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Review Article

POSSIBLE REACTIONS ON COUMARIN MOLECULE

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ABSTRACT
Many naturally occurring substances, traditionally used in the medicines contain the coumarin moiety. Coumarin is a simple scaffold widespread in nature and it is found in a number of plants as well as fungi and some bacteria. In the last years, it gains attention due to its ability to interact with diverse enzymes and receptors in living organisms. Coumarin based compounds having potential not only in the medicinal chemistry but also in the cosmetic and also in fragrances. It is chemically a Benzopyran 2-one. It possess a wide range of pharmacological activitiesincluding anti-cancer, anticoagulant, antibacterial, anti-inflammatory, anti- oxidant, antidiabetic, antiparkinson's activity and also found antihepatitis C activity. Its versatile range of activities makes it a versatile scaffold in a medicinal chemistry. Therefore, in this review we analyzed a various research articles, reviews and the data found from them are collected. Here in this overview, we collectvarious literature on the synthesis of possible reaction on coumarin molecule.

Keywords: 7-hydroxy 4 methyl coumarin, Anti-inflammatory, Methods of synthesis,Natural Coumarins.

1. INTRODUCTION
Coumarin is basically Benzopyran 2 ones [1], widely found in plants, fungi and bacteria [2]. Coumarin word is derived from the french word, and is isolated in 1820 by Vogel from theTonka bean *Dipteryx orodata,wild,* fabaceae [3]. They are isolated from many parts of plants such as roots, flowers, seeds, leaves fruits as secondary metabolites. Seo *et al* and Bai *et al* isolated coumarins from theroots of *Angelica dahurica* [4, 5]. Iranshahi *et al* isolated coumarins from the roots of *Ferula flabelliloba* while Peng *et al* also isolated coumarins from the roots of *Clausena excavate* [6-7]. Many of coumarins are found in theflowers of various species of *Bombax ceiba*, *Peltophorum pterocarpum, and Trifolium repens* [8-10]. Joselin et al investigated the presence of coumarins from the Apocyanaceae. Among this family, some species include *Allamanda cathartica, Allamanda violaceae, Wrightia tinctoria* and *Nerium oleander* [11]. The leaves of plants also a good source of coumarins. Wang *et al* extracted the leaves of bamboos species and determines 12 coumarin compounds [12]. Other species includes leaves of *Zanthoxylum scinifolium* [13] and *Zanthoxylum avicennae* [14]. Coumarins are divided into four main types including simple coumarins, furano coumarins, pyrano coumarins andpyrano substituted coumarins. Coumarin is known for its different pharmacological activities such as anticoagulant [15], anticancer [16], antibacterial and antituberculosis [17], antileishmanial agent, antifungal [18].

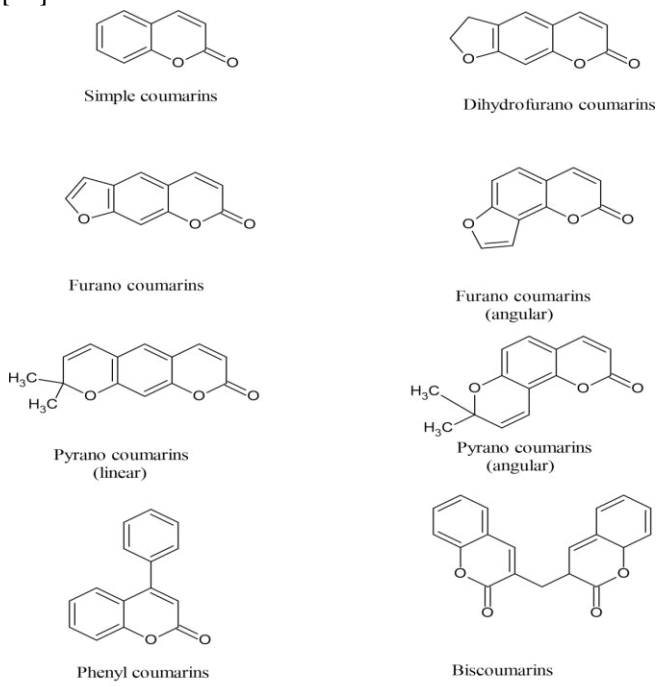


Fig. 1: Natural coumarins

Coumarin has an important role in the action of plant growth with the phenolic hydroxyl group which have capability to prevent the formation of hydroxy-icosatetraenoic acid and hydroxyheptadecatrienoic acid in the arachidonic pathway [19].

2. METHODS OF COUMARIN SYNTHESIS

Coumarin can be synthesized by various methods such as Pechmann condensation, Knoevenagel Condensation, Wittig reaction, Reformatsky reaction, Kostanecki-Robinson reaction, Claisen reaction etc.

2.1. Pechmann condensation

In 1883, a German chemist reported an important novel condensation reaction for synthesis of Coumarin. Pechmann condensation is carried out in acidic condition between resorcinol and ethyl acetoacetate. It involves esterification or tranesterificationto create new ring [20]. Pechmann reaction is catalyzed by several acid catalyst such a H_2SO_4, $ZnCl_2$, $POCl_3$, PPA, $AlCl_3$, HCl, Phosphoric acid and trifluoroacetic acid [21].

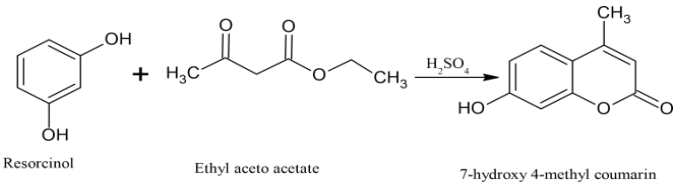


Fig. 2: Pechman condensation between Resorcinol and Ethylacetoacetate

2.2. Knoevenagel Condensation

The Knoevenagel reaction involves reaction between aldehyde or ketones and active methylene compound. In this reaction ammonia, amines, pyridine and piperadine are used as catalyst [22]. The condensation of 2-hydroxybenzaldehyde with diethyl malonate in the presence of Piperadine gives an ethyl coumarin-3-carboxylate. Other various catalyst used in this reaction are such as magnesium alumino phosphates, sodium methoxide, 1-n-buty-3-methylimidazolium bromide/ Pottasium carbonate, zinc chloride [23].

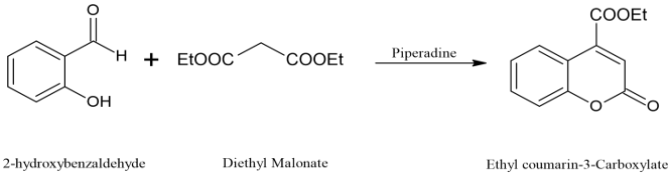


Fig. 3: Knoevenagel Condensation between Aldehyde and diethyl malonate

2.3. Wittig Reaction

In General, wittig reaction is carried out by suitable hydroxyl benzaldehyde with wittig reagent which can be further converted into a corresponding coumarin. Various different catalyst are used for this reaction such as bismuth(lll) nitrate [24].

Shaabani *et al* reported a synthesis of coumarin derivatives by a one pot condensation reaction using ethyl bromoacetate with o-hydroxybenzaldehyde under PPh3 at 80°C [25].

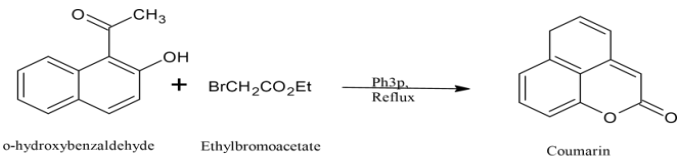


Fig. 4: Wittig Reaction between hydroxybenzal-dehyde and ethyl bromoacetate

2.4. Reformatsky reaction

The Reformatsky reaction is the reactionof a carbonyl compounds usually an aldehyde or ketone with an alpha haloester in the presence of zinc to give a beta hydroxy ester [26].

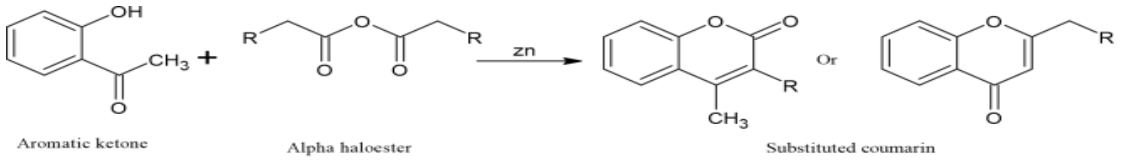


Fig. 5: Reformatsky reaction between a ketone and alpha haloester

2.5. Kostanecki Robinson reaction

The Kostanecki Robinson reaction of o- hydroxy aryl alkyl ketones with an acid anhydride in the presence of sodium salt of an acid produces coumarins by the carbon- carbon bond formation were chromones (4- H 1-benzopyaran-4-ones) found to be a major product [27].

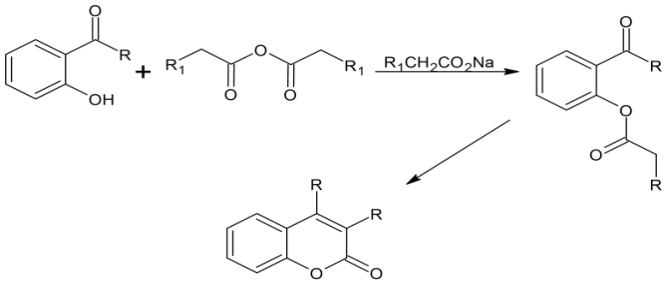


Fig. 6: General synthetic route of formation of coumarin by Kostanecki Robinson reaction.

2.6. Hydroxy Coumarin derivatives

Sakineh Asghari *et al* synthesized novel coumarin derivatives by reacting 7-hydroxy coumarins with acetylenic diesters and arylaldehyde in a catalytic amount of the NEt_3 in the presence of dry tetrahydrofuran at room temperature. Compounds were obtained in the good yield. It was also observed that high yield was found using NEt_3 ascshown in Scheme 1 [28].

2.7. Synthesis of Novel Chalcone and tetrazole fuzed pyrido [2,3-c] Coumarin derivatives

Pallabhi *et al.* reported synthesis of some novel tetrazole fuzed pyrido [2,3-c] coumarin derivatives from a one pot three component reaction. In the procedure, 4- hydroxy coumarin was first treated with the Vilsmier reagent [DMF+$POCl_3$] to obtain a key intermediate i.e. 4-chloro-3-formylcoumarin. Treatment of 4-chloro 3-formyl coumarin with sodium azide and cyanoacetamide for 3 hr at 50°Cin the presence of catalyst triethylamine using dimethylformamide as solvent obtain tetrazolo [4'5':1] pyrido[2,3-c] coumarin derivative in excellent yield, reaction as shown in Scheme 2.

From the above reaction it is observed that ethylcyanoacetate and malononitriles are more beneficial than others [29].

2.8. Synthesis of benzylpyrazolyl Coumarins

Pratha *et al.* synthesized benzyl pyrazolyl coumarin derivative by a green one pot four component reaction between Aryl hydrazine/hydrazine hydrate, ethyl acetoacetate, aromatic aldehyde and 4-hydroxy-coumarin. A mixture of 10% glacial acetic acid and 5 ml water, hydrazine (1 mmol) ethyl acetoacetate (1mmol), aromatic aldehyde (1mmol) and 4-hydroxyl coumarin (1mmol) were added and heated to reflux to obtain benzyl pyrazolyl coumarin derivative. The formation of compounds appeared as pale yellow solids, reaction is shown in Scheme 3 [30].

2.9. Synthesis of 7-amido coumarin derivatives

Tiwari *et al.* synthesized a series of 7-benzamido coumarin derivatives by reacting aminocoumarins and aromatic acids or hetero aromatic acids with acetonitriles. Then the reaction mixture was refluxed, upon completion quenched by water and evaporated the solvent, remaining residues were dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4. Purified the product by column Chromatography [31]. Reaction is shown in Scheme 4.

2.10. Synthesis of coumarinyl pyridine and coumarinyl pyrimidine hybrids

Ehab and Mohamed *et al.* synthsized coumarinyl pyridine and coumarinyl pyrimidine hybrids. Coumarinyl chalcone hybrids were prepared by Claisen schmidt reaction and 3-acetylcoumarin with the aromatic aldehydes. Then the reactions proceed by refluxing the reactant in ethyl alcohol and piperadine. Reaction is shown in Scheme 5.

The reaction of chalcone scaffolds with the malononitriles in the presence of glacial acetic acid and ammonium acetate yields 2-aminonicotinonitrile (Scheme 6).

Chalcone Scaffolds react with the ethyl cyanoacetate in refluxing glacial acetic acid in ammonium acetate yields the 2- hydroxynicotinonitrile derivatives (Scheme 7).

The reaction of Chalcone derivatives with the thiourea by refluxing in ethanolic solution of C_2H_5ONa obtains aryl coumarinyl pyrimidines (Scheme 8) [32].

2.11. Synthesis of new series of chromene based 1, 2,4 oxadiazones derivative

By the literature survey it is revealed that chromene based enones and quinoline based oxadiazones shows potent antibacterial activity.

In a research Baral synthesized chromene fused oxadiazole derivatives. Initially chromene nitrile was prepared by green and efficient one pot two component approach using salicyldehyde and acrylonitrile in the presence of DABCO under the solvent free condition after that thecompound was treated with hydroxylamine hydrochloride using Et_3N in ethanol for 2 hr to obtain N'-hydroxy-2H- chromene carboximidamide, reaction is shown in Scheme 9 [33].

2.12. Synthesis of thiazolyl coumarin derivatives

Donia *et al.* synthesized a three component one pot synthesis of new thiazolyl coumarin derivatives from

the different aromatic aldehydes, 3-acetyl hydroxy-coumarin and thiourea in the presence of DMC and ammonium acetate.

The mechanism behind the synthesis was simply the amine group and thiourea attacks the carbonyl group then the dehydration formed by protonation and the intermediate leads to the formation of intermediate ll. After the cyclization there was formation of product [34], reaction is shown in Scheme10.

2.13. Synthesis of N1-(Coumarin-7-yl) Amida-drazones and related Congener

Mohammad *et al.* synthesized a series of a new N1-(coumarinyl-7-yl) amidadrazones. For the reaction, first hydrazonoyl chloride was prepared by direct coupling of 4- methyl coumarin 7- diazonium chloride with 3-chloropentane 2, 4-dione in aqueous solution sodium acetate. Then piperazine, N- substitited piperazines and cyclic amines was added to N-(4-methyl coumarin-7-yl) nitrile imine to obtain amidarazones as a product [35], reaction is shown in Scheme 11.

2.14. Synthesis of coumarin imidazole hybrid derivatives

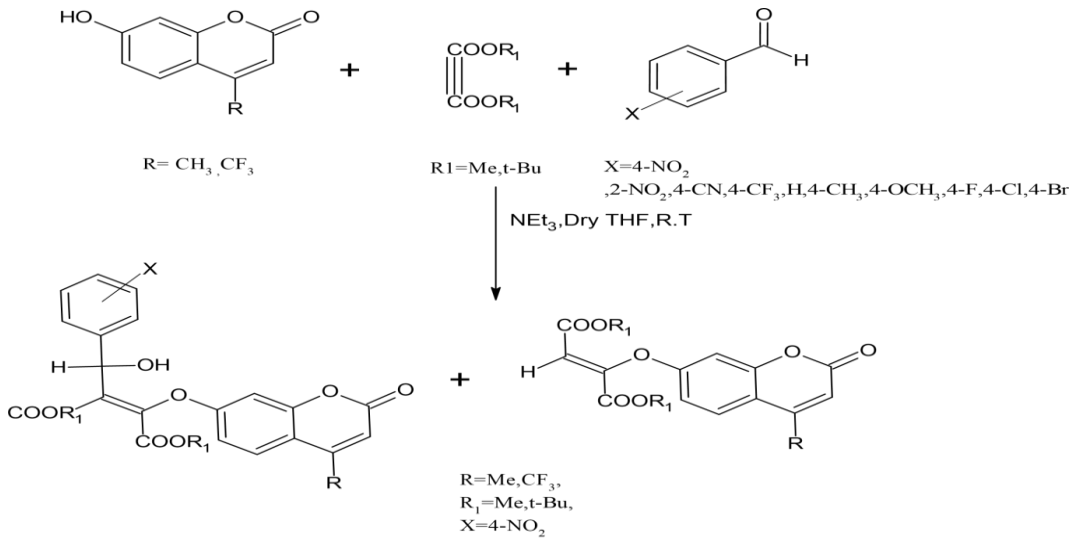
Megharaja reported synthesis of the coumarin imidazole hybrid derivative by reaction of 4-formylcoumarin and 1,2 diketone with the ammonium acetate in the presence of acid catalyst to obtain desired coumarin imidazole hybrid derivative and it was further reacted with p-tolunesulfonyl chloride in the presence of TEA at 0-5℃ overnight to obtain compound. Then it was treated with sodium hydroxide in the presence of ethanol at 80℃for 4-5 hour to obtaine a desired product [36]. Reaction is shown in Scheme 12.

2.15. Synthesis of Coumarin derivatives containing pyrazole and indenone group

Kenchappa *et al* synthesized novel coumarin derivatives by reacting 6-substituted 3 -acetyl coumarin with p-substituted phenyl hydrazine hydrochloride in the presence of dry ethanol using sodium acetate at room temperature. The product obtained was further refluxed with vilsemier reagent for about 6 hr to give formyl pyrazole compound. Further, 3-(6 substituted-2-oxo-2H-chromen-7-yl)-l-(4-Substitued)-1H-pyrazole-4- Carbaldehyde derivatives reacted with 5,-dimethoxy 2,3-dihydro-1H inden-1 one at room temperature for about 8 hour gives 6-Substituted-3- (1-(4 Substituted 4(Z)-(5,6-dimethoxy-1- oxo-1H-inden-2(3H)-ylidene methyl) 1-H pyrazol-3-yl)-2H-2 methyl derivatives (Scheme 13) [37].

2.16. Synthesis of Coumarin sulfonamide isoxazole derivatives

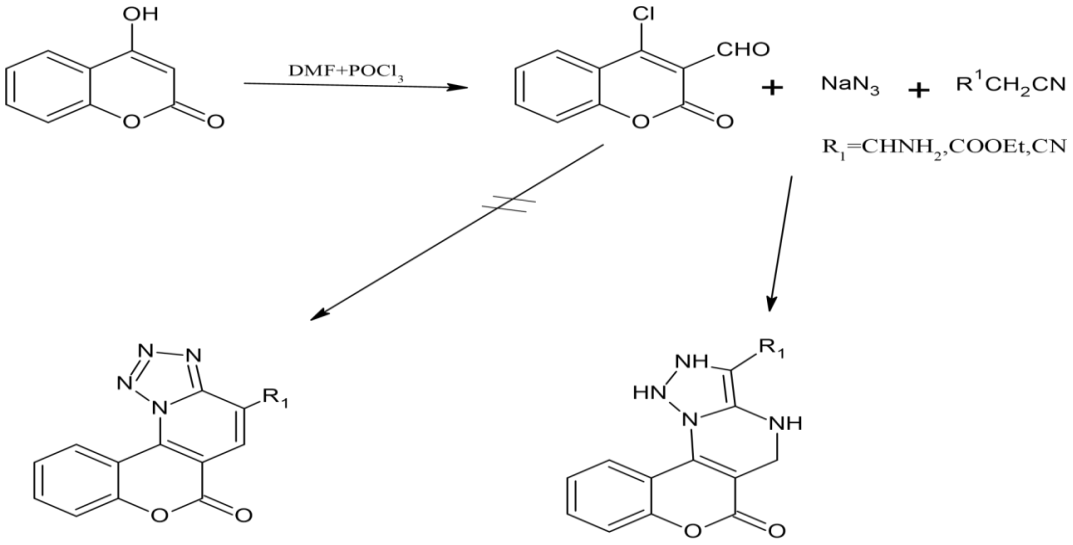
Sheida *et al.* synthesized novel isoxazole sulfonamide derivatives by the following procedure. In the first step coumarin 3-carboxylic acid chloride was prepared by coumarin carboxylic acid with the $SOCl_2$. In the second step, coumarin acid chloride was treated with 3-amino-5-Methyl isoxazole to produce amide 7. Then the amide 7 is treated with chlorosulfonic acid to obtain desired product. Finally, the product reacted with different amines in the presence of sodium hydrogen carbonate at room temperature produces corresponding sulfonamides derivatives [38]. Reaction is shown in Scheme 14.



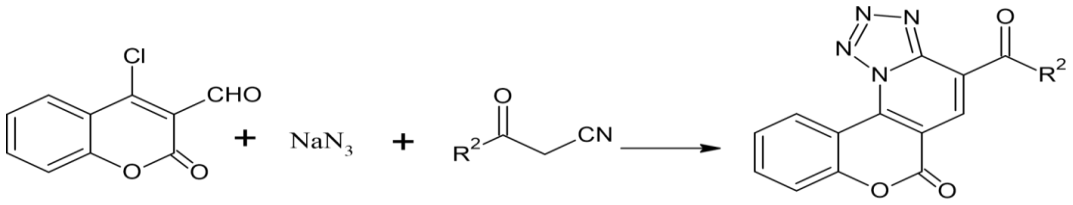
Scheme 1: Synthesis of 7-hydroxy coumarin derivatives

2.17. Synthesis of Imidazole coumarin derivatives

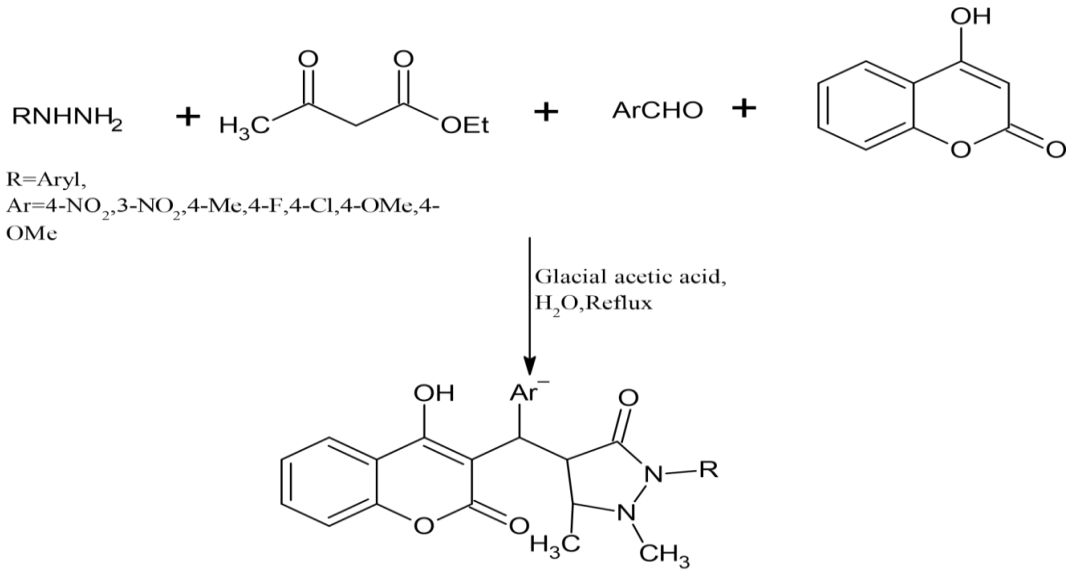
Shwn-chen *et al.* synthesized Imidazole coumarin derivatives as antiviral agent against Hepatitis C virus. Here, 1H-imidazole 2-thiol reacted with the 3-(Chloromethyl) coumarins in the presence of aqueous ammonia and acetonitrile to obtain a corresponding imidazole coumarin derivatives (Scheme 15).



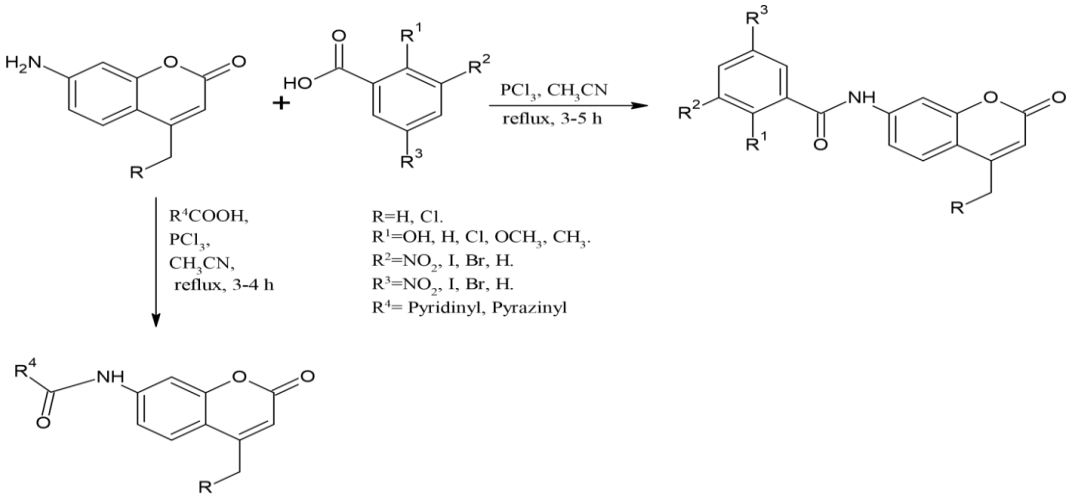
Scheme 2a: Synthesis of novel Chalcone and coumarin derivative



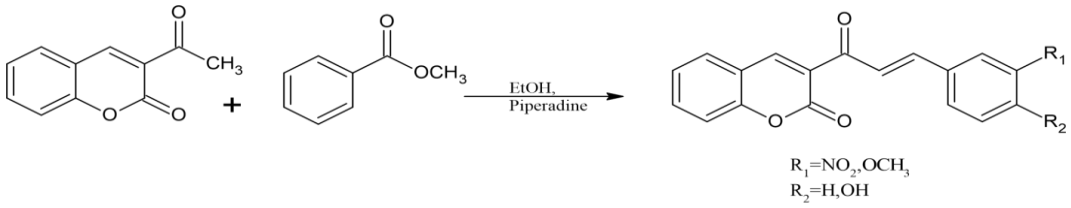
Scheme: 2b



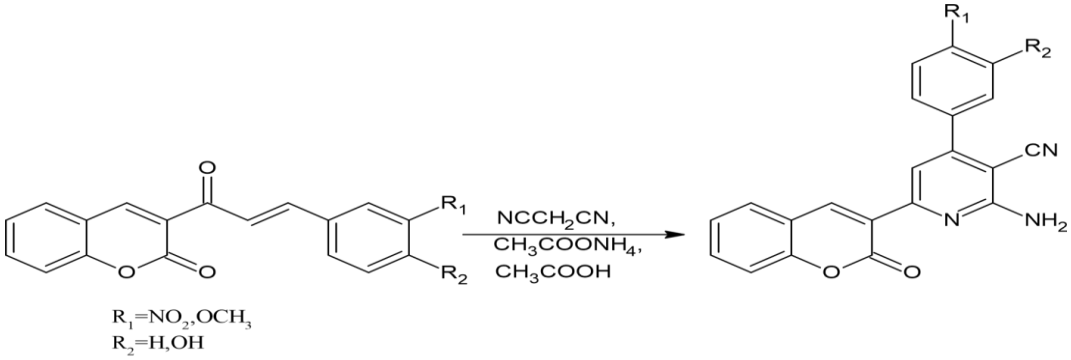
Scheme 3: Green synthesis of benzopyrazolyl coumarin



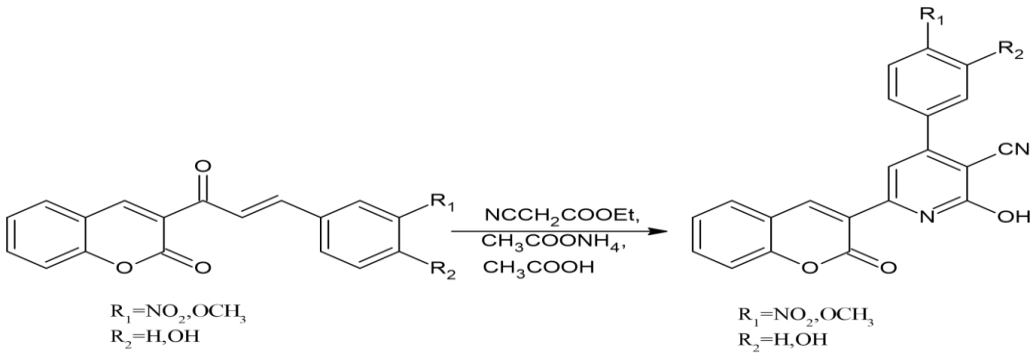
Scheme 4: Synthesis of 7-amidocoumarins



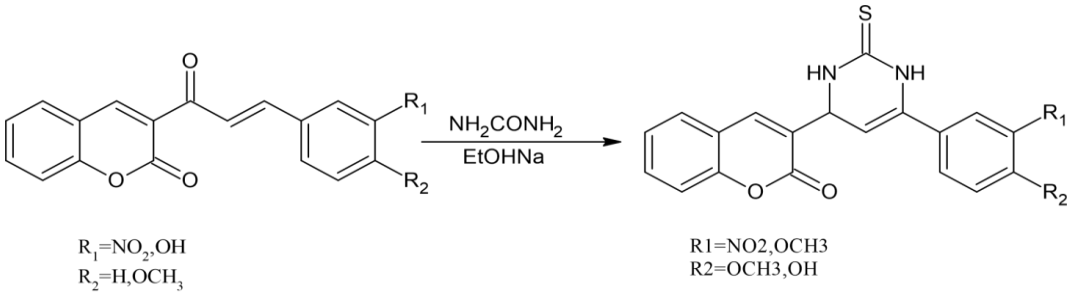
Scheme 5: Synthesis of coumarin chalcone derivatives



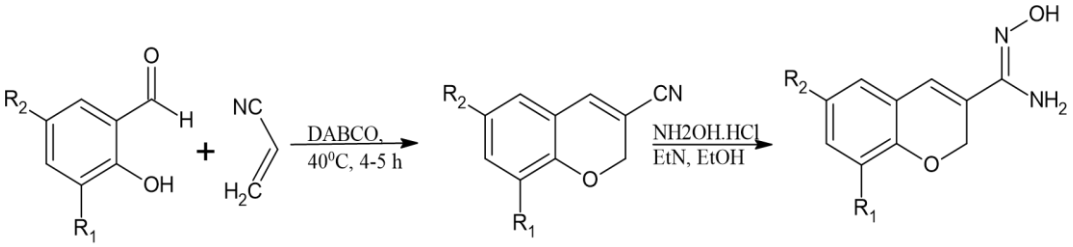
Scheme 6: Synthesis 2-aminonicotinonitrile derivatives



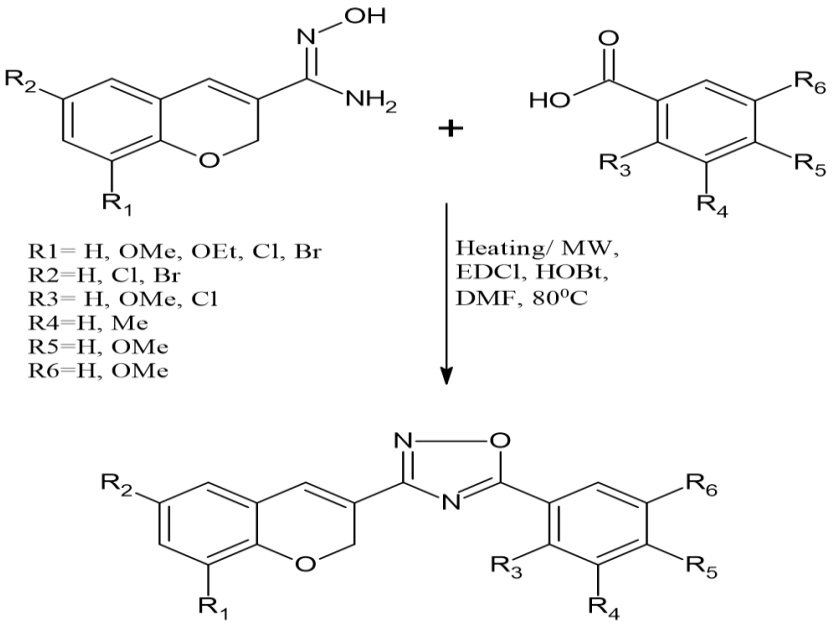
Scheme 7: Synthesis 2-hydroxynicotinonitrile derivatives



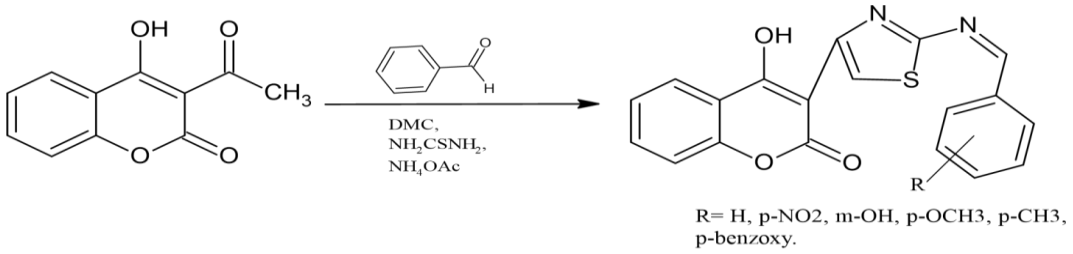
Scheme 8: Synthesis aryl coumarinyl pyrimidine derivatives



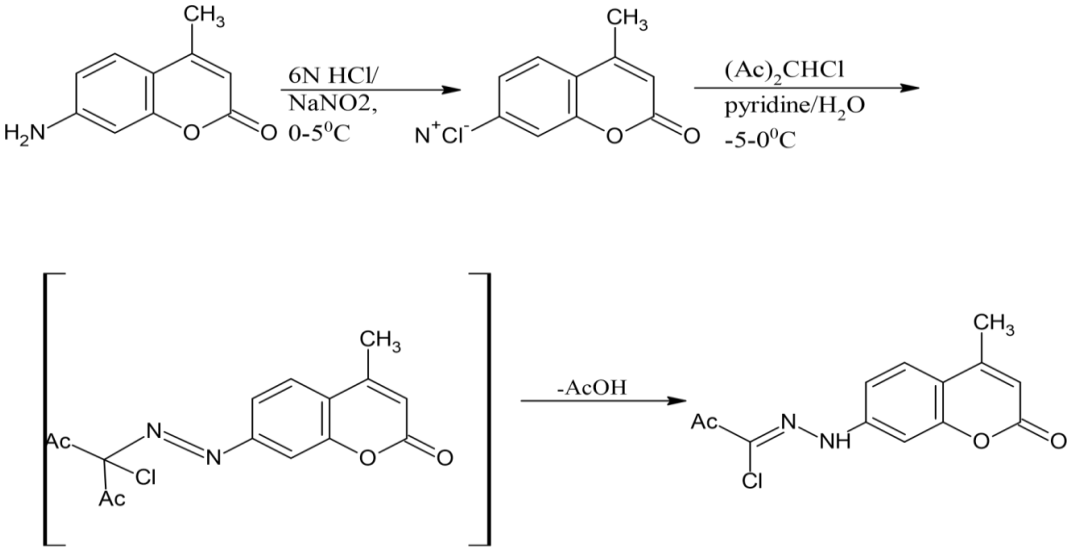
Scheme 9a: Synthesis of chromene-3-carbonitrile and N′-hydroxy-2-*H*-chromene-3-carboximide



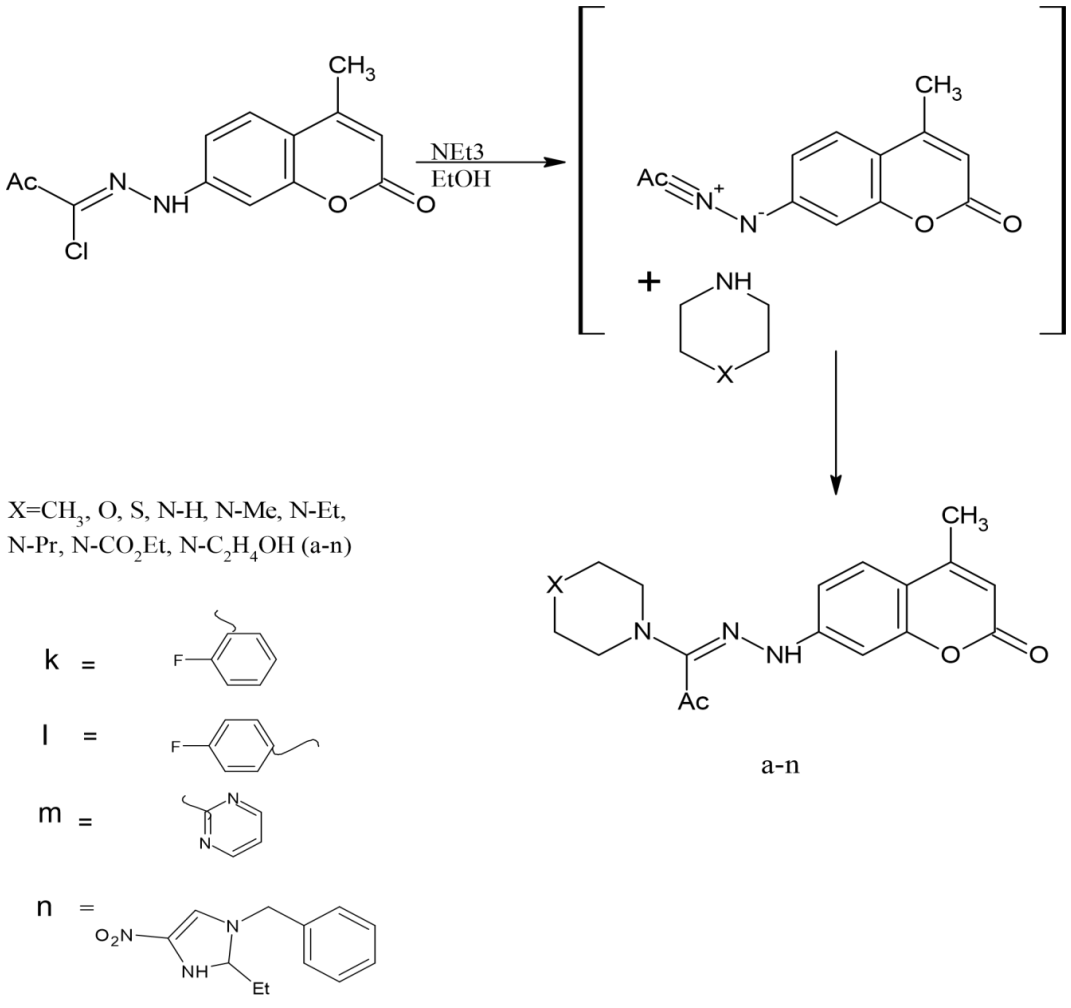
Scheme 9b: Synthesis of chromene fused oxadiazole derivative



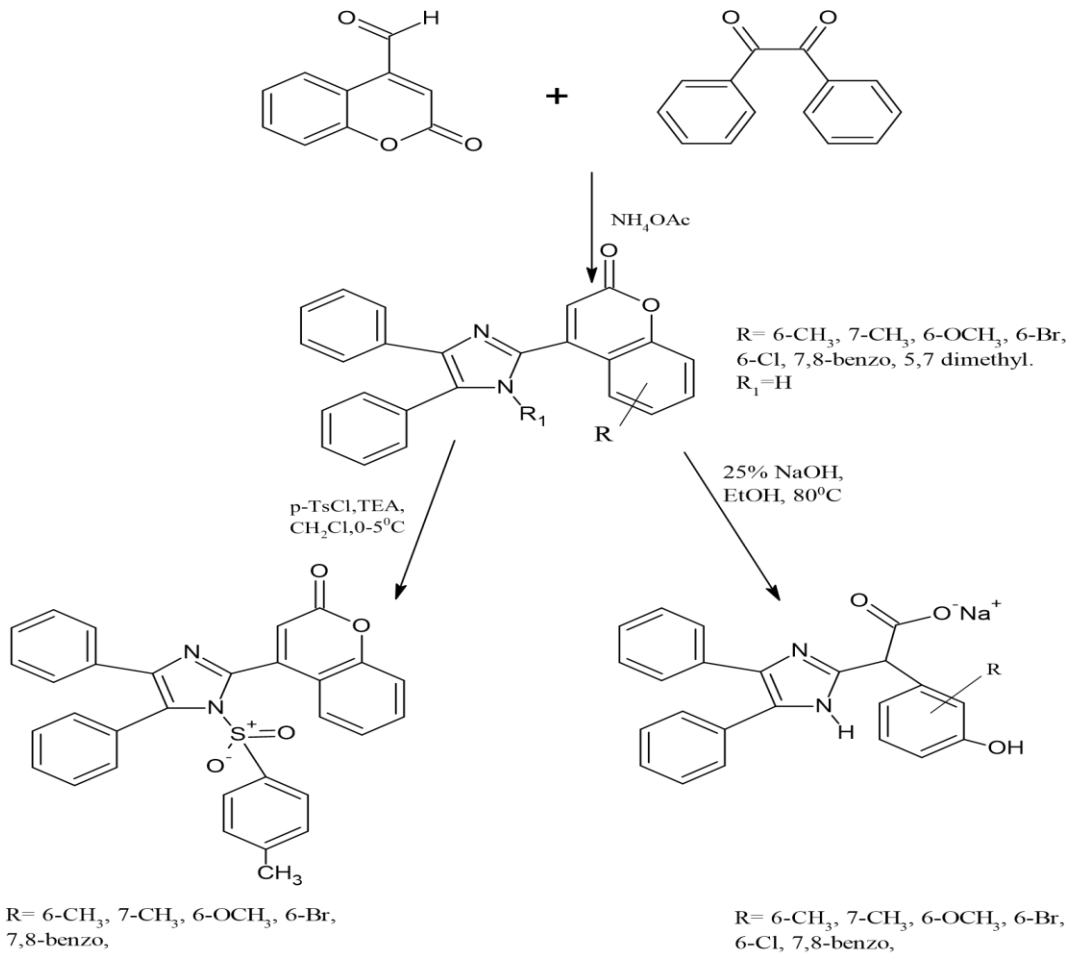
Scheme 10: Synthesis of thiazolyl coumarin derivatives



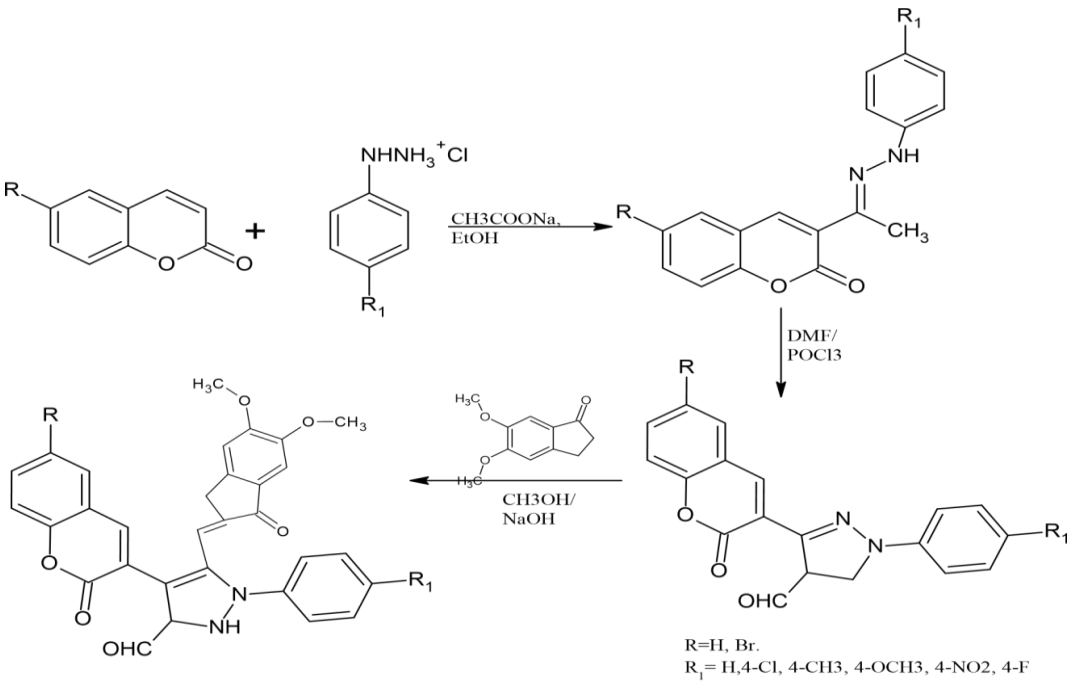
Scheme 11a: Synthesis of N-(4-methyl-2-oxo-2H-chromen-7-yl)-2-oxopropanehydrazonoyl chloride



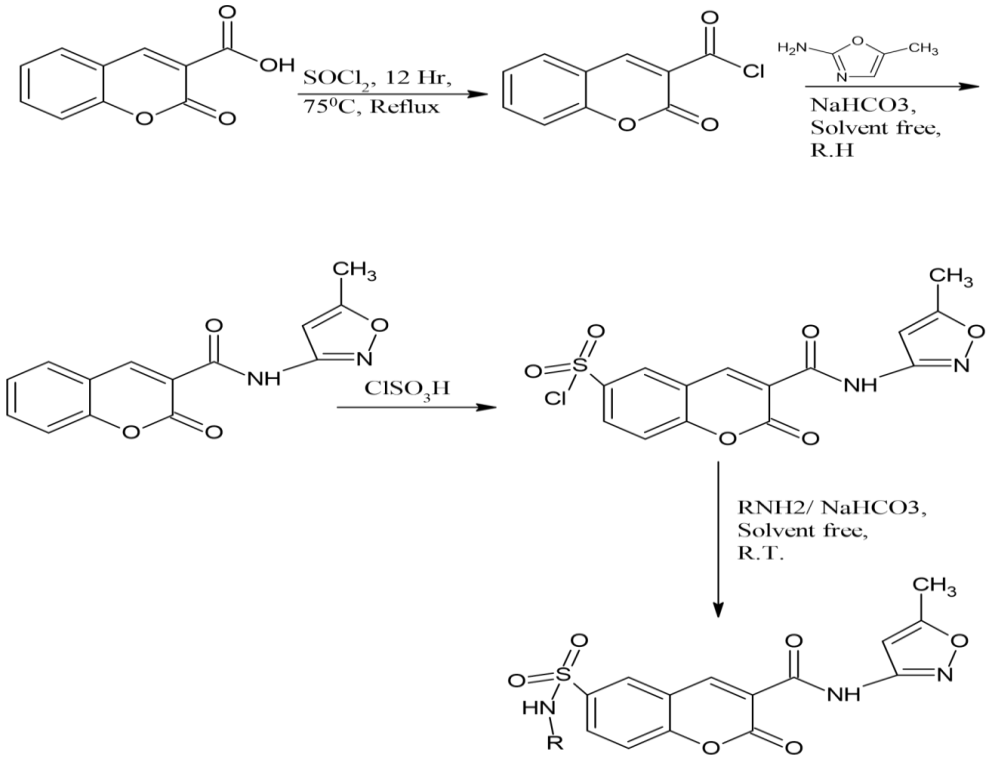
Scheme 11a: Synthesis of 4-methyl-7{2-[2-oxo-1-(substututed-N-hexahydroazinyl)propylidene]-hydrazinyl}-2H-2-ones



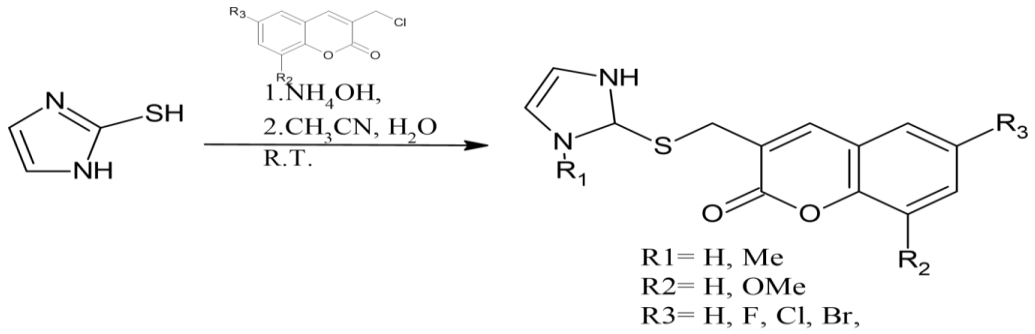
Scheme 12: Synthesis of coumarin imidazole hybrid derivatives



Scheme 13: Synthesis of pyrazole and indolene containing coumarin



Scheme 14: Synthesis of novel coumarin isoxazole sulfonamide hybrid compound



Scheme 15: Synthesis of imidazole coumarin conjugates

3. CONCLUSION

The present review gives an overview about the coumarin scaffold, as it posseses both the Nucleophilic and Eletrophilic nature that's why it undergoes several Number of Substitution reactions. The coumarin scaffold recently considered as a potential candidate because of it's wide range of pharmacological and biological activities.

Conflict of interest
None declared

Source of funding
None declared

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