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REVIEW

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 conditioners, 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].

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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)-1*H*-1,2,3-triazol-4-yl]coumarins **12** (Scheme 2) [23].

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

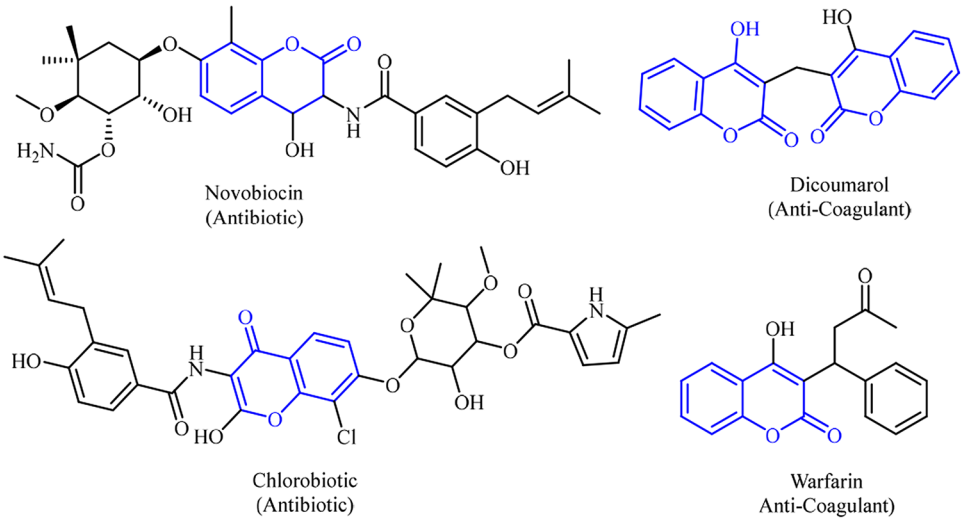
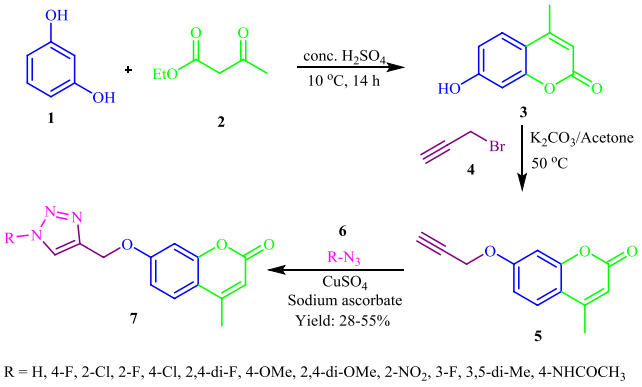
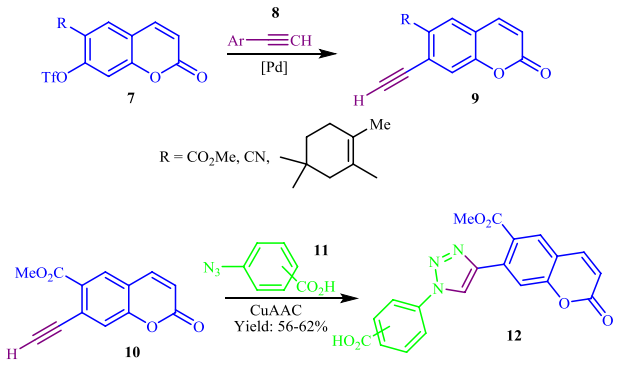


Fig. 1 Commercially available biologically active coumarins



Scheme 1 Synthesis of coumarin–triazole derivatives



Scheme 2 Synthesis of coumarin–triazoles from arylalkyne

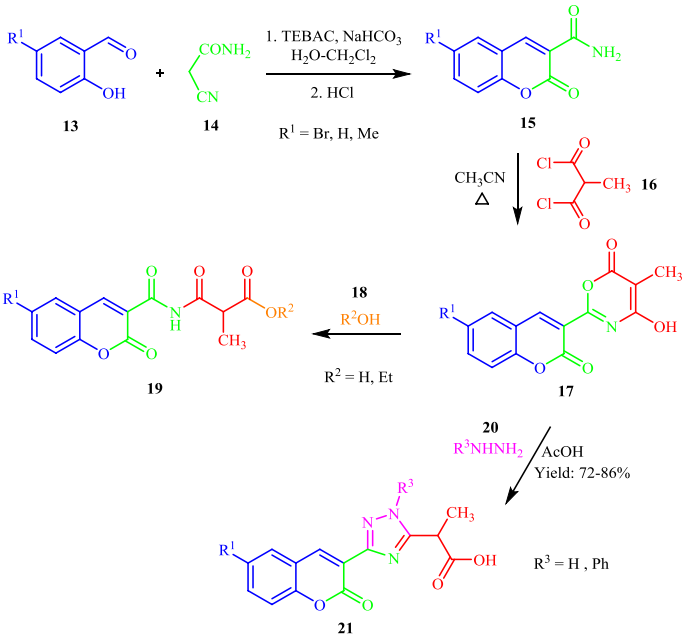
chloride in the presence of phase-transfer catalyst to yield corresponding coumarin-3-carboxamides **15** that led to corresponding 1,3-oxazines/coumarins **17** via reaction with methylmalonylchloride **16** in aprotic solvents such as carbon-tetrachloride, benzene, 1,2-dichloroethane and acetonitrile 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 **3** 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 ethanols 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].

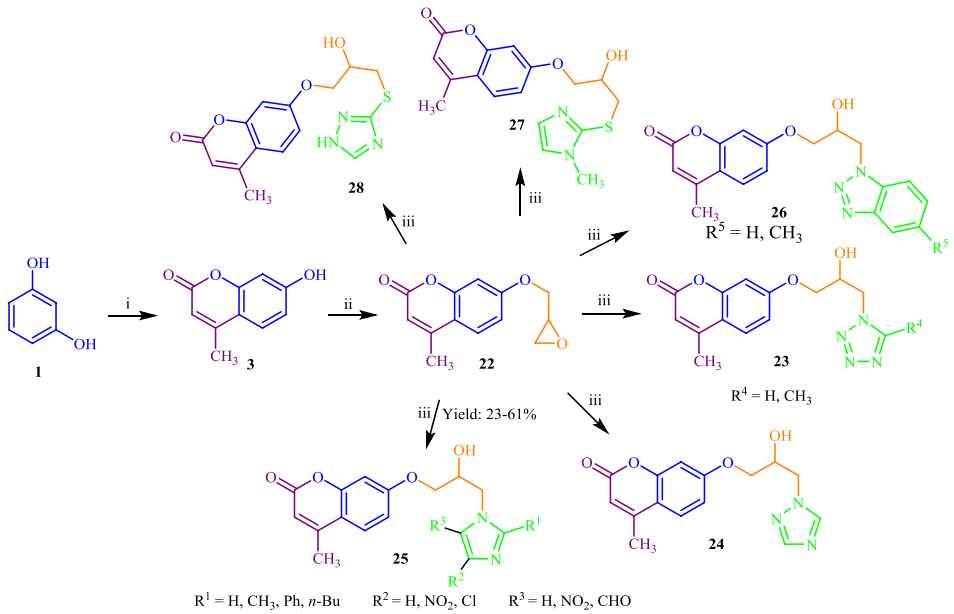
A library of novel triazole-tethered isatin–coumarin hybrids **36** were synthesized by click chemistry approach. The reaction of isatins **29** with 1,2-dibromoalkanes **30** afforded compound **31**, and further reaction of **31** with NaN_3 in DMF led to 1-(4-azidoalkyl)indoline-2,3-dione **32**. 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_2CO_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-((1-(substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methoxyimino)ethyl)-2*H*-chromen-2-one derivatives **41** via the click reaction of

Scheme 3 Synthesis of coumarins containing triazole derivatives



Scheme 4 Synthetic route of coumarin-derived mono-azolyl ethanols

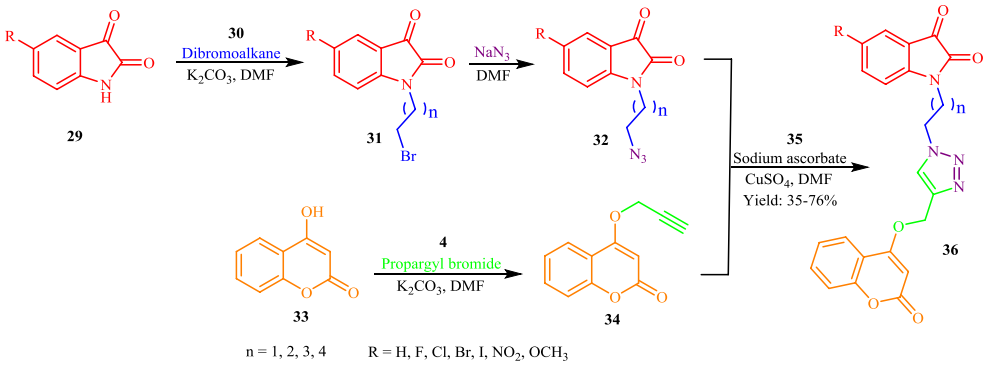


(i) ethyl acetoacetate, concentrated H_2SO_4, 0–5 °C, 2–3 h;(ii) epichlorohydrin, K_2CO_3, reflux, 4–6 h; (iii) azoles, K_2CO_3, EtOH, 70 °C, 2-4 h.

(*E*)-3-(1-((prop-2-yn-1-yloxy)imino)ethyl)-2*H*-chromen-2-one **40** and aryl azide **6** in the presence of sodium ascorbate and $CuSO_4$-$5H_2O$ in THF:H_2O (Scheme 6). Most of the synthesized compounds exhibited reasonable neuroprotectivity and toxicity activities against H_2O_2-induced $PC1_2$ cell lines [27].

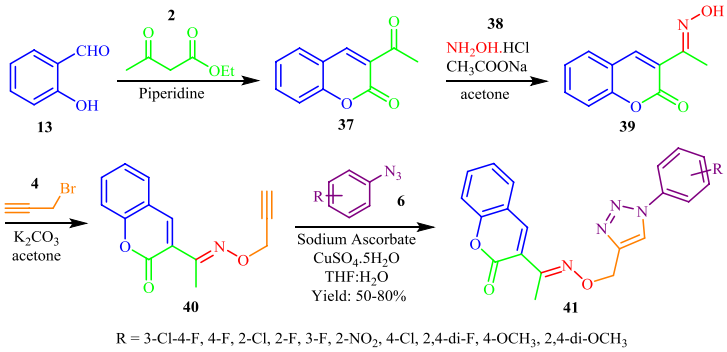
A series of N^1-(2,3,5-tri-*o*-benzoyl-*β*-D-ribofuranosyl)-C^4-(coumarin-7-oxymethyl)-1,2,3-triazoles **46** have been synthesized using Cu catalyzed Huisgen–Sharpless–Meldal [3 + 2] dipolar cycloaddition reaction between 1-azido-2,3,5-*tri*-*o*-benzoyl-*β*-D-ribofuranose **44** and 7-propargyloxycoumarins **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

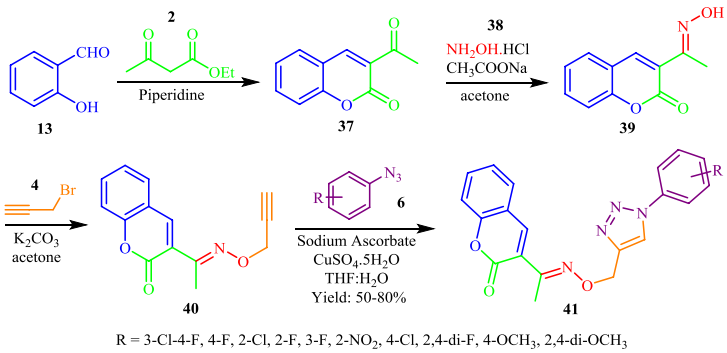


Scheme 5 Synthesis of triazole-linked isatin–coumarin hybrids

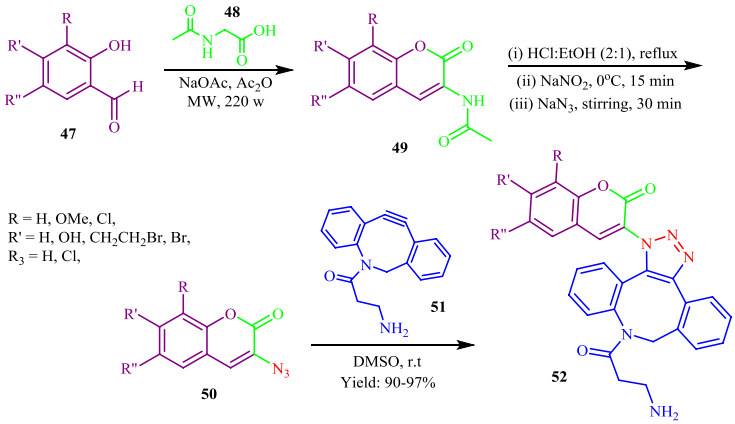
Scheme 6 Synthesis of novel 1,2,3-triazole-tethered coumarin derivatives



Scheme 7 Preparation of N^1-(β-*D*-ribofuranosyl)-C^4-(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 $CuSO_4{\cdot}5H_2O$ 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].

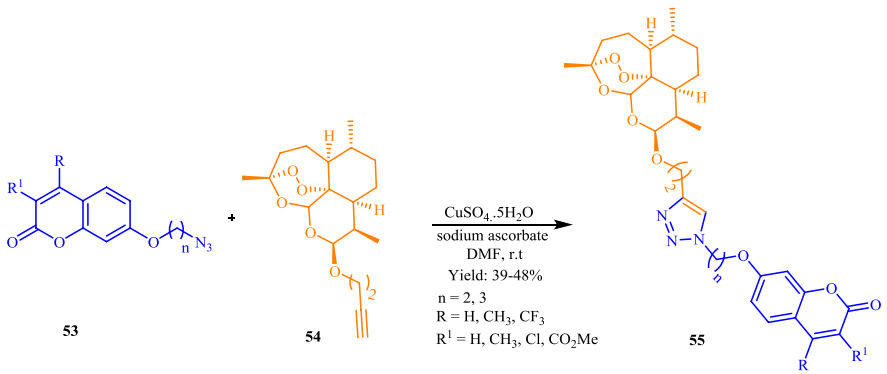
The synthesis of coumarinyl thiazolotriazole derivatives **61** is outlined in Scheme 61. Starting from coumarinyl hydrazide **56**, reacting with potassium thiocyanate in the presence of HCl afforded coumarinyl carbothioamide **57,** which on intramolecular dehydrative cyclization produced corresponding 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 propargylbromide **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].

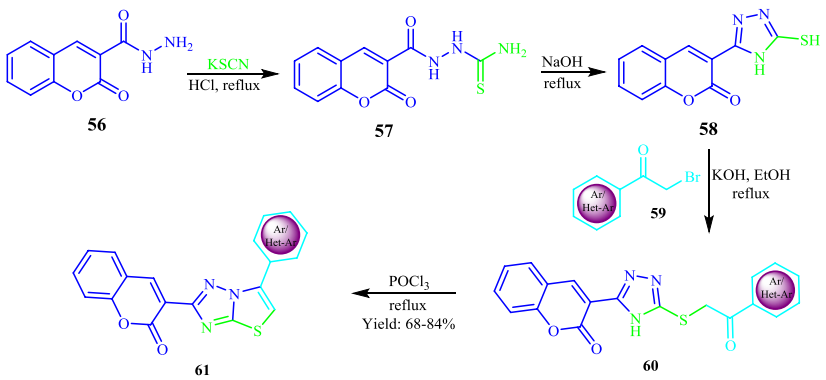
Chromen-triazol **69** was readily synthesized via click reaction of tripropagyl trindane **67** with coumarin azide **68** in the presence of Cu catalyst. The acetylenic substrate **67** was prepared for a high yield using condensing propagyl amine to tricarboxylic acid **66** in the presence of carbonyldiimidazole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

The reaction of anthranilic acids **70** and cyclohexanone **71** in refluxing $POCl_3$ 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 K_2CO_3 in acetonitrile to give compounds **74**. Compounds **75** were obtained via the reaction of compounds **74** with NaN_3 in EtOH. Finally,

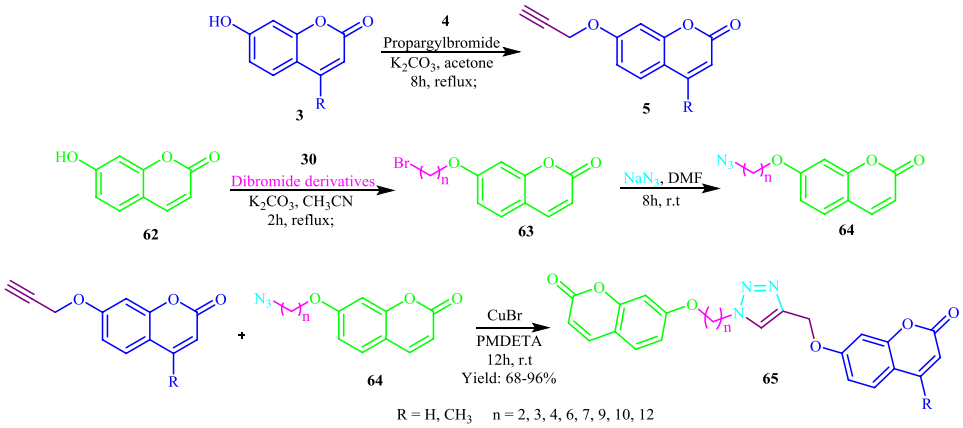
Scheme 9 Synthesis of novel dihydroartemisinin–coumarin hybrids **55**



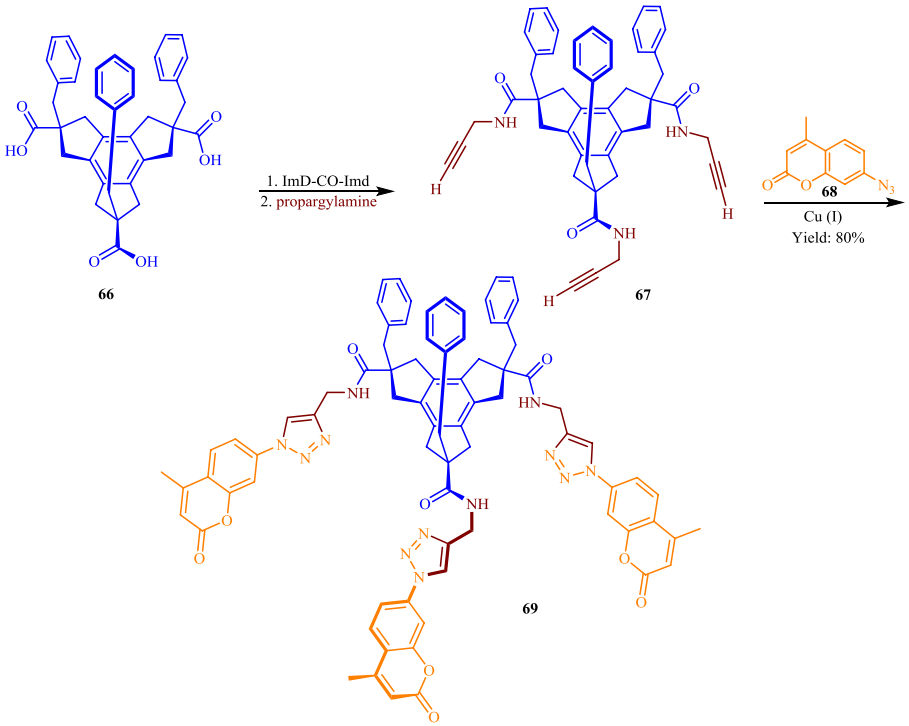
Scheme 10 Synthesis of coumarinyl thiazolotriazole hybrids **61**



Scheme 11 Synthesis of new triazole ring-substituted *bis*-coumarin derivatives



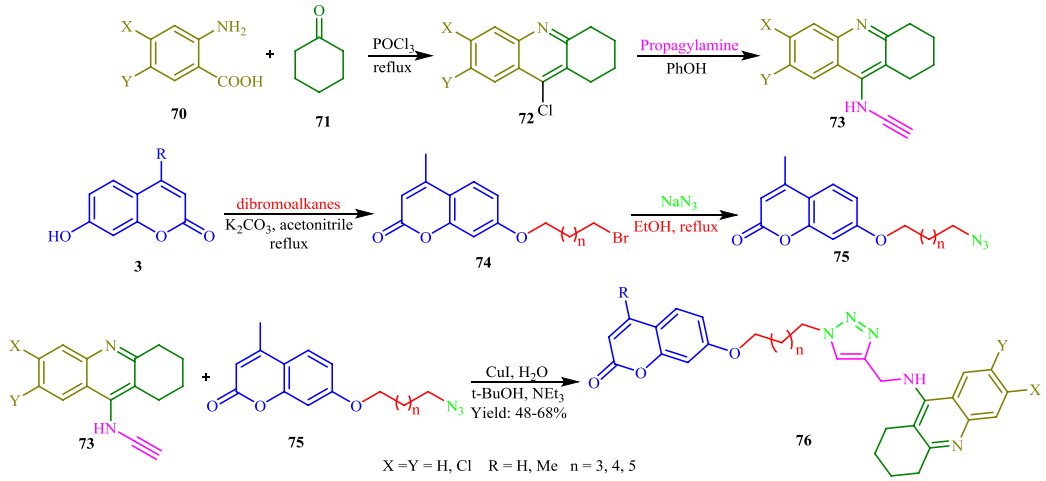
Scheme 12 Synthesis of triazole trindane–coumarin



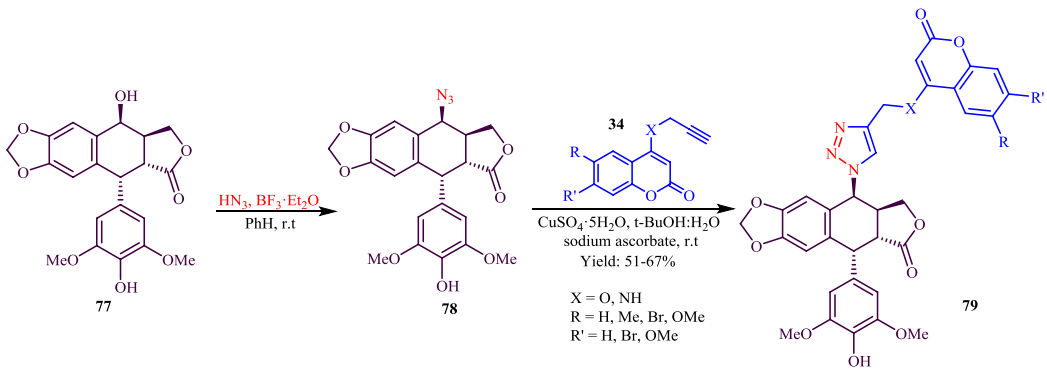
the target molecules **76** were prepared by click reaction of compounds **73** with azide analogs **75** in the presence of Et_3N along with a catalytic amount of CuI at room temperature. Some of the products displayed the good anti-BChE activity much more active than tacrine and donepezil as the reference drugs (Scheme 13) [34].

4β-N^3-4′-Demethyl-epipodophyllotoxin **78** was prepared via treating 4′-demethylepipodophyllotoxin **77** with a benzene solution of hydrazoic acid in the presence of boron trifluoride etherate ($BF_3{\cdot}Et_2O$). Then, the target compounds **79** were prepared by click reaction of the compound **78** and coumarin **34** in the presence of $CuSO_4{\cdot}5H_2O$ 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 H_2SO_4 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 DMF/H_2O solvent (Scheme 15) [36].

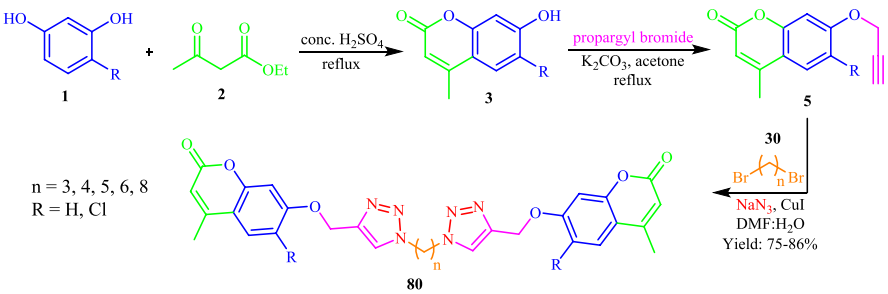


Scheme 13 Synthesis of tacrine–coumarin hybrids **76**



Scheme 14 Preparation of novel conjugates of podophyllotoxin and coumarin

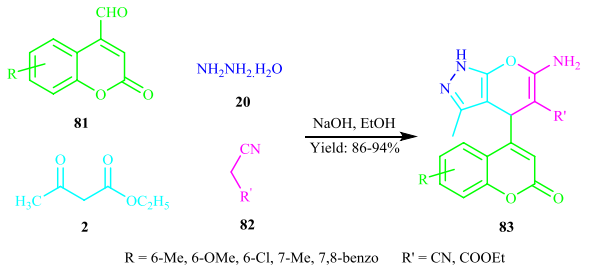
Scheme 15 Preparation of dimers of coumarin-tethered 1,2,3-triazole hybrids



Coumarins containing pyrazole core

A green, eco-friendly method has been developed, and a series of coumarin-pyrano[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 acetoacetate **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, Yalcın 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^2,N^4,N^4-tetramethyl-1,3,5-triazine-2,4-diamine **90**. Also, compound **86** was prepared for cycloaddition reaction 4-(diethylamino)-2-hydroxybenzaldehyde



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

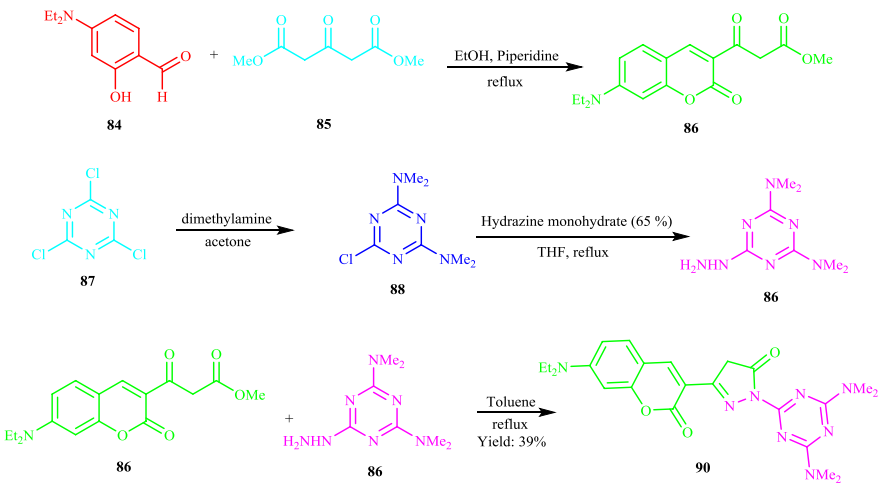
84 with dimethyl 3-oxopentanedioate **85** in the presence of catalytic amounts of piperidine in EtOH under reflux conditions (Scheme 17) [38].

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-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **94** and flavone or amine at 40–50 °C. Compound **94** was obtained as a result of the condensation of 3-cinnamoyl-2*H*-chromen-2-one compound **92** with hydrazine **20** in EtOH at 40–60 °C followed by cyclization with 2-bromoacetic acid **93** (Scheme 18). The results of initial evaluation showed that some derivatives exhibited better TNF-α and IL-6 inhibitory activity [18].

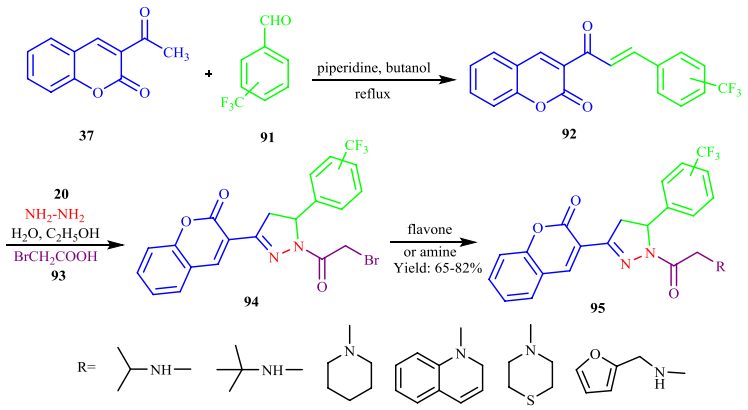
A series of substituted 3-(4-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-ones **104** were prepared through a stepwise procedure. Reduction of 3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **97** by $NaBH_4$, also reaction with $SOCl_2$ in benzene led to the formation of 3-(4-(chloromethyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **99**. The reaction of potassium *o*-ethyl carbonodithioate **100** with compound **99** under reflux condition afforded carbonodithioate **101**. Chromen 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-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-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-2*H*-chromen-2-one **107** was prepared by 1-(2,4-dihydroxyphenyl) ethanone **106** and ethyl acetoacetate **2** in the presence

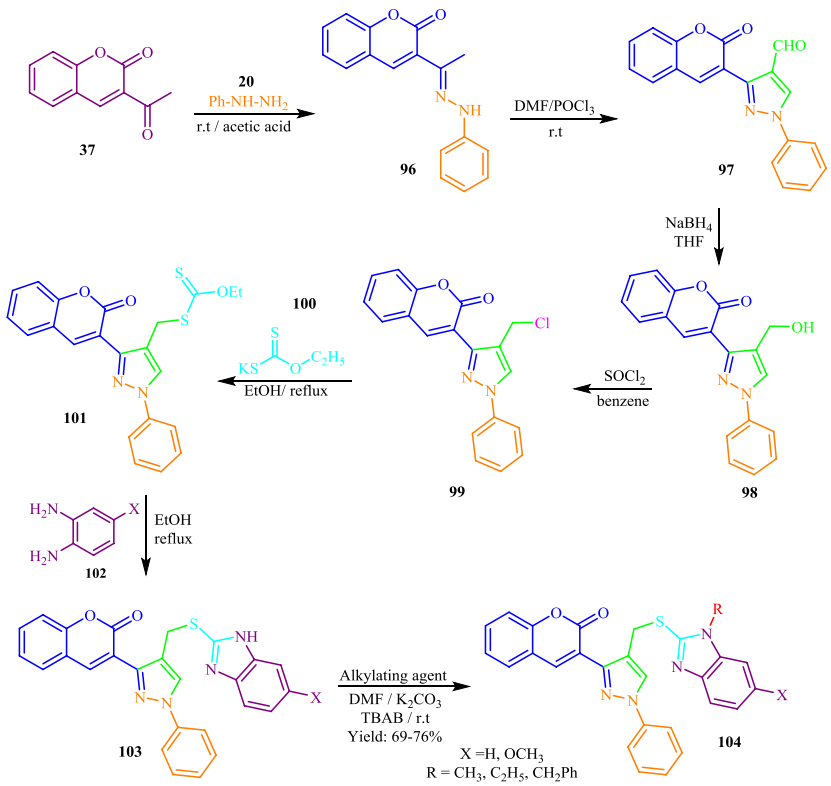
Scheme 17 Synthesis of novel coumarin–pyrazole–triazine-based fluorescence chemosensor



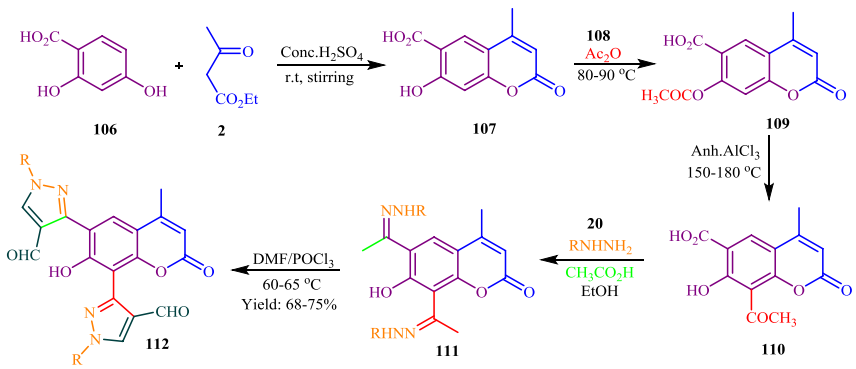
Scheme 18 Synthesis of new arylpyrazoline–coumarins



Scheme 19 Synthesis of novel substituted benzo[*d*]imidazol–pyrazol–chromens



Scheme 20 Synthesis of coumarin-appended *bis*(formylpyrazole) derivatives



of sulfuric acid via Pechmann reaction. The treatment of **107** with acetic anhydride **108** to give 6-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl acetate **109**, prepared on subjecting to Fries rearrangement using $AlCl_3$ as a catalyst, afforded 1,1′-(7-hydroxy-4-methyl-2-oxo-2*H*-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-1*H*-pyrazol-4-yl)(*p*-tolylamino)methyl)-4-hydroxy-2*H*-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 Ac_2O 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 $AlCl_3$ 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].

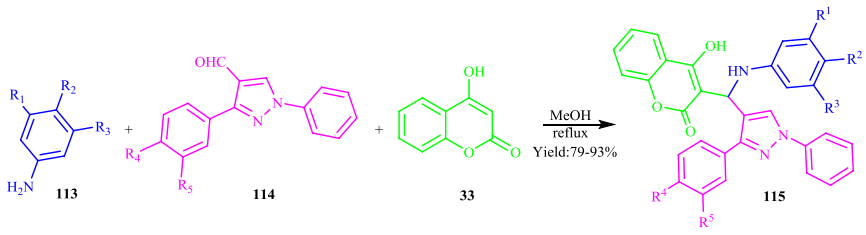
In another attempt, Saeed et al. synthesized a large series of coumarinyl–pyrazolinyl-substituted thiazoles derivatives **7**. The acetylcoumarin **37** was treated with various aldehydes **119**; this afforded the chalcones **124** in excellent yields. The chalcones **124** underwent inter-molecular 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-2*H*-chromen-3-yl)-1-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)-5-aryl-1*H*-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].

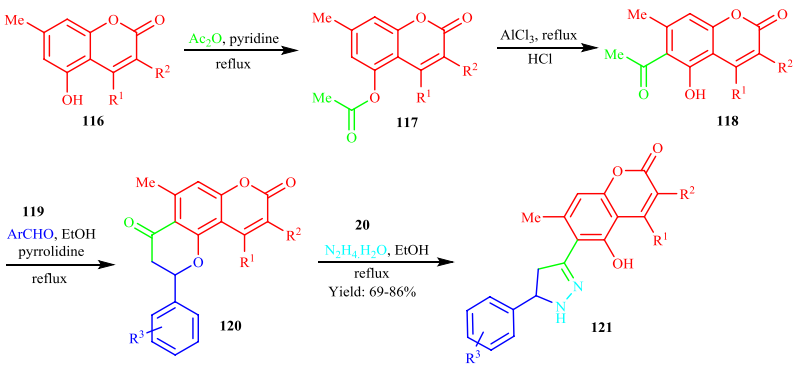
One-pot synthesis of some substituted benzylpyrazolyl coumarins **131** was carried out under solvent-free reaction of phenylhydrazine **120**, ethyl acetoacetate **2**, 4-hydroxycoumarin **33** and various aldehydes **119** in the presence of Nb-Zr/KIT-6 as an effective, recyclable and green catalyst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

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

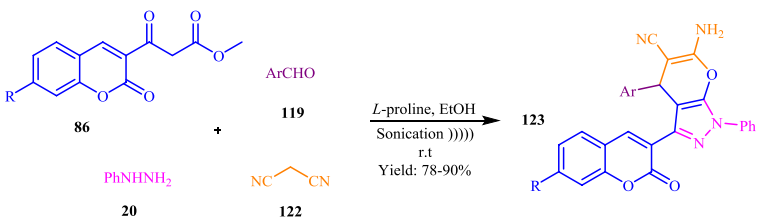
Scheme 21 Synthesis of pyrazole-aniline-linked coumarin



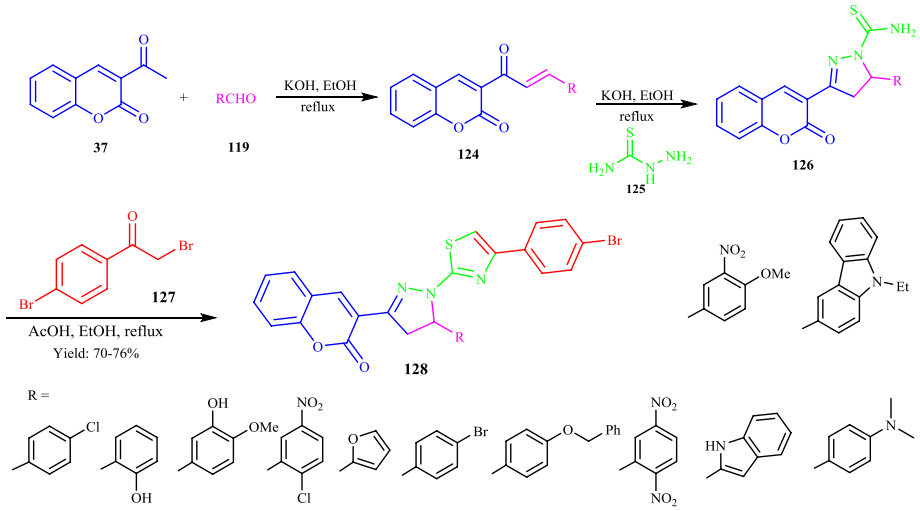
Scheme 22 Synthesis of 6-pyrazolinylcoumarin derivatives



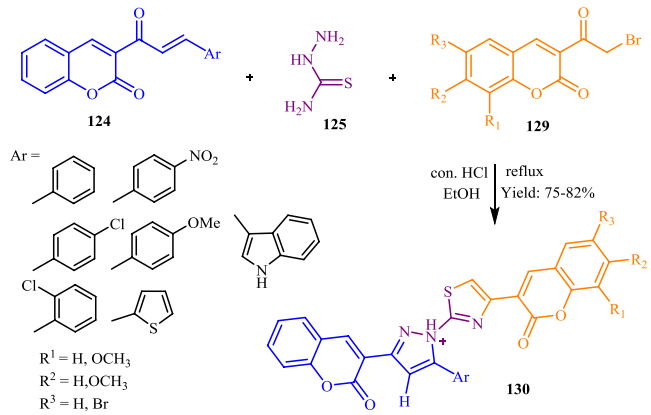
Scheme 23 One-pot synthesis of coumarin-containing dihydropyrano[2,3-*c*]pyrazoles



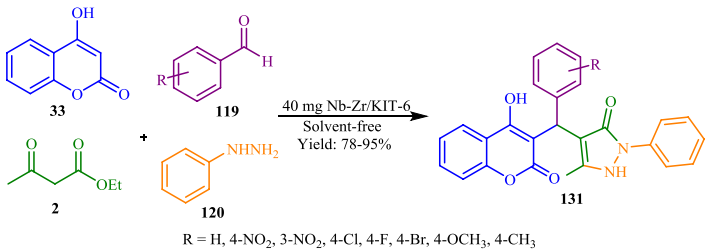
Scheme 24 Synthesis of coumarinyl–pyrazolinyl-substituted thiazoles derivatives



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



Scheme 26 One-pot synthesis of benzylpyrazolyl coumarin



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 pyrazol **135**, which was further treated with $POCl_3$ 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 K_2CO_3 and Cs_2CO_3 in CH_3CN 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 $POCl_3$ in pyridine as solvent and catalyst (Scheme 28) [48].

Coumarins containing imidazole core

Li et al. synthesized several molecules containing chromeno[3,4-*d*]imidazol-4(1*H*)-one **149**. Phenylamino derivatives **145** were prepared by reaction of compound **144** with a solution of iron and NH_4Cl in EtOH: H_2O.

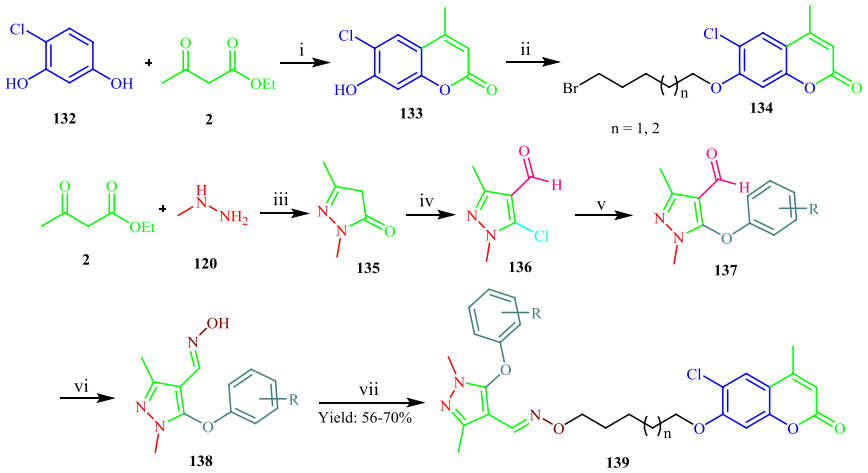
Subsequent cyclization of **145** with 1,1′-carbonyldiimidazole **146** in acetic acid afforded chromeno-imidazole **147**. Final products **149** were prepared via the reaction of **147** with boric acid **148** in the presence of K_2CO_3 and $PdCl_2$ at ambient temperature in dioxane/water (Scheme 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-1*H*-imidazol-2-yl)-2*H*-chromen-2-ones **155** were prepared through reaction of compound **152** with *p*-toluenesulfonyl chloride **154** in the presence of catalytic amounts of Et_3N (Scheme 30) [50].

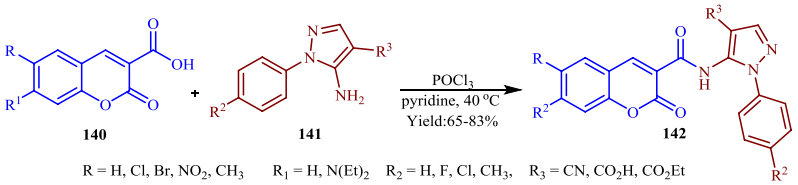
7-Hydroxy coumarin **62** reacted with various alkyl bromides **30** under reflux conditions in the presence of K_2CO_3 to yield coumarin derivatives **63** in high yield, and further reaction of **63** with imidazoles **156** in CH_3CN led to coumarin–imidazoles **157** (Scheme 31) [51].

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 isocyanidesin

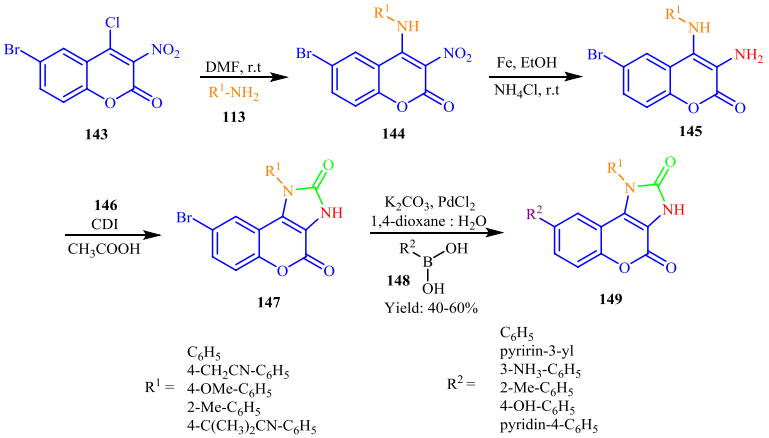
Scheme 27 Preparation of coumarin/pyrazole hybrids



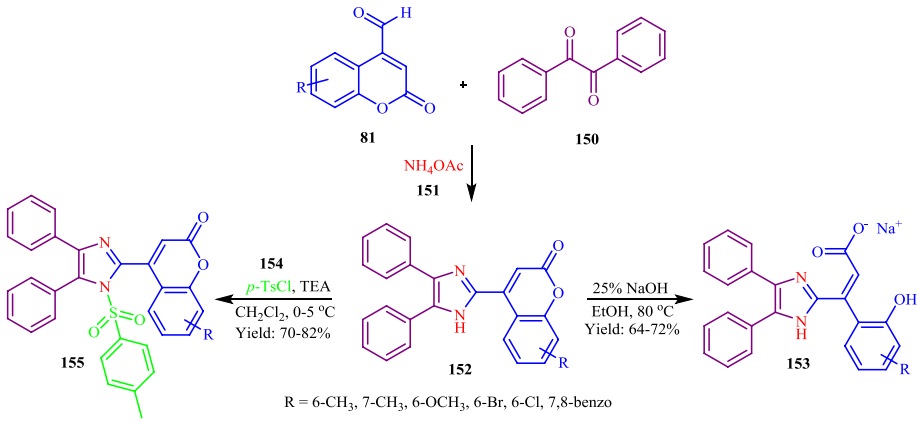
Scheme 28 Synthesis of novel coumarin–pyrazole carboxamide derivatives

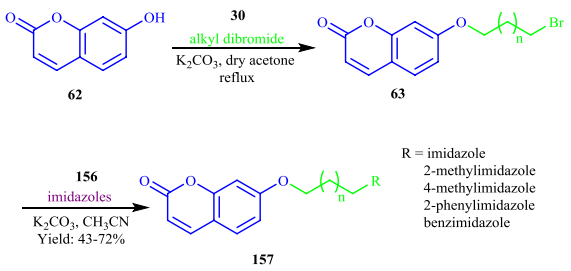


Scheme 29 Synthesis of 2,3-dihydrochromeno[3,4-*d*] imidazol-4(1*H*)-one derivatives



Scheme 30 Synthesis of coumarin–imidazole hybrid and phenylimidazoloacrylates





Scheme 31 Synthesis of coumarin derivatives containing imidazole agents

160 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 multi-component 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].

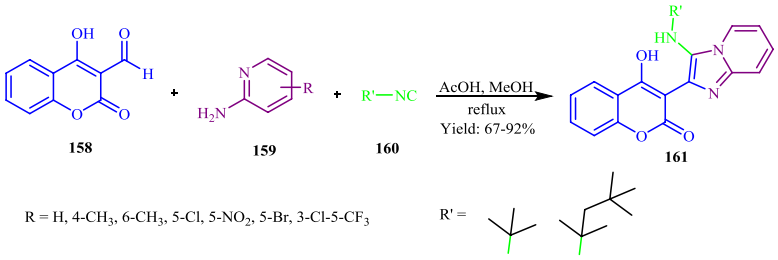
7-(4-Bromobutoxy)-2*H*-chromen-2-one **63** was prepared via reaction of 7-hydroxy-2*H*-chromen-2-one **62** with 1,4-dibromobutane in the presence of anhydrous K_2CO_3 and triethylamine. Then, **63** was transformed to 7-(4-(1*H*-benzo[*d*]imidazol-1-yl)butoxy)-2*H*-chromen-2-one **166** via reaction with benzimidazole in the presence of anhydrous K_2CO_3 and anhydrous acetonitrile (Scheme 34) [54].

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

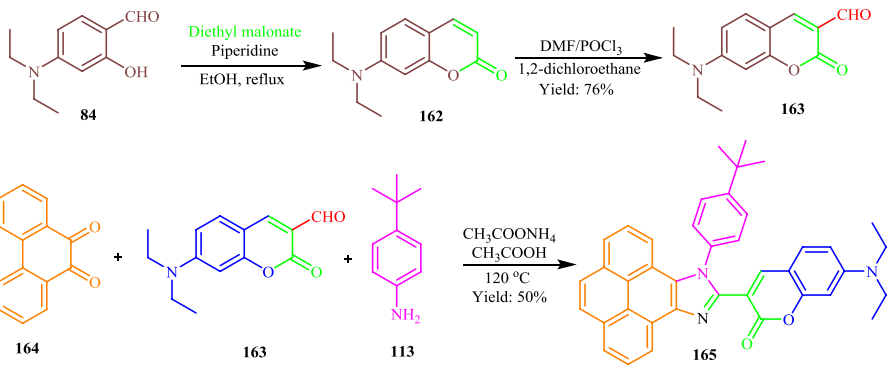
Coumarin derivatives **169** containing imidazole skeleton as potential anti-bacterial agents were synthesized from 7-hydroxy coumarin **168** by reacting with corresponding amines and triethylamine in anhydrous EtOH at reflux conditions (Scheme 36) [56].

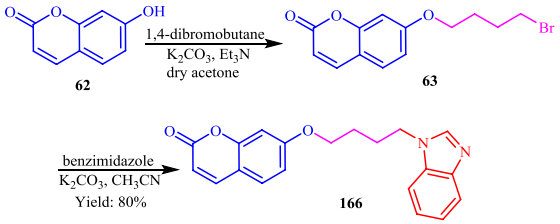
Four donor–acceptor triphenylamine- and *N*-phenyl carbazole-based coumarin dyes were synthesized from the reaction of aldehydes (**170** and **175**) with 2-(1*H*-benzo[*d*] imidazol-2-yl) acetonitrile **171** or 2-(benzo[*d*]thiazol-2-yl) acetonitrile **172** intermediate in the presence of piperidine in EtOH. The results showed that the synthesized rigid donor-π-acceptor coumarins are better candidates for NLO materials (Scheme 37) [57].

Scheme 32 Synthesis of imidazo[1,2-*a*]pyridine-4-hydroxy-2*H*-coumarins



Scheme 33 Synthesis of pyreno[4,5-*d*]imidazol-coumarin





Scheme 34 Synthesis of 7-(4-(1*H*-benzo[*d*]imidazol-1-yl)butoxy)-2*H*-chromen-2-one

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].

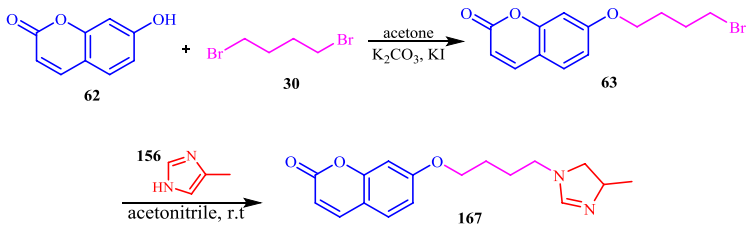
Coumarins containing theophylline core

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 K_2CO_3 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].

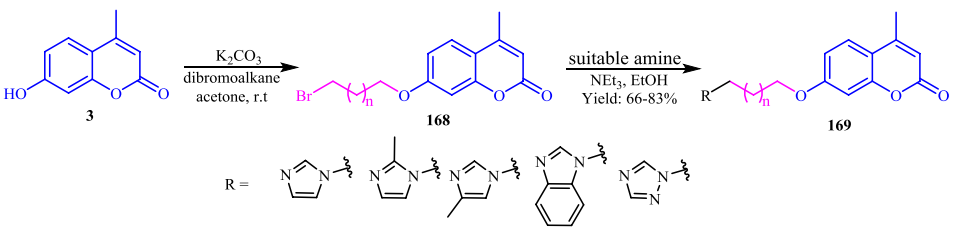
Coumarins containing quinolone core

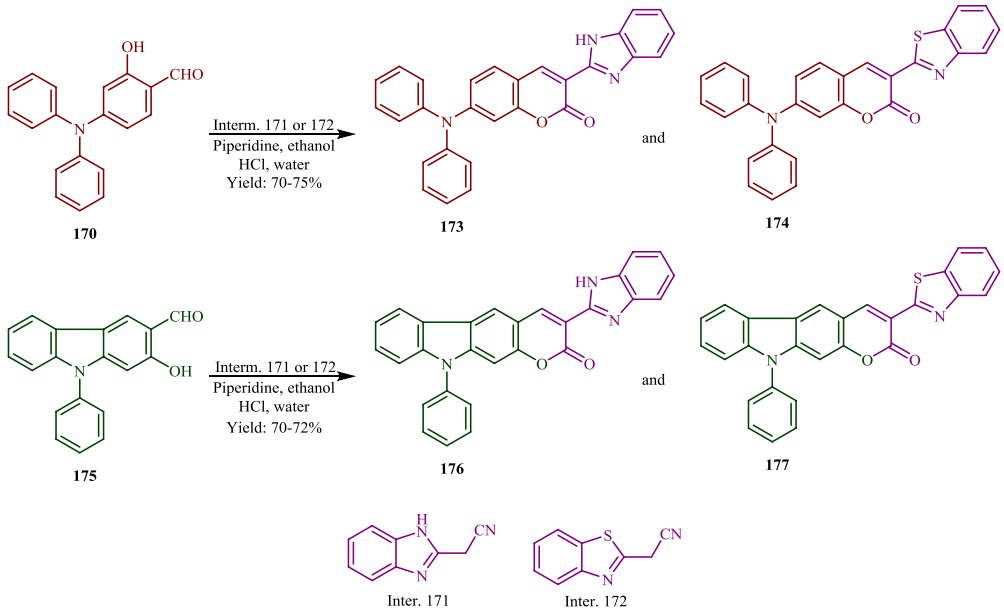
In an interesting procedure, the reaction of various dibromides **30** with 7-hydroxy-4-methyl coumarins **3** under reflux condition yielded bis-coumarins **182** in the presence of an alkaline catalyst. The bromoalkoxy derivatives of 7-hydroxy-4-methyl coumarins **168** were prepared through the bromoalkylation 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

Scheme 35 Synthesis of 7-(4-(4-methyl-4,5-dihydro-1*H*-imidazol-1-yl)butoxy)-2*H*-chromen-2-one

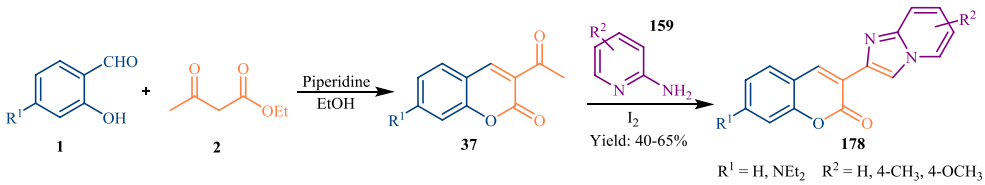


Scheme 36 Synthesis of coumarin derivatives containing imidazole skeleton



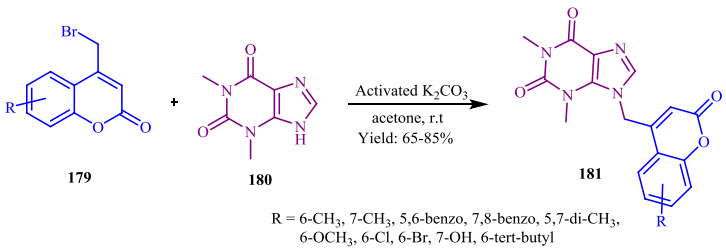


Scheme 37 Synthesis of NLOphoric coumarin dyes



Scheme 38 The synthesis of 3-imidazolyl coumarin derivatives **178**

Scheme 39 Synthesis of coumarin–theophylline hybrids

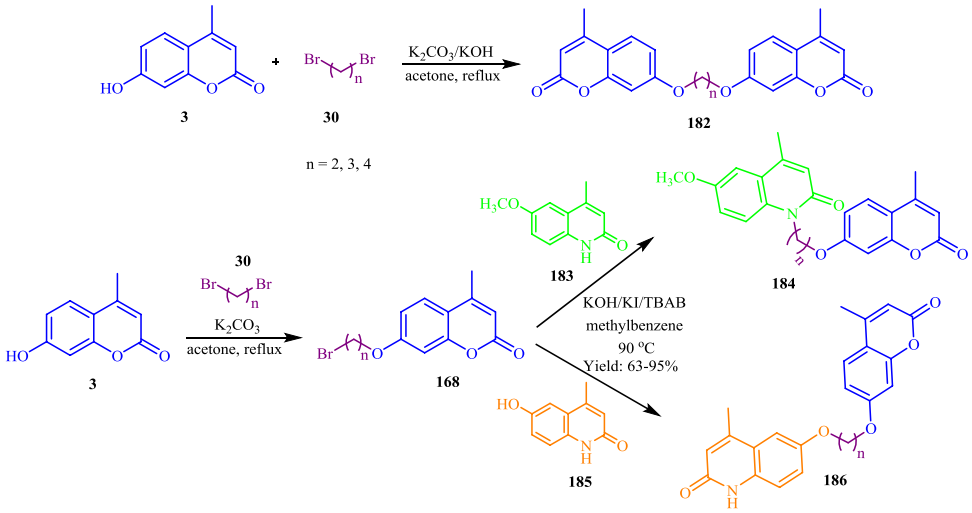


reaction between 7-bromoalkoxy-4-methyl coumarins **168** with 6-methoxy-4-methyl quinolone **183** and 6-hydroxy-4-methylquinolone **185**, respectively (Scheme 40) [59].

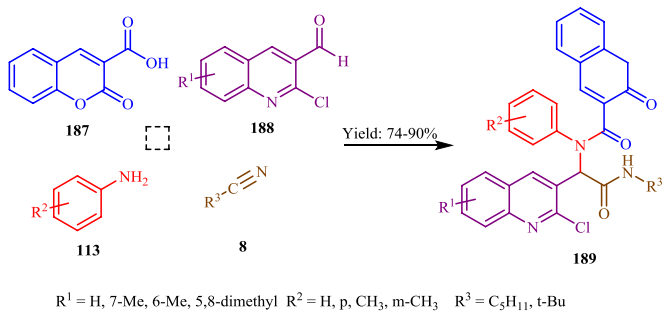
A simple method was developed for the synthesis of quinoline–coumarin derivatives **189** by an Ugi four-component reaction involving coumarin-3-carboxylic acid **187**, 2-chloroquinoline-3-carbaldehyde derivatives **188**, cyclohexyl isocyanide **8** and various amines **113** in methanol. Cytotoxic effects of all products were studied in A2780 human ovarian cancer cells (Scheme 41). Two synthesized compounds (R^1=5,8-dimethyl and R^2=H or *m*-CH_3) 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-2*H*-chromene-3-carboxylic acid *N*′-[2-(quinolin-8-yloxy)-acetyl]-hydrazide analogs **192** and 2-oxo-2*H*-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

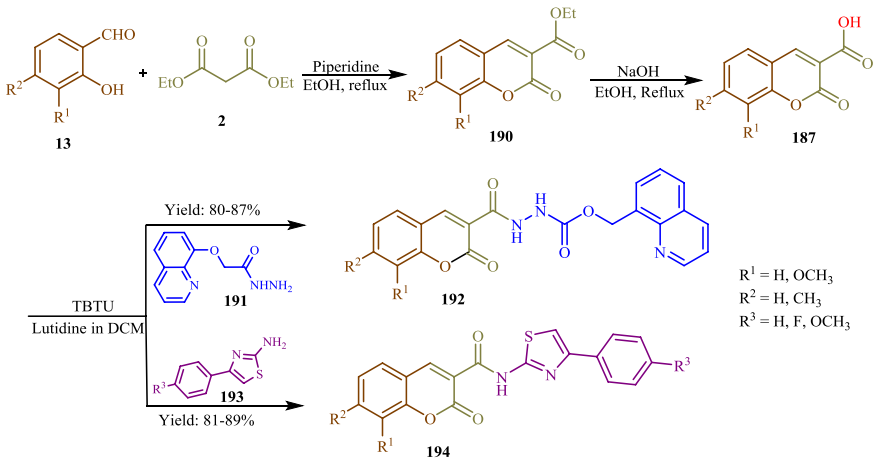
Scheme 40 Synthesis of coumarin–quinoline analogs



Scheme 41 Synthesis of quinoline–coumarin scaffolds by Ugi reaction



Scheme 42 Synthesis of chromene–quinolin analogs (**192**) and chromene–thiazol analogs (**194**)



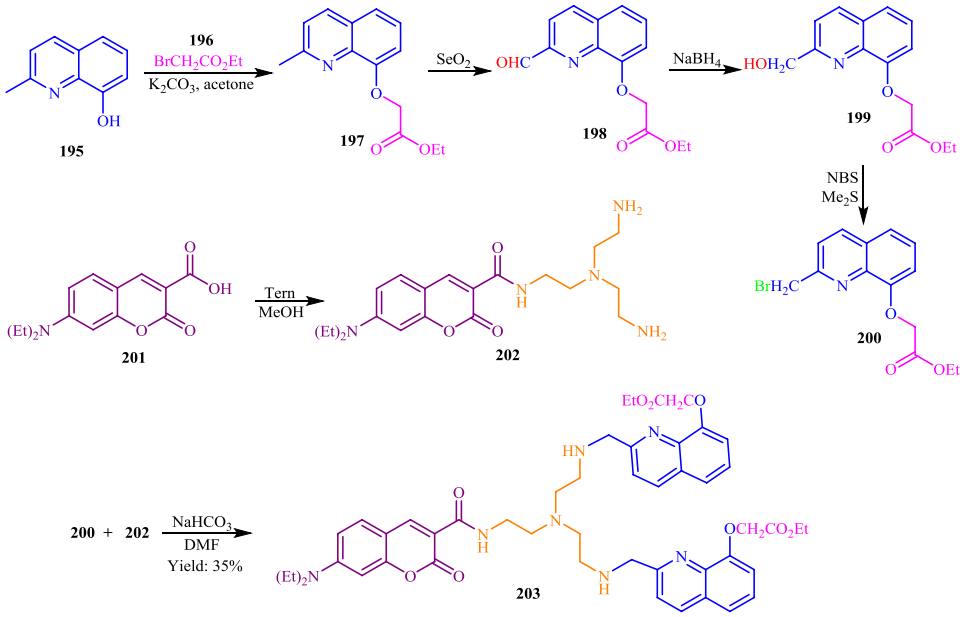
activity in comparison with chromene–quinolin analogs [61].

2-Methylquinolin-8-ol **195** reacted with ethyl bromoacetate **196** in the presence of K_2CO_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].

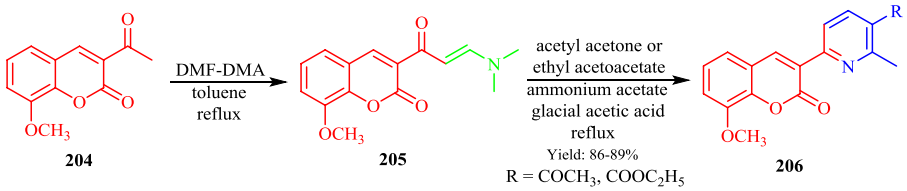
Coumarins containing pyridine core

Treatment of 3-acetyl-8-methoxy-2*H*-chromen-2-one derivatives **204** with equimolar of imethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene afforded the corresponding enaminone **205** which upon condensation with

Scheme 43 Synthesis of coumarin–quinoline **203**



Scheme 44 Synthesis of pyridine hybrids **206**



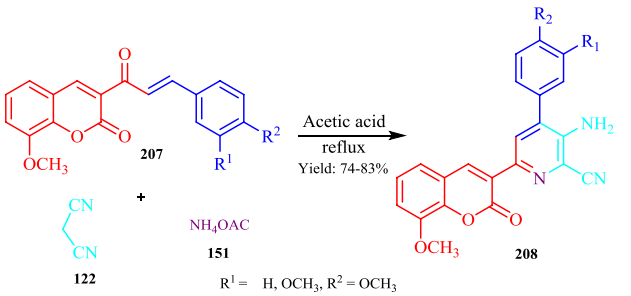
acetyl acetone or ethyl acetoacetate in glacial acetic acid in the presence of ammonium acetate furnished pyridine hybrids **206** (Scheme 44) [63].

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 salicylaldehydes **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(1*H*)-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_2CO_3 to afford the intermediate **220**. Then, the protecting group on pyridinone



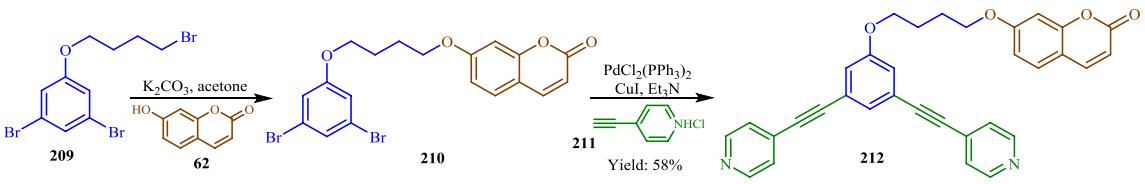
Scheme 45 Synthesis of picolinonitrile derivatives **208**

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].

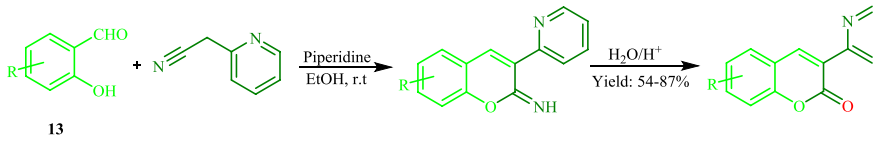
Coumarins containing pyrimidine core

4-Amino-2-(3-hydroxyphenyl)-6a,10a-dihydro-5*H*-chromeno[4,3-*d*]pyrimidin-5-one **229** was obtained

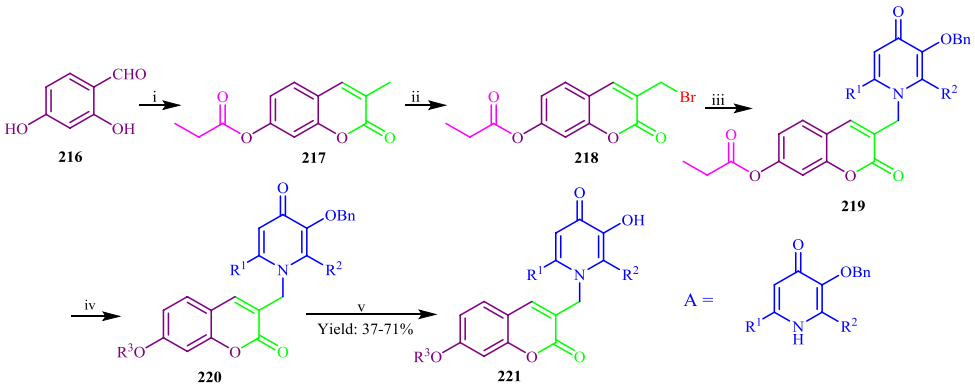


Scheme 46 Synthesis of coumarin having two pyridyl groups

Scheme 47 Preparation of 3-(pyridin-2-yl)coumarin derivatives



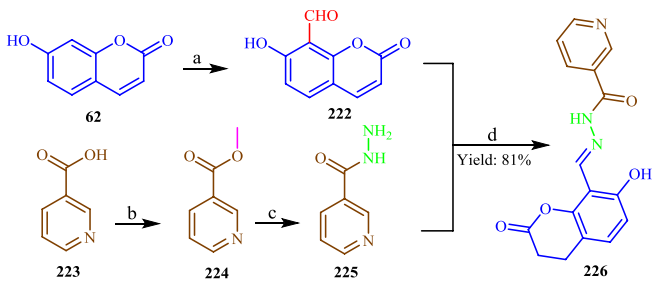
Scheme 48 Synthesis of hydroxypyridinonecoumarin hybrids



R_1 = H, CH_3 R_2 = H, CH_3, CH_2CH_3 R^3 = propargyl, benzyl, 3-chlorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 3,5-difluorobenzyl

(i) Propionic anhydride, sodium propionate, triethylamine, 170 °C, 10 h. (ii) NBS, BPO, CCl_4, reflux, 12 h (iii)A, K_2CO_3, acetonitrile, reflux, 6 h. (iv) Propargyl bromide or corresponding substituted benzyl bromide, K_2CO_3, 50% acetone-H_2O, reflux, 6 h. (v) BCl_3, anhydrous DCM, - 48 °C to r.t. 12 h.

Scheme 49 Synthesis of (*E*)-*N*′-((7-hydroxy-2-oxochroman-8-yl)methylene)nicotinohydrazide



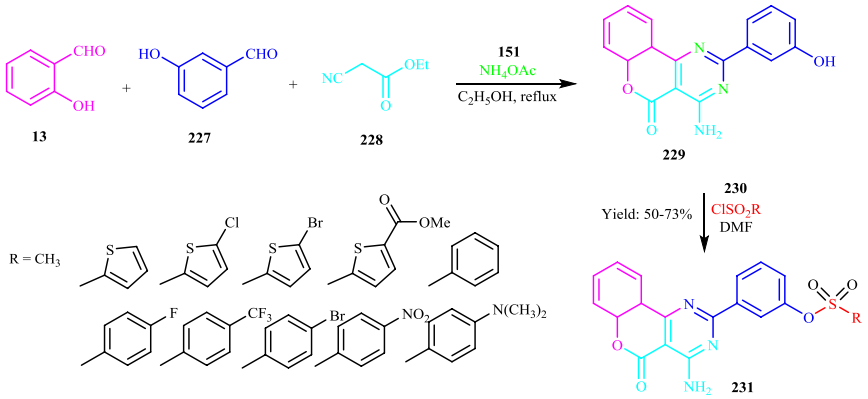
a) urotropine, acetic acid, 90 °C; b) MeOH, concentrated sulfuric acid, 75 °C; c) MeOH, hydrazine hydrate, room temperature; d) EtOH, reflux.

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].

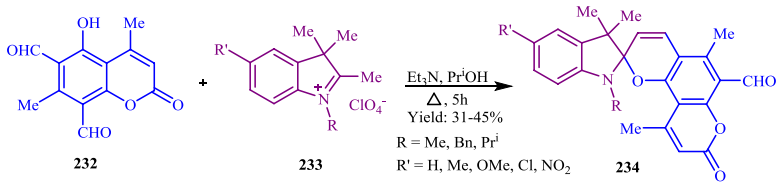
Coumarins containing indole core

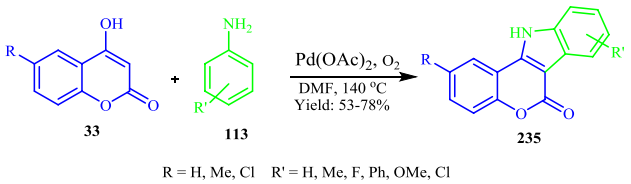
Novel photochromic indolinospiropyrans containing coumarin **234** were obtained via the reaction of 5-hydroxy-4,7-dimethyl-2-oxo-2*H*-chromene-6,8-dicarbaldehyde **232** with 1-R-5-R′-2,3,3-trimethyl-3*H*-indol-1-ium perchlorate **233** in the presence of catalytic amounts of Et_3N under reflux conditions (Scheme 51) [69].

Scheme 50 Synthesis of 3′-sulfonate-substituted 2-phenyl-benzopyranopyrimidine derivatives

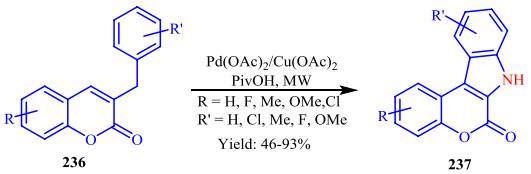


Scheme 51 Synthesis of indolinospiropyrans **234**





Scheme 52 Preparation of indole–coumarin derivatives



Scheme 53 Synthesis of indolo[2,3-*c*]coumarins

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 O_2 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

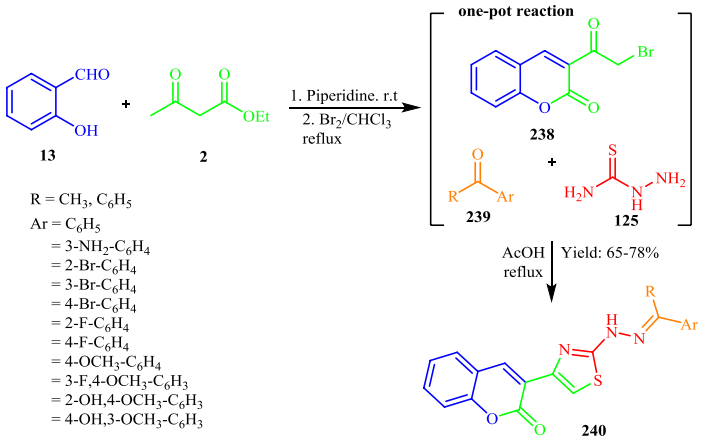
A series of coumarinyl thiazoles **240** have been synthesized as shown in Scheme 30. First, the 3-(2-bromoacetyl)-2*H*-chromen-2-one **238** was readily synthesized through condensation between salicylaldehyde **13** and ethyl acetoacetate **2** catalyzed by piperidine and subsequent bromination. Then,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

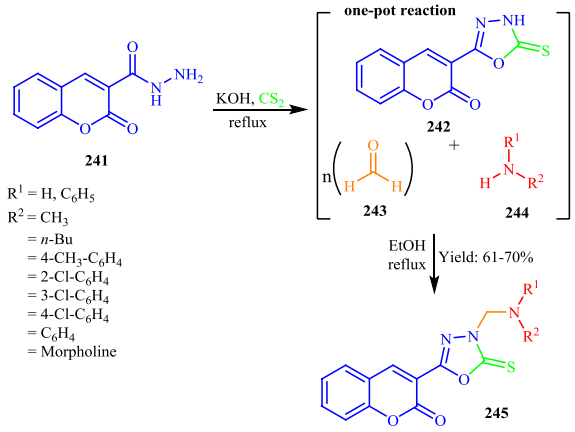
In another attempt, the coumarinyl hydrazide **241** was reacted with carbon disulfide in the presence of ethanolic solution of KOH under reflux conditions to afford corresponding 3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one **242**. The resultant compound **242** was treated with paraformaldehyde **243** and various amines **244** in one-pot reaction to get the coumarinyl oxadiazole-2(3*H*)-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)-2*H*-chrome-2 ones **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-[6-[(2-benzoylbenzofuran-5-yl) methyl]-2-oxo-2*H*-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 K_2CO_3 led to formation of 5-[(2-benzoylbenzofuran-5-yl)methyl]-2-hydroxybenzaldehyde **254**. Further cyclization reaction of compound **254** with ethylacetoacetate **2** in the presence of piperidine afforded 3-acetyl-6-[(2-benzoylbenzofuran-5-yl)methyl]-2*H*-chromen-2-one

Scheme 54 Synthesis of coumarinyl thiazole analogs via one-pot reaction





Scheme 55 Synthesis of coumarin–oxadiazole-2(3*H*)-thione hybrids

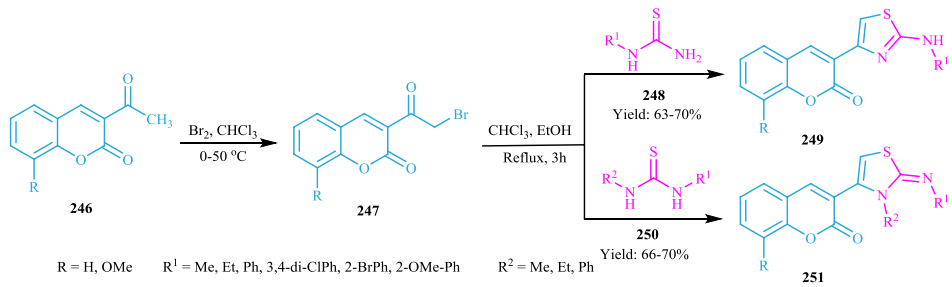
255. 3-(2-Aminothiazol-5-yl)-6-[(2-benzoylbenzofuran-5-yl) methyl]-2*H*-chromen-2-one **168** obtained from the reaction of **255** with thiourea **256** in the presence of catalytic amount of iodine. Finally, condensation of **257** into triphosgene **258** and different amines **244** led to 1-[5-[6-[(2-benzoylbenzofuran-5-yl)methyl]-2-oxo-2*H*-chromen-3-yl]thiazol-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-2*H*-chromen-2-one **3** was formed through Pechmann reaction between resorcinol **1** and ethyl acetoacetate **2**. Then, 4-methyl-7-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one **261** was prepared via reacting 7-hydroxy-4-methyl-2*H*-chromen-2-one **3** with excess of epichlorohydrin **260** in the presence of K_2CO_3 under reflux conditions. The synthesis of target compounds **262** was accomplished from the nucleophilic opening of oxirane with diverse anilines **113** in EtOH under refluxing condition (Scheme 58) [75].

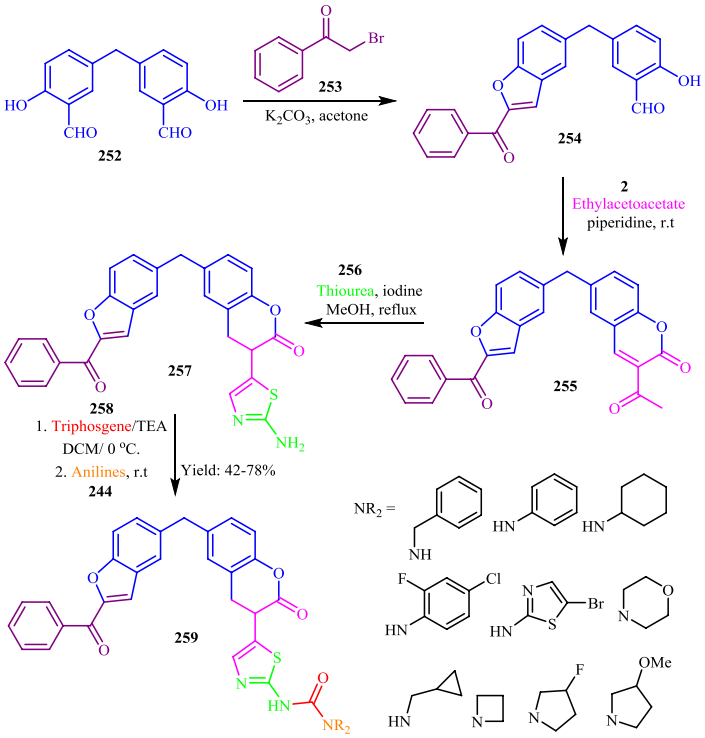
In another attempt, coumarin–benzothiazole derivatives were synthesized in two steps (Scheme 59). In first step, substituted benzothiazole derivatives **264** were prepared via reacting substituted aniline **113**, and potassium thiocyanate **263** in the presence of bromine in glacial acetic acid. In second step, substituted benzothiazole derivatives **264** were reacted with 4-methyl-7-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one **261** to afforded final compounds **265** (Scheme 59). Products showed anti-inflammatory and analgesic activities. The presence of $–OCH_3$ 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 benzohydrazide 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

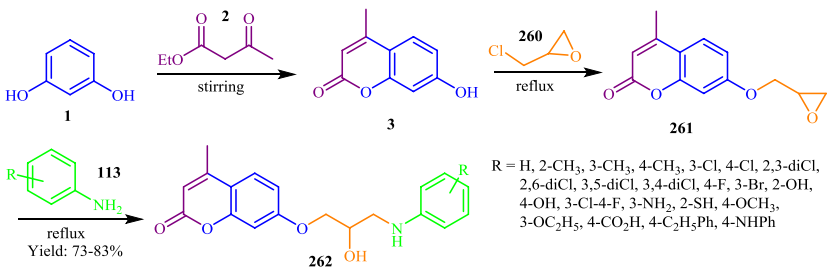
Scheme 56 Synthesis of new thiazolyl–coumarin hybrids



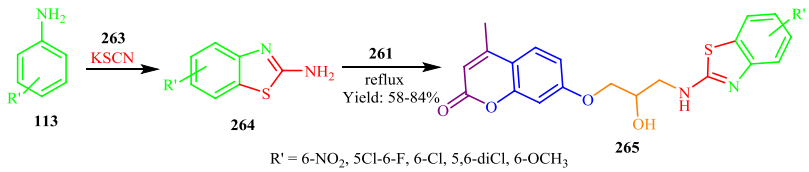
Scheme 57 Synthesis of novel 1-[5-[6-[(2-benzoylbenzofuran-5-yl)methyl]-2-oxo-2*H*-chromen-3-yl]thiazol-2-yl]ureas



Scheme 58 Synthesis of 7-substituted coumarin derivatives **262**



Scheme 59 Synthesis of coumarin–benzothiazole derivatives **265**



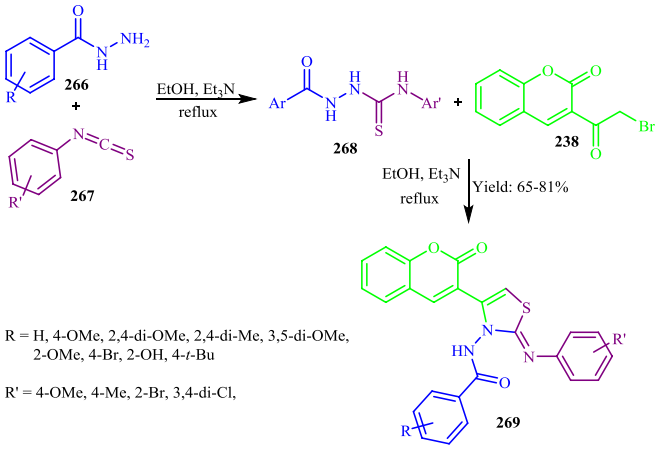
3-(bromoacetyl) coumarin **238** in the presence of catalytic amount of Et_3N, to afford 3-thiazolyl coumarin derivatives **269** (Scheme 60). All compounds showed inhibitory activity in the range of IC50 = 0.12 ± 0.01–16.20 ± 0.23 μM as compared to standard acarbose (IC50 = 38.25 ± 0.12 μM), also found to be non-toxic [76].

3-Acetylcoumarin derivatives **37** were brominated using Br_2 in $CHCl_3$ solvent to give bromoacetyl analogs **238**. In order to synthesis coumarins **272**, dimethyl *N*-cyanodithioimidocarbonate **270** was treated with suitable amines and Na_2S to produce intermediates **8**, which reacted with 3-(bromoacetyl)coumarins **238** in DMF. Also, the reaction of phenylisothiocyanates **267** with cyanamide and sodium methoxide afforded intermediate **273** that treated with coumarin **238** to give coumarins **274** (Scheme 61) [77].

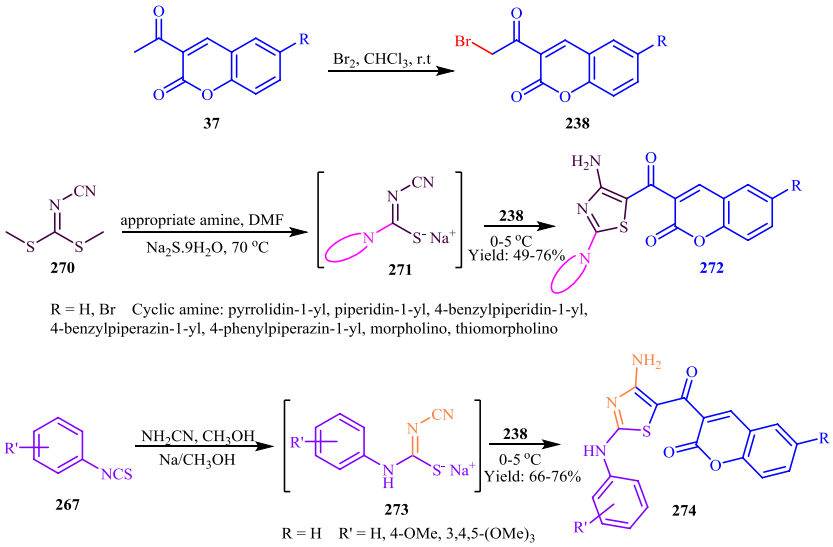
The reaction of *α*-bromoacetylcoumarin **238** with thioacetamide in MeOH at room temperature furnished 3-(2-methylthiazol-4-yl)-2*H*-chromen-2-one **275**, whereas refluxing compound **238** with potassium thiocyanate in EtOH at room temperature afforded 3-(2-ethoxythiazol-4-yl)-2*H*-chromen-2-one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

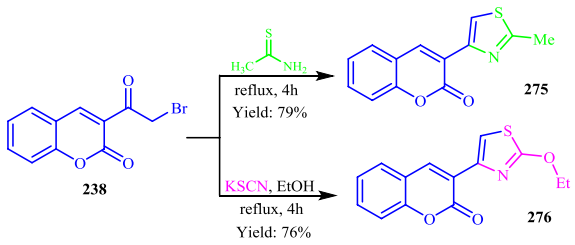
1-Hydroxy-2-naphthaldehyde **277** reacted with ethylacetoacetate **2** in the presence of piperidine to yield corresponding 2-acetyl-3*H*-benzo[*f*]chromen-3-one **278** that led

Scheme 60 Syntheses of 3-thiazolyl coumarin derivatives



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





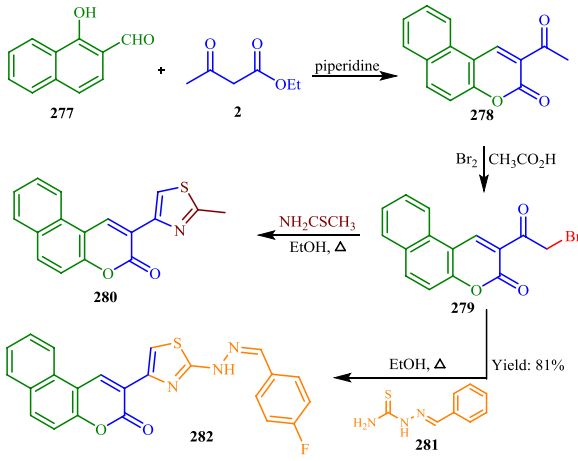
Scheme 62 One-pot synthesis of thiazolyl–coumarin hybrids

to corresponding 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one **4279** via bromination. Compound **279** reacted with 2-(4-fluorobenzylidene) hydrazine carbothioamide **281** 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].

A new fluorescent sensor **285** was synthesized using Schiff base reaction connected by 7-(*N*,*N*-diethylamino) coumarin-3-aldehyde **163** and 2-hydrazinobenzothiazole **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_2CO_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



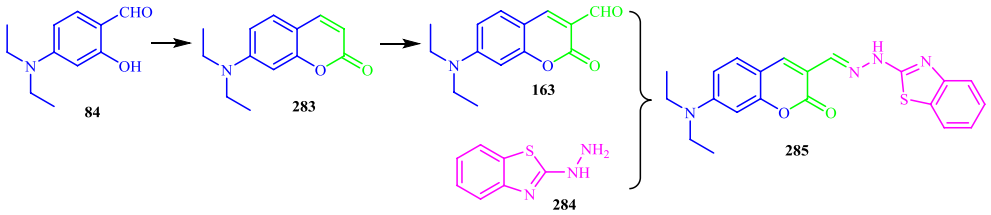
Scheme 63 Synthesis of benzocoumarin derivatives

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].

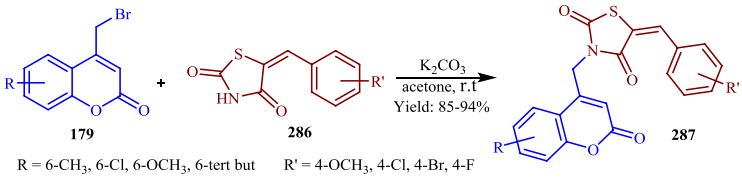
Coumarins **296** reacted with 3-aryl-5-(chloromethyl)-1,2,4-oxadiazole analogs **297** by using KI and K_2CO_3 in acetone to give coumarin-1,2,4-oxadiazole hybrids **298** in good yields (Scheme 68). All synthesized compounds were screened for their anticonvulsant activities [84].

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).

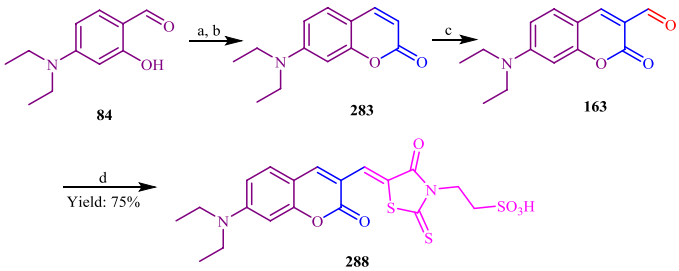


Scheme 64 Syntheses procedure of coumarin **285**

Scheme 65 Synthetic route for the preparation of coumarin–thiazolidine derivatives

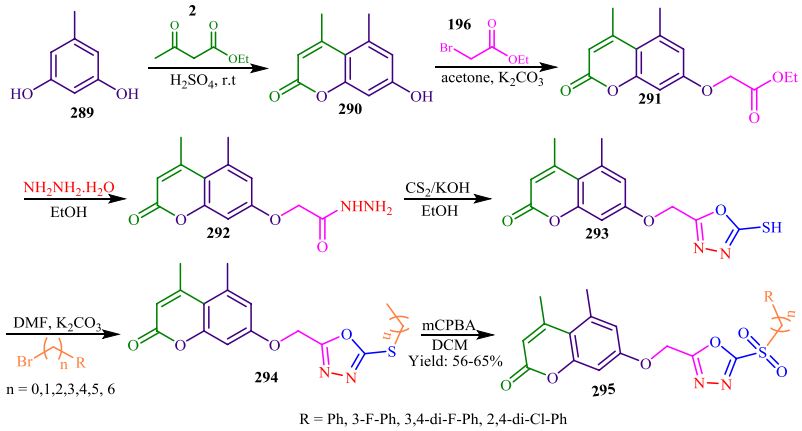


Scheme 66 Synthetic route to thioxothiazolidin–coumarin

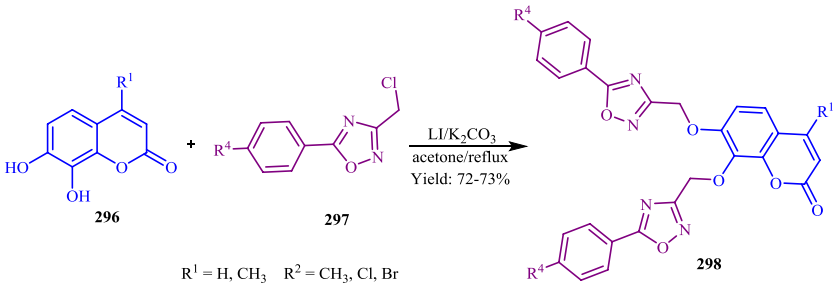


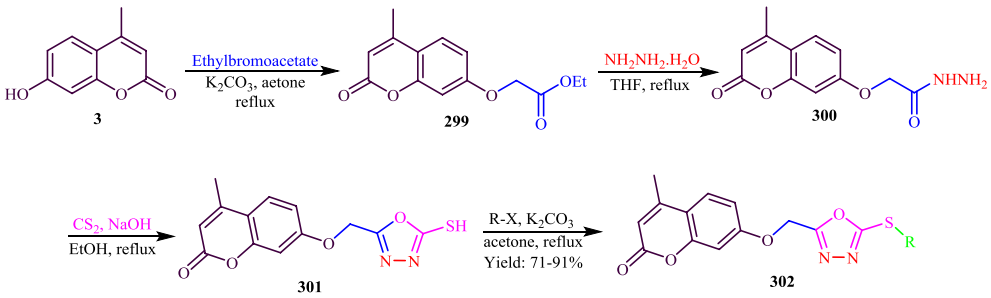
Reagents and conditions: a) Diethyl malonate, piperidine, reflux; b) HCl, AcOH, reflux; c) $POCl_3$, DMF d) 3, 2-(4-oxo-2-thioxotetrahydrothiophen-3-yl)ethanesulfonic acid, MeOH, piperidine

Scheme 67 Synthetic pathway of 1,3,4-oxadiazole derivatives



Scheme 68 Synthesis of new coumarin-1,2,4-oxadiazole hybrids





Scheme 69 Synthesis of coumarin-1,3,4-oxadiazole hybrids

All of the synthesized coumarin hybrids showed anticancer activity [85].

Coumarins containing imide band

Base-catalyzed Claisen–Schmidt condensation of 3-acetyl-8-methoxy-2*H*-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-2*H*-chromene-3-carboxylic acid **187** with anilines in dry DMF in the presence of DIEA and propyl phosphoric acid anhydride (T_3P). Also, coumarin-3-carboxamide derivatives **306** were obtained via reaction of 2-oxo-2*H*-chromene-3-carboxylic acid **187** with hydrazine hydrochloride derivatives in anhydrous CH_2Cl_2 (Scheme 71). All products were evaluated in vitro for their antifungal activities against *Alternaria solani*, *Botrytis cinerea*, *Gibberella zeae*, *Cucumber anthrax*, *Rhizoctorzia solani* and *Alternaria leaf spot* [87].

A new series of 3-formylcoumarin derivatives **309** were synthesized through reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **308** with various known

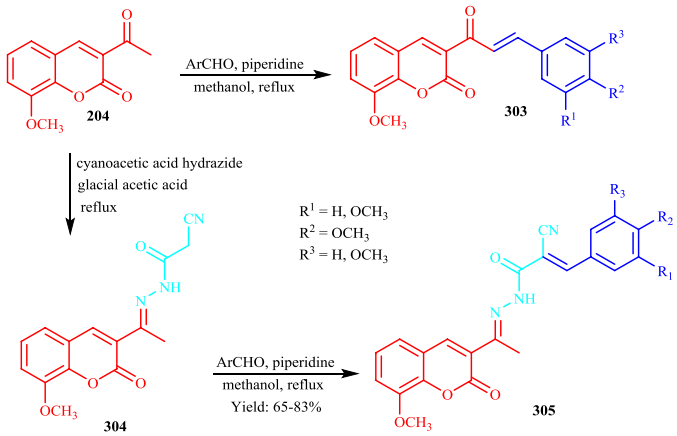
benzohydrazides **266** in the presence of acetic acid (Scheme 72). All derivatives indicated an acceptable degree of thymidine phosphorylase inhibition with IC50 values ranging between 0.90 ± 0.01 and 53.50 ± 1.20 lM [88].

Coumarin-3-carboxamides bearing tryptamine moiety **310** were achieved in reasonable yields from the reaction of coumarin-3-carboxylic acids **187** with $SOCl_2$ and tryptamine in the presence of catalytic amounts of K_2CO_3 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].

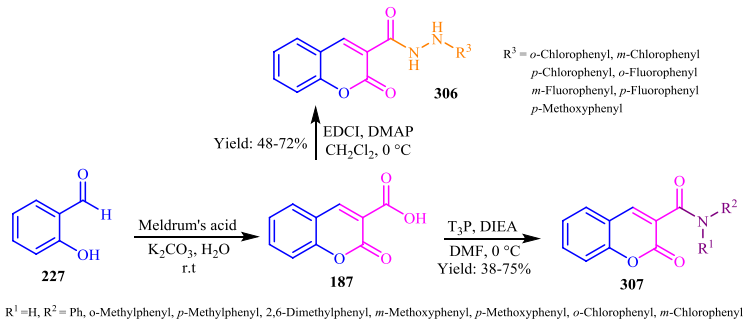
The synthetic method of fused tricyclic coumarins **313** was outlined in Scheme 74. At first, a series of cyano acetamide derivatives **311** were prepared via simple reaction of amines with equivalent amount of ethylcyanoacetate **228**. Also, resorcinol **1** and ethylacetoacetate were treated under 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 Et_3N 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 CH_2Cl_2

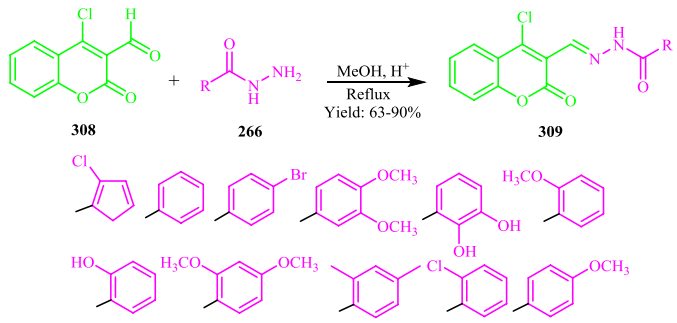
Scheme 70 Synthesis of chalcone derivatives **303** and acrylohydrazides **305**



Scheme 71 Synthetic routes for the coumarin-3-carboxamide derivatives



Scheme 72 Synthesis of 3-formylcoumarin analogs



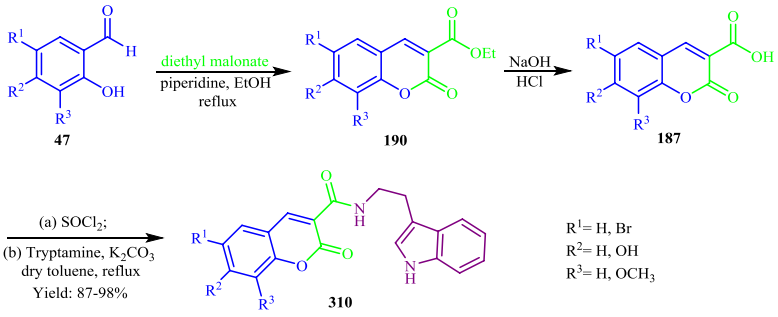
to afford **316**. Hydrogenation of compound **316** via Fe/NH_4Cl obtained **317**. Final products **318** were obtained through addition of **187** to intermediate **317** in dry CH_2Cl_2 (Scheme 75) [91].

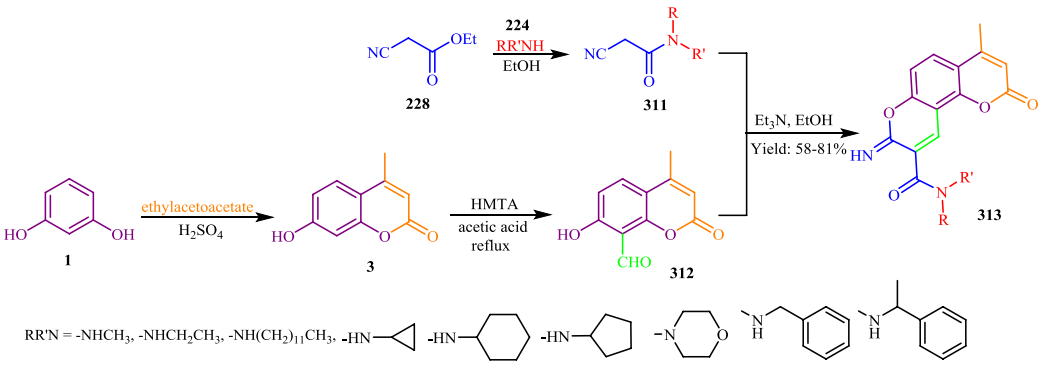
Vafadarnejad et al. synthesized several coumarin–pyridinium hybrid derivatives **322** by Ellman's method. *N*-Ethyl-2-oxo-2*H*-chromene-3-carboxamide-pyridine derivatives **320** were prepared by condensation of 2-oxo-2*H*-chromene-3-carboxylic acid **187** and compound **319** in CH_3CN. Additional 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-2*H*-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-2*H*-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

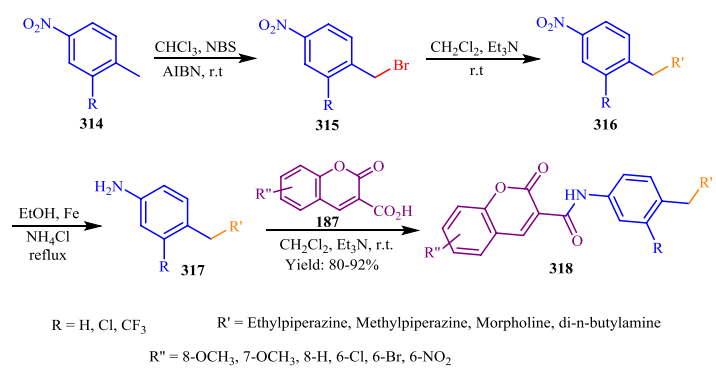
Scheme 73 Synthesis of coumarin-3-carboxamides bearing tryptamine moiety

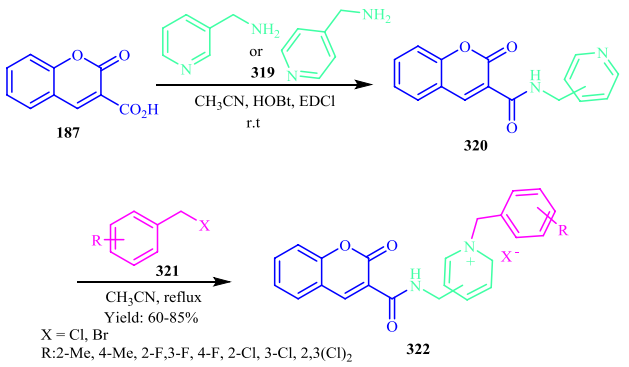




Scheme 74 Synthetic pathway of fused tricyclic coumarin derivatives

Scheme 75 Synthesis of coumarin-3-carboxamide derivatives





Scheme 76 Synthesis of coumarin–pyridinium hybrids **322**

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

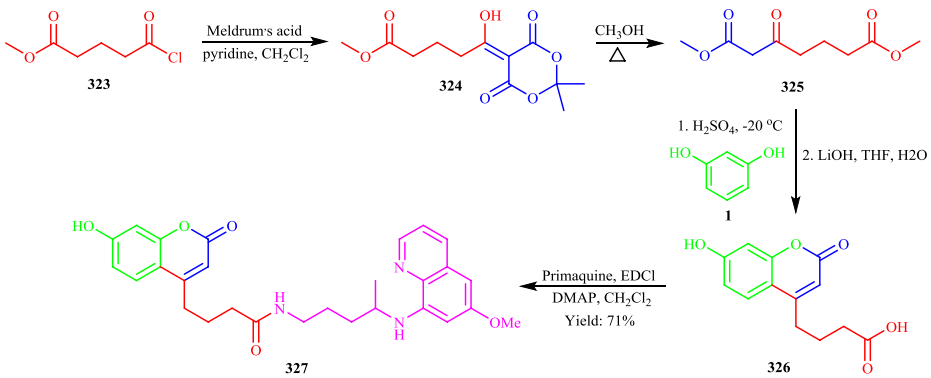
The target compounds were prepared according to published method which involved converting 7-amino-4-methyl-2*H*-chromen-2-one **329** to its diazonium salt upon reaction with 3-chloropentane-2,4-dione afforded *N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)-2-oxopropanehydrazonoyl chloride **330**. Reaction of chromen **330** 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].

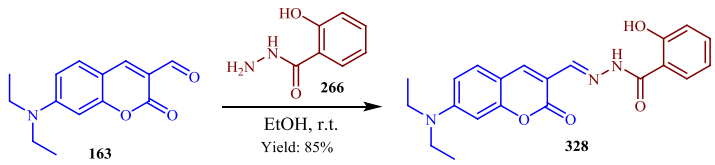
The starting material, 4-bromomethyl coumarins **179** were synthesized via Pechmann cyclization of phenols **335** with ethyl 4-bromoacetoacetate **334** using H_2SO_4 as cyclizing agent. The synthesized coumarins **179** on treating with 4,4-dimethylpiperidine-2,6-dione **336** in the presence of anhydrous K_2CO_3 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].

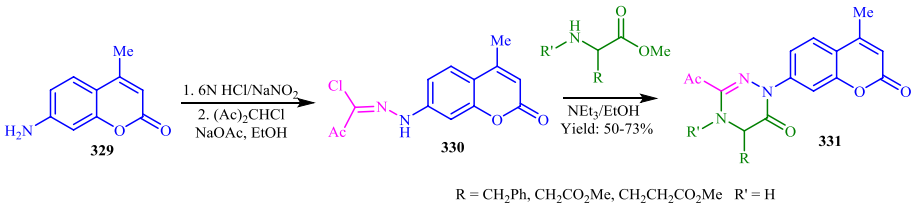
Scheme 77 Synthesis of the primaquine–coumarin probe (PQCP)



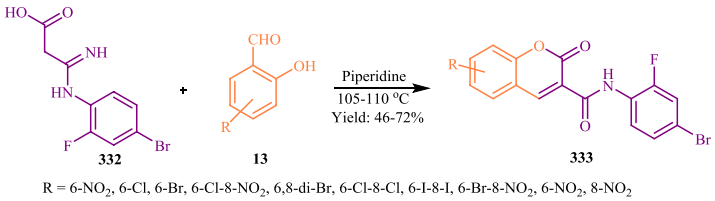
Scheme 78 Synthesis of the coumarin-based sensor **328**

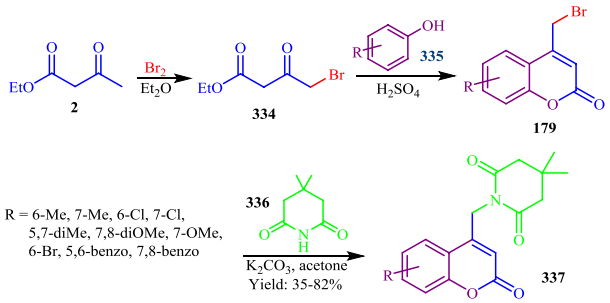


Scheme 79 Synthesis of coumarin–triazine



Scheme 80 Synthesis of coumarins through Knoevenagel condensation





Scheme 81 Synthesis of coumarin–cyclic-imide derivatives

Methionine methyl ester-modified coumarin **340** was synthesized by reaction of ethyl-7-(diethylamino)-2-oxo-2*H*-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 Cu^{2+} (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].

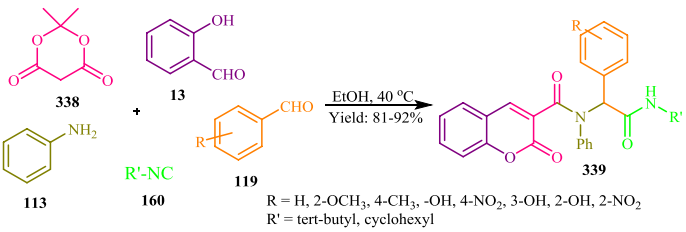
Oxime ethers **343** obtained from 4-bromomethy coumarins **179** and benzil monooxime **342** have undergone an unusual transformation into coumarin-4-carboxamides **344** (Scheme 85) [101].

Coumarins containing cyano band

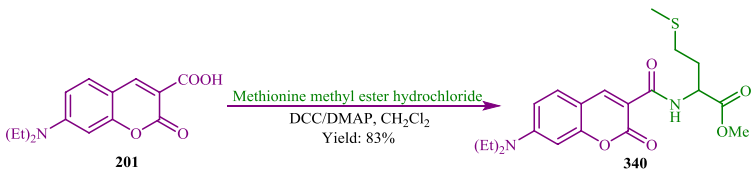
New 3-cyanocoumarin derivatives **347** were prepared by reaction of 2-(2-chlorobenzylidene)malononitrile **345** with resorcinol or 3-methoxyphenol **346**, and then further oxidation of **347** and replacement reaction with acetic anhydride in reflux conditions led to 4-(2-chlorophenyl)-3-cyano-2-oxo-2*H*-chromen-7-yl 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

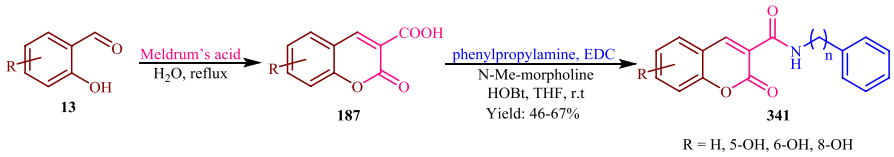
Scheme 82 Synthesis of coumarin via Knoevenagel-Ugi reaction



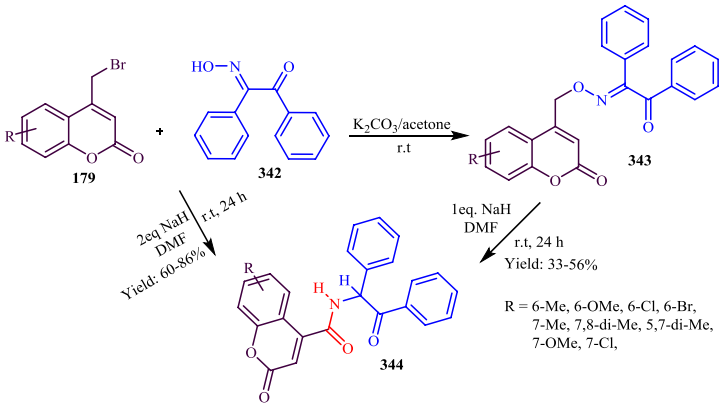
Scheme 83 Synthesis of methionine methyl ester-modified coumarin

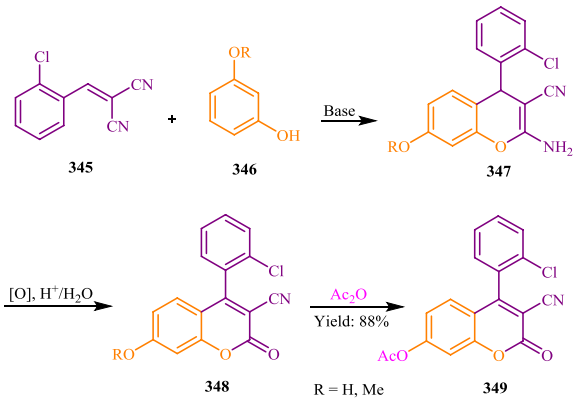


Scheme 84 Preparation of anti-austerity 7-hydroxycoumarins



Scheme 85 Reaction of benzil monooxime with 4-bromomethyl coumarins





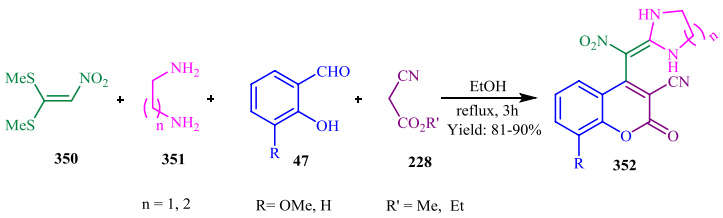
Scheme 86 Synthesis of new coumarin derivatives based on 2-(2-chlorobenzylidene)malononitrile

1,1-*bis*(methylsulfanyl)-2-nitroethene **350**, 1,*n*-diamine **351**, salicylaldehyde **47** and malononitrile or alkyl cyanoacetate **228** at reflux condition in ethanol (Scheme 87) [103].

Bardasova et al. synthesized some new 4-alkyl-6,8-dibromo-7-hydroxy-2-oxo-2*H*-chromene-3-carbonitriles **354** via the bromination of 2-amino-4-alkyl-4*H*-chromene-3-carbonitriles **353** with bromine in acetic acid, followed by hydrolysis (Scheme 88) [104].

Compound **357** was prepared via coupling of 7-(diethylamino)coumarin-3-aldehyde **163** and 2-(1-(4-aminophenyl) ethylidene)malononitrile **356**. The compounds **358** and **359** were prepared to mix **357** with acetic anhydride by conventional and microwave irradiation procedures, respectively.

Scheme 87 Synthesis of 3-cyanocoumarin via one-pot reaction



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

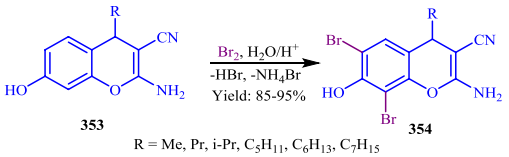
As depicted in Scheme 90, 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde **312** was formed via the reaction of **3** and hexamine then reaction of **312** with malononitrile in the presence of triethylamine which led to a coumarin-based fluorescent probe **360** (Scheme 90) [106].

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].

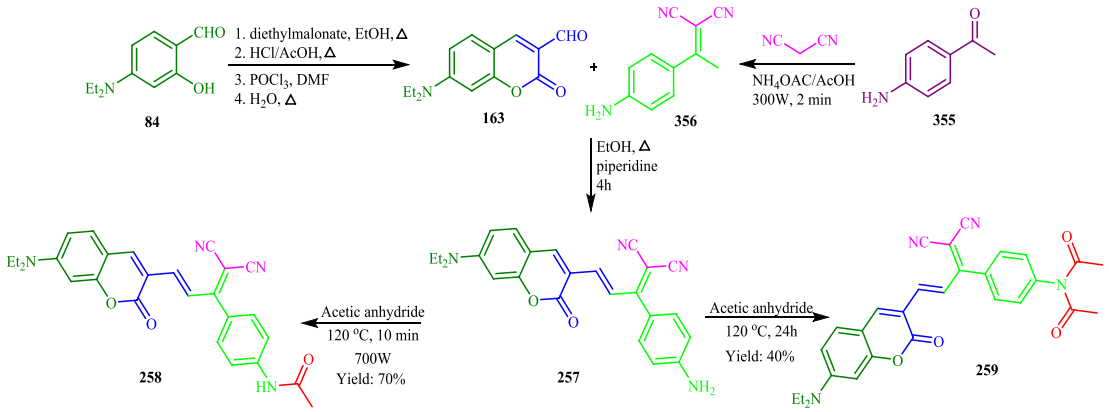
Coumarins containing alkyl and aryl groups

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

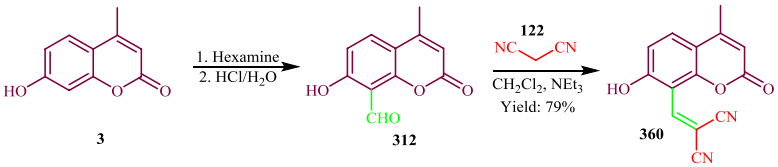


Scheme 88 Synthesis of 4-alkyl-6,8-dibromo-7-hydroxy-2-oxo-2*H*-chromene-3-carbonitriles

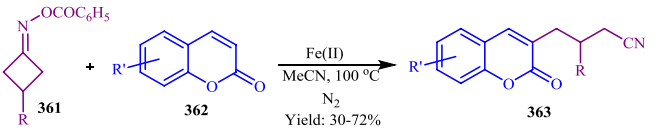


Scheme 89 Synthetic pathway of the dyes

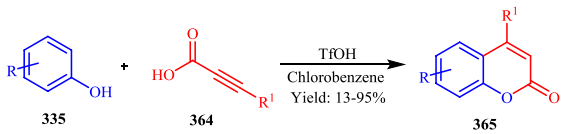
Scheme 90 Synthesis of 2-((7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)methylene) malononitrile



Scheme 91 Synthesis of coumarins via radical C–C bond cleavage

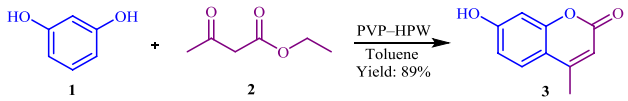


R = H, Ph, CH_2CN, $(CH_2)_3CN$ R' = 6-CH_3, 7-OMe, 8-Me, 4-Me-7-OMe, 6-NO_2, 6,8-di-Cl, 6,8-di-Me



R = H, 2-CH_3, 3-CH_3, 4-CH_3, 3,5-CH_3, 4-Ph, 3-OCH_3, 4-OCH_3, 2-Cl, 3-Cl, 4-Cl, 3-OH
R^1 = Ph, 4-NO_2-Ph

Scheme 92 Synthesis of coumarin derivatives from phenols and propiolic acids



Scheme 93 Synthesis route of 7-hydroxy-4-methyl coumarin by PVP–HPW

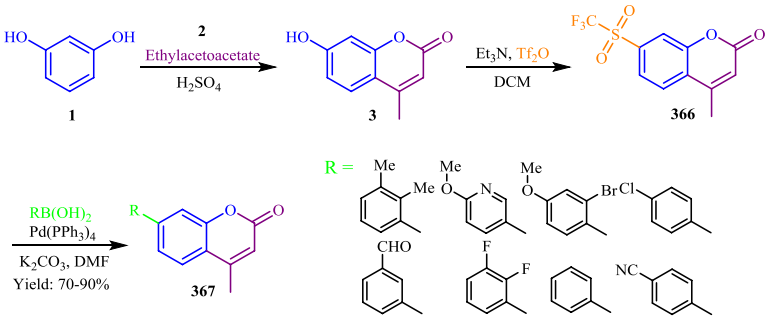
preparation of 7-hydroxy-4-methyl coumarin **3** (Scheme 93) [109].

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-2*H*-chromen-7-yl trifluoromethanesulfonate **366** and 4-methyl-2-oxo-2*H*-chromen-6-yl trifluoromethanesulfonate **370** in good yields. 7-Hydroxy-4-methyl-2*H*-chromen-2-one **3** prepared by cyclization of resorcinol **1** with ethylacetoacetate **2** in the presence of H_2SO_4. Subsequent reaction of **3** with trifluoromethanesulfonic anhydride (Tf_2O) afforded 4-methyl-7-((trifluoromethyl)sulfonyl)-2*H*-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 $Pd(PPh_3)_4$ and K_2CO_3 in DMF (Schemes 94, 95) [110].

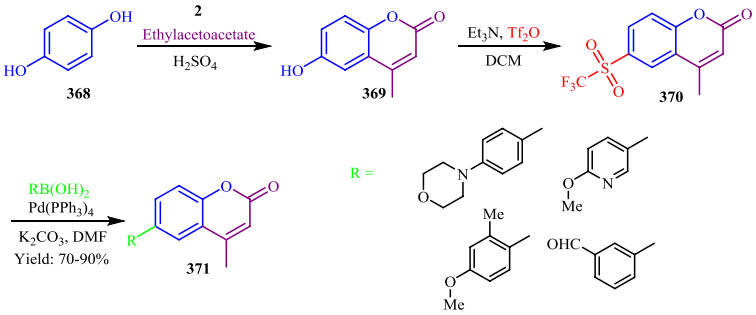
Also, 6-(aryl and heteryl)-4-methyl coumarins **371** were prepared according to the previous reported method, only with the difference that hydroquinone is used instead of resorcinol. The synthesized compounds **227** and **9** were tested for anti-proliferative activity against different human cancer cell lines such as SiHa, MDAMB-231, and PANC-1; some of the products displayed distinctive effects (Scheme 95) [110].

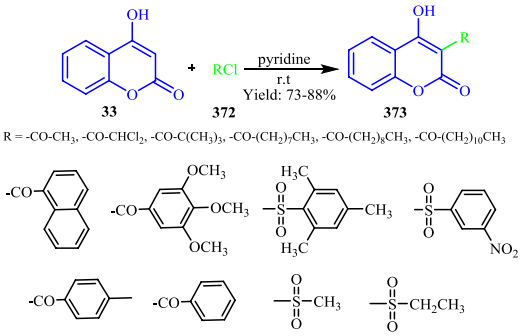
An effective synthesis of 2-acylated and sulfonated 4-hydroxycoumarins **373** has been achieved via the reaction of 4-hydroxycoumarin **33** with acyl chloride **372** in the

Scheme 94 Preparation of 7-(aryl and heteryl)-4-methyl coumarins

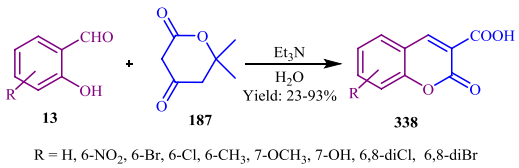


Scheme 95 Preparation of 6-(aryl and heteryl)-4-methyl coumarins

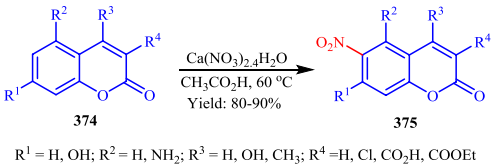




Scheme 96 Synthesis of 2-acylated and sulfonated 4-hydroxycoumarins



Scheme 97 Preparation of coumarin-3-carboxylic acid



Scheme 98 Nitration of coumarins by $Ca(NO_3)_2.4H_2O$

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 ($Ca(NO_3)_2.4H_2O$ as a mild and regioselective reagent to nitration of hydroxycoumarin **374** in the presence of acetic acid at 60 °C (Scheme 98) [113].

6,7-Dihydroxy coumarin derivatives **378** were obtained as a result of cyclization of benzene-1,2,4-triyl triacetate **376** 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 propiolic acid or ethyl acetoacetate, respectively (Scheme 99). Synthesized compounds containing the CH_2Cl 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

of the obtained acetoxy derivatives, in the presence of HCl, to achieve the final substituted hydroxy-3-arylcoumarins **384** (Scheme 100) [115].

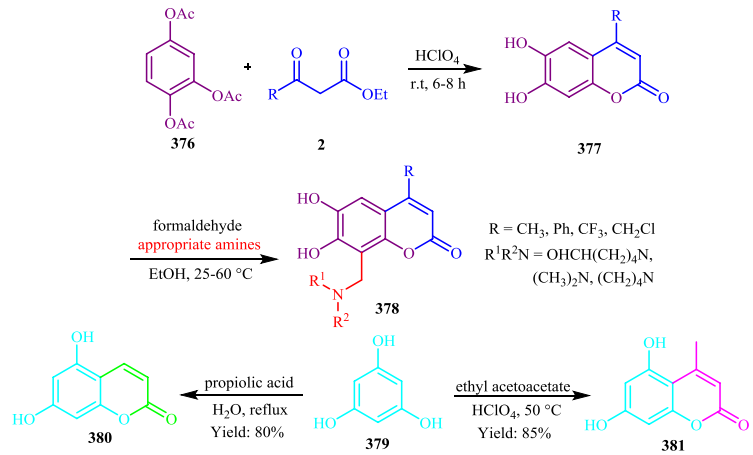
Yamaji et al. synthesized two isomeric compounds (**386a** and **386b)** to have fused skeletons of coumarin and fluorene via photochemical cyclization of olefin **385** (Scheme 101). The synthesized compounds showed different absorption and fluorescence features in solution [116].

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 Et_3N 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].

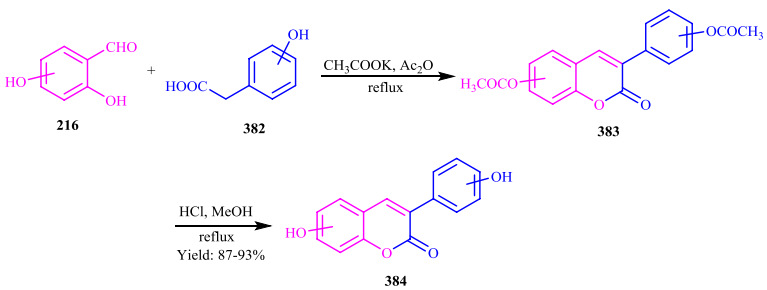
The *β*-keto ester **396** was obtained using reacting *p*-hydroxyacetophenone **393** with ethyl 2-bromoisobutyrate **394** in the presence of K_2CO_3 in acetonitrile, followed via reacting with diethyl carbonate in the presence of sodium hydride. The subsequent Knoevenagel condensation reaction of *β*-keto ester **396** into various salicylaldehydes yielded the favorite coumarin–chalcone fibrates **397**. Furthermore, compounds **398** and **399** were prepared from the corresponding fibrates **397** by reduction and hydrolysis, respectively (Scheme 103) [118].

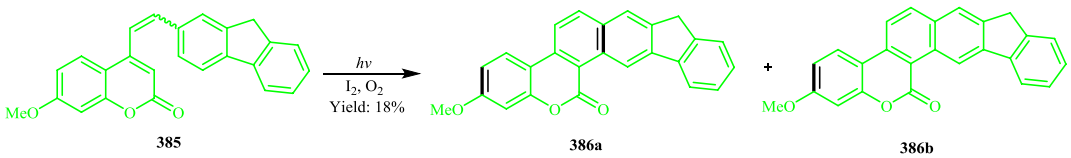
4-Arylcoumarin derivatives **402** were prepared through a stepwise procedure. *o*-methoxy-4-phenylchromenones **401** synthesized by cyclization reaction of phenols **335** with ethyl-3,4-dimethoxybenzoylacetate **400** and CF_3COOH under heat in reasonable yields and short reaction times. Finally, the reaction of compound **401** with boron tribromide in CH_2Cl_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

Scheme 99 Synthesis of hydroxylcoumarin derivatives as antioxidant agents



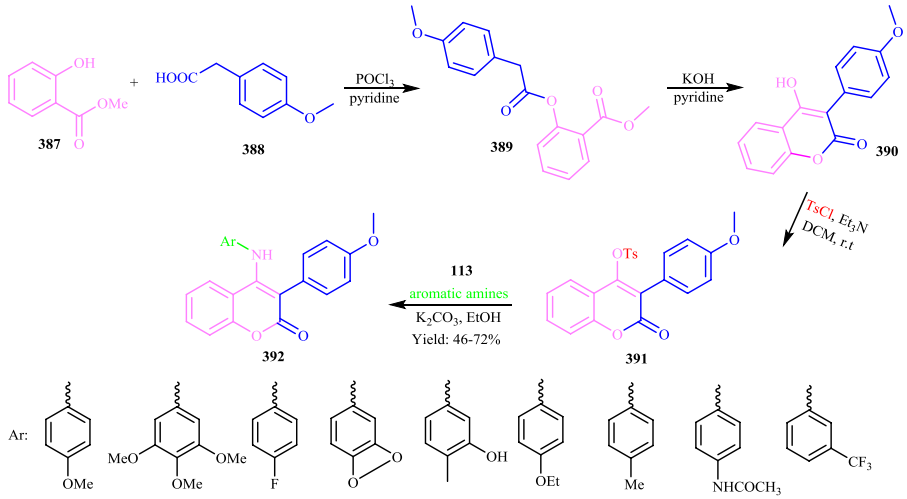
Scheme 100 Synthesis of hydroxyl-substituted 3-arylcoumarins

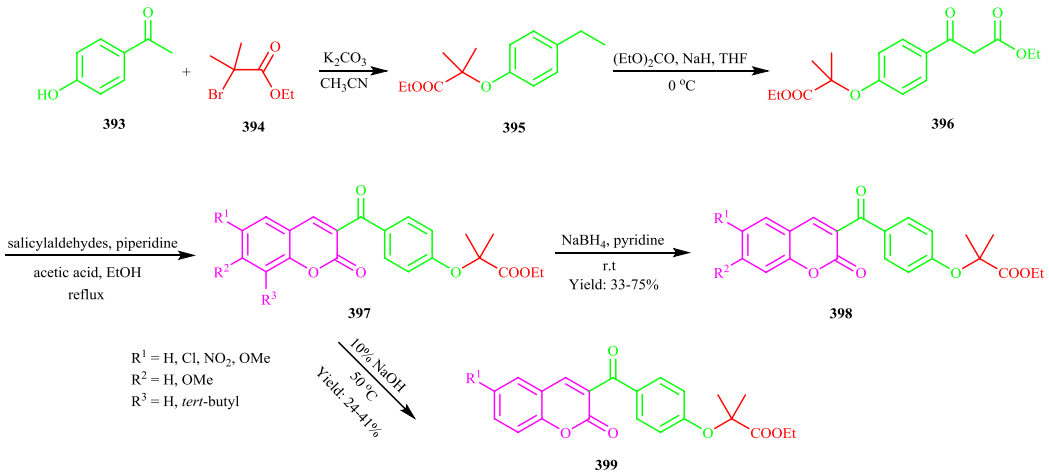




Scheme 101 Photocyclization procedure from compound **385** to compounds **386a** and **386b**

Scheme 102 Synthesis of novel 3-substituted 4-anilinocoumarin derivatives





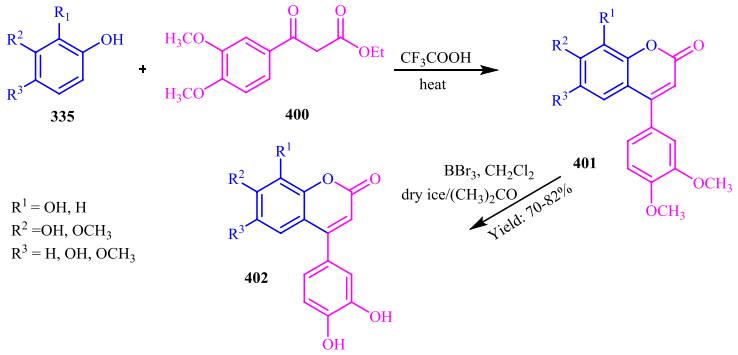
Scheme 103 Synthesis of novel structural class of coumarin–chalcones

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].

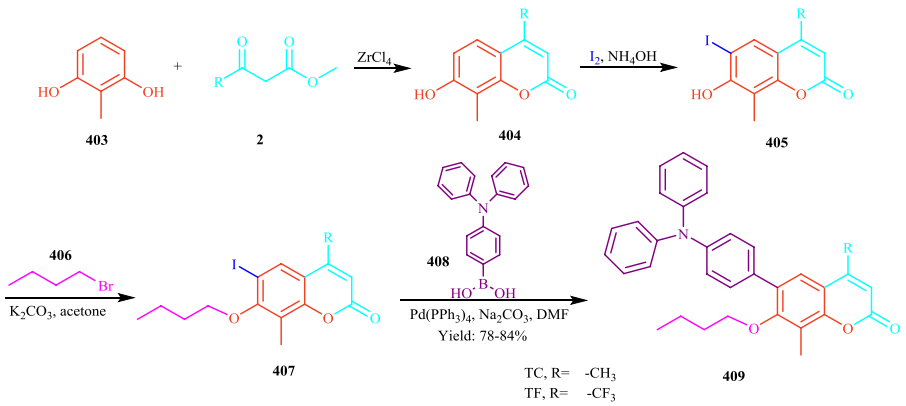
7-Butoxy-6-(4-(diphenylamino)phenyl)-4,8-dimethyl-2*H*-chromen-2-one (TC) and 7-butoxy-6-(4-(diphenylamino) phenyl)-8-methyl-4-(trifluoromethyl)-2*H*-chromen-2-one (TF) **409** were prepared through a stepwise procedure. Condensation of 2-methylbenzene-1,3-diol **403** via methyl 3-oxobutanoate **2** in the presence of $ZrCl_4$ led to formation of 7-hydroxy-4,8-dimethyl-2*H*-chromen-2-one derivatives **404**. The reaction of compound **404** with iodine afforded compound **405**. Chromen derivatives **407** were obtained from the reaction of 7-hydroxy-6-iodo-4,8-dimethyl-2*H*-chromen-2-one **405** with 1-bromobutane **406** in the presence of catalytic amount of K_2CO_3. Finally, the reaction of chromens **407** with (4-(diphenylamino) phenyl) boronic acid **408** in the presence of Na_2CO_3 led to formation of final product **409** (Scheme 104, 105) [120].

4-Methyl-6,7-dihydroxycoumarin **377** has been selected as a key intermediate to prepare new coumarin derivatives. The reaction of 4-methyl-6,7-dihydroxycoumarin **377** with triflic anhydride (Tf_2O) in the presence of Et_3N afforded *bis*(triflate) **410**. Reaction of **410** with arylboronic acids **411** in the presence of K_3PO_4, and $Pd(PPh_3)_4$ via Suzuki–Miyaura reaction led to 4-methyl-6,7-diarylcoumarines **412**. Also, reaction of **377** with bromine afforded the brominated product **413** in good yield. Compound **413** was converted into *bis*-triflate **414**. Suzuki–Miyaura cross-coupling reaction of **414** with various arylboronic acids **411** in 1,4-dioxane afforded the 4-methyl-3,6,7-*tris*(aryl) coumarines **415** (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].

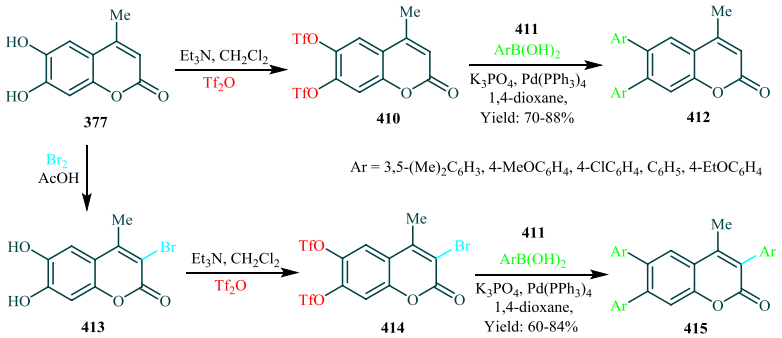
Scheme 104 Synthesis of 4-arylcoumarin derivatives



Scheme 105 Synthetic routes for of two bichromophores with a triphenylamine–coumarin dyad structure



Scheme 106 Synthesis of arylated coumarins by Suzuki–Miyaura cross-coupling



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].

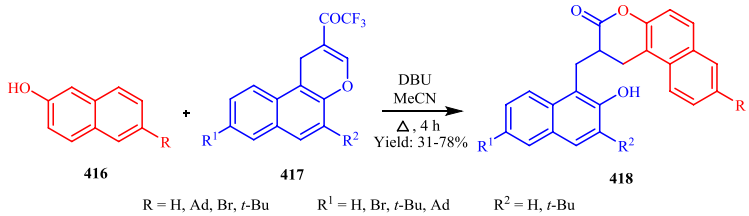
The target compound, 6-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]hexanoate **420** was prepared of the reaction 7-hydroxy-4-methyl coumarin **3** with ethyl-6-bromohexanoate **419** in the presence of anhydrous potassium carbonate in dry DMF (Scheme 108). Molecular docking studies showed that the molecule 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 luminol-enhanced chemiluminescence technique [124].

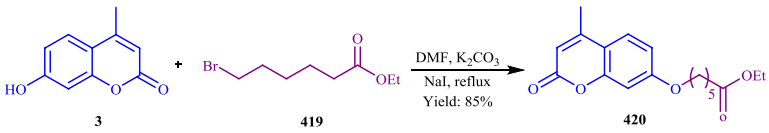
Benzo[*h*]coumarins **423** were prepared through Knoevenagel condensation method by reacting hydroxylnaphthalene aldehyde **422** into cyano-methylene-benzazoles **82** containing NH, O and S elements, respectively, as the active methylene compounds (Scheme 110) [125].

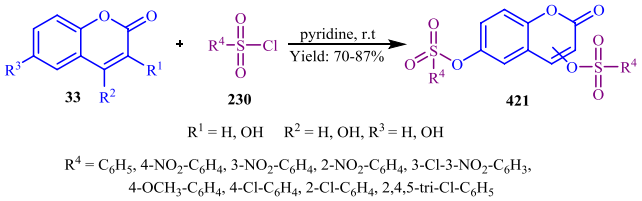
New polyphenolic hybrid–coumarin derivatives **431–433** were synthesized according to the outlined

Scheme 107 Synthesis of benzo[*f*]coumarins from 2-trifluoroacetyl-1*H*-benzo[*f*] chromenes and 2-naphthols

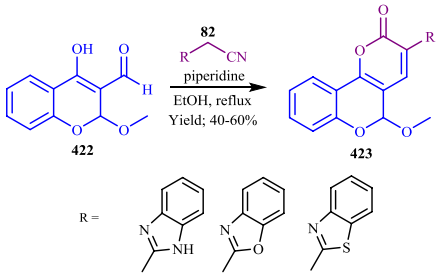


Scheme 108 Synthesis of ethyl 6-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]hexanoate





Scheme 109 Synthesis of coumarin sulfonates

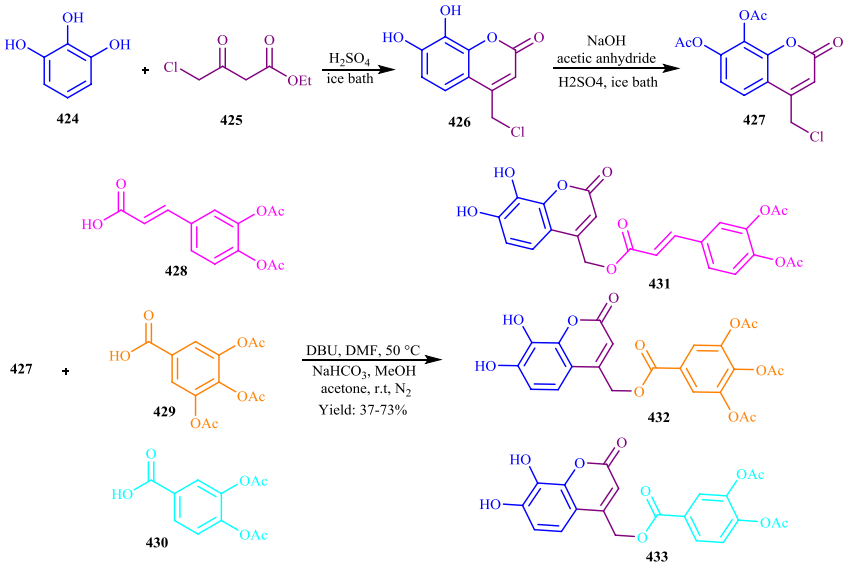


Scheme 110 Synthesis of benzo[*h*]coumarins

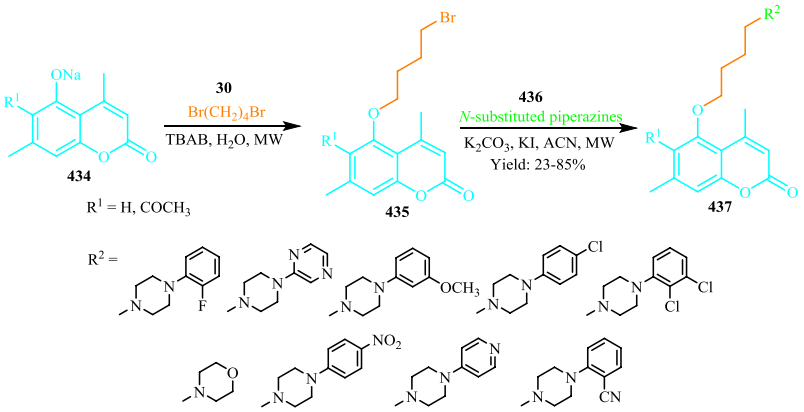
Scheme 111. The reaction of benzene-1,2,3-triol **424** with ethyl 4-chloro-3-oxobutanoate **425** afforded 4-chloromethyl-7,8-dihydroxycoumarin **295**, further reaction of **426** with acetic anhydride in the presence of NaOH led to 4-(chloromethyl)-2-oxo-2*H*-chromene-7,8-diyl diacetate **427**. The 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 deacylation of hydroxyl groups by $NaHCO_3$ 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 K_2CO_3 and KI under microwave irradiation (Scheme 112). The synthesized compounds exhibited reasonable anti-bacterial, antifungal and anti-tumor activities [127].

Scheme 111 Synthesis of new polyphenolic hybrid–coumarins



Scheme 112 Synthesis of a new series of 5-[4-(4-aryl-1-piperazinyl)butoxy]coumarins



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_2CO_3 under microwave irradiation, respectively. Compound **438** was converted to aryl/heteroarylpiperazinylpropoxy/butoxychomen-2-one **439** by stirring with two equivalents of appropriate amine under microwave irradiation in the presence of KI and K_2CO_3 in acetonitrile (Scheme 113) [128].

A new 7-(bromomethoxy)-2*H*-chromen-2-ones **440** were synthesized via reaction between 7-hydroxy-2*H*-chromen-2-one **3**, α,ω-dibromoalkane **30** and powdered K_2CO_3 in acetone. Reaction of **440** with benzylamines **441**, powdered K_2CO_3 and a catalytic amount of KI in acetonitrile led to coumarin derivatives **442**. Further, reaction of **442** with powdered K_2CO_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].

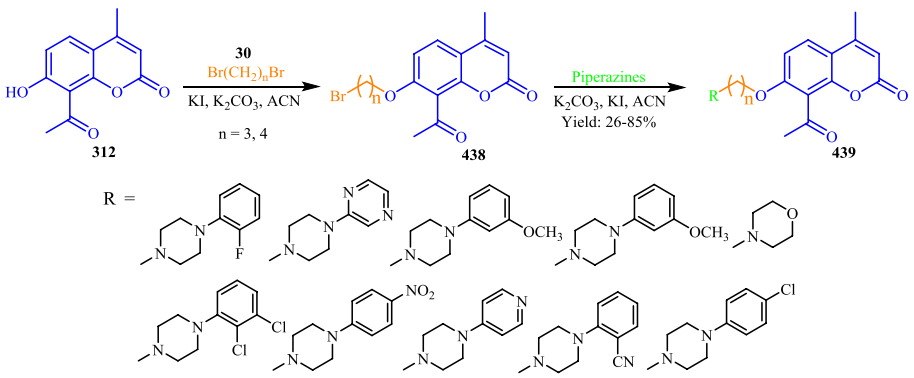
A new class of coumarin derivatives **451** and **452** were synthesized via Williamson etherification reaction of 4-hydroxy-2*H*-chromen-2-one **33** or 7-hydroxy-2*H*-chromen-2-one **62** with alkyl halogenides **450** in the presence of potassium carbonate in DMF (Scheme 116). All prepared compounds were evaluated for their in vitro antimicrobial 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)-2*H*-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].

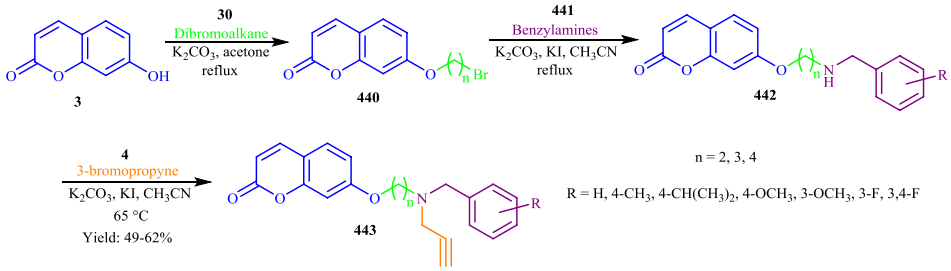
The condensation reaction between 3-acetylcoumarin **37** with various benzene sulfonyl hydrazide derivatives **455** was carried out in the presence of acetic acid glacial in EtOH to give novel coumarin–benzenesulfonohydrazide derivatives **456** (Scheme 118) [133].

A metal- and oxidant-free photo catalysis procedure for the direct trifluoromethylation of coumarin derivatives by

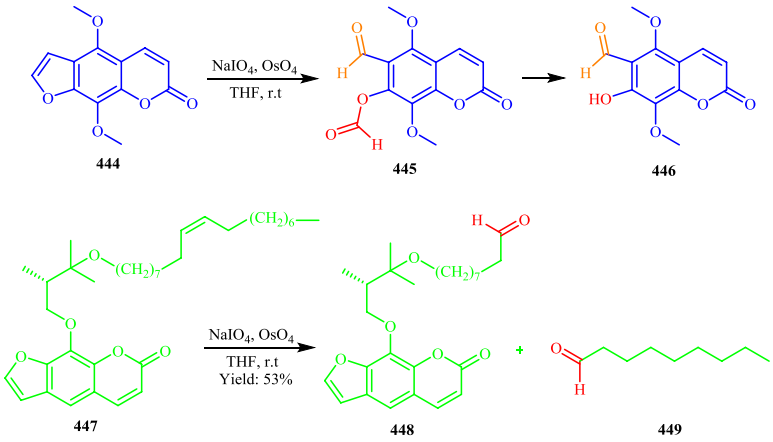
Scheme 113 Synthesis of aryl/heteroarylpiperazinyl derivatives of 7-hydroxycoumarin



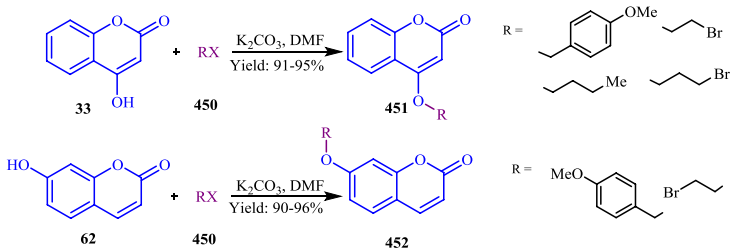
Scheme 114 Synthesis of coumarin–pargyline hybrids

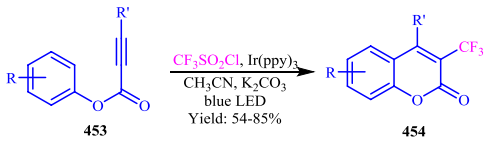


Scheme 115 Preparation of anti-inflammatory coumarins via oxidation reaction



Scheme 116 Synthesis of novel coumarin derivatives from alkyl halogenides





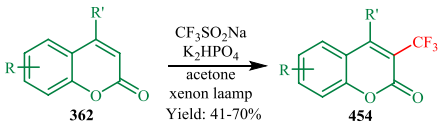
R = H, 7-Me, 7-t-Bu, 7-F, 7-Cl, 7-Br7-I, 7-CF3, 5-Me
R' = Ph, 4-Me-Ph, 4-F-Ph, 4-Cl-Ph, 4-OMe-Ph, 4-CO2Et-Ph,

Scheme 117 Synthesis of trifluoromethylated coumarins

sodium triflinate as the CF_3 source under xenon lamp irradiation was developed (Scheme 119) [134].

The chemodosimeter **458** was prepared via the esterification of coumarin **3** using phenyl chloromethanethioate **457** and *N*-Ethyldiisopropylamine in CH_2Cl_2 solvent at room temperature (Scheme 120). The compound **458** could be used to detect the concentrations of Hg^{2+} in water [135].

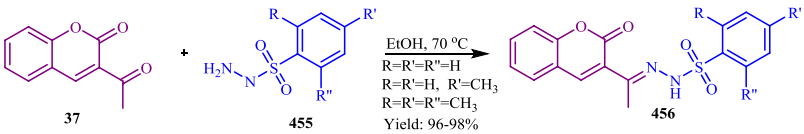
An efficient and convenient strategy for the preparation of 3-sulfonyl coumarins **461** through ipso-cyclization/1,2-ester migration from substituted phenyl-3-phenylpropiolates **459**



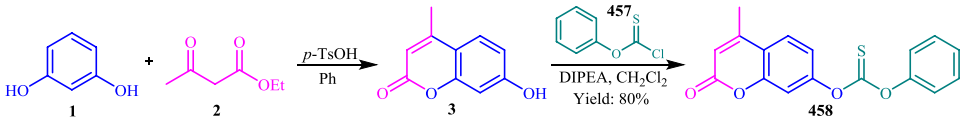
R = H, 6-Me, 6,8-di-Me, 6-t-butyl, 7-OMe, 7-OCOMe, 6-Cl, 6-Br, 6-NO2 R' = H, Me, Ph

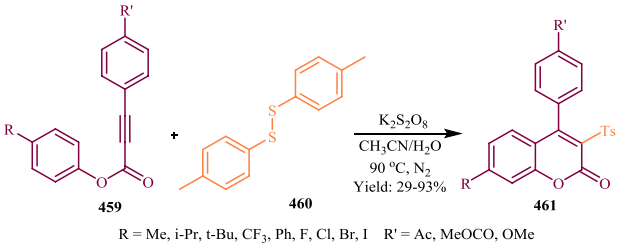
Scheme 119 Trifluoromethylation reaction of coumarins

Scheme 118 Synthesis of coumarin–benzenesulfonohydrazide derivatives



Scheme 120 Preparation of coumarin–carbonothioate **458**





Scheme 121 Synthesis of 3-sulfonyl 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*-toluen sulfonic 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 H_2SO_4. 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].

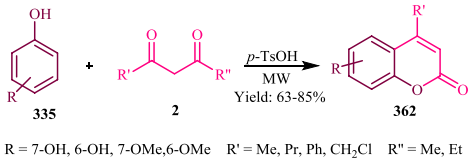
A series of novel coumarin-based 2,4-dinitrophenylhydrazones **467** were synthesized via the reaction of substituted 3-benzoyl coumarins **465** with 2,4-dinitrophenylhydrazine **466** in dimethylformamide and used as photosensitizers on zinc nanocones (Scheme 125) [140].

Phloroglucinol **379** was treated with ethyl cetoacetate or trifluoroacetoacetate **2** in acetic acid and catalyzed by H_2SO_4 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 aminocoumarin **470** (Scheme 126). The results displayed that the target molecules can suppress colon cancer cells [5].

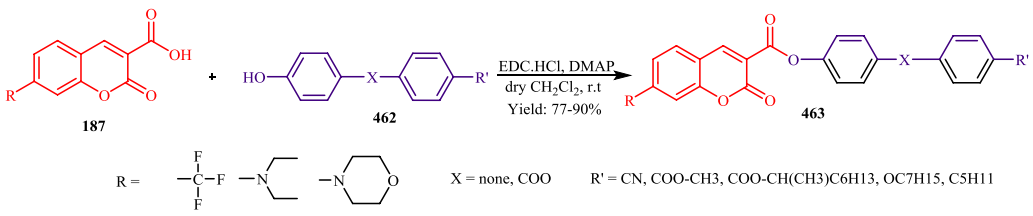
Intermediate **472** was obtained through Pechmann condensation reaction of 3,5-dihydroxybenzaldehyde **289** and 2-ethoxymethylene-3-oxobutanoic acid ethyl ester **471** using sodium in EtOH. Finally, the target compounds **473** were synthesized via the Mannich reaction of intermediate **472**, paraformaldehyde (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].

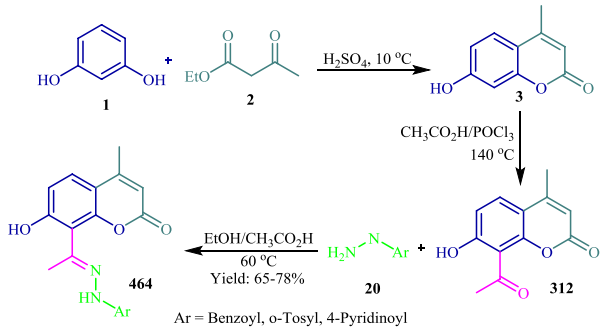
3-Acetyl-7-hydroxy-2*H*-chromen-2-one **472** was synthesized via Knoevenagel condensation of 2,4-dihydroxy benzaldehyde **216** into ethyl acetoacetate **2** in the presence of piperidine in ethanol. Compound **474** on reaction with 4-hydroxy benzaldehyde **393** in the presence of catalytic amount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



Scheme 123 Synthesis of coumarins by Pechmann–Duisberg condensation



Scheme 122 Synthesis of new set of coumarin derivatives



Scheme 124 Synthesis of coumarin–hydrazone derivatives

gave (*E*)-7-hydroxy-3-[3-(4-hydroxyphenyl)acryloyl]-2*H*-chromen-2-one **476**. Compound **476** was alkylated with various *n*-alkyl bromides by dry K_2CO_3 to give *bis*-alkyloxy derivatives **477** (Scheme 129) [143].

Tri and *bis*-coumarins

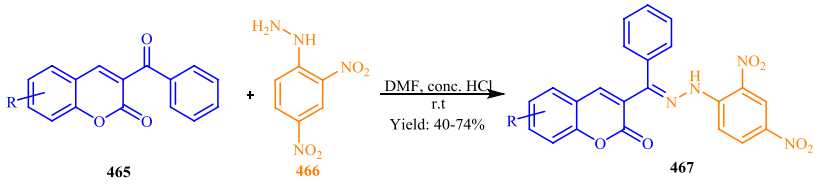
Zolfigol et al. developed effective methods for the synthesis of *bis*-coumarin derivatives **478** via the reaction between 4-hydroxycoumarin **33** with aromatic aldehydes **119** in the presence of trityl bromide (TrBr) as a homogenous and neutral organocatalyst or $[Fe_3O_4@SiO_2@(CH_2)_3\text{-Im-}SO_3H]Cl$ (MNPs) 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-diazabicyclo[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].

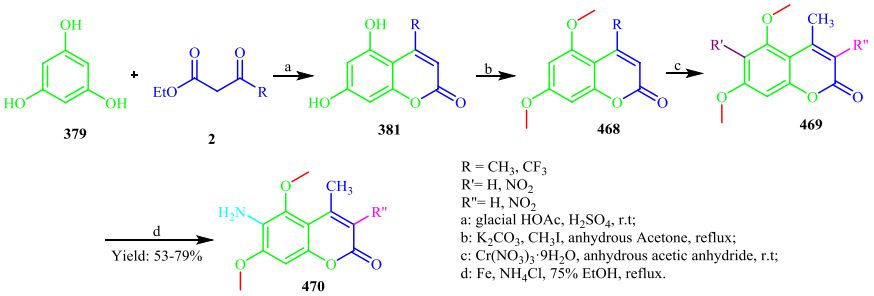
They also made a novel nanostructured molten salt $\{[1,4\text{-DHPyrazine}][C(CN)_3]_2\}$ (NMS), and it was used as an efficient and recyclable catalyst for the synthesis of novel 3,3′-(piperazine-1,4-diylbis(arylmethylene))*bis*(4-hydroxy-2*H*-chromen-2-one) derivatives (Scheme 132) [146].

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

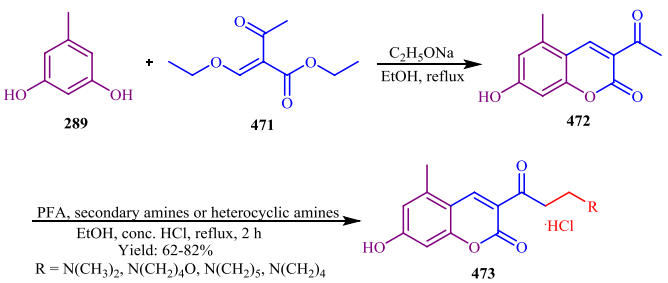
Scheme 125 Synthesis of coumarin-based 2,4-dinitrophenylhydrazones



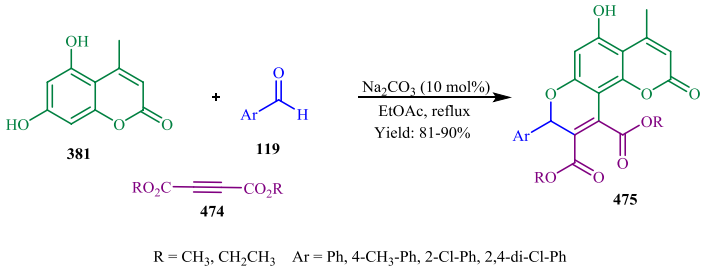
Scheme 126 Preparation of aminocoumarin **470**



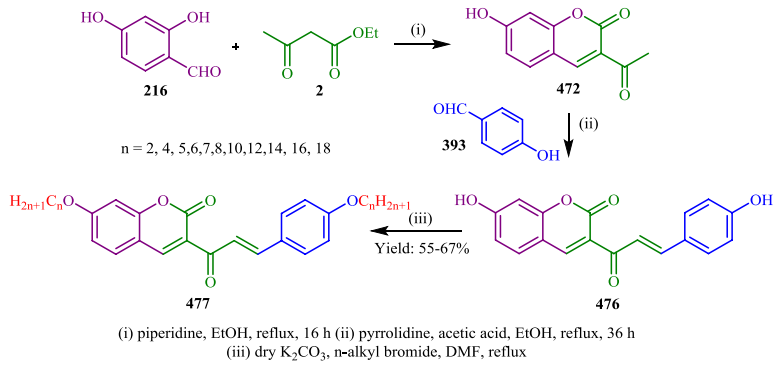
Scheme 127 Synthesis of coumarin Mannich base derivatives



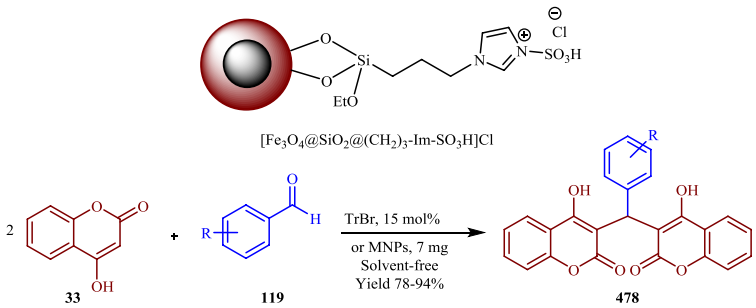
Scheme 128 Synthesis of pyrano[2,3-*h*]coumarins



Scheme 129 Synthesis of chalcones containing coumarin



Scheme 130 Preparation of *bis*-coumarin derivatives by TrBr or MNPs



(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].

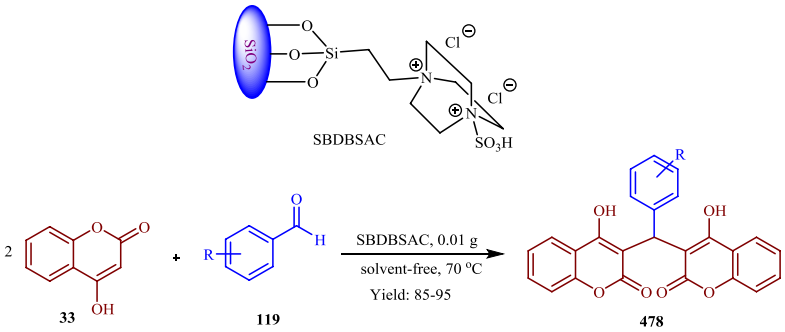
Bis-benzocoumarin **488** was prepared in a three-step reaction. First, reaction of compound **485** with HCl in EtOH at room temperature furnished (R)-2,2′-dihydroxy-[1,1′-binaphthalene]-3,3′-dicarbaldehyde **486**. Next, the reaction of **486** in the presence of diethyl malonate **2** in short reaction 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 acetylcoumarin **491** with 2-(4-diethylamino-2-hydroxybenzoyl)benzoic acid **490** and conc. H_2SO_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].

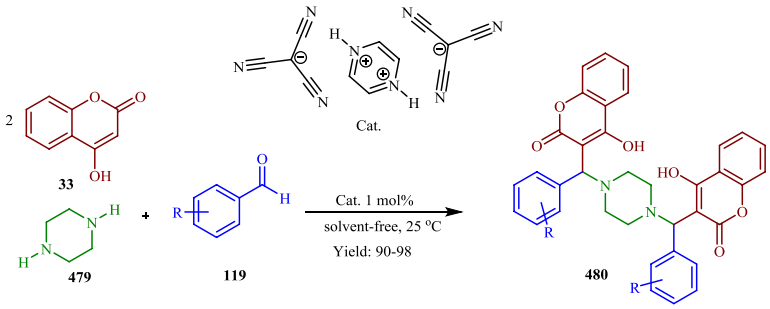
Coumarin conjugate **496** was easily prepared by condensation reaction 3-acetyl-7-diethylaminocoumarin **163** with 7-diethylaminocoumarin-3-carbaldehyde **491** in the presence of piperidine in EtOH. The target molecule **496** displayed high quantum yield because of strong ICT effect (Scheme 137) [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_2CO_3, TBAB and $Pd(pph_3)_4$ (Scheme 138) [152].

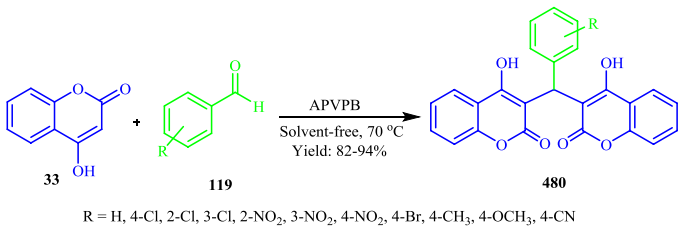
Scheme 131 The preparation of *bis*-coumarin catalyzed by SBDBSAC



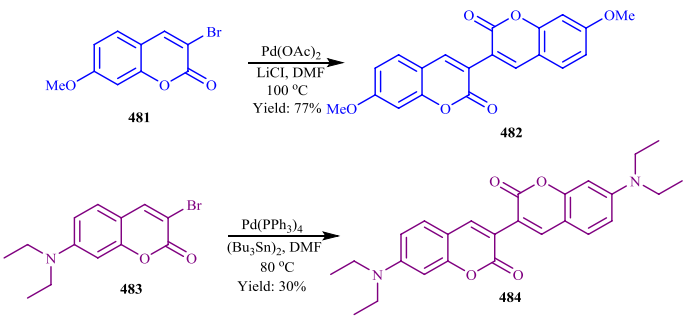
Scheme 132 Synthesis of 3,3′-(piperazine-1,4-diyl-*bis*(arylmethylene))*bis*(4-hydroxy-2*H*-chromen-2-one) derivatives



Scheme 133 Synthesis of novel *bis*-coumarin derivatives



Scheme 134 Synthesis of 3,3′-bis-coumarin via coupling reaction

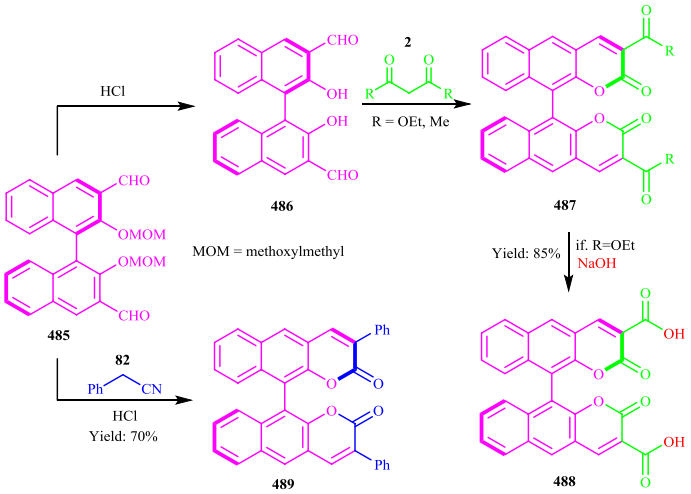


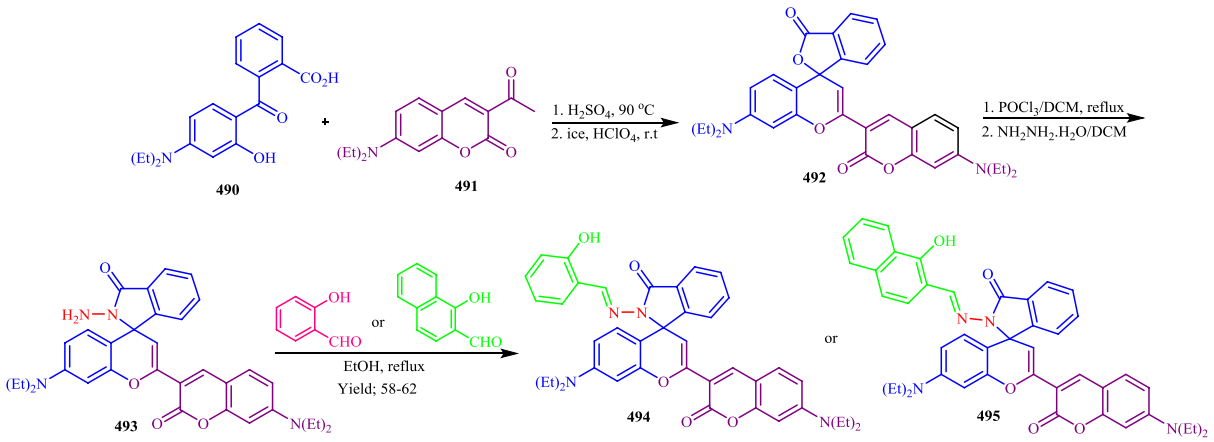
Synthesis of *bis*-coumarin derivatives started with refluxing 4-hydroxy coumarin **33** with 4-nitrobenzaldhyde **119** to form bis-coumarin **480**. Then, compound **480** was reduced to analog **480′**. Compound **480′** was further treated with CS_2 to form intermediate which is further reflux with 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].

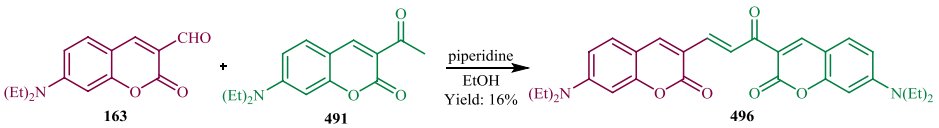
Scheme 135 Synthesis of luminogens based on bis-benzo-coumarin





Scheme 136 Preparation of coumarin–benzopyrylium-based sensors

Scheme 137 Synthesis route of coumarin conjugate



8-Formyl-7-hydroxycoumarin **222** was synthesized via the reaction of 7-hydroxy-2*H*-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-aminothyl)-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].

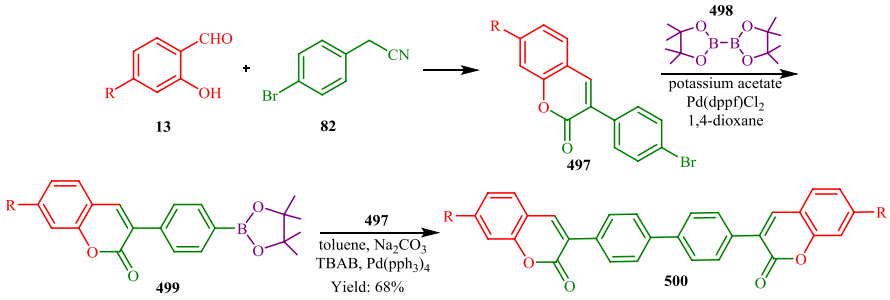
Coumarins containing pyridone core

Synthesis of coumarin–pyridone conjugate molecules **507** was carried out via one-pot reaction between (*E*)-3-(3-arylacryloyl)-2*H*-chromen-2-ones **505**, ethyl 2-nitroacetate **506** and NH_4OAc 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].

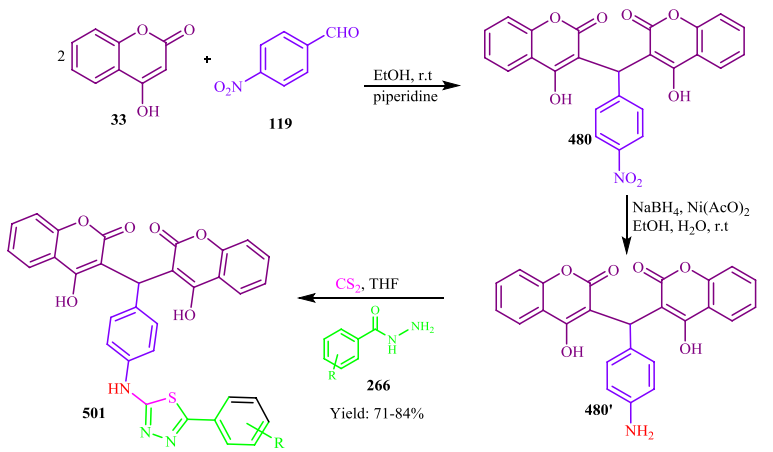
Coumarins containing pyrane core

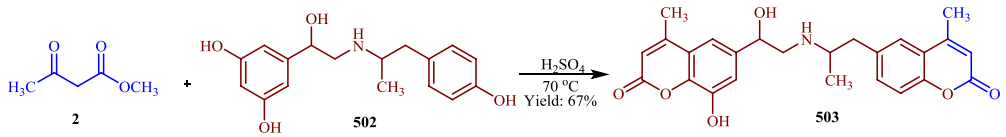
An efficient and straightforward procedure for the syntheses of isoxazoline/isoxazole-fused coumarins **513** and **514** from the corresponding 7-*o*-propargyloxy coumarin oximes **511** and 7-*o*-allyloxy-coumarin oximes **512** is

Scheme 138 Synthesis of coumarin–biphenyl derivatives



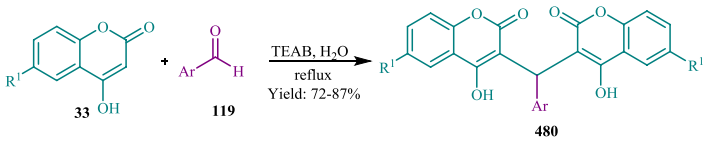
Scheme 139 Synthesis of hybrid *bis*-coumarin





Scheme 140 Synthesis of coumarin through von Pechmann condensation

Scheme 141 Synthesis of *bis*-coumarin derivatives by TEAB

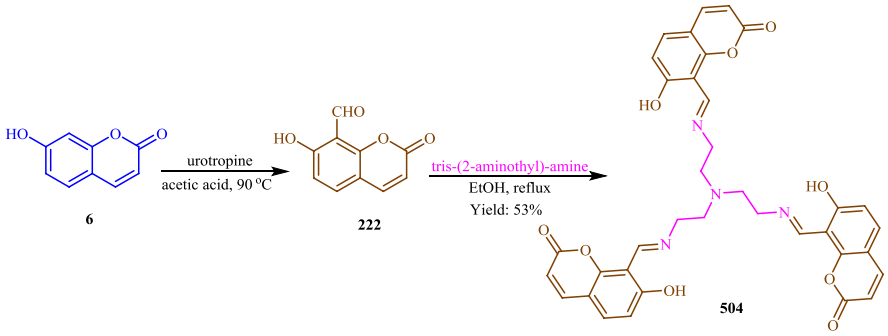


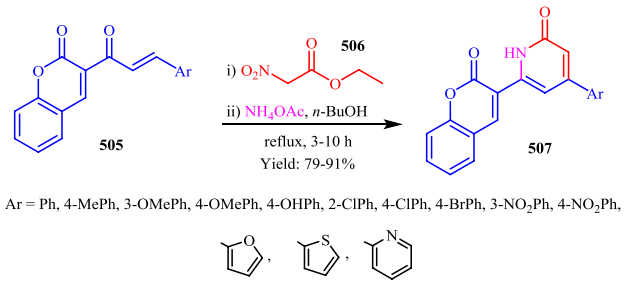
presented. 7-Allyloxy-coumarin-8-carbaldehydes **509** and **510** were prepared via condensation of coumarin-8-carbaldehyde **222** into 3-bromoprop-1-yne **4**, 3-bromoprop-1-ene **508** in DMF, and further condensation with $NH_2OH{\cdot}HCl$ led to **511** and **512**, respectively. In the last step, 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 CH_3SO_3H and P_2O_5 afforded 5,7-dihydroxy-2-methylchroman-4-one **516**, 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 $BF_3{\cdot}Et_2O$ gave 5,7-dihydroxy-2,2-dimethyl-4-chromanone

Scheme 142 Synthesis of a tripodal coumarin-derived





Scheme 143 Synthesis of coumarin–pyridone conjugates molecules

520, which can be readily converted to the target compounds **521** through Pechmann reactions (Scheme 146). The synthesized compounds showed anticancer activities against SHG-44, H1299, MCF7 and HCT-116 cell lines in vitro [159].

Coumarins containing oxazole core

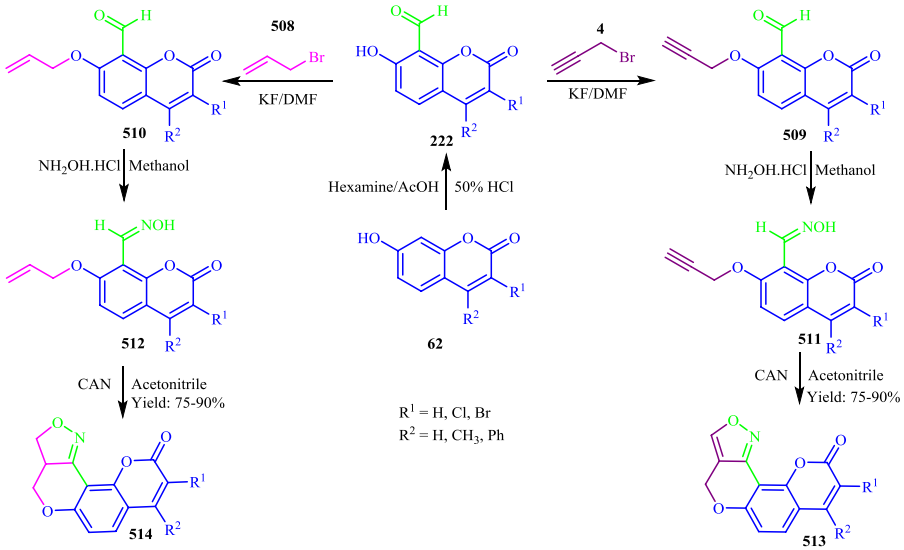
The synthetic route of coumarin–benzoxazoles is shown in Scheme 146. First, it is the coupling of salicylaldehyde **13**, ethyl cyanoacetate **522** and *o*-aminophenol **523** to form intermediate **524**. The chlorination of intermediate **524** with oxalyl chloride in the presence of organic base 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 K_2CO_3 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].

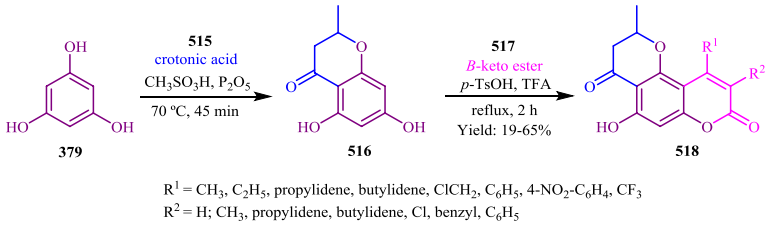
Coumarins containing furan core

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.

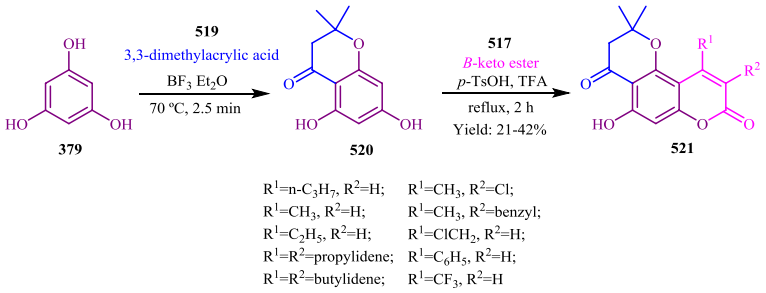
Scheme 144 Synthesis of pyrano isoxazoline/isoxazole-annulated coumarins



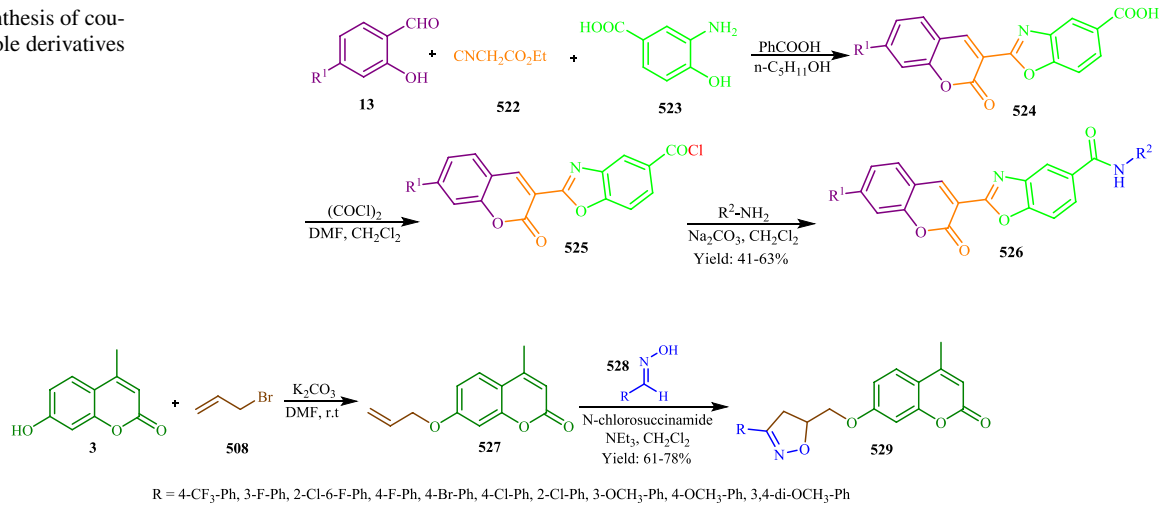
Scheme 145 Synthesis of pyrano[2,3-*f*]chromene-4,8-dione from crotonic acid



Scheme 146 Synthesis of pyrano[2,3-*f*]chromene-4,8-dione from 3,3-dimethylacrylic acid



Scheme 147 Synthesis of coumarin–benzoxazole derivatives



Scheme 148 Synthesis of coumarin-tethered isoxazoline derivatives

4-Methyl-6,9-diphenyl-2*H*-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 **534** were formed in one-pot four-component reaction of 4-chloro-3-formylcoumarin **308**, secondary amines **244**, dialkyl acetylenedicarboxylates **476** and diversely substituted isocyanides **160** in benzene under reflux conditions in reasonable yields (Scheme 150) [163].

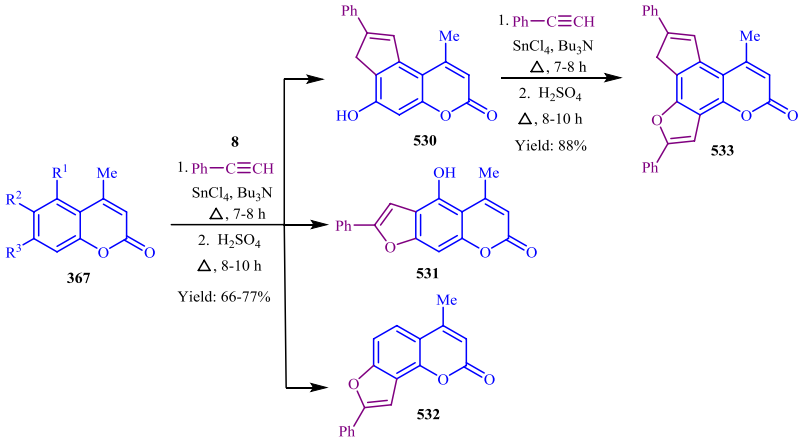
Two photochromic coumarin-based dithienylethenes **536** and **537** were prepared through one-pot nucleophilic additional reaction of 7-hydroxy-2*H*-chromen-2-one **62** and 1,2-*bis*(2,5-dimethylthiophen-3-yl)ethyne **535** in the presence of $Pd_2(dba)_3.CHCl_3$ catalyst (Scheme 151) [164].

In an efficient and quite environmental-friendly method, 2-aryl-4*H*-furo[3,2-*c*]chromen-4-one derivatives **538** were obtained from reaction of 4-hydroxy-2*H*-chromen-2-one **33** with various ethynylbenzenes **8** in the presence of I_2/TBHP-mediated and dioxane under reflux conditions (Scheme 152) [165].

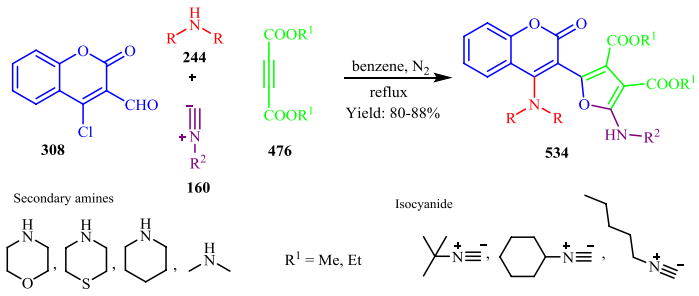
The synthesis of furo[3,2-*c*]coumarins **539** was carried out via one-pot three-component reaction of two *equiv*. 4-hydroxycoumarin **33** and one *equiv*. of various aldehydes **119** in the presence of a catalytic amount of I_2 in DMSO (Scheme 153) [166].

A new and efficient method for the synthesis of furo[3,2-*c*]coumarin derivatives **540** was developed via copper-catalyzed radical/radical cross-coupling of ketoxime

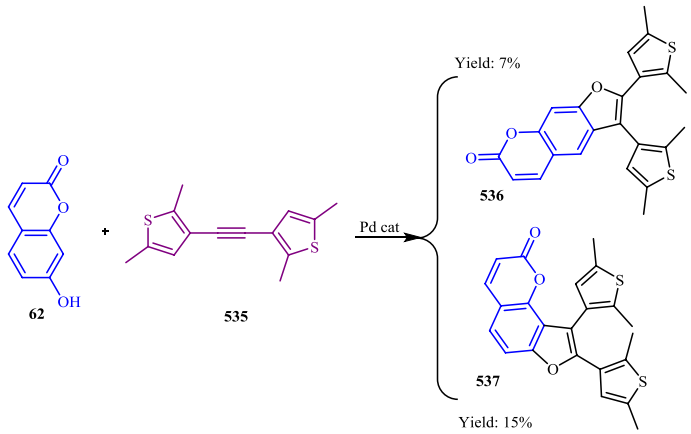
Scheme 149 Synthesis of new furocoumarin derivatives



Scheme 150 Preparation of novel 3-furyl coumarins



Scheme 151 Synthesis of coumarin-based dithienylethenes



carboxylates **528** with 4-hydroxycoumarins **33** in dioxane (Scheme 154) [167].

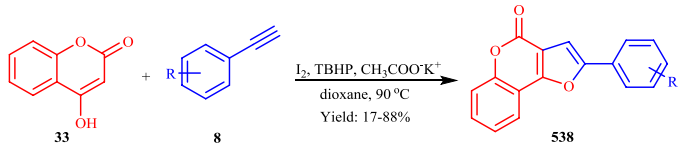
Coumarins containing thiophene core

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

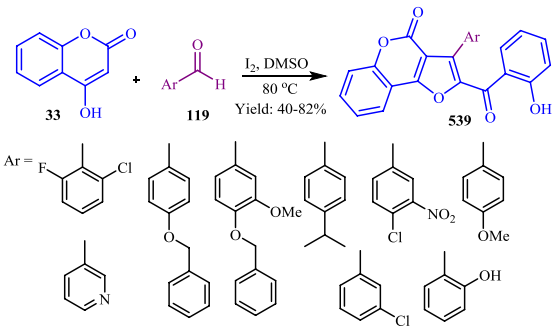
The coumarin–thiophene hybrids **545** were synthesized using the one-pot, three-component reaction of 3-acetylcoumarins **37**, malononitrile **122** and elemental sulfur under MWI conditions. All the synthesized compounds **3** have high thermal stability, and they can be applicable as optical dyes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

Bromobenzene was reacted into indole derivative **546** under $Pd(OAc)_2$ as catalysis to give *N*-phenylindoline derivative **551**. After the bromination, **551** was transformed into boronate with $B(OMe)_3$. 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

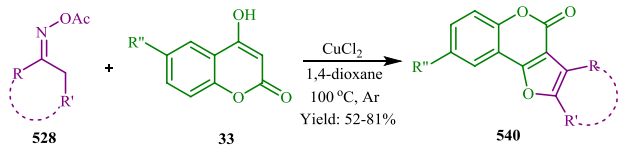
Scheme 152 Synthesis of furo[3,2-*c*]coumarins via I_2/TBHP-mediated reaction



R = H, 4-OMe, 4-Me, 4-i-butyl, 4-OEt, 4-Et, 4-F, 4-Br, 4-Cl, 3-OMe, 2-F, 3-F



Scheme 153 Synthesis of furo[3,2-*c*]coumarins



R = Ph, 4-Me-Ph, 4-OMe-Ph, thiophene, furan, naphthalene R' = H, Et R'' = H, Me, Cl, OMe

Scheme 154 Synthesis of 3-aryl furocoumarins

cyanoacetic acid. Also, 6-bromo-3-thiophenylcoumarin **547** reacted with indole derivative **546** to afford the coupling product **548**. Compound **548** was transformed into the aldehyde derivative **549** which further reacted with cyanoacetic acid to give dye **550**. (Scheme 157) [170].

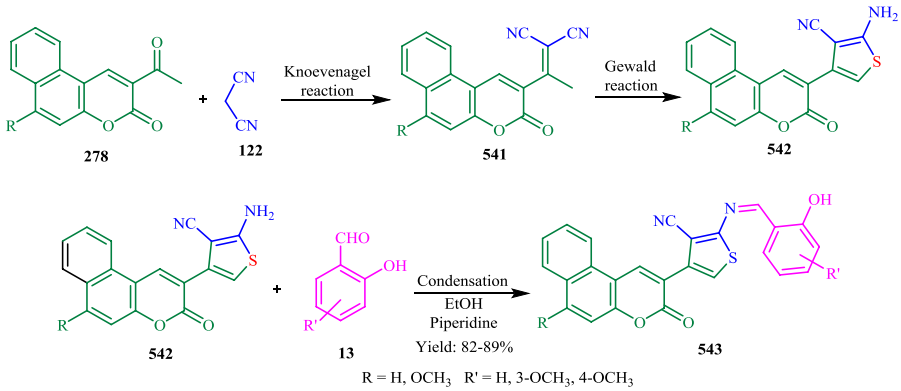
Reaction of 3-bromo-7-(*t*-butyl)-2*H*-chromen-2-one **557** with boronic acid derivatives in the presence of KCO_3 and $Pd(PPh_3)_4$ afforded compound **561–563**. Reaction of the synthesized compounds with cyanoacetic acid in chloroform led to coumarin-based dyes **564-566** (Scheme 158) [171].

Coumarins containing azo-group

3-Phenyl azo-4-hydroxycoumarin, PAHC **568** was synthesized by reacting aniline diazonium salt **567** with 4-hydroxy coumarin **33**. PAHC thin films have been grown successfully on the glass and quartz substrates via using thermal evaporation technique under high vacuum (Scheme 159) [172].

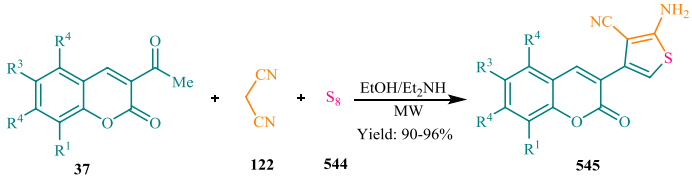
A series of coumarin-based disperse disazo dyes **571** were synthesized by coupling reaction to 4-hydroxycoumarin **33** with diazonium salt of

Scheme 155 Schematic representation for the synthesis of Schiff bases

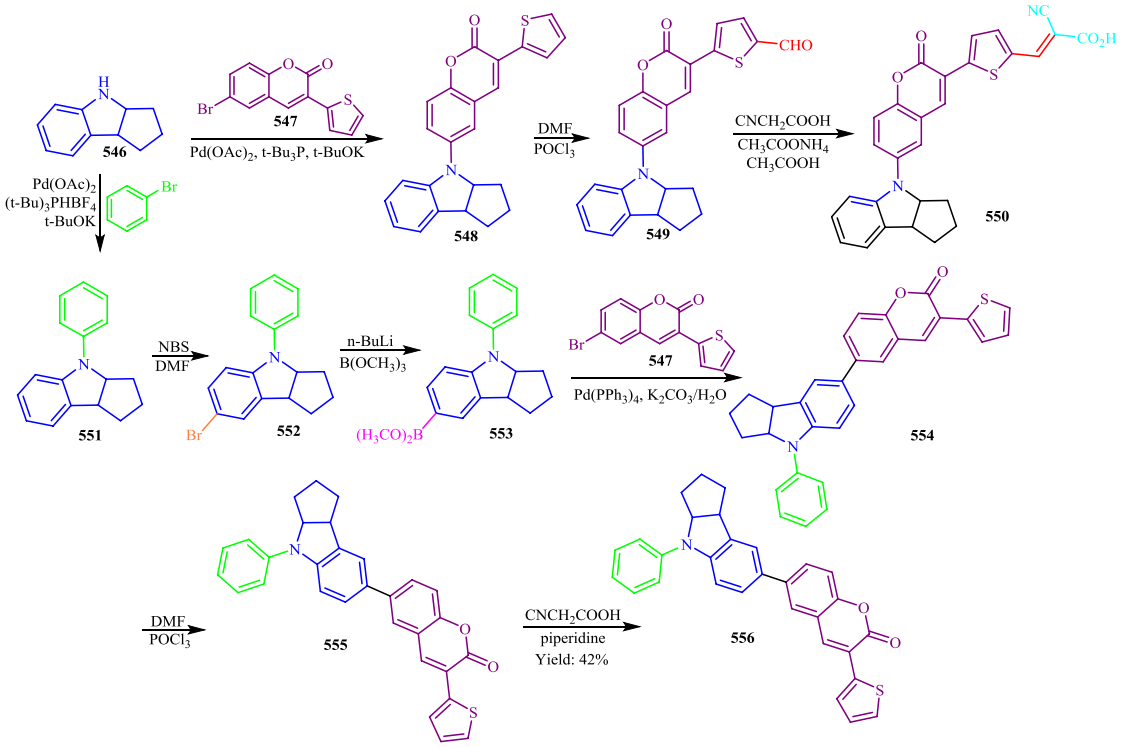


R = H, OCH_3 R' = H, 3-OCH_3, 4-OCH_3

Scheme 156 Synthesis of coumarin–thiophene hybrids



R^1 = H, OMe, OEt R^2 = H, NEt_2, OMe, OH R^3 = H, Br, Cl, OH R^4 = H, CH=CH=CH=CH



Scheme 157 Synthesis of indoline-linked coumarin

5-amino-4-arylazo-3-methyl-1*H*-pyrazoles **570** in the presence of Na_2CO_3 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 $NaNO_2$/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].

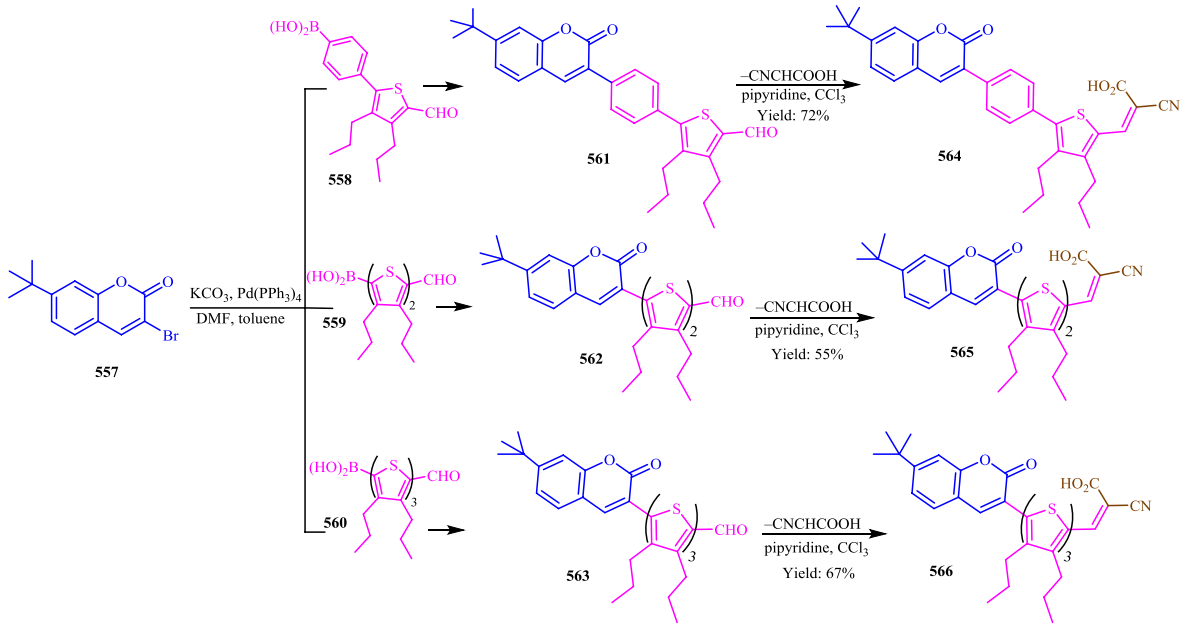
Complexes of coumarins with metals

7-Hydroxy-4-methyl coumarin **3** was synthesized via the Pechmann condensation and formylated 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].

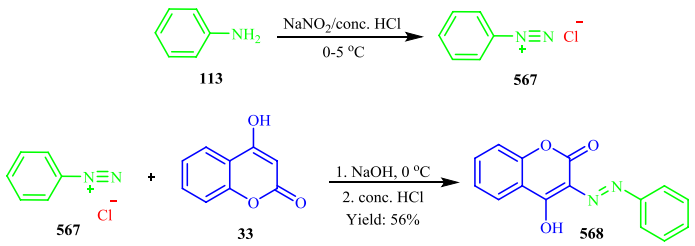
Several coumarin-substituted silver (I) *N*-heterocyclic carbene (NHC) complexes **582** and **585** were synthesized via the interaction of the corresponding imidazolium **583** or benzimidazolium chlorides **580** and Ag_2O in dichloromethane at room temperature (Scheme 164). The anti-microbial activities 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].

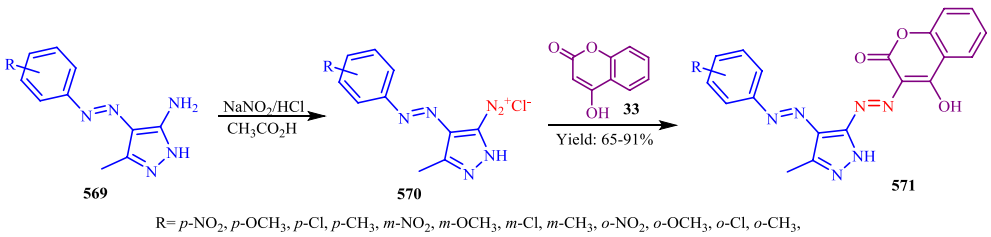
The synthetic method for symmetrical silicon-linked coumarin–oxadiazole derivatives **393** is summarized in Scheme 165. An important intermediate, silylbenzohydrazide moiety **591**, was prepared quantitatively via the reaction of **590** with excess amounts of hydrazine monohydrate under reflux conditions. 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

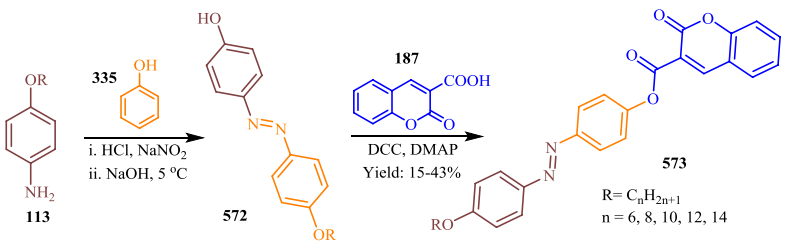
Scheme 159 Synthesis of 3-phenyl azo-4-hydroxycoumarin



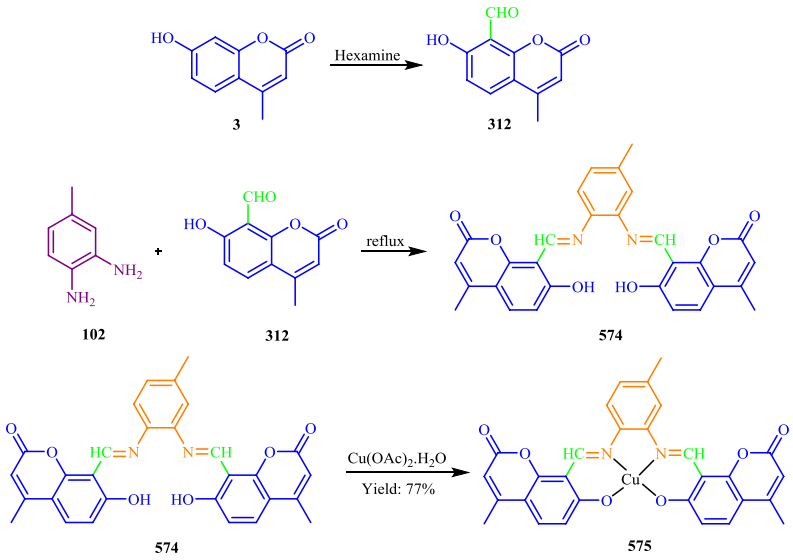


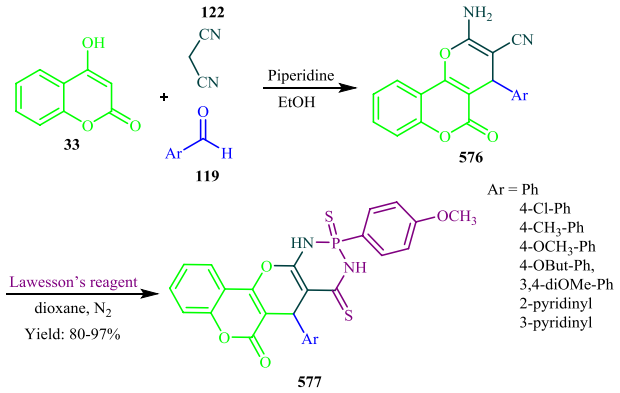
Scheme 160 Synthesis of coumarin-based disperse disazo dyes

Scheme 161 Synthesis of azo-coumarin esters



Scheme 162 Preparation of CuL complex





Scheme 163 Synthesis of diazaphosphinanes derivatives

Co(II), Ni(II) and Cu(II) complexes are prepared by Schiff bases **598** and **599**, derived from 8-formyl-7-hydroxy-4-methyl coumarin **312** 3-chloro-8-formyl-7-hydroxy-4-methyl coumarin **596** 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/benzylbenzimidazole **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].

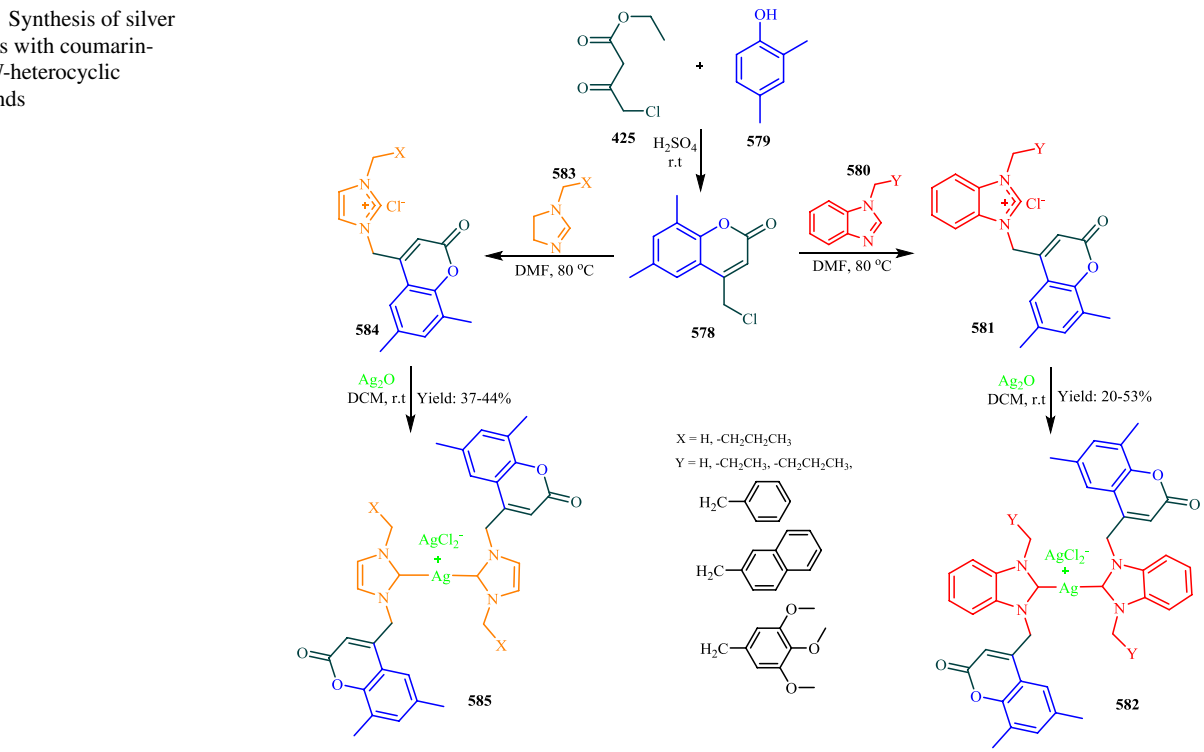
7,8-Dihydroxy-3-(3-methylphenyl)coumarin **607** was obtained from the reaction of compound **606** in the presence of pyridinium hydrochloride and silica gel as support material by microwave irradiation under solvent-free conditions. The reactions of compound **610** with one *equiv*. of 7,8-dihydroxy-3-(3-methylphenyl)coumarin **3** in the presence of Na_2CO_3 in dry xylene gave 2,2-*bis*[spiro(7,8-dioxy-3-(3-methylphenyl)coumarin)]-4,4,6,6-*bis*[spiro(2′,2″-dioxy-1′,1″-biphenylyl)]cyclotriphosphazene **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-dioxy-3-(3-methylphenyl)coumarin)]-6,6-*bis*[spiro(2′,2″-dioxy-1′,1″-iphenylyl)]cyclotriphosphazene **613** (Scheme 168) [181].

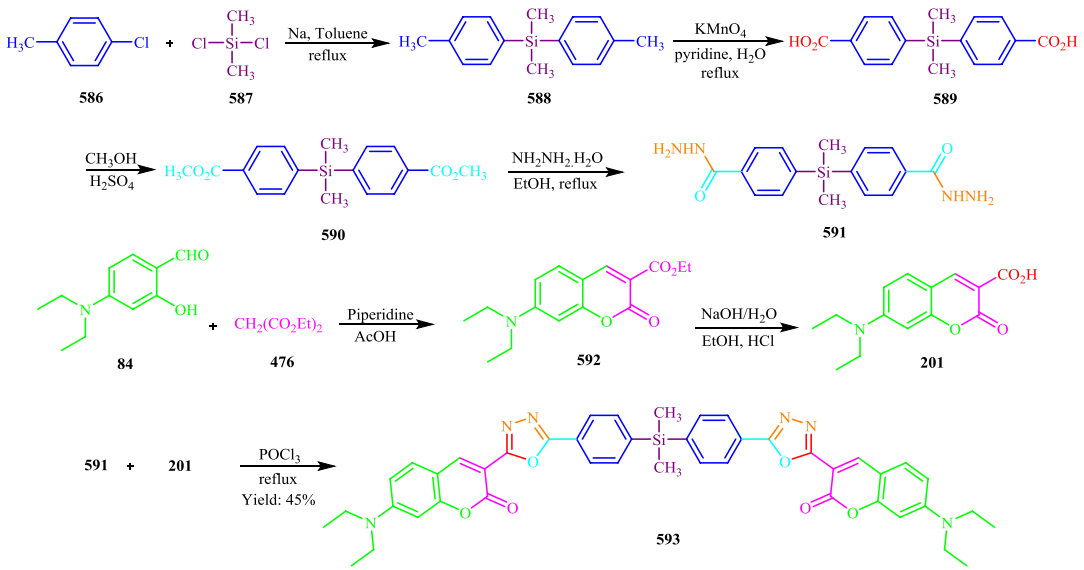
Ruthenium(II) half-sandwich complexes **616** containing coumarin ligands with the general formula [Ru(arene)(L_2)Cl]Cl synthesized from reaction dichlorido(*p*-cymene) ruthenium(II)dimer **614** with 3-aminocoumarin **615** in dry CH_2Cl_2 (Scheme 169) [182].

The synthetic pathway for copper complex is shown in Scheme 169. 7-*N*,*N*-dimethylamino-2-oxo-2*H*-3-coumarate **592** was obtained in an cyclization reaction of 4-(diethylamino)-2-hydroxybenzaldehyde **617** with diethyl malonate **476** in basic media; additional reaction of **592** with hydrazine monohydrate **20** afforded 7-(diethylamino)-2-oxo-2*H*-chromene-3-carbohydrazide **618**, Compound **620** was synthesized from compound **618** and 2,6-pyridine dicarboxaldehyde **619**. Finally, copper complex **621** was prepared from compound **620** and $Cu(ClO_4)_2$ in ethanol (Scheme 170) [183].

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

Scheme 164 Synthesis of silver (I) complexes with coumarin-substituted *N*-heterocyclic carbene ligands





Scheme 165 Preparation of silicon-linked coumarin–oxadiazole derivatives

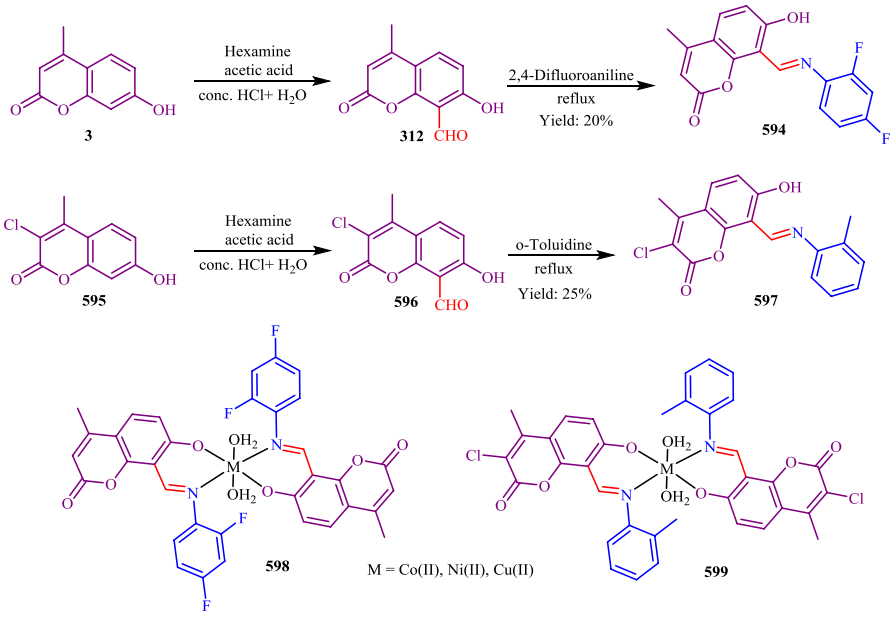
nickel, led to paramagnetic substance **624** (Scheme 171) [184].

A new binuclear Cu (II) complex, $[Cu_2L_2(NO_3)_4]$ has been prepared through complexation of $Cu(NO_3)_2{\cdot}3H_2O$ with coumarin-3-formyl-(3-(aminomethyl) pyridine (L) (Scheme 172) [185].

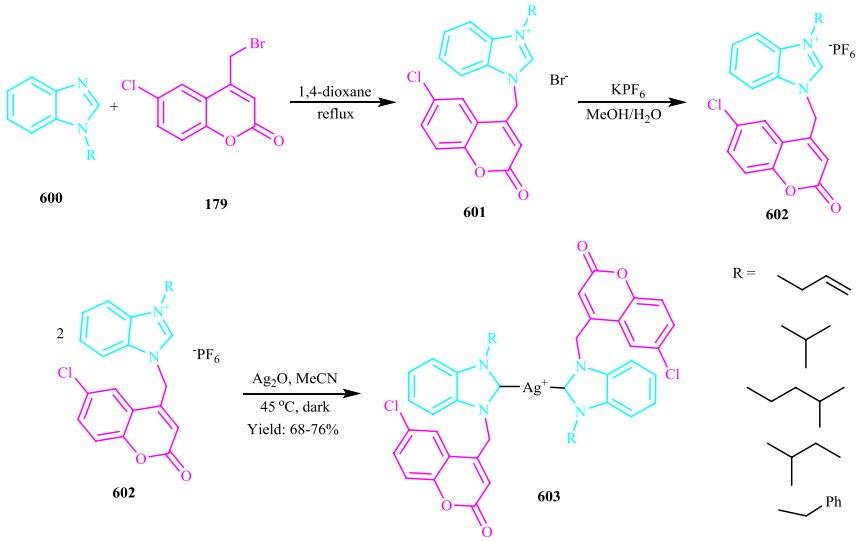
Fumed silica was chemically modified with 3-aminopropyl)triethoxysilane as coupling agent linked to a coumarin derivative in DMF solvent (Scheme 173) [186].

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

Scheme 166 Synthesis of Schiff bases of Co(II), Ni(II) and Cu(II) complexes



Scheme 167 Synthesis of silver(I)complexes derived from coumarin–tethered *N*–heterocyclic carbenes



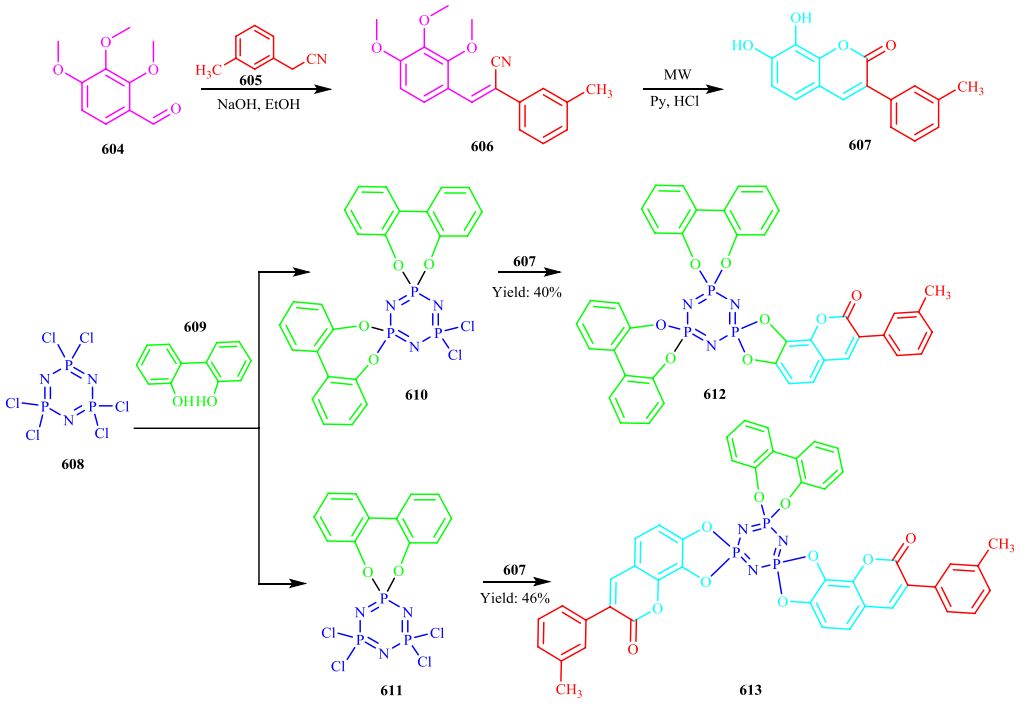
tetra-iodo zinc(II) or tetra-iodo indium(III) acetate phthalocyanines **633** through the Sonogashira coupling reaction for the preparation of the coumarin-substituted phthalocyanines **634**, respectively (Scheme 174) [187].

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*-$[RuCl_2(DMSO)_4]$ and the corresponding ligand **635** in EtOH (Scheme 175) [188].

Imidazol-coumarin **639** was obtained conveniently by condensation reaction of coumarin **618** into 1*H*-imidazole-2-carbaldehyde **638**. Subsequently, the complex Cu^{2+} was also synthesized via reaction of imidazol-coumarin **639** with $Cu(ClO_4)_2{\cdot}6H_2O$ 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].

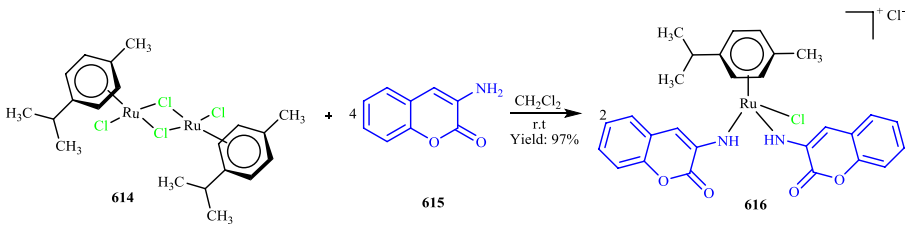
The target molecule **4** was prepared via a synthetic route as shown in Scheme 176. Condensation reaction 2,4-dihydroxybenzaldehyde **216** with ethyl benzoylacetate **641** catalyzed by piperidine produced compound **642** in good yield. Imination of coumarin **642** with benzhydrazide in the presence of tosic acid afforded the target molecule **643**. Among various metal ions, product **643** is able to detect Cu^{2+} 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

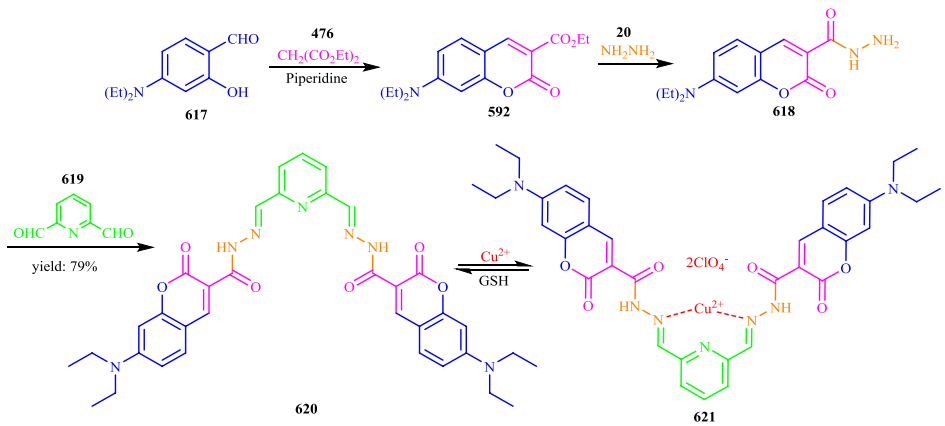


Scheme 168 Synthesis of dioxyphenylcoumarin-substituted cyclotriphosphazene compounds

Scheme 169 Preparation of complexes of Ru(II) with aminocoumarins



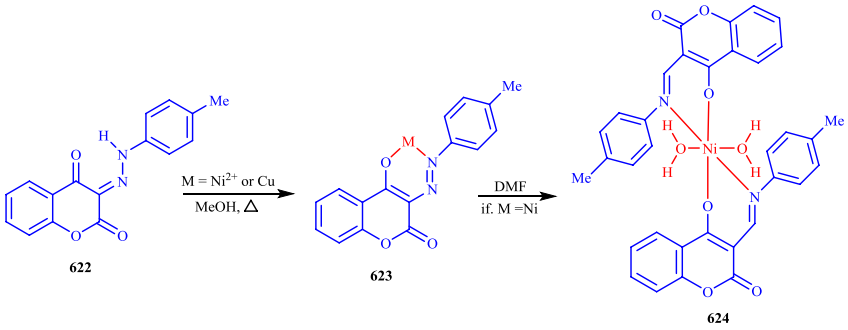
Scheme 170 Synthesis of a coumarin–copper complex

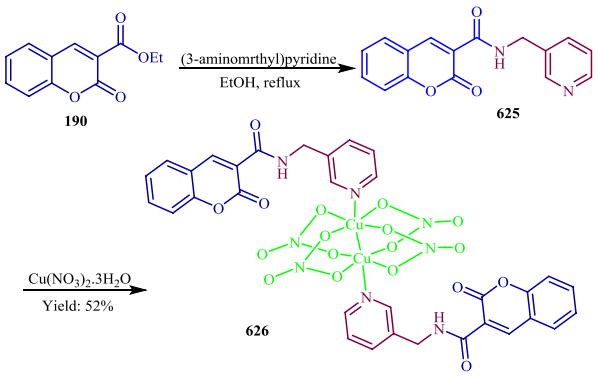


the presence of DCC/DMAP under an inert (Ar) atmosphere (Scheme 178). Studies have shown that ferrocene–coumarin conjugates are potential candidates for developing metallodrugs with anticancer activity [191].

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

Scheme 171 Synthesis of nickel and copper chelate complexes with coumarin-azo ligand





Scheme 172 Synthesis of copper (II) complexes **626**

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].

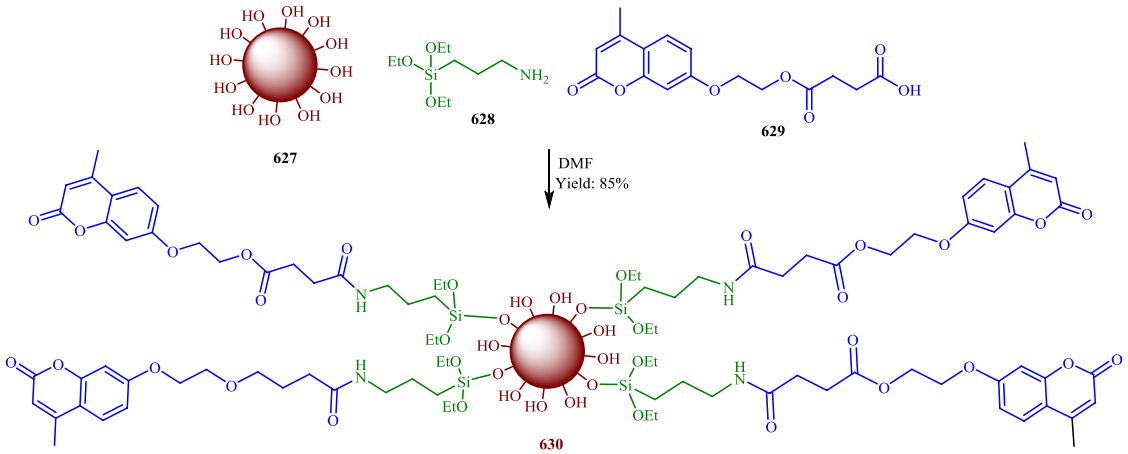
Other coumarins

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-hydantoin 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-2*H*-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].

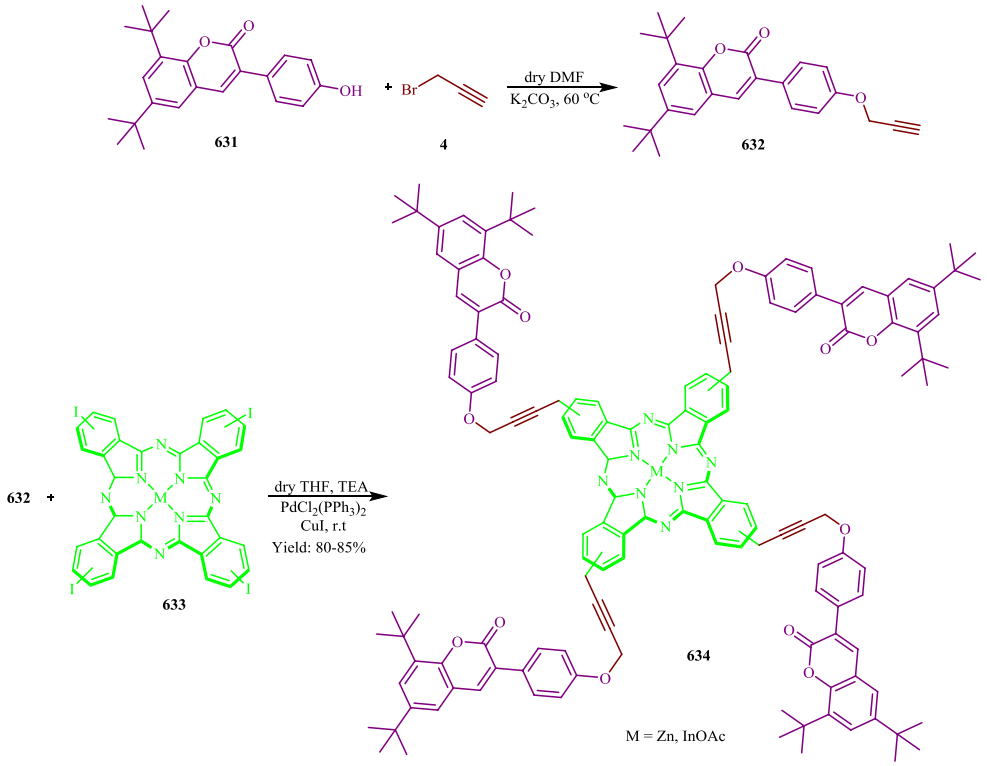
New set of coumarins **670** contains trifluromethyl, diethylamino and morpholino produced via reaction of different coumarin 3-carboxylic acids **187** and various phenyl esters **669** with peripheral alkyl, ester and polar cyano moieties in the presence of EDC.HCl/DMAP as esterification agent (Scheme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

Coumarin–pyrene-based fluorescent probes (*E*)-7-(diethylamino)-3-((pyren-1-ylimino)

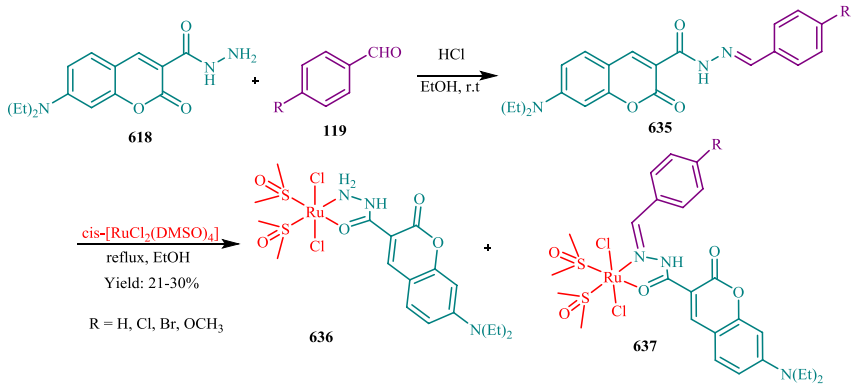


Scheme 173 Synthesis of modified SiNPs

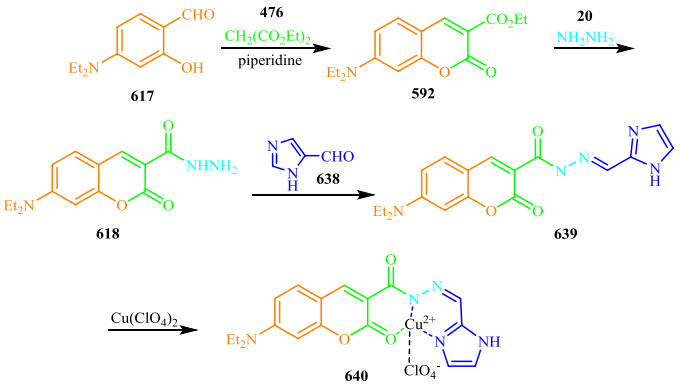
Scheme 174 Synthesis of 6,8-di-*tert*-butyl-3-[*p*-(propynyl) phenoxy]coumarin-substituted phthalocyanine complexes



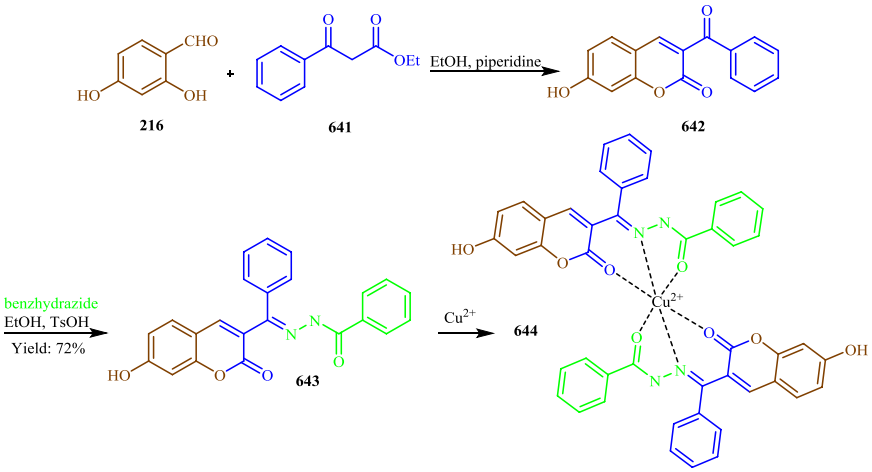
Scheme 175 Synthesis of the coumarin-*N*-acylhydrazone ligands and Ru (II) complexes



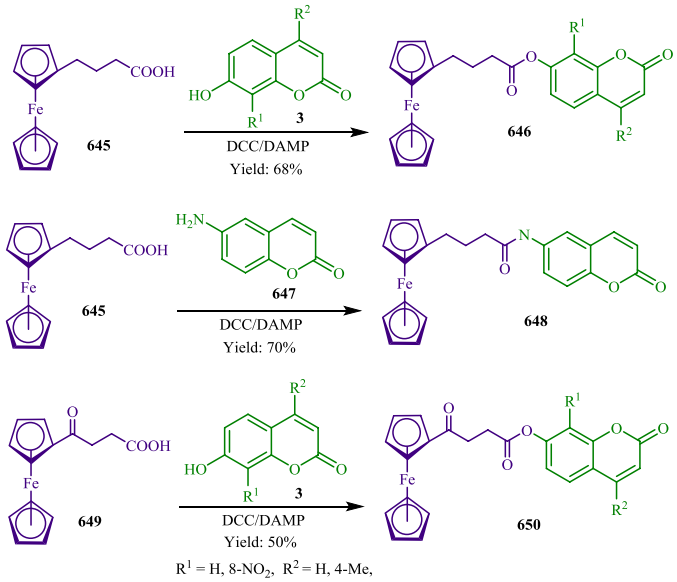
Scheme 176 Synthetic route of coumarin **639** and the presumable structure of complex **639**-Cu^{2+}



Scheme 177 Synthesis of coumarin-based multi-functional chemosensor



Scheme 178 Synthesis of the ferrocene–coumarin



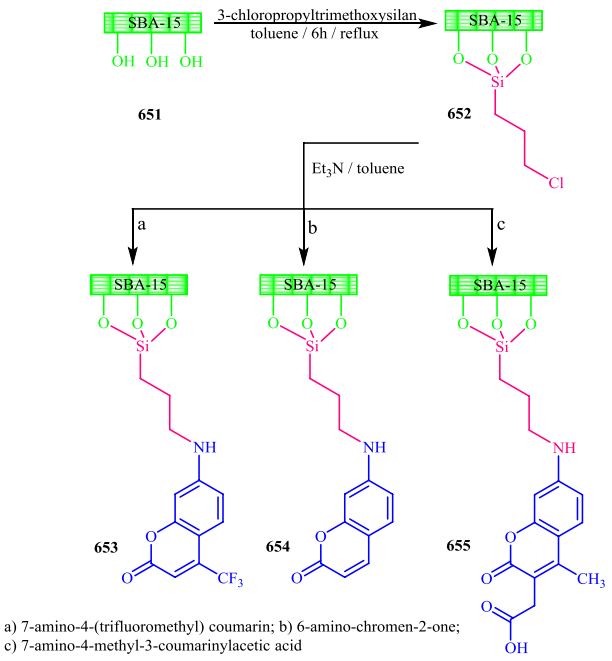
methyl)-2*H*-chromen-2-one **672** and (*E*)-7-(diethylamino)-3-((pyren-1-ylmethylimino)methyl)-2*H*-chromen-2-one **674** were prepared via reaction of 7-diethylaminocoumarin-3-aldehyde **163** with 1-aminopyrene **4671** or 1-(aminomethyl) pyrenehydrochloride **673** in MeOH at 50 °C, respectively (Scheme 184) [196].

2-(1-(2-Oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide derivatives **676** were prepared via multi-component one-pot reaction of 2-oxo-2*H*-chromene-3-carbaldehyde **37**, isothiocynates **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-2*H*-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*-Ethyldiisopropylamine in CH_2Cl_2 at room temperature (Scheme 186) [135].

A series of novel coumarin-oxime ether conjugates **679** with therapeutically interesting properties were synthesized via SN_2 reaction of bromomethyl coumarins **179** with butane-2,3-dione monoxime **678** in the presence of anhydrous K_2CO_3 (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 K_2CO_3 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



Scheme 179 Schematic protocol for functionalization of SBA-15

designed as multi-target agents for the treatment of Alzheimer's disease [199].

A series of coumarin-derived imino sulfonates **683** were synthesized by cyclization reaction of various salicylaldehydes **13** and chlorosulfonamide **682** (Scheme 189) [200].

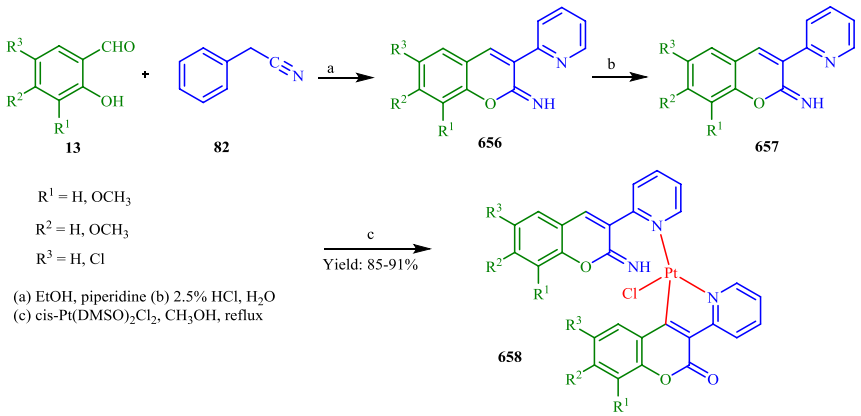
The reaction of 7-hydroxycoumarin **62** with epichlorohydrin in the presence of K_2CO_3 led to the formation of oxiranes **684**, which on regioselective nucleophilic ring opening with a series of suitable amines such as cyclopropyl amine, butyl amine, cyclohexyl amine and morpholine in EtOH at room temperature afforded coumarinyl amino alcohols **685** with good yield (Scheme 190). The products showed significant results for its biological properties assessed in terms of decent anti-bacterial, antioxidant cytotoxicity activities [13].

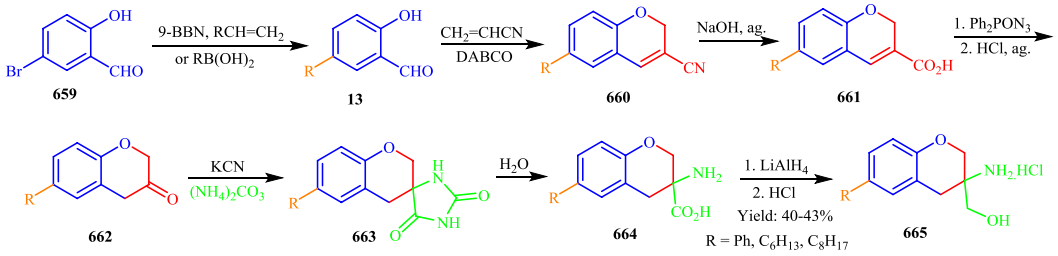
Vashisht et al. synthesized a coumarin-based azomethine colorimetric probe **687** tailored via reaction of 4-hydroxy-2-oxo-2*H*-chromene-3-carbaldehyde **158** with *N*-(2-aminoethyl)-1,3-propanediamine **686** under reflux conditions (Scheme 191) [201].

Condensation reaction of 4-(2-bromoethoxy)-2*H*-chromen-2-one **688** with dithiocarbamate salt **689** in absolute ethanol afforded 2-(2-oxo-2*H*-chromen-4-yloxy)ethyl pyrrolidine-1-carbodithioate derivatives **690** 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 **312** was synthesized via a hydrolysis reaction under acidic conditions aldol between 7-hydroxy-4-methyl-2*H*-chromen-2-one **3** and hexaminc. 8-(Hydrazonomethyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one **691** was synthesized through a reaction of **312** and hydrazine hydrate in EtOH (Scheme 193). Target

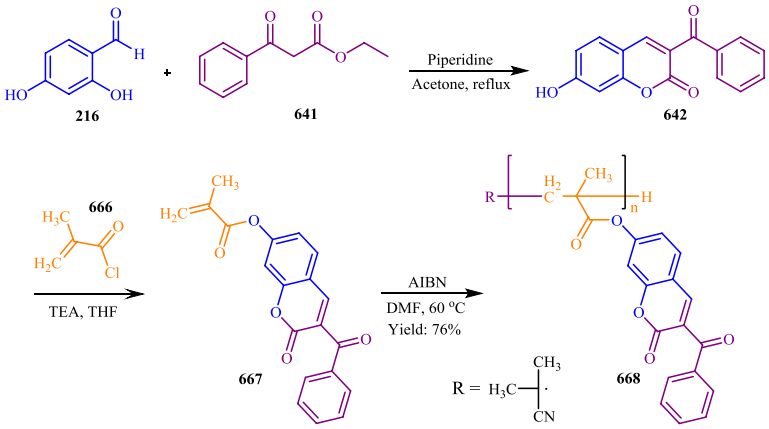
Scheme 180 Synthesis of novel organoplatinum (II) complexes with quinoline–coumarin derivatives

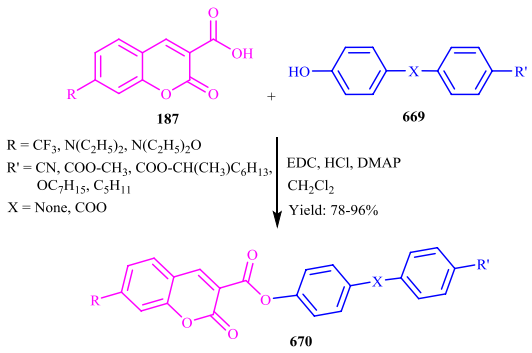




Scheme 181 Synthesis of amino alcohol derivatives containing coumarin moieties

Scheme 182 Preparation of poly(3-benzoyl coumarin-7-yl-methacrylate) [poly(BCMA)]





Scheme 183 Synthetic route for the coumarin derivatives

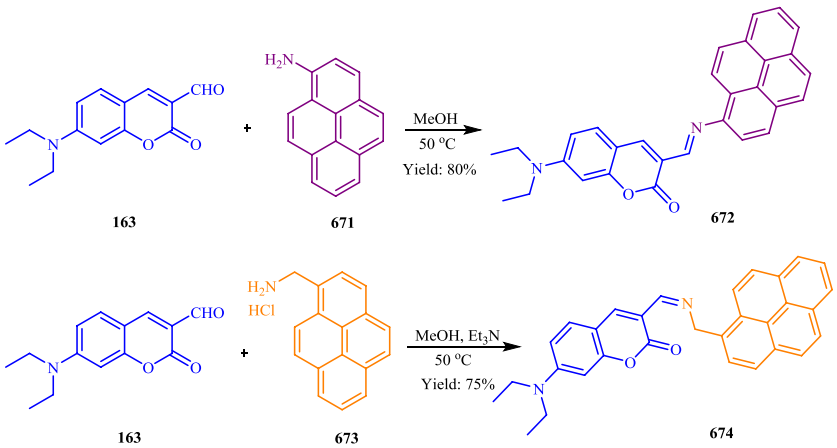
compound **3** showed high sensitivity to detect of ClO^- in living cells [203].

Coumarin derivatives **692** were reacted with the corresponding α,ω-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].

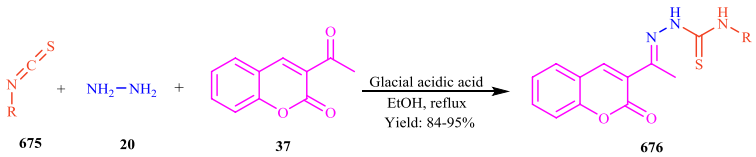
Condensation reaction of 4-bromomethyl coumarins **179** into 1-(4-(4-hydroxyphenyl)piperazin-1-yl)ethanone **695** in the presence of dry K_2CO_3 afforded coumarin–piperazine derivatives **696** as potent anti-microbial and anti-inflammatory agents (Scheme 195) [205].

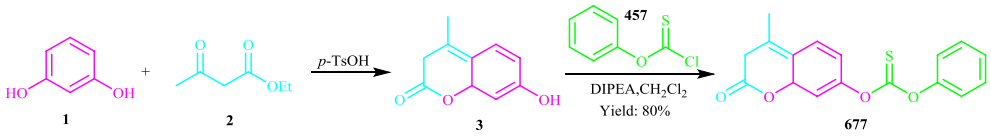
Scheme 196 displays the synthetic rout for coumarin derivative **701**. First, compound **699** was obtained through refluxing malonate ester **697** with compound **698** in toluene. Further coupling compound **699** with acetate chloride **700**

Scheme 184 Synthesis of coumarin–pyrene conjugate **672** and **674**



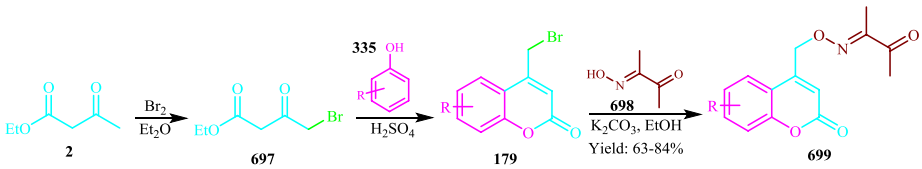
Scheme 185 Synthetic protocol of novel coumarin–thiosemicarbazone derivatives



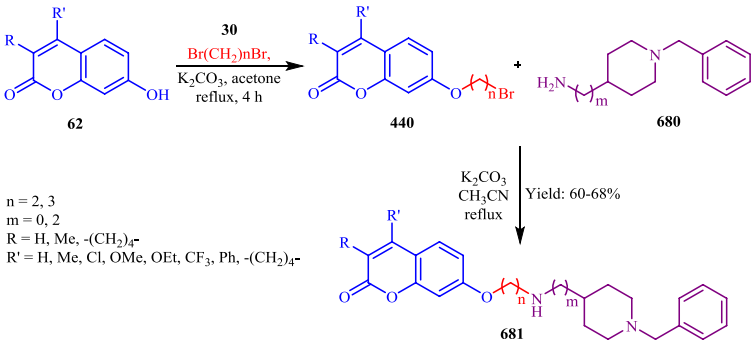


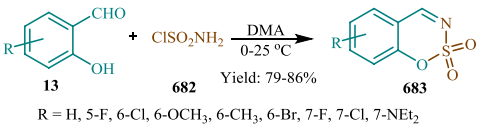
Scheme 186 Synthesis of coumarin–carbonothioate

Scheme 187 Synthesis of novel coumarin-oxime ethers as potential anti-tubercular agents



Scheme 188 Synthesis of donepezil–coumarin hybrids





Scheme 189 Synthesis of coumarin-derived imino sulfonates

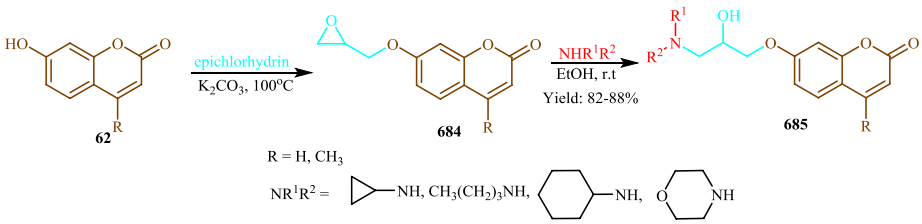
in CH_2Cl_2 afforded coumarin derivative **701** in good yield (Scheme 196) [206].

The reaction of coumarin **702** and benzoic acid **703** in conc. H_2SO_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].

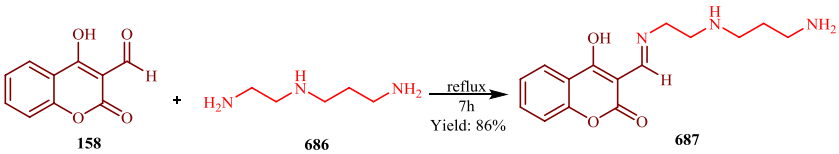
Conclusions

This review article contains the effective procedures of the synthesis of several symmetrical and asymmetrical coumarins containing heterocycles core such as triazole,

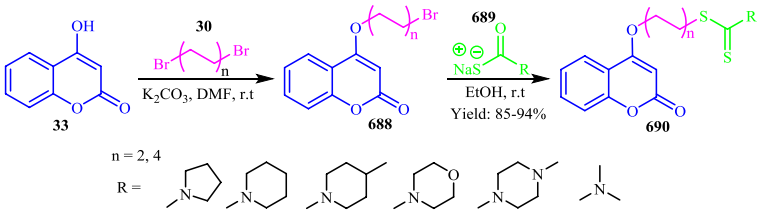
Scheme 190 Synthesis of coumarin derivatives by *Candida albicans*



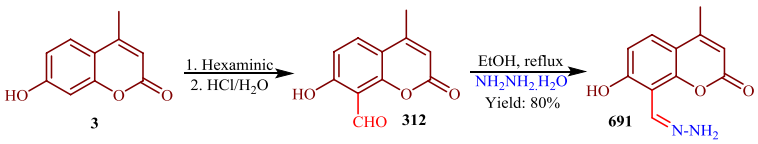
Scheme 191 Systematic route for the synthesis of coumarin **687**

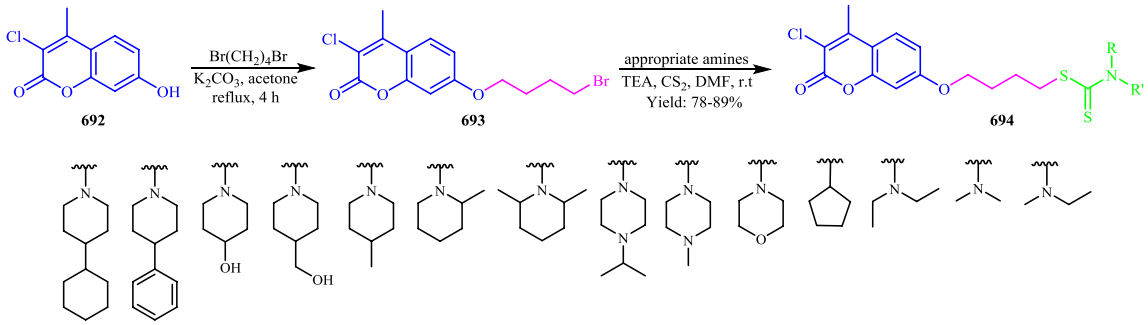


Scheme 192 Synthesis of novel coumarin derivatives bearing dithiocarbamate moiety



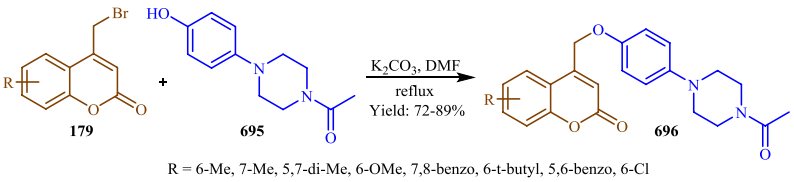
Scheme 193 Synthesis of a novel coumarin-based fluorescent probe with fine selectivity and sensitivity



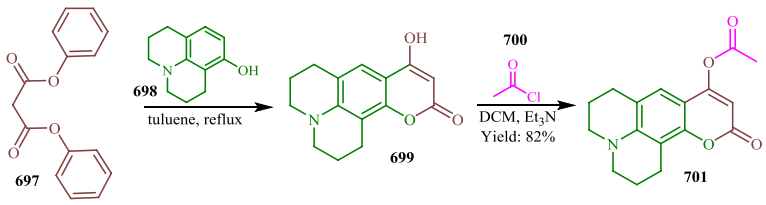


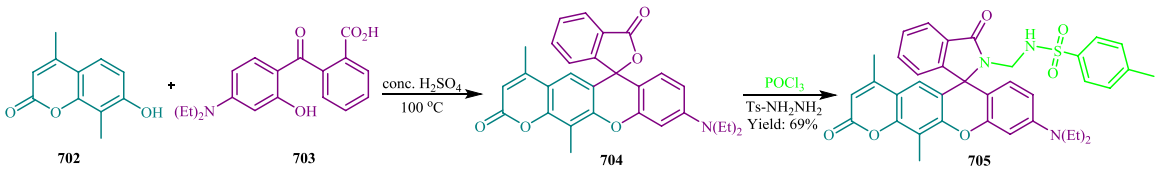
Scheme 194 Synthesis of coumarin–dithiocarbamate hybrids

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.

References

1. Y. Tanaka, W. Fujii, H. Hori, Y. Kitagawa, K. Ozaki, Toxicol. Lett. **99**, 280 (2017)
2. M. Zhu, L. Ma, J. Wen, B. Dong, Y. Wang, Z. Wang, J. Zhou, G. Zhang, J. Wang, Y. Guo, C. Liang, S. Cen, Y. Wang, Eur. J. Med. Chem. **186**, 111900 (2020)
3. Y.-P. Liu, G. Yan, Y.-T. Xie, T.-C. Lin, W. Zhang, J. Li, Y.-J. Wu, J.-Y. Zhou, Y.-H. Fu, Bioorg. Chem. **97**, 103699 (2020)
4. J.-W. Zhao, Z.-H. Wu, J.-W. Guo, M.-J. Huang, Y.-Z. You, H.-M. Liu, L.-H. Huang, Eur. J. Med. Chem. **181**, 111520 (2019)
5. M.-H. Lin, J.-S. Wang, Y.-C. Hsieh, J.-H. Zheng, E.-C. Cho, Chem.-Biol. Interact. **309**, 108708 (2019)
6. Y. Eker, E. Senkuytu, Z. Olcer, T. Yildirim, G.Y. Ciftci, J. Mol. Struct. **1209**, 127971 (2020)
7. M. Sanduja, J. Gupta, H. Singh, P.P. Pagare, A. Rana, J. Saudi Chem. Soc. **24**, 251 (2020)
8. E.Y. Ahmed, N.A. Abdel Latif, M.F. El-Mansy, W.S. Elserwy, O.M. Abdelhafez, Bioorg. Med. Chem. **28**, 115328 (2020)
9. S. Koparde, K.M. Hosamani, D.A. Barretto, S.D. Joshi, Chem. Data Collect. **15**, 41 (2018)
10. K. Ostrowska, Saudi Pharm. J. **28**, 220 (2020)
11. H. Wang, W. Xu, Biochem. Biophys. Res. Commun. **489**, 1 (2017)
12. S.N. Mangasuli, K.M. Hosamani, P.B. Managutti, Heliyon **5**, e01131 (2019)
13. Ambreen, S. Haque, V. Singh, D. Katiyar, M.T. Ali Khan, V. Tripathi, H. El Enshasy, M. Pasupuleti, B.N. Mishra, Process Biochem. **87**, 138 (2019)
14. M.Y. Ali, S. Jannat, H.A. Jung, R.J. Choi, A. Roy, J.S. Choi, Asian Pac. J. Trop. Med. **9**, 103 (2016)
15. S.N. Mangasuli, K.M. Hosamani, H.C. Devarajegowda, M.M. Kurjogi, S.D. Joshi, Eur. J. Med. Chem. **146**, 747 (2018)
16. C. Zaragoza, J. Monserrat, C. Mantecon, L. Villaescusa, F. Zaragoza, M. Alvarez-Mon, Vasc. Pharmacol. **87**, 139 (2016)
17. H.M. Revankar, S.N.A. Bukhari, G.B. Kumar, H.-L. Qin, Bioorg. Chem. **71**, 146 (2017)
18. L.Z. Chen, W.W. Sun, L. Bo, J.Q. Wang, C. Xiu, W.J. Tang, J.B. Shi, H.P. Zhou, X.H. Liu, Eur. J. Med. Chem. **138**, 170 (2017)
19. L.K.A.M. Leal, A.H. Silva, G.S. de Barros Viana, Rev. Bras. Farmacogn. **27**, 794 (2017)
20. M.Z. Hassan, H. Osman, M. Ashraf Ali, M. Jawed Ahsan, Eur. J. Med. Chem. **123**, 236 (2016)
21. H. Liu, D.-G. Xia, Z.-W. Chu, R. Hu, X. Cheng, X.-H. Lv, Bioorg. Chem. **100**, 103907 (2020)
22. N. Yadav, D. Agarwal, S. Kumar, A.K. Dixit, R.D. Gupta, S.K. Awasthi, Eur. J. Med. Chem. **145**, 735 (2018)
23. A.V. Lipeeva, E.E. Shults, Chem. Heterocycl. Compd. **53**, 1302 (2017)
24. N.M. Chernov, P.V. Filippova, I.P. Yakovlev, V.E. Zakhs, A.V. Belyakov, Russ. J. Gen. Chem. **86**, 1292 (2016)
25. X.-M. Peng, K.V. Kumar, G.L.V. Damu, C.-H. Zhou, Sci. China Chem. **59**, 878 (2016)
26. H. Singh, J.V. Singh, M.K. Gupta, A.K. Saxena, S. Sharma, K. Nepali, P. Mohinder, S. Bedi, Bioorg. Med. Chem. Lett. **27**, 3974 (2017)
27. M.A. Kumari, C.V. Rao, S. Triloknadh, N. Harikrishna, S. Venkataramaiah, N. Rajendra, C. Trinath, W.D.Y. Suneetha, Res. Chem. Intermed. **44**, 1989 (2018)
28. S. Srivastava, D. Bimal, K. Bohra, B. Singh, P. Ponnan, R. Jain, M. Varma-Basil, J. Maity, M. Thirumal, A.K. Prasad, Eur. J. Med. Chem. **150**, 268 (2018)
29. S. Sinha, A.P. Kumaran, D. Mishra, P. Paira, Bioorg. Med. Chem. Lett. **26**, 5557 (2016)
30. H. Yu, Z. Hou, Y. Tian, Y. Mou, C. Guo, Eur. J. Med. Chem. **151**, 434 (2018)
31. I. Khan, A. Khan, S.A. Halim, A. Saeed, S. Mehsud, R. Csuk, A. Al-Harrasi, A. Ibrar, Int. J. Biol. Macromol. **142**, 345 (2020)
32. B. Zengin Kurt, A. Dag, B. Dogan, S. Durdagi, A. Angeli, A. Nocentini, C.T. Supuran, F. Sonmez, Bioorg. Chem. **87**, 838 (2019)
33. J.E. Park, T. Anand, V. Bharadwaj, S.K. Sahoo, H.-J. Choi, J. Photochem. Photobiol. A **383**, 111990 (2019)
34. Z. Najafi, M. Mahdavi, M. Saeedi, E. Karimpour-Razkenari, N. Edraki, M. Sharifzadeh, M. Khanavi, T. Akbarzadeh, Bioorg. Chem. **83**, 303 (2019)
35. S.-Y. Hao, S.-L. Feng, X.-R. Wang, Z. Wang, S.-W. Chen, L. Hui, Bioorg. Med. Chem. Lett. **29**, 2129 (2019)
36. D. Ashok, S. Gundu, V.K. Aamate, M.G. Devulapally, R. Bathini, V. Manga, J. Mol. Struct. **1157**, 312 (2018)
37. B.M. Chougala, S. Samundeeswari, M. Holiyachi, L.A. Shastri, S. Dodamani, S. Jalalpure, S.R. Dixit, S.D. Joshi, V.A. Sunagar, Eur. J. Med. Chem. **125**, 101 (2017)
38. E. Yalcın, M. Alkış, N. Seferoglu, Z. Seferoglu, J. Mol. Struct. **1155**, 573 (2018)
39. D. Srikrishna, P.K. Dubey, Res. Chem. Intermed. **44**, 4455 (2018)
40. R. Nagamallu, B. Srinivasan, M.B. Ningappa, A.K. Kariyappa, Bioorg. Med. Chem. Lett. **26**, 690 (2016)
41. J. Kovvuri, B. Nagaraju, C. Ganesh Kumar, K. Sirisha, C. Chandrasekhar, A. Alarifi, A. Kamal, J. Saudi Chem. Soc. **22**, 665 (2018)

42. Y. Garazd, M. Garazd, R. Lesyk, Saudi Pharm. J. **25**, 214 (2016)
43. M. Seydimemet, K. Ablajan, M. Hamdulla, W. Li, A. Omar, M. Obul, Tetrahedron **72**, 7599 (2016)
44. A. Saeed, P.A. Mahesar, P.A. Channar, Q. Abbas, F.L. Larik, M. Hassan, H. Raza, S.-Y. Seo, Bioorg. Chem. **74**, 187 (2017)
45. N.O. Mahmoodi, S. Ghodsi, Res. Chem. Intermed. **43**, 661 (2017)
46. N. Mahdizadeh Ghohe, R. Tayebee, M.M. Amini, Mater. Chem. Phys. **223**, 268 (2019)
47. H. Dai, M. Huang, J. Qian, J. Liu, C. Meng, Y. Li, G. Ming, T. Zhang, S. Wang, Y. Shi, Y. Yao, S. Ge, Y. Zhang, Y. Ling, Eur. J. Med. Chem. **166**, 470 (2019)
48. H. Liu, Z.-L. Ren, W. Wang, J.-X. Gong, M.-J. Chu, Q.-W. Ma, J.-C. Wang, X.-H. Lv, Eur. J. Med. Chem. **157**, 81 (2018)
49. X. Han, J. Luo, F. Wu, X. Hou, G. Yan, M. Zhou, M. Zhang, C. Pu, R. Li, Eur. J. Med. Chem. **114**, 232 (2016)
50. M. Holiyachi, S. Samundeeswari, B.M. Chougala, N.S. Naik, J. Madar, L.A. Shastri, S.D. Joshi, S.R. Dixit, S. Dodamani, S. Jalalpure, V.A. Sunagar, Monatsh. Chem. **149**, 595 (2018)
51. Y. Hu, W. Chen, Y. Shen, B. Zhu, G.-X. Wang, Bioorg. Med. Chem. Lett. **29**, 1749 (2019)
52. P. Manvar, F. Shaikh, R. Kakadiya, K. Mehariya, R. Khunt, B. Pandey, A. Shah, Tetrahedron **72**, 1293 (2016)
53. Y. Wang, Y. Li, T. Yu, W. Su, H. Ma, Y. Zhao, X. Li, H. Zhang, Dyes Pigments **173**, 107958 (2020)
54. Y.-F. Shen, L. Liu, C.-Z. Feng, Y. Hu, C. Chen, G.-X. Wang, B. Zhu, Fish Shellfish Immun. **81**, 57 (2018)
55. G. Liu, C. Wang, H. Wang, L. Zhu, H. Zhang, Y. Wang, C. Pei, L. Liu, Virus Res. **268**, 11 (2019)
56. Y. Hu, Y. Shen, X. Tu, X. Wu, G.-X. Wang, Eur. J. Med. Chem. **143**, 958 (2018)
57. S.B. Yadav, S. Kothavale, N. Sekar, J. Photochem. Photobiol. A **382**, 111937 (2019)
58. Z. Zhou, A. Zheng, Y. Cui, Z. Lin, W. Niu, Y. Zhang, J. Gao, Y. Li, Tetrahedron **75**, 2958 (2019)
59. L. Pan, X.-Z. Li, D.-A. Sun, H. Jin, H.-R. Guo, B. Qin, Chin. Chem. Lett. **27**, 375 (2016)
60. S. Taheri, M. Nazifi, M. Mansourian, L. Hosseinzadeh, Y. Shokoohiniad, Bioorg. Chem. **91**, 103147 (2019)
61. T. Prashanth, B.R.V. Avin, P. Thirusangu, V.L. Ranganatha, B.T. Prabhakar, J.N.N. Sharath Chandra, S.A. Khanum, Biomed. Pharmacother. **112**, 108707 (2019)
62. X. Meng, D. Cao, Z. Hu, X. Han, Z. Li, D. Liang, W. Ma, Tetrahedron Lett. **59**, 4299 (2018)
63. H.A.H. Elshemy, M.A. Zaki, Bioorg. Med. Chem. **25**, 1066 (2017)
64. D. Zhang, D. Li, X. Li, W. Jin, Dyes Pigments **152**, 43 (2018)
65. T. Pivetta, E. Valletta, G. Ferino, F. Isaia, A. Pani, S. Vascellari, C. Castellano, F. Demartin, M.G. Cabiddu, E. Cadoni, J. Inorg. Biochem. **177**, 101 (2017)
66. C. Zhang, K. Yang, S. Yu, J. Su, S. Yuan, J. Han, Y. Chen, J. Gu, T. Zhou, R. Bai, Y. Xie, Eur. J. Med. Chem. **180**, 367 (2019)
67. G. Zhu, Y. Huang, C. Wang, L. Lu, T. Sun, M. Wang, Y. Tang, D. Shan, S. Wen, J. Zhu, Spectrochim. Acta A **210**, 105 (2019)
68. N. Lv, M. Sun, C. Liu, J. Li, Bioorg. Med. Chem. Lett. **27**, 4578 (2017)
69. A.V. Metelitsa, O.G. Nikolaeva, A.S. Cheprasov, O.Y. Karlutova, A.A. Burtseva, A.D. Dubonosov, V.A. Bren, V.I. Minkin, J. Photochem. Photobiol. A Chem. **321**, 12 (2016)
70. A. Dey, M. Ashif Ali, S. Jana, S. Samanta, A. Hajra, Tetrahedron Lett. **58**, 313 (2017)
71. C.-X. Gu, W.-W. Chen, B. Xu, M.-H. Xu, Tetrahedron **75**, 1605 (2019)
72. A. Ibrar, Y. Tehseen, I. Khan, A. Hameed, A. Saeed, N. Furtmann, J. Bajorath, J. Iqbal, Bioorg. Chem. **68**, 177 (2016)
73. H. Osman, S.K. Yusufzai, M.S. Khan, B.M. AbdRazik, O. Sulaiman, S. Mohamad, J.A. Gansau, M.O. Ezzat, T. Parumasivam, M.Z. Hassan, J. Mol. Struct. **1166**, 147 (2018)
74. B. Shankar, P. Jalapathi, M. Nagamani, B. Gandu, K.R. Kudle, Monatsh. Chem. **148**, 999 (2017)
75. P. Srivastava, V.K. Vyas, B. Variya, P. Patel, G. Qureshi, M. Ghate, Bioorg. Chem. **67**, 130 (2016)
76. U. Salar, M. Taha, K.M. Khan, N.H. Ismail, S. Imran, S. Perveen, S. Gul, A. Wadood, Eur. J. Med. Chem. **122**, 196 (2016)
77. A. Ayati, T.O. Bakhshaiesh, S. Moghimi, R. Esmaeili, K. Majidzadeh-A, M. Safavi, L. Firoozpour, S. Emami, A. Foroumadi, Eur. J. Med. Chem. **155**, 483 (2018)
78. A. Saeed, M. Arif, M.F. Erben, U. Florke, J. Simpson, Spectrochim. Acta A **198**, 290 (2018)
79. M.A. El-Fattah, H.A. El-Wahab, M.S. Bashandy, R.A. El-Eisawy, F.A. El-hai, M. Saeed, Prog. Org. Coat. **111**, 57 (2017)
80. S. Feng, Q. Gao, X. Gao, J. Yin, Y. Jiao, Inorg. Chem. Commun. **102**, 51 (2019)
81. S.N. Mangasuli, K.M. Hosamani, P. Managutti, D.A. Barretto, S.D. Joshi, Chem. Data Collect. **17**, 327 (2018)
82. M.E. Aliaga, M. Gazitua, A. Rojas-Bolanos, M. Fuentes-Estrada, D. Durango, O. Garcia-Beltran, Spectrochim. Acta A **224**, 117372 (2020)
83. S. Dhawan, N. Kerru, P. Awolade, A. Singh-Pillay, S.T. Saha, M. Kaur, S.B. Jonnalagadda, P. Singh, Bioorg. Med. Chem. **26**, 5612 (2018)
84. M. Mohammadi-Khanaposhtani, N. Ahangar, S. Sobhani, P.H. Masihi, A. Shakiba, M. Saeedi, T. Akbarzadeh, Bioorg. Chem. **89**, 102989 (2019)
85. N. Sridhar Goud, S. Mahammad Ghouse, M. Arifuddin, M. Alvala, A. Angeli, C.T. Supuran, Bioorg. Chem. **87**, 765 (2019)
86. H.A.H. Elshemy, M.A. Zaki, Bioorg. Med. Chem. **25**, 1066 (2016)
87. X. Yu, P. Teng, Y.-L. Zhang, Z.-J. Xu, M.-Z. Zhang, W.-H. Zhang, Fitoterapia **127**, 387 (2018)
88. M. Taha, S.A.A. Shah, M. Afifi, S. Imran, S. Sultan, F. Rahim, N.H. Ismail, K.M. Khan, Bioorg. Chem. **78**, 17 (2018)
89. S. Ghanei-Nasab, M. Khoobi, F. Hadizadeh, A. Marjani, A. Moradi, H. Nadri, S. Emami, A. Foroumadi, A. Shafiee, Eur. J. Med. Chem. **121**, 40 (2016)
90. S.J. Basha, P.B. Kumar, P. Mohan, K.K. Viswanath, D.S. Rao, E. Siddhartha, D.M. Manidhar, A.D. Rao, V. Ramakrishna, A.G. Damu, Eur. J. Med. Chem. **107**, 219 (2016)
91. D. Yao, J. Wang, G. Wang, Y. Jiang, L. Shang, Y. Zhao, J. Huang, S. Yang, J. Wang, Y. Yu, Bioorg. Chem. **68**, 112 (2016)
92. F. Vafadarnejad, M. Mahdavi, E. Karimpour-Razkenari, N. Edraki, B. Sameem, M. Khanavi, M. Saeedi, T. Akbarzadeh, Bioorg. Chem. **77**, 311 (2018)
93. A. McQueen, L.D. Blake, A. Azhari, M.T. Kemp, T.W. Mc Gaha Jr., N. Namelikonda, R.W. Larsen, R. Manetsch, D.E. Kyle, Bioorg. Med. Chem. Lett. **27**, 4597 (2017)
94. H. Chen, P. Yang, Y. Li, L. Zhang, F. Ding, X. He, J. Shen, Spectrochim. Acta A **224**, 117384 (2020)
95. M.N. Abu-Aisheh, A. Al-Aboudi, M.S. Mustafa, M.M. El-Abadelah, S.Y. Ali, Z. Ul-Haq, M.S. Mubarak, Heliyon **5**, e01552 (2019)
96. M.S. Khan, R. Agrawal, M. Ubaidullah, M.I. Hassan, N. Tarannum, Heliyon **5**, e02615 (2019)
97. D.S. Reddy, M. Kongot, V. Singh, N. Maurya, R. Patel, N. Kumar Singhal, F. Avecilla, A. Kumar, Bioorg. Chem. **92**, 103212 (2019)
98. S. Kumar, K. Mukesh, K. Harjai, V. Singh, Tetrahedron Lett. **60**, 8 (2019)
99. C.-B. Bai, H.-Y. Fan, R. Qiao, S.-N. Wang, B. Wei, Q. Meng, Z.-Q. Wang, J.-X. Liao, J. Zhang, L. Zhang, S.-S. Chen, H. Miao, Spectrochim. Acta A **216**, 45 (2019)

100. S. Awalea, T. Okada, D.F. Dibwe, T. Maruyama, S. Takahara, T. Okada, S. Endo, N. Toyooka, Bioorg. Med. Chem. Lett. **29**, 1779 (2019)
101. S. Samundeeswari, L.A. Shastri, B.M. Chougala, M. Holiyachi, M.V. Kulkarni, Tetrahedron Lett. **58**, 1996 (2017)
102. N. Bardasov, N.L. Malyshkina, A.Y. Alekseeva, O.V. Ershov, D.V. Timrukova, A.O. Grigoreva, Russ. J. Org. Chem. **53**, 47 (2017)
103. M. Bayat, M. Rezaei, Monatsh. Chem. **148**, 2097 (2017)
104. I.N. Bardasov, A.Y. Alekseeva, N.L. Malyshkina, O.V. Ershov, M.D. Surazhskaya, D.A. Grishanov, Russ. J. Org. Chem. **52**, 983 (2016)
105. B. Aydıner, J. Photochem. Photobiol. A Chem. **382**, 111916 (2019)
106. M. Shangguan, X. Jiang, Z. Lu, W. Zou, Y. Chen, P. Xu, Y. Pan, L. Hou, Talanta **202**, 303 (2019)
107. P. Gao, Y.-B. Cheng, F. Yang, L.-N. Guo, X.-H. Duan, Tetrahedron Lett. **60**, 150967 (2019)
108. H. Choi, J. Kim, K. Lee, Tetrahedron Lett. **57**, 3600 (2016)
109. S. Li, X. Qi, B. Huang, Catal. Today **276**, 139 (2016)
110. Y.J. Rao, E.Y. Goud, Y. Hemasri, N. Jain, S. Gabriella, Russ. J. Gen. Chem. **86**, 184 (2016)
111. U. Rashid, F. Rahim, M. Taha, M. Arshad, H. Ullah, T. Mahmood, M. Ali, Bioorg. Chem. **66**, 111 (2016)
112. W.-Y. Pan, Y.-M. Xiao, H.-Q. Xiong, C.-W. Lu, Res. Chem. Intermed. **42**, 7057 (2016)
113. H.K. Chaudhari, A. Pahelkar, B.S. Takale, Tetrahedron Lett. **58**, 4107 (2017)
114. C. Chen, W. Ping, Z. Liwei, Y. Ling, F. Yiming, H. Wenzhong, G. Guangbo, Chem. Res. Chin. Univ. **33**, 194 (2017)
115. N. Robledo-O Ryan, M.J. Matos, S. Vazquez-Rodriguez, L. Santana, E. Uriarte, M. Moncada-Basualto, F. Mura, M. Lapier, J.D. Maya, C. Olea-Azar, Bioorg. Med. Chem. **25**, 621 (2017)
116. M. Yamaji, H. Okamoto, K. Goto, S. Kato, F. Tani, Y. Nakamura, Tetrahedron Lett. **59**, 1216 (2018)
117. G. Luo, M. Muyaba, W. Lyu, Z. Tang, R. Zhao, Q. Xu, Q. You, H. Xiang, Bioorg. Med. Chem. Lett. **27**, 867 (2017)
118. H. Niu, W. Wang, J. Li, Y. Lei, Y. Zhao, W. Yang, C. Zhao, B. Lin, S. Song, S. Wang, Eur. J. Med. Chem. **138**, 212 (2017)
119. O. Danis, S. Demir, C. Gunduz, M.M. Alparslan, S. Altun, B. Yuce-Dursun, Res. Chem. Intermed. **42**, 6061 (2016)
120. H. Yan, X. Meng, B. Li, S. Ge, Y. Lu, Dyes Pigments **146**, 479 (2017)
121. A.M. Hamdy, Z. Khaddour, N.A. Al-Masoudi, Q. Rahman, C. Hering-Junghans, A. Villinger, P. Langer, Bioorg. Med. Chem. **24**, 5115 (2016)
122. V.A. Osyanin, D.V. Osipov, Y.V. Popova, I.A. Semenova, Y.N. Klimochkin, Chem. Heterocycl. Compd. **52**, 1012 (2016)
123. M.S. Shetty, B.R. Bharath, N.L. Rani, M.A. Sridhar, N.K. Lokanath, N.V.A. Kumar, Chem. Data Collect. **14**, 17 (2017)
124. U. Salar, K.M. Khan, A. Jabeen, A. Faheem, M.I. Fakhri, S.M. Saad, S. Perveen, M. Taha, A. Hameed, Bioorg. Chem. **69**, 37 (2016)
125. U. Warde, N. Sekar, Opt. Mater. **72**, 346 (2017)
126. K. Perez-Cruz, M. Moncada-Basualto, J. Morales-Valenzuela, G. Barriga, P. Navarrete-Encina, L. Núñez-Vergara, J.A. Squella, C. Olea-Azar, Arab. J. Chem. **11**, 525 (2017)
127. K. Ostrowska, D. Grzeszczuk, D. Maciejewska, I. Mlynarczuk-Bialy, A. Czajkowska, A. Sztokfisz, L. Dobrzycki, H. Kruszewska, Monatsh. Chem. **147**, 1615 (2016)
128. K. Ostrowska, K. Miodzikowska, M. Giuch-Lutwin, A. Grybos, A. Siwek, Eur. J. Med. Chem. **137**, 108 (2017)
129. H.-L. Yang, P. Cai, Q.-H. Liu, X.-L. Yang, F. Li, J. Wang, J.-J. Wu, X.-B. Wang, L.-Y. Kong, Eur. J. Med. Chem. **138**, 715 (2017)
130. W. Wei, X.-W. Wu, G.-G. Deng, X.-W. Yang, Phytochemistry **123**, 58 (2016)
131. S.-Y. Zhang, D.-J. Fu, H.-H. Sun, X.-X. Yue, Y.-C. Liu, Y.-B. Zhang, H.-M. Liu, Chem. Heterocycl. Compd. **52**, 374 (2016)
132. M.-J. Bu, G.-P. Lu, C. Cai, Catal. Commun. **114**, 70 (2018)
133. K.N. Chethan Prathap, N.K. Lokanath, J. Mol. Struct. **1158**, 26 (2018)
134. N. Lin, Y. Li, X. Hao, K. Jin, R. Zhang, C. Duan, J. Fluorine Chem. **214**, 42 (2018)
135. Q. Li, Y. Hu, H.-N. Hou, W.-N. Yang, S.-L. Hu, Inorg. Chim. Acta **471**, 705 (2018)
136. H. Ren, M. Zhang, A.Q. Zhang, Tetrahedron **74**, 4435 (2018)
137. H.T. Srinivasa, H.N. Harishkumar, B.S. Palakshamurthy, J. Mol. Struct. **1131**, 97 (2017)
138. F.A. Vargas-Soto, C.L. Cespedes-Acuna, P.M. Aqueveque-Munoz, J.E. Alarcon-Enos, Food Chem. Toxicol. **109**, 1118 (2017)
139. P. Govindaiah, N. Dumala, I. Mattan, P. Grover, M.J. Prakash, Bioorg. Chem. **91**, 103143 (2019)
140. K.V. Basavarajappa, Y. Arthoba Nayaka, H.T. Purushothama, R.O. Yathisha, M.M. Vinay, B.J. Rudresha, K.B. Manjunatha, J. Mol. Struct. **1199**, 126946 (2020)
141. D. Tao, Y. Wang, X.-Q. Bao, B.-B. Yang, F. Gao, L. Wang, D. Zhang, L. Li, Eur. J. Med. Chem. **173**, 203 (2019)
142. H.M. Tanuraghaj, M. Farahi, Tetrahedron Lett. **60**, 557 (2019)
143. S.D. Durgapal, R. Soni, S.S. Soman, A.K. Prajapati, J. Mol. Liq. **297**, 111920 (2020)
144. M. Zarei, M.A. Zolfigol, A.R. Moosavi-Zare, E. Noroozizadeh, J. Iran. Chem. Soc. **14**, 2187 (2017)
145. A.R. Moosavi-Zare, M.A. Zolfigol, E. Noroozizadeh, A. Zare, M. Zarei, Can. J. Chem. **95**, 16 (2017)
146. S. Baghery, M.A. Zolfigol, R. Schirhagl, M. Hasani, Catal. Lett. **147**, 2083 (2017)
147. E. Noroozizadeh, A.R. Moosavi Zare, M.A. Zolfigol, M. Zarei, R. Karamian, M. Asadbegy, S. Yari, S.H. Moazzami, J. Iran. Chem. Soc. **15**, 471 (2018)
148. Y. Yamaguchi, N. Nishizono, D. Kobayashi, T. Yoshimura, K. Wada, K. Oda, Bioorg. Med. Chem. Lett. **27**, 2645 (2017)
149. S. Chen, W. Liu, Z. Ge, W. Zhang, K. Wang, Z. Hu, Spectrochim. Acta A **193**, 141 (2018)
150. M.G. Choi, Y.J. Lee, I.J. Chang, H. Ryu, S. Yoon, S.-K. Chang, Sens. Actuators B Chem. **268**, 22 (2018)
151. K.-P. Wang, Y. Lei, J.-P. Chen, Z.-H. Ge, W. Liu, Q. Zhang, S. Chen, Z.-Q. Hu, Dyes Pigments **151**, 233 (2018)
152. H. Zhang, Q. Luo, Y. Mao, Y. Zhao, T. Yu, J. Photochem. Photobiol. A Chem. **346**, 10 (2017)
153. M. Alomari, M. Taha, S. Imran, W. Jamil, M. Selvaraj, N. Uddin, F. Rahim, Bioorg. Chem. **92**, 103235 (2019)
154. M.A. Omar, M.A. Hammad, M. Awad, Spectrochim. Acta A **204**, 702 (2018)
155. U. Salar, A. Nizamani, F. Arshad, K. Mohammed Khan, M. Imran Fakhri, S. Perveen, N. Ahmed, M. Iqbal Choudhary, Bioorg. Chem. **91**, 103170 (2019)
156. Y. Tang, Y. Huang, Y. Chen, L. Lu, C. Wang, T. Sun, M. Wang, G. Zhu, Y. Yang, L. Zhang, J. Zhu, Spectrochim. Acta A **218**, 359 (2019)
157. R. Khajuria, S. Mahajan, A. Kapoor, K.K. Kapoor, J. Chem. Sci. **129**, 1549 (2017)
158. C. Krishna, M.V. Bhargavi, Y.J. Rao, G.L.D. Krupadanam, Russ. J. Gen. Chem. **87**, 1857 (2017)
159. L. Hongshuang, W. Xiaming, Z. Ruize, H. Liqiang, D. Guiyun, X. Yuliang, X. Chengcai, L. Furong, Y. Guirong, H. Junfen, Chem. Res. Chin. Univ. **33**, 187 (2017)
160. J. Sun, M. Zheng, J. Jia, W. Wang, Y. Cui, J. Gao, Dyes Pigments **164**, 287 (2019)

161. G.S. Lingaraju, K.S. Balaji, S. Jayarama, S.M. Anil, K.R. Kiran, M.P. Sadashiva, Bioorg. Med. Chem. Lett. **28**, 3606 (2018)
162. Y. Selim, M. El-Ahwany, Chem. Heterocycl. Compd. **53**, 867 (2017)
163. V.P. Jalli, S. Krishnamurthy, T. Moriguchi, A. Tsuge, J. Chem. Sci. **128**, 217 (2016)
164. Y. Li, H. Lan, S. Xiao, Res. Chem. Intermed. **44**, 6489 (2018)
165. X. Chu, Z. Tang, J. Ma, L. Ha, L. Feng, C. Ma, Tetrahedron **74**, 970 (2018)
166. T.A. Fattah, A. Saeed, Y.M. Al-Hiari, V. Kasabri, I.M. Almasri, S. AlAlawi, F.A. Larik, P.A. Channar, J. Mol. Struct. **1179**, 390 (2019)
167. M. He, Z. Yan, W. Wang, F.Z.S. Lin, Tetrahedron Lett. **59**, 3706 (2018)
168. I. Yahaya, M. Chemchem, B. Aydıner, N. Seferoglu, F. Erva Tepe, L. Aclk, N. Aytuna Cerci, M. Turk, Z. Seferoglu, J. Photochem. Photobiol. A Chem. **368**, 296 (2019)
169. I. Yahaya, N. Seferoglu, Z. Seferoglu, Tetrahedron **75**, 2143 (2019)
170. S. Jiang, Y. Chen, Y. Li, L. Han, J. Photochem. Photobiol. A Chem. **384**, 112031 (2019)
171. A. Dhar, N. Siva Kumar, P. Kumar Paul, S. Roy, R.L. Vekariya, Org. Electron. **53**, 280 (2018)
172. M.M. Makhlouf, H.M. Zeyada, Synth. Met. **211**, 1 (2016)
173. F. Ylldırım, A. Demircall, F. Karcl, A. Bayrakdar, P.T. Tasll, H.H. Kart, J. Mol. Liq. **223**, 557 (2016)
174. E. Madiahlagan, B.N. Sunil, Z. Ngaini, G. Hegde, J. Mol. Liq. **292**, 111328 (2019)
175. V. Sharma, E.K. Arora, S. Cardoza, Chem. Pap. **70**, 1493 (2016)
176. M. Gardelly, B. Trimech, M.A. Belkacem, M. Harbach, S. Abdelwahed, A. Mosbah, J. Bouajila, H.B. Jannet, Bioorg. Med. Chem. Lett. **26**, 2450 (2016)
177. M.O. Karatas, B. Olgundeniz, S. Gunal, I. Ozdemir, B. Allcl, E. Çetinkaya, Bioorg. Med. Chem. **24**, 643 (2016)
178. L. Zhang, Y. Xia, M. Li, D. Li, R. Hou, Tetrahedron **72**, 7438 (2016)
179. C.T. Prabhakara, S.A. Patil, S.S. Toragalmath, S.M. Kinnal, P.S. Badami, J. Photochem. Photobiol. **157**, 1 (2016)
180. G. Achar, K. Uppendranath, V.C. Ramya, A. Biffis, R.S. Keri, S. Budagumpi, Polyhedron **123**, 470 (2017)
181. E. Elgazzar, A. Dere, F. Ozen, K. Koran, A.G. Al-Sehemi, A.A. Al-Ghamdi, A. Orhan Gorgulu, F. El-Tantawy, F. Yakuphanoglu, Phys. B **515**, 8 (2017)
182. A. Skoczynska, M. Małecka, M. Cieslak, J. Kazmierczak-Baranska, K. Krolewska-Golinska, A. Leniart, E. Budzisz, Polyhedron **127**, 307 (2017)
183. G. He, J. Li, Z. Wang, C. Liu, X. Liu, L. Ji, C. Xie, Q. Wang, Tetrahedron **72**, 272 (2017)
184. A.I. Uraev, V.G. Vlasenko, A.S. Burlov, N.I. Makarova, K.A. Lyssenko, D.A. Garnovskii, Mendeleev Commun. **28**, 205 (2018)
185. W. Lu, F. Huang, H. Hua, J. Chen, S. Qiu, F. Zhao, J. Shi, L. Xu, S. Yang, X. Chi, J. Mol. Struct. **1192**, 115 (2019)
186. C. Salgado, M.P. Arrieta, L. Peponi, D. Lopez, M. Fernandez-Garcia, Prog. Org. Coat. **123**, 63 (2018)
187. O.S. Can, A. Kus, E.N. Kaya, M. Durmus, M. Bulut, Inorg. Chim. Acta **465**, 31 (2017)
188. P.S.V.B. de Almeida, T.M. Pereira, A.E. Kummerle, G.P. Guedes, H. Silva, L.L. de Oliveira, A.P. Neves, Polyhedron **171**, 20 (2019)
189. G. He, X. Hua, N. Yang, L. Li, J. Xu, L. Yang, Q. Wang, L. Ji, Bioorg. Chem. **91**, 10317 (2019)
190. H. Li, X. Sun, T. Zheng, Z. Xu, Y. Song, X. Gu, Sens. Actuators B Chem. **279**, 400 (2019)
191. J.-N. Wei, Z.-D. Jia, Y.-Q. Zhou, P.-H. Chen, B. Li, N. Zhang, X.-Q. Hao, Y. Xu, B. Zhang, J. Organomet. Chem. **902**, 120968 (2019)
192. M. Tudose, D.C. Culita, M. Voicescu, A.M. Musuc, A.C. Kuncser, C. Bleotu, M. Popa, L. Marutescu, M.C. Chifiriuc, A. Nicolescu, C. Deleanu, Microporous Mesoporous Mater. **288**, 109583 (2019)
193. Q.-P. Qin, Z.-F. Wang, X.-L. Huang, M.-X. Tan, B.-Q. Zou, H. Liang, Eur. J. Med. Chem. **184**, 111751 (2019)
194. W. Yi, S. Guanglei, T. Qi, Z. Baozhen, W. Ensi, Chem. Res. Chin. Univ. **32**, 357 (2016)
195. A. Kurt, O.K. Topsoy, Russ. J. Appl. Chem. **90**, 2019 (2017)
196. M.A. Wani, P.K. Singh, R. Pandey, M.D. Pandey, J. Lumin. **171**, 159 (2016)
197. R.H. Vekariya, K.D. Patel, D.P. Rajani, S.D. Rajani, H.D. Patel, J. Assoc. Arab Univ. Basic Appl. Sci. **23**, 10 (2017)
198. D.S. Reddy, M. Kongot, S.P. Netalkar, M.M. Kurjogi, R. Kumar, F. Avecilla, A. Kumar, Eur. J. Med. Chem. **150**, 864 (2018)
199. S.-S. Xie, J.-S. Lan, X. Wang, Z.-M. Wang, N. Jiang, F. Li, J.-J. Wu, J. Wang, L.-Y. Kong, Bioorg. Med. Chem. **24**, 1528 (2016)
200. B. Wei, J. Zhou, J.-J. Xu, J. Cui, F.-F. Ping, J.-J. Ling, Y.-J. Chen, Eur. J. Med. Chem. **184**, 111779 (2019)
201. D. Vashisht, K. Kaur, R. Jukaria, A. Vashisht, S. Sharma, S.K. Mehta, Sens. Actuators B Chem. **280**, 219 (2019)
202. S.N. Mangasuli, K.M. Hosamani, P.B. Managutti, J. Mol. Struct. **1195**, 58 (2019)
203. L. Jin, X. Tan, L. Dai, C. Zhao, W. Wang, Q. Wang, Talanta **202**, 190 (2019)
204. Q. He, J. Liu, J.-S. Lan, J. Ding, Y. Sun, Y. Fang, N. Jiang, Z. Yang, L. Sun, Y. Jin, S.-S. Xie, Bioorg. Chem. **81**, 512 (2018)
205. S. Koparde, K.M. Hosamani, V. Kulkarni, S.D. Joshi, Chem. Data Coll. **16**, 197 (2018)
206. P. Qu, X. Ma, W. Chen, D. Zhu, H. Bai, X. Wei, C. Shu, M. Xu, Spectrochim. Acta A **210**, 381 (2019)
207. J.-H. Zhu, K.M.-C. Wong, Sens. Actuators B Chem. **267**, 208 (2018)