Overview on developed synthesis procedures of coumarin heterocycles

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Abstract
Considering highly valuable biological and pharmaceutical properties of coumarins, the synthesis of these heterocycles has been considered for many organic and pharmaceutical chemists. This review includes the recent research in synthesis methods of coumarin systems, investigating their biological properties and describing the literature reports for the period of 2016 to the middle of 2020. In this review, we have classified the contents based on co-groups of coumarin ring. These reported methods are carried out in the classical and non-classical conditions particularly under green condition such as using green solvent, catalyst and other procedures.

Keywords Coumarins · Biological · Pharmaceutical · Heterocycles

Introduction
Coumarins or benzopyran-2-ones are a group of nature-occurring lactones first derived from Tonka beans in 1820. Those compounds are valuable kinds of oxygen containing heterocycles widely found in nature, so that they have been routinely employed as herbal medicines since early ages. More than 1300 coumarin derivatives have been identified, which are mainly obtained from the secondary metabolite in green plants, fungi and bacteria [1]. This led to an incentive for researchers around the world to investigate the nature and identification of this molecule. Since the reporting of the first synthetic route in 1882, this moiety has found its place in fabric conditioner, certain perfumes and in medicinal industry especially as anti-coagulants, viz. warfarin and dicoumarol; also some others such as naturally occurring coumarins moieties have been reported (Fig. 1). Also, many synthetic coumarins with a type of pharmacophoric groups at C-3, C-4 and C-7 positions have been intensively screened for different biological properties. In recent years, there has been considerable amount of researches with coumarins being tested for anti-HIV [2, 3], anticancer [4–8], anti-microbial [9, 10], anti-tumor [6, 11], antioxidant [12, 13], anti-Alzheimer [14], anti-tuberculosis [15], anti-platelet activity [16], COX inhibitors [17], anti-inflammatory [18], anti-asthmatic [19], anti-viral [20] and DNA gyrase inhibitors [21].

Discussion

Coumarins containing triazole core

An efficient method was reported by Awasthi et al. for the synthesis of coumarin–triazole derivatives 7 via the alkylation reaction of 7-hydroxy-4-methyl coumarin 3 with propargyl bromide 4 in dry acetone and anhydrous potassium carbonate at 50 °C and then reaction with various sodium azides 6 (Scheme 1). Most of the synthesized compounds 7 exhibited anti-plasmodial activity against chloroquine-sensitive strain of plasmodium falciparum [22].

7-Alkynyl-substituted coumarins 9 were prepared by a Sonogashira reaction of 6-substituted-7-(trifluoromethylsulfonyloxy)coumarins 7 with terminal acetylenes 8. Also, the reaction of 7-ethynyl-substituted coumarins 10 with azidobenzoic acids 11 in the presence of copper (II) sulfate and sodium ascorbate was used to synthesize the respective 7-[(1-carboxyphenyl)-1H-1,2,3-triazol-4-yl]coumarins 12 (Scheme 2) [23].

Salicylaldehyde and its derivatives 13 reacted with cyanoacetamide 14 in a two-phase system water–methylene

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chloride in the presence of phase-transfer catalyst to yield corresponding coumarin-3-carboxamides 15 that led to corresponding 1,3-oxazines/coumarins 17 via reaction with methylmalonylchloride 16 in aprotic solvents such as carbon-tetrachloride, benzene, 1,2-dichloroethane and acetonitrile at the boiling point. Complete hydrolysis of 1,3-oxazines/coumarins led to N-acylmalonamic acids 19, and also the reaction of 1,3-oxazines/coumarins with hydrazines or phenylhydrazine 20 in glacial acetic acid led to coumarins containing 1,2,4-triazole derivatives 21 (Scheme 3) [24].

In an interesting procedure, the reaction of epichlorohydrin with 7-hydroxy-4-methyl-2\(H\)-chromen-2-one under reflux conditions yielded 4-methyl-7-(oxiran-2-ylmethoxy)-2\(H\)-chromen-2-one 22 and then reaction of 22 with various azoles led to a series of coumarin-derived azolyl ethanol including imidazolyl 23, triazolyl 24, tetrazolyl 25, benzotriazolyl 26, thiol-imidazolyl 27 and thiol-triazolyl ones 28 (Scheme 4). Some of the prepared compounds display suitable logPow extent, excellent anti-bacterial and antifungal activities [25].

A library of novel triazole-tethered isatin–coumarin hybrids 36 were synthesized by click chemistry approach. The reaction of isatins 29 with 1,2-dibromoalkanes 30 afforded compound 31, and further reaction of 31 with Na\(_3\) in DMF led to 1-(4-azidoalkyl)indoline-2,3-dione 32. On the other hand, 4-(prop-2-ynyloxy)-2\(H\)-chromen-2-one 36 was prepared by reaction of 4-hydroxycoumarin 33 with propargyl bromide 4 in the presence of K\(_2\)CO\(_3\) at room temperature. The final triazole-linked isatin–coumarin hybrids 36 were prepared via cyclization of 4-(prop-2-ynyloxy)-2\(H\)-chromen-2-one 34 with 1-(4-azidoalkyl)indoline-2,3-dione analogs 32 in the presence of catalytic amount of copper sulfate and sodium ascorbate in DMF at room temperature (Scheme 5). Most of the synthesized hybrids showed cytotoxic activity against a panel of four human cancer cell lines (THP-1, COLO-205, HCT-116 and PC-3) [26].

An efficient method was reported by Venkata et al. to synthesize a series of novel 3-((1-(substituted phenyl)-1\(H\)-1,2,3-triazol-4-yl)methoxymino)ethyl)-2\(H\)-chromen-2-one derivatives 41 via the click reaction of...
(E)-3-(1-((prop-2-yn-1-yloxy)imino)ethyl)-2H-chromen-2-one 40 and aryl azide 6 in the presence of sodium ascorbate and CuSO$_4$·5H$_2$O in THF:H$_2$O (Scheme 6). Most of the synthesized compounds exhibited reasonable neuroprotective and toxicity activities against H$_2$O$_2$-induced PC12 cell lines [27].

A series of N$^1$-(2,3,5-tri-o-benzoyl-β-d-ribofuranosyl)-C$^4$-(coumarin-7-oxymethyl)-1,2,3-triazoles 46 have been synthesized using Cu catalyzed Huisgen–Sharpless–Meldal [3+2] dipolar cycloaddition reaction between 1-azido-2,3,5-tri-o-benzoyl-β-d-ribofuranose 44 and 7-propargylocoumarins 43. The debenzoylation of the resulted triazole derivatives 5 with sodium methoxide in methanol led to the formation of targeted compounds, N$^1$-(β-d-ribofuranosyl)-C$^4$-(coumarin-7-oxymethyl)-1,2,3-triazoles 46 in good yields (Scheme 7) [28].

A series of potential anticancer triazolylcoumarins 52 have been synthesized as shown in Scheme 8. The starting 3-acetamido coumarin analogs 49 were prepared by using a choice of substituted salicylaldehyde 47 and N-acetyl...
Scheme 5 Synthesis of triazole-linked isatin–coumarin hybrids

Scheme 6 Synthesis of novel 1,2,3-triazole-tethered coumarin derivatives

Scheme 7 Preparation of $N^1$-(β-D-ribofuranosyl)-C$^6$-(coumarin-7-oxymethyl)-1,2,3-triazoles

Scheme 8 Plausible pathway for the synthesis of 3-(triazolyl) coumarins
glycine 48 in the presence of acetic anhydride under microwave conditions. These coumarins 49 were then refluxed with HCl/EtOH mixture and further treated with sodium nitrite followed by sodium azide to get the desired 3-azido coumarin derivatives 50. Finally, DBCO 51 was treated with 3-azidocoumarin analogs 50 in DMSO at ambient temperature for 30 min (Scheme 8). The results showed that compound 6 (R=H, R′=OH, R″=H and R=R″=Cl, R′=H) exhibited maximum quantum yield and strong cellular uptake in the MCF-7 cell line [29].

A new class of dihydroartemisinin–coumarin hybrids 55 were synthesized via cyclization reaction of azide–coumarin derivatives 53 with alkynes 54 in the presence of CuSO4·5H2O and sodium ascorbate in DMF (Scheme 9). Those coumarins were identified to have a great anticancer activity against two cancer cell lines (MDA-MB-231 and HT-29) [30].

The synthesis of coumarinyl thiazolotriazole derivatives 61 is outlined in Scheme 61. Starting from coumarinyl hydrazide 56, reacting with potassium thiocyanate in the presence of HCl afforded coumarinyl carbothioamide 57, which on intramolecular dehydrative cyclization produced corresponding coumarinyl-3-mercapto-1,2,4-triazole 58. Next, coupling with acetophenones 59 yielded the corresponding ethanones 60 which in the final step were cyclized to coumarinyl integrated thiazolo[3,2-b][1,2,4]triazole derivatives 61 upon treatment with phosphorus oxychloride (Scheme 10) [31].

The synthesis of the bis-coumarins 65 is depicted in Scheme 1. 7-Hydroxycoumarin 3 was reacted with propargyl bromide 4 to obtain coumarin derivatives 5. On the other hand, 7-hydroxycoumarin 62 was also reacted with alkyl bromides 30 and then it was treated with sodium azide to get other compound required for the synthesis of the target compounds. The bis-coumarin derivatives 65 were synthesized via copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) reaction between coumarin 5 and compound 64 (Scheme 11) [32].

Chromen-triazole 69 was readily synthesized via click reaction of tripropagyl trindane 67 with coumarin azide 68 in the presence of Cu catalyst. The acetylenic substrate 67 was prepared for a high yield using condensing propargyl amine to tricarboxylic acid 66 in the presence of carboxyldimidazole carbonyl activating reagent in DMA (Scheme 12) [33].

The reaction of anthranilic acids 70 and cyclohexanone 71 in refluxing POCl3 gave 1,2,3,4-tetrahydroacridines 72. Compounds 72 were treated with propargylamine in phenol to afford propargylated acridine analogs 73. On the other hand, coumarins 3 were reacted with various dibromoalkanes in the presence of anhydrous K2CO3 in acetonitrile to give compounds 74. Compounds 75 were obtained via the reaction of compounds 74 with NaN3 in EtOH. Finally,
the target molecules 76 were prepared by click reaction of compounds 73 with azide analogs 75 in the presence of Et₃N along with a catalytic amount of CuI at room temperature. Some of the products displayed the good anti-BChE activity much more active than tacrine and donepezil as the reference drugs (Scheme 13) [34].

4β-Ν³,4′-Demethyl-epipodophyllotoxin 78 was prepared via treating 4′-demethylpipodophyllotoxin 77 with a benzene solution of hydrazoic acid in the presence of boron trifluoride etherate (BF₃·Et₂O). Then, the target compounds 79 were prepared by click reaction of the compound 78 and coumarin 34 in the presence of CuSO₄·5H₂O and sodium ascorbate at room temperature (Scheme 14). Some of the synthesized compounds 79 displayed high cytotoxicities against A549, HepG2, HeLa, and LoVo cells with IC₅₀ values of 4.9–17.5 μM [35].

Pechmann condensation of various resorcinols 1 with ethyl acetoacetate 2 in the presence of H₂SO₄ gave substituted coumarins 3. Coumarins 3 upon reaction with propargyl bromide and potassium carbonate in acetone under reflux conditions afforded the compounds 5. Antimicrobial coumarin–triazole derivatives 80 were synthesized via nucleophilic substitution reaction of compound 5 with dibromoalkanes 30 and sodium azide in DMP/H₂O solvent (Scheme 15) [36].
**Coumarins containing pyrazole core**

A green, eco-friendly method has been developed, and a series of coumarin-pyran[2,3-c]pyrazoles \(83\) have been synthesized by a multi-component reaction (MCR). Coumarin–pyrazoles \(83\) have been synthesized via the reaction of substituted 4-formylcoumarin \(81\), ethyl acetooacetate \(2\), hydrazine hydrate \(20\) and malononitrile or ethylcyanoacetate \(82\) in the presence of catalytic amounts of NaOH in reasonable yields (Scheme 16) [37].

In another attempt, Yalcin et al. synthesized a large series of fluorescence coumarin–pyrazole–triazine-based chemosensor (CPT) bearing 5-hydroxypyrazole \(65\) as a receptoric part through the reaction of compound \(61\) with 6-hydrazinyl-N\(^2\),N\(^5\),N\(^4\),N\(^4\)-tetramethyl-1,3,5-triazine-2,4-diamine \(90\). Also, compound \(86\) was prepared for cycloadition reaction 4-(diethylamino)-2-hydroxybenzaldehyde.
with dimethyl 3-oxopentanedioate 85 in the presence of catalytic amounts of piperidine in EtOH under reflux conditions (Scheme 17) [38].

An efficient method was reported by Chen et al. for the synthesis of pyrazoline–coumarin derivatives 95 by the reaction of 3-(1-(2-bromoacetyl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-2H-chromen-2-ones 104 were prepared through a stepwise procedure. Reduction of 3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde 97 by NaBH₄, also reaction with SOCl₂ in benzene led to the formation of 3-(4-(chloromethyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one 99. The reaction of sodium ethyl carbonodithioate 100 with compound 99 under reflux condition afforded carbonodithioate 101. Chromene derivatives 103 were obtained from the reaction of diamines 102 with 101 in EtOH under reflux conditions. Finally, substitution of hydrogen atom on imidazole ring with different alkyls led to substituted 3-(4-((1H-benzo[d]imidazol-2-ylthio)methyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-ones 104 (Scheme 19) [39].

The synthetic procedure adopted to obtain the coumarin–pyrazole hybrids is depicted in Scheme 20. The starting material 6-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one 107 was prepared by 1-(2,4-dihydroxyphenyl) ethanone 106 and ethyl acetoacetate 2 in the presence of 1-(2,4-dihydroxyphenyl) acetonitrile 20 and NaBH₄.

Scheme 16 Synthesis of various coumarin-substituted pyrano[2,3-c]pyrazoles

Scheme 17 Synthesis of novel coumarin–pyrazole–triazine-based fluorescence chemosensor

Scheme 18 Synthesis of new arylpyrazoline–coumarins
of sulfuric acid via Pechmann reaction. The treatment of 107 with acetic anhydride 108 to give 6-acetyl-4-methyl-2-oxo-2H-chromen-7-yl acetate 109, prepared on subjecting to Fries rearrangement using AlCl₃ as a catalyst, afforded 1,1′-(7-hydroxy-4-methyl-2-oxo-2H-chromene-6,8-diyl) diethanone 110. The condensation of the compound 110 into hydrazine derivatives 20 in ethyl alcohol and a catalytic amount of acetic acid under reflux conditions produced the corresponding bis-hydrazones 111, which were subsequently reacted under Vilsmeier–Haack condition and furnished the target molecules 112 in excellent yield (Scheme 20) [40].

A series of 3-((1,3-diphenyl-1H-pyrazol-4-yl)(p-tolylamino)methyl)-4-hydroxy-2H-chromen-2-ones 115 were prepared through reaction of aniline derivatives 113, pyrazole aldehyde derivatives 114 and 4-hydroxy coumarin 33 in MeOH under reflux conditions (Scheme 21). Most of the pyrazole-aniline-linked coumarins exhibited potential antimicrobial activity against both Gram-positive and Gram-negative bacterial strains [41].

Yana et al. synthesized novel 6-pyrazolinylcoumarins 94. 5-Acetoxy-7-methyl coumarins derivatives 117 were prepared by 5-hydroxy-7-methyl coumarins 116 in the presence of catalytic amounts of pyridine in Ac₂O under reflux conditions. 6-Acetyl-5-hydroxy-7-methyl coumarins 118 were obtained as a result of the reaction 5-acetoxy-7-methyl coumarins 117 with AlCl₃ under reflux condition. Claisen–Schmidt condensation of 118 with aromatic aldehydes 119 in the presence of pyrrolidine led to 2-aryl-5-methyl-2,3-dihydropyrano-[2,3-f]chromen-4,8-diones 120. Finally,
6-[5-aryl-4,5-dihydropyrazol-3-yl]-5-hydroxy-7-methyl coumarins 121 were obtained from reaction of hydrazine 20 with 2-aryl-5-methyl-2,3-dihydropyrano[2,3-f]chromen-4,8-diones 120 in EtOH (Scheme 22) [42].

An efficient method was reported by Ablajan et al. to synthesize coumarin-containing dihydropyrano[2,3-c]pyrazoles 123 via four-component reaction of β-dicarbonyl compound 86, phenylhydrazine 20, aromatic aldehydes 119 and malononitrile 122 in EtOH catalyzed by L-proline under ultrasonic irradiation. This procedure provides several advantages, such as simple workup procedure, shorter reaction time, environmental friendliness and higher yields (Scheme 23) [43].

In another attempt, Saeed et al. synthesized a large series of coumarinyl–pyrazolinyl-substituted thiazoles derivatives 7. The acetylcoumarin 37 was treated with various aldehydes 119; this afforded the chalcones 124 in excellent yields. The chalcones 124 underwent inter-molecular cyclization with thiosemicarbazide 125 in the presence of KOH; this led to smooth formation of coumarinyl pyrazolines 100. Finally, the coumarinyl pyrazolinyl 126 condensed with α-halo ketones 127 provided the coumarinyl pyrazolinyl 1,3-thiazoles 128 in good yields (Scheme 24). The results showed that all of the coumarinyl–pyrazolinyl derivatives exhibited significant mushroom tyrosinase inhibitory activities [44]. A series of 3-(2-oxo-2H-chromen-3-yl)-1-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)-5-aryl-1H-pyrazol-1-ium bromides 130 have been prepared via one-pot three-component cyclocondensation of different coumarin chalcones 124, thiosemicarbazide 125 and 2-bromocoumarin derivatives 129 under reflux conditions (Scheme 25). Most of the synthesized compounds showed antioxidant, anti-bacterial and antifungal activities [45].

One-pot synthesis of some substituted benzylpyrazolyl coumarins 131 was carried out under solvent-free reaction of phenylhydrazine 120, ethyl acetooacetate 2, 4-hydroxycoumarin 33 and various aldehydes 119 in the presence of Nb-Zr/KIT-6 as an effective, recyclable and green catalyst (Scheme 26) [46].

The synthesis route for our aimed molecules 10 is presented in Scheme 1. Firstly, 4-chlorobenzene-1,3-diol 132

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**Scheme 21** Synthesis of pyrazole-aniline-linked coumarin

![Scheme 21](image_url)

**Scheme 22** Synthesis of 6-pyrazolinylcoumarin derivatives

![Scheme 22](image_url)

**Scheme 23** One-pot synthesis of coumarin-containing dihydropyrano[2,3-c]pyrazoles

![Scheme 23](image_url)

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was treated with ethylacetoacetate 2 under acidic condition to form coumarin 133. Then coumarin 133 was condensed with dibromoalkane to get compounds 134 in high yields. The reaction of ethylacetoacetate 2 with methylhydrazine 120 gave pyrazole 135, which was further treated with POCl₃ and DMF to produce aldehyde 136. Compound 136 was reacted with various phenols to afford the corresponding carbaldehydes 137. Subsequently, carbaldehydes 137 were treated with hydroxylamine in the presence of KOH as alkali to generate the oximes 138. Finally, the target molecules 139 were prepared via the reaction of oximes 138 with compounds 134 in the presence of K₂CO₃ and Cs₂CO₃ in CH₃CN at reflux (Scheme 27). The synthesized hybrids 139 exhibited good to excellent anti-tumor activities [47].

To synthesize coumarin–pyrazole carboxamide derivatives 142, coumarin-3-carboxylic acid 140 with pyrazole analogs 141 was reacted in the presence of POCl₃ in pyridine as solvent and catalyst (Scheme 28) [48].

**Scheme 24** Synthesis of coumarinyl–pyrazolinyl-substituted thiazoles derivatives

**Scheme 25** Preparation of coumarine–thiazol–pyrazoles 130

**Scheme 26** One-pot synthesis of benzylpyrazolyl coumarin

Li et al. synthesized several molecules containing chromeno[3,4-<i>d</i>]imidazol-4(1H)-one 149. Phenylamino derivatives 145 were prepared by reaction of compound 144 with a solution of iron and NH₄Cl in EtOH: H₂O.
Subsequent cyclization of 145 with 1,1′-carbonyldiimidazole 146 in acetic acid afforded chromeno-imidazole 147. Final products 149 were prepared via the reaction of 147 with boric acid 148 in the presence of K$_2$CO$_3$ and PdCl$_2$ at ambient temperature in dioxane/water (Scheme 29). Product 149 bearing imidazole moiety showed dramatic anticancer activity against HCT116 and MCF-7 [49].

Anti-bacterial coumarin–imidazoles 152 were achieved in reasonable yields from cyclization reaction of substituted 4-formylcoumarin 81 with benzil 150 and ammonium acetate 151 in acetic acid under reflux condition. The 4-(4,5-diphenyl-1-tosyl-1H-imidazol-2-yl)-2H-chromen-2-ones 155 were prepared through reaction of compound 152 with p-toluene-sulfonyl chloride 154 in the presence of catalytic amounts of Et$_3$N (Scheme 30) [50].

7-Hydroxy coumarin 62 reacted with various alkyl bromides 30 under reflux conditions in the presence of K$_2$CO$_3$ to yield coumarin derivatives 63 in high yield, and further reaction of 63 with imidazoles 156 in CH$_3$CN led to coumarin–imidazoles 157 (Scheme 31) [51].

A series of imidazo[1,2-a]pyridine-coumarin 161 hybrids were synthesized through Blackburn–Bienayme multi-component reaction of 4-hydroxy-3-formylcoumarin 158 with heterocyclic 2-aminoazines substrate 159 and isocyanides in Scheme 27

**Scheme 27** Preparation of coumarin/pyrazole hybrids

**Scheme 28** Synthesis of novel coumarin–pyrazole carboxamide derivatives

**Scheme 29** Synthesis of 2,3-dihydrochromeno[3,4-d] imidazol-4(1H)-one derivatives
in the presence of acetic acid under reflux conditions (Scheme 32). The prepared derivatives proved to be able to interfere with allosteric site of NS5B protein [52].

The compound 165 was synthesized via one-pot multicomponent reaction of the pyrene-4,5-dione 164, ammonium acetate, 4-(tert-butyl)aniline 113 and 7-(diethylamino)coumarin-3-carbaldehyde 163 in acetic acid as the medium. Furthermore, 7-(diethylamino)coumarin-3-carbaldehyde 163 was obtained via two-step reactions from 4-(diethylamino)-2-hydroxybenzaldehyde 84. First, 7-diethylamino-coumarin 162 was synthesized from Knoevenagel condensation reaction of 4-(diethylamino)-2-hydroxybenzaldehyde 84 with diethyl malonate, and then the subsequent Vilsmeier–Haack formylation of 7-diethylamino-coumarin 162 in 1,2-dichloroethane produced 7-(diethylamino)coumarin-3-carbaldehyde 163 (Scheme 33) [53].

7-(4-Bromobutoxy)-2H-chromen-2-one 63 was prepared via reaction of 7-hydroxy-2H-chromen-2-one 62 with 1,4-dibromobutane in the presence of anhydrous K₂CO₃ and triethylamine. Then, 63 was transformed to 7-(4-(1H-benzo[d]imidazol-1-yl)butoxy)-2H-chromen-2-one 166 via reaction with benzimidazole in the presence of anhydrous K₂CO₃ and anhydrous acetonitrile (Scheme 34) [54].

The reaction of 7-hydroxy-2H-chromen-2-one 62 with 1,4-dibromobutane 30 afforded 7-(4-bromobutoxy)-2H-chromen-2-one 63. Further reaction of 63 with 4-methyl-1H-imidazole 156 in tacetonitrile led to 7-(4-(4-methyl-4,5-dihydro-1H-imidazol-1-yl)butoxy)-2H-chromen-2-one 167. This study showed that this compound can be used to control rhabdovirus infection in fish aquacultures (Scheme 35) [55].

Coumarin derivatives 169 containing imidazole skeleton as potential anti-bacterial agents were synthesized from 7-hydroxy coumarin 168 by reacting with corresponding amines and triethylamine in anhydrous EtOH at reflux conditions (Scheme 36) [56].

Four donor–acceptor triphenylamine- and N-phenyl carbazole-based coumarin dyes were synthesized from the reaction of aldehydes (170 and 175) with 2-(1H-benzo[d]imidazol-2-yl) acetonitrile 171 or 2-(benzo[d]thiazol-2-yl)acetonitrile 172 intermediate in the presence of piperidine in EtOH. The results showed that the synthesized rigid donor-π-acceptor coumarins are better candidates for NLO materials (Scheme 37) [57].
3-Imidazolyl coumarin compounds 178 were synthesized through the condensation reaction of salicylaldehyde derivatives 1 into ethyl acetoacetate 2 catalyzed followed by the [3 + 2] cycloaddition reaction of 3-acetylcoumarin 37 and 2-aminopyridine 159 catalyzed by iodine. The compounds exhibited dual efficient luminescence, which was blue fluorescence with the highest fluorescence quantum yield being more than 0.9, and also displayed favorable yellow solid-state fluorescence (Scheme 38) [58].

Coumarins containing theophylline core

Mangasuli et al. synthesized new coumarin–theophylline hybrids 181 via the reaction of theophylline 180 with the substituted 4-bromomethyl coumarin 179 in the presence of K₂CO₃ as activated catalyst (Scheme 39). All final products have shown excellent anti-tubercular activity, and of course, electron-donating compounds displayed significant anti-microbial activity [15].

Coumarins containing quinolone core

In an interesting procedure, the reaction of various dibromides 30 with 7-hydroxy-4-methyl coumarins 3 under reflux condition yielded bis-coumarins 182 in the presence of an alkaline catalyst. The bromoalkoxy derivatives of 7-hydroxy-4-methyl coumarins 168 were prepared through the bromoalkylation of 7-hydroxy-4-methyl coumarin 3 with various dibromides 30. Finally, a complex catalyst system of KOH, KI and tetrabutyl ammonium bromide (TBAB) was developed to prepare compounds 184 and 186 in high yield. Compounds 184 and 186 were then prepared by the...
reaction between 7-bromoalkoxy-4-methyl coumarins 168 with 6-methoxy-4-methyl quinolone 183 and 6-hydroxy-4-methylquinolone 185, respectively (Scheme 40) [59].

A simple method was developed for the synthesis of quinoline–coumarin derivatives 189 by an Ugi four-component reaction involving coumarin-3-carboxylic acid 187, 2-chloroquinoline-3-carbaldehyde derivatives 188, cyclohexyl isocyanide 8 and various amines 113 in methanol. Cytotoxic effects of all products were studied in A2780 human ovarian cancer cells (Scheme 41). Two synthesized compounds (R1=5,8-dimethyl and R2=H or m-CH3) displayed more anticancer activity than other derivatives [60].

Compounds 190 were synthesized via Knoevenagel condensation of substituted salicylaldehydes 13 and diethylmalonate 2 in the presence of piperidine. Then, compounds 190 on hydrolysis afforded coumarin-3-carboxylic acids 187. Finally, 2-oxo-2H-chromene-3-carboxylic acid N’-[2-(quinolin-8-yloxy)-acetyl]-hydrazide analogs 192 and 2-oxo-2H-chromene-3-carboxylic acid (4-phenyl-thiazol-2-yl)-amide analogs 194 were synthesized in good yield through coupling coumarin-3-carboxylic acids 187 with quinoline acetic hydrazide 191 and 2-amino-4-phenyl thiazoles 193, respectively, using TBTU as a coupling agent (Scheme 42). Chromene–thiazol analogs showed better anti-neoplastic activity than the other synthesized compounds.
activity in comparison with chromene–quinolin analogs [61].

2-Methylquinolin-8-ol 195 reacted with ethyl bromoacetate 196 in the presence of K$_2$CO$_3$ to yield compound 197 that led to ethyl 2-((2-formylquinolin-8-yl)oxy)acetate 198 via oxidation. Compounds 198 reacted with NaBH$_4$ to form ethyl 2-((2-(hydroxymethyl)quinolin-8-yl)oxy)acetate 199 that led to compound 200 via bromination. On the other hand, coumarin 202 reacted with compound 200 in the presence of NaHCO$_3$ to yield corresponding coumarin–quinoline 203 (Scheme 43) [62].

**Coumarins containing pyridine core**

Treatment of 3-acetyl-8-methoxy-2H-chromen-2-one derivatives 204 with equimolar of imethylformamide–dimethylacetal (DMF–DMA) in refluxing toluene afforded the corresponding enaminone 205 which upon condensation with
acetyl acetone or ethyl acetoacetate in glacial acetic acid in the presence of ammonium acetate furnished pyridine hybrids 206 (Scheme 44) [63].

The picolinonitrile derivatives 208 were prepared through the reaction of chalcone derivatives 207 with malononitrile 122 using ammonium acetate 151 in the presence of glacial acetic acid under reflux conditions (Scheme 45). The synthesized hybrids showed cytotoxic activity against liver cancer [63].

The coumarin derivative 3, having two pyridyl cores for metal coordination, was prepared by a nucleophilic substitution reaction and a subsequent Pd-catalyzed Sonogashira coupling (Scheme 46) [64].

2-Iminocoumarins 214 were prepared via Knoevenagel condensation between substituted salicyaldehydes 13 and 2-pyridylacetonitrile 213. The resulting 2-iminocoumarins were converted to 3-(pyridin-2-yl)coumarin derivatives 215 by acid hydrolysis of the imines (Scheme 47) [65].

According to Scheme 48, coumarin-based hybrids 219 were prepared via reaction between the pyridin-4(1H)-one (A) and 3-bromomethyl coumarin 218. The gathered intermediates 219 were refluxed in 50% acetone–water solution, subsequently treated with propargyl bromide or corresponding benzyl bromide in the presence of K$_2$CO$_3$ to afford the intermediate 220. Then, the protecting group on pyridinone moiety was removed to obtain the final compounds 221 (Scheme 48) [66].

A new coumarin derivative 226 was synthesized through the condensation reaction of 8-formyl-7-hydroxycoumarin 222 with niacin hydrazide 225 under reflux conditions and used as an efficient turn-on fluorescent chemosensor for Al$^{3+}$ (Scheme 49) [67].

**Coumarins containing pyrimidine core**

4-Amino-2-(3-hydroxyphenyl)-6a,10a-dihydro-5H-chromeno[4,3-d]pyrimidin-5-one 229 was obtained...
through the one-pot reaction of salicylic aldehyde 13, 3-hydroxybenzaldehyde 227, ethyl cyanoacetate 228 and ammonium acetate 151 under reflux conditions. Then, 3'-sulfonate-substituted 2-phenyl-benzopyranopyrimidine derivatives 231 were obtained from reaction of compound 229 with sulfonyl chlorides 230 in DMF (Scheme 50). The results displayed that all of the derivatives had desirable effect on resisting tumor cell proliferation [68].

Coumarins containing indole core

Novel photochromic indolinospiropyrans containing coumarin 234 were obtained via the reaction of 5-hydroxy-4,7-dimethyl-2-oxo-2H-chromene-6,8-dicarbaldehyde 232 with 1-R-5-R\(^{-1}\)-2,3,3-trimethyl-3H-indol-1-ium perchlorate 233 in the presence of catalytic amounts of Et\(_3\)N under reflux conditions (Scheme 51) [69].
Hajra et al. described a palladium-catalyzed cross-dehydrogenative coupling reaction of coumarin 33 and aniline 113 for the synthesis of indole–coumarin derivatives 235. The reported method is simple, and O₂ is used as sole oxidant (Scheme 52) [70].

Chen et al. reported an efficient palladium-catalyzed/microwave-assisted intramolecular cross-dehydrogenative coupling reaction for facile synthesis of indolo[2,3-c]coumarins 237 in high yields (Scheme 53) [71].

**Coumarins containing thiazole and diazole core**

A series of coumarinyl thiazoles 240 have been synthesized as shown in Scheme 30. First, the 3-(2-bromoacetyl)-2H-chromen-2-one 238 was readily synthesized through condensation between salicylaldehyde 13 and ethyl acetocetate 2 catalyzed by piperidine and subsequent bromination. Then, condensation of intermediate 238 with various acetoephones 239 and thiosemicarbazide 125 in the presence of glacial acetic acid as catalyst led to the coumarinyl thiazole 240 (Scheme 54) [72].

In another attempt, the coumarinyl hydrazide 241 was reacted with carbon disulfide in the presence of ethanolic solution of KOH under reflux conditions to afford corresponding 3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one 242. The resultant compound 242 was treated with paraformaldehyde 243 and various amines 244 in one-pot reaction to get the coumarinyl oxadiazole-2(3H)-thione hybrids 245 (Scheme 55) [72].

A series of thiazole-containing coumarin derivatives 249 and 251 were synthesized as pharmacophore hybrids through Hantzsch cyclization of 3-(2-bromoacetyl)-2H-chromene-2-one 247 with various N-substituted thiourea 248 or N,N-di-substituted thiourea 250 derivatives (Scheme 56). Some of the synthesized compounds displayed considerable potency against anti-bacterial, anti-tubercular and anti-viral agents [73].

A series of novel 1-[5-[(2-benzoylbenzofuran-5-yl)methyl]-2-oxo-2H-chromen-3-yl][thiazol-2-yl]urea derivatives 171 were prepared through a stepwise procedure. Cyclization reaction of compound 252 with phenacyl bromide 253 in the presence of K₂CO₃ led to formation of 5-[(2-benzoylbenzofuran-5-yl)methyl]-2-hydroxybenzaldehyde 254. Further cyclization reaction of compound 254 with ethylacetocetate 2 in the presence of piperidine afforded 3-acetyl-6-[(2-benzoylbenzofuran-5-yl)methyl]-2H-chromen-2-one.
255. 3-(2-Aminothiazol-5-yl)-6-[(2-benzoylbenzofuran-5-yl)methyl]-2H-chromen-2-one obtained from the reaction of 255 with thiourea in the presence of catalytic amount of iodine. Finally, condensation of 255 into triphosgene and different amines led to 1-[5-{6-[(2-benzoylbenzofuran-5-yl)methyl]-2-oxo-2H-chromen-3-yl]thiazol-2-yl]urea derivatives 259 (Scheme 57). Most of the synthesized compounds exhibited a promising anti-microbial activity and cytotoxicity [74].

The synthetic method for the synthesis of 7-substituted coumarin derivatives 262 involves three steps. Initially, 7-hydroxy-4-methyl-2H-chromen-2-one 3 was formed through Pechmann reaction between resorcinol 1 and ethyl acetooacetate 2. Then, 4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one 261 was prepared via reacting 7-hydroxy-4-methyl-2H-chromen-2-one 3 with excess of epichlorohydrin 260 in the presence of K2CO3 under reflux conditions. The synthesis of target compounds 262 was accomplished from the nucleophilic opening of oxirane with diverse amines 113 in EtOH under refluxing condition (Scheme 58) [75].

In another attempt, coumarin–benzothiazole derivatives were synthesized in two steps (Scheme 59). In first step, substituted benzothiazole derivatives 264 were prepared via reacting substituted aniline 113, and potassium thiocyanate 263 in the presence of bromine in glacial acetic acid. In second step, substituted benzothiazole derivatives 264 were reacted with 4-methyl-7-(oxiran-2-ylmethoxy)-2H-chromen-2-one 261 to afforded final compounds 265 (Scheme 59). Products showed anti-inflammatory and analgesic activities. The presence of –OCH3 and –Cl groups in 265 at C6-position of benzothiazole ring were found very important substitutions for potent activity [75].

3-Thiazolylcoumarin derivatives 269 were prepared through one-pot and two-step reactions and screened for in vitro α-glucosidase inhibitory activity. In first step, various benzoxyadrazide derivatives 266 were treated with benzene isothiocyanates 267 in EtOH to afford thiosemicarbazide intermediates 268. In second step, resulted intermediate went under cyclization reaction when treated with...
3-(bromoacetyl) coumarin 238 in the presence of catalytic amount of Et₃N, to afford 3-thiazolyl coumarin derivatives 269 (Scheme 60). All compounds showed inhibitory activity in the range of IC₅₀ = 0.12 ± 0.01–16.20 ± 0.23 μM as compared to standard acarbose (IC₅₀ = 38.25 ± 0.12 μM), also found to be non-toxic [76].

3-Acetylcoumarin derivatives 37 were brominated using Br₂ in CHCl₃ solvent to give bromoacetyl analogs 238. In order to synthesis coumarins 272, dimethyl N-cyanodithioimidocarbonate 270 was treated with suitable amines and Na₂S to produce intermediates 8, which reacted with 3-(bromoacetyl)coumarins 238 in DMF. Also, the reaction of phenylisothiocyanates 267 with cyanamide and sodium mehtoxide afforded intermediate 273 that treated with coumarin 238 to give coumarins 274 (Scheme 61) [77].

The reaction of α-bromoacetylcoumarin 238 with thiocetamide in MeOH at room temperature furnished 3-(2-methylthiazol-4-yl)-2H-chromen-2-one 275, whereas refluxing compound 238 with potassium thiocyanate in EtOH at room temperature afforded 3-(2-ethoxythiazol-4-yl)-2H-chromen-2-one 276 (Scheme 62) [78].

1-Hydroxy-2-naphthaldehyde 277 reacted with ethylacetoacetate 2 in the presence of piperidine to yield corresponding 2-acetyl-3H-benzo[f]chromen-3-one 278 that led
A new fluorescent sensor 285 was synthesized using Schiff base reaction connected by 7-(N,N-diethylamino) coumarin-3-aldehyde 163 and 2-hydrizinobenzothiazole 284. CHT fluorescent sensor was used for fluorescent imaging of Cu^{2+} ions in A549 and MCF-7 cells, showing its potential applications in live cell imaging (Scheme 64) [80].

Condensation reaction of 4-bromomethyl coumarin 179 into (E)-5-benzylidenethiazolidine-2,4-diones 286 in the presence of anhydrous K_{2}CO_{3} in acetone at room temperature was done to obtain anti-microbial coumarin–thiazolidine derivatives 287 (Scheme 65) [81].

The target molecule 288 was prepared in four steps, as shown in Scheme 1. Firstly, 4-(diethylamino)-2-hydroxybenzaldehyde 84 was condensed into diethyl malonate in the presence of piperidine, cyclized and decarboxylated in one step to afford 7-(diethylamino)-2\(H\)-chromen-2-one 283. Subsequently, the compound was formylated (Vilsmeier–Haack) to obtain 7-(diethylamino)-2-oxo-2\(H\)-chromene-3-carbaldehyde 163, which was condensed with corresponding 2-(2-bromoacetyl)-3\(H\)-benzo[f]chromen-3-one 4279 via bromination. Compound 279 reacted with 2-(4-fluorobenzylidene) hydrazine carbothioamide to form 2-(2-(2-(4-fluorobenzylidene)hydrazinyl)thiazol-4-yl)-3\(H\)-benzo[f]chromen-3-one 282. Also, compound 279 reacted with thioacetamide to form 2-(2-methylthiazol-4-yl)-3\(H\)-benzo[f]chromen-3-one 280 (Scheme 63). The synthesized benzocoumarins showed anti-bacterial activity [79].

Scheme 60 Syntheses of 3-thiazolyl coumarin derivatives

Scheme 61 Synthesis of new coumarins bearing 2,4-diamino-thiazole-5-carbonyl moiety

Scheme 62 One-pot synthesis of thiazolyl–coumarin hybrids

Scheme 63 Syntheses of 3-thiazolyl coumarin derivatives

Scheme 64 Synthesis of new coumarins bearing 2,4-diamino-thiazole-5-carbonyl moiety

Scheme 65 One-pot synthesis of thiazolyl–coumarin hybrids
2-(4-oxo-2-thioxotetrahydrothiophen-3-yl) ethanesulfonic acid to yield the target molecule \(288\) (Scheme 66) [82].

A series of \(S\)-benzylated or \(S\)-alkylated-coumarins \(294\) were synthesized by reacting 7-((5-mercapto-1,3,4-oxadiazol-2-yl)methoxy)-4,5-dimethyl-2\(H\)-chromen-2-one \(293\) with various alkyl and benzyl halides in the presence of \(K_2CO_3\) at room temperature. 2-((4,5-Dimethyl-2-oxo-2\(H\)-chromen-7-yl)oxy)acetohydrazide \(292\) was used to be cyclized in the presence of \(CS_2\) and \(K_2CO_3\) in \(EtOH\) to obtain 5-mercapto-1,3,4-oxadiazol-2-yl \(293\). After successful formation of coumarins \(294\), their oxidation was performed by using \(m\)-CPBA as oxidizing agent in DCM to produce 1,3,4-oxadiazole derivatives \(295\) in good yields (Scheme 67) [83].

Coumarins \(296\) reacted with 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole analogs \(297\) by using \(KI\) and \(K_2CO_3\) in acetone to give coumarin-1,2,4-oxadiazole hybrids \(298\) in good yields (Scheme 68). All synthesized compounds were screened for their anticonvulsant activities [84].

Ethyl 2-(4-methyl-2-oxo-2\(H\)-chromen-7-yloxy) acetate \(299\) was prepared by reaction of 7-hydroxy-4-methyl coumarin \(3\) with ethyl bromoacetate and anhydrous potassium carbonate in dry acetone. The 2-((4-methyl-2-oxo-2\(H\)-chromen-7-yl)oxy) acetohydrazide \(300\) was synthesized of compound \(299\) by reacting with hydrazine hydrate in THF under reflux conditions. Then, the cyclization of chromen \(300\) was achieved by refluxing with carbon disulfide in basic conditions; thus, chromen \(301\) was obtained. Finally, the target coumarin-1,3,4-oxadiazole hybrids \(302\) were prepared by refluxing various halides with compound \(301\) (Scheme 69).
All of the synthesized coumarin hybrids showed anticancer activity [85].

**Coumarins containing imide band**

Base-catalyzed Claisen–Schmidt condensation of 3-acetyl-8-methoxy-2H-chromen-2-one 204 with different aldehydes using piperidine as catalyst yielded chalcone hybrids 303. Condensation of 204 into cyanoacetylhydrazine in methanol containing acetic acid afforded acetohydrazide derivative 304 and subsequent coupling of different substituted with various aldehydes yielded acrylohydrazides 305 (Scheme 70) [86].

A large library of coumarin-3-carboxamide derivatives 307 were prepared through reaction of 2-oxo-2H-chromene-3-carboxylic acid 187 with anilines in dry DMF in the presence of DIEA and propyl phosphoric acid anhydride (T3P). Also, coumarin-3-carboxamide derivatives 306 were obtained via reaction of 2-oxo-2H-chromene-3-carboxylic acid 187 with hydrazine hydrochloride derivatives in anhydrous CH2Cl2 (Scheme 71). All products were evaluated in vitro for their antifungal activities against *Alternaria solani*, *Botrytis cinerea*, *Gibberella zeae*, *Cucumber anthrax*, *Rhizoctonia solani* and *Alternaria leaf spot* [87].

A new series of 3-formylcoumarin derivatives 309 were synthesized through reaction of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde 308 with various known
benzohydrazides 266 in the presence of acetic acid (Scheme 72). All derivatives indicated an acceptable degree of thymidine phosphorylase inhibition with IC50 values ranging between 0.90 ± 0.01 and 53.50 ± 1.20 nM [88].

Coumarin-3-carboxamides bearing tryptamine moiety 310 were achieved in reasonable yields from the reaction of coumarin-3-carboxylic acids 187 with SOCl2 and tryptamine in the presence of catalytic amounts of K2CO3 in dry toluene under reflux condition (Scheme 73). Then, in vitro assessment of the synthesized compounds 310 revealed that most of them had notable activity toward acetylcholinesterase (AChE) [89].

The synthetic method of fused tricyclic coumarins 313 was outlined in Scheme 74. At first, a series of cyano aceta-
mide derivatives 311 were prepared via simple reaction of amines with equivalent amount of ethylcyanoacetate 228. Also, resorcinol 1 and ethylacetoacetate were treated under Pechmann conditions to give 7-hydroxy-4-methyl coumarin 3, and then compound 3 was treated with hexamethylenetetramine in glacial acetic acid and underwent Duff formylation, to provide 8-formyl-7-hydroxy-4-methyl coumarin 312. Subsequently, compound 312 was condensed with various N-substituted cyano acetamide derivatives 311 in the presence of Et3N afforded the final products 313 (Scheme 74). The biological evaluation showed that most of these molecules were potent and selective AChE inhibitors, which are 2–220 folds more potent than the positive control, galantamine [90].

In an interesting procedure, compound 314 was reacted with N-bromosuccinimide (NBS) in the presence of AIBN to yield 315, which was then condensed into appropriate amines in the presence of triethylamine in CH2Cl2.
to afford 316. Hydrogenation of compound 316 via Fe/NH₄Cl obtained 317. Final products 318 were obtained through addition of 187 to intermediate 317 in dry CH₂Cl₂ (Scheme 75) [91].

Vafadarnejad et al. synthesized several coumarin–pyridinium hybrid derivatives 322 by Ellman’s method. N-Ethyl-2-oxo-2H-chromene-3-carboxamide-pyridine derivatives 320 were prepared by condensation of 2-oxo-2H-chromene-3-carboxylic acid 187 and compound 319 in CH₃CN. Additional reaction of 320 with appropriate benzyl halides 321 under reflux conditions afforded final products 322 (Scheme 76) [92].

The preparation route of the primaquine–coumarin probe (PQCP) is shown in Scheme 77. Meldrum’s acid was acylated using methyl 5-chloro-5-oxovalerate 323 and subsequently treated with MeOH to provide β-keto ester 325. Then, β-keto ester 325 was first reacted with resorcinol 1 under acidic conditions and hydrolyzed by lithium hydroxide to provide 4-(7-hydroxy-2-oxo-2H-chromen-4-yl) butanoic acid 326. Finally, primaquine and coumarin butanoic acid 326 were coupled under standard EDCI/DMAP coupling conditions to yield the probe PQCP 327 (Scheme 77) [93].

The coumarin-based sensor 328 was designed and synthesized of reaction 7-(diethylamino)-2-oxo-2H-chromene-3-carbaldehyde 163 with 2-hydroxybenzohydrazide 266 in ethanol solution at room temperature (Scheme 78). Generally, Shen et al. introduced a new strategy to design coumarin-based functional sensor for Cu(II) detection with

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**Scheme 73** Synthesis of coumarin-3-carboxamides bearing tryptamine moiety

**Scheme 74** Synthetic pathway of fused tricyclic coumarin derivatives

**Scheme 75** Synthesis of coumarin-3-carboxamide derivatives

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fluorescence “OFF” switching mechanism via blocking intramolecular charge transfer (ICT) [94].

The target compounds were prepared according to published method which involved converting 7-amino-4-methyl-2H-chromen-2-one to its diazonium salt upon reaction with 3-chloropentane-2,4-dione afforded N-(4-methyl-2-oxo-2H-chromen-7-yl)-2-oxopropanehydrazonoyl chloride. Reaction of chromen with the appropriate amino acid methyl ester led to the formation of compounds 331 (Scheme 79) [95].

The coumarin derivatives 333 were synthesized via reaction of substituted salicylaldehyde 13 and N-(substituted) phenyl malonic acid 332 through Knoevenagel condensation reaction in the presence of piperidine as catalyst (Scheme 80). All synthesized compounds showed moderate to good anti-bacterial and antifungal activities [96].

The starting material, 4-bromomethyl coumarins 179 were synthesized via Pechmann cyclization of phenols 335 with ethyl 4-bromoacetooacetate 334 using H₂SO₄ as cyclizing agent. The synthesized coumarins 179 on treating with 4,4-dimethylpip eridine-2,6-dione 336 in the presence of anhydrous K₂CO₃ afforded coumarin-cyclic-imide derivatives 337 with good yields (Scheme 81) [97].

Anti-bacterial coumarins 339 were achieved in reasonable yields from one-pot, five-component sequential Knoevenagel-Ugi reaction of Meldrum’s acid 338, salicylaldehyde 13, aniline 113, isocyanides 160 with aldehydes 119 in the absence of catalysts in EtOH (Scheme 82). The synthesized products displayed good anti-bacterial activities against both Gram-positive and Gram-negative strains [98].
Methionine methyl ester-modified coumarin 340 was synthesized by reaction of ethyl-7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate 201 with methionine methyl ester hydrochloride in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). The results showed that compound 340 could be used as a colorimetric chemosensor for Cu²⁺ (Scheme 83) [99].

Dihydroxybenzyldehyde 13 was subjected to condensation reaction with Meldrum's acid in water to obtain carboxylic acid 187. It was then converted to a series of anti-austerity 7-hydroxycoumarins 341 via the condensation reaction with appropriate amines by using EDC and HOBt or HOAt (Scheme 84) [100].

Oxime ethers 343 obtained from 4-bromomethycoumarins 179 and benzil monooxime 342 have undergone an unusual transformation into coumarin-4-carboxamides 344 (Scheme 85) [101].

### Coumarins containing cyano band

New 3-cyanocoumarin derivatives 347 were prepared by reaction of 2-(2-chlorobenzylidene)malononitrile 345 with resorcinol or 3-methoxyphenol 346, and then further oxidation of 347 and replacement reaction with acetic anhydride in reflux conditions led to 4-(2-chlorophenyl)-3-cyano-2-oxo-2H-chromen-7-yl acetate 349 (Scheme 86). Study of optical properties of the synthesized compound showed that it is strong fluorescence in purple and blue areas [102].

3-Cyanocoumarine derivatives 352 were prepared via multi-component one-pot reaction of prepared...
Bardasova et al. synthesized some new 4-alkyl-6,8-dibromo-7-hydroxy-2-oxo-2H-chromene-3-carbonitriles via the bromination of 2-amino-4-alkyl-4H-chromene-3-carbonitriles with bromine in acetic acid, followed by hydrolysis (Scheme 88) [104].

Compound 357 was prepared via coupling of 7-(diethylamino)coumarin-3-aldehyde and 2-(1-(4-aminophenyl)ethylidene)malononitrile. The compounds 358 and 359 were prepared to mix 357 with acetic anhydride by conventional and microwave irradiation procedures, respectively.

The results showed that these compounds could be used as dyes (Scheme 89) [105].

As depicted in Scheme 90, 7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde was formed via the reaction of 3 and hexamine then reaction of 312 with malononitrile in the presence of triethylamine which led to a coumarin-based fluorescent probe 360 (Scheme 90) [106].

Cyclobutanone oxime ester 361 reacted with coumarins 362 containing electron donating and electron withdrawing groups in the presence of iron as catalyst to give the target products 363 in moderate to good yields (Scheme 91) [107].

**Coumarins containing alkyl and aryl groups**

Coumarin derivatives 365 were prepared through Bronsted acid-mediated condensation, intramolecular cyclization of phenols 335 and propiolic acids 364 in the presence of trifluoromethanesulfonic acid (TfOH) in excellent yield (Scheme 92) [108].

Li et al. introduced polyvinylpyrrolidone-supported phosphotungstic acid (PVP–HPW) as an effective catalyst in...
preparation of 7-hydroxy-4-methyl coumarin 3 (Scheme 93) [109].

Two various series of analogs of 6,7-aryl/hetaryl coumarins 367 and 371 have been synthesized by using Suzuki–Miyaura across coupling reaction of 4-methyl-2-oxo-2H-chromen-7-yl trifluoromethanesulfonate 366 and 4-methyl-2-oxo-2H-chromen-6-yl trifluoromethanesulfonate 370 in good yields. 7-Hydroxy-4-methyl-2H-chromen-2-one 3 prepared by cyclization of resorcinol 1 with ethylacetoacetate 2 in the presence of H2SO4. Subsequent reaction of 3 with trifluromethanesulfonic anhydride (Tf2O) afforded 4-methyl-7-((trifluromethyl)sulfonyl)-2H-chromen-2-one 366. 7-(aryl

and heteryl)-4-methyl coumarins 367 obtained through condensation of coumarin triflate 366 with boronic acids in the presence of Pd(PPh3)4 and K2CO3 in DMF (Schemes 94, 95) [110].

Also, 6-(aryl and heteryl)-4-methyl coumarins 371 were prepared according to the previous reported method, only with the difference that hydroquinone is used instead of resorcinol. The synthesized compounds 227 and 29 were tested for anti-proliferative activity against different human cancer cell lines such as SiHa, MDAMB-231, and PANC-1; some of the products displayed distinctive effects (Scheme 95) [110].

An effective synthesis of 2-acylated and sulfonated 4-hydroxycoumarins 373 has been achieved via the reaction of 4-hydroxycoumarin 33 with acyl chloride 372 in the
The presence of dry pyridine as catalyst at room temperature (Scheme 96) [111].

The preparation of coumarin-3-carboxylic acids 187 in excellent yields was realized by a triethylamine catalyzed Knoevenagel-intramolecular cyclization tandem reaction of various ortho-hydroxyaryl aldehydes 13 with Meldrum’s acid 338. This method has advantages such as clean reaction conditions, using much less water as solvent, a cheap and eco-friendly catalyst, simple workup procedure and easy isolation (Scheme 97) [112].

Chaudhari and co-worker introduced calcium nitrate (Ca(NO₃)₂.4H₂O as a mild and regioselective reagent to nitration of hydroxycoumarin 374 in the presence of acetic acid at 60 °C (Scheme 98) [113].

Hydroxy-3-arylcoumarins 384 were synthesized via a two-step strategy. The first step is a Perkin–Oglialoro condensation of various hydroxybenzaldehydes 216 and arylacetic acids 382, using potassium acetate in acetic anhydride under reflux conditions, to obtain the precursor acetoxy-3-arylcoumarins 383. The second step is hydrolysis and 1,3-diketone 2 followed by reaction with formaldehyde and appropriate amines. Also, a new series of hydroxy coumarins 380 and 381 were synthesized in one-pot procedure from the reaction of phloroglucinol 379 with propionic acid or ethyl acetoacetate, respectively (Scheme 99). Synthesized compounds containing the CH₂Cl group showed high antioxidants activity [114].

Hydroxy-3-arylcoumarins 384 were synthesized via a two-step strategy. The first step is a Perkin–Oglialoro condensation of various hydroxybenzaldehydes 216 and arylacetic acids 382, using potassium acetate in acetic anhydride under reflux conditions, to obtain the precursor acetoxy-3-arylcoumarins 383. The second step is hydrolysis and 1,3-diketone 2 followed by reaction with formaldehyde and appropriate amines. Also, a new series of hydroxy coumarins 380 and 381 were synthesized in one-pot procedure from the reaction of phloroglucinol 379 with propionic acid or ethyl acetoacetate, respectively (Scheme 99). Synthesized compounds containing the CH₂Cl group showed high antioxidants activity [114].
of the obtained acetoxy derivatives, in the presence of HCl, to achieve the final substituted hydroxy-3-arylcoumarins \(384\) (Scheme 100) [115].

Yamaji et al. synthesized two isomeric compounds (\(386a\) and \(386b\)) to have fused skeletons of coumarin and fluorene via photochemical cyclization of olefin \(385\) (Scheme 101). The synthesized compounds showed different absorption and fluorescence features in solution [116].

The synthetic method of compounds \(256\) is shown in Scheme 76. Intermediate \(252\) was easily obtained from the reaction of methyl salicylate \(387\) and 4-methoxyphenylacetic acid \(388\). The 3-(4-methoxyphenyl)-4-hydroxy coumarin \(390\) was prepared from intermediate \(389\) via intramolecular Claisen condensation. Further treatments with TsCl in the presence of \(\text{Et}_3\text{N}\) afforded the 3-(4-methoxyphenyl)-4-tosyloxy coumarin \(391\). The target compounds \(392\) were generated by nucleophilic substitution of \(391\) with nine kinds of anilines \(113\) (Scheme 102). Some of the coumarin derivatives \(392\) exhibited better anti-proliferative activities against the tested cells than positive control (5-Fluorouracil) [117].

4-Arylcoumarin derivatives \(402\) were prepared through a stepwise procedure. \(\alpha\)-methoxy-4-phenylchromenones \(401\) synthesized by cyclization reaction of phenols \(335\) with ethyl-3,4-dimethoxybenzoylectate \(400\) and \(\text{CF}_3\text{COOH}\) under heat in reasonable yields and short reaction times. Finally, the reaction of compound \(401\) with boron tribromide in \(\text{CH}_2\text{Cl}_2\) at room temperature afforded 4-arylcoumarin derivatives \(402\) (Scheme 104). Products were screened for their antioxidant capacity, ability to chelate iron ions and scavenge the

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**Scheme 99** Synthesis of hydroxycoumarin derivatives as antioxidant agents

**Scheme 100** Synthesis of hydroxyl-substituted 3-arylcoumarins

**Scheme 101** Photocyclization procedure from compound \(385\) to compounds \(386a\) and \(386b\)

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1,1-diphenyl-1-picrylhydrazyl (DPPH) radical as well. The results demonstrate that compounds bearing dihydroxyl groups at 6- and 7-positions of the benzopyrone ring of the arylcoumarin structure showed best antioxidant [119].

7-Butoxy-6-(4-(diphenylamino)phenyl)-4,8-dimethyl-2H-chromen-2-one (TC) and 7-butoxy-6-(4-(diphenylamino)phenyl)-8-methyl-4-(trifluoromethyl)-2H-chromen-2-one (TF) were prepared through a stepwise procedure. Condensation of 2-methylbenzene-1,3-diol via methyl 3-oxobutanoate in the presence of ZrCl4 led to formation of 7-hydroxy-4,8-dimethyl-2H-chromen-2-one derivatives. The reaction of compound with iodine afforded compound . Chromen derivatives were obtained from the reaction of 7-hydroxy-6-iodo-4,8-dimethyl-2H-chromen-2-one with 1-bromobutane in the presence of catalytic amount of K2CO3. Finally, the reaction of chromens with (4-(diphenylamino)phenyl) boronic acid in the presence of Na2CO3 led to formation of final product (Scheme 104, 105) [120].

4-Methyl-6,7-dihydroxy coumarin 377 has been selected as a key intermediate to prepare new coumarin derivatives. The reaction of 4-methyl-6,7-dihydroxy coumarin 377 with triflic anhydride (Tf2O) in the presence of Et3N afforded bis(triflate). Reaction of bis(triflate) with arylboronic acids in the presence of K3PO4, and Pd(PPh3)4 via Suzuki–Miyaura reaction led to 4-methyl-6,7-diarylcoumarines. Also, reaction of 377 with bromine afforded the brominated product in good yield. Compound was converted into bis-triflate. Suzuki–Miyaura cross-coupling reaction of bis-triflate with various arylboronic acids in 1,4-dioxane afforded the 4-methyl-3,6,7-tris(aryl) coumarines (Scheme 106). All compounds were tested for their in vitro anti-HIV-1 (strain IIIb) and HIV-2 (strain ROD) activities in human (MT-4) cells based on an MTT assay [121].
A series of 3\(H\)-benzo[f]chromen-3-ones 418 containing the 2-hydroxybenzyl or (2-hydroxy-1-naphthyl)methyl substituents in position 2 were prepared via the reaction of 2-naphthols 416 with 2-trifluoroacetyl-1\(H\)-benzo[f]chromenes 417 in the presence of DBU. The reaction includes 1,4-addition and intramolecular haloform type reaction followed by opening of the dihydropyran ring (Scheme 107) [122].

The target compound, 6-[(4-methyl-2-oxo-2\(H\)-chromen-7-yl)oxy]hexanoate 420 was prepared of the reaction 7-hydroxy-4-methyl coumarin 3 with ethyl-6-bromo-hexanoate 419 in the presence of anhydrous potassium carbonate in dry DMF (Scheme 108). Molecular docking studies showed that the molecule is a potent MMP9 inhibitor to yield anti-rheumatoid arthritis activity [123].

Coumarins containing a hydroxy group at positions 3, 4 or 6 (33) reacted with commercially available various substituted sulfonyl chlorides 230 in THF in the presence of triethyl amine as base to afford the desired coumarin sulfonates 421 (Scheme 109). The products were investigated for their effects on oxidative burst activity of zymosan-stimulated whole blood phagocytes using a luminal-enhanced chemiluminescence technique [124].

Benzo[h]coumarins 423 were prepared through Knoevenagel condensation method by reacting hydroxynaphthalene aldehyde 422 into cyanomethylene-benzazoles 82 containing NH, O and S elements, respectively, as the active methylene compounds (Scheme 110) [125].

New polyphenolic hybrid–coumarin derivatives 431–433 were synthesized according to the outlined
Scheme 107 Synthesis of benzo[f]coumarins from 2-trifluoroacetyl-1H-benzo[f]chromenes and 2-naphthols

Scheme 108 Synthesis of ethyl 6-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]hexanoate

Scheme 109 Synthesis of coumarin sulfonates

Scheme 110 Synthesis of benzo[h]coumarins

Scheme 111 Synthesis of new polyphenolic hybrid–coumarins

The reaction of benzene-1,2,3-triol 424 with ethyl 4-chloro-3-oxobutanoate 425 afforded 4-chloromethyl-7,8-dihydroxycoumarin 295, further reaction of 426 with acetic anhydride in the presence of NaOH led to 4-(chloromethyl)-2-oxo-2H-chromene-7,8-diyl diacetate 427. The reaction of protected halo-coumarin 427 with acylated acid derivatives 428-430 in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dry DMF and decylation of hydroxyl groups by NaHCO₃ in acetone formed the desired polyphenolic derivatives (Scheme 111) [126].

6-Substituted-5-(4-bromobutoxy)-4,7-dimethyl coumarins 435 were prepared via reaction of compound 434 with 1,4-dibromobutane 30 in the presence of catalytic amounts of KI under microwave irradiation. Then, 435 was transformed to 5-[4-(4-aryl-1-piperazinyl)butoxy]coumarins 437 via reaction with corresponding N-substituted piperazine 436 in acetonitrile in the presence of K₂CO₃ and KI under microwave irradiation (Scheme 112). The synthesized compounds exhibited reasonable anti-bacterial, antifungal and anti-tumor activities [127].
The preparation of aryl/heteroarylpiperazinyl derivatives 439 was achieved through the efficient synthetic route outlined in Scheme 113. 8-Acetyl-7-hydroxy-4-methylchromen-2-one 312 converted to 8-acetyl-7-(3-bromopropoxy)-4-methylchromen-2-one or 8-acetyl-7-(4-bromobutoxy)-4-methylchromen-2-one 438 via the reaction with 1,3-dibromopropane or 1,4-dibromobutane 30 in the presence of KI and K$_2$CO$_3$ under microwave irradiation, respectively. Compound 438 was converted to aryl/heteroarylpiperazinylpropoxy/butoxychromen-2-one 439 by stirring with two equivalents of appropriate amine under microwave irradiation in the presence of KI and K$_2$CO$_3$ in acetonitrile (Scheme 113) [128].

A new 7-(bromomethoxy)-2H-chromen-2-ones 440 were synthesized via reaction between 7-hydroxy-2H-chromen-2-one 3, α,ω-dibromoalkane 30 and powdered K$_2$CO$_3$ in acetone. Reaction of 440 with benzylamines 441, powdered K$_2$CO$_3$ and a catalytic amount of KI in acetonitrile led to coumarin derivatives 442. Further, reaction of 442 with powdered K$_2$CO$_3$, 3-bromopropyne, a catalytic amount of KI in acetonitrile afforded 443 (Scheme 114). Some of the coumarin derivatives exhibited high anti-proliferative activities against 5-fluorouracil [129].

Anti-inflammatory coumarins with short- and long-chain hydrophobic groups were obtained by oxidation reaction of compounds 444 and 447 in the presence of NaIO$_4$ and OsO$_4$ (Scheme 115) [130].

A new class of coumarin derivatives 451 and 452 were synthesized via Williamson etherification reaction of 4-hydroxy-2H-chromen-2-one 33 or 7-hydroxy-2H-chromen-2-one 62 with alkyl halogenides 450 in the presence of potassium carbonate in DMF (Scheme 116). All prepared compounds were evaluated for their in vitro anti-microbial activities against E. coli and M. albicans and also their in vitro anti-proliferative activities against five selected human cancer cell lines (EC109, MGC-803, PC-3, MCF-7 and EC9706). 7-(2-bromoethoxy)-2H-chromen-2-one exhibited the highest growth inhibition against MCF-7 cell line [131].

An efficient strategy for the synthesis of trifluoromethylated coumarins via visible-light photoredox catalysis was developed using fac-Ir(ppy)$_3$ as the photocatalyst and trifluoromethanesulfonyl chloride as the trifluoromethylation reagent under mild conditions (Scheme 117) [132].

The condensation reaction between 3-acetylcoumarin 37 with various benzene sulfonyl hydrazide derivatives 455 was carried out in the presence of acetic acid glacial in EtOH to give novel coumarin–benzenesulfonylhydrazide derivatives 456 (Scheme 118) [133].

A metal- and oxidant-free photo catalysis procedure for the direct trifluoromethylation of coumarin derivatives by
sodium triflinate as the CF₃ source under xenon lamp irra-
dication was developed (Scheme 119) [134].

The chemodosimeter was prepared via the esterifica-
tion of coumarin using phenyl chloromethanethioate and 
N-Ethyldiisopropylamine in CH₂Cl₂ solvent at room
temperature (Scheme 120). The compound 458 could be 
used to detect the concentrations of Hg²⁺ in water [135].

An efficient and convenient strategy for the preparation of 
3-sulfonyl coumarins through ipso-cyclization/1,2-ester 
migration from substituted phenyl-3-phenylpropionate 459

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An efficient and convenient strategy for the preparation of 
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sodium triflate as the CF₃ source under xenon lamp irra-
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The chemodosimeter 458 was prepared via the esterifica-
tion of coumarin 3 using phenyl chloromethanethioate 457 and 
N-Ethyldiisopropylamine in CH₂Cl₂ solvent at room

coumarin–pargyline hybrids

Preparation of anti-inflammatory coumarins via oxidation reaction

Synthesis of novel coumarin derivatives from alkyl halogenides

Synthesis of trifluoromethylated coumarins

Synthesis of coumarin–benzenesulfonylhydrazide derivatives

Trifluoromethylation reaction of coumarins

Scheme 114  Synthesis of coumarin–pargyline hybrids

Scheme 115  Preparation of anti-inflammatory coumarins via oxidation reaction

Scheme 116  Synthesis of novel coumarin derivatives from alkyl halogenides

Scheme 117  Synthesis of trifluoromethylated coumarins

Scheme 118  Synthesis of coumarin–benzenesulfonylhydrazide derivatives

Scheme 119  Trifluoromethylation reaction of coumarins
with disulfide 460 and potassium persulfate as sulfonylating reagents was developed by Zhanga et al. (Scheme 121) [136].

New set of coumarin derivatives 463 were prepared by reacting different coumarin 3-carboxylic acids 187 with diverse phenyl esters 462 in the presence of EDC.HCl/DMAP as esterification agent (Scheme 122) [137].

Enos et al. have synthesized some coumarins derivatives 362 via Pechmann–Duisberg condensation of different phenols 335 and ethyl acetoacetate 2 in the presence of p-toluenesulfonic acid as a catalyst (Scheme 123) [138].

Coumarin derivatives 464 were prepared of 7-hydroxy-4-methyl coumarin 3 as a precursor, which was synthesized from resorcinol 1 and ethyl acetoacetate 2 in the presence of H2SO4. Further, the formed compound 3 was acylated using acetic acid in the presence of phosphorus oxychloride. Acylatedcoumarin 312 was reacted with various hydrazides 20 to afford the final compounds 464 (Scheme 124). All the compounds showed good to moderate anticancer activities against A-549, Hela, SKNSH, MCF-7 human cancer cell lines [139].

A series of novel coumarin-based 2,4-dinitrophenylhydrazones 467 were synthesized via the reaction of substituted 3-benzoyl coumarins 465 with 2,4-dinitrophenylhydrazine 466 in dimethylformamide and used as photosensitizers on zinc nanocones (Scheme 125) [140].

Phloroglucinol 379 was treated with ethyl cetoacetate or trifluoroacetoacetate 2 in acetic acid and catalyzed by H2SO4 to give coumarin 381. Methylation of compound 381 yielded 5,7-dimethoxycoumarin 468, and then nitration of 468 obtained compound 469. Reduction of 469 yielded amidocoumarin 470 (Scheme 126). The results displayed that the target molecules can suppress colon cancer cells [5].

Intermediate 472 was obtained through Pechmann condensation reaction of 3,5-dihydroxybenzaldehyde 289 and 2-ethoxymethylene-3-oxobutanoic acid ethyl ester 471 using sodium in EtOH. Finally, the target compounds 473 were synthesized via the Mannich reaction of intermediate 472, paraformaldehyde (PFA) and secondary amines in EtOH (Scheme 127). All the target compounds showed anti-inflammatory and neuroprotective effects in vitro studies [141].

The one-pot and multi-component reaction between 5,7-dihydroxy-4-methyl coumarin 381, aromatic aldehydes 119 and dialkyl acetylenedicarboxylate 474 catalyzed by sodium carbonate leads to the formation of a new group of pyrano[2,3-h]coumarin derivatives 475. Excellent yields, high atom-economy, mild reaction conditions and simple procedure are the major features of this method (Scheme 128) [142].

3-Acetyl-7-hydroxy-2H-chromen-2-one 472 was synthesized via Knoevenagel condensation of 2,4-dihydroxybenzaldehyde 216 into ethyl acetoacetate 2 in the presence of piperidine in ethanol. Compound 474 on reaction with 4-hydroxy benzaldehyde 393 in the presence of catalytic amount of acetic acid and pyrrolidine in EtOH

Scheme 120 Preparation of coumarin–carbonothioate 458

Scheme 121 Synthesis of 3-sulfonyl coumarins

Scheme 122 Synthesis of new set of coumarin derivatives

Scheme 123 Synthesis of coumarins by Pechmann–Duisberg condensation
gave (E)-7-hydroxy-3-[3-(4-hydroxyphenyl)acryloyl]-2H-chromen-2-one 476. Compound 476 was alkylated with various n-alkyl bromides by dry K2CO3 to give bis-alkyloxy derivatives 477 (Scheme 129) [143].

**Tri and bis-coumarins**

Zolfigol et al. developed effective methods for the synthesis of bis-coumarin derivatives 478 via the reaction between 4-hydroxycoumarin 33 with aromatic aldehydes 119 in the presence of trityl bromide (TrBr) as a homogenous and neutral organocatalyst or [Fe3O4@SiO2@(CH2)3-Im-SO3H]Cl (MNP) as a heterogeneous, acidic and nano-magnetic catalyst under solvent-free conditions. The advantages of the proposed method are efficiency, generality, high yields, short reaction times, cleaner reaction profile and simplicity (Scheme 130) [144].

Zolfigol et al. introduced silica-bonded 1,4-diaza-bicyclo[2.2.2]octane-sulfonic acid chloride (SBDBSAC) as a nanostructured heterogeneous catalyst in preparation of bis-coumarins 478 via the condensation reaction between arylaldehydes 119 and 4-hydroxycoumarin 33 (Scheme 131) [145]. They also made a novel nanostructured molten salt {[1,4-DHPyrazine][C(CN)3]2} (NMS), and it was used as an efficient and recyclable catalyst for the synthesis of novel 3,3’-(piperazine-1,4-diylibis(arylmethylene))bis(4-hydroxy-2H-chromen-2-one) derivatives (Scheme 132) [146].

Various bis-coumarins 480 were prepared via multicomponent one-pot reaction 4-hydroxycoumarin 33 with arylaldehydes 119 in the presence of acetic acid-functionalized poly(4-vinylpyridinium) bromide (APVPB) as a green and reusable catalyst under solvent-free conditions.
All of the synthesized bis-coumarins showed antioxidant, anti-inflammatory and antifungal activity [147]. Bis-coumarin derivatives 482 and 484 were prepared via coupling reaction of two equiv. 7-Substituent coumarin 481 and 483 in the presence of Pd catalyst in DMF (Scheme 134). Synthesized compounds showed aromatase inhibitory activities [148]. Bis-benzocoumarin 488 was prepared in a three-step reaction. First, reaction of compound 485 with HCl in EtOH at room temperature furnished (R)-2,2'-dihydroxy-1,1'-binaphthalene-3,3'-dicarbaldehyde 486. Next, the reaction of 486 in the presence of diethyl malonate 2 in short reaction time yielded corresponding bis-benzocoumarin 487 that resulted in bis-benzocoumarin 488 under basic hydrolysis (Scheme 135) [149].

Bis-coumarin–benzopyrylium-conjugated compound 492 was prepared via the reaction of acetyl coumarin 491 with 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid 490 and conc. H$_2$SO$_4$. Treatment of compound 492 with POCl$_3$, followed by reaction with hydrazine hydrate, afforded a coumarin–benzopyrylium hydrazide 493 in good yield. The desired copper-selective sensors (494 and 495) were obtained from the reaction of 493 with salicylaldehyde or 2-hydroxy-1-naphthaldehyde under reflux in EtOH (Scheme 136) [150].

Coumarin conjugate 496 was easily prepared by condensation reaction 3-acetyl-7-diethylaminocoumarin 163 with 7-diethylaminocoumarin-3-carbaldehyde 491 in the presence of potassium acetate. Then, 499 was transformed to coumarin–biphenyl derivatives 500 via reaction with other 3-(4-bromophenyl)coumarins 497 in the presence of Na$_2$CO$_3$, TBAB and Pd(pph$_3$)$_4$ (Scheme 138) [152].

(Scheme 133). All of the synthesized bis-coumarins showed antioxidant, anti-inflammatory and antifungal activity [147].

Bis-coumarin derivatives 482 and 484 were prepared via coupling reaction of two equiv. 7-Substituent coumarin 481 and 483 in the presence of Pd catalyst in DMF (Scheme 134). Synthesized compounds showed aromatase inhibitory activities [148]. Bis-benzocoumarin 488 was prepared in a three-step reaction. First, reaction of compound 485 with HCl in EtOH at room temperature furnished (R)-2,2'-dihydroxy-1,1'-binaphthalene-3,3'-dicarbaldehyde 486. Next, the reaction of 486 in the presence of diethyl malonate 2 in short reaction time yielded corresponding bis-benzocoumarin 487 that resulted in bis-benzocoumarin 488 under basic hydrolysis (Scheme 135) [149].

The coumarin–benzopyrylium-conjugated compound 492 was prepared via the reaction of acetyl coumarin 491 with 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid 490 and conc. H$_2$SO$_4$. Treatment of compound 492 with POCl$_3$, followed by reaction with hydrazine hydrate, afforded a coumarin–benzopyrylium hydrazide 493 in good yield. The desired copper-selective sensors (494 and 495) were obtained from the reaction of 493 with salicylaldehyde or 2-hydroxy-1-naphthaldehyde under reflux in EtOH (Scheme 136) [150].

Coumarin conjugate 496 was easily prepared by condensation reaction 3-acetyl-7-diethylaminocoumarin 163 with 7-diethylaminocoumarin-3-carbaldehyde 491 in the presence of piperidine in EtOH. The target molecule 496 displayed high quantum yield because of strong ICT effect (Scheme 137) [151].

Different coumarins 5 were prepared via condensation of 3-(4-bromophenyl)coumarins 497 into bis(pinacolato) diboron 498 in the presence of potassium acetate. Then, 499 was transformed to coumarin–biphenyl derivatives 500 via reaction with other 3-(4-bromophenyl)coumarins 497 in the presence of Na$_2$CO$_3$, TBAB and Pd(pph$_3$)$_4$ (Scheme 138) [152].
Synthesis of bis-coumarin derivatives started with refluxing 4-hydroxy coumarin 33 with 4-nitrobenzaldehyde 119 to form bis-coumarin 480. Then, compound 480 was reduced to analog 480'. Compound 480' was further treated with CS$_2$ to form intermediate which is further reflux with various benzoyl hydrazides 266 to form the target compounds 501 (Scheme 139) [153].

Chromene 503 was synthesized through von Pechmann condensation reaction of methyl 3-oxobutanoate 2 and 5-(1-hydroxy-2-((1-(4-hydroxyphenyl)propan-2-yl)amino)ethyl)benzene-1,3-diol 502 in acidic media at 70 °C (Scheme 140) [154].

Bis-coumarin derivatives 480 were prepared via reacting 6-fluoro-4-hydroxy, 4-hydroxy and 6-chloro-4-hydroxy coumarins 33 with various benzaldehydes 119 in the presence of tetraethylammonium bromide (TEAB) as catalyst. A group of synthesized compounds showed good antiglycation activities compared to the standard routine (Scheme 141) [155].
8-Formyl-7-hydroxycoumarin 222 was synthesized via the reaction of 7-hydroxy-2H-chromen-2-one 62 with urotropine in acetic acid. Then, a tripodal coumarin-derived Schiff base was prepared through the reaction of compound 222 with tris-(2-aminoethyl)-amine in EtOH under reflux conditions. This compound acts as a recognition unit for the highly selective and sensitive detection of Cd\(^{2+}\) (Scheme 142) [156].

**Coumarins containing pyridone core**

Synthesis of coumarin–pyridone conjugate molecules 507 was carried out via one-pot reaction between (E)-3-(3-arylacryloyl)-2H-chromen-2-ones 505, ethyl 2-nitroacetate 506 and NH\(_4\)OAc under reflux conditions in n-BuOH (Scheme 143). Most of the compounds revealed mild anti-bacterial activity, and a number of compounds showed good inhibitory potential against all the tested fungal organisms [157].

**Coumarins containing pyrane core**

An efficient and straightforward procedure for the syntheses of isoxazoline/isoxazole-fused coumarins 513 and 514 from the corresponding 7-o-propargyloxy coumarin oximes 511 and 7-o-allyloxy-coumarin oximes 512 is
presented. 7-Allyloxy-coumarin-8-carbaldehydes 509 and 510 were prepared via condensation of coumarin-8-carbaldehyde 222 into 3-bromoprop-1-yne, 3-bromo-prop-1-ene in DMF, and further condensation with NH₂OH·HCl led to 511 and 512, respectively. In the last step, intramolecular cyclization reaction on compounds 511 and 512 in acetonitrile afforded isoxazoline/isoxazole-fused coumarins 513 and 514 (Scheme 144). All compounds demonstrated high cytotoxic activity against three human cancer cell lines [158].

The preparation of pyrano[2,3-f]chromene-4,8-dione derivatives 518 is shown in Scheme 78. Initially, the reaction of phloroglucinol 379 with crotonic acid 515 in the presence of CH₃SO₃H, P₂O₅ afforded 5,7-dihydroxy-2-methylchroman-4-one, which was then cyclized with various β-keto esters 517 in trifluoroacetic acid (TFA) using p-toluenesulfonic acid (p-TsOH) as catalyst (Scheme 145) [159].

Similarly, Friedel–Crafts acylation of phloroglucinol 379 with 3,3-dimethylacrylic acid 519 in the presence of BF₃·Et₂O gave 5,7-dihydroxy-2,2-dimethyl-4-chromanone.
The synthesized compounds showed anticancer activities against SHG-44, H1299, MCF7 and HCT-116 cell lines in vitro [159].

Coumarins containing oxazole core

The synthetic route of coumarin–benzoxazoles is shown in Scheme 146. First, it is the coupling of salicylaldehyde 13, ethyl cyanoacetate 522 and o-aminophenol 523 to form intermediate 524. The chlorination of intermediate 524 with oxalyl chloride in the presence of organic base DMF produced intermediate 525. Further, the target products 526 were synthesized in the amidation with aromatic amine in moderate yield (Scheme 147) [160].

Allyl derivative 527 was synthesized in good yield through the nucleophilic substitution reaction of 7-hydroxy coumarin 3 with allyl bromide 508 using K₂CO₃ in DMF. In a typical reaction, aldoximes 528 were chlorinated with N-chlorosuccinimide and reacted with allylated coumarin 527 in the presence of triethyl amine to yield target compounds 529 (Scheme 148) [161].

Coumarins containing furan core

Synthesis of angular furocoumarins 530, 531 and 532 and difurocoumarins 533 has been carried out starting from substituted coumarins 367 and phenyl acetylene 8 leading to the target compounds via styrylcoumarin intermediates (Scheme 149). Synthesized derivatives were evaluated for inhibition of cell proliferation of human breast carcinoma, human gastric carcinoma and human lung cancer, exhibiting anti-proliferative activity.
4-Methyl-6,9-diphenyl-2H-difuro[3,2-f:2′,3′-h]chromen-2-one exhibited the highest inhibition of cell proliferation on all cell lines [162].

3-Furyl coumarin derivatives were formed in one-pot four-component reaction of 4-chloro-3-formylcoumarin, secondary amines, dialkyl acetylenedicarboxylates and diversely substituted isocyanides in benzene under reflux conditions in reasonable yields (Scheme 150) [163].

Two photochromic coumarin-based dithienylethenes were prepared through one-pot nucleophilic addition reaction of 7-hydroxy-2H-chromen-2-one and 1,2-bis(2,5-dimethylthiophen-3-yl)ethyne in the presence of Pd2(dba)3.CHCl3 catalyst (Scheme 151) [164].

In an efficient and quite environmental-friendly method, 2-aryl-4H-furo[3,2-c]chromen-4-one derivatives were obtained from reaction of 4-hydroxy-2H-chromen-2-one with various ethylbenzenes in the presence of I2/TBHP-mediated and dioxane under reflux conditions (Scheme 152) [165].

The synthesis of furo[3,2-c]coumarins was carried out via one-pot three-component reaction of two equiv. 4-hydroxycoumarin and one equiv. of various aldehydes in the presence of a catalytic amount of I2 in DMSO (Scheme 153) [166].

A new and efficient method for the synthesis of furo[3,2-c]coumarin derivatives was developed via copper-catalyzed radical/radical cross-coupling of ketoxime.
carboxylates 528 with 4-hydroxycoumarins 33 in dioxane (Scheme 154) [167].

**Coumarins containing thiophene core**

Schiff bases 543 were obtained via a Schiff reaction between the coumarin–thiophene hybrid molecules 542 and \( o \)-vanil- lin, salicylaldehyde or 4-methoxy salicylaldehyde to afford 543 in good yields (Scheme 155) [168].

The coumarin–thiophene hybrids 545 were synthesized using the one-pot, three-component reaction of 3-acetylcoumarins 37, malononitrile 122 and elemental sulfur under MWI conditions. All the synthesized compounds 3 have high thermal stability, and they can be applicable as optical dyes (Scheme 156) [169].

Bromobenzene was reacted into indole derivative 546 under \( \text{Pd(OAc)}_2 \) as catalysis to give \( \text{N-phenylindoline} \) derivative 551. After the bromination, 551 was transformed into boronate with \( \text{B(OMe)}_3 \). The boronate of 551 reacted directly with 6-bromo-3-thiophenylcoumarin via Suzuki coupling reaction to synthesize compound 554. The aldehyde group was reacted into the thiophene ring of 554 via Vilsmeier reagent to afford the aldehyde 555. Dye 556 was synthesized through Knoevenagel condensation of 555 into
cyanoacetic acid. Also, 6-bromo-3-thiophenylcoumarin reacted with indole derivative to afford the coupling product. Compound was transformed into the aldehyde derivative which further reacted with cyanoacetic acid to give dye (Scheme [170]).

Reaction of 3-bromo-7-(t-butyl)-2H-chromen-2-one with boronic acid derivatives in the presence of KCO₃ and Pd(PPh₃)₄ afforded compound. Reaction of the synthesized compounds with cyanoacetic acid in chloroform led to coumarin-based dyes (Scheme [158] [171]).

### Coumarins containing azo-group

3-Phenyl azo-4-hydroxycoumarin, PAHC was synthesized by reacting aniline diazonium salt with 4-hydroxycoumarin. PAHC thin films have been grown successfully on the glass and quartz substrates via using thermal evaporation technique under high vacuum (Scheme [159] [172]). A series of coumarin-based disperse disazo dyes were synthesized by coupling reaction to 4-hydroxycoumarin with diazonium salt of...
5-amino-4-arylazo-3-methyl-1H-pyrazoles 570 in the presence of Na₂CO₃ in water (Scheme 160) [173].

A variety of novel coumarin-azo bearing aliphatic chains 5 were synthesized as depicted in Scheme 1. 4-Alkoxyaniline 113 was coupled with phenol 335 in the presence of NaNO₂/HCl and NaOH, and then the reaction of 4-[(E)-alkoxyphenyldiazenyl]phenol 572 with coumarin-3-carboxylic acid 187 at 5 °C yielded 4-[(E)-alkyloxyphenyldiazenyl]phenyl coumarinate 573 (Scheme 161). The studies have shown that the synthesized azo coumarins can be used in optical storage devices [174].

**Complexes of coumarins with metals**

7-Hydroxy-4-methyl coumarin 3 was synthesized via the Pechmann condensation and formulated at the eighth position through the Duff’s reaction to give 4-methyl-7-hydroxy-8-formyl coumarin 312. The reaction of 3,4-diaminotoluene 102 with 4-methyl-7-hydroxy-8-formyl coumarin 312 in ethanol led to Schiff base 574. Finally, Cu-Schiff base complex 575 was prepared from reaction Schiff base 574 with copper acetate monohydrate in EtOH (Scheme 162) [175].

A series of α-aminocarbonitriles 576 were obtained via condensation reaction of 4-hydroxycoumarin 33 into malononitrile 122 and various arylaldehydes 119, which was reacted with Lawesson’s reagent to give the diazaphosphinanes 577 as diastereoisomers (Scheme 163). The synthesized compounds were appraised for their cytotoxic activities in vitro against two tumor cell lines HCT-116 and MCF-7. The results display a medium cytotoxic activity for most compounds [176].

Several coumarin-substituted silver (I) N-heterocyclic carbene (NHC) complexes 582 and 585 were synthesized via the interaction of the corresponding imidazolium 583 or benzimidazolium chlorides 580 and Ag₂O in dichloromethane at room temperature (Scheme 164). The anti-microbial activities of carbene precursors and silver NHC complexes were examined against standard strains: Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli and the fungi Candida tropicalis and Candida albicans. Results indicated that all the compounds inhibited the growth of all bacteria and fungi strains and some complexes performed good activities against various microorganisms [177].

The synthetic method for symmetrical silicon-linked coumarin-oxadiazole derivatives 393 is summarized in Scheme 165. An important intermediate, silylbenzohydrazide moiety 591, was prepared quantitatively via the reaction of 590 with excess amounts of hydrazine monohydrate under reflux conditions. Finally, the reaction of 591 and coumarin acid 201 in phosphoryl chloride as the refluxing solvent eventually produced symmetrical silicon-linked coumarin-oxadiazole derivatives 593 (Scheme 165) [178].
Scheme 158 Synthesis routes of the coumarin dyes

Scheme 159 Synthesis of 3-phenylazo-4-hydroxycoumarin

Scheme 160 Synthesis of coumarin-based disperse disazo dyes

Scheme 161 Synthesis of azo-coumarin esters
Co(II), Ni(II) and Cu(II) complexes are prepared by Schiff bases and, derived from 8-formyl-7-hydroxy-4-methyl coumarin with 2,4-difluoroaniline/o-toluidine, respectively. The Schiff bases and their metal complexes were appraised for antifungal (Aspergillus Niger and Rhizopus oryzae), anti-bacterial (Pseudomonas aureginosa and Proteus mirabilis), anthelmintic (Pheretima posthuma) and DNA cleavage (Calf Thymus DNA) activities (Scheme 166) [179].

A series of sterically tuned benzimidazolium hexafluorophosphate derivatives 602 contain chlorocoumarin substituents prepared by the reaction of 1-alkyl/benzyl-benzimidazole 600 with 4-bromomethyl-6-chlorocoumarin 179 followed by salt metathesis reaction using potassium hexafluorophosphate. Corresponding bis-NHC silver complexes 603 were prepared in excellent yields by the reaction of salts 602 with silver(I) oxide under dark following in situ deprotonation protocol (Scheme 167). Disk diffusion studies indicated that few of the complexes have excellent anti-bacterial activities against E. coli bacteria [180].

7,8-Dihydroxy-3-(3-methylphenyl)coumarin 607 was obtained from the reaction of compound 606 in the presence of pyridinium hydrochloride and silica gel as support material by microwave irradiation under solvent-free conditions. The reactions of compound 610 with one equiv. of 7,8-dihydroxy-3-(3-methylphenyl)coumarin 3 in the presence of Na2CO3 in dry xylene gave 2,2-bis[spiro(7,8-dioxo-3-(3-methylphenyl)coumarin)]-4,4,6,6-bis[spiro(2',2''-dioxo-1',1''-biphenyl)]cyclophosphazene 612. The reactions of 611 with two equiv. of 7,8-dihydroxy-3-(3-methylphenyl)coumarin 607 gave 2,2,4,4-bis[spiro(7,8-dioxo-3-(3-methylphenyl)coumarin)]-6,6-bis[spiro(2',2''-dioxo-1',1''-biphenyl)]cyclophosphazene 613 (Scheme 168) [181].

Ruthenium(II) half-sandwich complexes 616 containing coumarin ligands with the general formula [Ru(arene)(L2)Cl]Cl synthesized from reaction dichlorido(p-cymene)(L2)Cl with 3-aminocoumarin 615 in dry CH2Cl2 (Scheme 169) [182].

Metal chelates 623 were prepared via reaction of compound 622 with copper and nickel acetates in MeOH. Crystallization of complex 623, when the nucleus is
nickel, led to paramagnetic substance 624 (Scheme 171) [184].

A new binuclear Cu (II) complex, \([\text{Cu}_2\text{L}_2(\text{NO}_3)_4]\) has been prepared through complexation of Cu(NO\(_3\))\(_2\)·3H\(_2\)O with coumarin-3-formyl-(3-(aminomethyl) pyridine (L) (Scheme 172) [185].

Fumed silica was chemically modified with 3-aminopropyl]triethoxysilane as coupling agent linked to a coumarin derivative in DMF solvent (Scheme 173) [186].

6,8-Di-tert-butyl-3-[\(p\)-(propynyl)phenoxy]coumarin 632 was synthesized via the reaction of 6,8-di-tert-butyl-3-(\(p\)-hydroxyphenyl)coumarin 631 with propargyl bromide 4 in DMF. The synthesized coumarin 632 was reacted with...
tetra-iodo zinc(II) or tetra-iodo indium(III) acetate phthalocyanines 633 through the Sonogashira coupling reaction for the preparation of the coumarin-substituted phthalocyanines 634, respectively (Scheme 174) [187].

Coumarin-N-acylhydrazone ligands 635 were obtained through acid-catalyzed reactions between compound 618 and the suitable benzaldehyde 119 at room temperature. Ru (II) complexes were prepared by reaction between cis-[RuCl₂(DMSO)₄] and the corresponding ligand 635 in EtOH (Scheme 175) [188].

Imidazol-coumarin 639 was obtained conveniently by condensation reaction of coumarin 618 into 1H-imidazole-2-carbaldehyde 638. Subsequently, the complex Cu²⁺ was also synthesized via reaction of imidazol-coumarin 639 with Cu(ClO₄)₂·6H₂O under reflux condition (Scheme 176). The fluorescence experiments of the product to various amino acid indicated that it had good selectivity and sensitivity to GSH [189].

The target molecule 4 was prepared via a synthetic route as shown in Scheme 176. Condensation reaction 2,4-dihydroxybenzaldehyde 216 with ethyl benzoylecetate 641 catalyzed by piperidine produced compound 642 in good yield. Imination of coumarin 642 with benzhydrazide in the presence of tosic acid afforded the target molecule 643. Among various metal ions, product 643 is able to detect Cu²⁺ ion by the naked eye with high selectivity and sensitivity (Scheme 177) [190].

A series of novel ferrocene–coumarin conjugates (646, 648 and 650) were synthesized through reaction between ferrocene derivatives (645, 649) and coumarins (3, 647) in...
the presence of DCC/DMAP under an inert (Ar) atmosphere (Scheme 178). Studies have shown that ferrocene–coumarin conjugates are potential candidates for developing metallo-drugs with anticancer activity [191].

Tudose et al. synthesized three novel fluorescent mesoporous silica composites via the covalent immobilization of 7-amino-4-(trifluoromethyl)coumarin, 7-amino-4-methyl-3-coumarinylacetic acid
and 6-amino-chromen-2-one inside the channels of mesoporous silica SBA-15 (Scheme 179) [192].

A series of novel organoplatinum (II) complexes bearing quinoline–coumarin derivatives were first designed. The designed complexes selectively displayed obvious cytotoxicities in comparison with cisplatin for A549/DDP cells and HeLa cervical carcinoma cells (Scheme 180) [193].

Other coumarins

A group of amino alcohol derivatives 665 containing coumarin moieties was synthesized with 5-bromosalicylaldehyde 659 as starting materials, 6-substituted-3-chromanone 662 as intermediates and Suzuki reaction and spiro-hydan- toin hydrolysis as key steps (Scheme 181) [194].

2,4-Dihydroxybenzaldehyde 216 reacted with ethyl 3-oxo-3-phenylpropanoate 641 in the presence of piperidine to yield corresponding 3-benzoyl-7-hydroxy-2H-chromen-2-one 642 that led to corresponding 3-benzoyl coumarin-7-yl-methacrylate (BCMA) monomer 667 via reacted with methacryloyl chloride 666 in THF. Compounds 667 reacted with AIBN initiator to form poly(3-benzoyl coumarin-7-yl-methacrylate) [poly(BCMA)] 668 through polymerization reaction (Scheme 182) [195].

New set of coumarins 670 contains trifluromethyl, diethylamino and morpholino produced via reaction of different coumarin 3-carboxylic acids 187 and various phenyl esters 669 with peripheral alkyl, ester and polar cyano moieties in the presence of EDC.HCl/DMAP as esterification agent (Scheme 183) [137].

Coumarin–pyrene-based fluorescent probes (E)-7-(diethylamino)-3-((pyren-1-ylimino)
Scheme 174  Synthesis of 6,8-di-tert-butyl-3-[(p-propynyl)phenoxy]coumarin-substituted phthalocyanine complexes

Scheme 175  Synthesis of the coumarin-N-acylhydrazone ligands and Ru (II) complexes

Scheme 176  Synthetic route of coumarin 639 and the presumable structure of complex 639-Cu²⁺
methyl)-2H-chromen-2-one 672 and (E)-7-(diethylamino)-3-((pyren-1-ylmethylamino)methyl)-2H-chromen-2-one 674 were prepared via reaction of 7-diethylaminocoumarin-3-aldehyde 163 with 1-aminopyrene 4671 or 1-(aminomethyl) pyrenehydrochloride 673 in MeOH at 50 °C, respectively (Scheme 184) [196].

2-(1-(2-Oxo-2H-chromen-3-yl)ethylidene)hydrazinecarbothioamide derivatives 676 were prepared via multi-component one-pot reaction of 2-oxo-2H-chromene-3-carbaldehyde 37, isothiocyanates 675 and hydrazine hydrate 20 in the presence of catalytic amount of glacial acetic acid in high to excellent yields (Scheme 185). All synthesized compounds showed excellent activity against E. coli MTCC 443 [197].

Li et al. synthesized a new coumarin–carbonothioate derivative 677. 7-Hydroxy-4-methyl-3,8a-dihydro-2H-chromen-2-one 3 was prepared via condensation of resorcinol 1 with ethyl 3-oxobutanoate 2 in p-TsOH. The chemodosimeter 677 was synthesized by the esterification of compound 3 using phenyl chloromethanethioate 457 and N-Ethylisopropylamine in CH2Cl2 at room temperature (Scheme 186) [135].

A series of novel coumarin-oxime ether conjugates 679 with therapeutically interesting properties were synthesized via SN2 reaction of bromomethyl coumarins 179 with butane-2,3-dione monoxime 678 in the presence of anhydrous K2CO3 (Scheme 187). Most of the synthesis compounds exhibited notable activities with minimum inhibitory concentration (MIC) in the range of 0.04–3.12 μg/mL−1 [198].

7-Hydroxy coumarins 62 reacted with α,ω-dibromoalkanes 30 under reflux conditions in the presence of K2CO3 to yield key intermediates 440 in high yield, and further reaction of 440 with commercially available compounds 680 in the presence of potassium carbonate in acetonitrile led to the target compounds 681 (Scheme 188). Donepezil–coumarin hybrids 681 were
179. Schematic protocol for functionalization of SBA-15

A series of coumarin-derived imino sulfonates were synthesized by cyclization reaction of various salicylaldehydes and chlorosulfonamide (Scheme 180) [201].

The reaction of 7-hydroxycoumarin with epichlorohydrin in the presence of K$_2$CO$_3$ led to the formation of oxiranes, which on regioselective nucleophilic ring opening with a series of suitable amines such as cyclopropyl amine, butyl amine, cyclohexyl amine and morpholine in EtOH at room temperature afforded coumarinyl amino alcohols with good yield (Scheme 189) [200].

Vashisht et al. synthesized a coumarin-based azomethine colorimetric probe tailored via reaction of 4-hydroxy-2-oxo-2$H$-chromene-3-carbaldehyde with $N$-(2-aminoethyl)-1,3-propanediamine under reflux conditions (Scheme 191) [201].

Condensation reaction of 4-(2-bromoethoxy)-2$H$-chromen-2-one with dithiocarbamate salt in absolute ethanol afforded 2-(2-oxo-2$H$-chromen-4-yl)oxyethyl pyrrolidine-1-carbodiethioate derivatives under both microwave and conventional conditions (Scheme 192). The titled compounds have emerged as potential candidate to be useful as anti-bacterial and antifungal agents [202].

8-Formyl-7-hydroxy-4-methyl-coumarin was synthesized via a hydrolysis reaction under acidic conditions aldol between 7-hydroxy-4-methyl-2$H$-chromen-2-one and hexaminc. 8-(Hydrazonomethyl)-7-hydroxy-4-methyl-2$H$-chromen-2-one was synthesized through a reaction of and hydrazine hydrate in EtOH (Scheme 193).
Compound 3 showed high sensitivity to detect of ClO\(^-\) in living cells [203].

Coumarin derivatives 692 were reacted with the corresponding \(\alpha,\omega\)-dibromoalkanes 30 under reflux conditions to give compounds 693. In next step, compounds 693 were treated with the appropriate amines, carbon disulfide and triethylamine in DMF to obtain coumarin–dithiocarbamate hybrids 694 (Scheme 194) [204].

Condensation reaction of 4-bromomethyl coumarins 179 into 1-(4-(4-hydroxyphenyl)piperazin-1-yl)ethanone 695 in the presence of dry K\(_2\)CO\(_3\) afforded coumarin–piperazine derivatives 696 as potent anti-microbial and anti-inflammatory agents (Scheme 195) [205].

Scheme 196 displays the synthetic rout for coumarin derivative 701. First, compound 699 was obtained through refluxing malonate ester 697 with compound 698 in toluene. Further coupling compound 699 with acetate chloride 700...
in CH$_2$Cl$_2$ afforded coumarin derivative 701 in good yield (Scheme 196) [206].

The reaction of coumarin 702 and benzoic acid 703 in conc. H$_2$SO$_4$ under reflux conditions afforded the coumarin-fused rhodol 704. The subsequent reaction of 704 with p-toluenesulfonyl hydrazide generated the product 705 (Scheme 197) [207].

**Conclusions**

This review article contains the effective procedures of the synthesis of several symmetrical and asymmetrical coumarins containing heterocycles core such as triazole,
Scheme 192 Synthesis of novel coumarin derivatives bearing dithiocarbamate moiety

Scheme 193 Synthesis of a novel coumarin-based fluorescent probe with fine selectivity and sensitivity

Scheme 194 Synthesis of coumarin–dithiocarbamate hybrids

Scheme 195 Synthetic route to synthesize coumarin–piperazines

Scheme 196 Synthesis of a coumarin-based fluorescent probe

Scheme 197 Synthesis of coumarin-fused rhodol derivative
pyrazole and imidazole, and applications testify the strength and vitality of this area of organic chemistry. However, the challenges of discovering new symmetrical systems and of understanding their properties also continue to stimulate research in the area. As it was observed in this study, coumarins and its derivatives are energetic compounds with a wide range of biological activities.

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Compliance with ethical standards

Conflict of interest The authors did not have any financial or personal relationships with other people or organizations during the study. Therefore, there was no conflict of interests in this article.

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