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Review of synthesis methods and evaluation of biological effects of coumarin compounds

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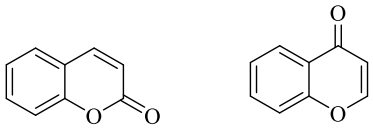
ABSTRACT: *Coumarins are a class of naturally occurring heterocyclic compounds characterized by a distinctive sweet aroma and notable biological activities, though some demonstrate toxicity. These phytochemicals have attracted significant attention in medicinal chemistry due to their diverse pharmacological properties. This study systematically evaluates four synthetic approaches for coumarin derivatives and investigates their structure-activity relationships. The research highlights the therapeutic potential of coumarin scaffolds, particularly their antioxidant, anti-inflammatory, and anticancer properties. Our findings offer theoretical explanations for coumarin bioactivity and contribute to rational drug design. Furthermore, we demonstrate reproducible synthetic protocols for preparing novel pyridocoumarin derivatives under optimized reaction conditions, expanding the structural diversity of this pharmacologically important class.*

KEYWORDS- *Coumarin, Pachmann reaction, Heck coupling, Wittig reaction, synthetic methodology, structure-activity relationship.*

I. INTRODUCTION

Coumarin is a heterocyclic organic compound characterized by its sweet aromatic odor and notable toxicity, widely distributed in various plant species. Chemists have developed particular interest in heterocyclic compounds due to their remarkable biological properties, making their synthesis highly valuable in pharmaceutical research. Oxygen, nitrogen, and sulfur represent the most prevalent heteroatoms in heterocyclic systems, though numerous other heteroatom-containing rings have been extensively characterized.

The family of known heterocyclic compounds continues to expand rapidly. Benzopyrans are systematically classified into two isomeric forms: benzo-α-pyran and benzo-γ-pyran. In chemical nomenclature, benzo-α-pyran is designated as coumarin, while benzo-γ-pyran is referred to as chromone (Scheme 1). The fundamental distinction between these two structures lies in the positional orientation of the carbonyl group within the pyran ring.



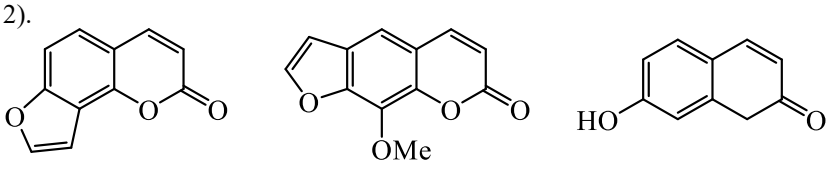
1 2

Scheme (1) Coumarin formula

Coumarin (H2-1-benzopyran-2-one) was first identified as an oxygenated heterocycle in 1820 and is known for its grassy, vanilla-like odor.

It was first isolated from tonka beans in 1822 and later from clover, yellow grass, and a flowering plant in the willow family. Coumarin is a white crystalline powder with a grassy odor and a sweet, invigorating, and characteristic aroma that is used to flavor detergents, soaps, and perfumes[1].

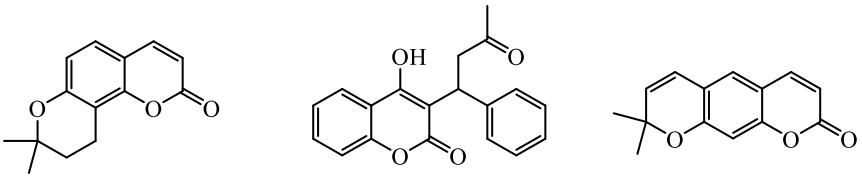
Coumarin is classified based on its chemical structure into simple coumarins, in which alkoxy, hydroxy, and alkyl groups are attached to a benzene ring (e.g., amblyophore), furanocoumarins, a furan ring attached to coumarin, linear furocoumarins (e.g., xanthotoxin), and nonlinear furocoumarins (angeligine) (Scheme 2).



Xanthotoxin Angeligin Umbelliferone

Scheme (2) Schematic of different forms of coumarin.

Pyranocoumarins consist of a six-membered ring attached to the coumarin moiety (such as sezelin and xanthilitin) of a coumarin with a substitution in the pyran ring (such as warfarin) (Scheme 3) [2].



Xanthyletin Warfarin Seselin

Scheme 3: Different forms of pyranocoumarins

Coumarins and their derivatives are a class of active heterocycles that possess a wide range of biological activities. Their antibacterial [3], antifungal [4], anti-inflammatory [5], antidepressant [6], anti-AIDS [7] and antitumor [8] activities have been demonstrated. In addition, coumarins and their derivatives are used as inhibitors of the lipoxygenase (LOX) and cyclooxygenase (COX) pathways of arachidonic acid [9]. Apart from their biological applications; they are also used as food additives, perfumes, cosmetics, brighteners and fluorescent and laser dyes. Their optical applications such as laser dyes, nonlinear optical chromophores, fluorescent bleaches, polymer science, solar cell absorbers have been extensively studied by coumarins [10-13].

Sources in Nature Coumarins constitute a special class of natural compounds that play a special role in nature and attention to their chemistry continues due to their benefits as bioactive substances. They are known as secondary plant metabolites and exhibit numerous and interesting biological properties. More than 1800 natural coumarins have been discovered [16]. 7-Hydroxycoumarin is the best known natural compound containing the coumarin nucleus and is found in carrots, coriander and hyacinth. It has been used in sunscreen, fluorescence indicator and dye [17]. Warfarin is a natural compound of 4-hydroxycoumarin and is isolated from the plant Zuberine, which is used to prevent blood clotting in the veins, lungs or heart [18]. Recently, six new coumarins have been extracted from the fruit and stem bark of the plant Colophyllum despar. Colophyllum includes 200 species and is widely distributed in tropical rainforests. Several species are traditionally used by indigenous peoples [19].

In this study, the results obtained allow us to better understand the medicinal properties of coumarin compounds and, through biological investigation of this research, we can gain deeper knowledge in the field of

Alzheimer's disease treatment, help reduce the risks of using pollutants, and thus promote a healthier and better society. This study addresses the question of whether coumarin derivatives have medicinal properties and can treat Alzheimer's disease.

Coumarin compounds, which have long been used in medicine as spices in various fields, contain the coumarin ring with various derivatives of aromatic amines, DMAD, etc. The main objectives of this study included the investigation of coumarin derivatives, physiological effects, and synthetic methods in the laboratory.

The research method in this study was a review and laboratory investigation using Wittig interactions in the laboratory and other methods of coumarin extraction, as a review of basic compounds and possible methods and mechanisms, to synthesize it.

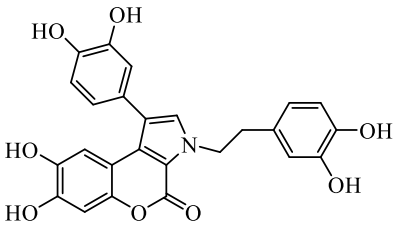
II. DISCUSSION AND CONTROVERSY

REVIEW OF METHODS FOR SYNTHESIS OF COUMARINS

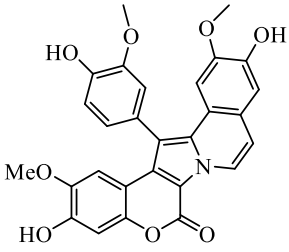
Due to its diverse biological applications, the preparation of coumarin derivatives has attracted the attention of chemists. Several methods have been developed for the synthesis of coumarin and its derivatives, such as the Pechmann condensation method, Perkin interaction, Nonagel condensation, Wittig interaction, etc.

PECHMANN INTERACTION

The Pechmann condensation interaction was first reported by Pechmann and Duisberg in 1883. This method for preparing coumarin has been widely used due to its ease of preparation and low cost of raw materials. In this method, the interaction between phenol and β-ketoester takes place in the presence of an acid catalyst (Schemes 4 and 5) [20].

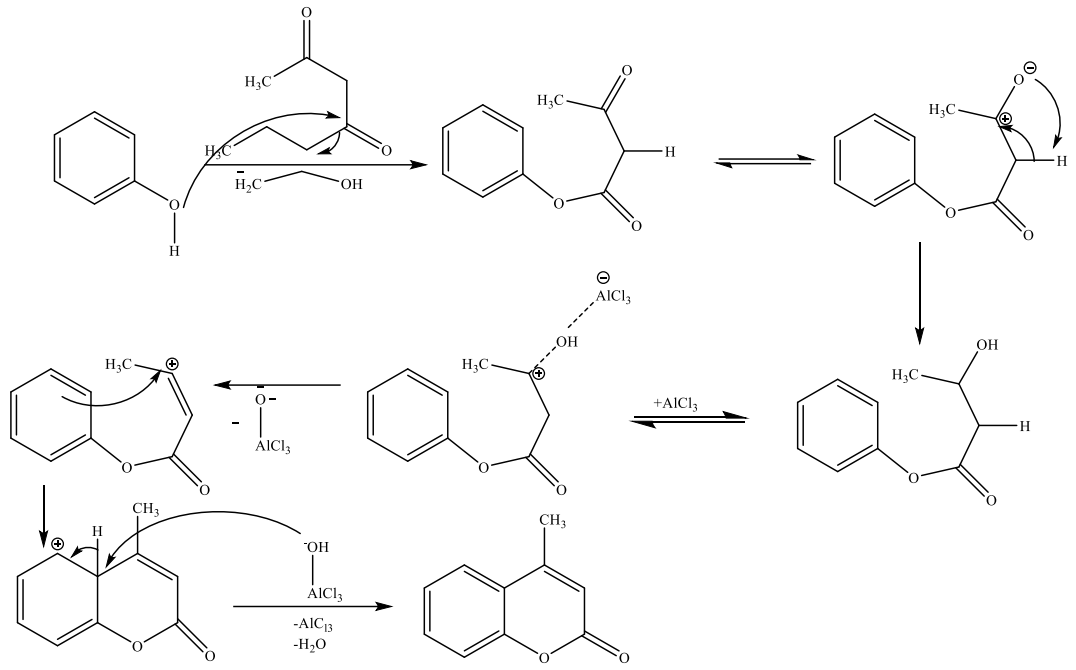


Ningalin B



Lamellarin D

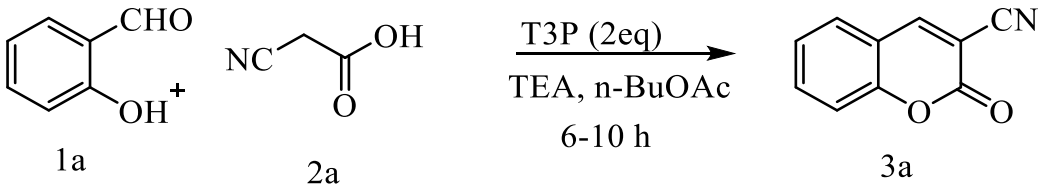
Scheme 4: Patchman interaction



Scheme 5: Patchman interaction mechanism

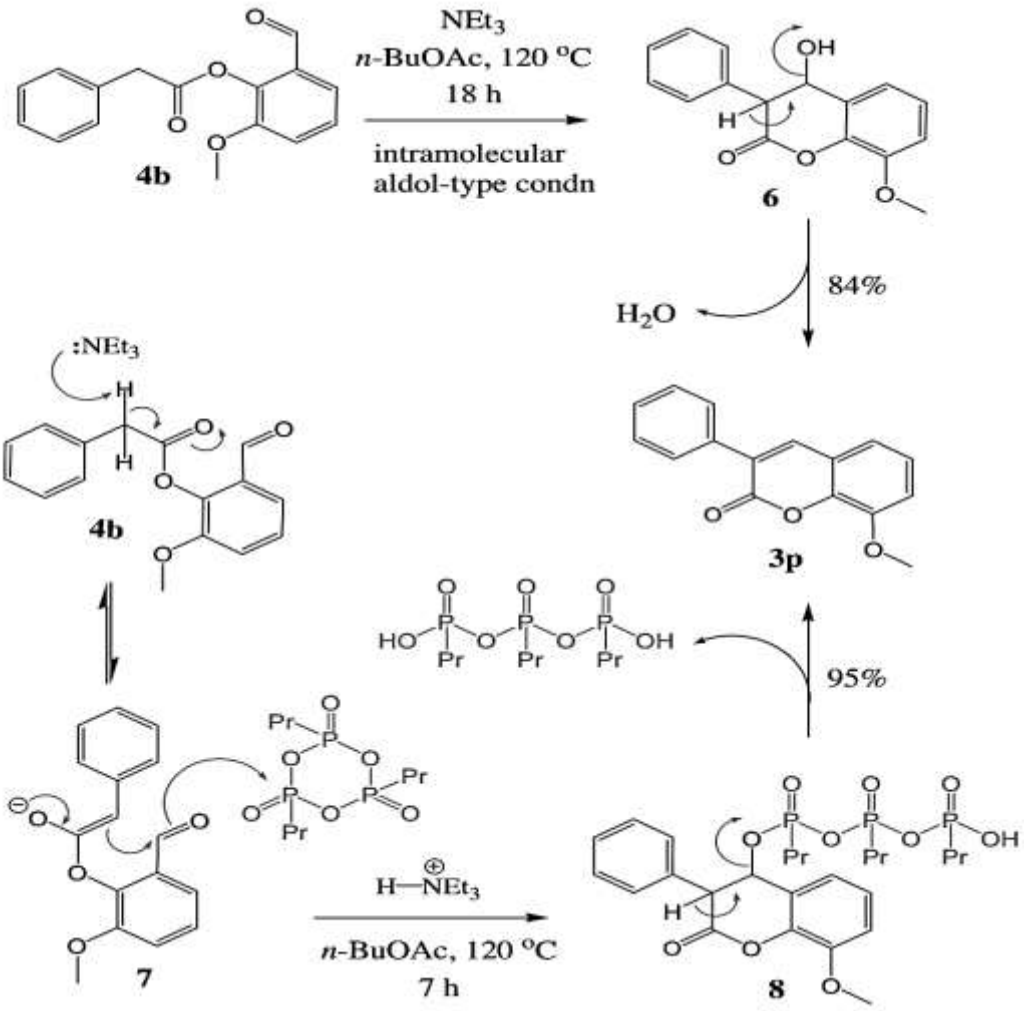
PERKIN INTERACTION

The Perkin interaction is another method for the synthesis of coumarins. For example, Augustin and co-workers reported the synthesis of a single coumarin group from salicylaldehyde and cyanoacetic acid using propylphosphonic anhydride (T3P) (Scheme 6)[21].



1a 2a 3a

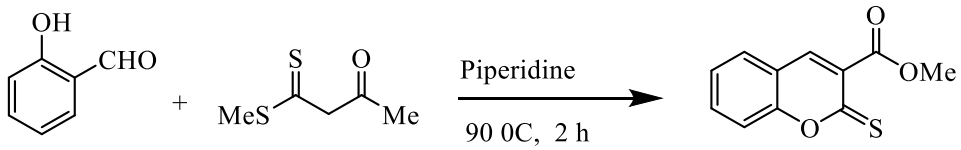
Scheme 6: Interaction of salicylaldehyde and cyanoacetic acid



Scheme 7: A sketch of the proposed mechanism for the synthesis of a coumarin derivative.

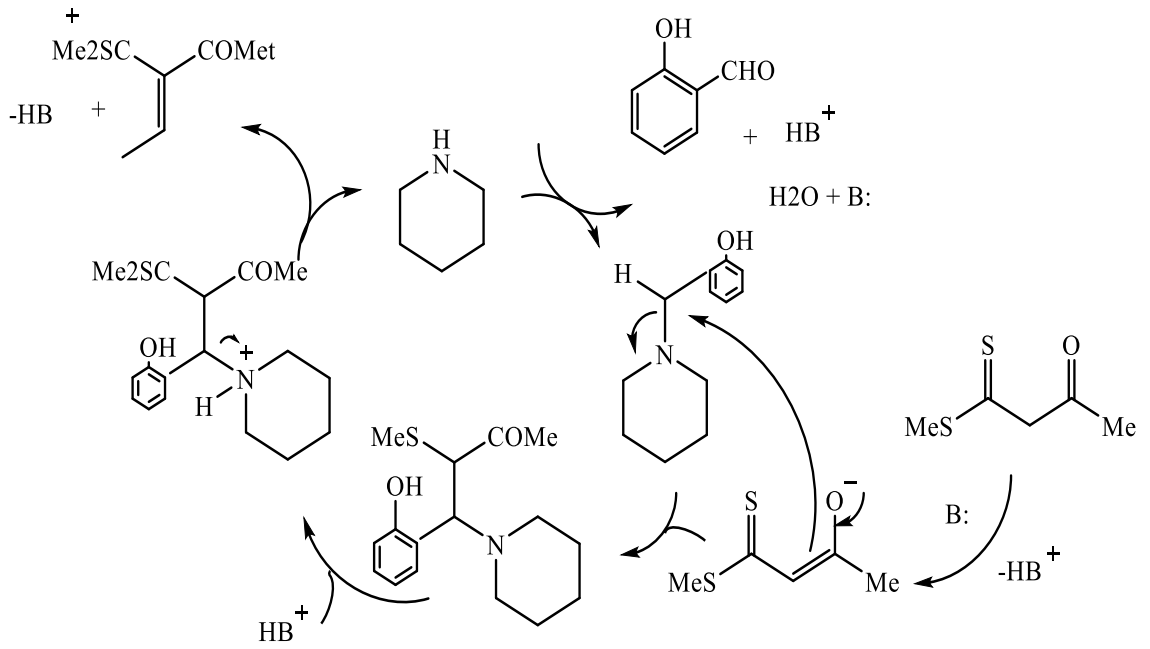
NOVONAGLE INTERACTION

The synthesis of coumarins via Novonagle interaction involves the condensation of aromatic aldehydes and activated methylene compounds in the presence of an amine. For example, Singh and co-workers reported the synthesis of methyl 2-thioxo-2H-chromo-3-carboxylate from the condensation of β-oxo dithioester and salicylaldehyde in the presence of piperidine under solvent-free conditions (Scheme 9) [22].



Scheme 9: Condensation interaction of β-oxo dithioester and salicylaldehyde

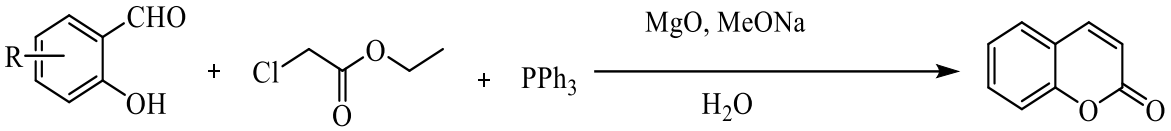
The mechanism of this interaction is shown in Figure 10.



Scheme 10: Mechanism of Neunagel interaction

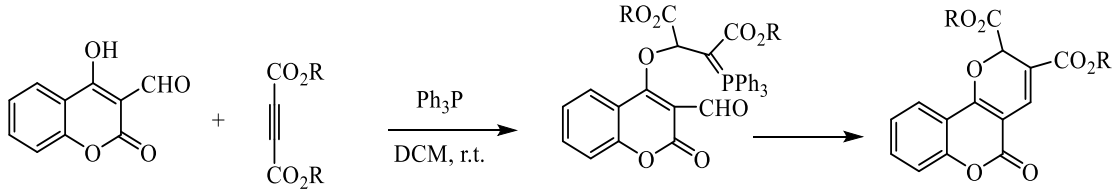
WITTIG REACTION

The Wittig reaction involves the reaction of an aromatic aldehyde or ketone with a phosphonite or phosphoric acids. For example, the reaction of salicylaldehyde and ethyl chloroacetate in the presence of triphenylphosphine and MgO/MeONa leads to the formation of coumarin (Scheme 11)[23].



Scheme 11: Interaction of ethyl chloroacetate and salicylaldehyde

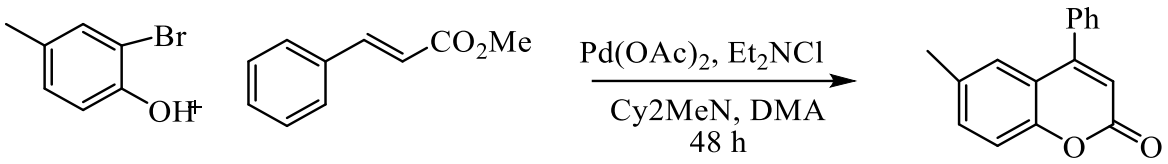
The Wittig reaction is one of the most important methods for the formation of carbon-carbon double bonds. Since its discovery in 1953 by Wittig and Gessler, the Wittig reaction has been widely used in the preparation of industrial and pharmaceutical materials. Rad Moghadam and his colleagues reported the synthesis of pyran-neo coumarin from triphenylphosphine, dialkylacetylene dicarboxylate, and 3-formyl-4-hydroxycoumarin in dichloromethane solvent at room temperature [24].



Scheme 12: Pyranocoumarin synthesis interaction

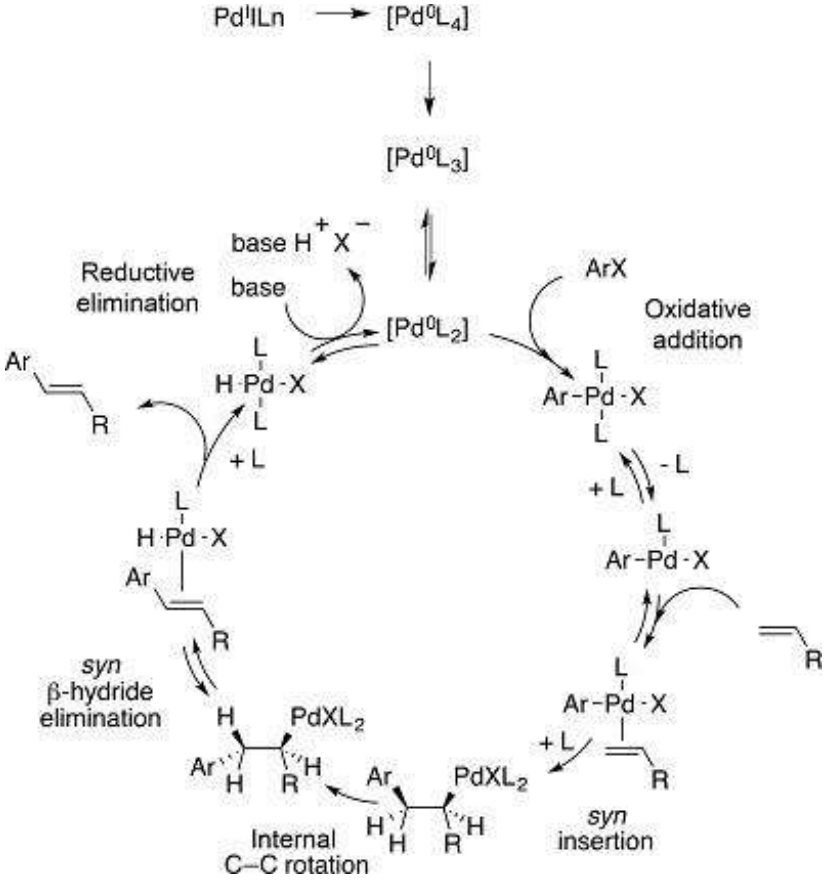
Heck interaction

The Heck interaction involves the palladium-catalyzed interaction between aryl hydrides and alkenes, leading to the coupling of alkenes. The interaction is carried out on 2-bromophenols and cinnamic acid esters to prepare coumarin derivatives (Scheme 13) [25].



Scheme 13: Interaction of bromophenols and cinnamic acid esters

The mechanism of the Heck interaction is shown in the following scheme.



Scheme 14: Possible mechanism of the Heck interaction

BIOLOGICAL INVESTIGATION AND MEDICINAL APPLICATIONS OF COUMARIN

Coumarins are of great interest due to their biological properties. In particular, the physiological, bacteriostatic and antitumor activities of these compounds make them attractive and are used in new therapeutic approaches. Coumarin and its derivatives are potential inhibitors of cell proliferation in various cancer cells [26]. In addition, 4-hydroxycoumarin and 7-hydroxycoumarin inhibit cell proliferation in gastric carcinoma cells [27]. A new series of coumarinylpyrazolines substituted at carbon 5 by aryl fusion of coumarinylpropan-1-one with phenylhydrazine in the presence of heated pyridine were synthesized. All the synthesized compounds have anti-inflammatory and analgesic activities. Compounds containing 4-chloro and

2,4-dichloro showed significant anti-inflammatory effects in acute inflammation of the rat paws compared to diclofenac as a standard drug. These compounds also showed significant antibacterial activity in a modified acetic acid-induced model [28].

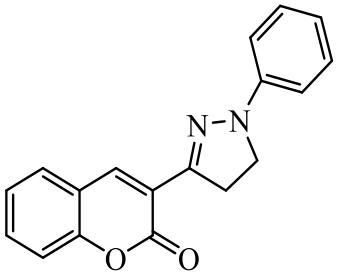


Figure 15: Structure of coumarinyl pyrazoline

Pradeep Kumar and co-workers reported the synthesis and antimicrobial activity of phenyl thiazolidinyl benzopyran-2-ones substituted at carbon 2. They evaluated the antibacterial and antifungal activity of the synthesized compounds against bacterial and fungal dysenteries [29]. Among the synthesized compounds, the compound with fluorine substitution showed good antimicrobial activity.

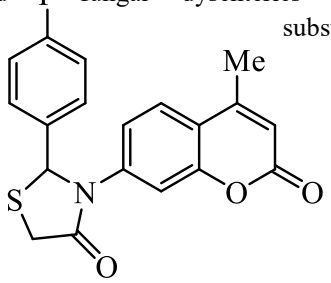


Figure 16: Structure of phenyl thiazolidinyl benzopyran 2-one

Mesole and isomesole 4-phenylcoumarins extracted from the tree Marillapluricostata are effective for the treatment of HIV-1. Mesole inhibits TNFα-induced transcription of HIV-1-LTR by targeting the nuclear factor-κB (NF-κB) pathway. Mesole does not inhibit NF-κB binding to DNA or phosphorylate and degrade a portion of NF-κBp65 in TNFα-stimulated cells. These results suggest the potential of the NF-κB transcription factor as a target for anti-HIV-1 compounds such as 4-phenylcoumarins, which could serve as lead compounds for the development of complementary therapeutic programs against AIDS.

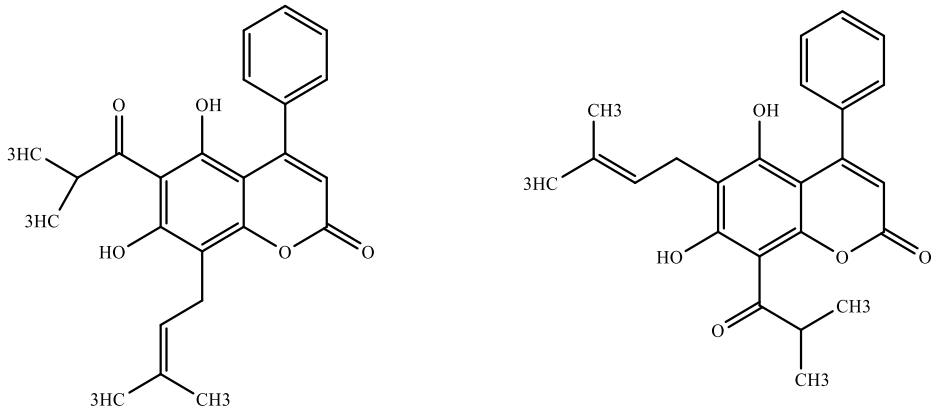
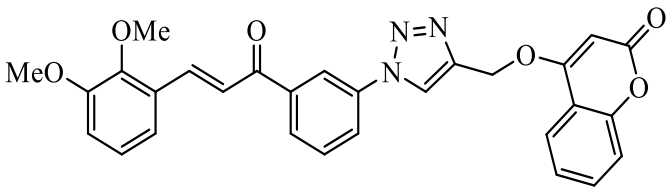


Figure 17: Structure of mesole (left) and isomisole (right) of 4-phenylcoumarin

A number of chalcone-coumarin derivatives with a 3,2,1-triazole ring attached via a dipolar cycloaddition of azide and alkyne. These molecules were investigated for their cytotoxic activity against cancer cells (HuCCA-1, HepG2, A549 and MOLT 3). Among the triazole hybrids, derivatives of the 2,3-dimethoxy triazole ring at position 3 have the strongest cytotoxic activity against MOLT-3 cells without affecting



normal cells [30].

Figure 18: Structure of chalcone-coumarin

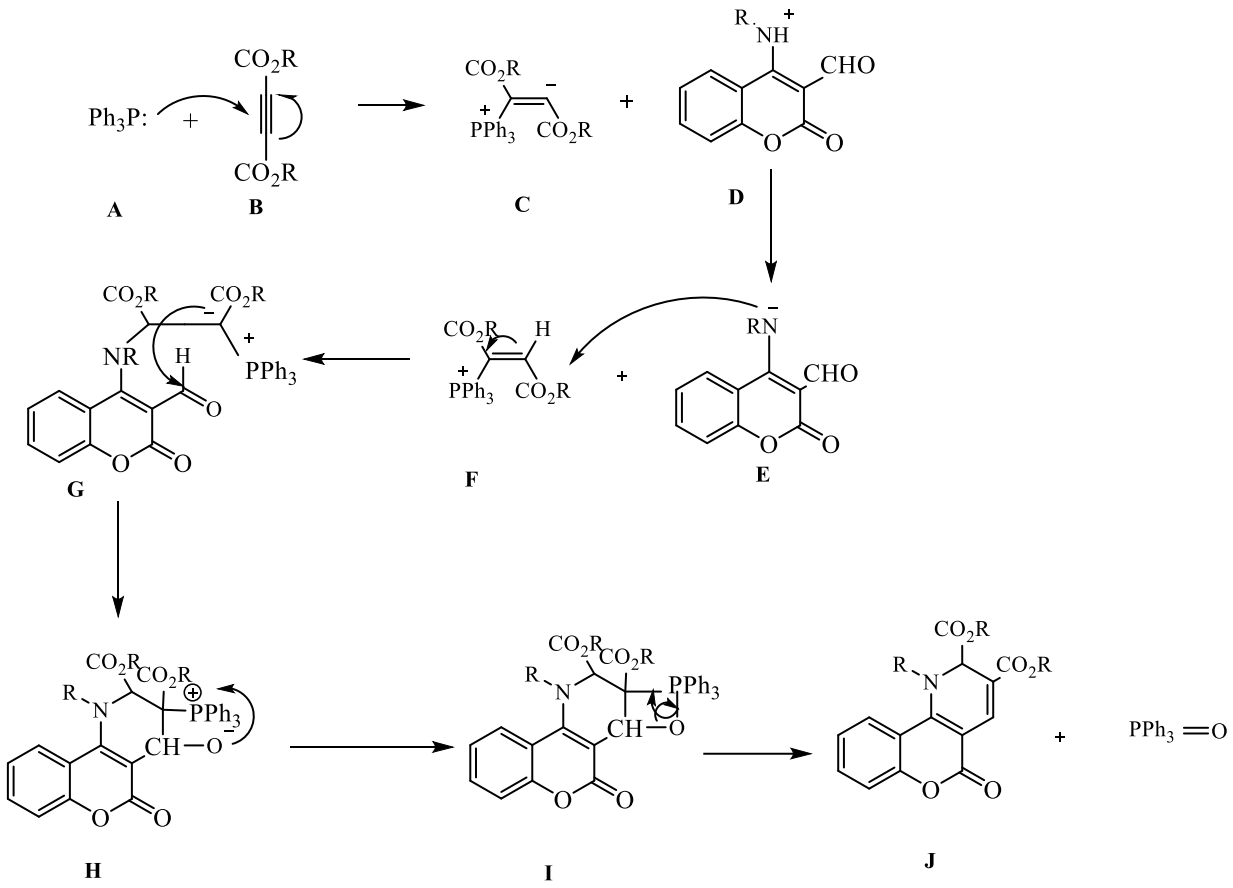
New derivatives of 2-(5-hydroxy-5-trifluoromethyl-4,5-dihydromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazole were synthesized from the condensation of 3-(2-bromoacetyl)coumarin with 5-hydroxy-5-trifluoro-4,5-dihydropyrazole-1-thiocarboxamide for antibacterial activity [31]

III. CONCLUSION

According to the obtained optimization conditions, the reproducibility of the interaction was investigated and studied with the aim of preparing a wide range of fused derivatives of pyridocoumarin

Based on the above observations and previous reports on the possible route for the interaction to reach the final product, it is proposed as Scheme 19.

From the nucleophilic attack of PPh3 on the ester group, the ion pair C is formed, which is protonated by NH-acid. Then, from the double base attack of NH-acid E on the vinylphosphonium ion F, the phosphorane G is formed. From the Wittig interaction between the phosphorane part of the molecule and the aldehyde part, the phosphine oxide product (J) is obtained.



Scheme 19: Possible mechanism for the synthesis of pyridocoumarins

In the laboratory, aminopyridocoumarin derivatives were synthesized via Wittig reaction as a convenient and useful method. The reaction system used was without the aid of transition metals and temperature, including the use of triphenylphosphine in the formation of the C-C bond. Pyridocoumarin derivatives were obtained under mild conditions, in high yields and in a short time.

High yields, easy separation conditions, ambient temperature, and short time are the advantages of this synthetic method.

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