibitory action. Hence the anti-alzheimer's study would deserve for further research.

CONCLUSION

Coumarin and its derivatives remains to be of a great interest to a large number of researchers due to their great pharmaceutical and industrial importance and it is astonishing that the synthetic publication far overshadow in numbers those relating to all other. Literature review divulges that the compounds having coumarin nucleus and itscomplexes have very simple synthetic process and possess extensive range of pharmacological actions like anti-coagulant, anti-viral, anti-oxidant, anti-inflammatory, anti- cancer, anti-fungal, anti-viral etc. The area of the production of coumarin rings endures to grow, and the organic chemistry will afford more and better methods for the synthesis of this mesmerizing heterocycle, consenting the discovery of new drug candidates more active,more specific and benign. The coumarin containing various marketed formulations are available with diverse mechanism of action.

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