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Review of Studies on Novel Drug Discovery of Coumarin Chalcone Derivatives, DFT Study and Its Biological Activity

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Abstract: *This review presents a orderly and complete survey of the method of preparation, the chemical reactivity, and the anti-microbial properties linked with this system Coumarins and chalcones are possible pharmacological and biologically active molecules got from the natural source. Coumarins and its chalcone have chief pharmacological activities such as antidiabetic, antitumor, and anti-inflammatory activity. This work elucidates the current information about synthesis practices, pharmacologic importance, and scientific applications of coumarinyl chalcone derivatives. The DFT worldwide chemical awareness signifiers were calculated for the created compounds and used to predict their comparative stability and reactivity.*
Index Terms: *3acetylcoumarin, biological activity, Chalcone, Coumarin, Density functional theory.*

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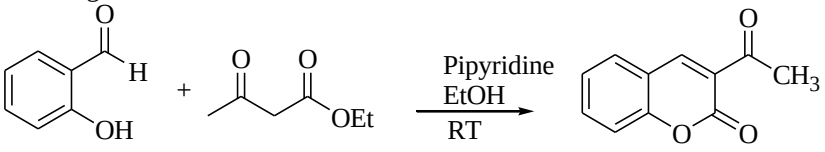
I. INTRODUCTION

Coumarins are pharmacologically vital compounds got from natural sources. Coumarin is 2H-chromen-2-one which fits to benzopyrone class [47]. Coumarin is an oxygen heterocyclic compound, which plays an important part in the kingdom of natural products and synthetic organic chemistry. Naturally happening coumarins are found in many plants, remarkably in high concentration in tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, Ceylon cinnamon, sweet clover, and bison grass. Coumarin was first remote from coumarone in 1820 and it has been used in perfumes since 1882 due to its enjoyable (sweet) smell. It was first synthesized in 1868 [49]. Coumarin based chalcones are reported for their anticancer [50] antioxidant, antibacterial [12], anti-inflammatory [38] antiviral [45], Trypanocidel [46], analgesic [16] and antiproliferative [30] activities. In the present study, a series of coumarin-based compounds containing a chalcone moiety were studied for their in vitro and in silico properties. The combination of coumarin chalcones has involved considerable attention of organic and medicinal chemists due to their wide usage in food seasonings, fragrances, pharmaceuticals, and agrochemicals [32]. The DFT worldwide chemical awareness descriptors (chemical hardness, total energy, electronic chemical potential and electrophilicity) were calculated for four manufactured compounds and used to predict their relative stability and reactivity [39]. The present review showed a broad view of the synthesis and biological properties expressed by compounds having a coumarin nucleus.

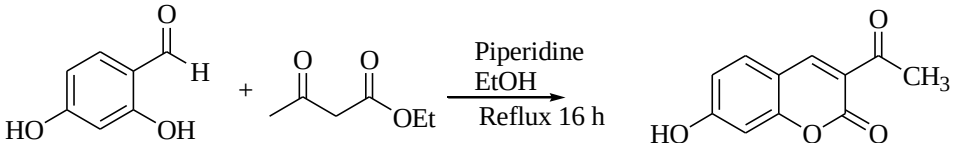
II. SYNTHESIS

Savita Patil *et al*[31] reported the synthesis of 3-Acetylcoumarin P was prepared from salicylaldehyde and ethyl acetoacetate in piperidine with present or absent of Ethanol for 2 to 6 hours at room temperature through Knovengel reaction.



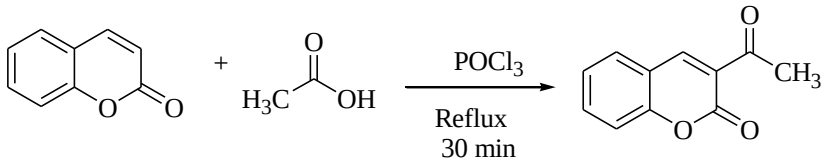
Salisaldehyde Ethylaceto acetate 3-acetyl coumarin

Shubhangi S.Soman et al [41] have synthesized 3-acetyl-7 hydroxy coumarin from 2,4-dihydroxy benzaldehyde and ethyl aceto acetate in catalytic amount of piperidine in ethanol with good yield.

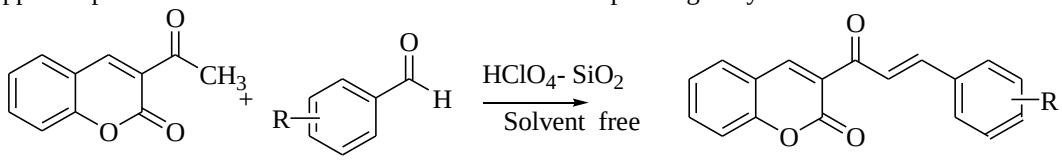


Ajani et al [5] reported microwaves assisted one opt reaction of salicylaldehyde with ethyl acetoacetate in piperidine to afford 3-acetylcoumarin with good yield.

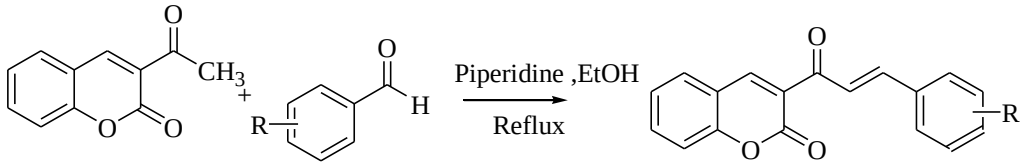
The Soby Devasia [42] was prepared 3-acetyl coumarin in his Ph.D. work from 2H-1-benzopyran-2-one in acetic acid phosphrous oxychloride The mixture was heated at reflux for 30 minutes. After cooling, the precipitate was collected and recrystallized from ethanol. The yield was 89% and the melting point was119-1210C.



Zeba N Siddique [51] was work on synthesis of coumarin chalcone derivative by green approach by using silica supported perchloric acid under solvent free condition to reported good yield.

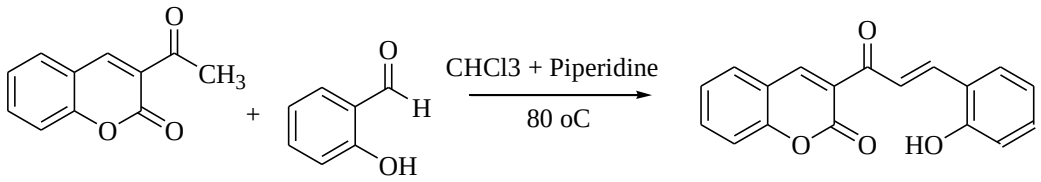


Saleta Vazquez-Rodriguez et al [36] was work on Synthesis and Trypanocidel Properties of New Coumarin-Chalcone Derivatives.

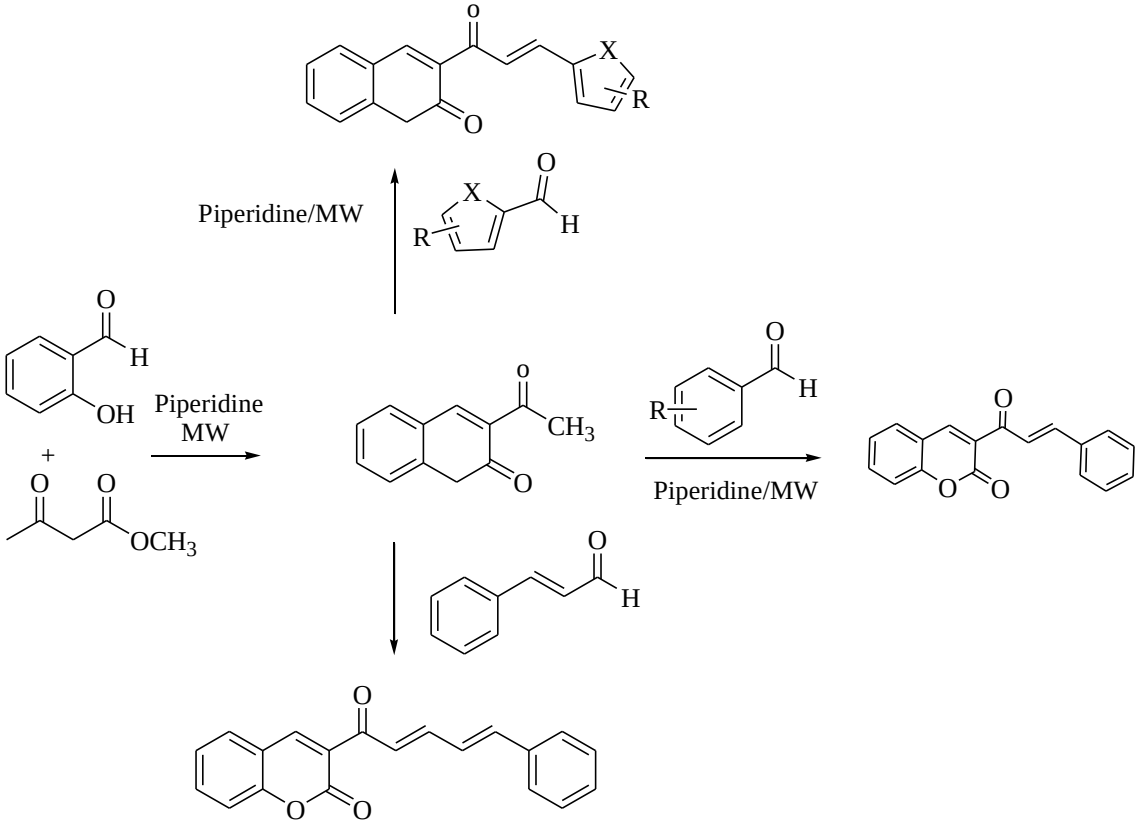


Savita Patil et al [31] was also synthesized the Coumarin-Chalcone Derivatives by same method as above discuss for the purpose, to confirmed the considerable antioxidant activity of new hydroxylated coumarin-chalcone hybrid compounds.

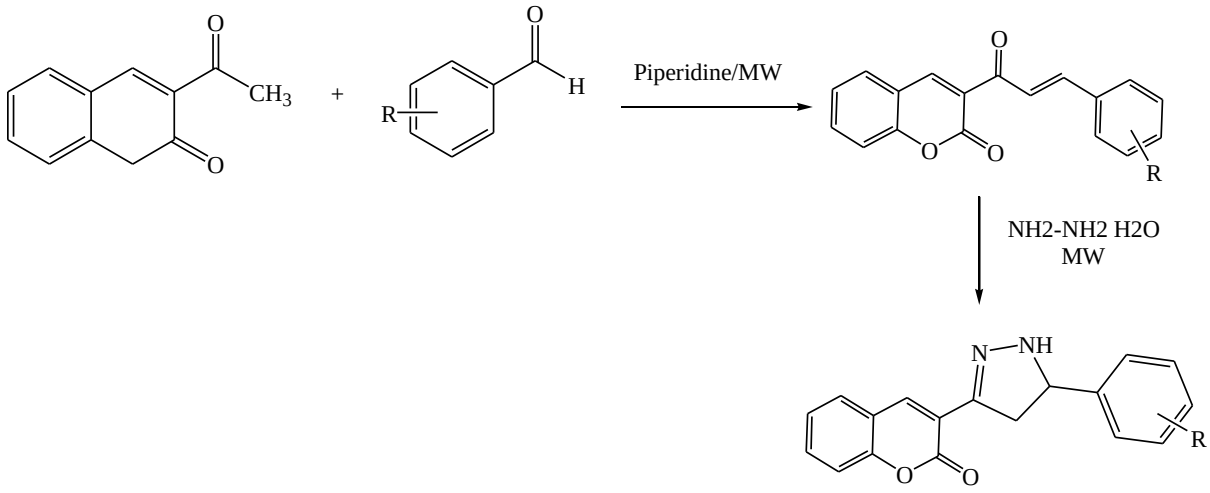
Afef Ghouili et al [2] was synthesized the 2-hydroxy coumarin chalcone by using Chloroform solvent in presence of Piperidine base reflux at 80^{o}C for the purpose of X-ray structure determination



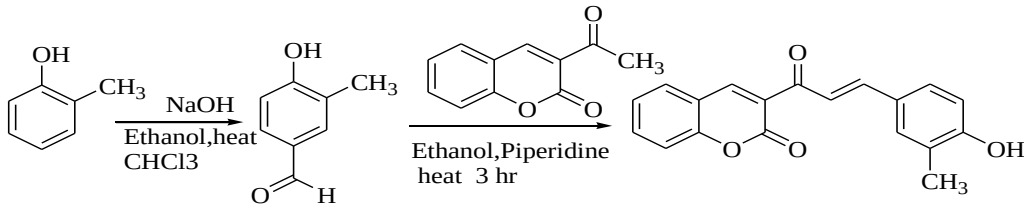
Ajani et al [4] reported microwaves assisted one opt reaction of salicylaldehyde with ethyl acetoacetate in piperidine to afford 3-acetylcoumarin and it was condensed with different aromatic aldehydes to give the corresponding chalcones respectively in high yield within 1-3 minutes.



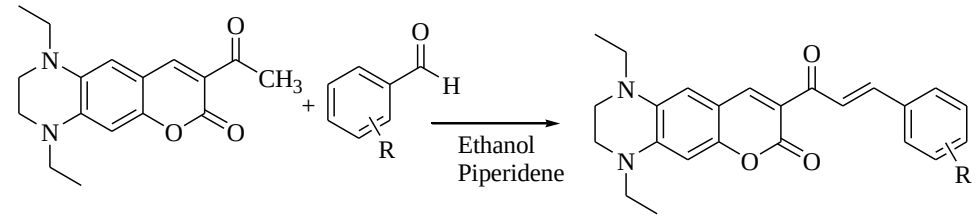
In addition, Ajani et al prepared a variety of 1H-pyrazol-3-yl)-2H-chromen-2-ones in higher yields at shorter reaction times via cyclization of the corresponding arylidene with hydrazine hydrate in the presence of microwave. The formed pyrazolines were investigated for their antimicrobial activities using agar diffusion method. The result showed that the most active antibacterial agent was 3-(5-(4-[diethylamino] phenyl)-4,5-dihydro-1H-pyrazol3-yl)-2H-chromen-2-one with MIC and MBC values of 3.92 ± 0.22 and 7.82 ± 0.43 mg/mL respectively that may be attributed to presence of N(Et)2 moiety.



Ismiyarto et al [14] was work on synthesis of 4-hydroxy 3-methyl benzaldehyde proceed through the Reimer Tieman reaction using chloroform and NaOH reagent and then it is reacted with 3-acetyl coumarin to formed 3-(3-(4-hydroxy 3-methyl phenyl) acryloyl coumarin for the purpose to check the antibacterial activity against Escherichia coli and Staphylococcus aureus.

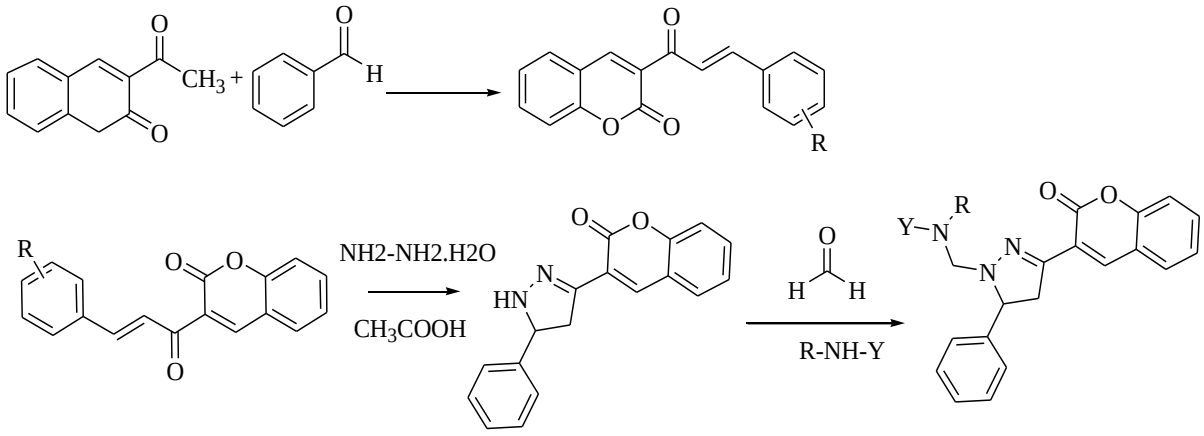


Amit R. Jagtap et al [15] was work on novel highly fluorescent coumarin chalcone by using 8-acetyl-1,4-diethyl-1,2,3,4-tetra hydro-7H-pyrano (2,3) quinoxaline 7 one and benzaldehyde with piperidine as a base for the purpose of spectral characteristic such as absorption maxima, emission maxima, extinction coefficient and fluorescent maxima of acetyl coumarin and coumarin chalcones.

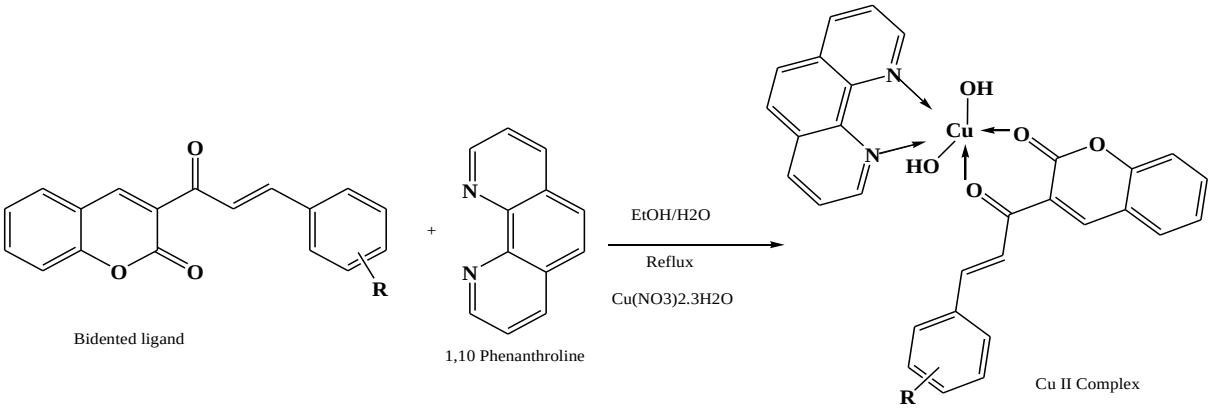


Laxminarayan et al [21] reported the synthesis of 3-(3-phenyl-acryloyl) chromen -2-one from 3-acetyl coumarin and benzaldehyde was stirred in water and methanol in presence of sodium hydroxide for 4 hr. and kept reaction mass for overnight in ice – bath then the product was treated NH2-NH2 to formed 3-(5-phenyl 4-5 dihydro-1H-pyrazol-3-yl)-chromen-2-one further reaction with aldehyde derivative and amino compounds in methanol to formed substituted pyrazole compound.

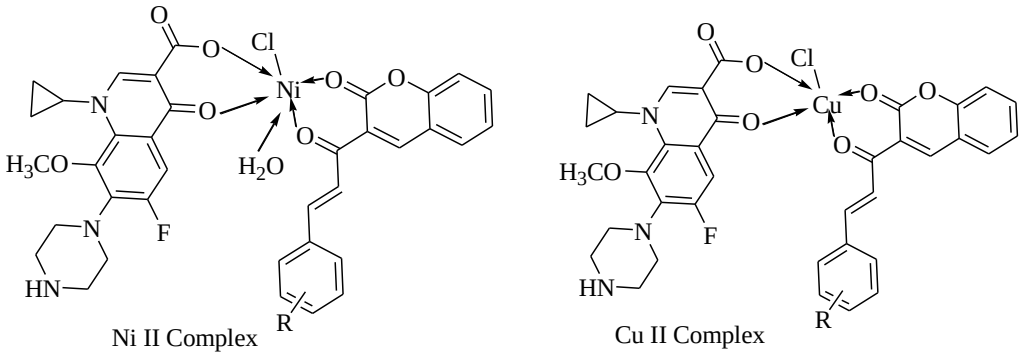
Laxminarayan et al [33] reported the additional work on the newly synthesized pyrazole compounds were screening for their antibacterial activity and antifungal activity.



Jiten C. Patel et al [28] were worked on neutral bidental ligands synthesized using Claisen-Schmidt condensation with 1:1 molar ration of 3- acetyl coumarin and different substituted aromatic aldehyde with piperidine as a catalyst in ethanol. Then by using this ligand to formed copper complex with the help of ethanolic solution of 10 Phenanthroline.

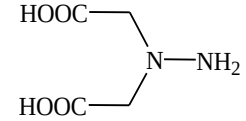


Jiten C. Patel et al [29] were assigned different geometry for Cu (II) and Ni (II) complexes on the basis of electronic magnetic moment value and thermogravimetric analysis. Jiten C. Patel et al study on its antimicrobial, Antituberculosis study and also works on thermal studies of Cu (II) Complex i.e. TG, DTG and DSc and metal interaction with two distinct biological compound is beneficial to prepared biologically potent agents against infectious disease.

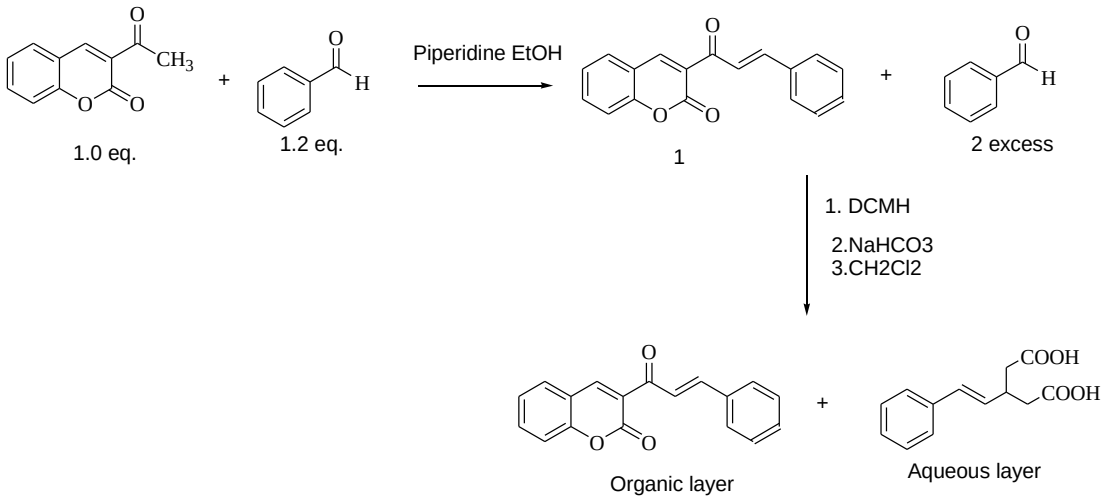


Maomin Zhen et al [23] was found to the N,N-dicarboxymethyl hydrazine (DCMH) is a chemoselactive derivatization reagent of carbonyl compound and its potential applications in organic synthesis was investigated for the first time. Maomin Zhen et al was found the application of DCMH as a novel and chemoselactive protective reagent of aldehyde. DCMH is remove the excess of aldehyde in the presence of ketone and also used in the isolation of aldehyde from natural plant products.

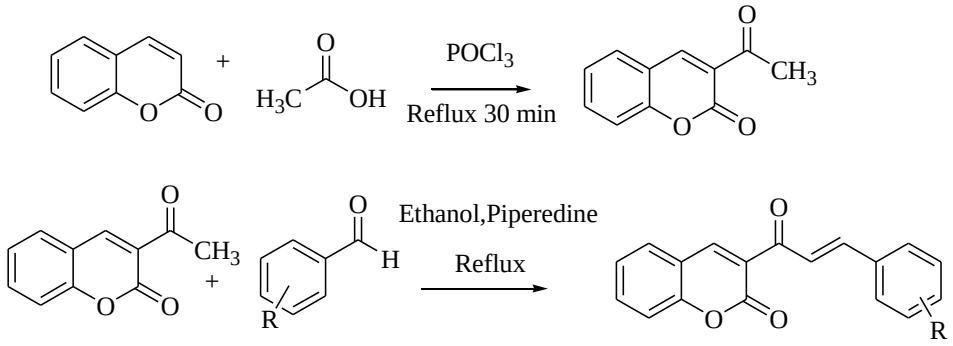
Structure of DCMH



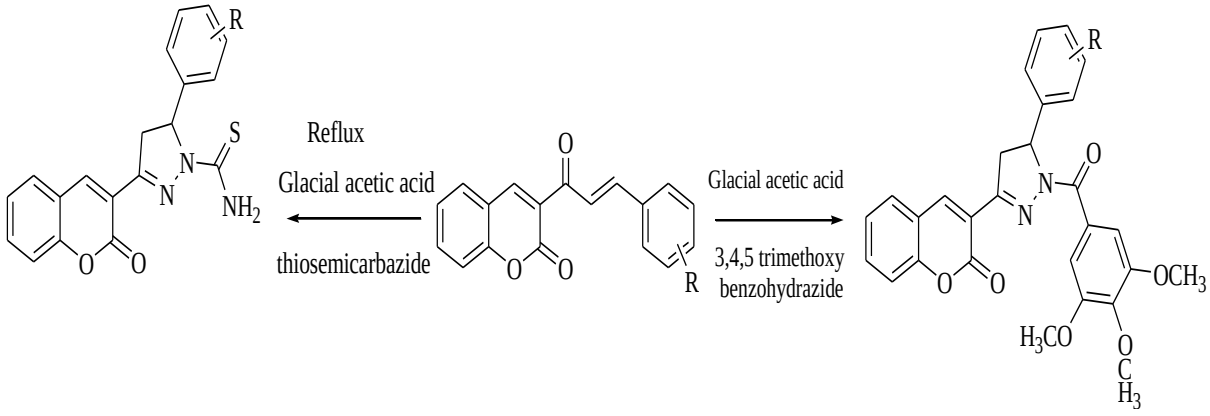
N.N-dicarboxymethyl hydrazine



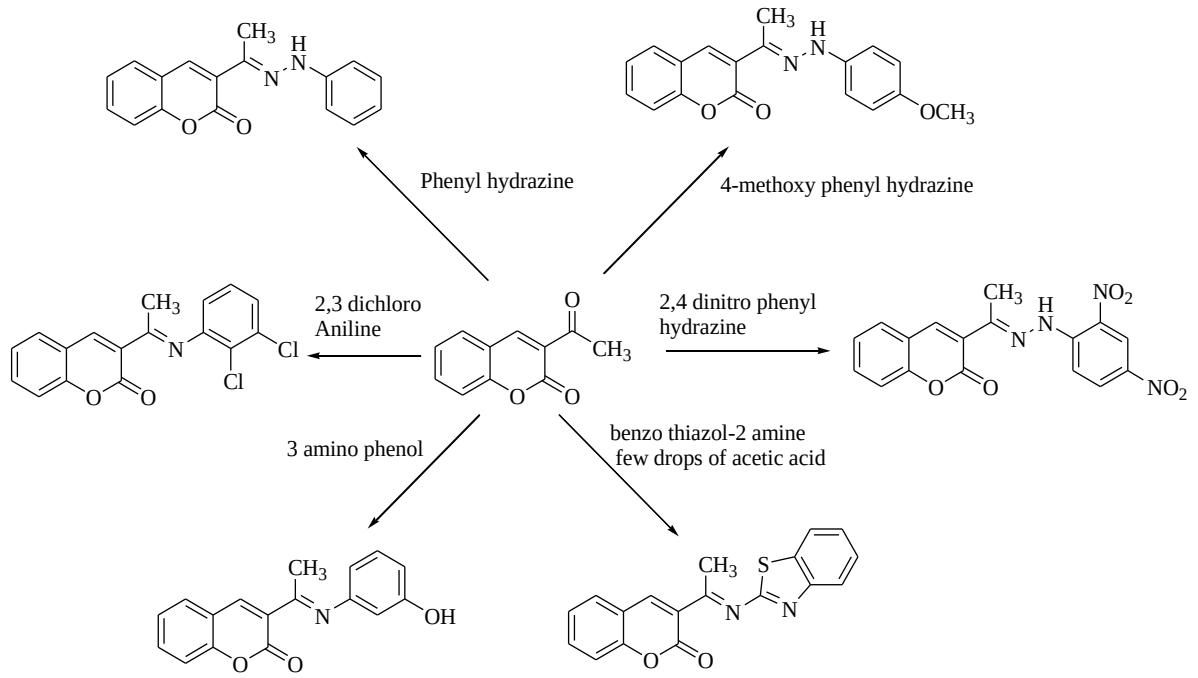
Soby Devasia [42] was studies on the Novel Discovery through isolation of lead molecules (coumarin) from plants and optimization using combinational approach in his Ph.D. thesis. Soby Devasia isolate the coumarin from Dipteryxodorata tree is called Tonka beans. Soby Devasia was synthesized the various chalcone derivative of 3-acetyl coumarin with different aldehyde derivative.



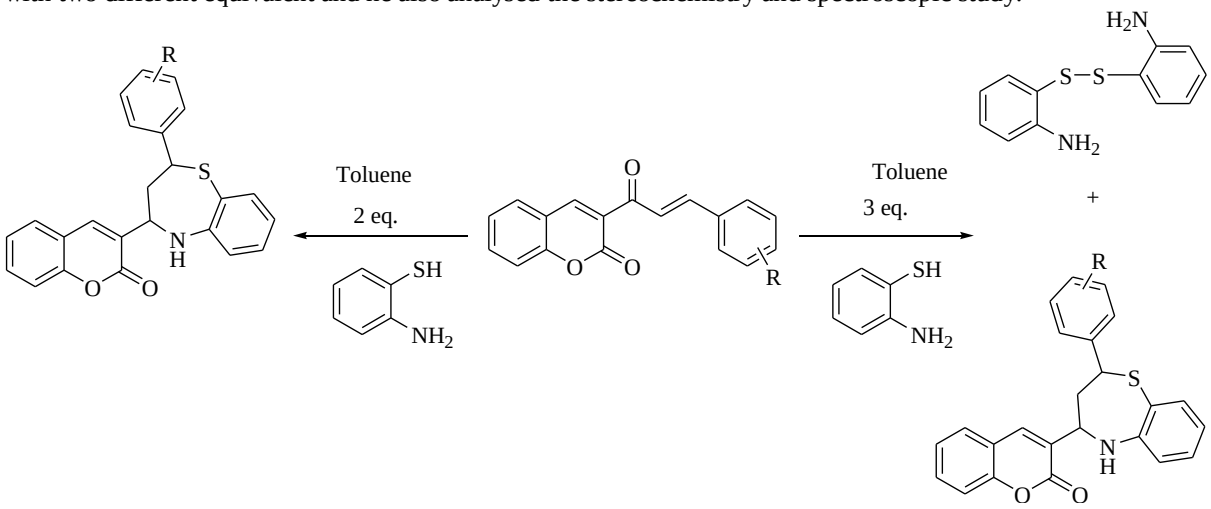
R = 4-OCH3, 4- C(CH3)3, 4-N(CH3)2, 4- Cl, 3,4- dimethoxy, 4-hydroxy-3-methoxy, 3-bromo-2-hydroxy



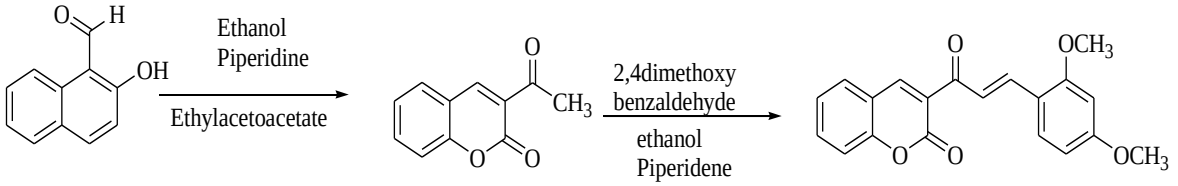
Soby Devasia [42] gives the idea about Drug likeness property of the coumarin compound and also gives the idea about Dock Score and conformation of the ligands.



Albert levai et al [6] was worked on 3-acetyl coumarin chalcone derivative is reactive with 2-aminothio phenol with two different equivalent and he also analysed the stereochemistry and spectroscopic study.

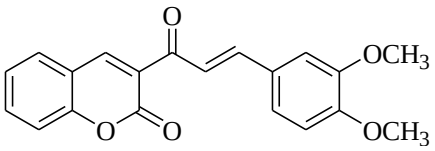


Muhammad Shabbir et al [40] have worked on synthesized coumarin appended chalcone derivatives (2-[3-(2,4-Dimethoxy-phynyl)-3H-benzo chromen-3-one) by Claisen Schmidt aldol condensation reaction and also studies on molecular geometry and electronic spectra by using DFT (Density Functional Theory) in the frame work on dual approach comprising of experimental and Quantum computational techniques.

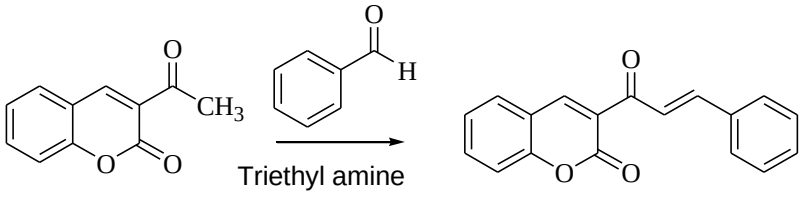


Rajendra Prasad et al [34]was synthesized and antimicrobial activity of some Novel Chalcone of 3-acetyl Coumarin. Rajendra Prasad et al synthesized five novel chalcone were ware prepared by refluxing 3-acetyl coumarin with heterocyclic aldehyde in the presence of piperidine in ethanol.

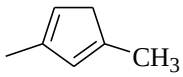
Rajendra Prasad et al shows antimicrobial activity i.e., Antibacterial and antifungal by cup plate method by using Muller Hinton agar medium.

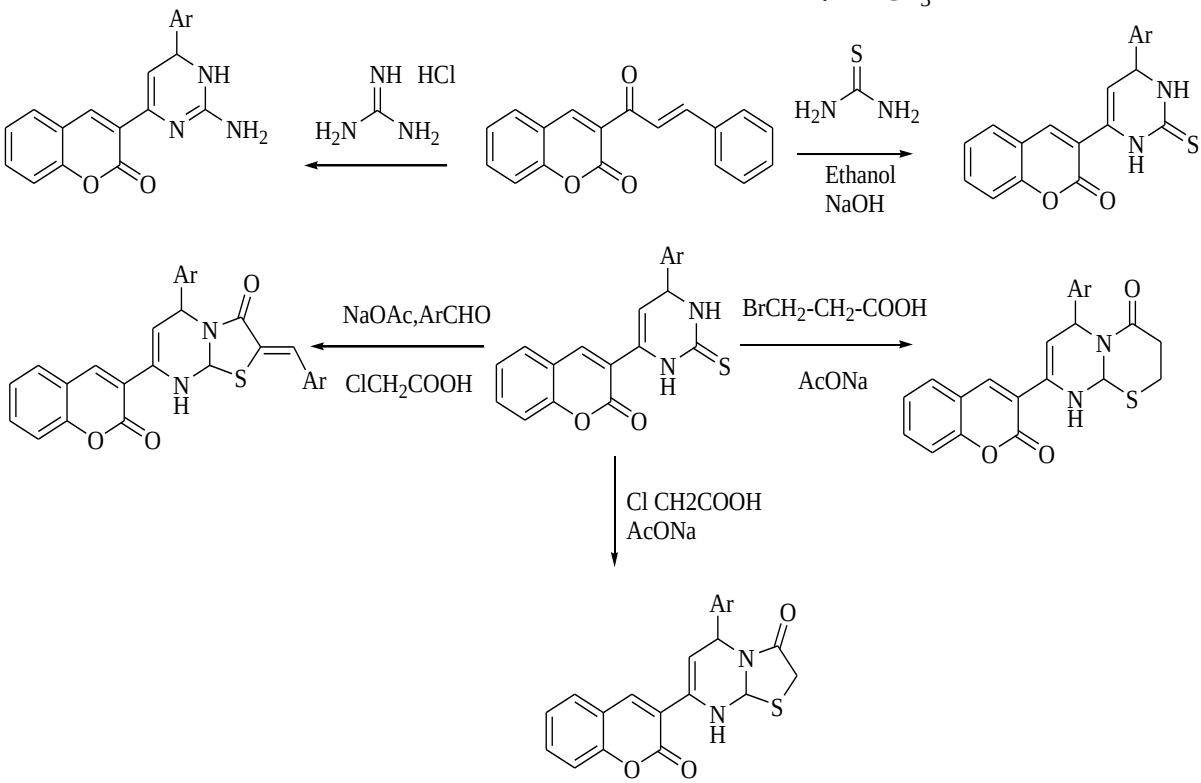


Nehad A. [27] was synthesized and antidepressant activity of some new coumarin derivative. Nehal A,et al synthesized different coumarin chalcone derivative by using triethyl amine in ethanol.

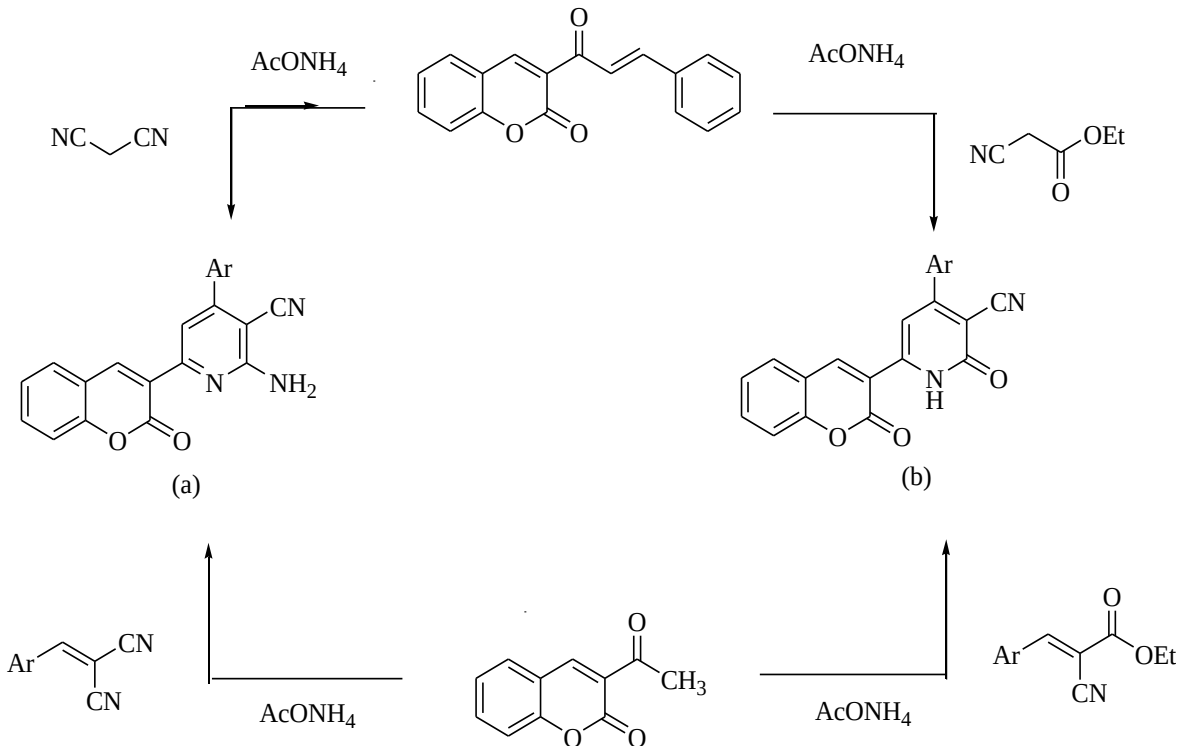


a = Ar = C_6H_5
b = Ar = C_6H_4F (P)
c = Ar = $C6H_4NO_2$ (P)
d = Ar = C_6H_4OH (P)

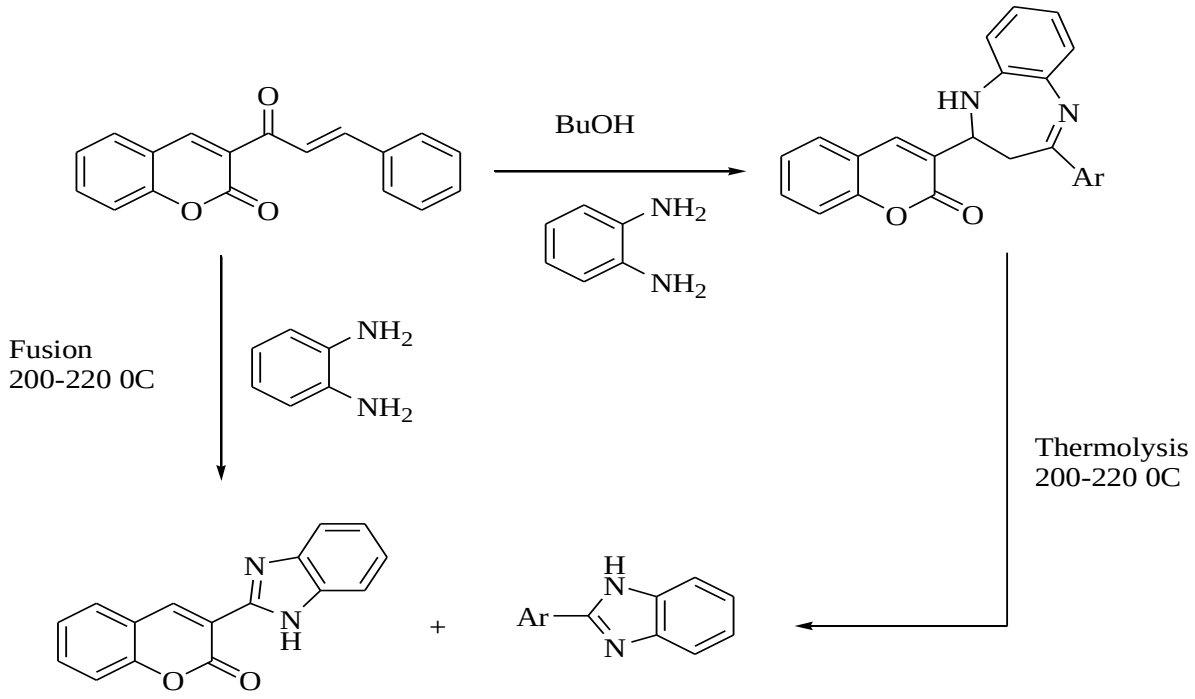
e = Ar = 



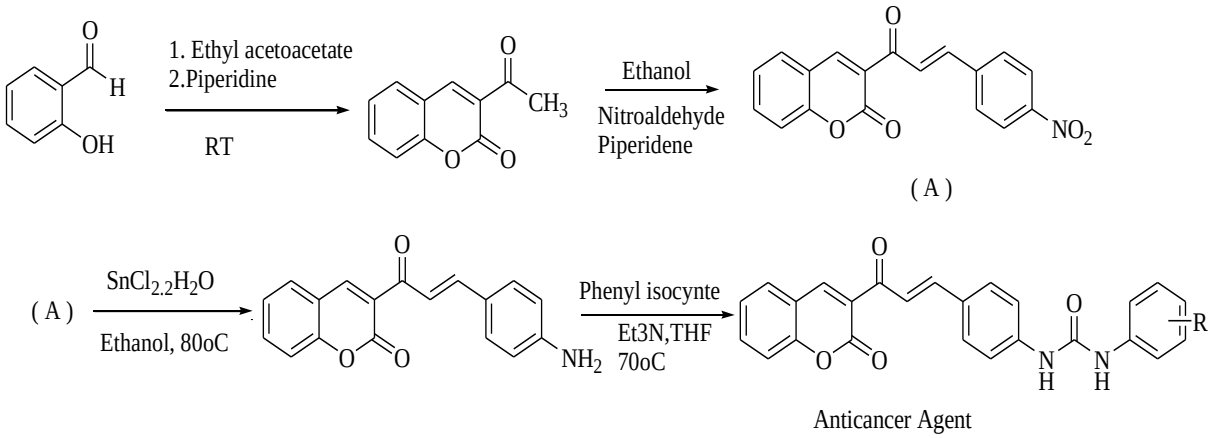
Nehad et al [27]gives the additional work to formation of compound a and b from coumarin chalcone derivatives by using malononitrile and ammonium acetate.



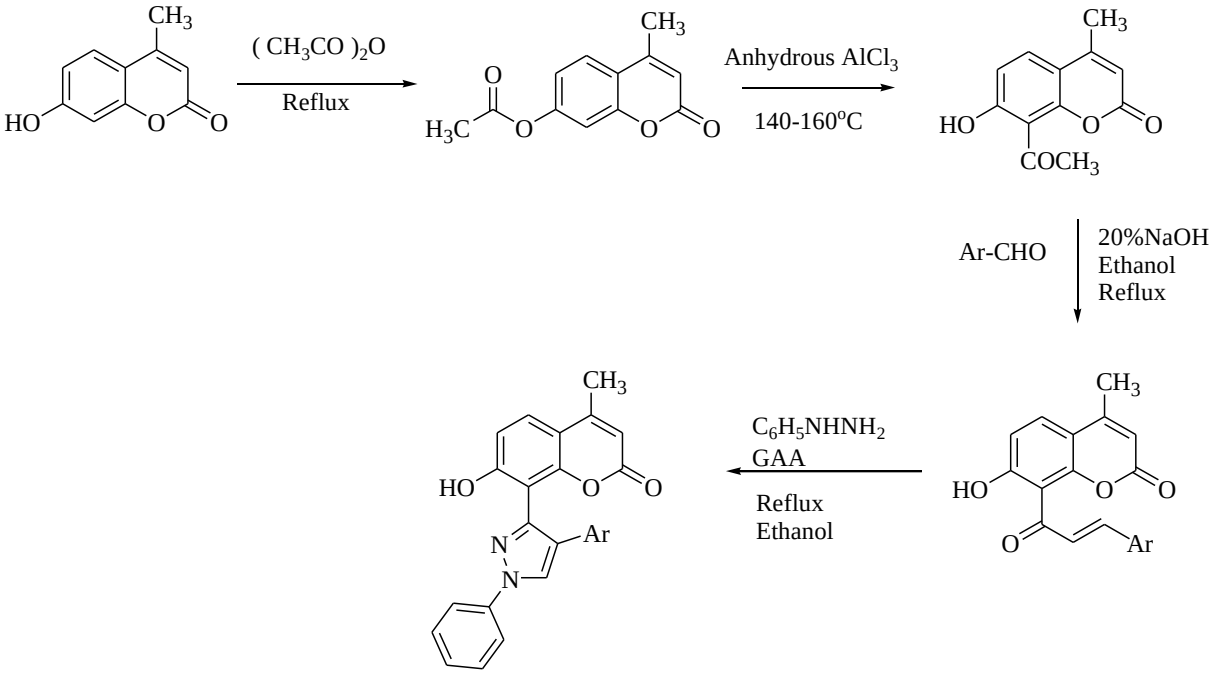
Nehal et al *(2005)* synthesized benzimidazoles compound by using OPD by different method.



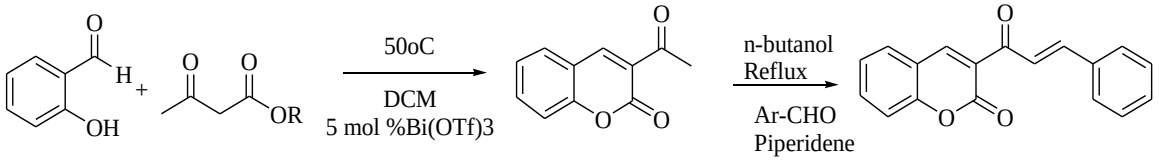
Belma Zengin Kurt [20] was synthesized 3-acetyl coumarin and coumarin chalcone derivative from the reported method by using 3 nitro benzaldehyde, then he reduced the nitro group and then formation of coumarin chalcone derivative containing urea moity as potential anticancer agent. Belma Zengin Kurt et al studies on cytotoxicity of the coumarin chalcone derivatives against H4IIE, Hep G2 and CHO were evaluated. He shows ability of these diaryl urea to inhibit the growth of cancer cells.



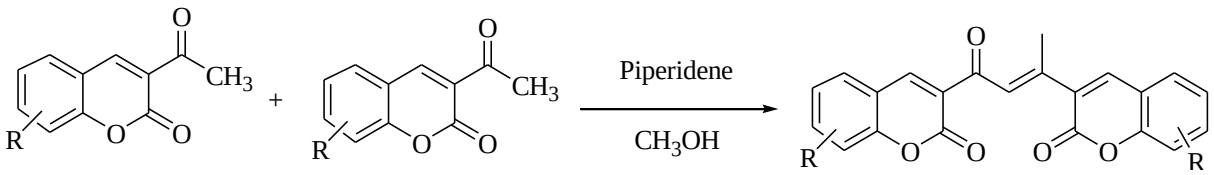
Balaji et al [7] reported the synthesis of coumarin chalcone by refluxing the 7-hydroxy -4-methyl coumarin and acetic anhydride for 1-5 hr. under anhydrous conditions to get 7-acetoxy-4-methyl coumarin then it is heated under anhydrous condition in an oil bath at 125^0C for 2 hr.at 145 to 160 ^{0}C to get 8-acetyl-7-hydroxy -4-methyl coumarin then it was stirred with substituted aromatic aldehyde in ethanol at room temperature to get the coumarin chalcones.



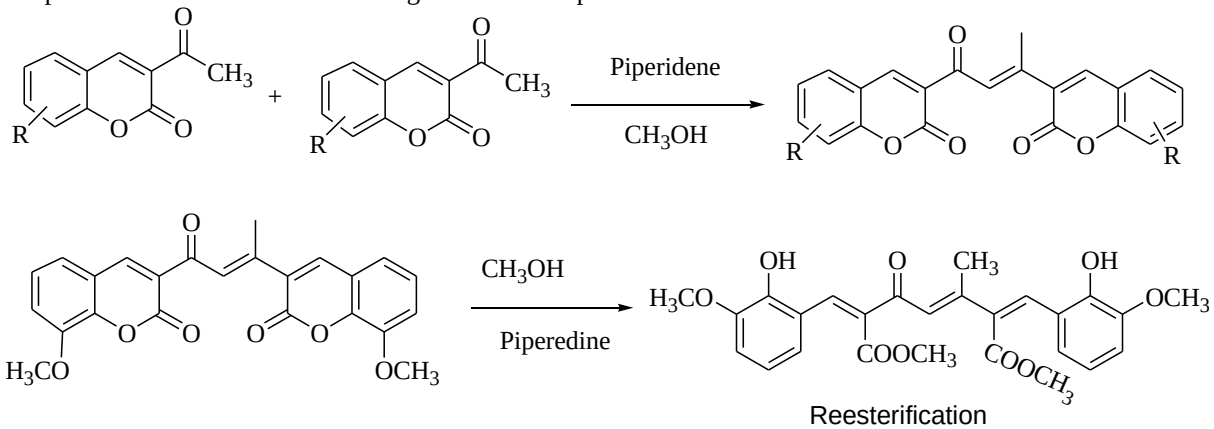
Khode et al [18] reported the synthesis of coumarinyl chalcones by reacting the salicylaldehyde with ethyl acetoacetate in the presence of piperidine with stirring at room temperature for 20 min then the resulting coumarin was reflux with aromatic aldehyde and piperidine in n-Butanol for 4 hr.



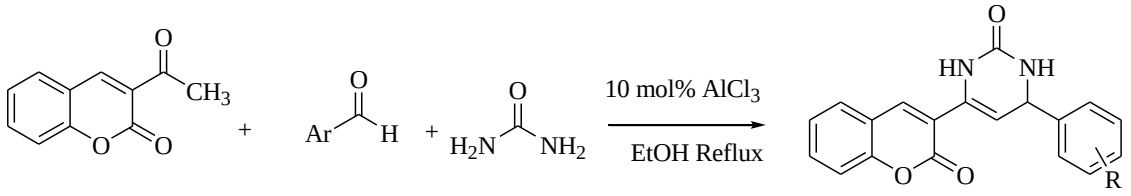
S. Stanchev et al [43] was reported the self-condensation of 3-acetyl coumarin by aldol reaction with piperidine and Methanol as a solvent. Stanchev et al was also elucidated the structure of self-condensed product by DFT density Functional Theory.



Stanche[43] reported the additional work on self-condensation of 3-acetyl-8-methoxy coumarin shows re-esterification reaction after aldol condensation. Which is leading to opening of the lactone ring.
Stanchev *et al* concluded electron donating substituent in the aromatic ring may facillated the aldol reaction but the presence of electronic withdrawing substituent impedes that reaction.

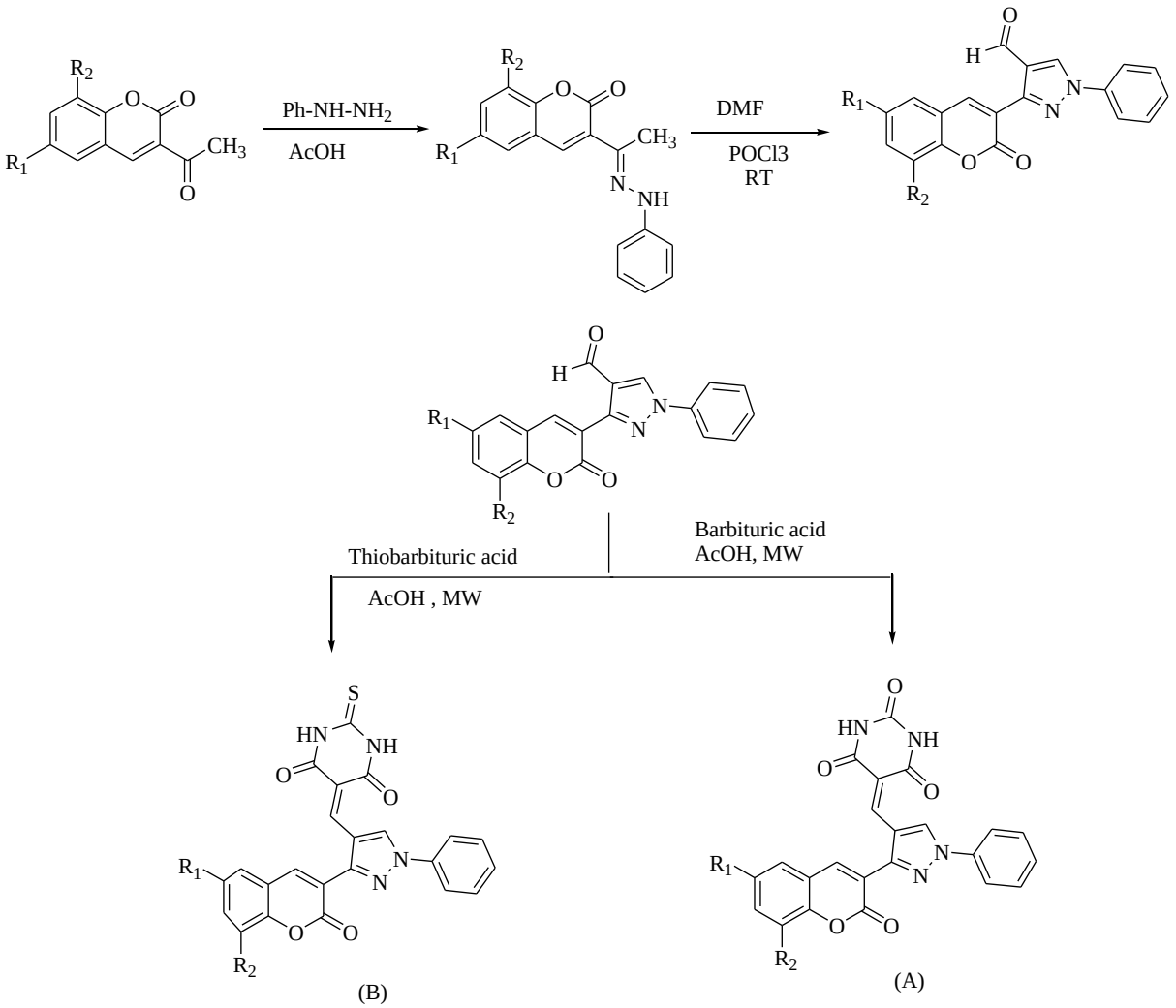


A. Radha [26] reported the coumarin derivatives were synthesized through of condensation.3-acetyl coumarin with number of substituted aromatic aldehyde and urea with a small amount of $AlCl_3$ as catalyst in ethanol.



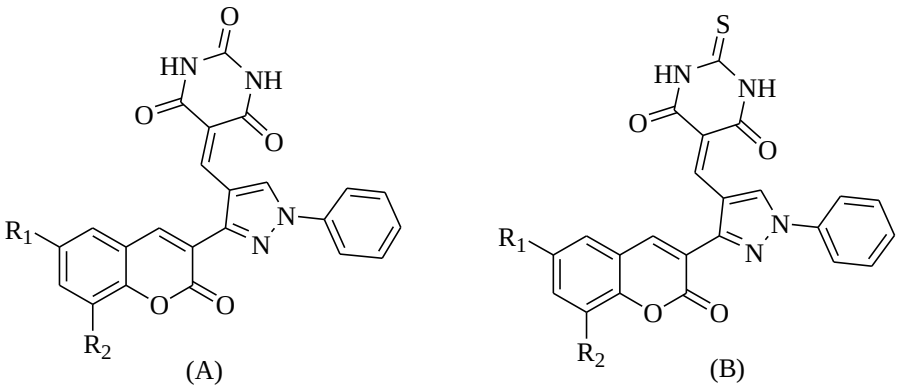
R = 4-OH, 4-OCH_3, 4-Cl, 4-Br , 4$N(CH_3)_2$

Vijaya Laxmiet al [48]was synthesized coumarin pyrazole barbiturate derivative followed by formylation (using DMF and $POCl_3$) and barbituric acid or thio-barbituric acid reaction.



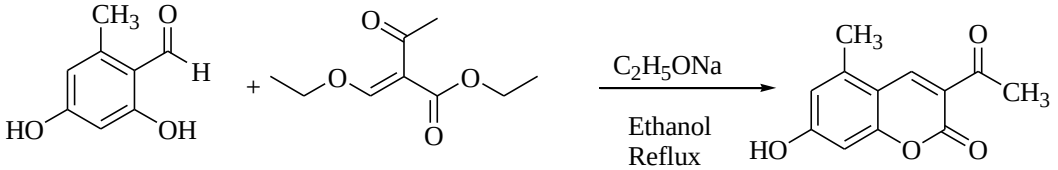
(B) (A)

Vijaya Laxmi *et al.* work on biological activity i.e. antibacterial and antifungal activity on following compounds.



(A) (B)

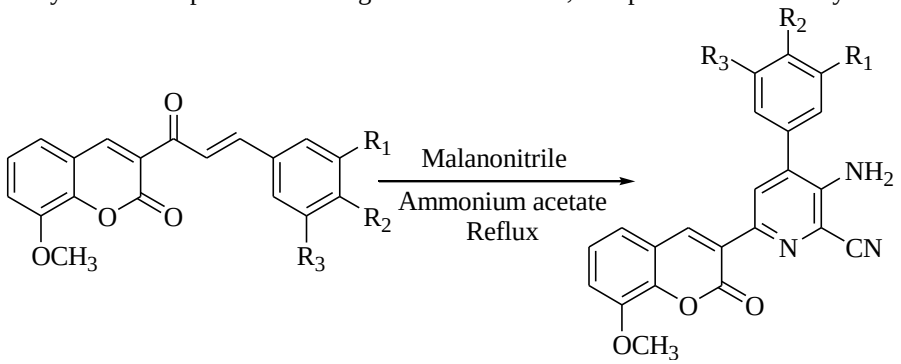
Deng Tao et al [9] reported the synthesis of 5 methyl-7- hydroxy-3-acetyl coumarin was obtained through Pitchman Condensation reaction of 3,5 dihydroxy benzaldehyde and 2-ethoxy methylene -3-oxo butanoic acid ethyl ester using sodium acetate in ethanol. The target molecule showed anti-inflammatory and neuroprotective effect in vitro studies.



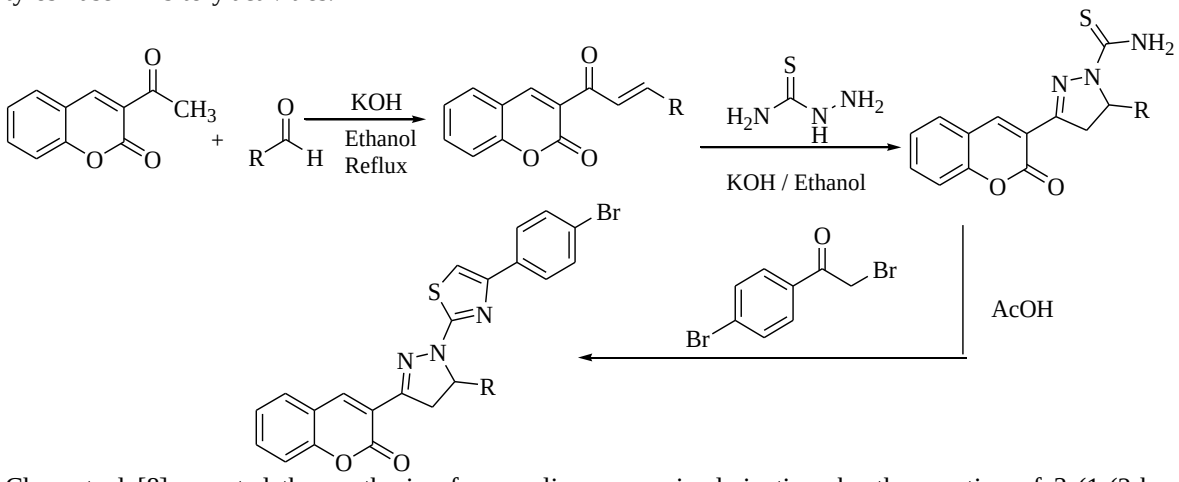
Heba A.H. Elshemy et al [13] reported the preparation of 8 methoxy-3-(3-substituted phenyl) acryloyl)-2H-Chromen-2-one from 3-acetyl-8-methoxy chromen-2-one and appropriate substituted benzaldehyde in methanol

by using piperidine as a catalyst. Coumarin chalcone farther react with malononitrile, ammonium acetate, glacial acetic acid under reflux to formed picolinonitrile derivatives .

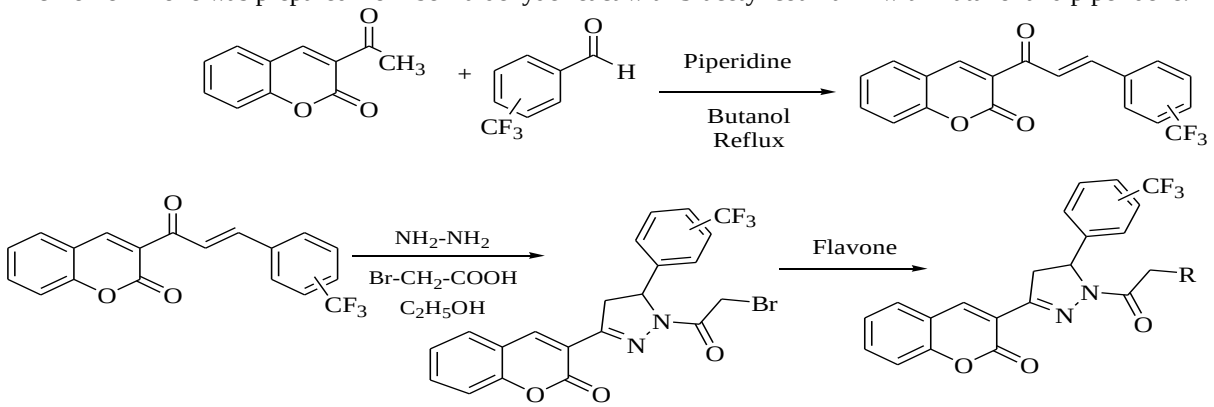
Heba A.H. Elshemy et al was reported the biological evaluation i.e., Antiproliferative activity



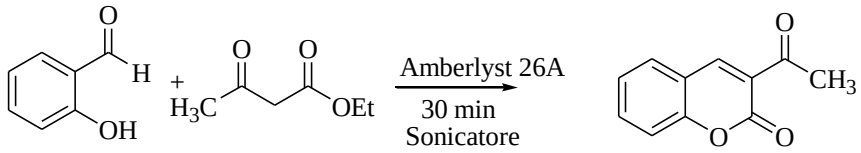
Saeed et al [35] synthesized a large series of coumarinyl pyrazolinyl substituted thiazole derivatives. The acetyl coumarin was treated with various aldehyde to gives the chalcone with good yield. The chalcone gives intermolecular cyclisation with thiosemicarbazide in presence of KOH to formation of coumarinyl pyrazolines. Finally, it reacts with alfa halo ketone to gives the coumarinyl pyrazolinyl 1,3 thiozole in good yield. The result showed that all of the coumarinyl-pyrazolinyl derivative exhibited significant mushroom tyrosinase inhibitory activities.



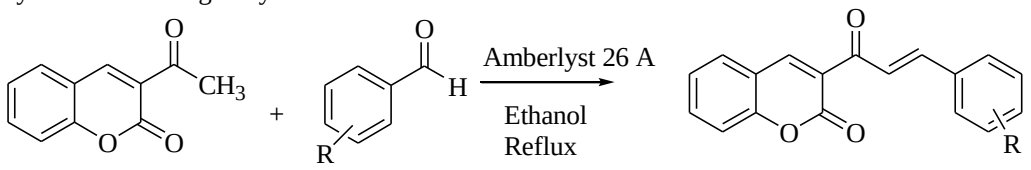
Chen et al [8] reported the synthesis of pyrazoline coumarin derivatives by the reaction of 3-(1-(2-bromo acetyl)-5-phenyl-4,5-dihydro -1H-pyrazol-3-yl)-2H-Chromen -2-one and flavone or amine at 40 -50 ^{o}C. The compound was obtained as a result of the condensation of 3-cinnamonyl -2H – chromen -2- one compound with hydrazine in ethanol at 40-60 ^{o}C followed by cyclization with 2-bromo-acetic acid. The 3-cinnamoyl-2Hchromen-2-one was prepared from benzaldehyde react with 3-acetyl coumarin with Butanol and piperidene.



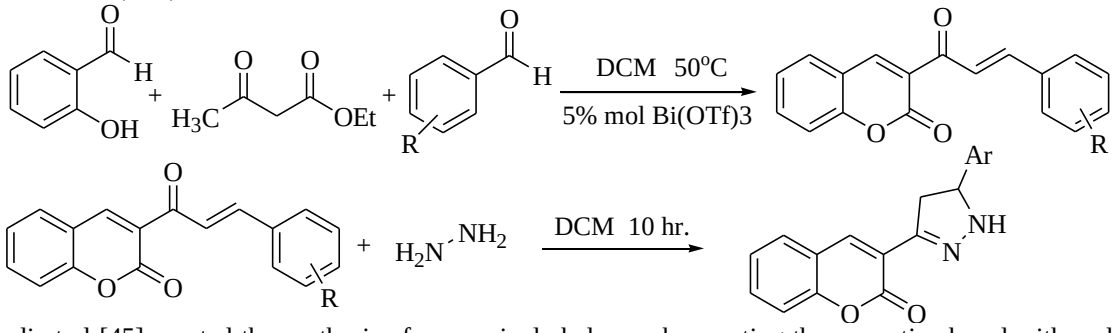
Mehmet Ersatir et al [25] reported cross aldol condensation reaction of 3-acetyl -2H-chromen-2 one by using Amberlyst 26 A as a catalyst. The synthesis of 3-acetyl coumarin from mixture of salicylaldehyde, ethyl acetate with 10 % w/w Amberlyst 26 A catalyst with good yield.



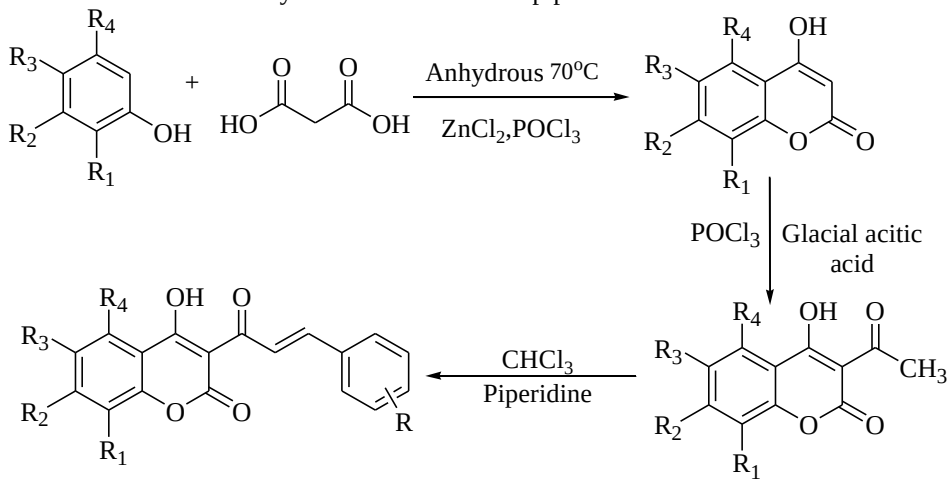
Mehmet Ersatir et al [25] synthesized the various coumarin chalcone derivative of aldehyde with Amberlyst 26A catalyst at 80 ^{o}C with good yield.



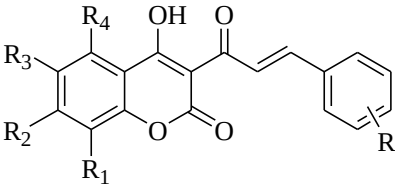
Mahmoud and El Remaily et al [22] reported the synthesis of bioactive coumarin chalcone compound by mixing of salicylaldehyde or methyl salicylaldehyde with ethyl acetoacetate in the presence of piperidine without any solvent to get 3-acetyl coumarin. Then the 3-acetyl coumarin was mixed with corresponding aldehyde in the presence of Bi $(OTf)_3$ at 50^{o}C.



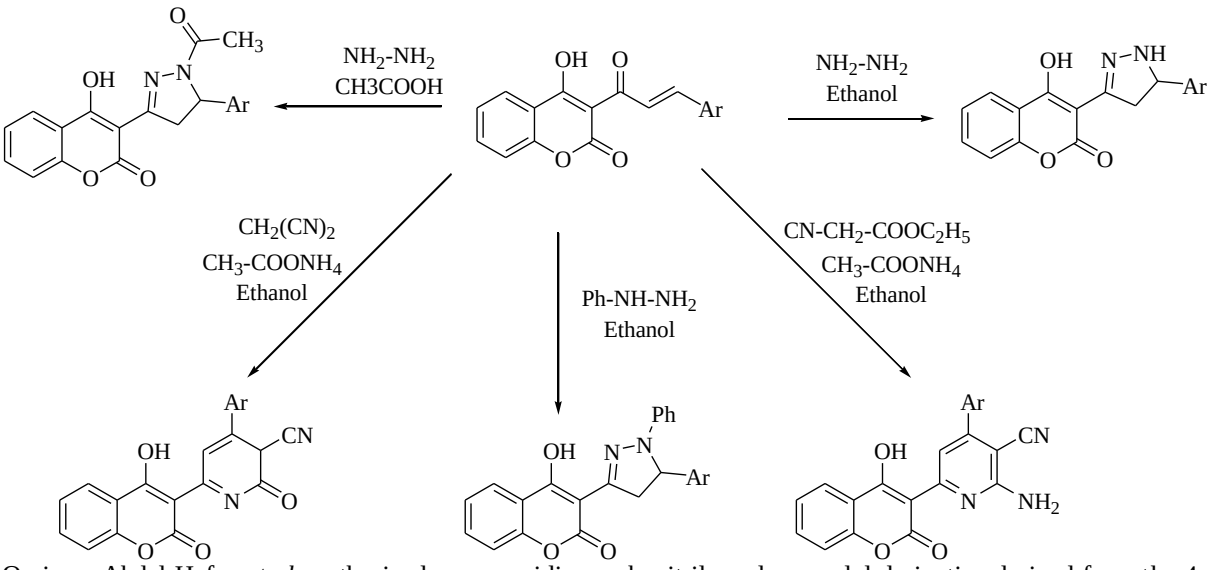
Trivedi et al [45]reported the synthesis of coumarinyl chalcones by reacting the aromatic phenol with malonic acid in the presence of phosphorus oxychloride and zinc chloride at 70 ^{o}C above for 20 h. and the resulting compound was acylated with glacial acetic acid and phosphorus oxychloride. Then the acetylated coumarin was reflux with substituted aromatic aldehyde in chloroform with piperidine at 80 ^{o}C about 1-1.5 hr.



Trivedi et al [45]reported screening of anti-HIV for coumarinyl chalcone, unfortunately no compound shows positive result for anti-HIV activity.

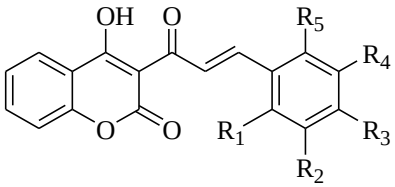


Omiama Abdel Hafez et al [11] was reported the reflux of 4-hydroxy-coumarin with acetic acid in the presence of phosphorous oxychloride leads to the formation of 3-acetyl-4-hydroxy coumarin which react with some aldehyde to yield the coumarin chalcone derivatives. The chalcone was cyclised with malononitrile in ethanol in the presence of ammonium acetate leads to the formation of pyridine carbonitriles while the reaction of coumarin chalcone with ethyl cyanoacetate given the oxy pyridine carbonitrile.



Omiama Abdel Hafez *et al* synthesized some pyridine carbonitrile and pyrazolyl derivative derived from the 4-hydroxy coumarin of expected antitumor and antimicrobial activity. Omiama Abdel Hafez et al reported the screening of coumarinyl chalcone derivative for antimicrobial activity compound with 4 chloro and 4-broma substituted on benzaldehyde benzene ring of chalcone to be active against bacteria and yeast but did not show activity against fungi.

Kuldeep Patel et al [19] was design synthesis and biological evaluation of some novel 3-cinnamoyl-4-hydroxy-2H-Chromen-2 -ones as antimalarial activity against chloroquine sensitive and chloroquine plasmodial strain resistant.

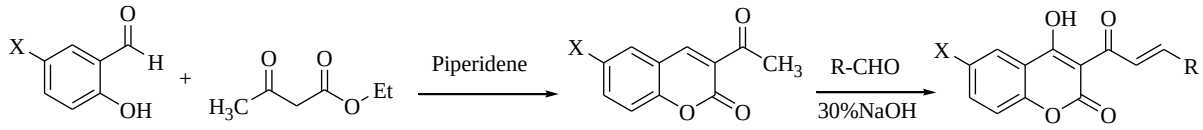


Kuldeep Patel et al [19] shows that ortho substitution in phenyl ring is not well tolerated for antimalarial activity. Among the para substituted compounds, nitro substitution on the phenyl ring shows highest antimalarial activity. The Order of potency decreases for the synthesized compound on the basis of substituent is

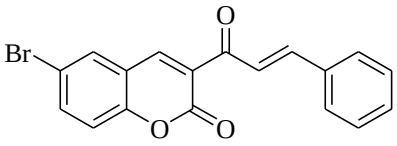
$$NO_2 > Cl > CH_3 > OCH_3 > N(CH)_2$$

Kuldeep Patel *et al* also work on replacement of furan ring in place of phenyl ring resulted in loss of antimalarial activity against chloroquine sensitive strain .

Jayashree et al [17] synthesized the different coumarin chalcone from 3-acetyl coumarin and aldehyde by using 30% NaOH in EtOH.



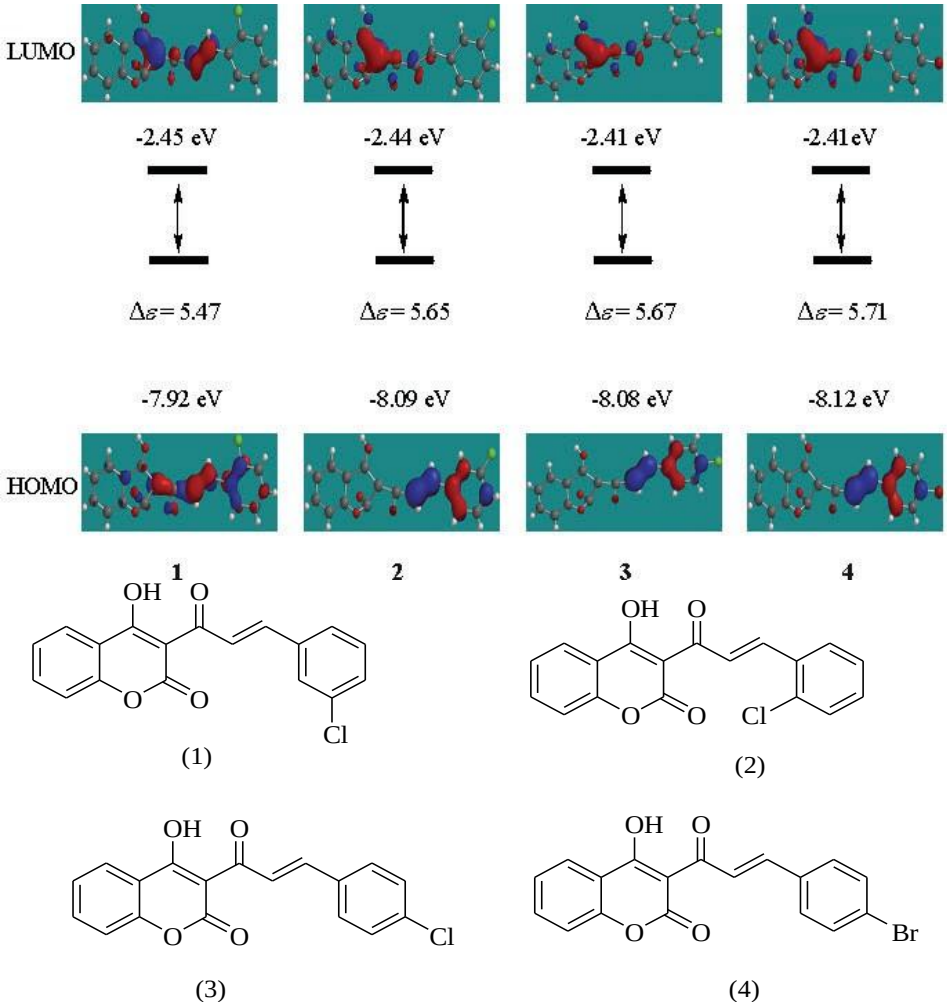
Jayashree et al [17] reported all coumarin chalcone were screened for their antioxidant, anti-inflammatory, analgesic and antibacterial activity. The compound with chloro and bromo group at the 6th position of coumarin chalcone shows anti-inflammatory and analgetic activity.



Saleta Vazquez-Rodriguez [36] was reported the synthesis and Trypanocidel properties of new coumarin chalcone derivatives. Saleta Vazquez-Rodriguez et al compounds were tasted against the epimastigote, trypomastigote and amastigote stages of the T cruzi parasite. The compound 4 was more active against the trypomastigote stage.

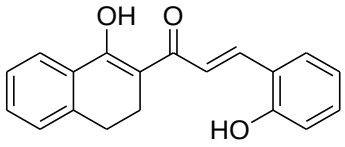
III DENSITY FUNCTIONAL THEORY (DFT)

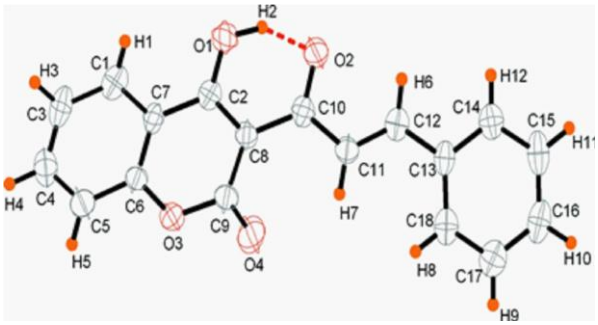
Selma Spirtovic Halilovic et al [39] reported DFT study and microbiology of some coumarin-based compounds containing a chalcone moiety. The quantum-chemical and physicochemical calculations specified that the calculated chemical consciousness descriptors of the molecules connected with antibacterial activity. Reduction of HOMO and increase of LUMO, that is, a reduction in the reactivity and an increase in the stability of the synthesized compounds increased their activity against the verified microorganisms. The most reactive derivative, compound 1, showed the lowest activity, indicating that the most chemically steady compound had the best antibacterial activity. The promising antibacterial activity of the compounds could be helpful in the synthesis of a large number of analogues for extensive antimicrobial studies, which could be used to develop more appropriate drug candidates. It could be concluded that these classes of compounds certainly hold promise towards good active leads in medicinal chemistry.



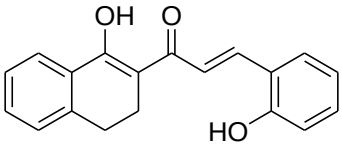
Frontier molecular orbitals of compounds 1–4

Afef Ghouili et al [2] reported the DFT study of 4-Hydroxy-3-[(E)-3-phenylprop-2-enoyl]- 2H-chromen-2-one molecule. The molecular structure of title compound showing 50% possible movement ellipsoids and the atomic numbering. Dashed line denotes hydrogen bond and also studied onFractional atomic coordinates and isotropic or equivalent isotropic displacement parameters,atomic displacement parameters, Geometric parameters i.e.Hydrogen-bond geometry.

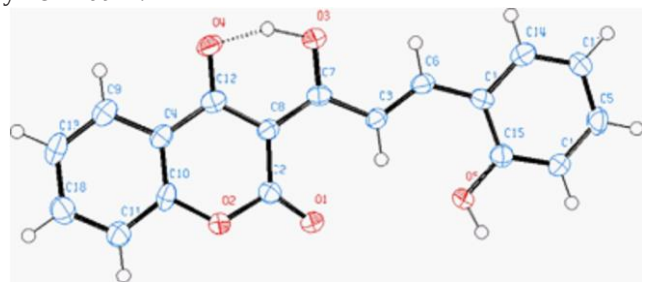




AfefGhouili [1] reported Synthesis, crystal structure and spectral characteristics of highly fluorescent chalcone-based coumarin in solution and in polymer matrix.

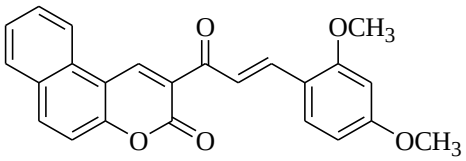


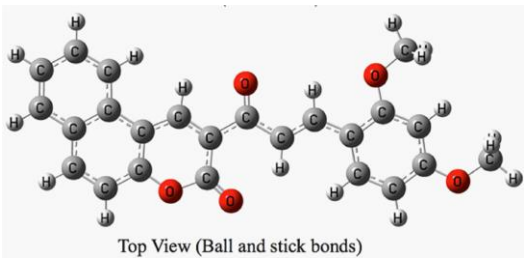
1-(1-Hydroxy-3,4-dihydro-naphthalen-2-yl)-3-(2-hydroxy-phenyl)-propenone



The 1-(1-Hydroxy-3,4-dihydro-naphthalen-2-yl)-3-(2hydroxy-phenyl)-propenone was synthesized and confirmed by different analysis, ^{1}H NMR, ^{13}C NMR FT-IR and UV–vis absorption spectra. The crystal structure of thecoumarin chalcone was investigated by single crystal X-ray diffraction. The structure exhibits intermolecular O–H…O hydrogen bonds linking the molecules into zigzag chains. The crystal packing is also stabilized by π–π stacking interactions. Afef Ghouili at al reported the bond length, bond angle also.

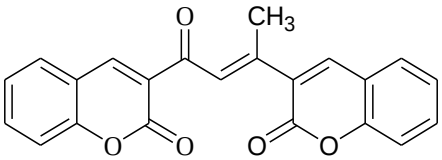
Shabbir Muhammad et al [40] reported design, nonlinear optical properties of coumarin appended chalcones, the experimental and theoretically calculated absorption and emission spectra showed peaks at 392 and 461 nm, which are found to be in agreement with their experimental peaks at 393 and 501 nm, respectively. Shabbir Muhammad et al reported the calculations of Nonlinear optical response properties indicated that the <μ> amplitudes of compounds on the basis of nature of substituent. and geometry of compounds.

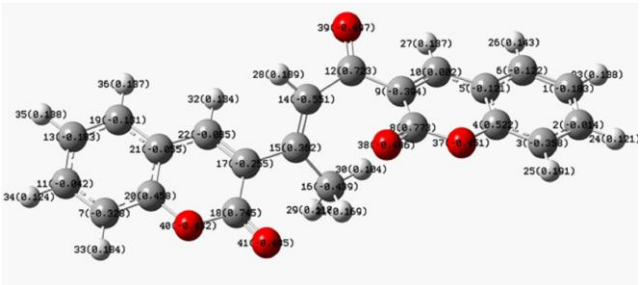




Top View (Ball and stick bonds)

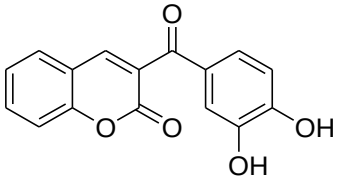
Stanchev S et al [43] reported Aldol condensation of 3-acetylcoumarin derivatives and extraordinary side reactions and its DFT study Its structure was also explained by DFT (Density Functional Theory) methods. Optimization with B3LYP/6-31G (d,p) method and calculation of the ESP (Electrostatic Potential) charges were made.





GloriaMazzone et al [24] reported Antioxidant properties of several Coumarin- Chalcone hybrids from theoretical insights. Gloria et al reportedcoumarin-chalconederivativesarenotcompletely planar systems since in allcases ringC is cruelwithrespecttotherestofthe molecule by around 20°.Though,conjugationanddelocalizationof the π electronsoccur in the two planar portions of the

considered compounds.Amongtheexaminedmechanisms,theHATpathwayisplannedasthemost favourable,sinceitrequiresthelowestamount of energy to yield place. All the considered compoundsyieldstablefundamentalspeciesupontheremoval of a hydrogenatominwhichtheoddelectronappearstobe delocalized as and aspossibleontheportionofthemoleculethatisradicalized.Thestabilityofsuch radicalsisenhanced bythepossibilitythattheyestablishinternalH-bondsbetweentheradicalized oxygenatomandvicinal hydroxyl groups, and bythe electronic properties of the other groups in the conjugatedsystem.



IV CONCLUSION

This paper explains the current synthetic technique for enlightening the superiority and yield of synthesized derivatives and current biological activities produced by synthesized coumarinyl chalcone derivatives through dissimilar mechanisms. This data may be useful for the research society for better understanding of coumarinyl chalcone derivatives regarding their synthetic mechanisms and particular pharmacophore required for display characteristic biological activities through different mechanism of actions and also useful to detect the various properties i.e., bond length, bond angle, dihedral angle, HOMO-LUMO study etc by Density functional Theory (DFT).

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