Comprehensive review on coumarins: Molecules of potential chemical and pharmacological interest

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ABSTRACT

Coumarins are one of the most important classes of heterocycles that occupies prime position in synthetic and pharmaceutical chemistry due to their diverse applications. Broad spectrum of biological activity and their utility as useful synthons, coumarins have attracted researchers to work on this moiety, which is instrumental in the development of coumarin chemistry. This review article provides up to date information about the natural sources, developments, exploration of new methodologies and varied biological activities of coumarins.

Key words: Antibacterial, antifungal, antioxidant, coumarins, formyl pyrazoles.

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INTRODUCTION

The attention of organic chemists has been directed towards the field of heterocyclic chemistry, because of their valuable utilities in the synthesis of variety of biologically active derivatives. Nitrogen, oxygen and sulfur are the most common heteroatoms, but heterocyclic rings containing other hetero atoms are also widely known. A vast number of heterocyclic compounds are known and this number is increasing rapidly. Among the various classes of heterocycles, we are selected coumarin, pyrazole, pyrans, oxazines, oxadiazole and thiadiazoles for the present study.

The fusion of pyrone ring with benzene nucleus gives rise to a class of heterocyclic compound known as benzopyrone, of which two distinct types are recognized. They are Benzo-α-pyrone **(1)** commonly called as coumarin, Benzo-γ-pyrone **(2)** commonly called as chromones, which differs from each other only in the position of the carbonyl group in the pyrone ring.
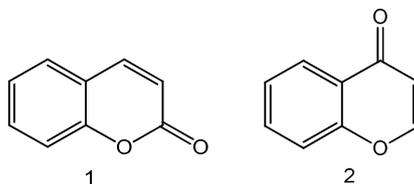

Coumarin is chemically 2H-1-benzopyran-2-one and was first identified in 1820's as an oxygen heterocycles, and is famous for its vanilla like or freshly-mowed hay fragrance. It was first isolated in 1822 from the tonka bean [1] and later from sweet clover, bison grass and woodruff. Coumarin is a crystalline white powder with a hay-like, sweet

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aromatic creamy odor with certain nutty shadings, much used in synthetic form as a fragrance chemical for perfumes and for fragranced soaps and detergents.

Coumarins are classified based on their chemical composition such as, simple coumarins which are hydroxylated, alkoxylated or alkylated on the benzene ring (e.g. Umbelliferone), Furanocoumarins, that contain a five membered furan ring attached to the coumarin moiety such as linear furanocoumarins (e.g. Xanthotoxin) and angular furanocoumarins (e.g. Angeligin).

| Umbelliferone | Xanthotoxin | Angeligin |
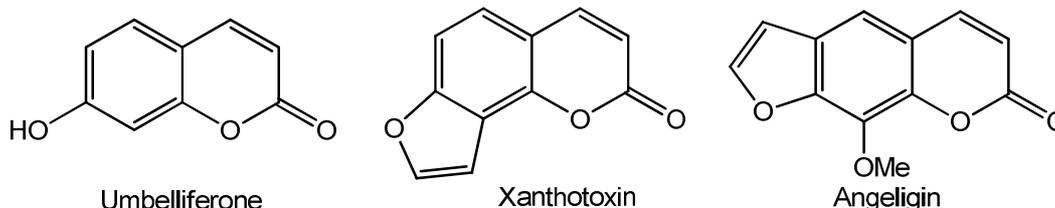
Pyrano coumarins containing a six membered ring attached to the coumarin moiety (e.g. Seselin and Xanthyletin). Coumarins with substituents in the pyrone ring (e.g. Warfarin) [2].

Seselin   Xanthyletin   Warfarin
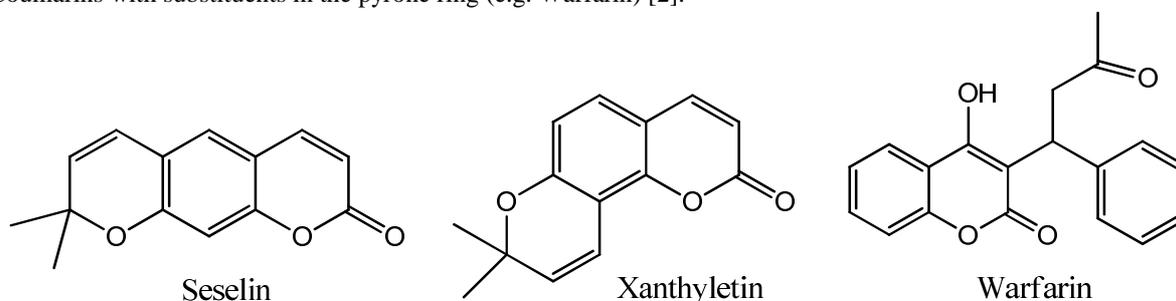
Coumarin and its derivatives considered as the most active classes of heterocycles, which possess a broad spectrum of biological activity. They have been proven to be active as antibacterial [3], antifungal [4], anti-inflammatory [5], antidepressant [6], anti-HIV [7] and antitumour agents [8]. Moreover, coumarin and its related derivatives have been used as inhibitors of lipoxygenase (LOX) and cyclooxygenase (COX) pathways of arachidonic acid meyabolism [9]. Besides the biological applications, the literature embodies their applications from the material view point such as additives in food, perfumes, cosmetics, optical brighteners and would dispersed fluorescent and laser dyes. Optical applications such as laser dyes, nonlinear optical chromophores, fluorescent whiteners, polymer science and solar energy collectors associated with coumarins have been extensively studied [10-13]. Coumarins are also found in selective microorganisms. Members of coumarins isolated from microbial sources are novobiocin from *streptomycin* and aflatoxin from *Aspergillus* species. They are used as enhancing agent in cosmetic products like soap, toothpaste, perfumes and alcoholic beverages [14]. It is also used as a neutralizer in rubber and plastic materials and also in paints and sprays to dilute the unpleasant odors [15].

NATURAL SOURCES OF COUMARINS
Coumarins form elite classes of naturally occurring compounds, which occupy a special role in nature and interest in its chemistry continues unabated because of its usefulness as biologically active agents. They occur widely as secondary plant metabolites and are known to exhibit numerous interesting biological properties. More than 1800 different natural coumarins have been discovered. Most of these coumarins are mono or deoxygenated in the aromatic ring [16]. The well-known natural compound containing coumarin nucleus is 7-hydroxycoumarin (umbelliferone) and is found in carrots, coriander and garden angelica. It has been used a sunscreen, a fluorescence indicator and as a dye indicator [17]. Warfarin is a naturally occurring compound containing the 4-hydroxy coumarin moiety. It has been isolated from woodruff as well as from lavender and is used to prevent clotting of blood in the veins, lungs or heart [18].

Recently six new coumarins have been isolated from the fruits and stem bark of *Calophyllumdispar* (Clusiaceae). The genus *Calophyllum*, which comprises of 200 species, is widely distributed in the tropical rain forest where

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several species are used in folk medicine [19]. Coumarin derivatives ningalin B and lamellarin D were derived from the marine alkaloids, which exhibit HIV-1 integrace inhibition, immunomodulatory activity and cytotoxicity [20,21].

Ningalin B   Lamellarin D
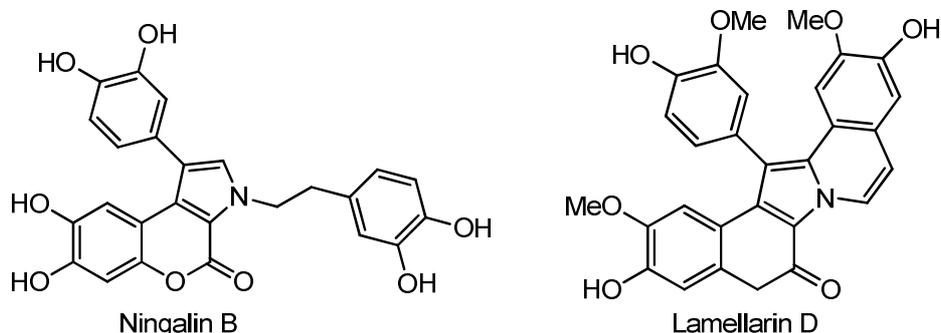
(+)-Calanolide A isolated from *Calophyllumlanigerum* is a non-nucleoside reverse transcriptase inhibitor with potent activity against HIV-1 [22]. (+)-Cordatolide A, a tetracyclic coumarin isolated from the leaves *C. cordatooblangum* in 1985 [23]. (+)-Inophyllum B isolated from *C. inophyllum* was found to be most active against HIV-reverse transcriptase [24].

(+)-Calanolide A   (+)-Cordatolide A   (+)-Inophyllum B
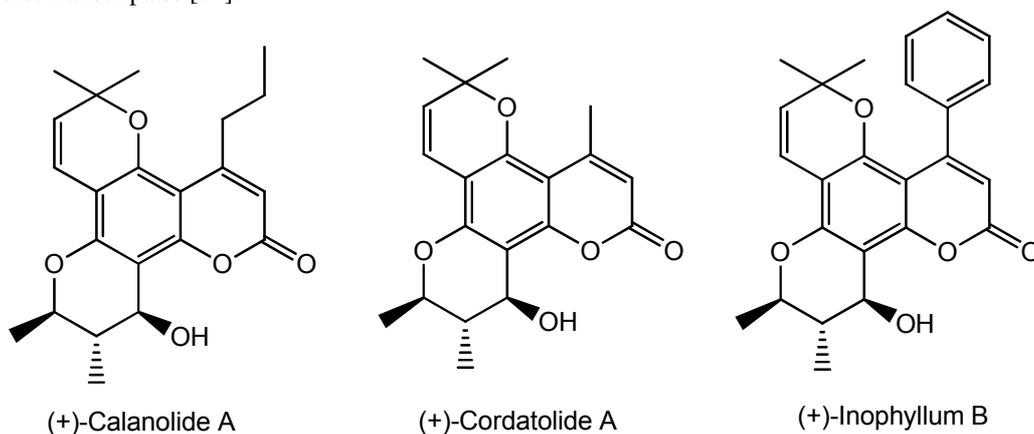
Miglietta A and coworkers [25] isolated Geiparyarin from the leaves of Geijeraparviflora as a new drug which targets tubulin. They investigated the antimicrotubular and cytotoxic effects of new synthetic aromatic derivatives of geiparvarin and observed that these drugs inhibited the polymerization of microtubular protein.

Geiparyarin
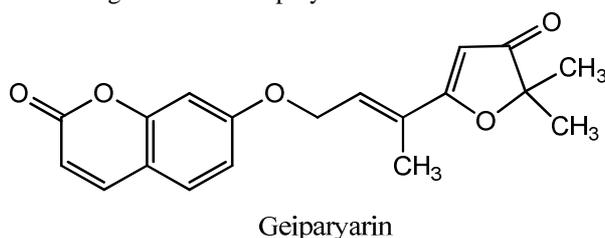
SYNTHESIS OF COUMARINS
Because of their varied biological applications, the preparation of coumarin analogues has attracted attention of organic chemists. Numerous methods have been developed for the synthesis of Coumarins that includes via Pechmann condensation, Perkin reaction, Knoevenagel condensation, Wittig reaction etc.

Pechmann condensation reaction was first reported by Pechmann and Duisberg in 1883. It has been widely employed for the synthesis of coumarins because of its preparative simplicity and inexpensive starting material. This method involves the reaction between phenol and β-keto ester in the presence of an acid catalyst (Scheme-1)[26].

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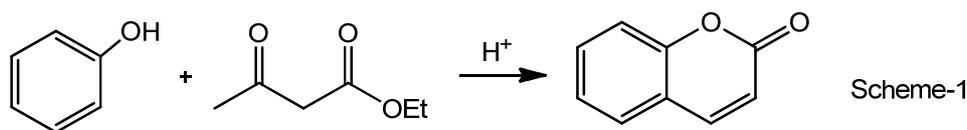
Scheme-1

Vahid *et al* [27] reported a solvent free one-pot synthesis of coumarins from substituted phenols and ethyl acetoacetate catalyzed by FeF$_3$ an environmentally friendly catalyst under microwave irradiation conditions (Scheme-2). The method offers high yield, short reaction time and easy isolation procedure.


Scheme-2

Sun and co-workers [28] have developed an alternative procedure for the pechmann condensation reaction employing Gallium (III) triiodide as a catalyst. This method has several advantages such as mild conditions, short reaction times, high yield and a simple operation. They carried out the reaction of 1-naphthol and ethyl acetoacetate in the presence of Gallium (III) triiodide as catalyst to obtain 4-methyl-2*H*-benzo[*H*]chromen-2-ones (Scheme-3).
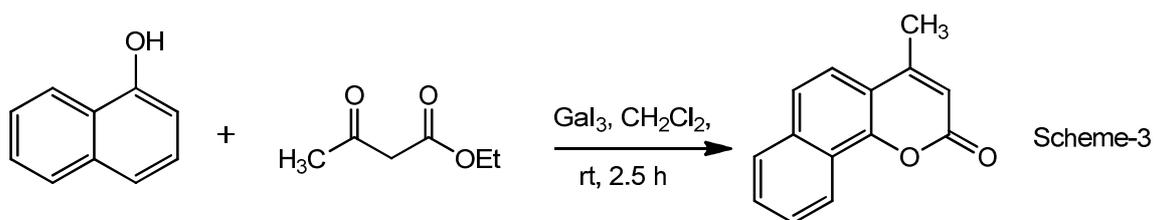

Scheme-3

Jalal Albadi and co-workers [29] reported the synthesis of coumarin derivatives from phenol and ethyl acetoacetate in the presence of catalyst poly (4-vinylpyridine)-CuI under solvent free conditions at 80 °C (Scheme-4). The catalyst was prepared by refluxing the poly (4-vinylpyridine) and CuI under N$_2$ atmosphere in ethanol. This catalyst can be recovered by simple filtration and recycled up to eight consecutive runs without any loss of their efficacy.
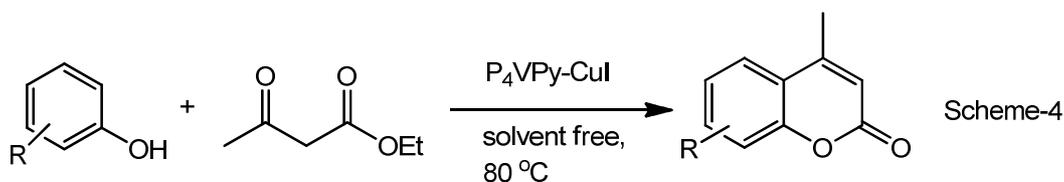

Scheme-4

Khaligh reported the green synthesis of coumarins from the mixture of phenols and β-keto esters at 40°C under solvent free conditions in the presence of [Msim] HSO$_4$ as a catalyst (Scheme-5). The catalyst was recovered effectively by separating through decantation and is reused five times with only a slight decrease in the catalytic activity [30].


Scheme-5
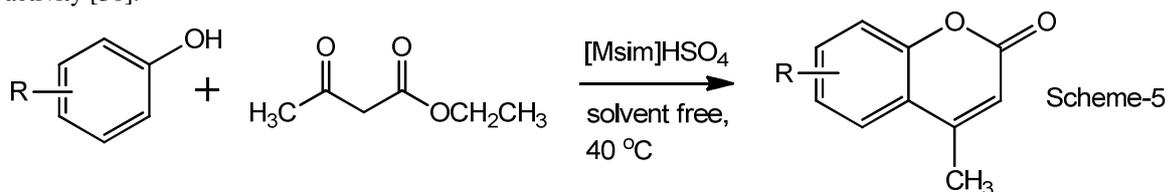
The Perkin reaction provides other useful method for the synthesis of coumarins. For instance, Augustine et al [31] reported the one-pot synthesis of coumarins from salicylaldehyde and cyano acetic acid mediated by propylphosphonic anhydride (T3P) (Scheme-6).
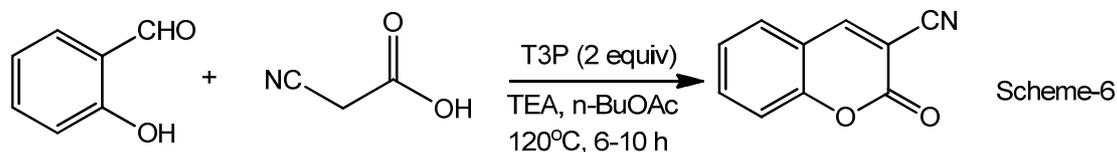

Synthesis of coumarins via Knoevenagel reaction involves the condensation of aromatic aldehydes and activated methylene compounds in the presence of amine. For instance, Singh and co-workers [32] reported a facile synthesis of 3-alkanoyl-2H-chromene-2-thiones by condensation of β-oxodithioesters and salicylaldehyde in the presence of piperidine under solvent free conditions (Scheme-7).
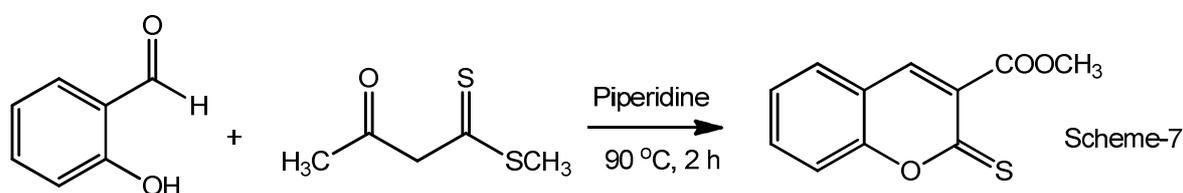

Wittig reaction approach involves the reaction of an aromatic aldehyde or ketone with a phosphonate or phosphorous ylide. For instance, the reaction of salicylaldehyde and ethyl chloroacetate in the presence of triphenylphosphine and MgO/MeONa produced coumarins in good yields (Scheme-8) [33].
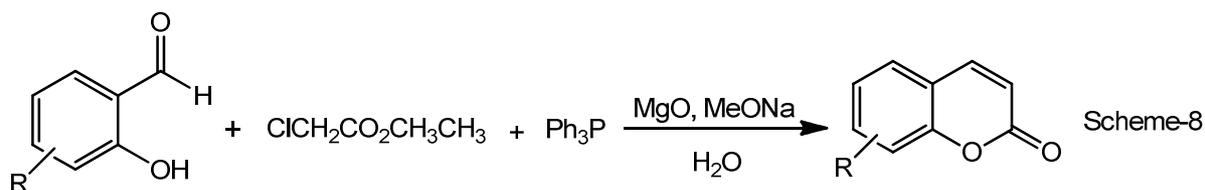

Yavari and co-workers [34] reported the one-pot multistep reaction for the synthesis of coumarins from 4-fluorophenol and dimethylacetylenedicarboxylate. In this reaction, the complex formed by the reaction of triphenylphosphine and dimethylacetylenedicarboxylate react with phenols to undergo aromatic electrophilic substitution, lactonization to provide 4-methoxycarbonyl coumarins (Scheme-9).
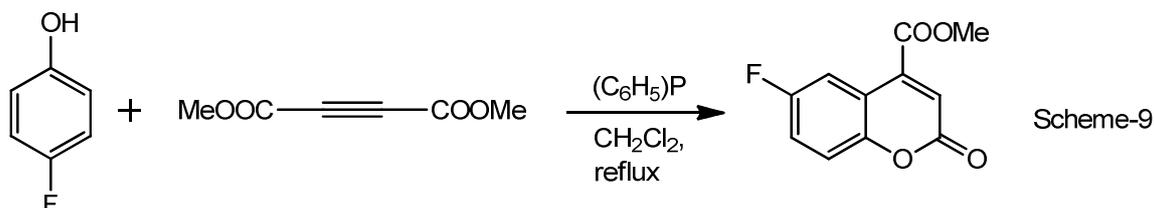

Heck coupling involves the palladium catalysed reaction between aryl halides and alkenes to provide coupled alkenes in a well-established manner. The reaction is applied on 2-bromophenols and cinnamic acid esters to provide coumarins derivatives (Scheme-10) [35].

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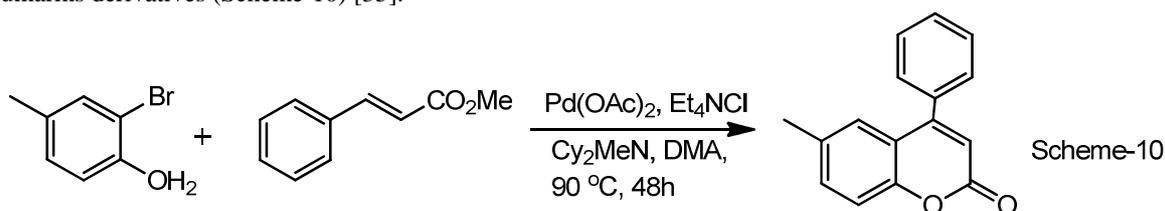
Iso-coumarins have been of considerable interest due to their unique biological properties. The iso-coumarins were synthesized by the reaction of benzoic acid and alkynes using rhodium catalyst. Benzoic acids efficiently undergo oxidative coupling with alkynes through regioselective C-H bond cleavage under rhodium catalysis to form highly substituted iso-coumarin derivatives. Compared with the other conventional multistep synthetic methods, this direct annulations process is intensely step economical [36]. Jia and coworkers [37] have developed a method for the preparation of coumarins by palladium(II) catalyzed and trifluoroacetic acid mediated intramolecular cycloisomerization of arylated alkynoates (Scheme-11).
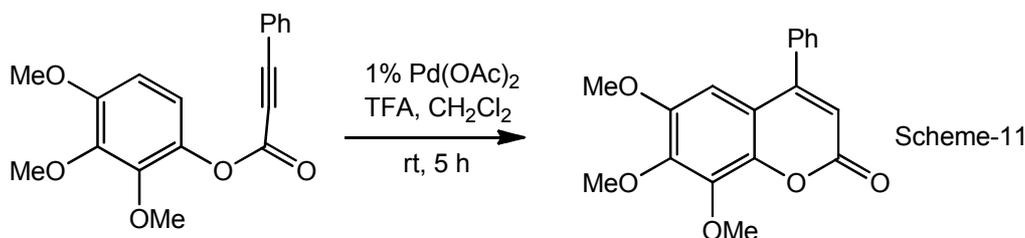

Selles *et al* [38] synthesized highly substituted fused coumarins in two steps starting from the boronic acids and enoltriflates. Firstly, Pd(TPP)$_4$ mediated coupling reaction produced the intermediate ester and then deprotection of phenolic hydroxyl group with BBr$_3$ lead to phenol which readily lactonized to provide coumarins (Scheme-12).
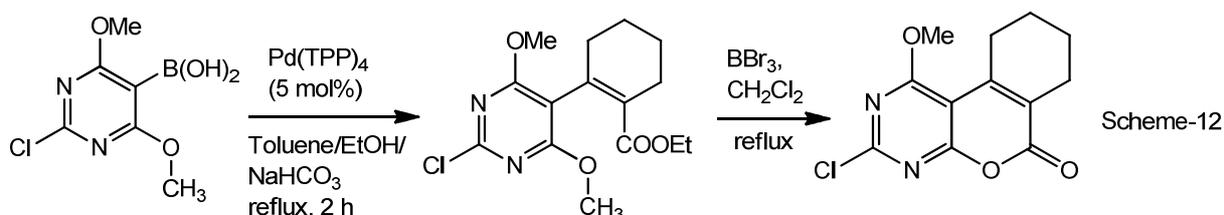

X. He *et al* [39] developed the FeCl$_3$ catalyzed multicomponent reaction for the synthesis of coumarin-3-carboxylic esters using salicylaldehyde, Meldrum's acid and alcohol as the starting materials (Scheme-13). The method is a highly economic and environmentally friendly way.
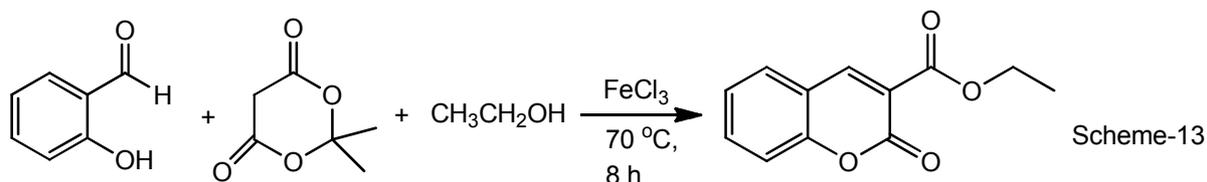

3-Bromocoumarins are synthesized by the treatment of α-halocarboxylic acid ester of salicylaldehyde by sodium or lithium tellurium triggered cyclization (Scheme-14). The reaction worked under non-basic conditions in THF. It was observed that the formation of coumarin was better with lithium telluride compared to sodium telluride [40].
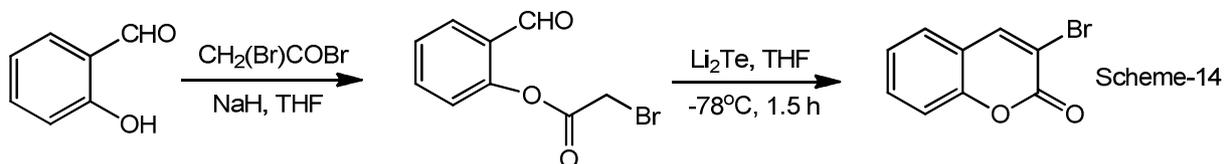
Coumarins were synthesized form variety of electron rich phenols and electron rich cinnamates under mild reaction condition in the presence of trifluoroacetic acid at room temperature. Electron deficient phenols gave low yield of coumarin products, restricting the utility of this procedure [41]. 3-Aryl coumarin derivatives were synthesized in excellent yield by the reaction of 2-chloro-2-arylacetaldehyde with salicylaldehyde catalysed by *N*-hetero-cyclic carbene (NHC) via umpolung reaction (Scheme-15) [42]. The method has experimentally simple and mild.

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Scheme-15
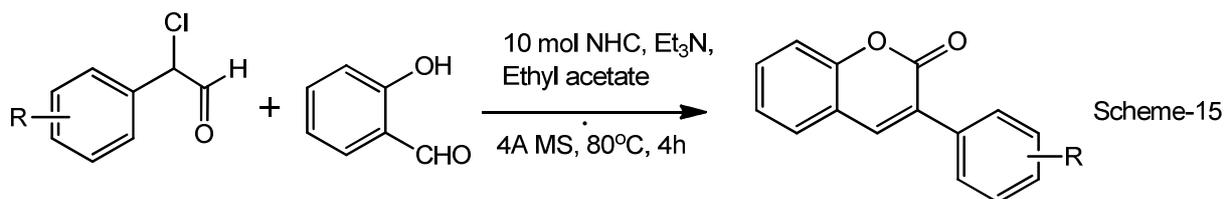
Kaye et al [43] synthesized the coumarin derivatives by Baylis-Hillman methodology. Salicylaldehyde reacts with t-butyl acrylate in the presence of DABCO used as a catalyst to form Baylis-Hillman adducts. These adducts were then reacted with HI in acetic acid to form 3-(iodomethyl)coumarin derivatives in good yields (Scheme-16).
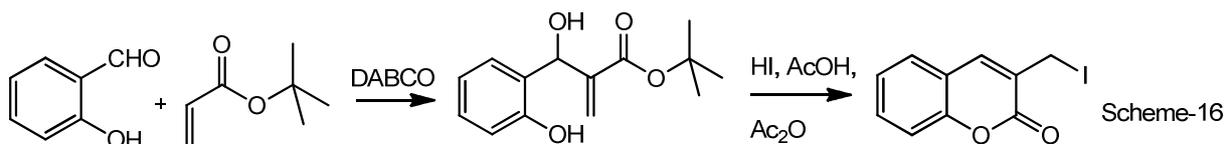

Scheme-16

Polito and co-workers [44] showed a simple and facile synthesis of coumarin scaffolds *via* ring closing methathesis using Grubbs catalyst (Scheme-17). It involves the esterification of 2-vinylphenol with acryloyl chloride to form acrylic ester. The olefin metathesis reaction was conducted on acrylic acid ester in the presence of catalyst in dichloromethane. The method is an alternative to existing procedures for coumarin synthesis, where, near neutral conditions exist for the ring formation.
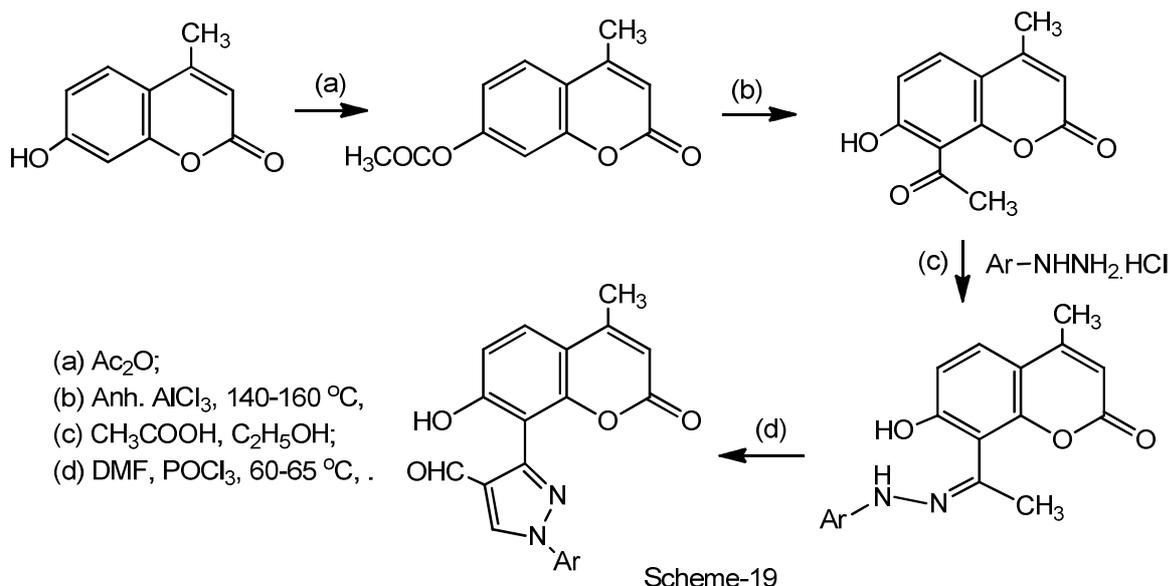

Scheme-17

Grubbs catalyst
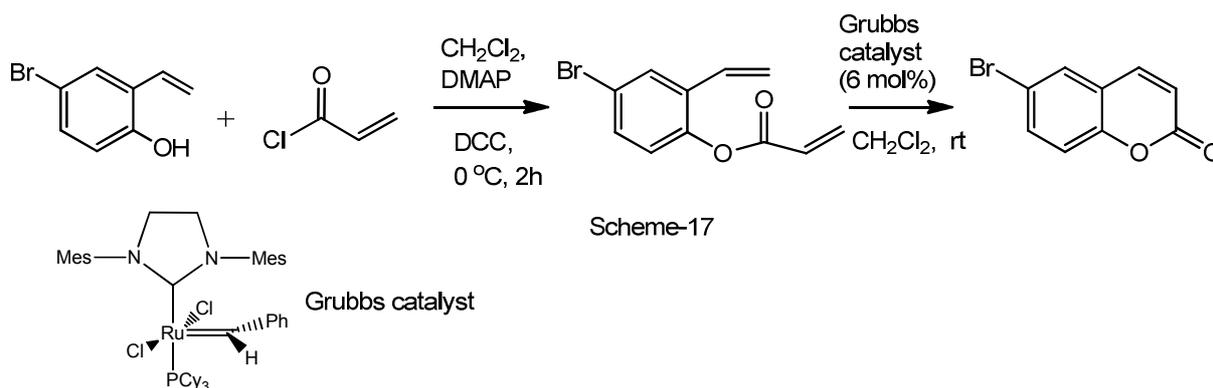
REACTIVITY OF COUMARINS

Coumarin and its derivatives are highly reactive because of the aliphatic moiety present in the coumarin, it is likely to undergo ring opening at the acyl centre. Carbon-6 on the aromatic ring can undergo electrophilic attack such as Friedel-Crafts acylation, sulphonation leading to the formation of 6-substituted derivatives. A methyl substituent on the coumarin nucleus may react differently depending on the position of attachment. Phenol group present in the C-7 position, it is easily undergo acylation, benzoylation and Friedel-Crafts reactions.

Coumarin based benzothiazole derivative was synthesized from the coumarin-3-formyl chloride. The precursor coumarin-3-formyl chloride was prepared form the coumarin-3-carboxylic acid and thionyl chloride in the presence of pyridine. These formyl chlorides are treated with 2-amino benzothiazole and triethylamine in dichloromethane at room temperature furnished the target compound N-(benzo[*d*]thiazol-2-yl)-2-oxo-2*H*-chromene-3-carboxamide (Scheme-18)[45].

Scheme-18

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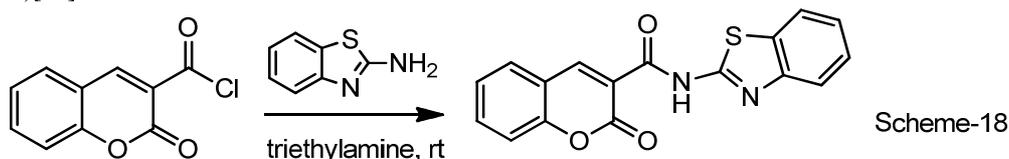
A series of coumarin appended formyl-pyrazoles were synthesized by a simple and accessible approach. The reaction of 8-acetyl-4-methyl-7-hydroxy coumarin and phenyl hydrazine hydrochlorides produces the intermediate compounds 8-acetyl-4-methyl-7-hydroxy coumarin hydrazones, which reacts with DMF in the presence of $POCl_3$ and yielded formyl-pyrazoles bearing coumarin moiety in good yield (Scheme-19). The synthesized new compounds and the intermediates 8-acetyl-4-methyl-7-hydroxy coumarin hydrazones prepared were screened in vitro for their antibacterial, antifungal antioxidant activities. The compounds having chloro substitution exhibited promising antifungal and antibacterial activity against the different organisms tested [46]. Later they were converted the formyl pyrazoles efficiently to fused pyrans [47].

(a) Ac_2O;
(b) Anh. $AlCl_3$, 140-160 °C,
(c) CH_3COOH, C_2H_5OH;
(d) DMF, $POCl_3$, 60-65 °C, .

Scheme-19

Sahoo *et al* [48] effectively transformed 8-Amino-7-hydroxy-4-methyl coumarins to a series of 6-methyl-2-methyl-8*H*-pyrano[2,3-*e*]benzoxazol-8-ones and 3-chloro-7-methyl-9*H*-pyrano[2,3-*e*]benzo-1, 4-oxazine-2, 9–diones (Scheme-20).
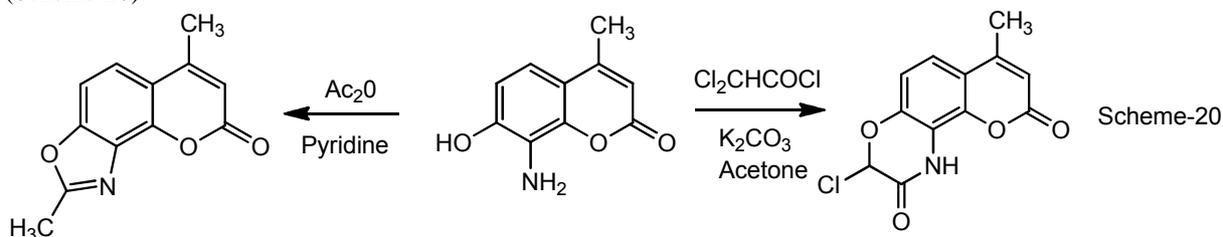
Scheme-20

Farahi and co-workers [49] reported a convenient synthesis of new sulphonamide-substituted coumarins from the *N*-sulfonylaldimines and 5,7-dihydroxy-4-methylcoumarin using NaOH (Scheme-21). The sulfonylaldimines were synthesized from the reaction of aromatic aldehydes and p-toluenesulfonamide in the presence of $AlCl_3$. Further, 5,7-dihydroxy-4-methylcoumarin was synthesized by the condensation of phloroglucinol and ethyl aceto acetate via the $ZrOCl_2/SiO_2$ catalyst.

Scheme-21
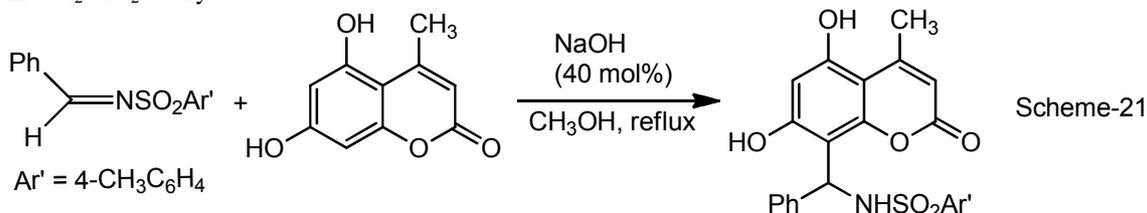
Liang Han and co-workers [50] synthesized novel coumarin-type dyes from the 7-diethylamino-3-(4-formylphenyl)coumarin. The 3-bromo-7-diethylaminocoumarin coupled with the 4-formylphenyl boric acid using tetrakis(triphenylphosphine)palladium in THF obtained the formyl coumarin. Satyanarayana Reddy *et al* [51]

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synthesized a 7*H*-benzopyrano[3, 2-*c*] coumarins achieved by the mild base promted reaction of 4-chloro-3-formylcoumarin with resorcinol in the presence of triethylamine and ethanol at room temperature (Scheme-22).


Scheme-22
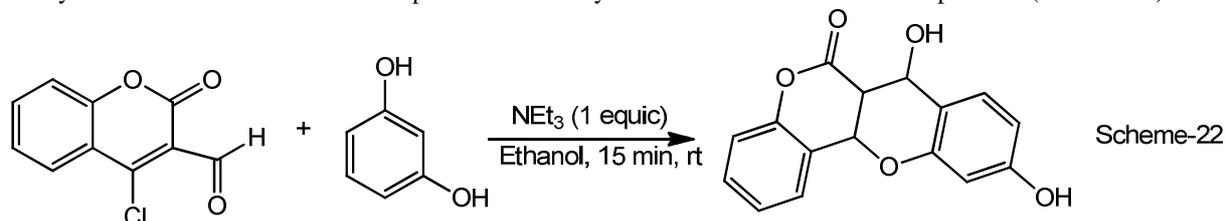
3-Benzoyl-2*H*-chromen-2-one was treated with ethyl ayanoacetate under basic condition; afford ethyl 10-cyano-9-hydroxy-6-oxo-7-phenyl-6*H*-benzo[*c*]chromen-8-caboxylate. The reaction pathway is assumed to proceed by nucleophillic addition of the carbanion to the ethylenic bond of 3-benzoyl-2*H*-chromen-2-one affording the expected pyranochromen,which in turn reacts with a second equivalent of ethyl cyanoacetateion, subsequent ring opening followed by recyclization and elimination of HCN affords the product (Scheme-23) [52].


Scheme-23
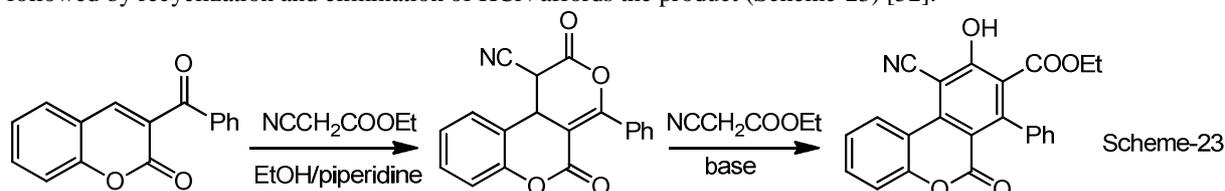
Omaima and co-workers [53] developed a convenient approach to the preparation of coumarin based pyrimidines, pyridinesand pyrazole derivatives. These key reactions involved the intermediate formation of chalcones (**3**), a facile synthesis of these synthesized α, β-unsaturated ketones involves condensation of 3-acetyl-4-hydroxy-coumarin with the appropriate aldehydes. Acetyl coumarins were prepared by the reaction of 4-Hydroxy coumarin with acetyl chloride in the presence of pyridine or piperidine. 4-Aryl-2-amino-6-(4-hydroxycoumarin-3yl)-pyridine-3-carbonitriles were prepared by the cyclization of the corresponding chalcones with malononitrile and ammonium acetate (**4**). On the other hand pyrimidin-2-thiones (**5**) were prepared by the cyclocondensation of the compound (**3**) with thiourea in 5% ethanolic potassium hydroxide solution. Further 5-Aryl-4,5-dihydro-3-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-pyrazol-1-carbothioamide (**6**) were prepared by refluxing a mixture of compound (**3**) and thiosemicarbazide in ethyl alcohol in the presence of glacial acetic acid. Similarly *N*-acetylpyrazolines (**7**) were obtained by refluxing the key intermediate chalcones with hydrazine hydrate in glacial acetic acid (Scheme-24).

Scheme-24
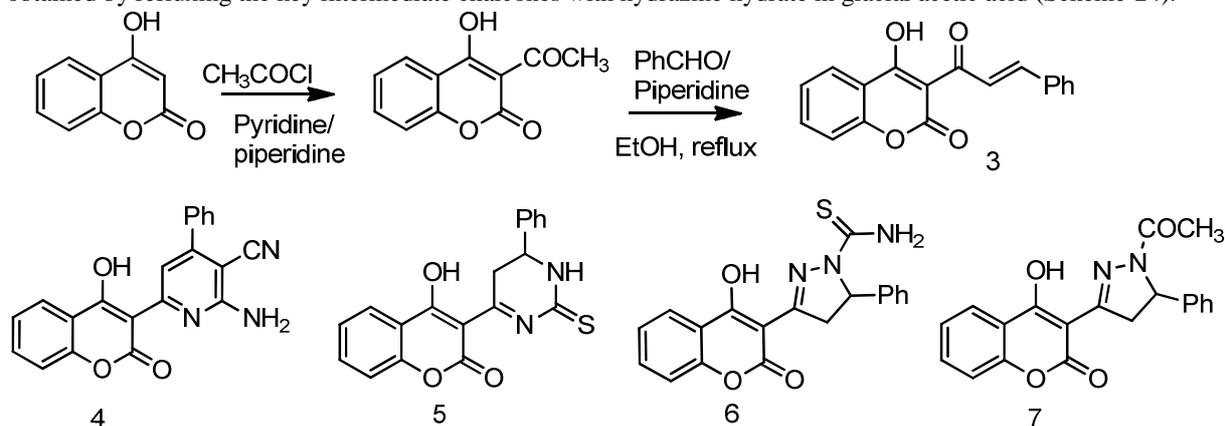
Series of coumarin based traizole and pyrazole derivatives are synthesized from the key intermediate (7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid hydrazide (**8**). Condensation of compound (**8**) with pentane-2,4-dione gave 4-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-7-hydroxy-2*H*-chromen-2-one (**9**), while with potassium isothiocyanate it gave a salt, which was converted directly to 7-hydroxy-4-[(5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-2*H*-chromen-2-one (**10**) by heating it in aqueous KOH followed by acidification with HCl in good yield. The intermediate (**8**) was prepared from (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid ester and 100% hydrazine hydrate (Scheme-25) [54].

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Scheme-25
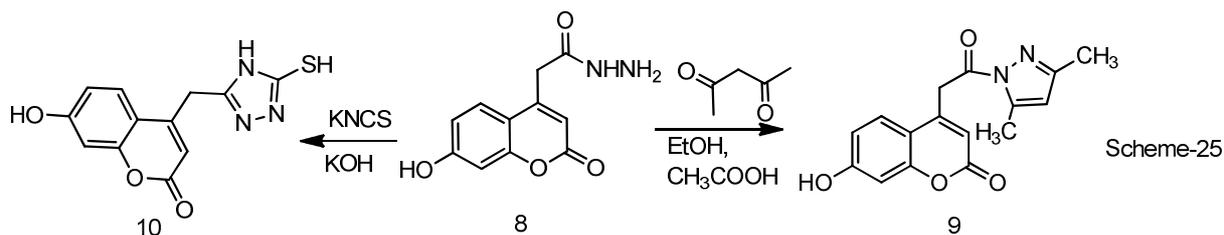
Triazole derivatives of 7-hydroxy-4-methyl coumarin was synthesized from the condensation of 7-(3-chloropropoxy)-4-methyl-2*H*-chromen-2-one with 1,2,4-triazole. 7-(3-chloropropoxy)-4-methyl-2*H*-chromen-2-one was in turn prepared from the 7-hydroxy-4-methylcoumarin refluxed with 1-bromo-3-chloropropane in the presence of anhydrous potassium carbonate for twelve hours [55]. Pallabi et al [56] transformed the 4-Hydroxy coumarin to 4-chloro-3-formyl coumarins with Vilsmeier reagent. They carried out one-pot three-component reaction of 4-chloro-3-formylcoumarins, sodium azide and alkyl or aryl acetonitriles to get novel tetrazole fused pyrido[2,3-*c*]coumarin derivatives. 1-Benzopyrano [3, 4-*c*]pyrrolidines are synthesized via 1,3-dipolar cycloaddition of *in situ* generated non stabilized azomethine ylide with 3-substituted coumarin and *N*-alkyl-α-amino acids (Scheme-26) [57].

Scheme-26
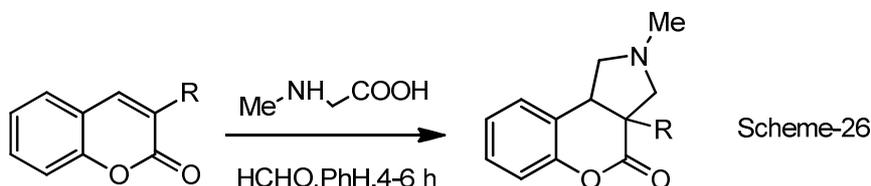
A series of (coumarin-3-yl)carbamates was synthesized by the mixture of 3-aminocoumarin dissolved in dichloromethane and pyridine. The mixture was cooled to 0°C. The corresponding acid chloride was added drop wise to the mixture and the mixture was stirred at room temperature for 3 h. after completion of the reaction, solvent was evaporated and the solid obtained was purified to give the desired (coumarin-3-yl) carbamates [58]. A substituted pyrido[2,3-*c*]coumarin derivatives have been synthesized from 3-amino-coumarins, aromatic aldehydes and alkynes in the presence of 10 mol% molecular iodine in acetonitrile through one-pot Povarov reaction under reflux condition (Scheme-27) [59].


Scheme-27
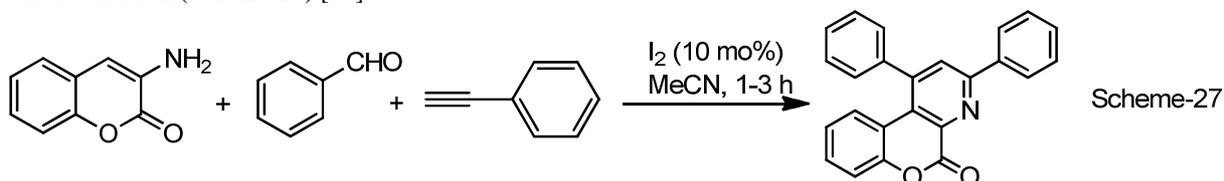
A novel 3-(1*H*-benzo[d]imidazole-2-yl)-7-bromo-2*H*-chromen-2-one (**12**) was synthesized by the 7-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**11**) and o-phenylenediamine in polyphosphoric acid under reflux condition for 12 h. Along with the compound (**12**) , 7-((2-aminophenyl) amino)-2-oxo-2H-chromen-3-carboxylic acid (**13**) (Scheme-28) was also obtained from this reaction which was separated through column chromatography. Compound (**11**) was synthesized by hydrolysis of 7-bromo-2-oxo-2*H*-chromene-3-carboxylic acid ethyl ester with sodium hydroxide [60].

Scheme-28
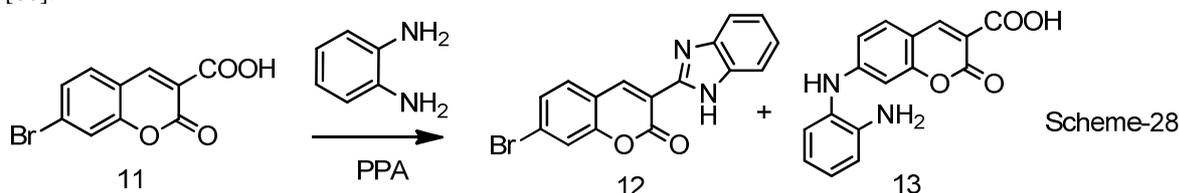
PHARMACEUTICAL APPLICATIONS OF COUMARINS
Coumarins are of great interest due to their biological properties. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive for further backbone derivatisation and screening a novel therapeutic agent. Both coumarin and coumarin derivatives have shown promise potential inhibitors of cellular proliferation in various tumor cell lines [59]. In addition it has been shown that 4-hydroxycoumarin and 7-hydroxy coumarin inhibited cell proliferation in a gastric carcinoma cell line [61].

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Series of novel 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines (**14**) were synthesized by various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenyl hydrazine in the presence of hot pyridine. All the synthesized compounds were screened in vitro anti-inflammatory and analgesic activities. Compounds having 4-Cl and 2, 4-Cl exhibited significant anti-inflammatory activity in model of acute inflammation such as carrageenan-induced rat paw edema compared with diclofenac as a standard drug. These compounds also found significant analgesic activity in acetic acid induced writhing model [62].

14
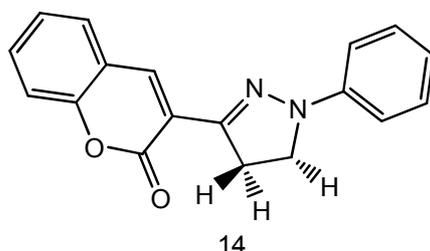
Pradeep kumar *et al* [63] reported the synthesis and antimicrobial activity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-ones (**15**). They have evaluated the synthesized compounds for antibacterial and antifungal activity against bacterial and fungal strains. Among the synthesized compounds, compound having fluro substitution has shown good antimicrobial activity.

15
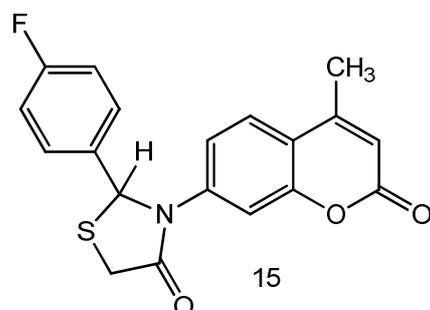
Mesuol (**16**) and isomesuol (**17**) are the 4-phenyl coumarins, isolated from the tree Marilapluricostata, suppress HIV-1 replication in Jurkat T cells [64]. Mesuol inhibits TNFα-induced HIV-1-LTR transcriptional activity by targeting the nuclear factor –κB (NF-κB) pathway. Mesuol does not prevent either the binding of NF-κB to DNA or the phosphorylation and degradation of NF-κBp65 subunit in TNFα-stimulated cells. These results highlight the potential of the NF-κB transcription factor as a target for anti-HIV-1 compounds such as 4-phenyl coumarins, which could serve as lead compounds for the development of additional therapeutic approaches against AIDS.

16

17
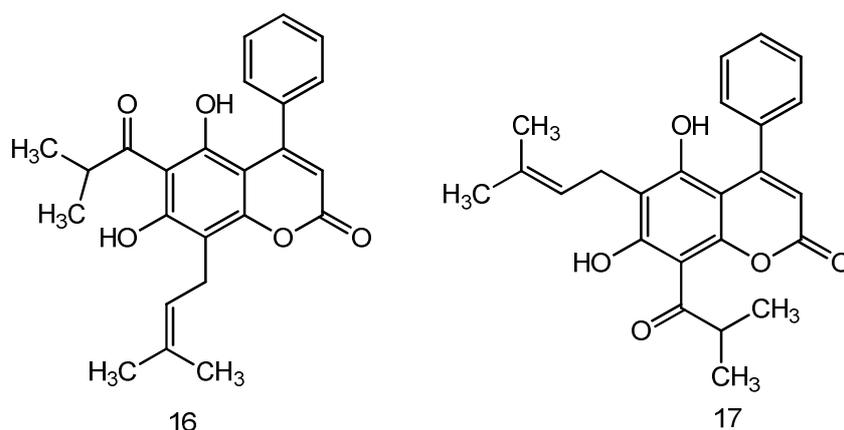
Series of chalcone-coumarin derivatives linked by the 1,2,3-triazole ring (**18**) were synthesized through the azide and alkyne dipolar cycloaddition. These molecules were evaluated for their cytotoxic activity against cancer cell lines (HuCCA-1, HepG2, A549 and MOLT-3). Among these triazole hybrid, the 2,3-dimethoxy derivatives

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containing triazole ring at position 3 shown to be the most potent cytotoxic compound against MOLT-3 cells lines without affecting normal cells [65].


18
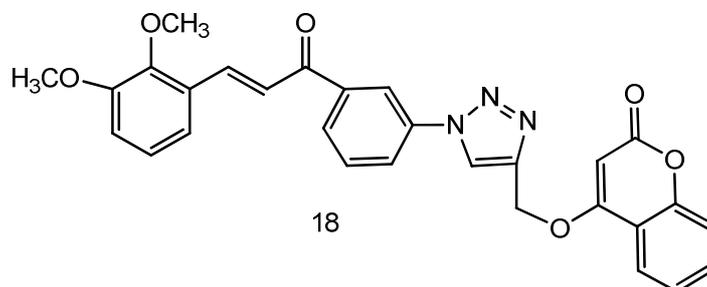
Ranjana *et al* [66] synthesized a series of novel 2-(5-hydroxy 5-trifluoromethyl-4,5-dihydromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazoles (**19**) by condensing 3-(2-bromoacetyl)coumarins with 5-hydroxy-5-trifluromethyl-4,5-dihydropyrazol-1-thiocarboxamides. All these new derivatives were screened for their antibacterial activity. The minimum inhibitory concentration of the synthesized compounds against different bacterial strains was determined by macro dilution tube method. Among these compounds, compound having Cl and F substituents were found to be most effective against *E.coli* and *P.mirabilis* when compared to the standard drug cefixime.

19
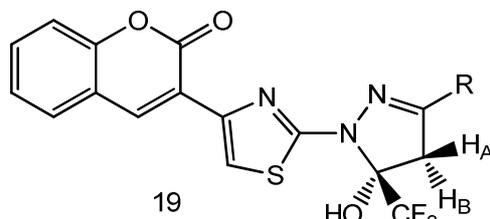
A new class of iodinated-4-aryloxymethylcoumarins (**20**, **21**) have been synthesized from the various 4-bromomethylcoumarins with 2-iodophenol, 3-iodophenol and 4-iodophenol respectively. All these compounds were screened for their *in vitro* anticancer activity against two cancer cell lines MDA-MB human adenocarcinoma mammary gland and A-549 human lung carcinoma by using MTT assay for the determination of MIC values. Among these, compound having chlorine at 6th and 7th position on coumarin and iodine at 4th position on phenoxy moiety exhibited potent anticancer activity [67].

20   21
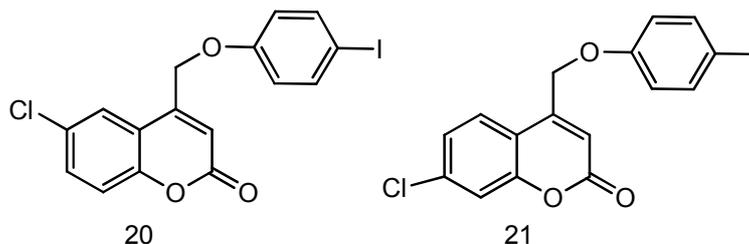
Koneni *et al* [68] synthesized a series of coumarin based aminopyran derivatives were synthesized and evaluated for their antidepressant effect on Swiss albino mice. Among the series, compound (**22**) exhibited significant activity in Forced Swimming Test (FST) at a very low dose of 0.5 mg/kg reduced the time of immobility by 86.5% as compared to the standard drug fluoxetine which reduced the immobility time by 69.8% at the dose of 20 mg/kg. Further all active compounds were screened for tail suspension test (TST). From this, it was proved that these hybrids did not produce any motor impairment effects. Hence coumarin-aminopyran derivatives may have potential therapeutic value for the management of mental depression.

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22
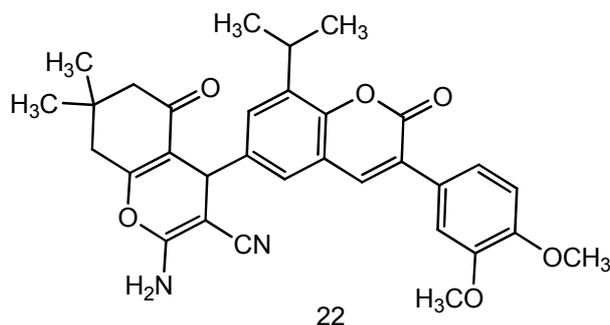
Series of novel coumarin-3-carboxamides (**23**) were synthesized and evaluated for their in vitro antioxidant activity and in vivo anti-inflammatory activity. These carboxamide coumarins possessed potent antioxidant and anti-inflammatory activities. On the basis of results, structure-activity relationships were developed in order to define the structural features required for activity [69]. Patel R B and co-workers synthesized a novel 3,4-dimethoxy phenyl ethyl 1,3,5-triazinyl thiourea derivative (PETT) (**24**) as antibacterial and anti-HIV agents [70].

23   **24**
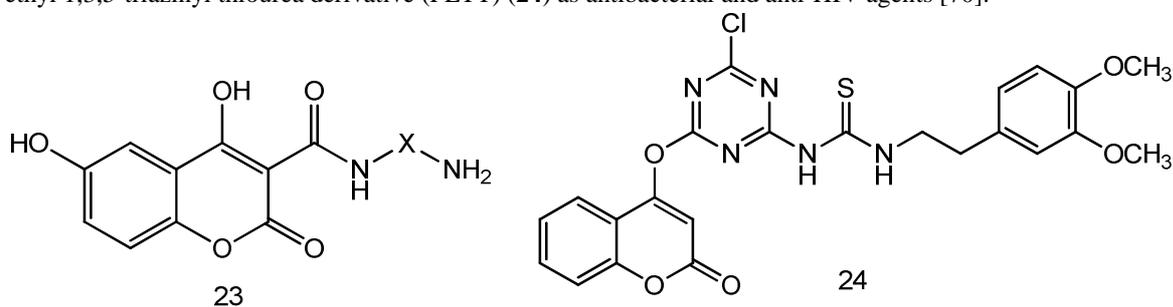
2-(substituted phenyl)-3-(4-methylcoumarinyl-7-oxyacetamido)-5-carboxymethyl-4-thiazolidione (**25**) was synthesized by the 4-methylcoumarinyl-7-ocyacetic acid [(substituted phenyl methylene)] hydrazides and thiomalic acid in glacial acetic acid under reflux condition. After completion of the reaction, the mixture was dissolved in sodium bicarbonate solution and re-precipitated by hydrochloric acid and recrystallized from ethanol. The obtained product was evaluated for antioxidant activity by DPPH assay. Among this, compound with unsubstituted phenyl substituent showed more than 95% antioxidant activity compared to standard ascorbic acid [71].

25
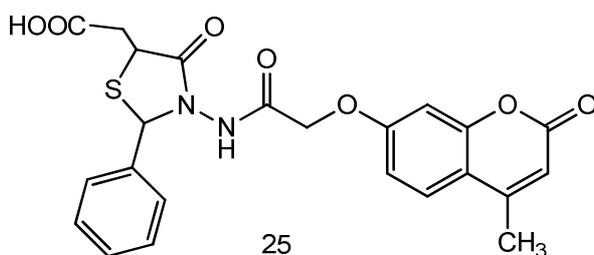
CONCLUSION

In the present review, attempt has been made to present the source, synthetic strategies, reactions and pharmaceutical applications of coumarins. Wide range of natural sources and new coumarin analogues are being discovered or synthesized on a regular basis. The coumarins are of great attention due to their therapeutic property. Their physiological, bacteriostatic, antioxidant, antitumor and other pharmaceutical properties make the coumarins as novel class for therapeutic applications. Synthetic procedure and clinical applications of coumarins for the treatment of several diseases were critically discussed.

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