REVIEW ARTICLE

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3-Acyl(aroyl)coumarins as synthon in heterocyclic synthesis

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Abstract: This review presents a systematic and comprehensive survey of the chemical reactivity of 3-acyl(aroyl) coumarins. The target compounds are important intermediates for the synthesis of a variety of synthetically useful and novel heterocyclic systems with different ring sizes such as isoxazole, pyrazole, 3*H*-triazolium salts, pyrimidine, pyridine, quinolone, benzoxocin, benzoxonin and benzoxepin.

Keywords: Coumarins; pyrazoles; thiazole; pyridine; heterocyclic; reduction.

1. Introduction

Coumarins (**II**) are the simple compounds (**I-V**) belonging to a large class of molecules known as benzopyrones.[1] Furthermore, coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry.[1]

They are widely used as additives in food, perfumes, cosmetics,[2] pharmaceuticals, optical brighteners[3] (e.g. 7-diethylamino-4-methylcoumarin),[4] dispersed fluorescent laser dyes,[5] antithrombotic and anticoagulants[6] (e.g. acenocoumarol),[4] and in treatment of bronchial asthma (e.g. intal)[4] and cancer.[7] Also, coumarin derivatives are novel lipid-lowering agents, possessing moderate triglyceride lowering activity.[8] Many coumarin derivatives can scavenge reactive oxygen species such as hydroxyl free radicals, superoxide radicals or hypochlorous acid to prevent free radical injury.[9] While certain coumarin derivatives function as human immunodeficiency virus integrase inhibitors and are used in treatment of

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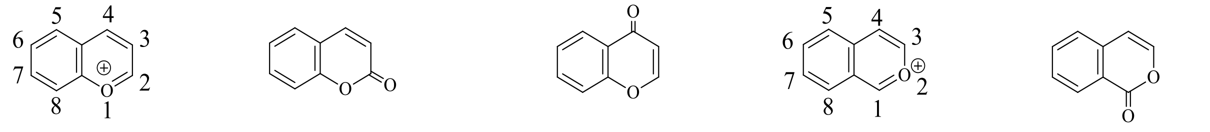
HIV infection,[10] the others are used as anti-invasive compounds against some serine proteases and matrix metalloproteases (MMPs).[11] Moreover, 6-nitro-7-hydroxycoumarin acts as a selective anti-proliferative agent.[12, 13] Two naturally occurring coumarins have been isolated and shown to inhibit the polymerization of tubulin and arrest cells in mitotic phase by inhibiting microtubule formation.[14] These coumarins act synergistically in inhibiting KB (human epidermoid carcinoma) cell proliferation.[14]



Chromylium **I** or (benzo[b]pyrylium) or 1-benzopyrylium

Coumarin **II** or 2H-1-benzopyran-2-one

Chromone **III** or 4H-1-benzopyran-4-one

Isochromylium **IV** or benzo[c]pyrylium or 2-benzopyrylium

Isocoumarin **V** or 1H-2-benzopyran-1-one

Figure 1. Skeleton of benzopyrones **I-V**

Coumarin derivatives usually occur as secondary metabolites in seeds, roots and leaves of many plant species *via* shikimate pathway. Their function includes waste products, plant growth regulators, fungistats and bacteriostats.[15] Anthocyanins[16] and flavones,[17] grouped together, are known as flavonoids,[18] and make up many flower pigments. Also, flavone and coumarin[19] derivatives have marked toxic and other physiological properties in animals, though they have no part in normal metabolism of animals. The isomeric 2-banzopyrylium[20] system is not naturally occurring; only a few isocoumarin derivatives[21] occurs as natural products and, therefore, much less work on these has been described.

Our review deals with the effective use of 3-acyl(aroyl)coumarin derivatives **1** in the synthesis of different polyfunctional heterocyclic compounds.

2. Reactivity

3-Acyl(aroyl)coumarins are difunctional compounds possessing electrophilic and nucleophilic properties. Typical nucleophilic position is C_{10}. Furthermore, C_9 of C=O and C_4 could act as an electrophile. These chemical properties have been used to design different heterocyclic moieties with different ring sizes such as oxazole, pyrazole, thiophene, thiazole, pyridine, diazepine, benzoxocin, benzoxonin, benzoxepin and pyrimidine (Figure 2).

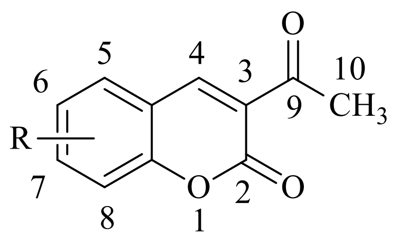
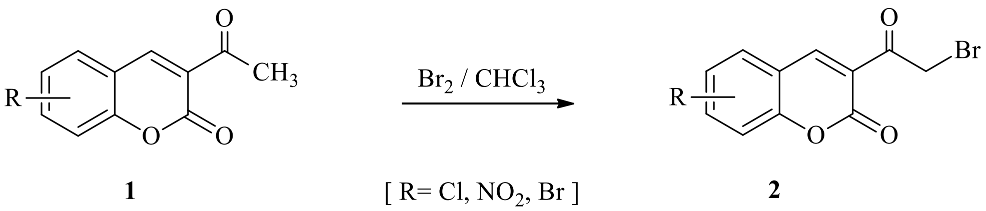


Figure 2. Reactivity of 3-acyl(aroyl)coumarins.

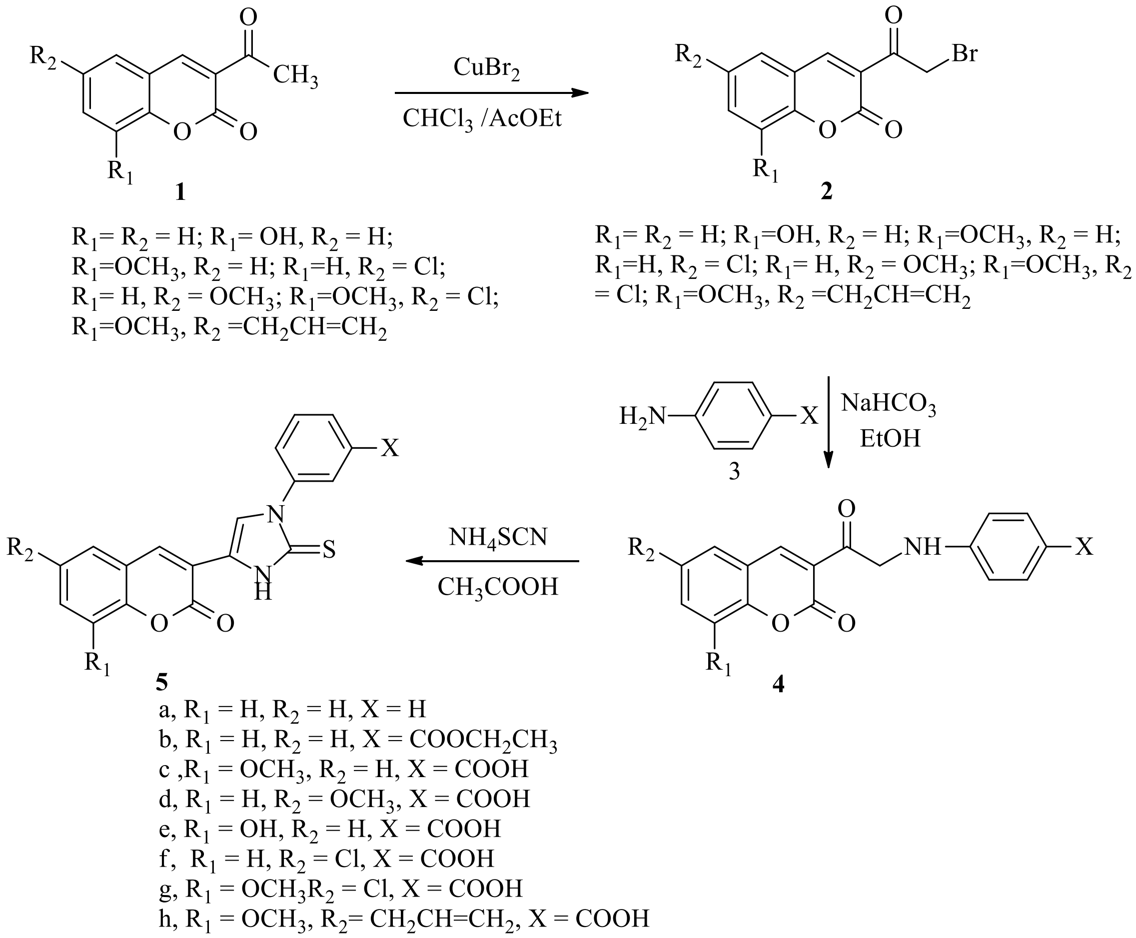
2.1. Bromination

Halogenation of **1** with bromine in chloroform afforded 3-bromoacetyl coumarin derivatives **2** (Scheme 1).[22, 23]



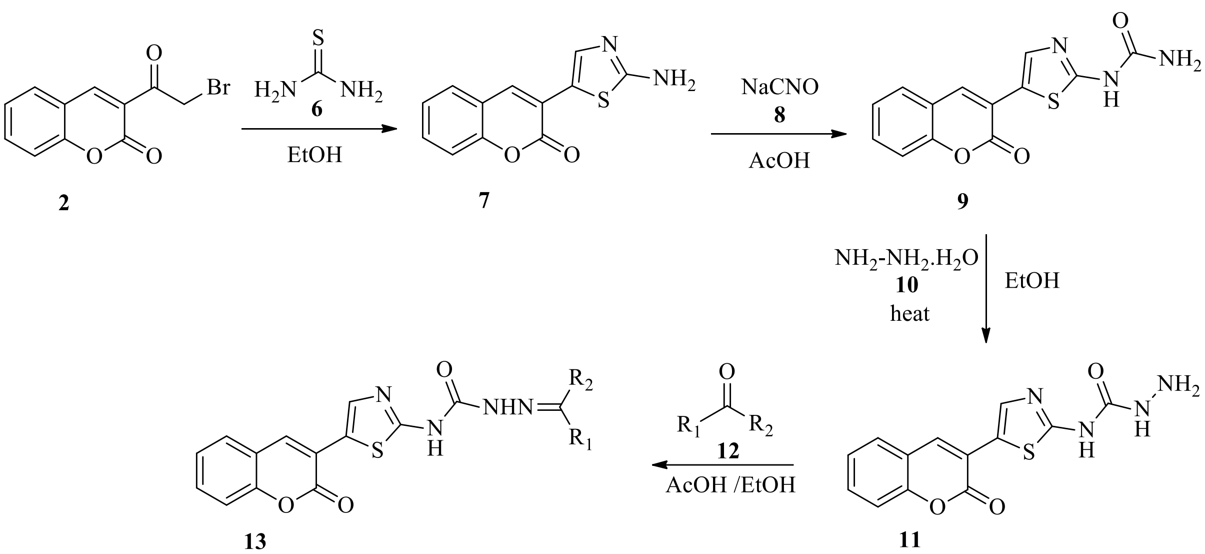
Scheme 1. Synthesis of 3-bromoacetylcoumarin derivatives **2**

Separately, La Pietra et. al prepared 3-bromoacetylcoumarin derivatives **2** *via* treating compound **1** with $CuBr_2$ in $CHCl_3$ / CH_3COOEt mixture. The reaction of 3-bromoacetylcoumarin derivatives **2** with the appropriate arylamine **3** (aniline, 3-aminobenzoic acid, ethyl 3-aminobenzoate) in ethanol in the presence of $NaHCO_3$ yielded compounds **4**. Derivatives **5a-h** were then obtained by treatment of compounds **4** with a large excess of ammonium thiocyanate in acetic acid (Scheme 2).[24,25]



Scheme 2. Synthesis of imidazoline derivatives **5**

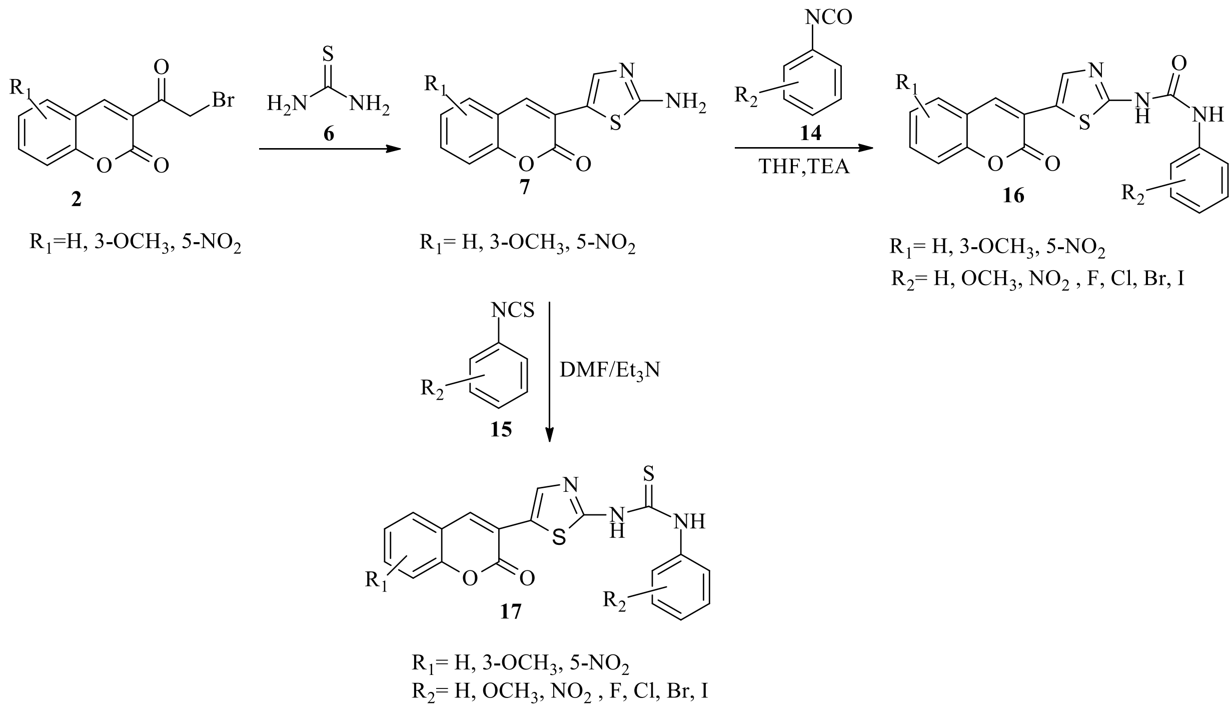
Kurt, B. Z. *et al.*,[26] carried out the reaction of 3-(bromoacetyl)-2*H*-chromen-2-one **2** in the presence of ethanol with thiourea **6**, which yielded 3-(2-amino-1,3-thiazol-4-yl)-2*H*-chromen-2-one **7**. This was reacted with sodium cyanate **8** in the presence of glacial acetic acid to produce *N*-[4-(2-oxo-2*H*chromen-3-yl)-1,3-thiazol-2-yl]urea **9**. Treatment of compound **9** with hydrazine hydrate **10** produced *N*-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]hydrazinecarboxamide **11,** which was condensed with different aromatic/ heteroaromatic aldehydes and ketones **12** to form (*1E*)-1-arylalkane-1-one-*N*-[4-(2-oxo-2*H*-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazones **13a-w** (Scheme 3).[26]



13a; R_1= C_6H_5, R_2= CH_3, **13b**; R_1= 4-Cl-C_6H_4, R_2= CH_3, **13c**; R_1=2,4-diClC_6H_3, R_2= CH_3, **13d**; R_1= 3,4-diClC_6H_3, R_2= CH_3, **13e**; R_1=2-OHC_6H_4, R_2= CH_3, **13f**; R_1=3-OHC_6H_4, R_2= CH_3, **13g**; R_1= 4-OHC_6H_4, R_2= CH_3, **13h**; R_1=2,4-diOHC_6H_3, R_2= CH_3, **13i**; R_1= 2-O$CH_3C_6H_4$, R_2= CH_3, **13j**; R_1= 3-O$CH_3C_6H_4$, R_2= CH_3, **13k**; R_1= 4-O$CH_3C_6H_4$, R_2= CH_3, **13l**; R_1= 2,4-diO$CH_3C_6H_3$, R_2= CH_3, **13m**; R_1= 3,4-diO$CH_3C_6H_3$, R_2= CH_3, **13n**; R_1= 4-BrC_6H_4,R_2= CH_3, **13o**; R_1= 2-$NO_2C_6H_4$, R_2= CH_3, **13p**; R_1=3-$NO_2C_6H_4$, R_2= CH_3,**13q**; R_1=4-$NO_2C_6H_4$, R_2= CH_3, **13r**; R_1=C_6H_5, R_2= H, **13s**; R_1=3-Cl-C_6H_4, R_2= H, **13t**; R_1=3-Cl-C_6H_4, R_2= H,**13u**; R_1=4-Cl-C_6H_4, R_2= H, **13v**; R_1= 4-N$(CH_3)_2C_6H_4$,R_2= H, **13w**; R_1=2-furyl, R_2= H.

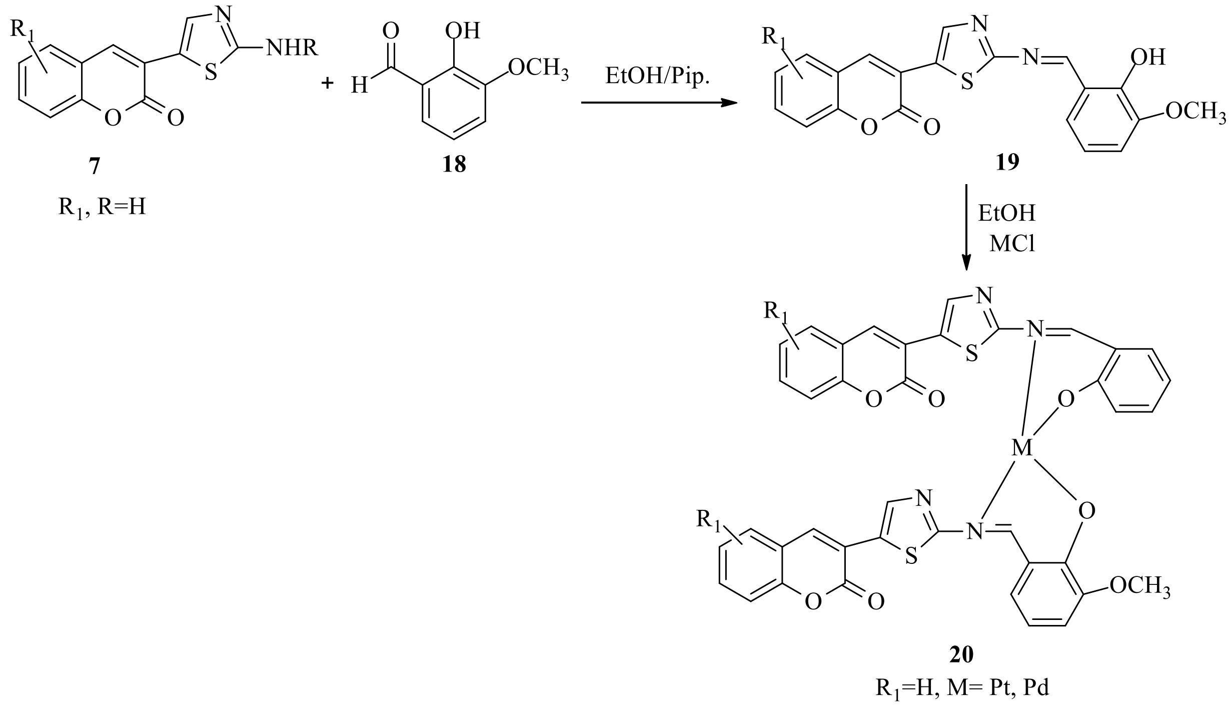
Scheme 3. Synthesis of (*1E*)-1-arylalkane-1-one-*N*-[4-(2-oxo-2*H*-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazones **13a-w**.

A series of coumarylthiazole derivatives containing arylurea/thiourea groups **17** and **18**, respectively, were obtained by the reactions of **2** with thiourea **6**, which was followed by treatment of the formed aminothiazole **7** with arylisocyanates **14** in THF and arylisothiocyanates **15** in DMF, respectively (Scheme 4).[27]



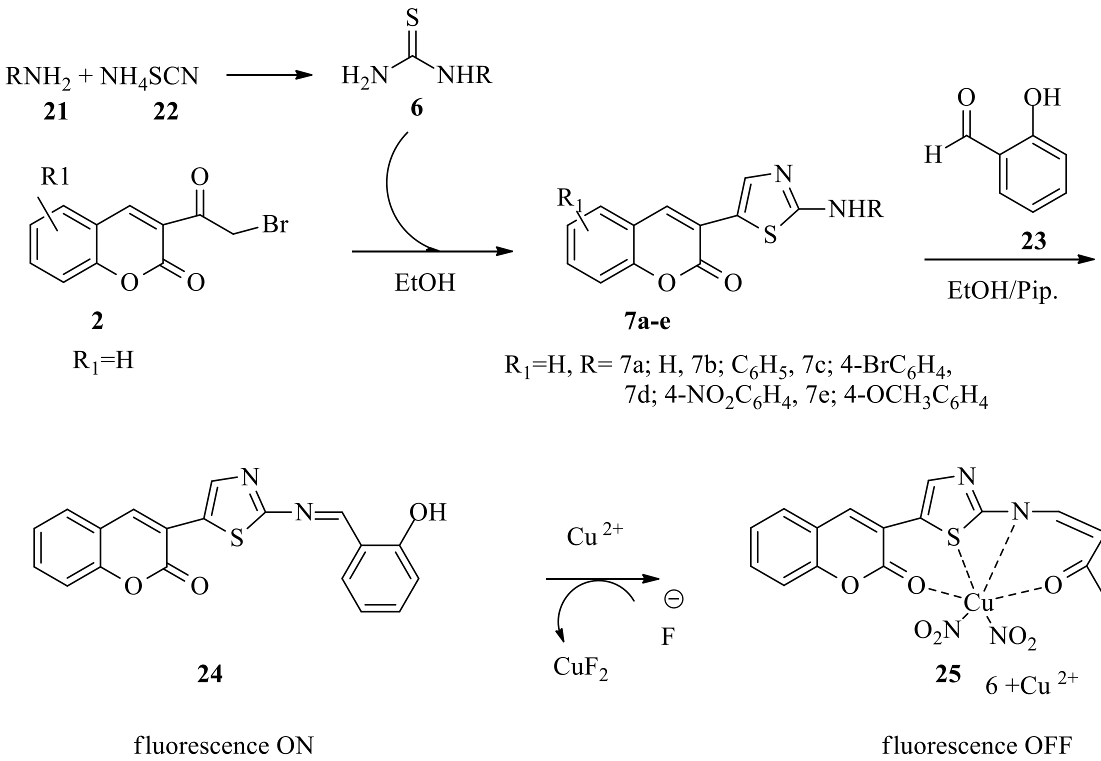
Scheme 4. Synthesis of new urea/thiourea substituted coumarylthiazole derivatives

Razi, et. al. prepared several thiazolylamine derivatives **19** by treating of compound **7** with the corresponding 2-hydroxy-3-methoxybenzaldehyde **18** in a basic ethanol solution. The Pd(II) and Pt(II) complexes **20** were synthesized by complexation of thiazolylamine derivatives **19** with Pd(II) and Pt(II), respectively (Scheme 5).[28]



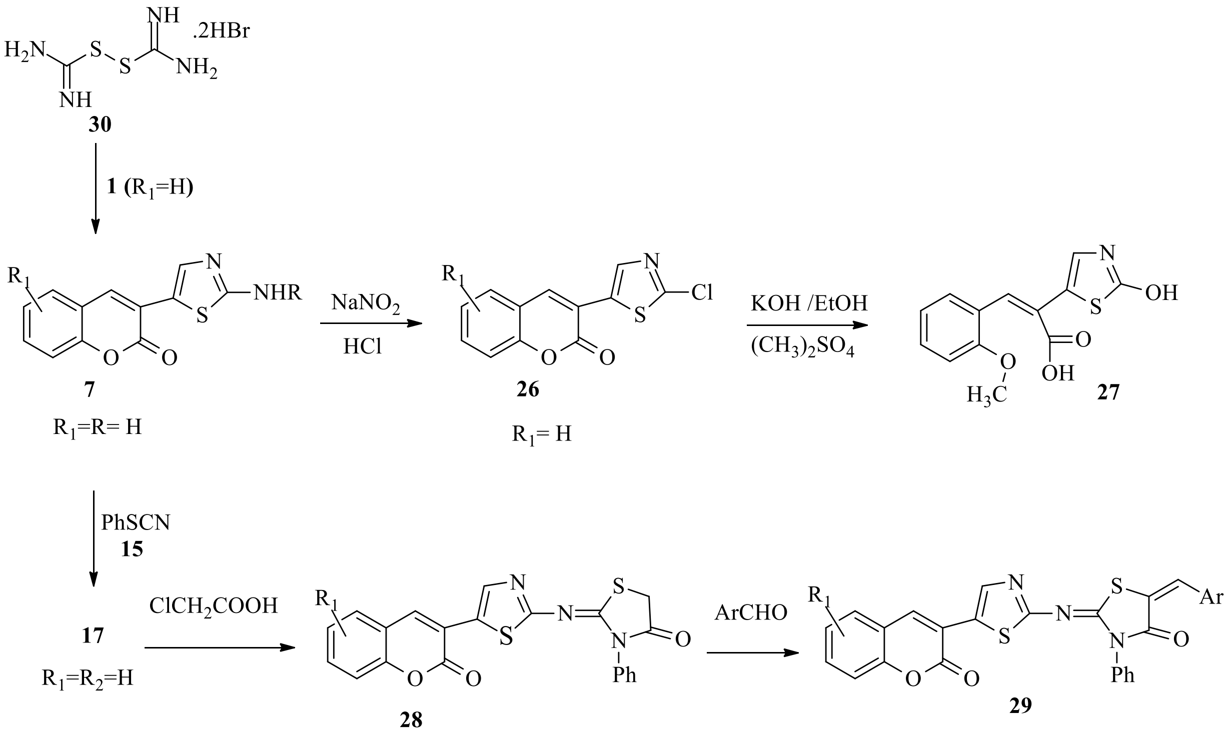
Scheme 5. Synthesis of Pd(II) and Pt(II) complexes **20**

Sahu, S. K. et al prepared a series from thiourea derivatives **6a–d** *via* the reaction of aniline derivatives **21** with ammonium thiocynate **22** under acidic condition. They were further reacted with compound **2** to obtain the aminothiazolylcoumarins **7a–e**. Reacting the derivatives **7a** with salicyl aldehyde gave the probe **24**, which showed good optical behavior in acetonitrile and, upon interaction with different metal ions and anions, displayed strong fluorescence quenching (~87%; switch-off) with Cu^{2+}. Moreover, **24**-Cu^{2+}(**25**), when tested toward different anions, only fluoride (F^-) gave copper displacement (as CuF_2) and demonstrated a fluorescence enhancement (switched-on) (Scheme 6).[29]



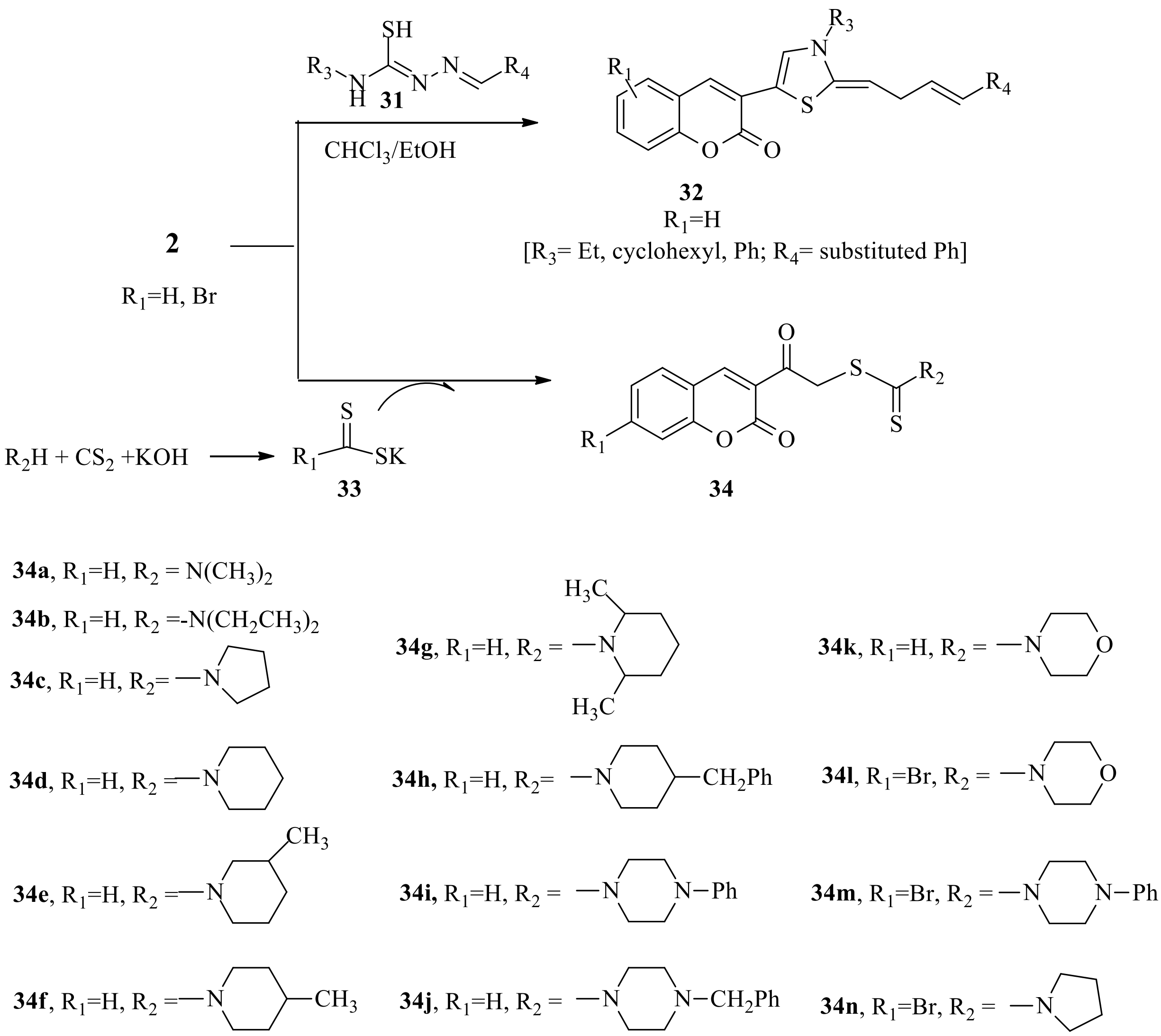
Scheme 6. Synthesis of probe **24**

Diazotization of aminothiazole **7** gave the 2-chloro derivative **26**, which was undergone alkaline hydrolysis in the presence of dimethyl sulfate to give the corresponding (*E*)-2-(2-chlorothiazol-5-yl)-3-(2-methoxyphenyl)acrylic acid **27**. Also, aminothiazole **7** was reacted with phenylisothiocyanate**15** to afford the unsymmetrical thiourea 1-(5-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)-3-phenylthiourea **17**, which was cyclized with chloroacetic acid to give (Z)-2-(5-(2-oxo-2*H*-chromen-3-yl)thiazol-2-ylimino)3-phenyl thiazolidin-4-one **28**. The reaction of **28** with different aromatic aldehydes gave the corresponding arylidene derivatives **29**.[30] Furthermore, aminothiazole **7** was obtained *via* condensation of 3-acetylcoumarin **1** with formamidine disulfide dihydrobromide **30** (Scheme 7).[31]



Scheme 7. Synthesis of arylidene derivatives **29**

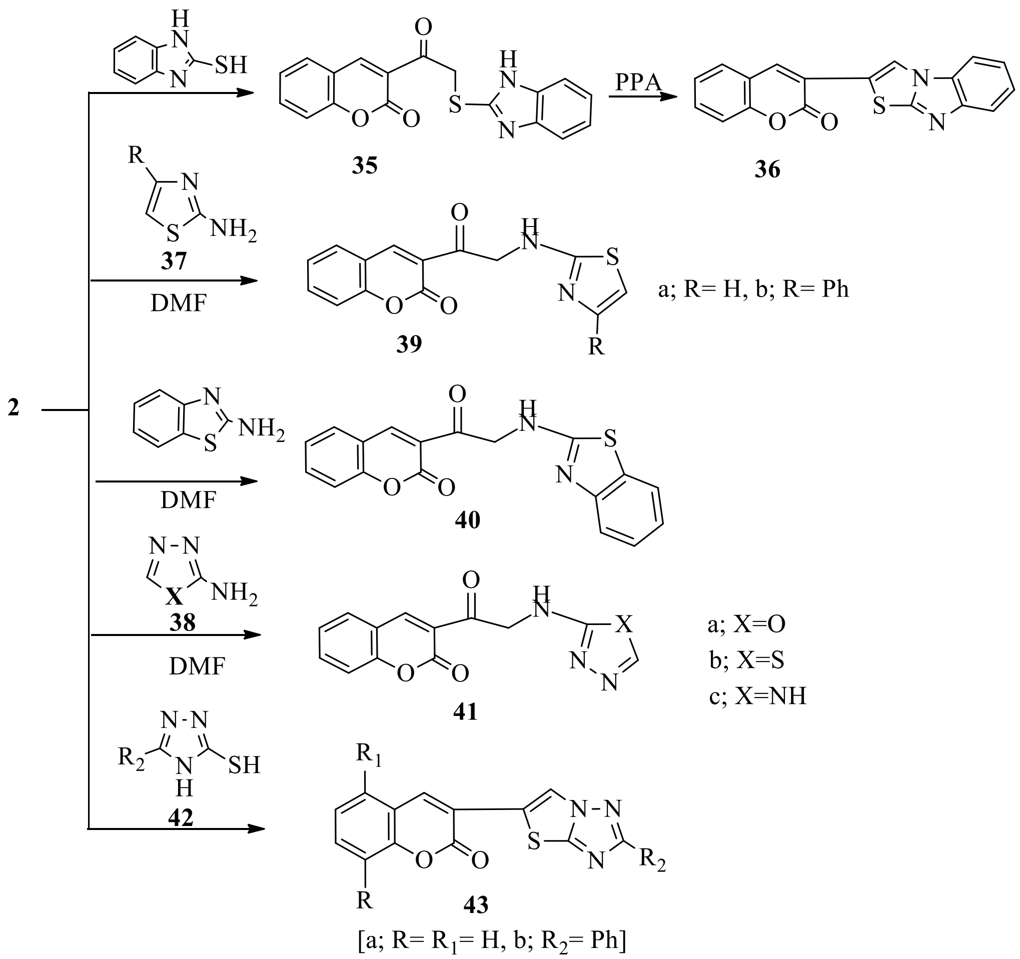
Cyclocondensation of 3-bromoacetylcoumarin **2** with R_3NHC (SH): NN: CHR_4 **31** in $CHCl_3$-EtOH gave the thiazolone derivatives **32** in 64-100% yield.[32] Furthermore, the reaction of 3-(α-bromoacetyl)coumarins **2** (R_1=H or Br) with potassium salts of dithiocarbamic acids **33** in ethanol afforded 3-[(*N*,*N*-disubstitutedthiocarbamoilthio)acetyl]coumarin derivatives **34a-n** (Scheme 8).[33]



Scheme 8. Synthesis of 3-[(*N*,*N*-disubstitutedthiocarbamoilthio)acetyl]coumarin derivatives **34a-n**

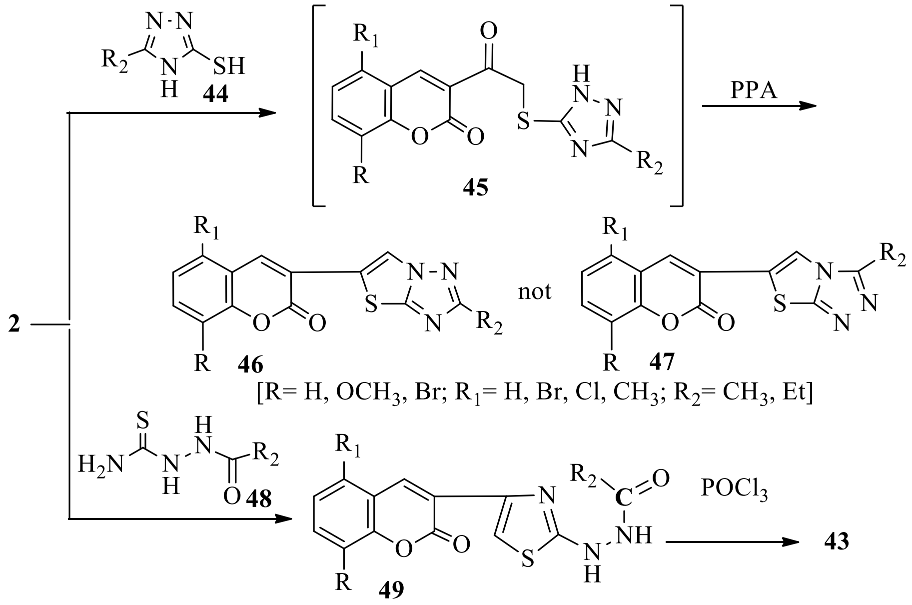
3-Bromoacetylcoumarin **2** was reacted with 2-mercaptobenzimidazole to give the corresponding 3-(2-1*H*-benzo[d]imidazol-2-ylthio)acetyl)-2*H*-chromen-2-one **35**, which was subjected to cyclization in polyphosphoric acid to give 3-(benzo[*d*]thiazolo[3,2-*a*]imidazol-2-yl)-2*H*-chromen-2-one **36**[34](Scheme 9).

Moreover, 3-bromoacetylcoumarin **2** was condensed with 2-aminothiazole **37a**, 2-amino-4-phenylthiazole **37b**, 2-aminobenzothiazole, 2-amino-1,3,4-thiadiazole **38a**, 3-amino-4*H*-1,2,4-triazole **38b** and 2-amino-1,3,4-oxadiazole **38c** in DMF to give the corresponding 2*H*-chromen-2-ones **39-41**, respectively.[29] On the other hand, the reaction of 3-bromoacetylcoumarin **2** with 3-substituted-5-mercapto-5-triazole **42a,b** gave 3-(2-phenylthiazolo[3,2-b](1,2,4)triazol-5-yl)-2H-chromen-2-one **43a,b** (Scheme 9).[34]



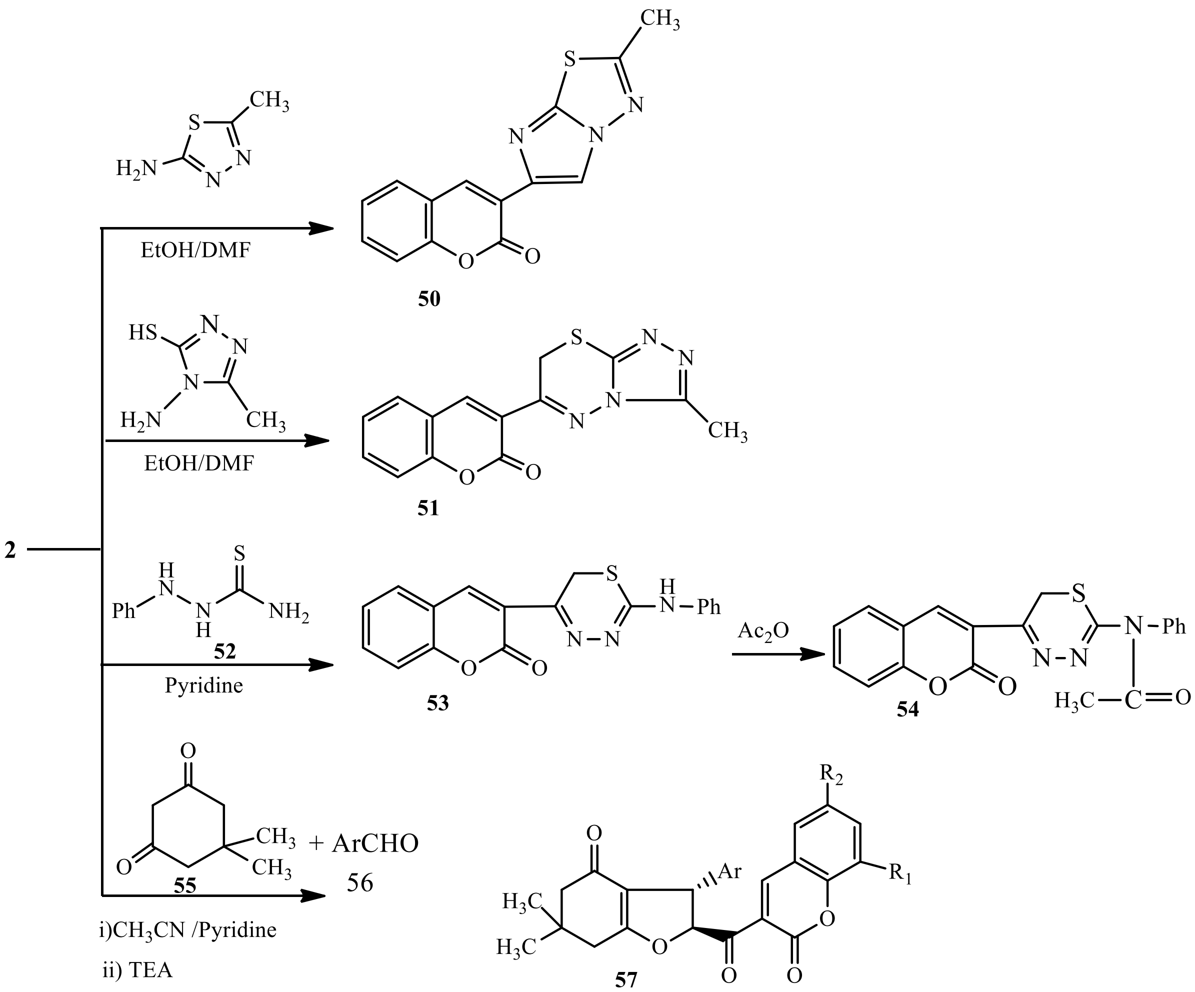
Scheme 9. Synthesis of thiazole derivatives **36, 39-41** and **43**

Rajeswar Rao, V. et. al. prepared a new series from 3-(2-alkylthiazolo[3,2-b][1,2,4] triazol-5-yl)-2*H*-chromen-2-one **46** by treating 3-bromoacetylcoumarin **2** (R= H, OCH_3, Br, R_2= H, Br, Cl, CH_3) with 3-alkyl-mercaptotriazole **44** in polyphosphoric acid. Also, the reaction of **2** (R= H, OCH_3, Br, R_2= H, Br, Cl, CH_3) with acetyl/propanoylthiosemicarbazide **48** gave 2-acetyl or propanoylhydrazinethiazolyl-coumarins **49**, which, on treatment with phosphoryl trichloride, afforded **43** (Scheme 10).[35]



Scheme 10. Synthesis of 2-acetyl or propanoyl hydrazinethiazolylcoumarins **49**

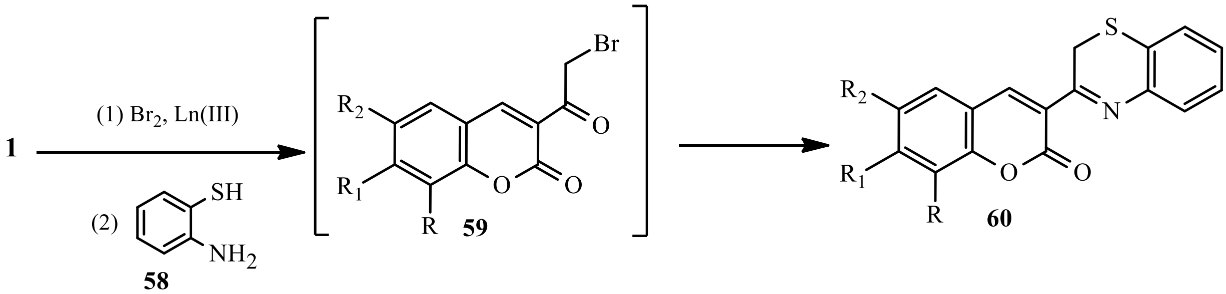
Cyclocondensation of 3-bromoacetylcoumarin **2** with 2-amino-5-methyl-1,3,4-thiadiazole gave 3-(2-methylimidazo[2,1-b](1,3,4) thiadiazol-6-yl)-2*H*-chromen-2-one **50**,[36] while its reaction with 1-amino-2-mercapto-5-methyl-1,3,4-triazole produced 3-(3-methyl-3,7-dihydro-2*H*-[1,2,4] triazolo[3,4-b][1,3,4]thiad-iazin-6-yl)-2*H*-chromen-2-one **51**[36] (Scheme 11). Moreover, bromoacetylcoumarin **2** was reacted with phenylthiosemicarbazide **52** in the presence of pyridine to give 3-(2-phenylamino)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-one **53** (Scheme 11).[37] The exocyclic N in compound **53** was acetylated by acetic anhydride to obtain the corresponding *N*-(5-(2-oxo-2*H*-chromen-3-yl)-6*H*-1,3,4-thiadiazin-2-yl)-*N*-phenylacetamide **54**. Furthermore, one-pot condensation of bromoacetylcoumarin **2**, pyridine, dimedone **55**, aromatic aldehydes **56** and triethylamine afforded the benzofuran derivatives **57** (Scheme 11).[38]



57a; R_1=R_2= H, Ar = Ph, **57b**; R_1=R_2= H, A r= 4-$CH_3C_6H_4$, **57c**; R_1=R_2= H, Ar = 4-$OCH_3C_6H_4$, **57d**; R_1=R_2= H, Ar = 3,4-di$CH_3C_6H_3$, **57e**; R_1=R_2=H, Ar= 4-N(CH_3)2C_6H_4, **57f**; R_1=R_2= 5,6-benzo, Ar= Ph, **57g**; R_1=R_2= 5,6-benzo, Ar= 4-$OCH_3C_6H_4$, **57h**; R_1=R_2= Br, Ar= 4-$CH_3C_6H_4$, **57i**; R_1=R_2= Br, Ar = 4-ClC_6H_4, **57j**; R_1=R_2= Br, Ar= 4-$CH_3C_6H_4$, **57k**; R_1=R_2=Br, Ar= Ph.

Scheme 11. Synthesis of imidazole **50,** 1,3,4-thiadiazine **51**, **54** and benzofurans **57**

Multiple component reactions of 3-acetylcoumarin derivatives **1** with bromine in the presence of Ln(III) catalyst and *o*-aminothiophenol **58** gave 3-(2*H*-1,4-benzothiazin-3-yl)-2*H*-1-benzopyran-2-ones **60** (Scheme 12).[39]

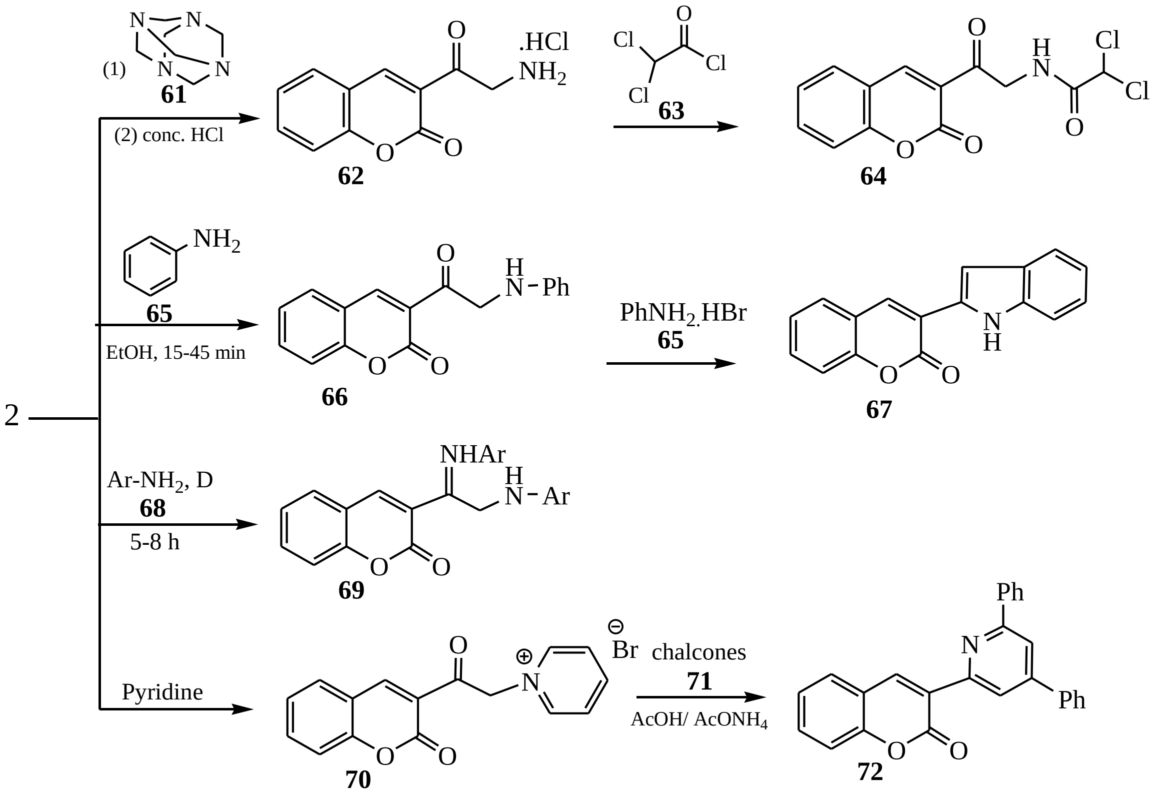


[R= H, OCH_3, Br, Cl; R= H, Br, Cl, NO_2; R_2= H, OH, CH_3]

Scheme 12. Synthesis of 1,3,4-thiadiazine **60**

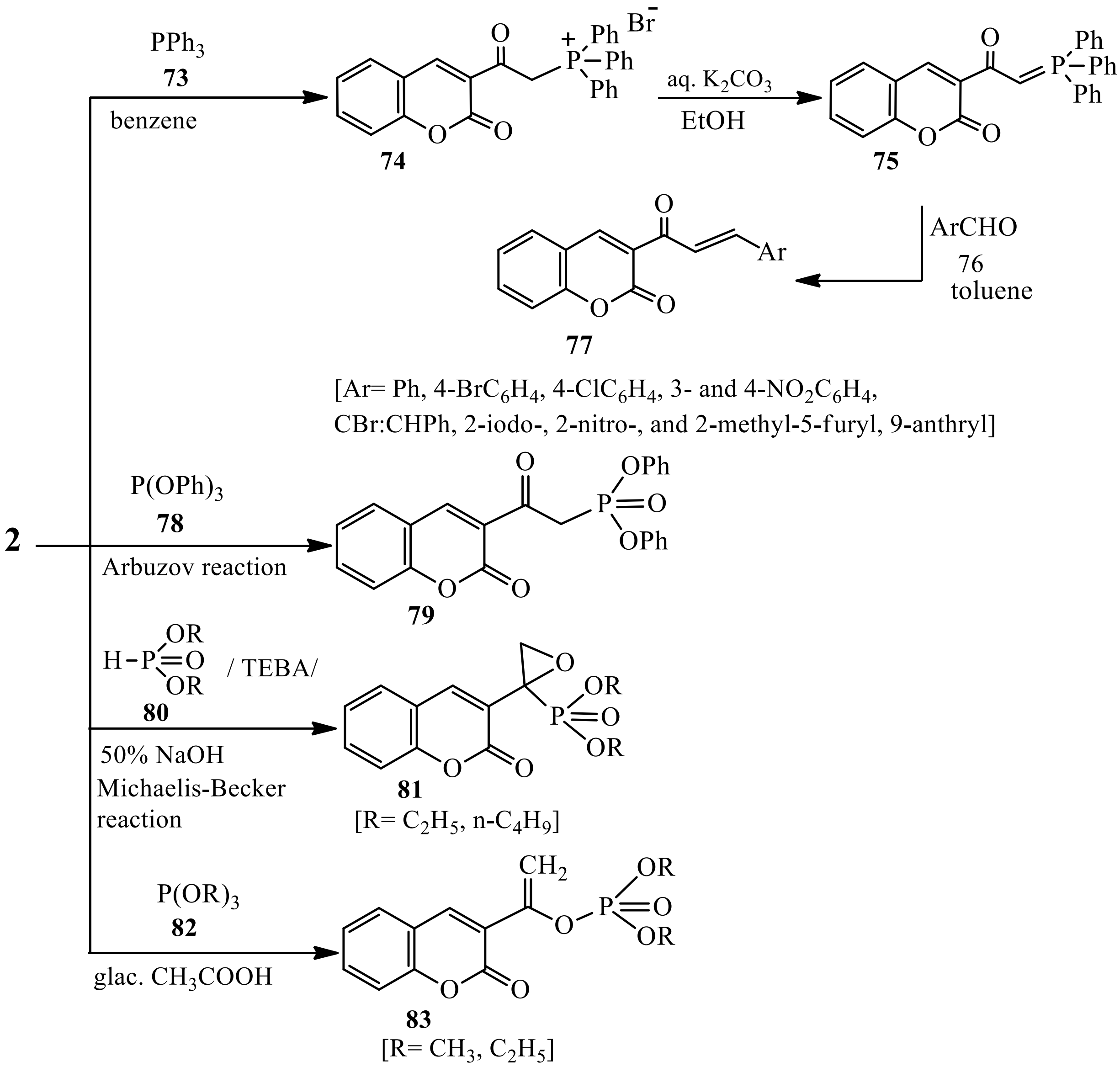
Sinnur, K. H. et al., developed a short and efficient synthesis for dichloroacetamidomethyl-3-coumarinylketone **64**. 3-Bromoacetylcoumarin **2** was reacted with hexamethylenetetramine **61** in concentrated alcoholic hydrochloric acid to produce the corresponding aminomethyl-3-coumarinyl ketone hydrochloride **62**. Treatment of **62** with dichloroacetyl chloride **63** gave the corresponding dichloroacetamidomethyl-3-coumarinyl ketone **64** (Scheme 13).[40]

3-Bromoacetylcoumarin **2**, following Bischler's procedure, was reacted with primary aromatic amines, i.e. aniline **65** in ethanol for 15-45 minutes to yield 3-(2-(phenylamino)acetyl)-2*H*-chromen-2-one **66**[30], which was condensed with the respective primary aromatic amine in the presence of catalytic amounts of the amine hydrobromide to give 3-(1*H*-indol-3-yl)-2*H*-chromen-2-one **67** (Scheme 13).[30] On the other hand, refluxing **2** with primary aromatic amines **68** for 5-8 hours gave the corresponding imino derivatives **69** (scheme 13). In a separate study, 3-bromoacetylcoumarin **2** was treated with pyridine to give the quaternary salt **70**, which, upon condensation with chalcone **71** in the presence of acetic acid and ammonium acetate, gave the corresponding 3-(4,6-diphenylpyridin-2-yl)-2*H*-chromen-2-one **72** (Scheme 13).[41]



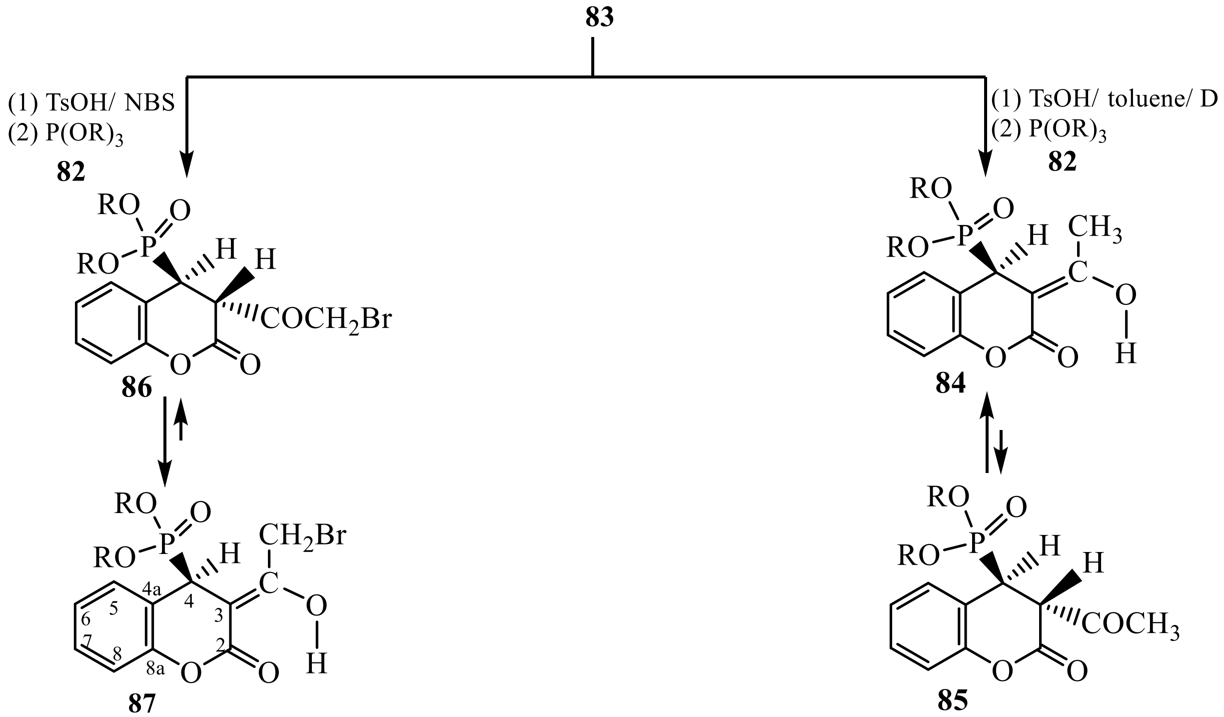
Scheme 13. Reaction of **3**-bromoacetylcoumarin **2** with amines

3-Bromoacetylcoumarin **2** was reacted with triphenylphosphine **73** in benzene to give (2-oxo-2-(oxo-2H-chromen-3-yl)ethyl)triphenylphosphonium **74** in 97.3%, which was treated with aq. K_2CO_3 in ethanol to obtain **75**. When it was reacted with various aromatic aldehydes **76** in toluene yielded only the *trans* isomer **77**. Moreover, **2** was transformed to 2-oxophosphonates **79** *via* Arbuzov reaction conditions (Scheme 14).[42-44] Also, 3-bromoacetylcoumarin transformation into the epoxyphosphonate derivatives **81** proceeded *via* Michaelis-Becker reaction conditions (Scheme 14),[45-47] Furthermore, 3-bromoacetylcoumarin was reacted with trialkylphosphites **82** in acetic acid to give enolphosphate **83** (Scheme 14).



Scheme 14. Reaction of **3**-bromoacetylcoumarin **2** with triphenylphosphine

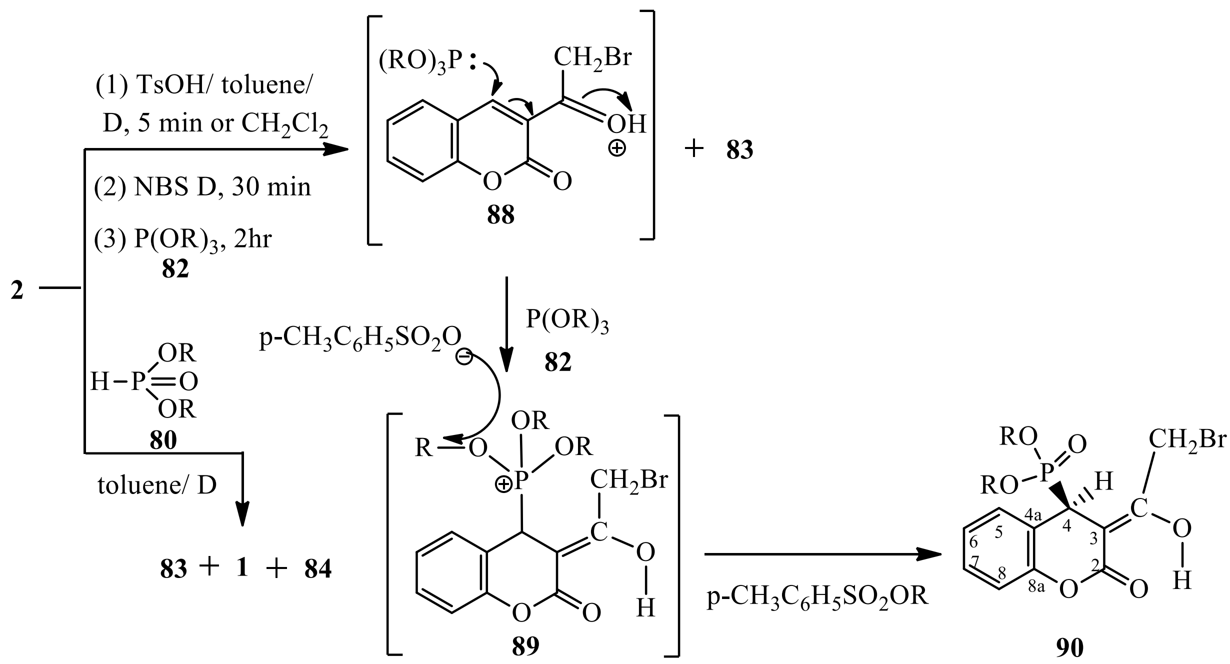
Enolphosphate **83** was reacted with trialkylphosphites **82** in refluxing toluene in the presence of *p*-toluenesulfonic acid (TsOH) to give the 1,4-adducts **84**/ **85**. Separately, **83** was obtained in 40-80% yield through the reaction of 3-acetylcoumarin **1** with dialkyl- and trialkylphosphites upon refluxing for 8-10 h. (Scheme 15).[48-51] Also, when enol phosphate **83** was reacted with trialkylphosphites **82** in the presence of *p*-toluenesulfonic acid and NBS, it gave the corresponding **86**/ **87** (Scheme 15).[52]



Scheme 15. Reaction of enolphosphate **83** with trialkyl phosphites **82**

The reaction of **2** with P(OR)3 in refluxing toluene in the presence of *p*-toluene sulfonic acid-was completely different to that of acetic acid,[52] giving new 1,4-addition products **90** along with the expected enol phosphates **83**.[52]

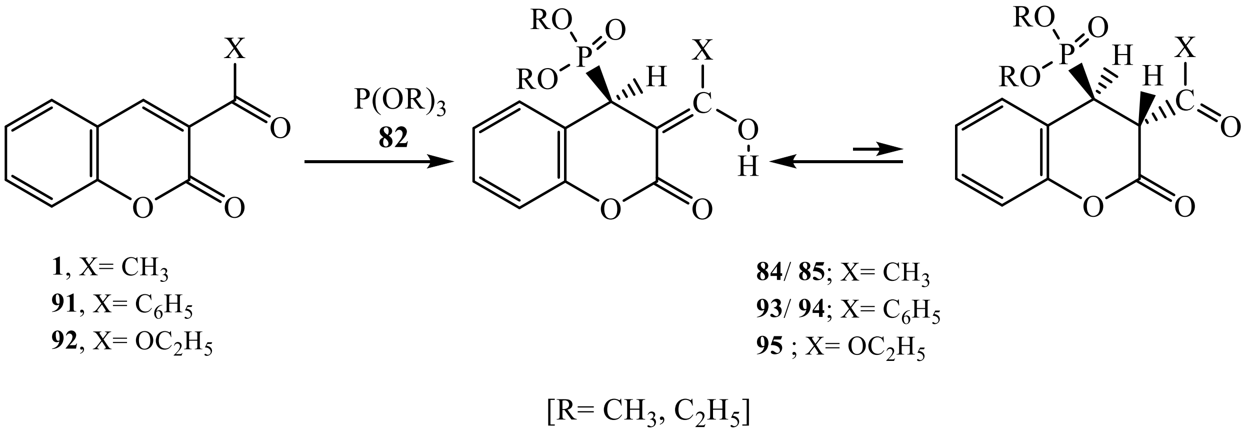
Furthermore, when 3-bromoacetylcoumarin **2** was reacted with dialkylphosphites in refluxing toluene, a complicated reaction mixture was obtained, i.e. 3-acetylcoumarin **1** (2-5 %), enol phosphates **83** (~ 20%) and **84**, which are the products of 1,4-additions of dialkylphosphites to 3-acetylcoumarin **1**. Compound **90** formed *via* the following mechanism (Scheme 16).[52]



Scheme 16. Synthesis of 4-dialkylphosphono-2-oxocoumarin derivatives **90**

2.2. Reactions of trialkylphosphites

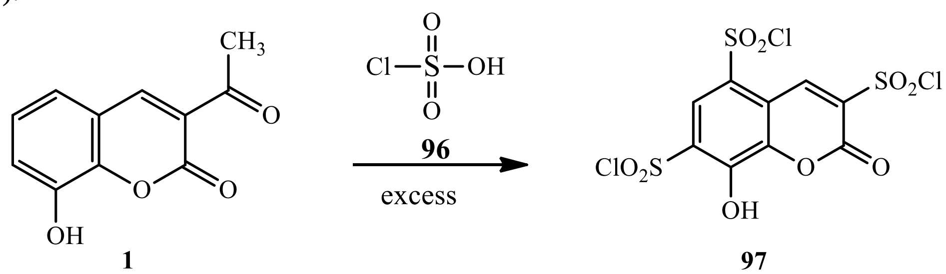
Reactions of trialkylphosphites **82** with 3-acetylcoumarin **1** as well as with 3-benzoylcoumarin **91** and 3-ethoxycarbonylcoumarin **92**, in the presence of *p*-toluenesulfonic acid under ultrasound irradiation gave the corresponding 4-dialkylphosphono-2-oxocoumarin derivatives **84/ 85**, **93/ 94** and **95**, respectively, in 60 to 95% yields (Scheme 17).[53]



Scheme 17. Synthesis of 4-dialkylphosphono-2-oxocoumarin derivatives **84**, **85**, **93**, **94** and **95**

2.3. Chlorosulfonation

3-Acetyl-8-methoxycoumarin **1** was subjected to chlorosulfonation reaction using excess chlorosulfonic acid **96** to give the corresponding 8-hydroxy-2-oxo-2*H*-chromen-3,5,7-trisulfonamide **97** (Scheme 18).[54]

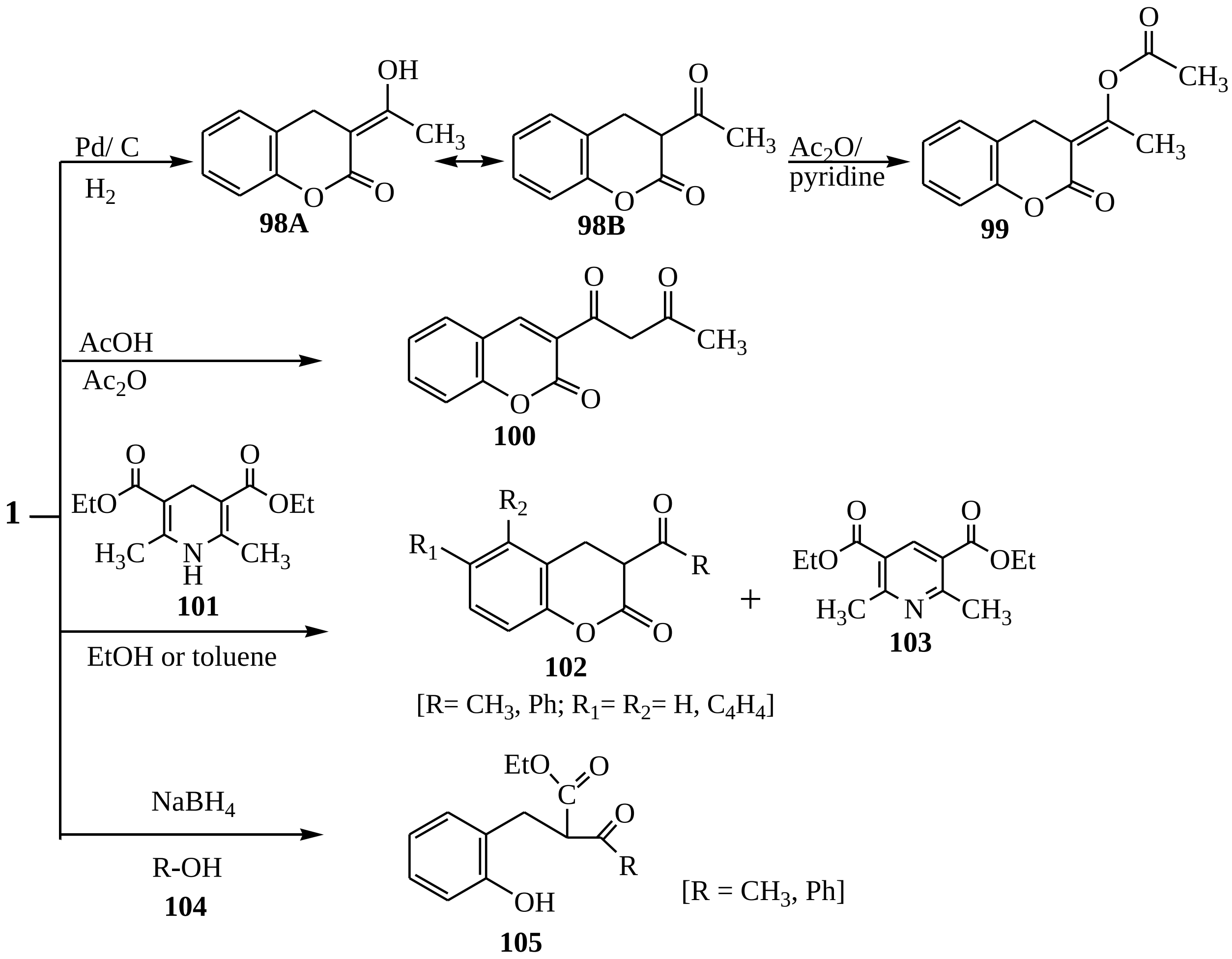


Scheme 18. Synthesis of 8-hydroxy-2-oxo-2*H*-chromen-3,5,7-trisulfonamide **97**

2.4. Reduction

3-Acetylcoumarin **1** was agitated with palladium-charcoal and hydrogen at 60 Ibs./ sq. at room temperature to give an excellent yield of 3-acetyl-3,4-dihydrocoumarin as a keto-enol mixture **98**. The keto form was isolated giving a negative ferric reaction, while the enol form was obtained as a sole product *via* acetylation of the mixture **98** to give the acetate **99**. Acetylation of 3-acetylcoumarin **1** with acetic acid and acetic anhydride produced the corresponding 3-acetylcoumarin derivative **100** (Scheme 19).[55]

Liu et al. reported the selective reduction of endocyclic double bond of the 3-substituted coumarin derivatives **1** by using Hantzsch 1,4-dihydropyridine (HEH) **101** as a reducing agent, which yielded 3,4-dihydrocoumarin derivatives **102** (Scheme 19).[56] Chemo-selective reduction of the endocyclic double bond in 3-substituted coumarin derivatives **1** took place by *o*-phenylenediamine and benzaldehyde to generate in situ 2-phenyl benzimidazoline.[57] Reduction of 3-acetyl and 3-benzoyl coumarin derivatives **1** occurred with sodium borohydride in alcohol to give the corresponding ethyl-2-(2-hydroxy benzyl)-3-oxo(butanoate) and 3-phenyl propanoate **105** (Scheme 19).[58]

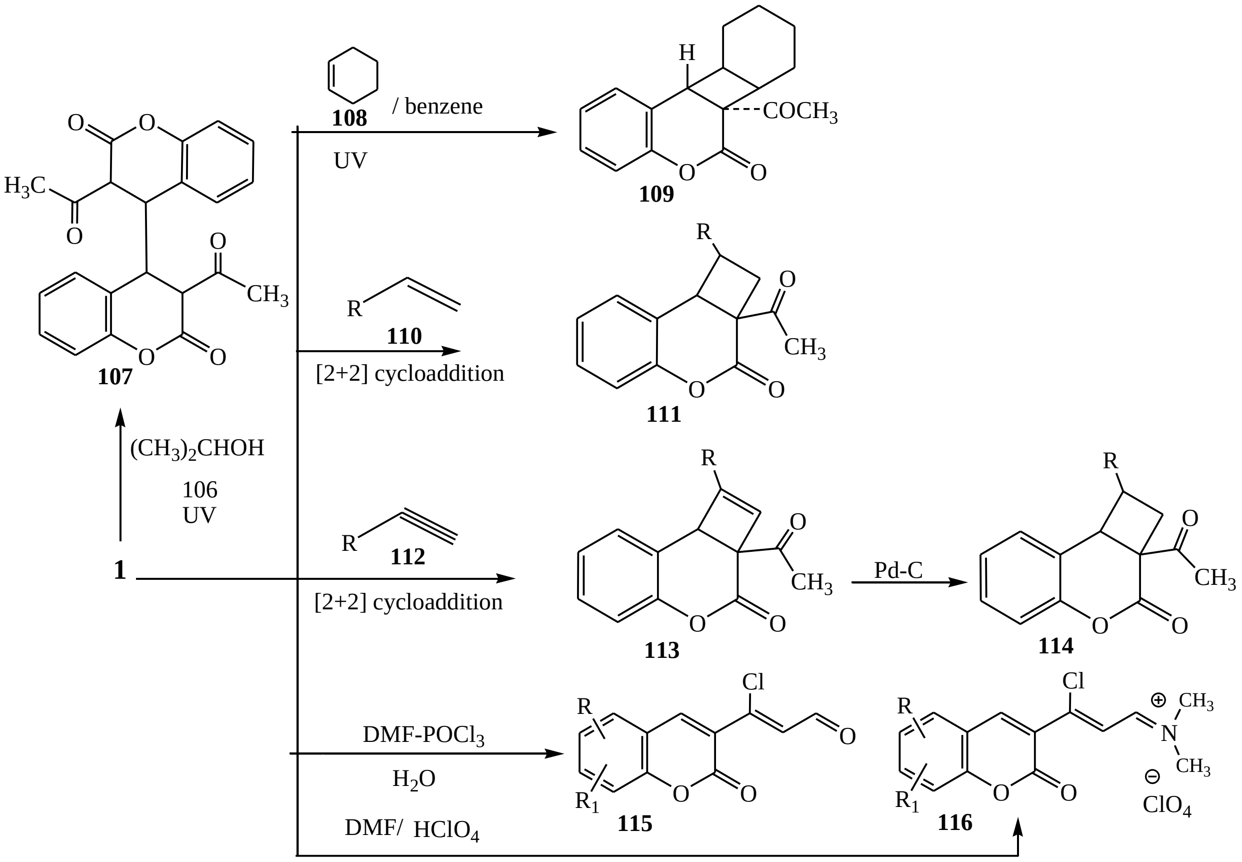


Scheme 19. Reduction of 3-acetylcoumarin derivatives **1**

2.5. Photoreduction

Photo reduction of 3-acetylcoumarin **1** in *i*-propyl alcohol **106** gave the dihydro dimer 3,3'-diacetyl-4,4'-bichroman-2,2'-dione **107**. Cyclobutanes **109** were formed by [2+2] cycloaddition of cyclohexene **108** with 3-acetylcoumarin **1** upon UV irradiation in benzene (Scheme 20).[59] Furthermore, photo [2+2] cycloaddition of olefins **110** with 3-acetylcoumarin **1** gave 1-exo-substituted 1,2,2a,8b-tetrahydro-3*H*-benzo[b]cyclobuta[d]pyran-3-one derivatives **111**. Endo-substituted 1,2,2a,8b-tetrahydro-3*H*-benzo[b]cyclobuta[d]pyran-3-one derivatives **114** were prepared by photo [2+2] cycloaddition of 3-acetylcoumarin **1** with acetylenes **112**, which was followed by hydrogenation of the formed 2a,8b-dihydro-3*H*-benzo[b]cyclobuta[d]pyran-3-one derivatives **113** over Pd-C (Scheme 20).[60]

Treatment of 3-acetylcoumarin **1** with dimethylformamide in the presence of phosphorus oxychloride or $HClO_4$ yielded chloropropeniminium salts **115** and aldehydes **116**, respectively (Scheme 20).[61]

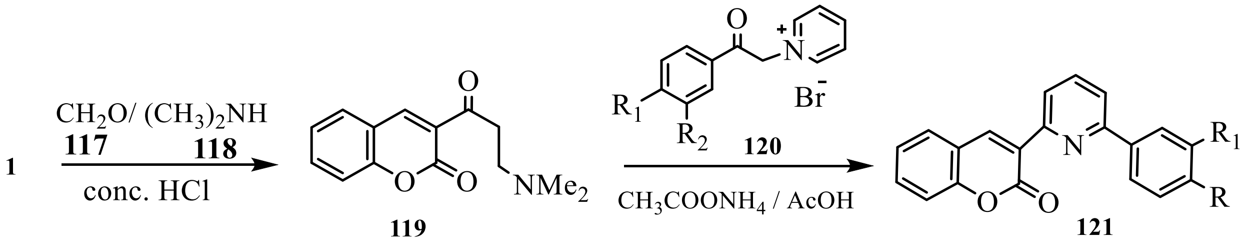


[R= H, 6-Br, 7-OH, 7-OMe, 7-NMe_2, 7-Pyrrolidione, 8-OMe, 7-NEt_2;
R_1= 5,6-CH=CHCH=CH, 7,8-CH=CHCH=CH;

Scheme 20. Photo and Vilsmier reaction of 3-acetylcoumarin derivatives **1**

2.6. Mannich reaction

Mannich base **119** of 3-acetylcoumarin **1** was prepared *via* condensation of the corresponding acetylcoumarin **1** with paraformaldehyde **117** and dimethylamine **118** in the presence of conc. HCl (Scheme 21)[62]. The reaction of **119** with substituted phenacylpyridiniumbromide salts **120** in the presence of ammonium acetate in refluxing acetic acid gave the corresponding 3-(6-arylpyridin-2-yl) **121** in moderate to good yields (scheme 21).[62]

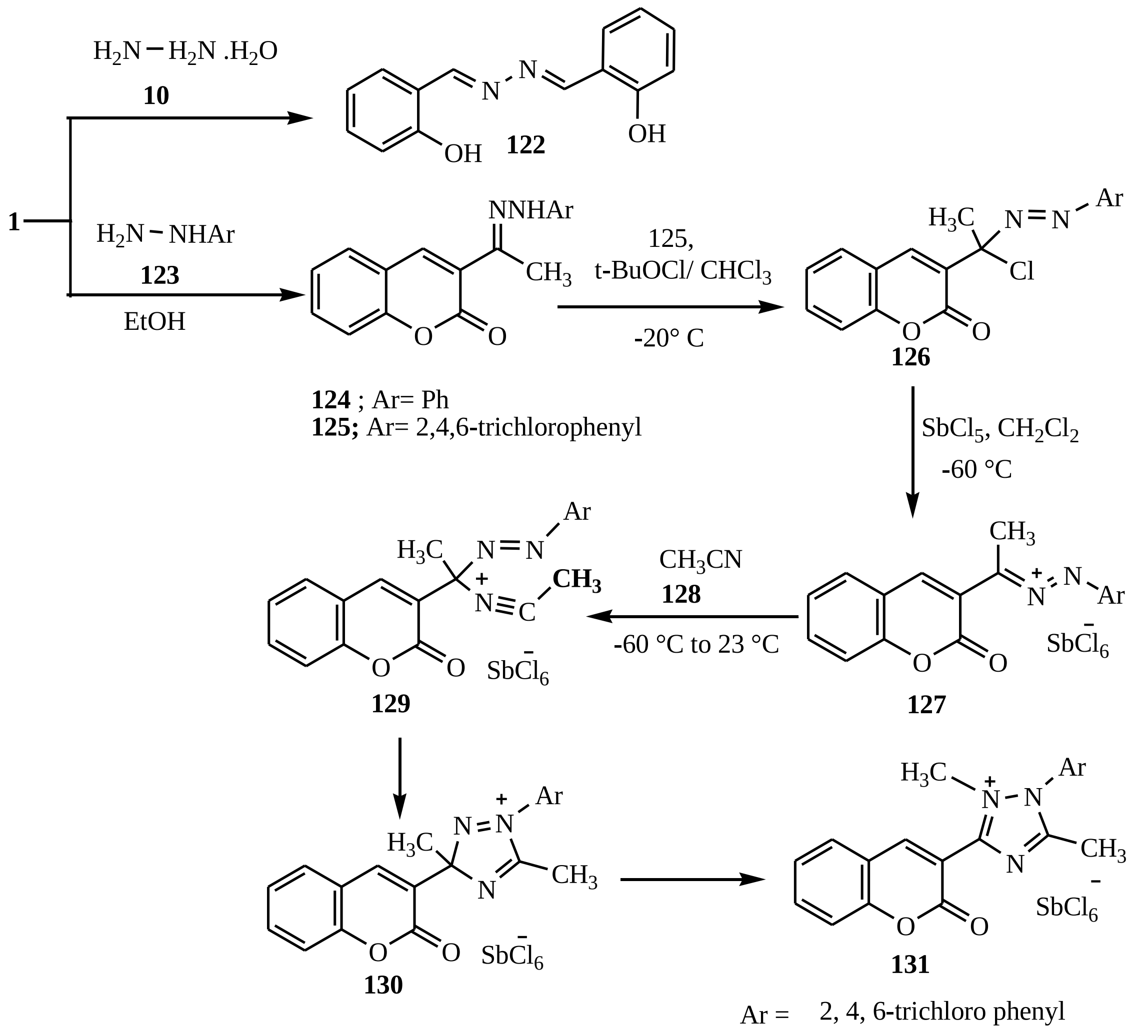


[R= H, CH_3, OCH_3, Cl, Br;
R_1= H, CH_3]

Scheme 21. Mannich reaction of 3-acetylcoumarin derivatives **1**

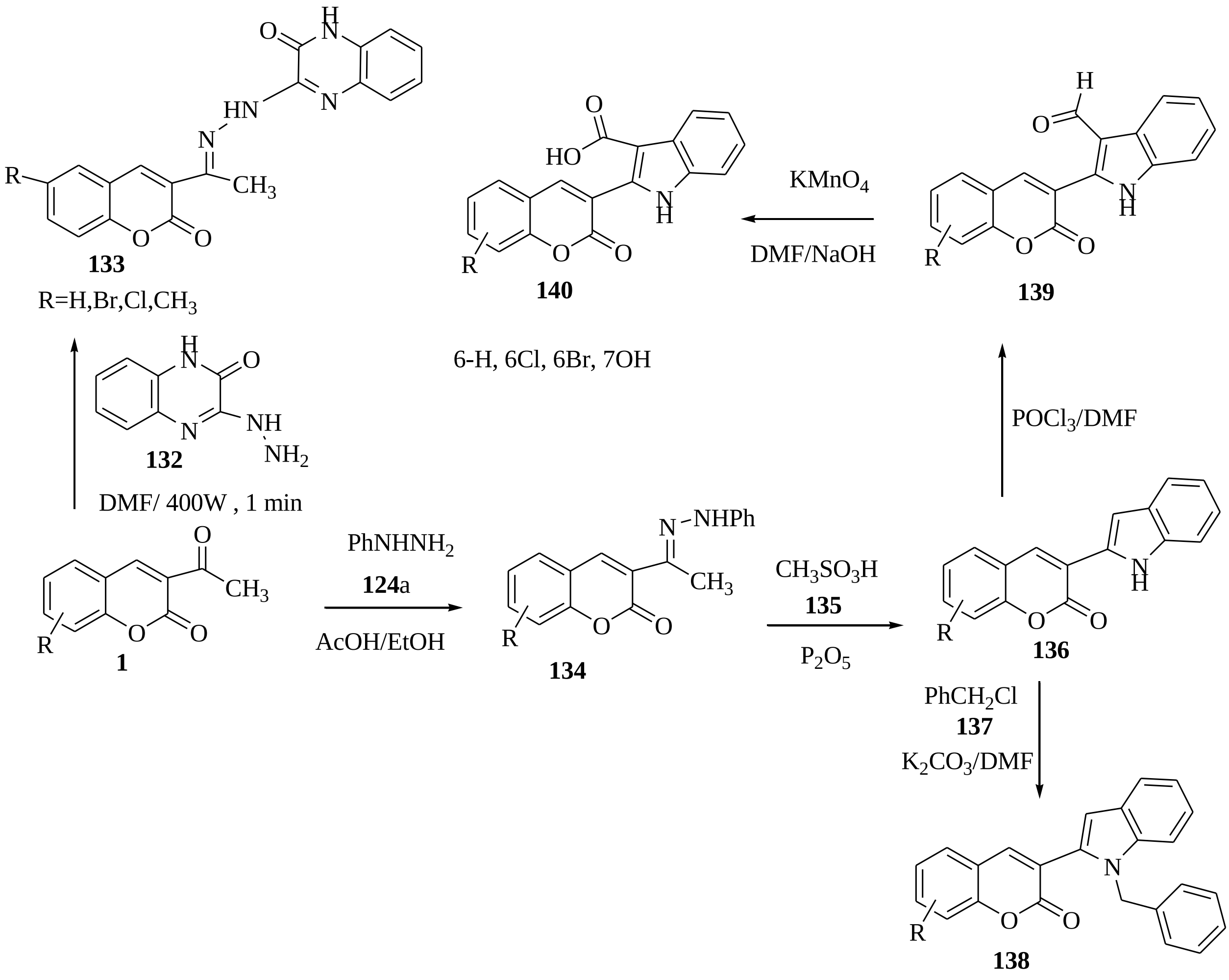
2.7. Reaction with hydrazine hydrate and its derivatives

It was reported that the reaction of hydrazine hydrate **10** with 3-acetylcoumarin **1** led to fission of the coumarin ring giving salicaldazine **122** (Scheme 22).[63] On the other hand, refluxing of 3-acetylcoumarin **1** with phenylhydrazine **123a**[64] or (2,4,6-trichlorophenyl)hydrazine **123b**[65] in ethanol gave the corresponding hydrazones **124** and **125**, respectively. Oxidation of **125** with tertbutylhypochlorite yielded chloroalkylazo **126**.[66-68] When **126** was treated with antimonypentachloride at 60 °C in dichloromethane, an orange precipitate **127** was formed. On addition of acetonitrile at room temperature 1*H*-triazolium salt **131** was afforded in 71% yield. The formation of **131** is assumed to take place *via* the formation of non-isolable acyclic intermediate **129**, followed by cyclization to afford the non-isolable tiazole **130**. This underwent Wagner-Meerwein type [1,2] shift of a methyl group to furnish the 1*H*-triazolium salts **131**(Scheme 22).[69-75]



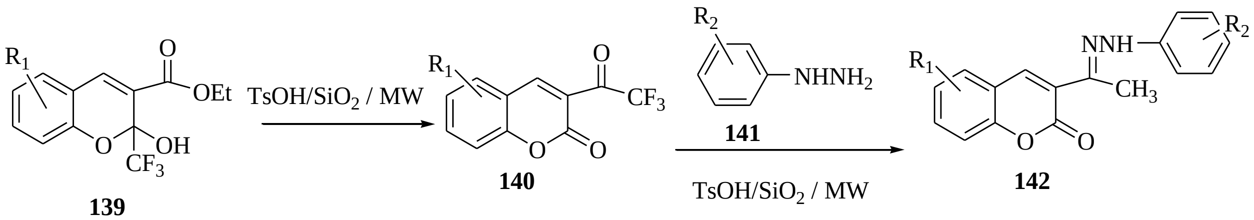
Scheme 22. Reaction of 3-acetylcoumarin derivatives **1** with hydrazine derivatives

Microwave irradiation of 3-hydrazinylquinoxalin-2(1*H*)-one **132** and 6-substituted acetylcoumarin **1** in dry DMF at 400 W for 1 min afforded the corresponding hydrazones **133**. Furthermore, treatment of substituted acetylcoumarins **1** with phenylhydrazine **124a** gave the hydrazone **134**.[76] Fischer indole synthesis of **134** in the presence of Eaton's reagent produced substituted 3-(1*H*-Indol-2-yl)chromen-2-ones **136**. Compounds **136** were allowed to undergo benzylation with beznyl chloride **137** and Vilsmeyer–Haack formylation to yield substituted 3-(1-benzyl-1*H*-indol-2-yl)-2*H*-chromen-2-ones **138** and 2-(2-oxo-2*H*-chromen-3-yl)-1*H*-indole-3-carbaldehydes **139**. Oxidation of **139** in the presence of potassium permanganate afforded 2-(2-oxo-2*H*-chromen-3-yl)-1*H*-indole-3-carboxylic acids **140** (Scheme 23).[77]



Scheme 23. Synthesis of substituted indolecoumarin derivatives **138**

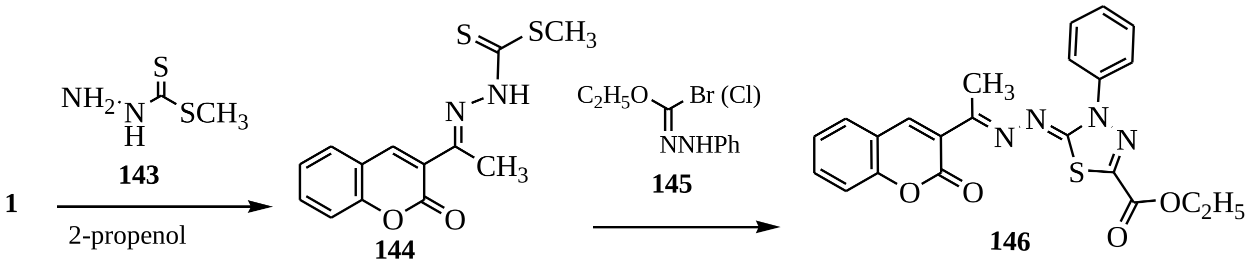
Sixteen novel fluoro-substituted coumarin hydrazones were synthesized from a series of ethyl 2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylates, using supported acid catalyst under microwave-assisted one-pot and solvent free conditions. The reaction was carried out in two steps under solid acid and microwave conditions. In step1, fluoro-substituted coumarin esters **139** were transformed into fluoro-substituted coumarin ketones **140**. Then, the ketones, **140**, which were not isolated from the mixture, were directly reacted with arylhydrazine to give the hydrazones **142** (Scheme 24).[78]



142a; R_1 = H, R_2 = H, **142 b**; R_1 = 6-Cl, R_2 =H, **142c**; R_1 = 8-Dichloro, R_2 = H, **142d**; R1 = 6, 8-Dibromo, R_2 = H, **142e**; R_1 = 8-CH_3, R_2 = OH, **142f**; R_1 = 8-CH_3CH_2, R_2 = OH, **142g**; R_1= H, R_2 = 4-F, **142h**; R_1= H, R_2 = 4-Cl, **142i**; R_1= H, R_2 = 4-Br, **142j**; R_1 = H, R_2 = 3-NO_2, **142k**; R_1 = H, R_2 = 3, 5-Dichloro, **142l**; R_1 = H, R_2 =4-CH_3O, **142m**; R_1, = H R_2 =4-CH_3, **142n**; R_1, = H R_2 =4-CF3, **142o**; R_1, = H, R_2 = 2, 4-Dimethyl, **142p**, R_1, = 6-Br; R_2 = H.

Scheme 24. Synthesis of fluorosubstituted coumarin hydrazones 142

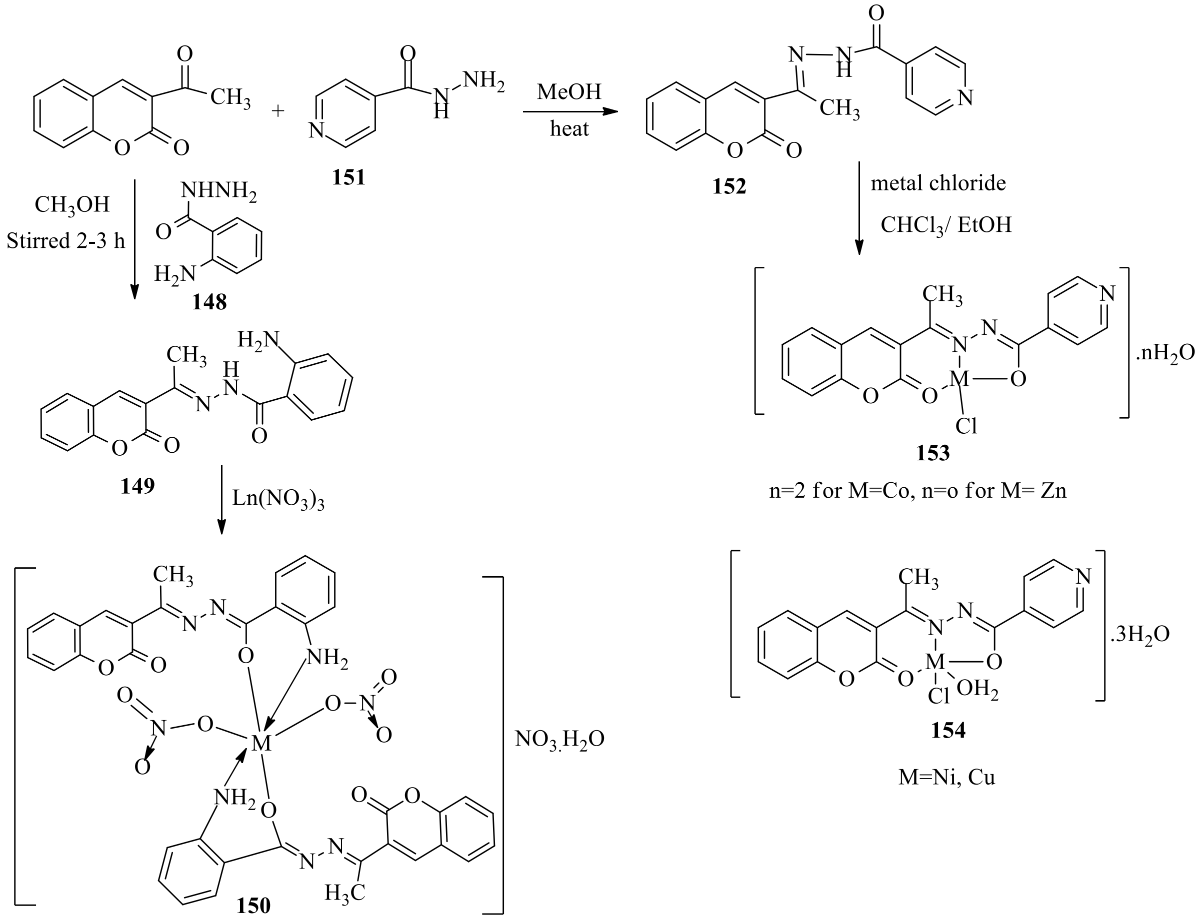
3-[(I*E*)-2-aza-I-methyl-2-[(methylthiothioxomethyl]vinyl]-2*H*-chromen- 2-one **144**, which prepared through the reaction of 3-acetylcoumarin **1** with methyl hydrazinecarbodithioate **143** in 2-propenol, was reacted with **145** to afford ethyl 2-[(2Z)-1,2-diaza-3-(2-oxo(2*H*-chromen-3-yl)but-2-enylidene]-3-phenyl-l,3,4-tbiadiazoline-5-carboxylate **146** (Scheme 25).[79]



Scheme 25. Synthesis of ethyl 2-[(2Z)-1,2-diaza-3-(2-oxo(2H-chromen-3-yl)but-2-enylidene]-3-phenyl l,3,4-tbiadiazoline-5-carboxylate **146**

2.8. Reaction with acid hydrazides and its derivatives

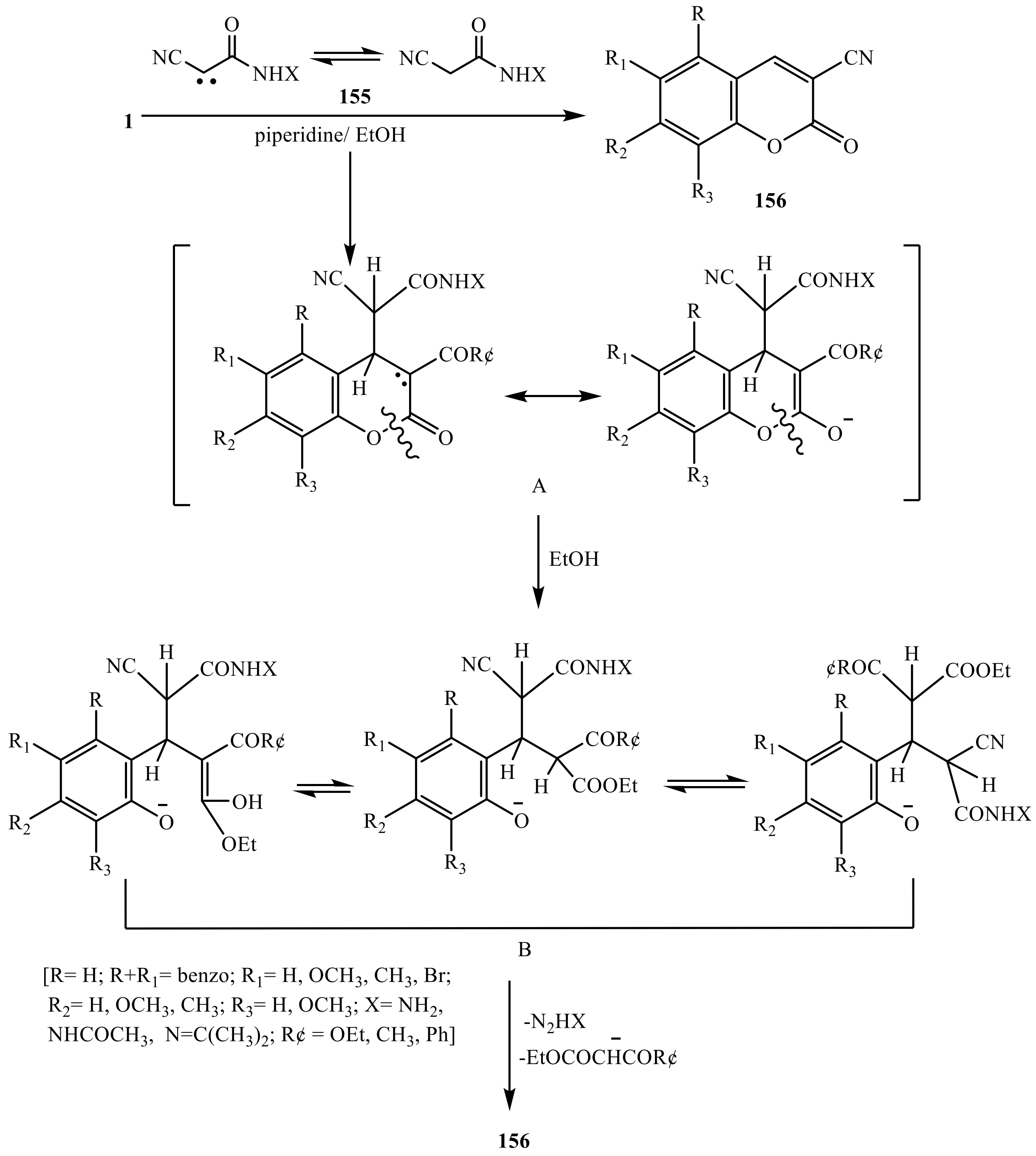
Aminobenzoylhydrazone **149**[80] was synthesized *via* condensation of 3-acetylcoumarin **1** with *o*-aminobenzoylhydrazide **148**. Also, the reaction of **148** with $Ln(NO_3)_3$ gave the corresponding complexes of the composition $[Ln(ACAB)_2(NO_3)_2(H_2O)_2]\cdot NO_3\cdot H_2O$ **150**, where Ln = La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III) and Y(III)[81]. Moreover, Hunoor et. al. synthesized Co(II), Ni(II), Cu(II) and Zn(II) complexes **153** and **154**, using a new heterocyclic Schiff base **152**, derived by condensation of isonicotinoylhydrazide **151** and 3-acetylcoumarin **1** in ethanol (Scheme 26).[82]



La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III) and Y(III)

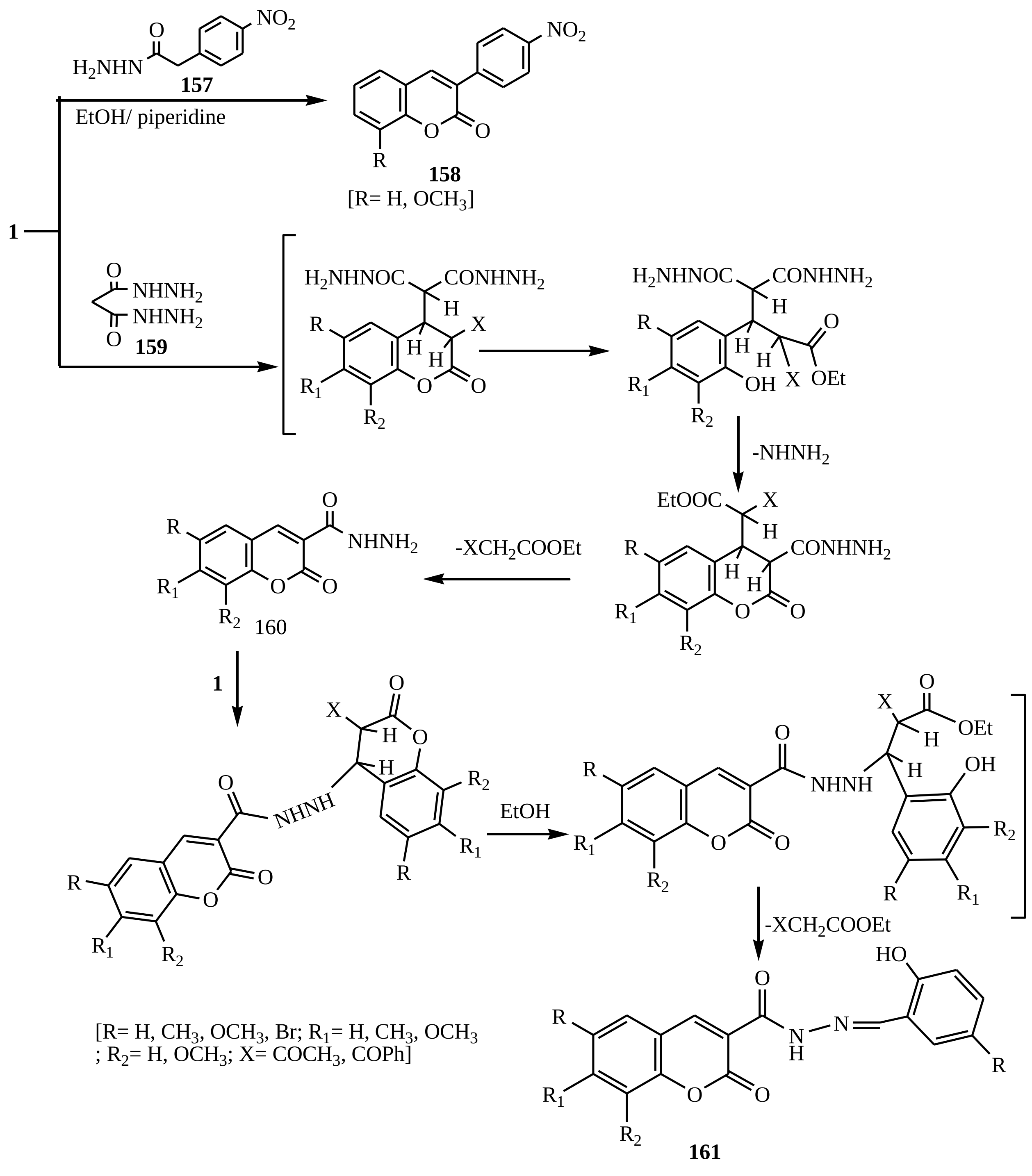
Scheme 26. Synthesis of Co(II), Ni(II), Cu(II) and Zn(II) complexes **153** and **154**

3-Substituted coumarin derivatives **1** were reacted with cyanoacetylhydrazine **155** and its N-acetyl and *N*-isopropylidene derivatives in the presence of piperidine at room temperature to give 3-cyano coumarin derivatives **156** (Scheme 27).[83]



Scheme 27. Synthesis of 3-cyanocoumarin derivatives **156**

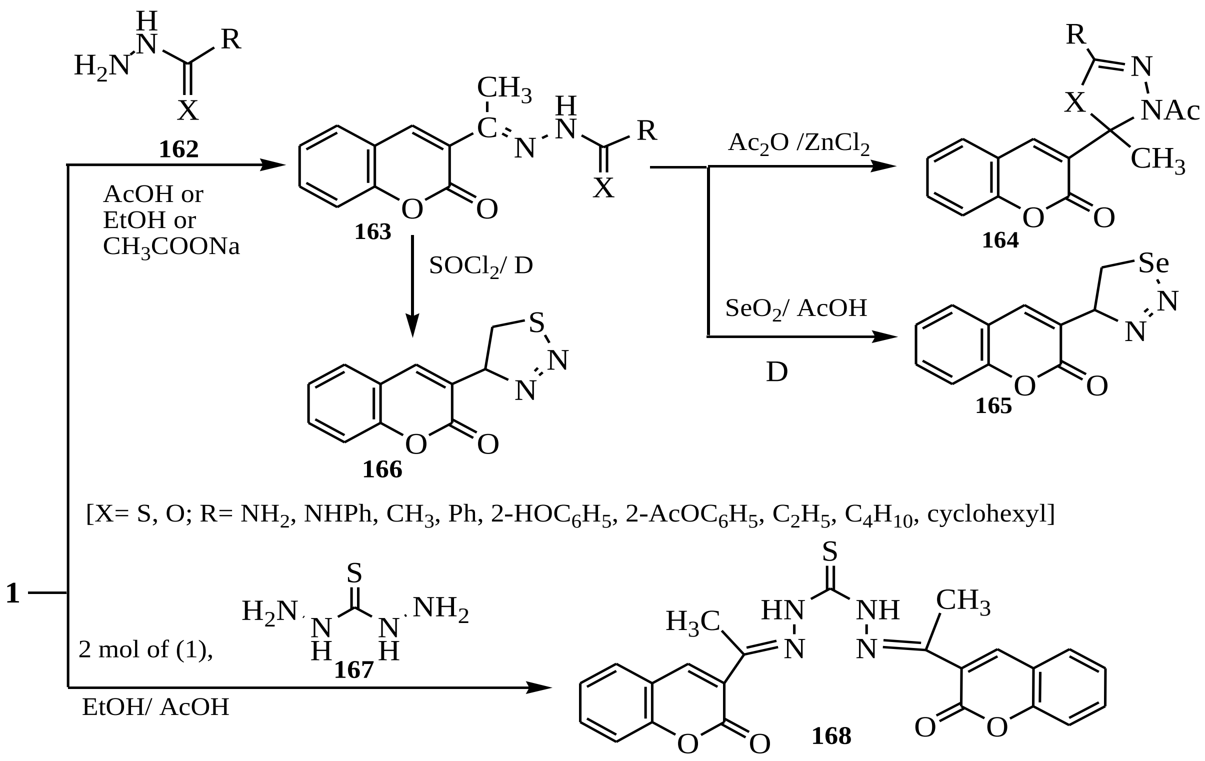
The reaction of 3-substituted coumarin derivatives **1** with hydrazide of *p*-nitrophenylacetic acid **157** in ethanol at 18-20 °C in the presence of catalytic amounts of piperidine gave the corresponding 3-(*p*-nitrophenyl)coumarin derivatives **158** (Scheme 28).[84] Furthermore, interaction of 3-substituted coumarin derivatives **1** with malonic acid dihydrazide **159** under Michael reaction conditions showed the conversion of **1** into coumarin-3-carboxylic acid hydrazide **160** (Scheme 28).[85] When the resulting hydrazide **160** was reacted with 3-substituted coumarin derivatives **1**, coumarin-3-carboxylic acid hydrazone derivatives **161** were obtained (Scheme 28).[85]



Scheme 28. Interaction of **1** with *p*-nitrophenylacetic acid and malonic acid hydrazide **157** and **159**

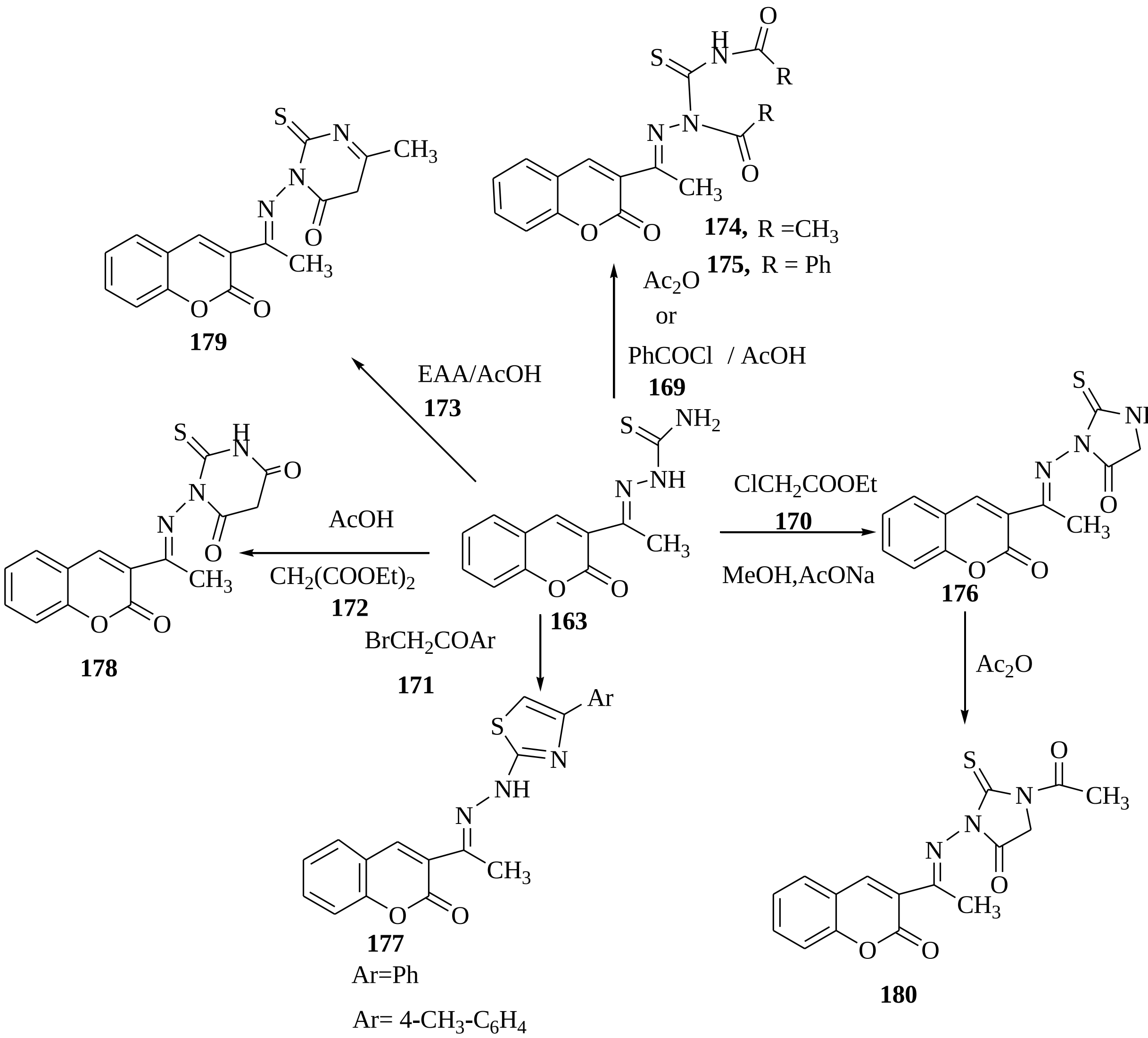
2.9. Reaction with thiosemicarbazide and semicarbazide

Condensation of 3-acetylcoumarin **1** with thiosemicarbazide or semicarbazide derivatives **162** in acetic acid or ethanol gave the corresponding hydrazone derivatives **163**.[86,87] Acetylation of **163** with Ac_2O/ $ZnCl_2$ formed 5-substituted-3-acetyl-2-(coumarinyl)-methyl-1,3,4-oxa(thia)diazoline derivatives **164** (Scheme 29).[88, 89] Moreover, 3-acetylcoumarin **1** was reacted with semicarbazide hydrochloride **162** in the presence of sodium acetate to give the semicarbazone hydrochloride **163**, which was subjected to oxidative cyclization using selenium dioxide in acetic acid to give 3-(1,2,3-selenadiazol-1,4-yl)coumarin **165**. Oxidative cyclization of the semicarbazone **163** with thionyl chloride produced the corresponding 3-(1,2,3-thiadiazol-4-yl)coumarin **166** (Scheme 29).[90,91] The bis-Schiff base **168** was prepared *via* refluxing of 3-acetylcoumarin **1** with thiocarbohydrazide **167** in ethanol/acetic acid (Scheme 29).[92]



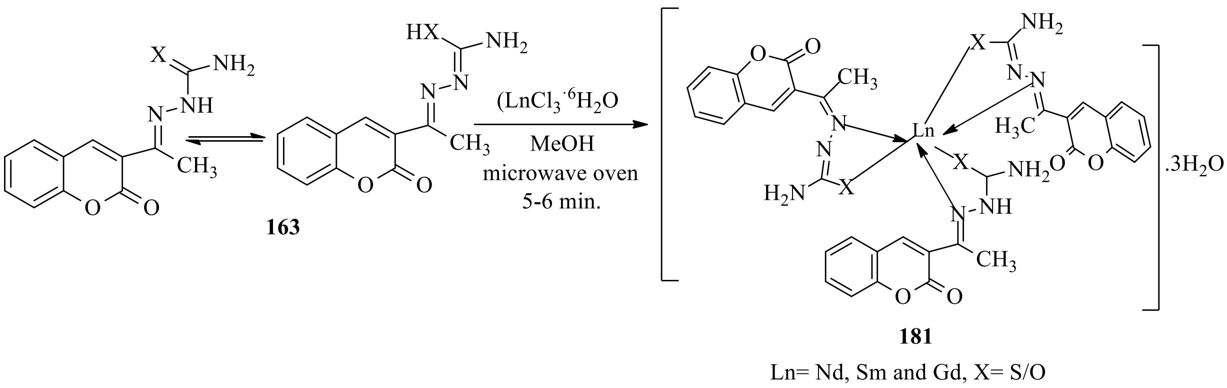
Scheme 29. Reaction of **1** thiosemicarbazide, semicarbazide **162** and thiocarbohydrazide **167**

Treatment of thiosemicarbazone **163** with acetic anhydride, benzoyl chloride **169**, ethyl chloroacetate **170**, ω-bromomethylketones **171** and dicarbonyl compounds **172** and **173** afforded the corresponding diacetyl **174** and dibenzoyl-thiosemicarbazone **175,** 3-(coumarin-3-ylethylidene)amino-2-thioxo-imidazolidin-4-one **176**, 5-aryl-2-[(coumarin-3-ylethylidene)-hydrazino]thiazole **177** and 1-(coumarin-3-ylethylidene)amino-2-thioxopyrimidine derivatives **178** and **179**, respectively. Acetylation of **176** with acetic anhydride gave 1-acetyl-2-thioxo-imidazolidin-4-one **180** (Scheme 30).[93]



Scheme 30. Reaction of thiosemicarbazone **163** with acetic anhydride, benzoyl chloride **169**, ethyl chloroacetate **170**, ω-bromomethylketones **171** and dicarbonyl compounds **172** and **173**

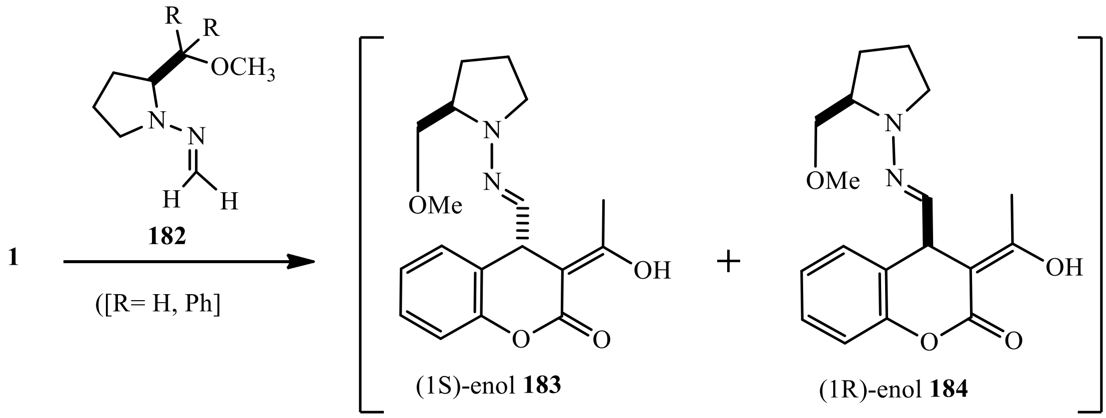
Reactions of hydrated lanthanide (III) chlorides; Ln = Nd, Sm and Gd, with the sodium salt of carbazone **163** in methanol in a microwave oven for 5–6 min. gave the corresponding complexes **181** (Scheme 31).[94]



Scheme 31. Reactions of hydrated lanthanide (III) chlorides; Ln = Nd, Sm and Gd, with the sodium salt of carbazone **163**

2.10. Reaction with chiral Formaldehyde N, N-dialkylhydrazones

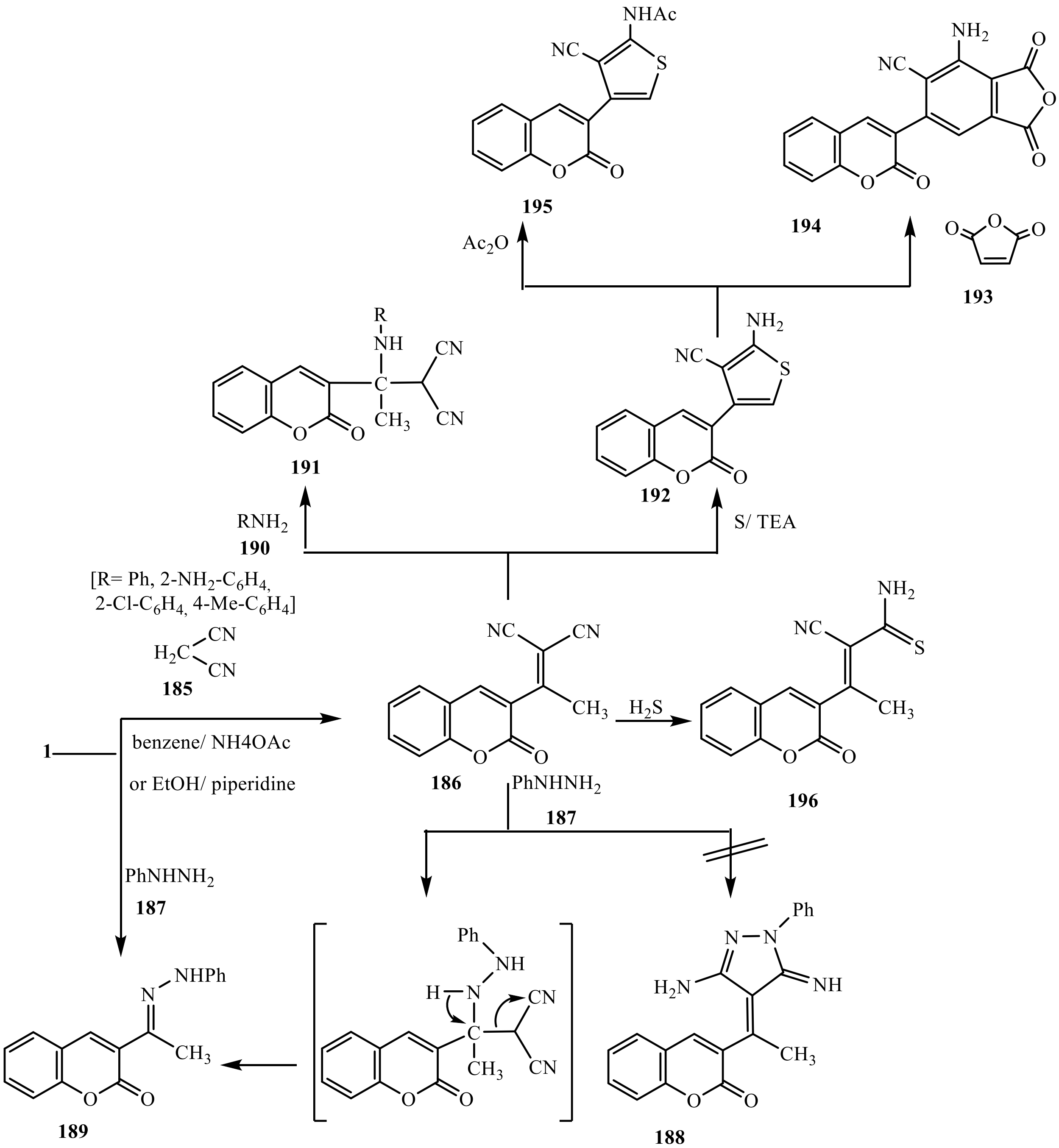
Michael addition of chiral formaldehyde *N*,*N*-dialkylhydrazone derivatives **182** to 3-acetylcoumarin **1** gave a 1.3:1 diastereoisomeric ratio of (1*S*)-trans/(1*R*)-trans **183** and **184** (Scheme 32).[95]



Scheme 32. Reaction of **1** with chiral formaldehyde *N, N*-dialkylhydrazones

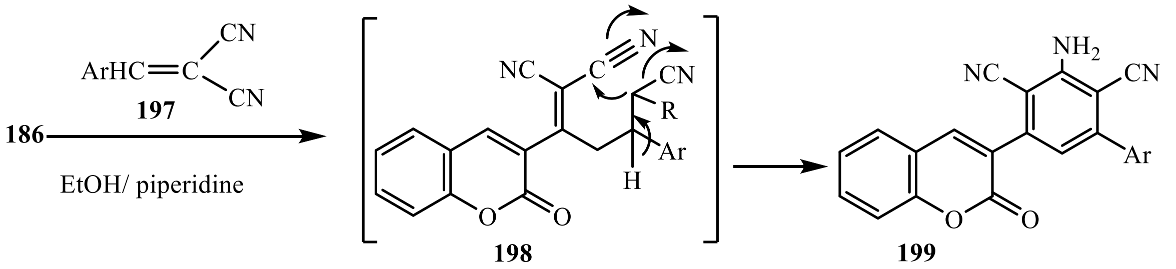
2.11. Reaction with active methylene components

Condensation of 3-acetylcoumarin **1** with malononitrile **185** in boiling benzene containing ammonium acetate and acetic acid afforded 3-(2,2-dicyano-1-methylvinyl)coumarin **186** (Scheme 33).[96] The reaction of compound **186** with phenylhydrazine **187** in boiling ethanol gave the imino compound **189**, while the pyrazoline derivatives **188** did not form.[97] The suggested structure for **188** was confirmed by its independent synthesis from **1**, i.e. refluxing it with phenylhydrazine**187** in boiling ethanol (Scheme 33)[64]. Also, interaction of **186** with primary aromatic amines **190** in boiling ethanol gave 3-(2,2-dicyano-1-arylamino-1-methylethyl)coumarin derivatives **191** by initial attack of the nucleophile at C-β of the olefinic bond of the dicyano derivatives. Furthermore, the reaction of **186** with sulfur in a Gewald reaction[98] produced 3-(5-amino-4-cyano-3-thienyl)coumarin **192**. In addition, the interaction of **192** with maleic anhydride **193** through a Diels-Alder reaction gave **194**, while its acetylation yielded the corresponding acylated compound **195**. Passing hydrogen sulfide gas into a solution of **186** in ethanol containing a few drops of triethylamine gave 3-(2-cyano-1-methyl-2-thiocarboxamidovinyl)coumarin **196** (Scheme 33).[96]



Scheme 33. Condensation of 3-acetylcoumarin **1** with malononitrile **185**

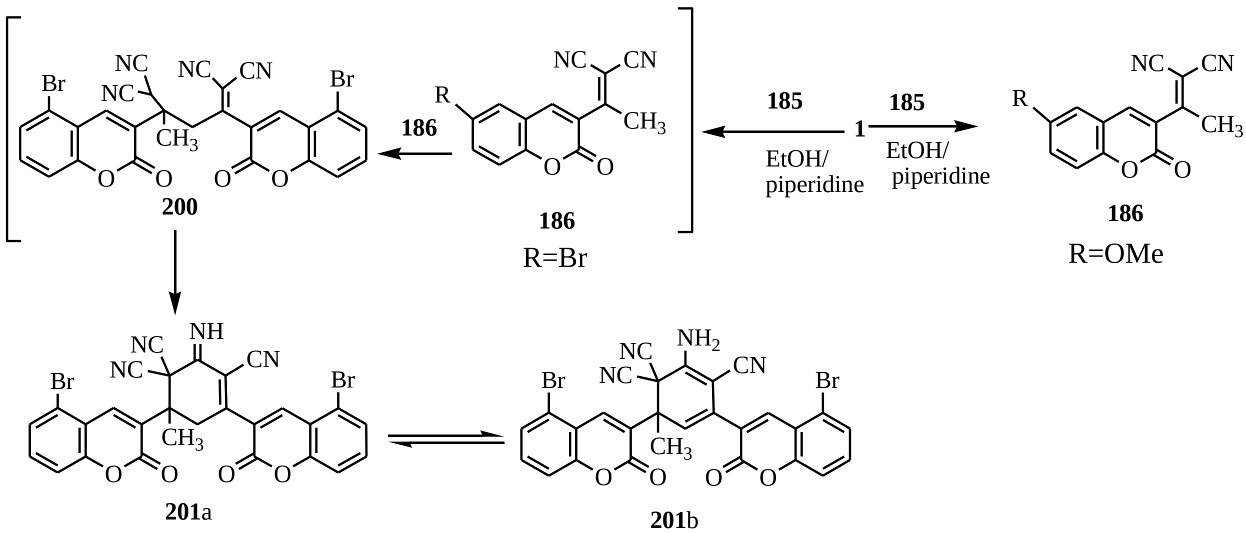
Condensation of compound **186** with substituted α-cyanocinnamonitrile derivatives **197** in boiling ethanol, containing a few drops of piperidine, gave coumarin derivatives **199** through the intermediate **198** (Scheme 34).[96]



[Ar= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NO_2-C_6H_4; R= CN, COOEt]

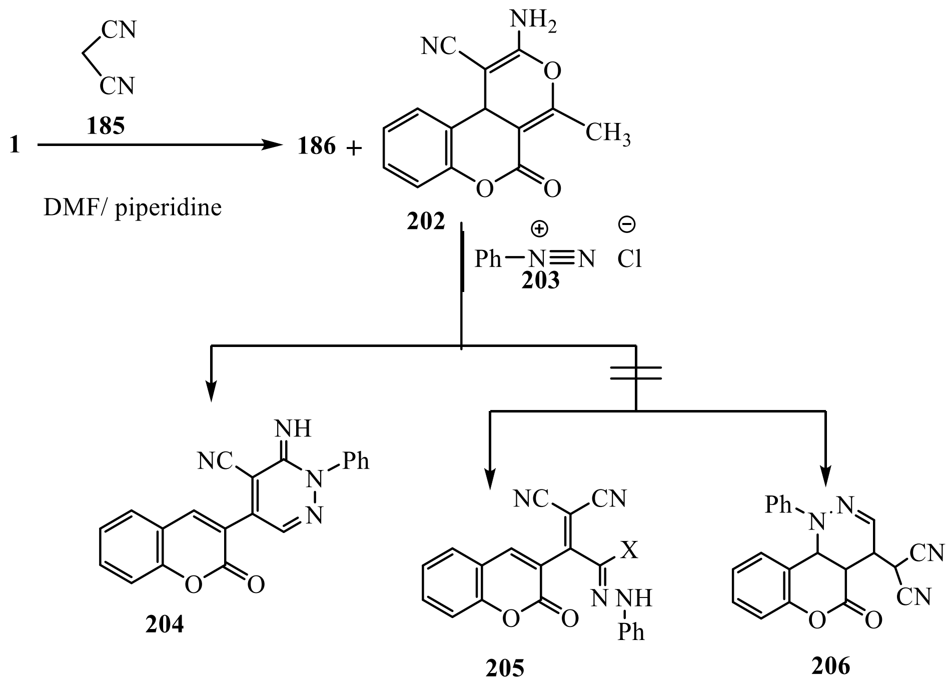
Scheme 34. Reaction of **186** with substituted α-cyanocinnamonitrile derivatives **197**

Knoevenagel condensation reaction of **1** (R=6-OCH_3) with malononitrile **185** in ethanol, containing a catalytic amount of piperidine, afforded compound **186** (R=6-OCH_3) as the main product. However, the product obtained from the reaction of 3-acetyl-5-bromocoumarin (R=5-Br) with malononitrile **185** is the benzopyran derivative **201b**. The corresponding mechanism for benzopyran derivatives involves the sequence of **186→200→201a** → **202b** (Scheme 35).[99]



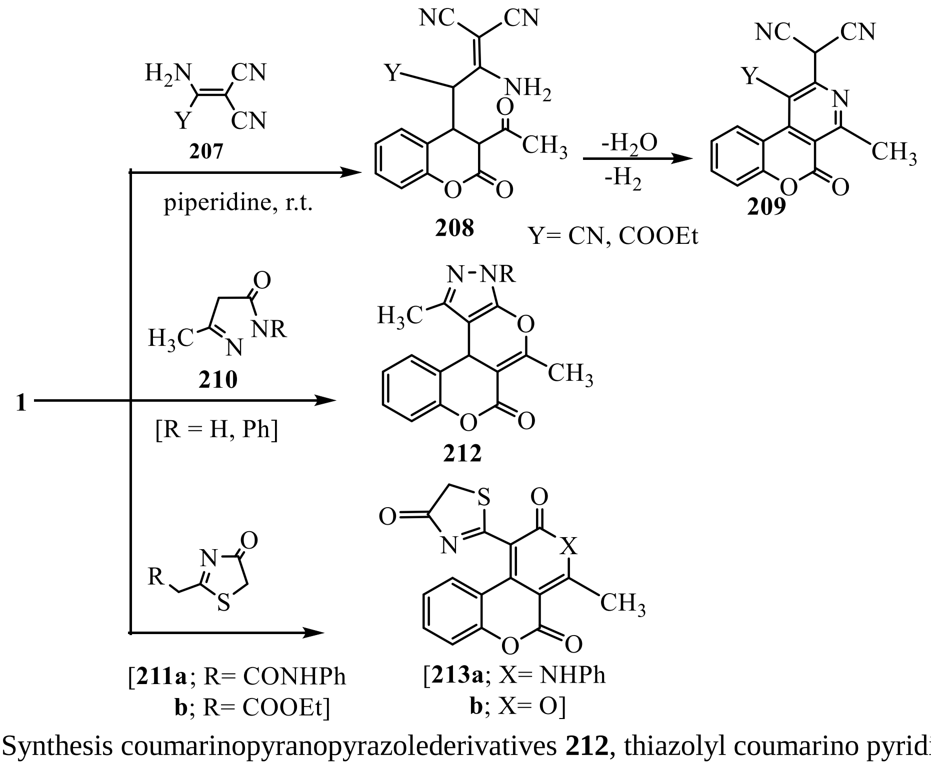
Scheme 35. Reaction of **1** with malononitrile under several conditions

Mohareb et al. reported that condensation of 3-acetylcoumarin **1** with malononitrile **185** in dimethylformamide, containing a catalytic amount of piperidine, gave a mixture of pyrano[3,4-c]coumarin derivatives **202** and **186**.[100] Coupling of **202** with benzenediazonium chloride **203**[100] gave the corresponding (coumarin-3-yl)-6-imino-1-phenyl-1,6-dihydropyridazin-5-carbonitrile **204**, not the compound **205** or **206** (Scheme 36).[100]



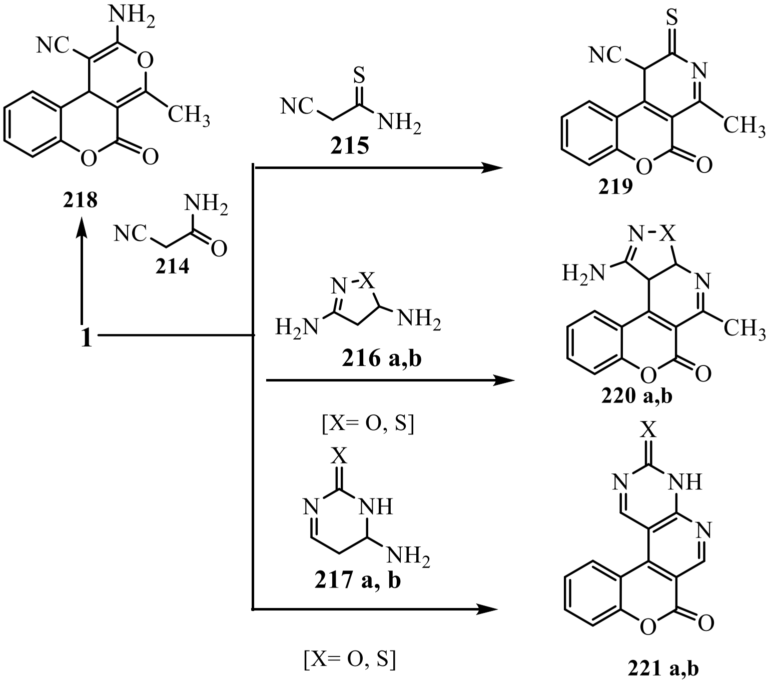
Scheme 36. Synthesis of (coumarin-3-yl)-6-imino-1-phenyl-1,6-dihydro-pyridazin-5-carbonitrile **204**

3-Acetylcoumarin **1** was reacted with 2-amino-1,1,3-tricyanopropene **207** in the presence of piperidine at room temperature to give the benzopyrano[3,4-c] pyridine derivative **209**. The reaction proceded *via* Michael addition of the active methylene group to the activated double bond to form the acyclic Michael intermediate **208**, which was cyclized to give **209** (Scheme 37).[101] Furthermore, the reaction of 3-acetylcoumarin **1** with different active methylene heterocyclic derivatives such as pyrazolone **210** and thiazolone **211a,b** yielded coumarinopyranopyrazole derivatives **212**, thiazolyl coumarinopyridine **213a** and coumarinopyranone **213b**, respectively (Scheme 37).[102]



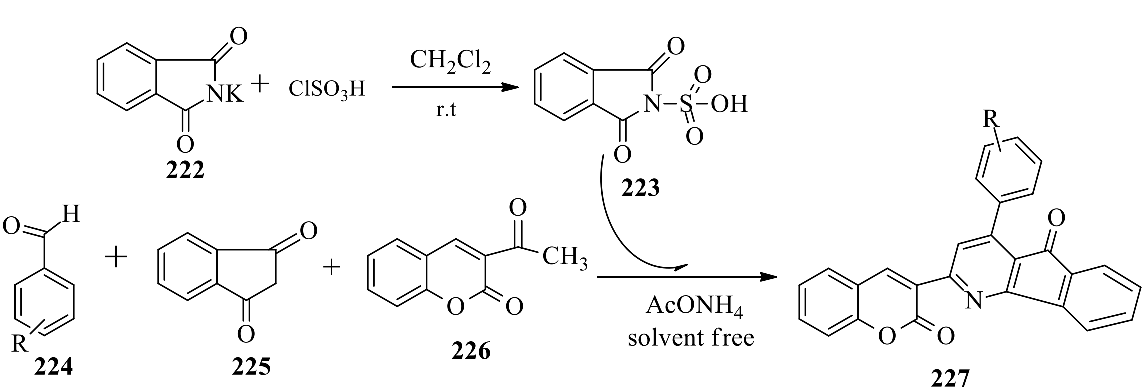
Scheme 37. Synthesis coumarinopyranopyrazolederivatives **212**, thiazolyl coumarino pyridine **213a** and coumarino pyranone **213b**

Benzopyronopyridine, pyrazolo[3,4-*d*]-pyridine, isoxazolo[5,4-*b*]-pyridine, pyrido[2,3-*d*]pyrimidine and pyrrolylcoumarin derivatives **218-221** were synthesized through the reaction of 3-acetylcoumarin **1** with the corresponding active methylene compounds (e.g., 2-cyanoacetamide **214**, 2-cyanoethanethioamide **215**, 4,5-dihydro isoxazole-3,5-diamine **216a**, 4,5-dihydroisothiazole -3,5-diamine **216b**, 6-amino-5,6-dihydro pyrimidine-2(1H)-one **217a** or 6-amino-5,6-dihydro pyrimidine-2(1H)-thione **217b** (Scheme 38).[103]



Scheme 38. Synthesis Benzopyronopyridine, pyrazolo[3,4-d]-pyridine, isoxazolo-[5,4-b]-pyridine, pyrido[2,3-d] pyrimidine, and pyrrolyl coumarin derivatives **218-221**

Facile and environmentally benign synthesis of some 2-(2-oxo-2*H*-chromen-3-yl)-4-aryl-indeno[1,2-b]pyridine-5-one derivatives **227** through the reaction of aromatic aldehydes **224**, 3-acetylcoumarin **226**, 1,3-indandione **225** and ammonium acetate using phthalimide-*N*-sulfonic acid (PISA) **223** as a catalyst is described in Scheme 39. The present method has some important features such as mild reaction conditions, short reaction time, less catalyst dosage and high yields with the green aspects by avoiding toxic catalysts and solvents. Furthermore, the catalyst can be reused for four times without any noticeable decrease in the catalytic activity (Scheme 39).[104]

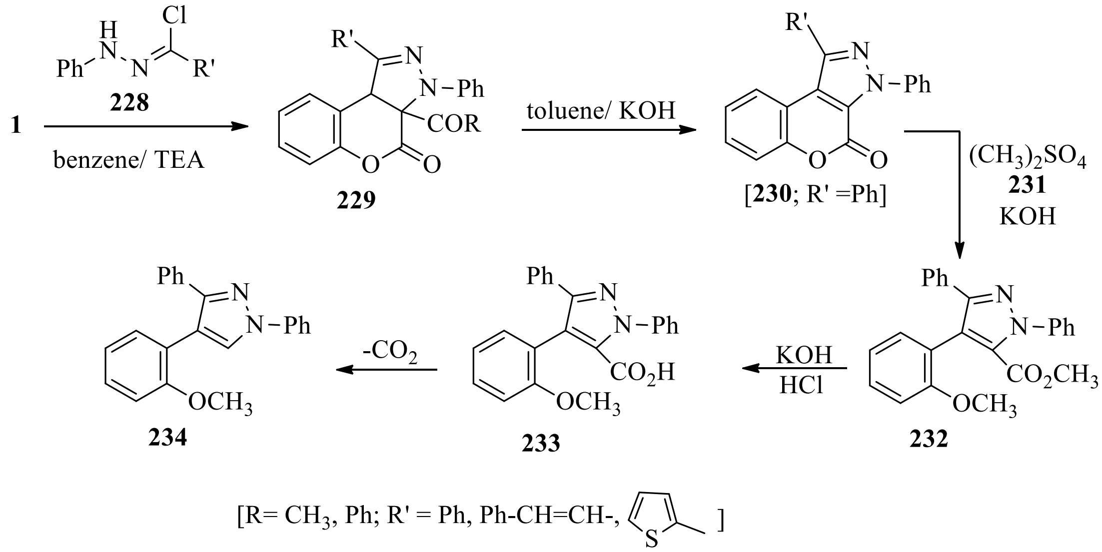


R=H, 4-f, 3-Br, 2-Cl, 4-CH_3, 4-OCH_3, 3,4-di-Cl, 2,4-di-Cl, 2-F, 2-CH_3, 3-NO_2, 4-Cl, 4-NO_2

Scheme 39. Synthesis of 2-(2-oxo-2H-chromen-3-yl)-4-aryl-indeno[1,2-b]pyridine-5-one derivatives **227**

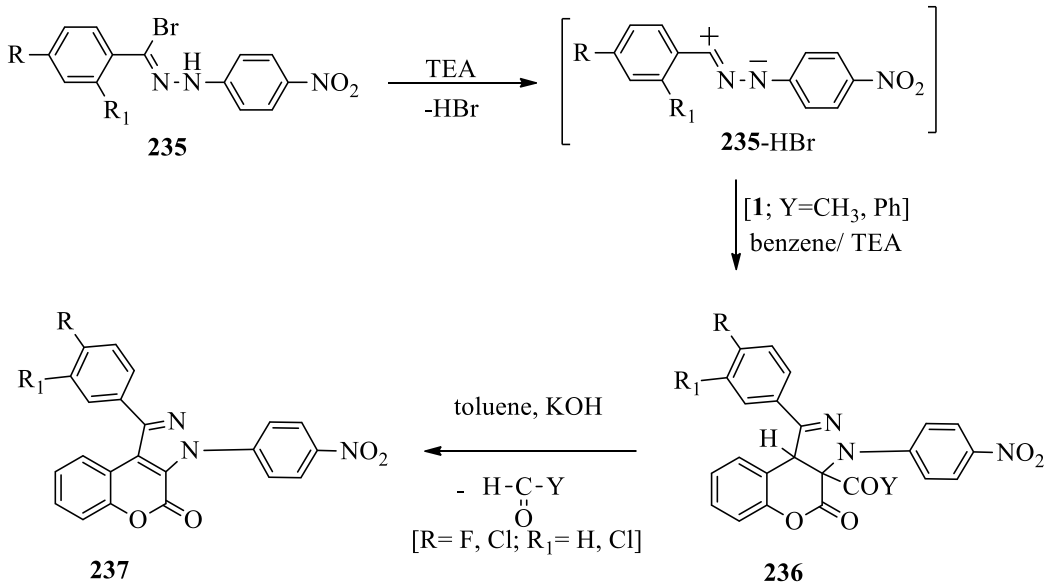
2.12. Reaction with hydrazonoyl halide derivatives

Cycloaddition reaction of *N*-phenylnitrileimine derivatives **228** with 3-substituted coumarin **1** in benzene in the presence of triethylamine gave the benzopyrano[3,4-*c*]pyrazole derivatives **229**, reflux of which in toluene in the presence of KOH led to deacylation, debenzoylation and dehydrogenation to give the corresponding pyrazole derivative **230** (Scheme 40).[105-108] Methylation of **230** afforded the substituted pyrazole **232**. Saponification of compound **232** produced the acid **233**, which was decarboxylated to yield 4-orthomethoxyphenyl-1,3-diphenylpyrazole **234** (Scheme 40).[106]



Scheme 40. Cycloaddition of **1** with nitrileimine **228**

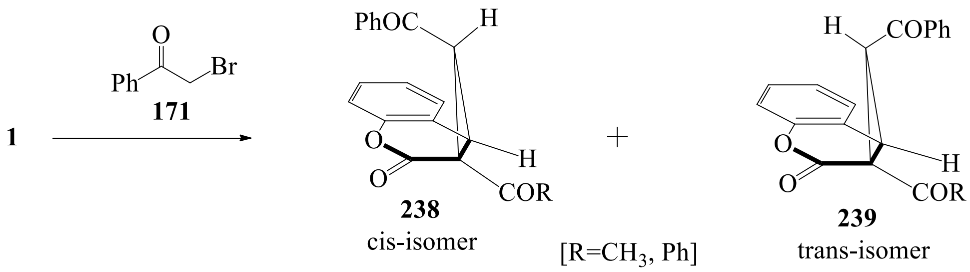
Cycloaddition reaction of 3-substituted coumarin **1** with hydrazonoyl bromide derivatives **235** in benzene in the presence of triethylamine gave the 1,3-dipolar cycloadducts 1-aryl-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]pyrazole-4(3*H*)-one derivatives **236**, which was aromatized by heating in aqueous potassium hydroxide in toluene to give the corresponding chromeno[3,4-c]pyrazol-4(3H)one derivatives **237** (Scheme 41).[109-111]



Scheme 41. Cycloaddition reaction of **1** with hydrazonoyl bromide derivatives **235**

2.13. Reaction with phenacyl bromide

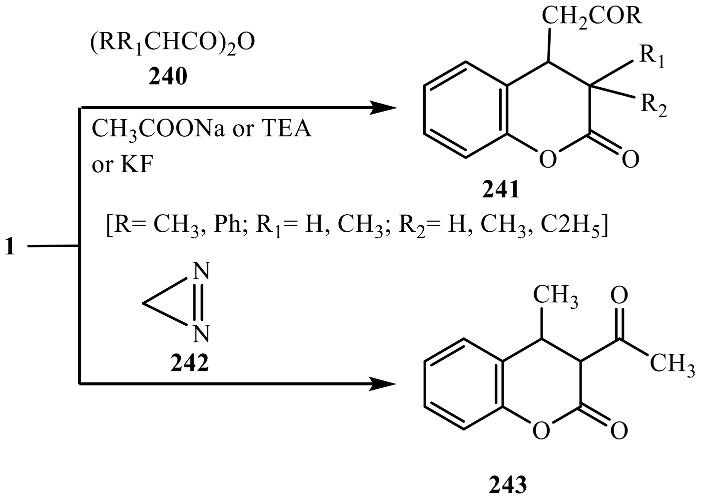
3-Substituted coumarin derivatives **1** were reacted with phenacyl bromide **171** in the presence of a base (e.g. EtONA, NaH, NaOH and DUB) to yield the cyclopropane derivatives **238** and **239** in moderate yields, which were improved by using catalyst such as Aliquat 336 or TPB under phase transfer conditions. These reactions have sterioselectivity (Scheme 42).[112]



Scheme 42. Cycloaddition reaction of **1** with phenacyl bromide **171.**

2.14. Acylation

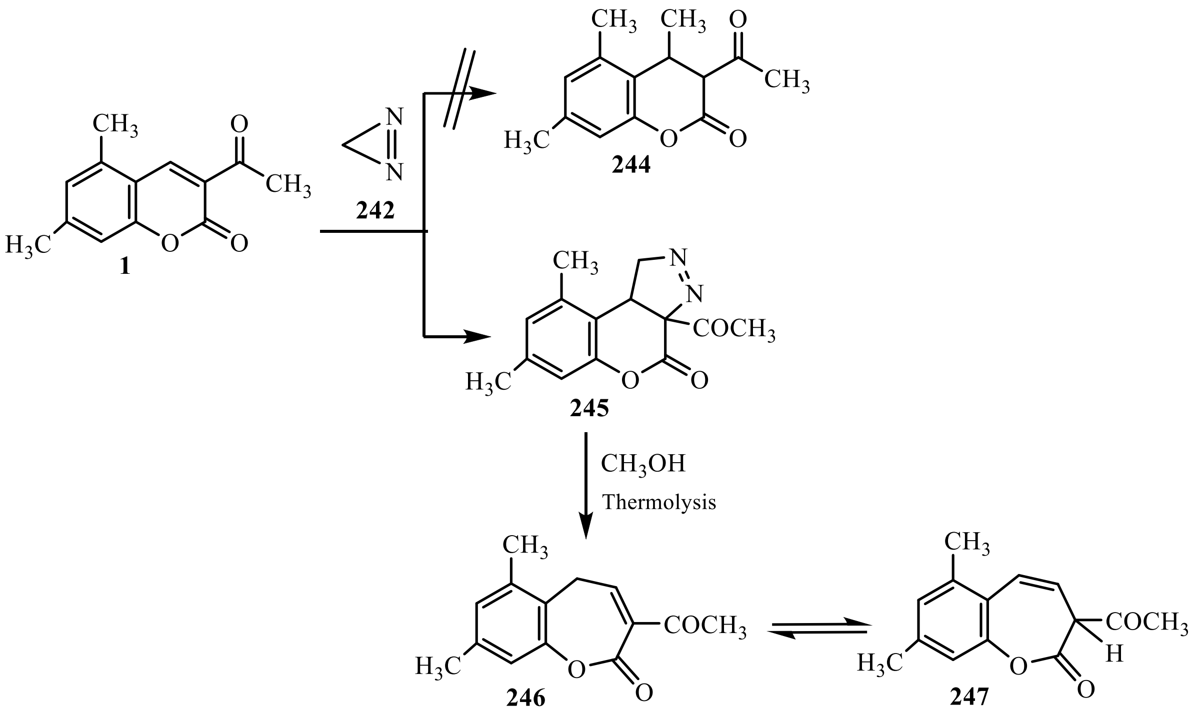
The reaction of 3-substituted coumarin **1** with acid anhydride derivatives (e. g. acetic, propionic, butyric and isobutyric acid anhydrides) **240** in the form of $(R_1R_2CHCO)_2O$ **240** in the presence of sodium acetate or triethylamine or potassium fluoride afforded dihydrolactones **241** (Scheme 43).[113]



Scheme 43. Reaction of **1** with acid anhydride **240** and diazomethane **242**

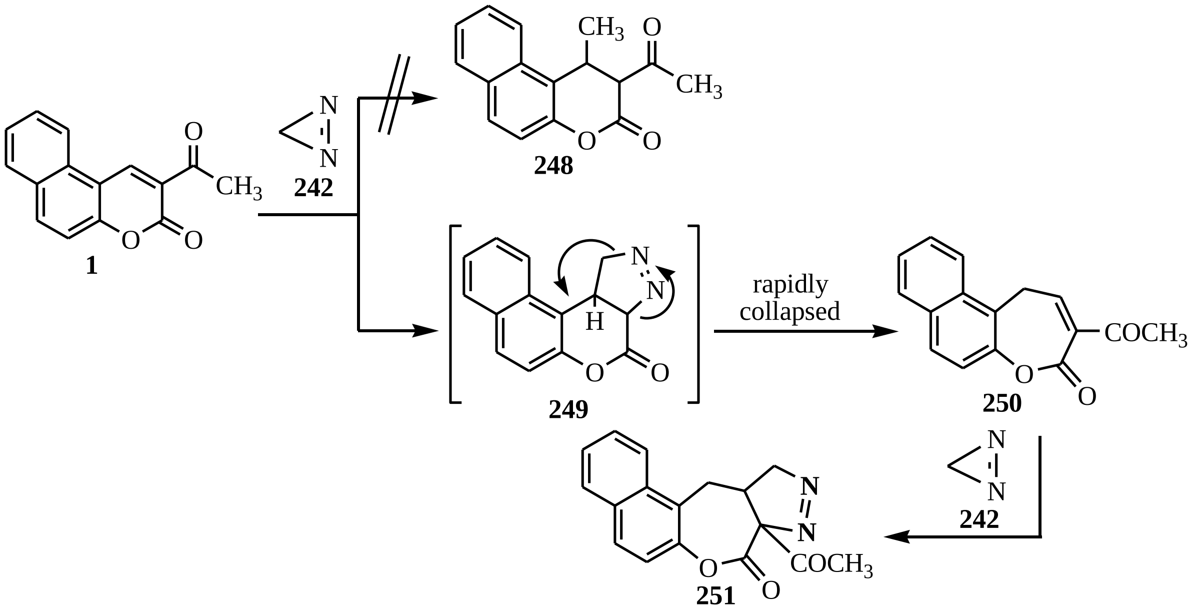
2.15. Reaction with diazo derivatives

Alkylation of 3-acetylcoumarin **1** with diazomethane **242** gave the 4-methylcoumarin **243** (Scheme 43). On the other hand, the substituents at the 5-position were interfered during the methylation process that 3-acetyl-5,7-dimethylcoumarin **1** rather than **244** gave a pyrazoline derivative **245**, which was then converted by methanol into the oxepin lactone derivative **246**. It tautomerises rapidly to its isomer **247**, which is more stable due to the extend conjugation (Scheme 44).[114, 115]



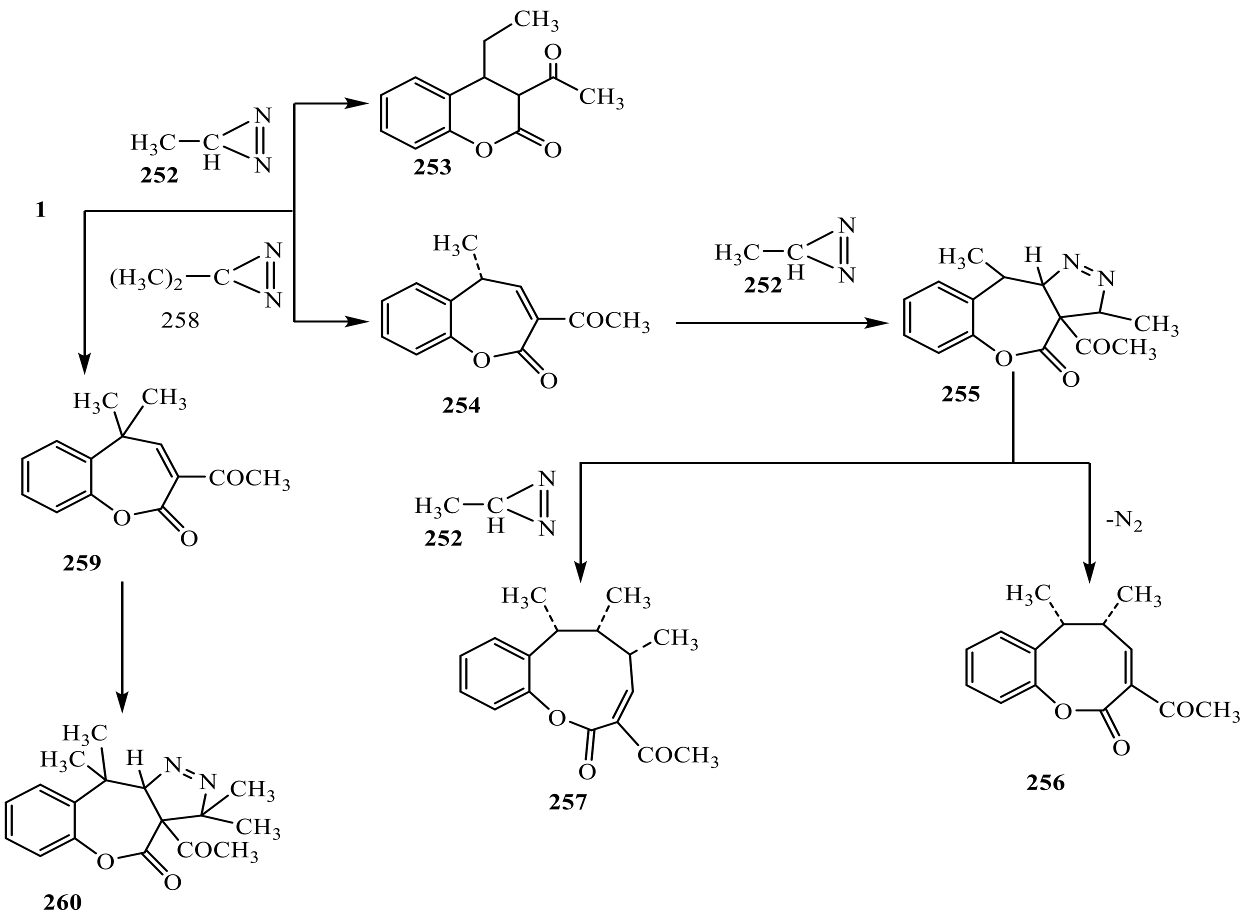
Scheme 44. Synthesis of oxepin lactone **247**

In 3-acetyl-5,6-benzocoumarin **1**, as methine group is smaller than a methyl group, a simple 4-methylation did not take place to obtain the compound **248**. The expected pyrazoline **249** was not detected as it rapidly collapsed to give the unsaturated lactone **250**, which was added to a second molecule of the reagent to produce the pyrazoline **251**(Scheme 45).[114]



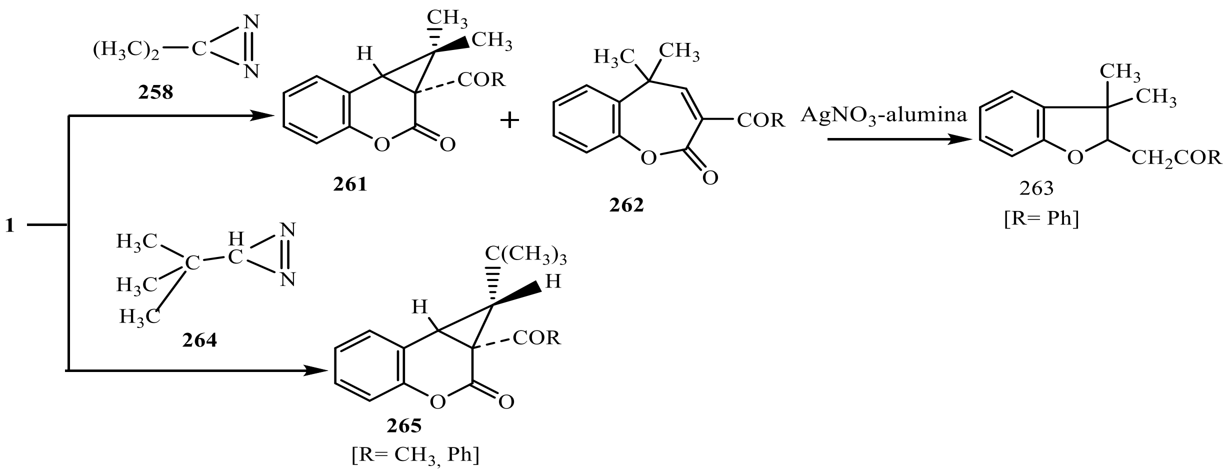
Scheme 45. Synthesis of pyrazoline **251**

Diazoethane alkylation of 3-acetylcoumarin **1** gave the corresponding 3-acetyl-4-ethylcoumarin **253** and expanded the lactone ring **254**, which reacted with a second molecule of diazoethane **252** to form the benzoxepinopyrazoline derivative **255**. It underwent a second ring expansion to form the benzoxocin derivative **256**. When the compound **255** was treated with diazoethane, a ring expansion took place giving the benzoxonin derivative **257** (Scheme 46).[116] Furthermore, 3-acetylcoumarin **1** underwent ring expansion upon treatment with 2-diazopropane **258**, which was followed by inverse cycloaddition of diazoalkane leading to a 3-acetyltetramethyl-4*H*-(1)benzoxepino[4,3-c]pyrazol-4-one derivative **260** (Scheme 46).[116]



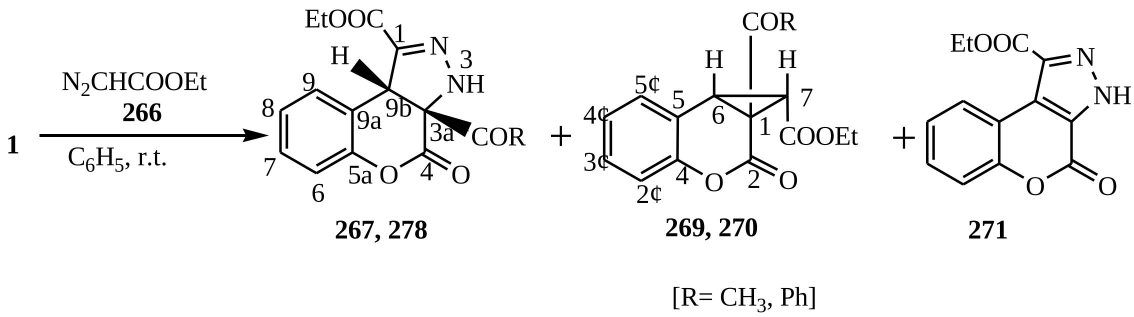
Scheme 46. Synthesis of benzoxocin, benzoxonin and benzoxepin derivatives **256, 257** and **260**

Similarly, the reaction of 3-benzoylcoumarin **1** with dimethyldiazomethane **258** gave the lactone **262** along with a small amount of cyclopropane derivative **261**. The compound **262** underwent $AgNO_3$-alumina induced ring contraction to yield the benzofuran derivative **263**. Also, diazopentane **264** converted 3-substituted coumarin **1** into **265** (Scheme 47).[117]



Scheme 47. Reaction of **1** with dimethyldiazomethane **258** and diazopentane **264**

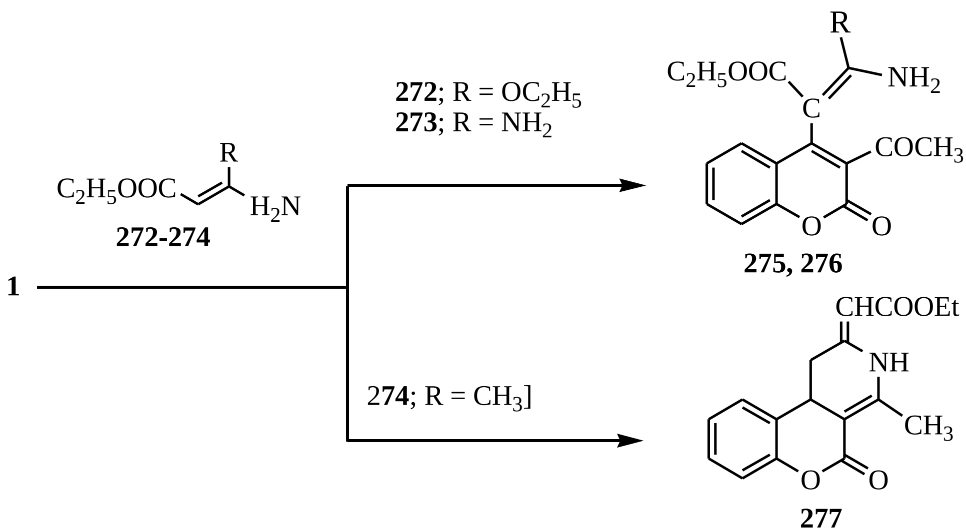
Cycloaddition reaction of ethyldiazoacetate **266** with 3-substituted coumarin **1** in benzene at room temperature or in silica gel gave a mixture of **267**, **268**, **269**, **270** and **271**. This is in agreement with the other analogous 1,3-dicycloaddition of diazo compounds to 3- or 4-substituted coumarin derivatives, where the terminal nitrogen of diazo moiety binds to the carbon atom of the benzopyran 3,4-double bond bearing the electronegative substituent (Scheme 48).[114,116-122]



Scheme 48. Reaction of **1** with ethyldiazoacetate **266**

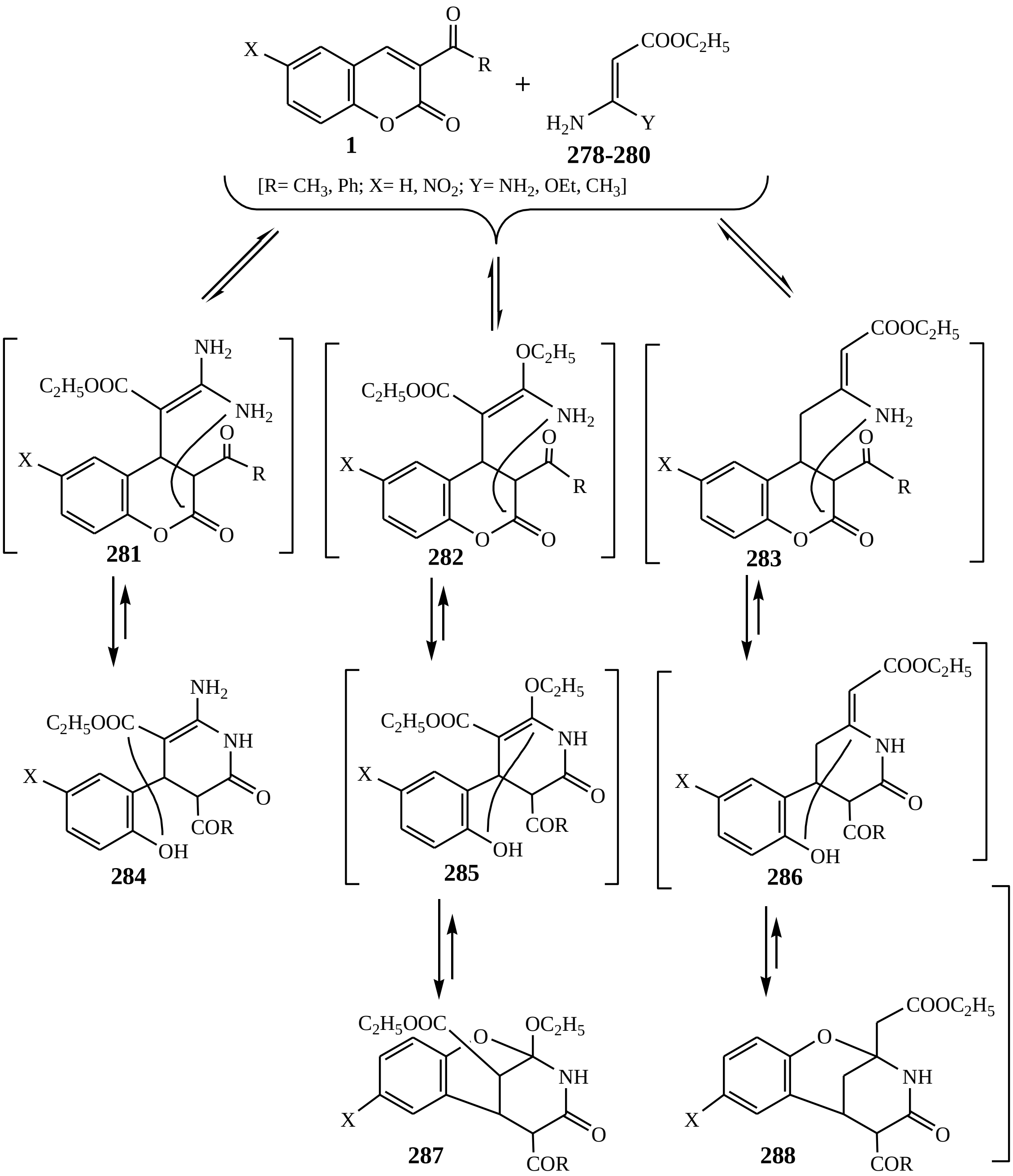
2.16. Reaction with enaminoesters and ethyl malonamate

Addition of the enaminoesters of 3-amino-3-ethoxy-acrylic acid ethyl ester **272** and 3,3-diamino-acrylic acid ethyl ester **273** to 3-substituted coumarin **1**, gave the adducts 3-amino-3-ethoxyacrylic acid ethyl ester derivatives **275, 276**. However, the adduct, produced from 3-substituted coumarin **1** and ethyl-1-amino-1-methylpropenoate **274**, was benzopyrano[3,4-c]pyridine derivative **277** (Scheme 49).[123]



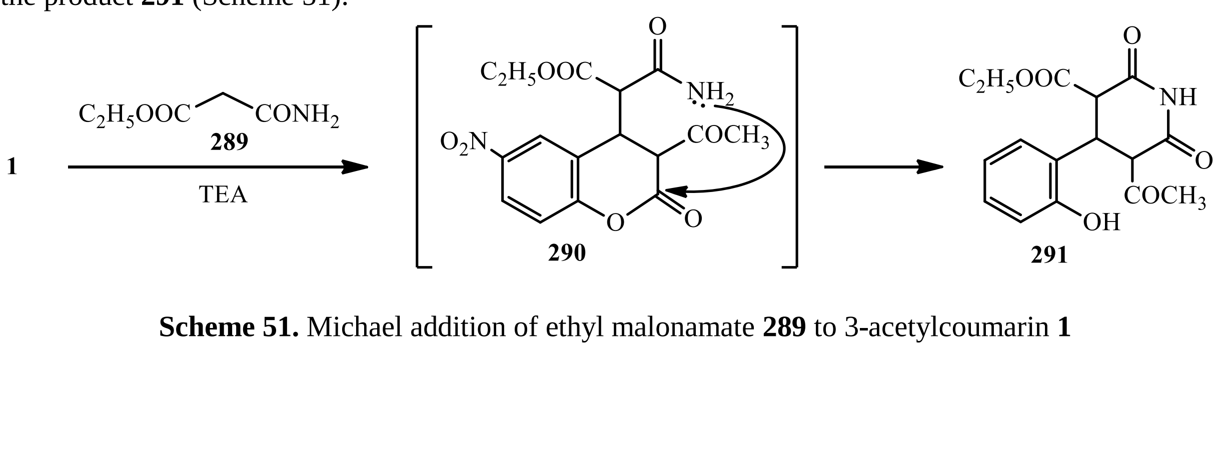
Scheme 49. Reaction of **1** with enaminoesters **272-274**

Raev et al. studied the addition of 3-aminopropenoate derivatives **278-280** to 3-substituted coumarin **1** to obtain the coumarinenaminoester adducts **284**, **287** and **288** *via* the intermediates **281**, **282**, **283**, **285** and **286**, respectively (Scheme 50).[124]



Scheme 50. Reaction of **1** with enaminoesters **278-280**

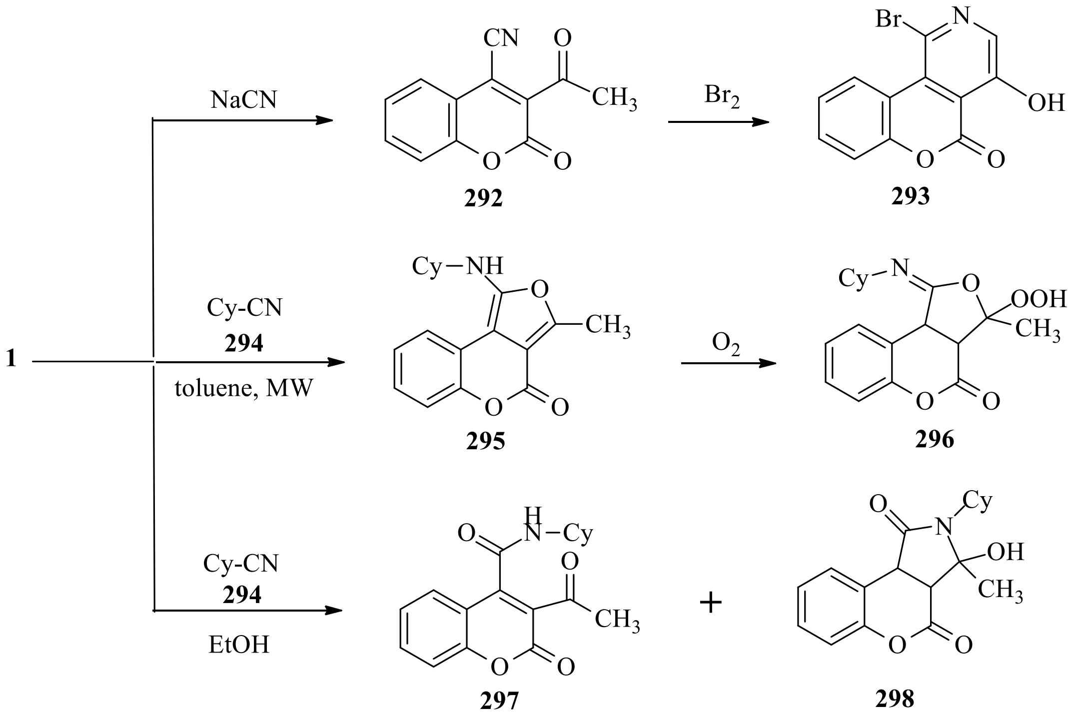
Michael addition of ethyl malonamate **289** to 3-acetylcoumarin **1** in the presence of triethylamine gave Michael adduct derivatives **290**, which underwent spontaneous intramolecular cyclization to yield the product **291** (Scheme 51).[125]



Scheme 51. Michael addition of ethyl malonamate **289** to 3-acetylcoumarin **1**

2.17. Reaction with sodium cyanide and isocyanide

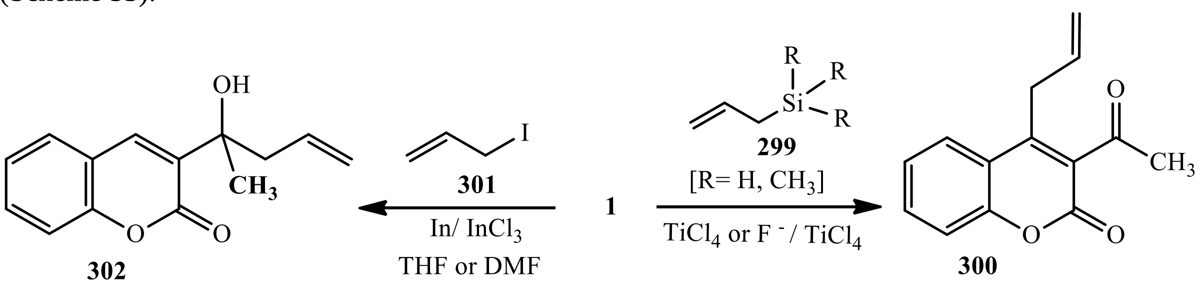
3-Acetylcoumarin **1** was reacted with sodium cyanide to give 3-acetyl-4-cyanocoumarin **292**, which was brominated to give benzopyrano[4,3-c]pyridine derivative **293** (Scheme 52).[126] Furthermore, 3-acetylcoumarin **1** was reacted with isocyanide **294** in toluene under microwave irradiation to furnish 2-aminofuran **295**, This combined very rapidly with triplet oxygen to afford hydroperoxide **296**, in addition the ketoamide **297** as well as the 5-hydroxy-pyrrolidone **298** was formed when the same reaction in refluxing ethanol was repeated (Scheme 52).[127]



Scheme 52. Reaction of **1** with sodium cyanide and isocyanide

2.18. Alkylation

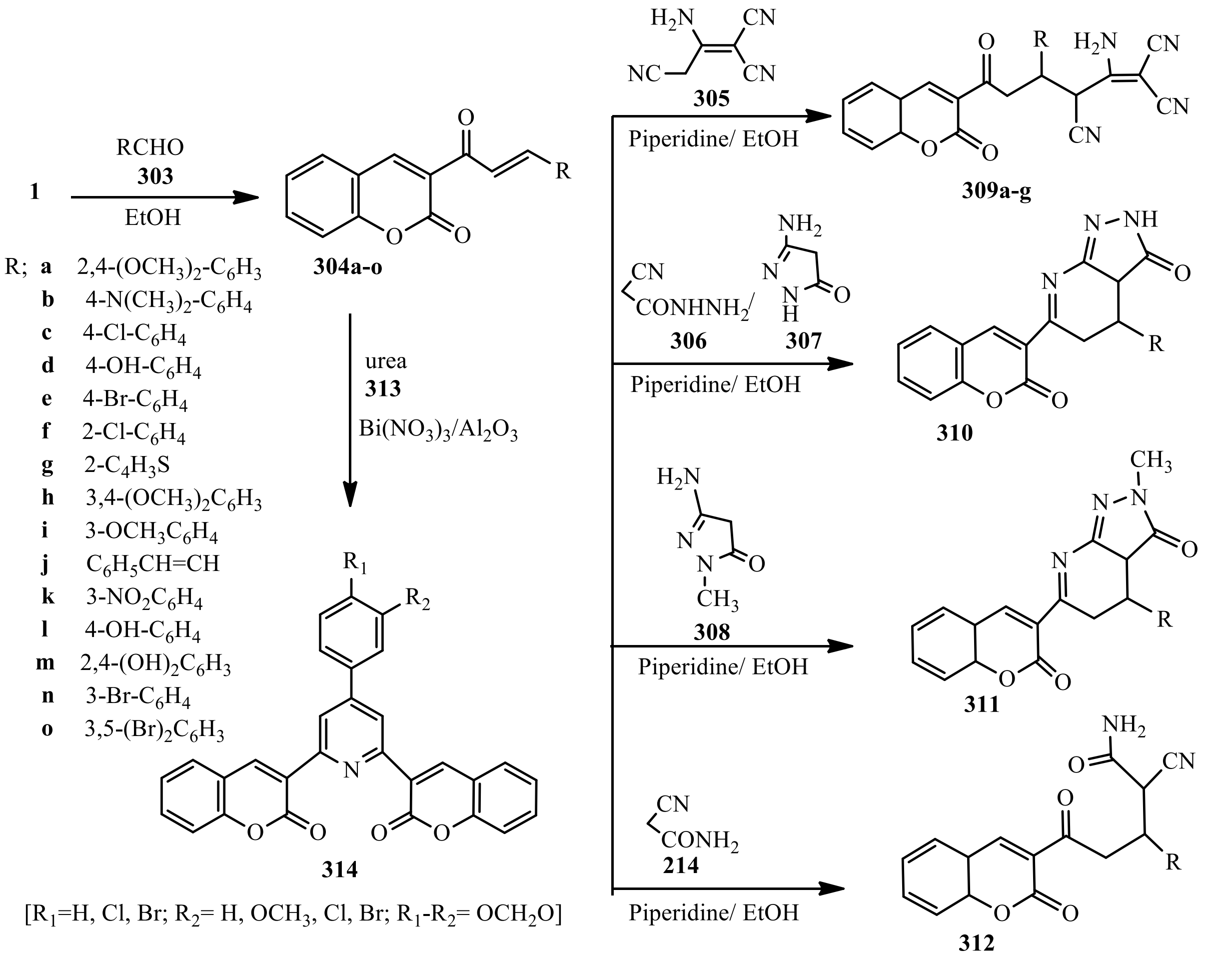
Alkylation of 3-acetylcoumarin **1** with allyl silane **299** in the presence of fluoride ion, titanium chloride[128] or trimethylallylsilane in the presence of titanium chloride[129] gave **300**. Also, interaction of 3-acetylcoumarin **1** with allyl iodide **301** in dimethylformamide or tetrahydrofuran in the presence of indium/ indium trichloride (In/ $InCl_3$) gave 1,2-addition product **302** in a high yield (Scheme 46)[130] (Scheme 53).



Scheme 53. Reaction of **1** with allyl silane and allyl iodide

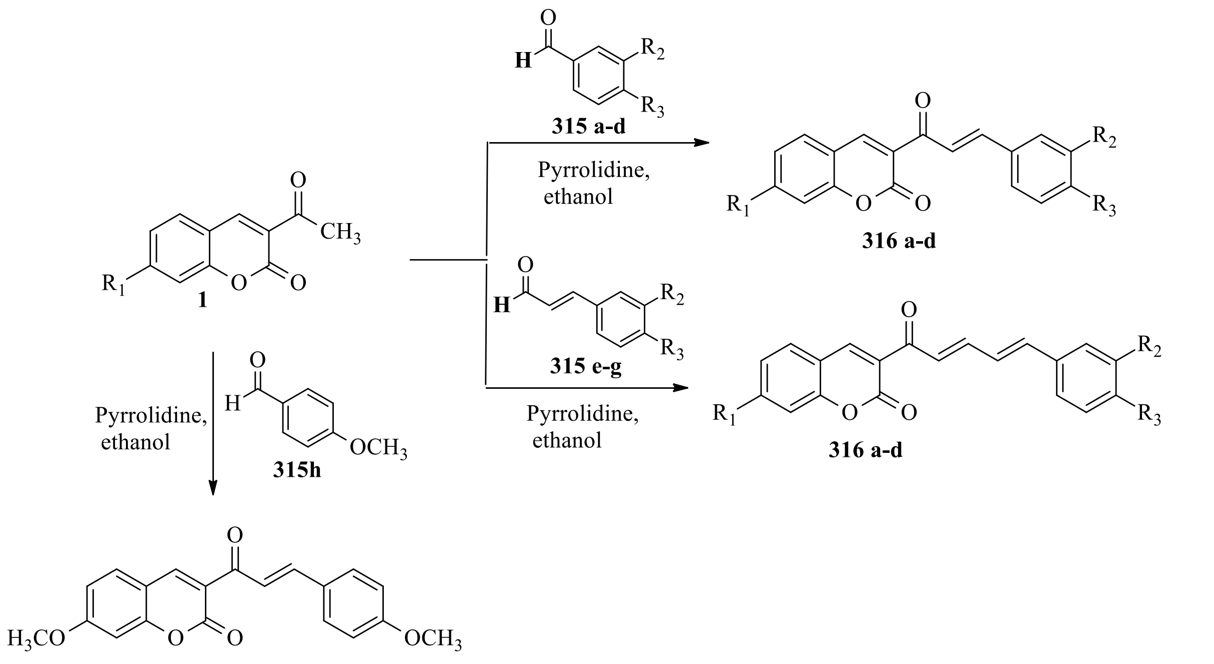
2.19. Reaction with aldehydes and ketones

3-Acetylcoumarin **1** reacted with aldehydes **303** in ethanol in the presence of piperidin, potassium hydroxide[135] or piperidine under solvent free condition to give the corresponding 3-cinnamoyl coumarin derivatives **304a-o**.[126,131-134] Michael addition of **304 a-g** with 2-amino-1,1,3-tricyanopropene **305**, cyanoethanoic acid hydrazide **306**, 3-aminopyrozol-5-one **307**, 3-amino-N-methylpyrazol-5-one **308** or cyanoacetamide **214** in the presence of piperidine gave 5-amino-3-aryl-4,6,6-tricyano-1-[2-(*H*)-oxo-1-benzopyran-3-yl]hex-5-en-1-one derivatives **309**, 4-aryl-3,3a,4,5-tetrahydro-6-[2(H)-oxo-1-benzopyran-3yl]-2-H/ methylpyrazolo-[3,4-b]pyridines **310** and **311** and 3-aryl-5-carboxamido-4-cyano 1-[2(H)-oxo-1-benzopyran-3-yl]pentan-1-one derivatives **312** (Scheme 54)[132]. Furthermore, a new efficient and eco-friendly methodology was developed for the synthesis of 4-aryl-2,6-dicoumarinyl pyridine derivatives **314** from coumarin chalcones **304** and urea **313**, using Bi(III) nitrate-Al_2O_3 as a catalyst (Scheme 54)[135].



Scheme 54. Reaction of **1** with aldehydes

Moreover, Seidel et al prepare a series from novel inhibitors of human histone deacetylases **316a-d**, **316h** and **316e-g**, via condensation of coumarin derivatives **1** with bezaldehyde derivatives **315a-d**, **315h** and cinnamaldehyde derivatives **315e-g** in ethanol in the presence of pyrrolidine (Scheme 55).[136]



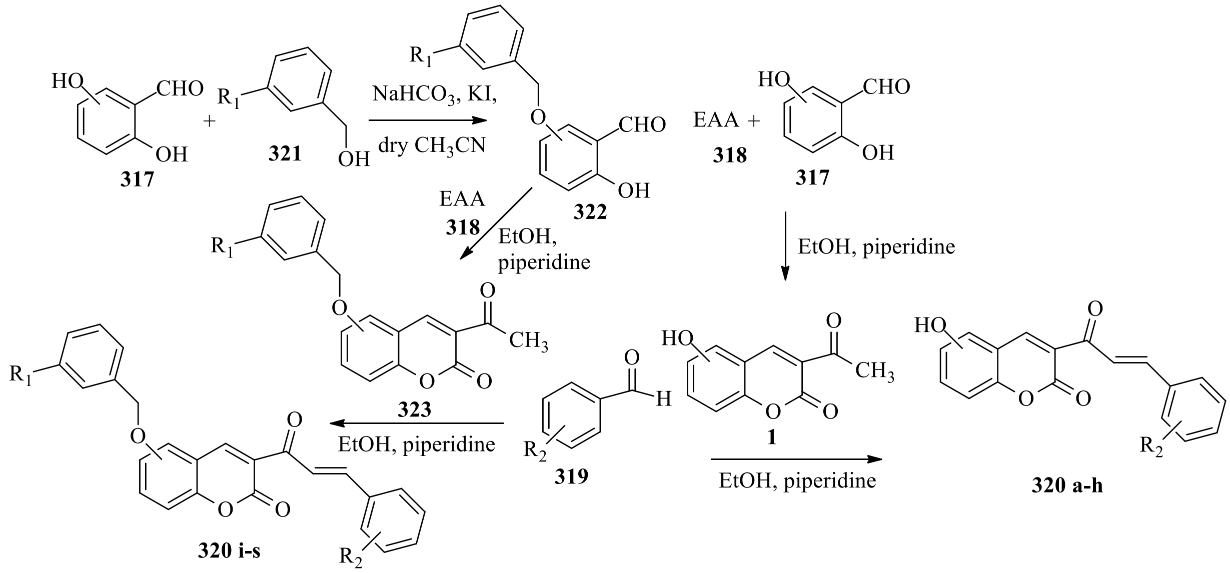
316a; R_1= H, R_2=H, R_3=H: **316b**; R_1= OCH_3, R_2= OCH_3, R_3=H: **316c**; R_1= OCH_3, R_2=OH, R_3= OCH_3: **316d**; R_1= OCH_3, R_2= OCH_3, R_3= OCH_3: **316e**; R_1= H ,R_2=H, R_3=H: **316f**; R_1= OCH_3 ,R_2= OCH_3, R_3=H: **316g**; R_1= OCH_3, R_2= OCH_3 ,R_3= OCH_3.

Scheme 55. Synthesis of cinnamaldehyde derivatives **316**

Molaverdi et. al. prepared **320a-s** via the routes illustrated in Scheme 56. Initially, commercial hydroxysalicylaldehyde **317** was converted to 6- or 7-hydroxy-3-acetylcoumarins **1** using ethyl acetoacetate **318** in the presence of catalytic amount of piperidine[137]. In the next step, 3-acetylcoumarins **1** were condensed with several aldehydes **319** in refluxing ethanol and in the presence of piperidine as a catalyst to afford the compounds **320a-h**. On the other hand, O-benzylation of hydroxysalicylaldehyde **317** in dry acetonitrile produced benzyloxysalicylaldehydes **322**. The reaction of **322** with ethyl acetoacetate **318** yielded the corresponding 3-acetylcoumarins **323**, which were subsequently condensed with appropriate aldehydes **319** to afford the final compounds **320i-s**.[138]

When the compound **304** was reacted with various 1-(aroylmethyl)-pyridinium bromide derivatives **324** in acetic acid in the presence of ammonium acetate, 3-(2-pyridyl)coumarin derivatives **325** were obtained.[138] Condensation of **304** with malononitrile or ethyl cyanoacetate **326** in the presence of ammonium acetate afforded cyanopyridine derivatives **327**. An alternative route for the synthesis of **327** by condensation of 3-acetylcoumarin **1** with malononitrile or ethyl cyanoacetate and aromatic aldehydes in the presence of ammonium acetate was also reported (Scheme 57).[139]

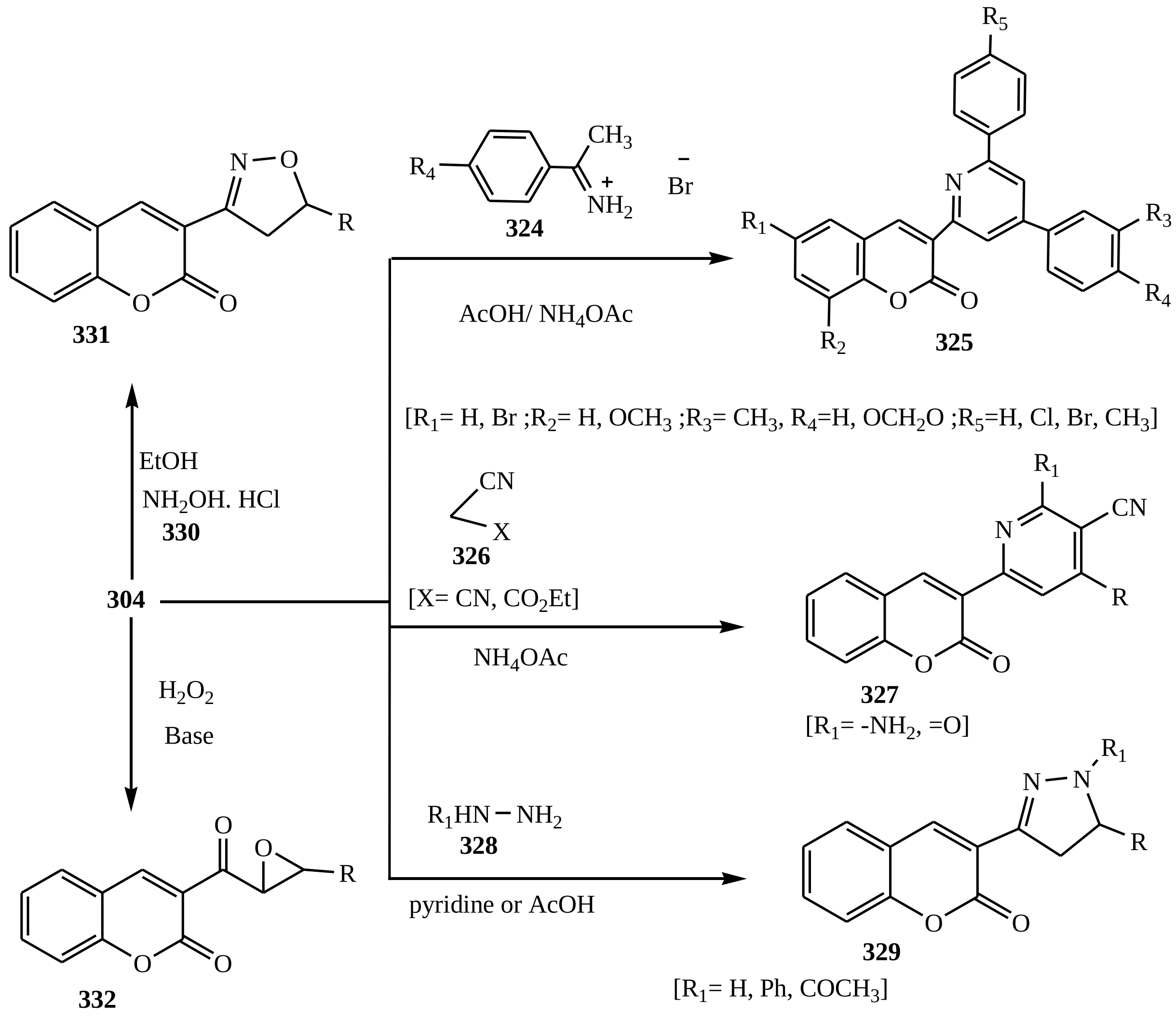
Furtheremore, a facile procedure for the synthesis of 3-(2-amino-3-cyano-4-arylpyrid-6-yl) coumarins **327** (R=NH_2, R_1= C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3-$NO_2C_6H_4$, 3,4-($OCH_2OC_6H_3$) were reported,[160] starting from 3-acetylcoumarin, aromatic aldehydes and malononitrile. The reactions were carried out on microwave irradiation in good yields with shorter time and easy work-up (Scheme 57).



320a; OH= 6 position , R_2=2,3-$(MeO)_2$, **320b**; OH= 6 position, R_2= 3,4,5-$(MeO)_3$, **320c**; OH= 6 position, R_2=3,4-(OCH_2O), **320d**; OH= 6 position, R_2= 4-(COOMe), **320e**; OH= 7 position , R_2=2,3-$(MeO)_2$, **320f**; OH= 7 position, R_2= 3,4,5-$(MeO)_3$, **316g;** OH= 7 position, R_2=3,4-(OCH_2O), **320h**; OH= 7 position, R_2= 4-(COOMe), **320i**; OCH_2Ar= 6 position, R_1=H, R_2= 2,3-$(MeO)_2$, **320j**; OCH_2Ar= 6 position, R_1=H, R_2= 3,4,5-$(MeO)_3$: **320k**; OCH_2Ar= 6 position, , R_1=H, R_2=3,4-(OCH_2O): **320l**; OCH_2Ar = 7 position, R_1=MeO, R_2= H, **320m**; OCH_2Ar= 7 position, R_1=MeO, R_2= 4-Me, **320n**; OCH_2Ar= 7 position, R_1=MeO, R_2= 2,4-Cl_2, **320o**; OCH_2Ar = 7 position, R_1=MeO, R_2= 2,6-Cl_2, **320p**; OCH_2Ar= 7 position, R_1=MeO, R_2= 4-MeO, **320q**; OCH_2Ar= 7 position, R_1=MeO, R_2= 2,3-$(MeO)_2$: **320r**; OCH_2Ar= 7 position, R_1=MeO, R_2= 2,5-$(MeO)_2$, **320s**; OCH_2Ar= 7 position, R_1=MeO, R_2= 3,4-(OCH_2O).

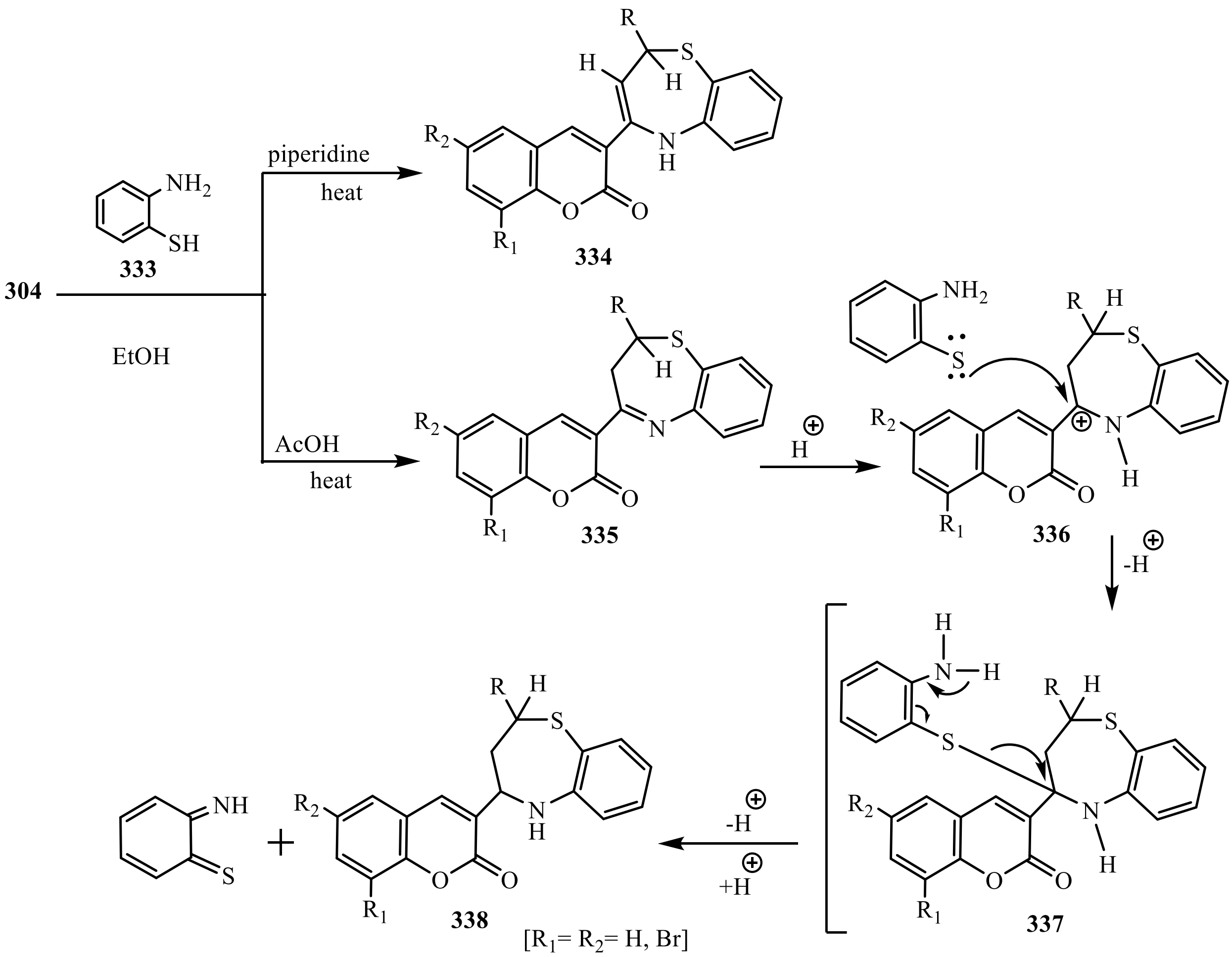
Scheme 56. Synthesis of substituted cinnamoylcoumarins **320a-s**

A series of 5-substituted aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazoline derivatives **329a-c** were synthesized by reacting **304a-c** with hydrazine derivatives **328** in the presence of hot pyridine[140] or acetic acid[142]. These compounds were screened for in vivo anti-inflammatory and analgesic activities at a dose of 200 mg/kg b.w[141]. Also, condensation of 3-acetyl-coumarin **1** with substituted benzaldehydes by using novel solvent-free method involving aheterogeneous catalyst, silica sulfuric acid, gave the corresponding chalcone **304 (**R=3,4,5-triCH_3O-C_6H_2; 3- $CH_3OC_6H_4$; 3,4-diCH_3O-C_6H_3; 4-CH_3O-C_6H_4; 2,5-diCH_3O-C_6H_3; 2,3,5-tri$CH_3OC_6H_2$; 2,4,5-tri$CH_3OC_6H_2$; 2-$CH_3OC_6H_4$; 2-ClC_6H_4, 2,5-di$CH_3OC_6H_4$. Treatment of **304** (R=3,4-di$CH_3OC_6H_3$) with hydrazine hydrate and phenyl hydrazine in the presence of acetic acid afforded pyrazolines **329** (R=3,4-di$CH_3OC_6H_3$, R_1=$COCH_3$ or C_6H_5) (Scheme 57).[143] Condensation of **304** with hydroxylamine hydrochloride **330** in ethanol gave the substituted isoxazolinocoumarin derivatives **331**.[144] Epoxidation of compound **304** using hydrogen peroxide in alkaline medium gave epoxy proprnoyl derivatives **332** (Scheme 57).[89]



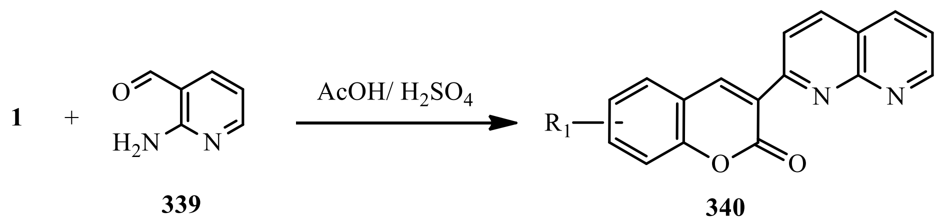
Scheme 57. Synthesis of pyridines **325**, **327**, pyrazolines **329**, isoxazoline **331** and oxirans **332**

Furthermore, compound **304** was reacted with 2-aminobenzenethiol **333** in ethanol in the presence of piperidine to yield 2-aryl-4-[2*H*-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothiazepine derivatives **334**. When the same reaction was repeated in the presence of acetic acid instead of piperidine, 2-aryl-4-[2*H*]-2-oxo-[1]benzopyran-3-yl]-2,3-dihydro-1,5-benzothiazepine derivatives **335** were produced. They were subjected to reduction with either sodium borohydride or *o*-aminothiophenol (*o*-ATP), contaminated with a little amount of di-O-aminophenyl disulphide in ethanol containing an acid (HCl or HBr) to give the tetrahydrobenzothiazepine derivatives **338**, through the intermediate **336** and **337** (Scheme 58).[145]



Scheme 58. Synthesis of tetrahydrobenzothiazepine derivatives **338**

Friedlander condensation of the 3-substituted coumarin derivatives **1** with 2-aminonicotinaldehyde **339** in the presence of glacial acetic acid containing a catalytic amount of conc. H_2SO_4 gave 3-(1, 8-naphthyridin-2-yl)-2*H*-1-benzopyran-2-one derivatives **340** (Scheme 59).[146]

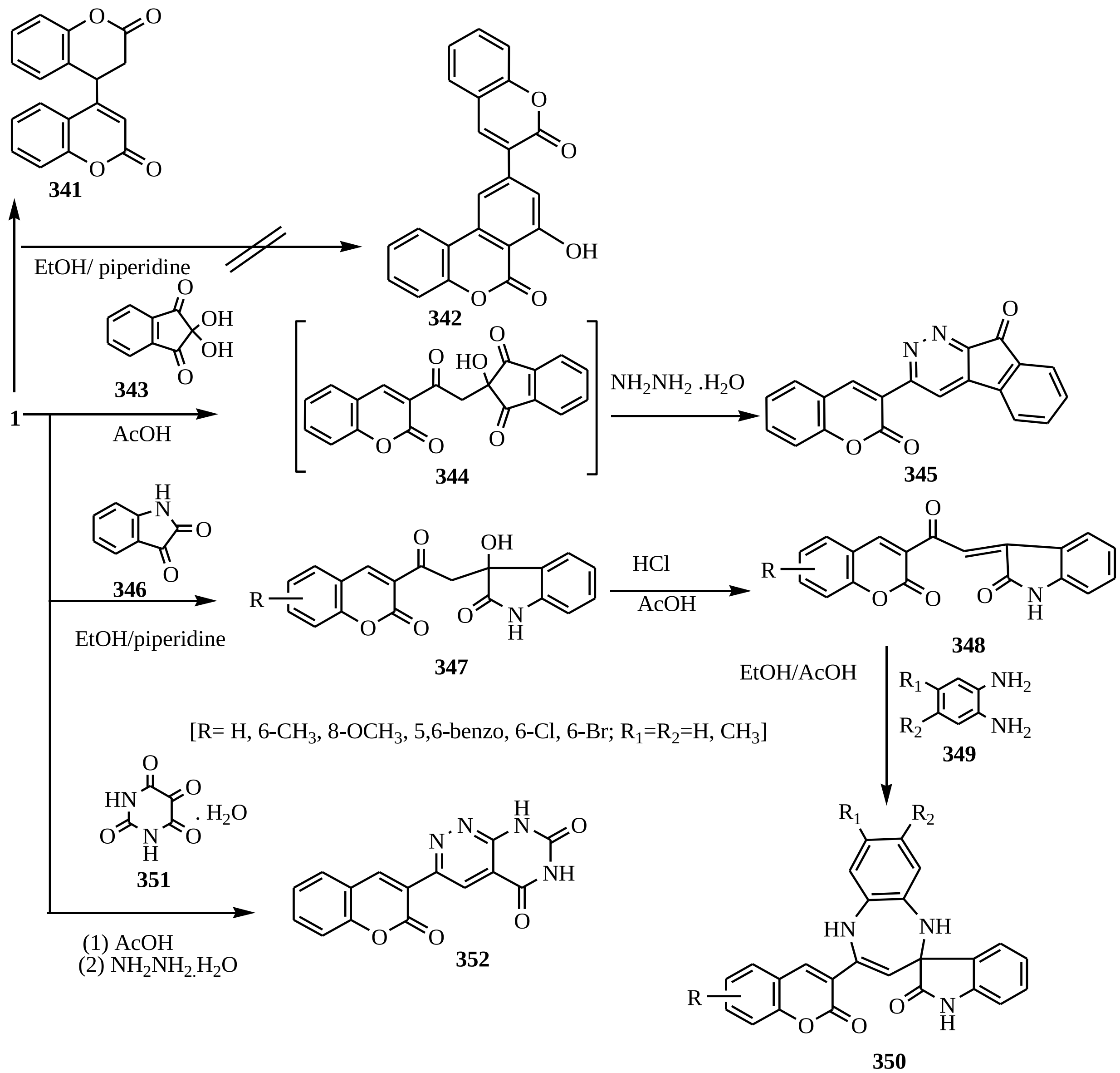


[R_1=H, 8-MeO, 7-HO, 6-Cl, 6-Br, 6, 8-Cl_2, 6, 8-Br_2, 6-NO_2, 8-NO_2, 5,6-benzo]

Scheme 59. Synthesis of 3-(1, 8-naphthyridin-2-yl)-2H-1-benzopyran-2-one derivatives **340**

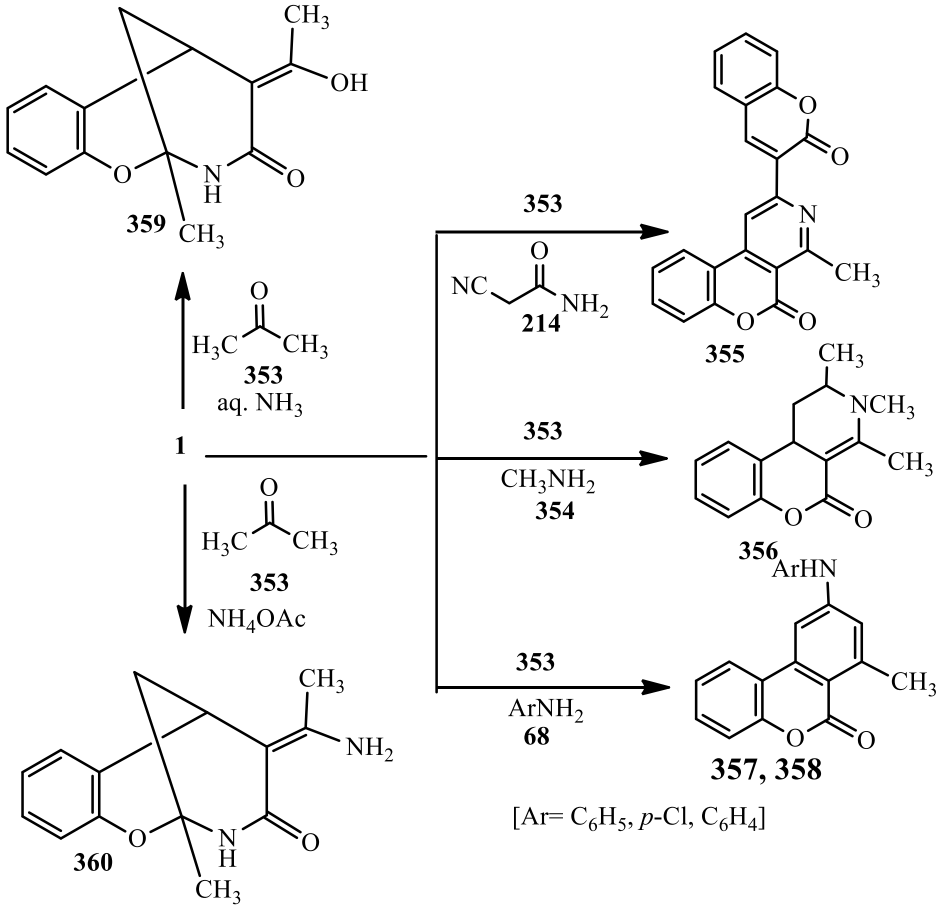
3-Acetylcoumarin **1**, refluxed in ethanol in the presence of piperidine, gave compound **341**, not **342**[147]. Moreover, the reaction of 3-acetylcoumarin **1** with ninhydrin **343** in ethanol in the presence of piperidine produced 2-hydroxy-2-[2-oxo-2-(2-oxo-2*H*-chromen-3-yl)-ethyl]indan-1,3-dione derivatives **344**, to which in-situ addition of hydrazine hydrate gave the corresponding 3-(2-oxo-2*H*-chromen-3-yl)-indeno[2,1-c]pyridazin-9-one derivatives **345** (Scheme 60).[148]

The reaction of 3-substituted coumarin derivatives **1** with isatin **346** in ethanol in presence of piperidine afforded the corresponding 3-[3'-hydroxy-2'-(oxo)indolo]acetylcoumarin derivatives **347**, which, on dehydration in HCl/AcOH, gave the corresponding α,β-unsaturated ketone derivatives **348**. Cyclocondensation reaction of compound **348** with substituted *o*-phenylenediamine derivatives **349** in ethanol in the presence of acetic acid afforded the novel 3-coumarinylspiro[indolo-1,5-benzodiazepine] derivatives **350** (Scheme 60).[149] Furthermore, the reaction of 3-acetylcoumarin **1** with alloxan monohydrate **351** in acetic acid, followed by treatment with hydrazine hydrate, afforded 3-(2-oxo-2*H*-chromen-3-yl)-6*H*, 8*H*-pyrimido[4,5-c]pyridazine-5,7-dione derivative **352** (Scheme 60).[150]



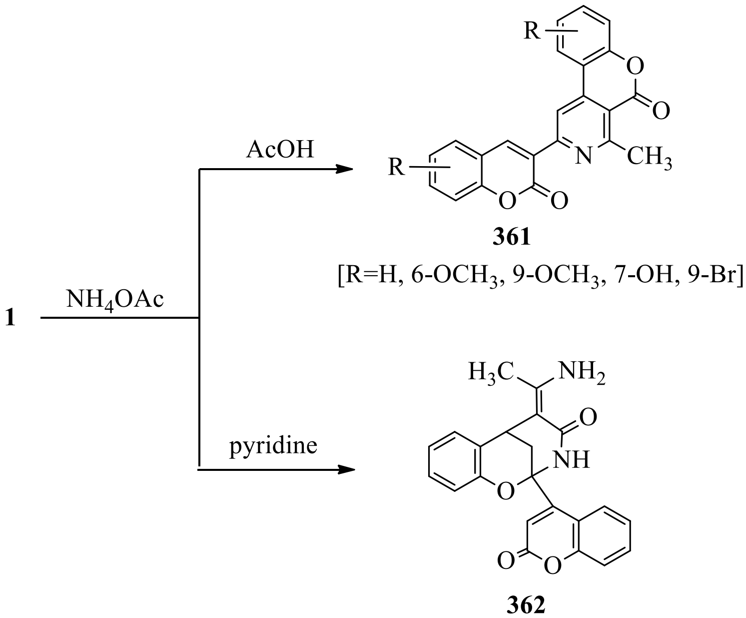
Scheme 60. Reaction of **1** with ninhydrin **343**, isatin **346** and alloxan **351**

3-Acetylcoumarin **1** was reacted with acetone **353** in the presence of cyanoacetamide **214**, [liprating ammonia which was reacted with 3-acetylcoumarin **1**], primary aliphatic amines **354** (e.g. methyl amine), primary aromatic amines **86** (e.g. aniline), aqueous ammonia or ammonium acetate to obtain the corresponding 2,4-dimethyl-5*H*-chromeno[3,4-c]pyridine-5-one **355**, 9-bromo-2,3,4-trimethyl-2,3-dihydro-1*H*-chromeno[3,4-c]pyridin-5(10b*H*)-one **356**, aminobenzocoumarin derivatives **357** and **258**, tricyclic derivatives **359** or enamine derivative **360**, respectively (Scheme 61).[151,152]



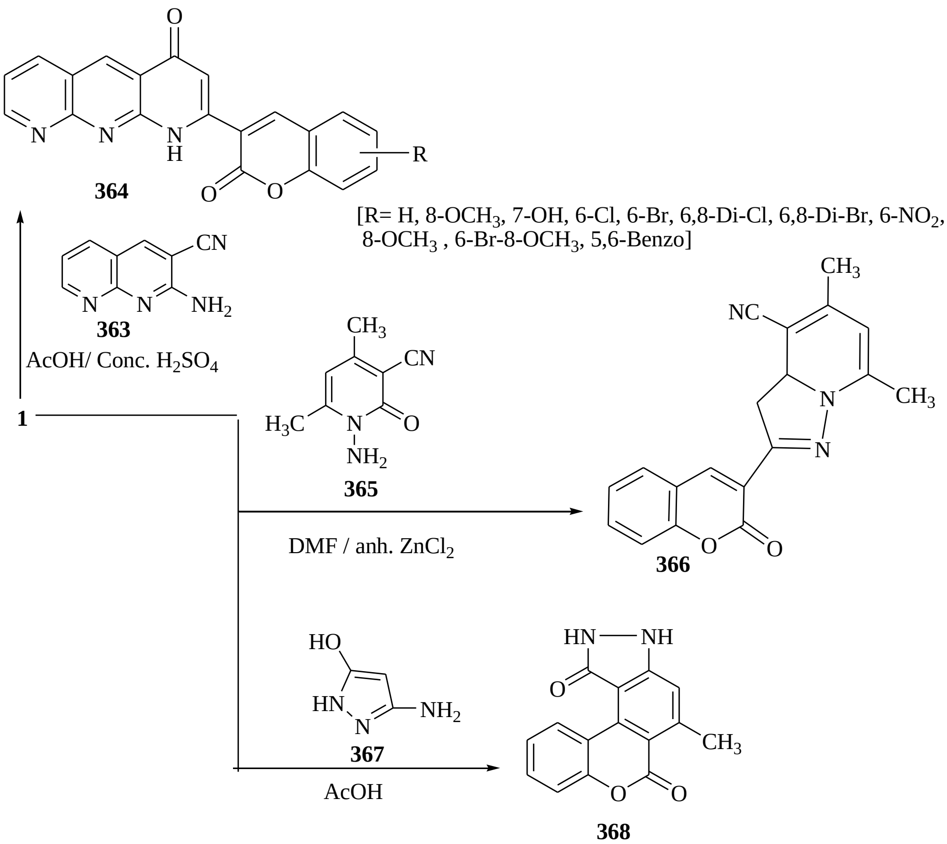
Scheme 61. Reaction of **1** with acetone **353**

Condensation of 3-substituted coumarin derivatives **1** with ammonium acetate afforded a chemoselective high yield of the corresponding (oxobenzopyranyl)benzopyranopyridinone derivatives **361** in boiling acetic acid or gave methanobenzoxazocine derivative **362** in boiling pyridine (Scheme 62).[153]



Scheme 62. Reaction of **1** with ammonium acetate

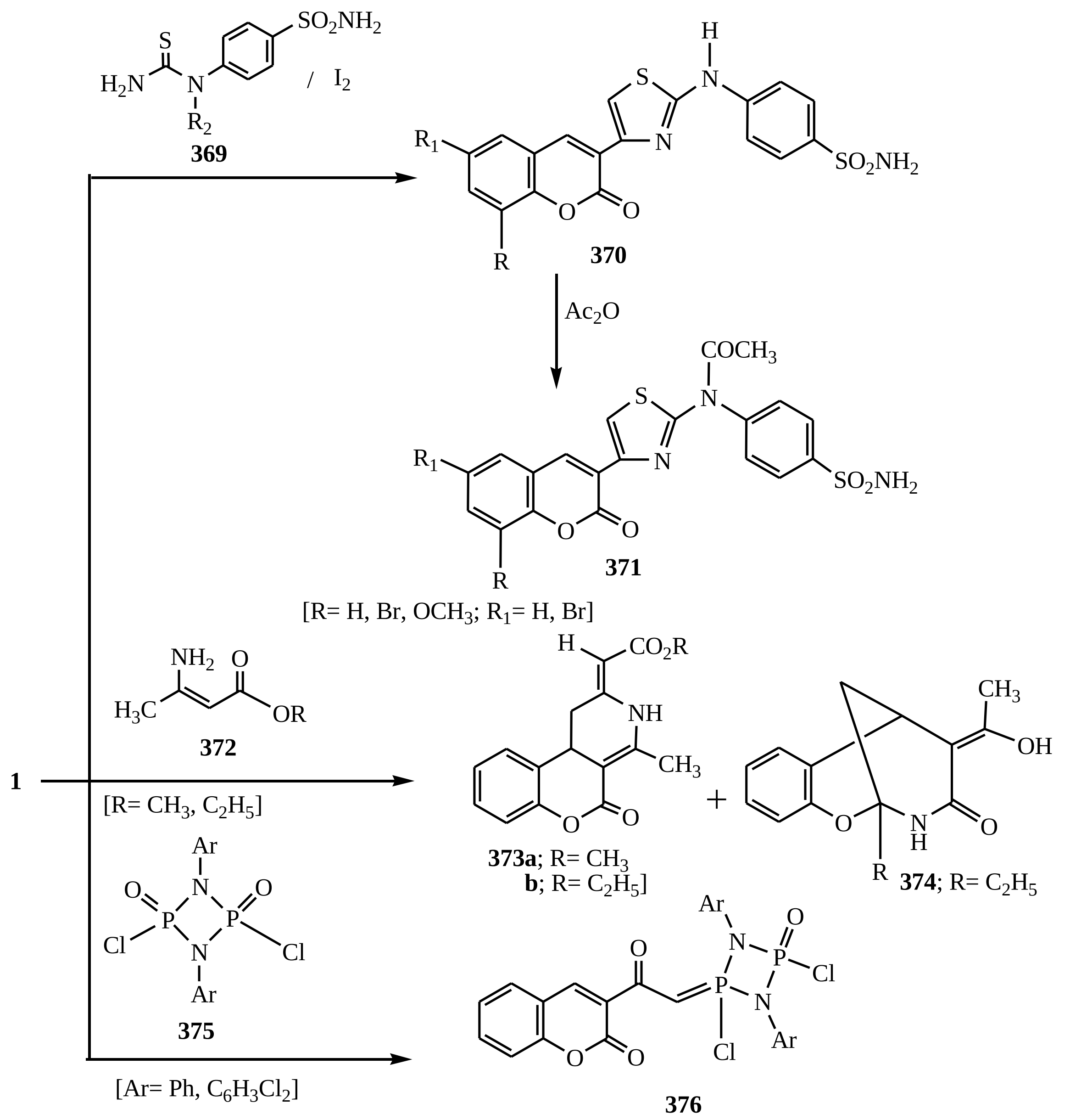
3-Acetylcoumarin **1** was reacted with 2-amino-3-cyano-1,8-naphthypyridine **363** in glacial acetic acid in the presence of a catalytic amount of concentrated sulfuric acid to give 2-(3-coumarinyl)-(1*H*)-anthyridinone derivatives **364**.[154] Moreover, condensation of 3-acetylcoumarin **1** with *N*-amino-3-cyano-4, 6-dimethyl-2-(1*H*)-pyridone **365** in dimethylformamide in the presence of anhydrous zinc chloride afforded the pyrazolo[1,5-a]pyridine derivatives **366**.[155] Furthermore, the reaction of **1** with 3-amino-1*H*-pyrazol-5(4*H*)-one **367** in acetic acid gave a comparable yield of poly heterocycle **368** (Scheme 63).[156]



Scheme 63. Reaction of **1** with heterocyclic amines **363, 365** and **367**

2.20. Reaction with thiourea derivatives

3-Substituted coumarin derivatives **1** were reacted with substituted thiourea derivatives **369** in the presence of iodine to give the substituted 3-(2-arylamino-4-thiazolyl)-2-1-benzopyran-2-one derivatives **370**, which were then converted into their acetyl derivatives **371**(Scheme 64)[157].



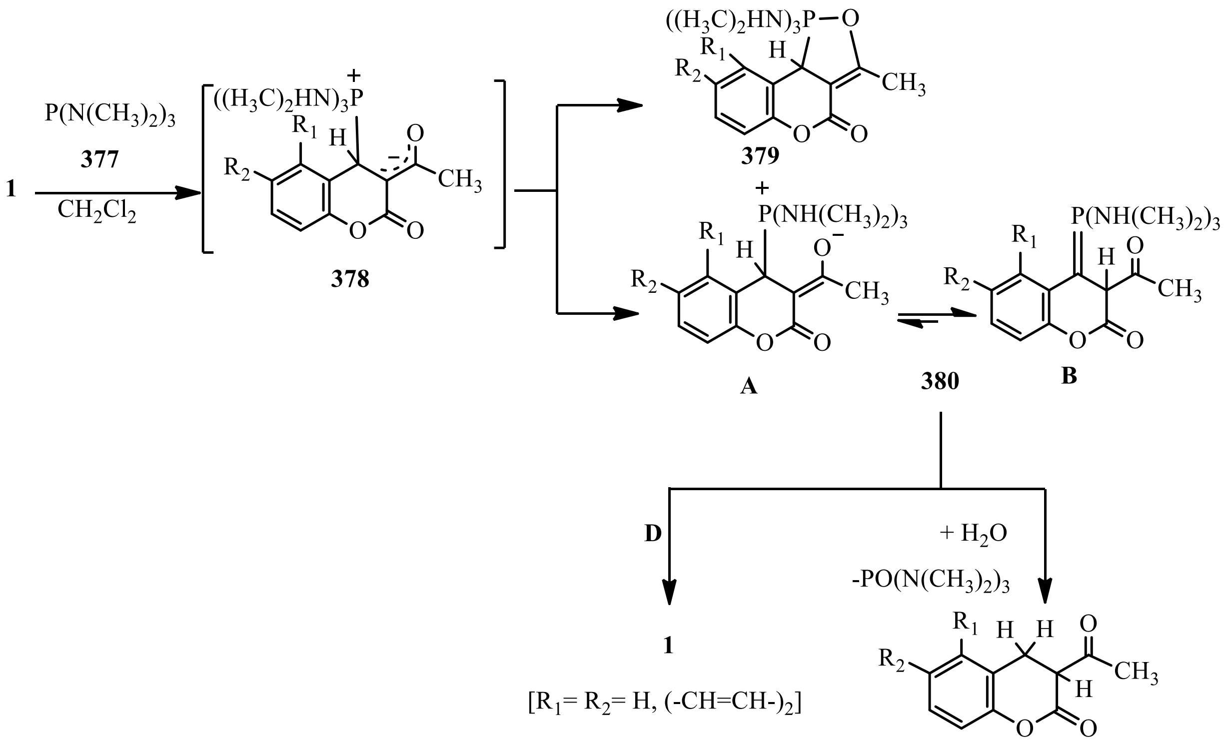
Scheme 64. Reaction of **1** with thioureas **369,** enamines **372** and 1,3-diarylhexachlorocyclo-diphosphazane **375**

2.21. Reaction with enamineone

Cyclocondensation reaction of 3-acetylcoumarin **1** with the enamine of methyl acetoacetate **372** afforded only benzopyranopyridine derivative **373a**, while using ethyl acetoacetate instead of methyl acetoacetate afforded **373b** together with tricyclic derivative **374** (scheme 64).[158]

2.22. Reaction with diphosphazane derivative and triaminophosphine

Condensation of 3-acetylcoumarin **1** with 1,3-diarylhexachlorocyclodiphosphazane derivatives **375** yielded the corresponding carbonyl methylene derivative **376** (Scheme 64).[159] 3-Substituted coumarin **1** was reacted with triaminophosphine **377** in methylene chloride at 5 ^{0}C to give the corresponding trisdimethylamino-2-acetyl(3*H*)naphtha[2,1-b][1*H*-3-oxo-pyran-1-yl]phosphorane **380** through the intermediate **378**. Treatment of **380** with water resulted in its conversion to the reduced form **381**. On heating the amino-ylide derivatives **380** above their melting points under reduced pressure, the starting material **1** was produced (Scheme 65).[50]



Scheme 65. Synthesis of dihydro-3-aceylcoumarins **381**

2.23. Reaction with lithium tetramethyl thallium

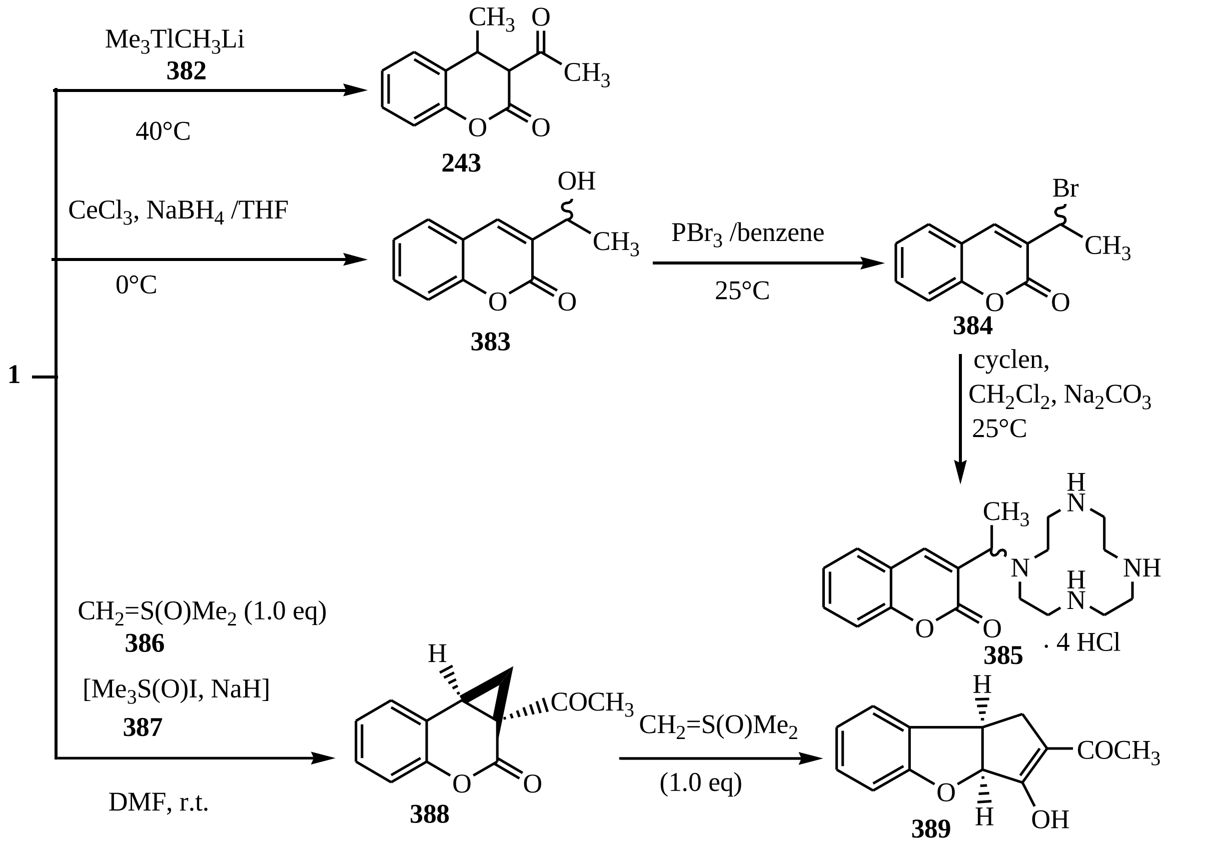
Condensation of 3-acetylcoumarin **1** with lithium tetramethyl thallium **382** at 40 ^{0}C gave the conjugated (1,4) addition product 4-methyl-3-acetyl coumarin **243** (Scheme 66).[160]

2.23.1. Reaction with $NaBH_4$/$CeCl_3$

Reduction of 3-acetylcoumarin **1** under Luche's condition ($NaBH_4$, $CeCl_3$) afforded the secondary alcohol **383**, which was brominated with PBr_3 to give the corresponding bromocoumarin derivative **384**. N-alkylation of **384** with 1,4,7,10-tetraazacyclododecane yielded the monosubstituted cyclen derivative **385** (Scheme 66).[161]

2.24. Reaction with dimethylsulfoxonium methylide

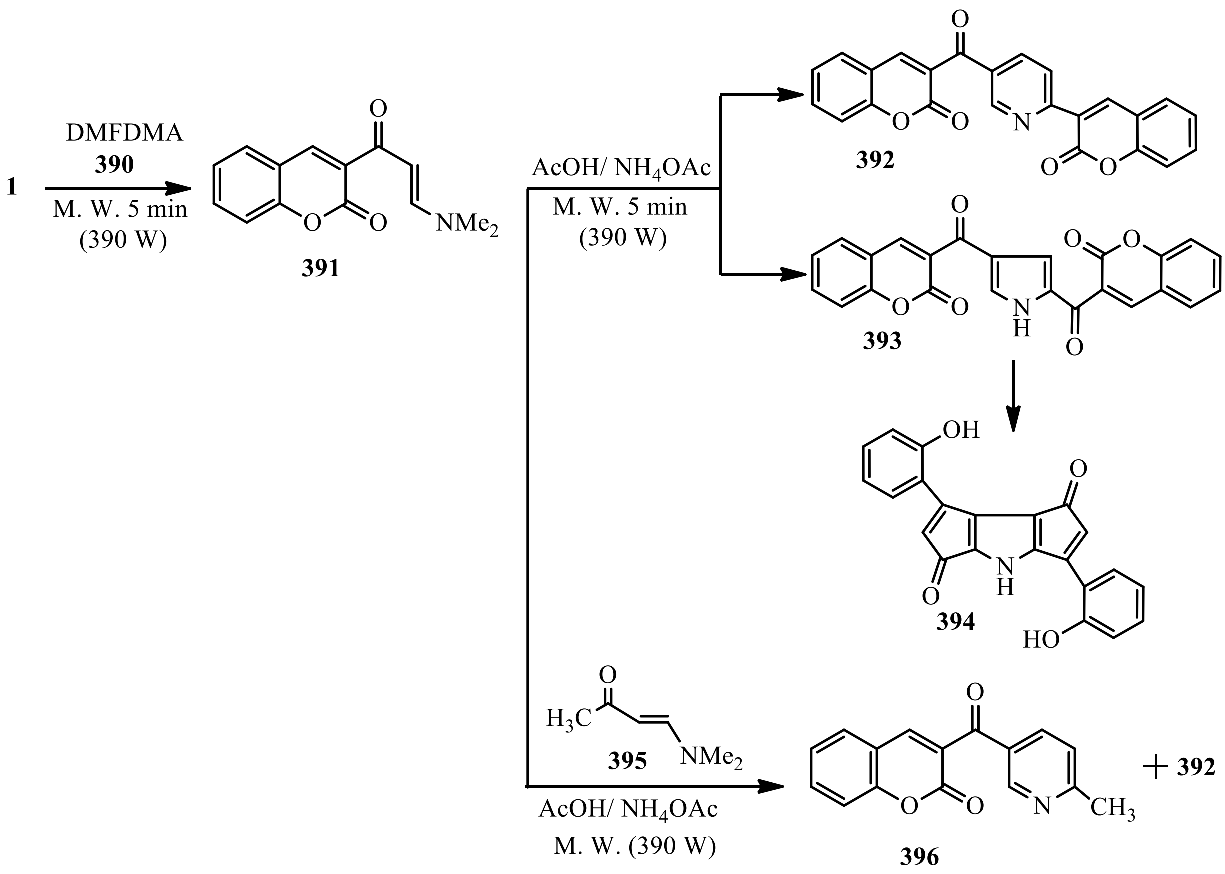
When 3-acetylcoumarin **1** was treated with 2.4 equivalent of dimethylsulfoxonium methylide **386** at room temperature in dimethylformamide or DMSO, novel (3a R*, 8a S*)-2-acetyl-3a,8b-dihydro-1*H*-cyclopenta-[b]benzofuran-3-ol **389** was obtained through **338** (Scheme 66).[162]



Scheme 66. Reaction of **1** with lithium tetramethyl thallium **382** , $CeCl_3$ and dimethylsulfoxonium **386**

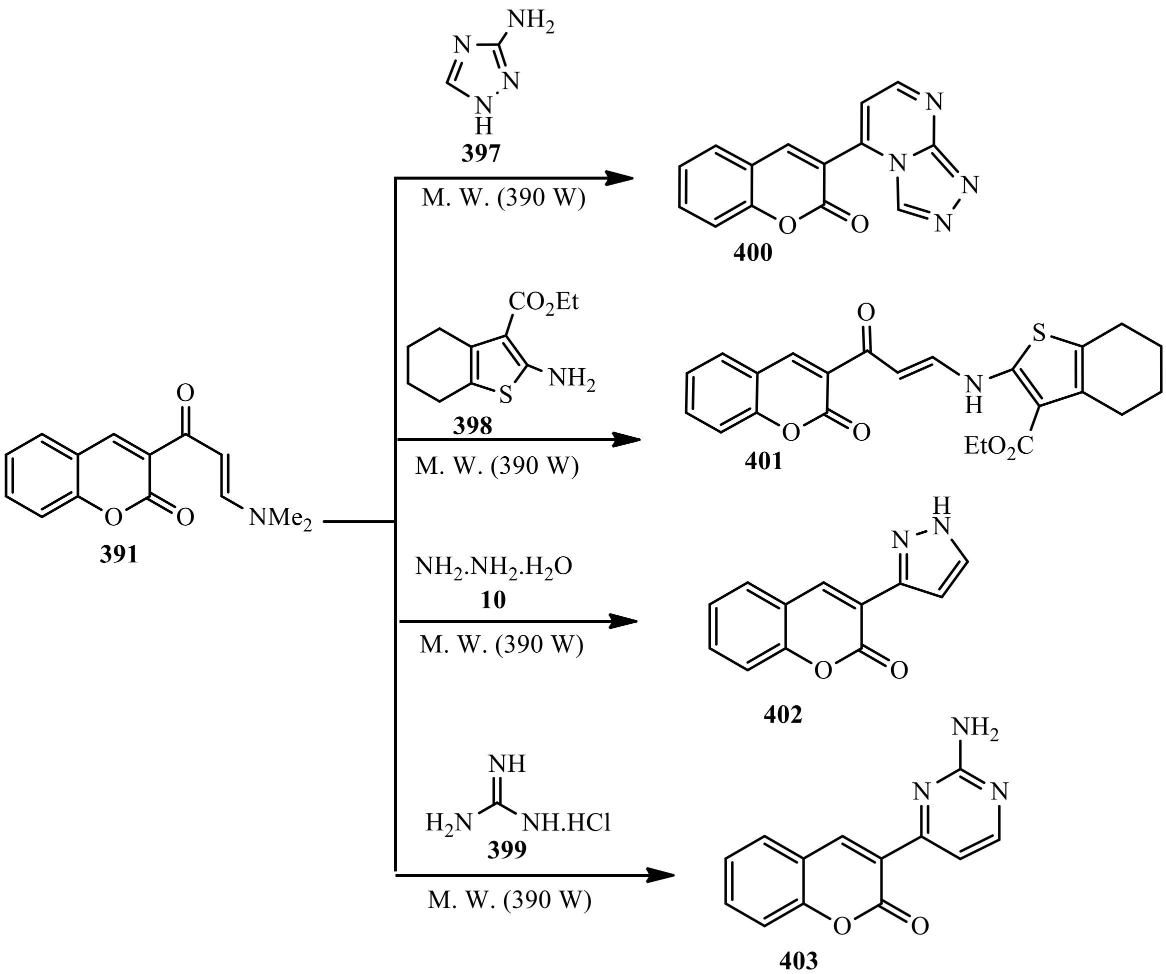
2.25. Reaction with dimethylformamide dimethylacetal

Enaminone **391**[163] was obtained by reacting 3-acetylcoumarin **1** with dimethylformamide dimethylacetal (DMFDMA) **390** in a microwave oven (390 W). The yield was found to be much higher than heating in a solvent. It was reported in the literature[163] that enaminone **391**, when refluxed in acetic acid in the presence of ammonium acetate, gave the pyridine derivative **392**, but the same reaction when occurred in a microwave oven (390 W) instead of refluxing, produced a compund with a molecular formula of $C_{22}H_{13}NO_4$, for which a structure, **394**, was suggested, through a Nenitzescu like cyclization[164] **393** and decarboxylation **394** products, respectively. Furthermore, the reaction of compound **391** with enaminone **395** in a microwave oven (390 W) gave a mixture of **396** and **392** (Scheme 67).[163,165]



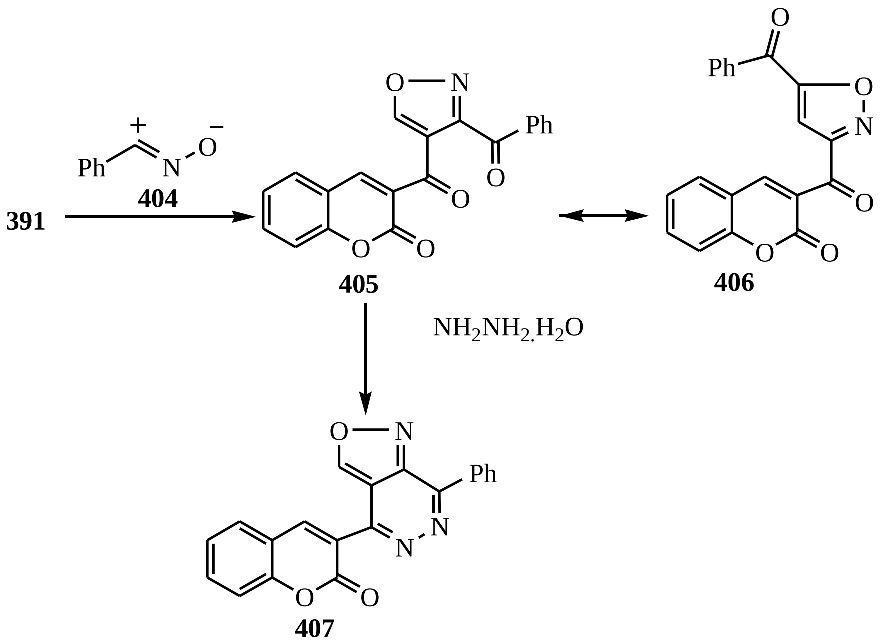
Scheme 67. Reaction of **1** with dimethylformamide dimethylacetal **390**

Furthermore, enaminone **391** was reacted with nitrogen nucleophiles in a microwave oven (390 W) such as 3(5)1,2,4-aminotriazole **397**, ethyl 2-amino tetrahydrobenzo-[b]thiophene-3-carboxylate **398**, hydrazine hydrate **10** and guanidine hydrochloride **399** to afford the corresponding 5-(coumarin-3-yl)-1,2,4-triazolo[4,3-a]pyrimidine **400**, 2-[3-oxo-3-(2-oxo-2*H*-chromen-3-yl)-propenyl-amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester **401**, 3-(coumarin-3-yl)-pyrazole **402** and 2-amino-4-(coumarin-3-yl)pyrimidine **403**, respectively (Scheme 68).[165]



Scheme 68. Reaction of enaminone **391** with nitrogen nucleophiles 10, **397-399**

The reaction of enaminone **391** with nitrile oxide **404** gave the isoxazole derivative **405**, rather than the potential isomeric product **406**. The isoxazole **405** was reacted with hydrazine hydrate to give the coumarinyl isoxazolopyridazine **407** (Scheme 69).[166]



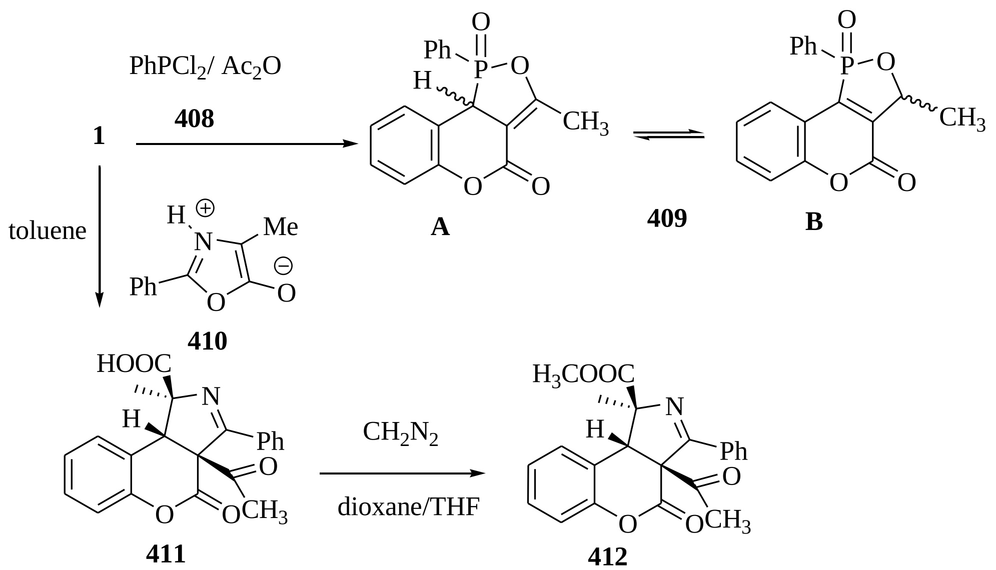
Scheme 69. Reaction of enaminone **391** with nitrile oxide **404**

2.26. Reaction with dichloro phenyl phosphine

Addition of dichloro phenyl phosphine ($PhPCl_2$) **408** to 3-acetylcoumarin **1** in the presence of acetic anhydride afforded coumarino[3,4-c]-3*H*-10-methyl-2-oxo-2-phenyl-1,2-oxaphosphole **409A**, which underwent an allylic rearrangement to give the isomeric coumarino[3,4-c]-9*H*-9-methyl-2-oxo-2-phenyl-1, 2-oxaphosphole **409**B (Scheme 70)[167].

2.27. Reaction with 4-methyl-2-phenyl-1,3-oxazol-5(4H)- one

Strirring of 3-acetyl coumarin **1** with 4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-one (MPO**4**) **410** under reflux in toluene afforded 3-acetyl[3,4-c]pyrrolecoumarin acid **411**. Furthermore, **411** was prepared in another route *via* triturating the same reactants together in a mortar rapidly and then reacting in a sealed vial in a bath set at 100 ^{0}C for 15–20 min. Stirring of **411** with fresh ethereal diazomethane solution in dioxane/THF at room temperature afforded the methyl ester **412** (Scheme 70).[168]



Scheme 70. Reaction of **1** with dichloro phenyl phosphine **408** and **4-**methyl-2-phenyl-1,3-oxazol-5(4H)- one **410**

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