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SYNTHETIC STRATEGIES AND PHARMACOLOGICAL ACTIVITY OF COUMARIN DERIVATIVES: AN OVERVIEW

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Abstract: Benzopyrones, also known as coumarins, are found in very significant amounts in plants, however they have also been found in microbes and animal sources. This family of chemicals was divided into various categories as a result of the structural diversity that was discovered there, ranging from simple coumarins to numerous other types of polycyclic coumarins, including furocoumarins and pyranocoumarins. Due to their wide range of biological activity, simple coumarins and their analogues are a vast family of chemicals that have garnered attention. They have demonstrated value as CNS-active chemicals, antitumor, anti-inflammatory, antioxidant, hepatoprotective, antiviral, and anti-HIV agents. Many plant habitats include coumarins, which may also serve as a chemical defense against predators. Warfarin, an anticoagulant that prevents deep vein thrombosis, blood clot formation, and pulmonary embolism, is used in prescriptions where it suppresses vitamin K production. There are a number of ways to make coumarins, with the Perkin reaction between salicylaldehyde and acetic anhydride being a well-known example. The investigation of various synthesis processes and the pharmacological effects of coumarins are included in the current review.

Index Terms **– Coumarin, anti-leishmania, anti-microbial, anti-viral, anti-oxidant.**

I. INTRODUCTION

Over 200 years ago, coumarins were first studied. The basic member of this class, coumarin, was first isolated from Coumarounaodorata Aube, that's where the name of this chemical family comes from. A common secondary metabolite found in many plant families and essential oils, coumarin has been employed as a scent in both food and cosmetic items. The benzo-pyrone (2H-1-benzopyran-2-one) for whom the systematic nomenclature was defined by IUPAC relates to the coumarin nucleus (Adelia et al. 2016). In addition to the discoveries achieved by isolating coumarins from the many different plant and animal species, there are also derivatives of synthetic origin, which greatly expand the number of coumarin molecules that are currently known. The ability to determine their chemical structures was made possible by technical advancement; therefore, it begs the question of what motivates people to be interested in the chemicals in this family. From a variety of options that could be listed.

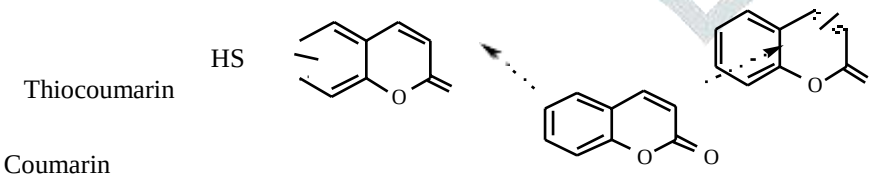


Figure 1- Structure of Coumarin

The plant world has a wide distribution of coumarins, which are noticeable in some species including Umbelliferae, Rutaceae, and Compositae. However, the precise functions of these substances are unclear and have generated some discussion. Since the first instance was recorded in 1812, several coumarins have been identified (Adelia et al. 2016). An outstanding work that offers a thorough analysis of naturally occurring coumarins was prepared by many researchers. Since then, this information has been revised (Ibrar et al., 2016; Otero et al., 2014).

1.1 Biosynthesis of simple coumarins and its derivatives

The biosynthetic pathway starts with the Sikmic acid pathway with the essential presence of through cinnamic acid. The C-2 hydroxylation a characteristic feature of this pathway, which produces a sidechain cleavage (in case of *Salix spp*.), or chain isomerization followed by lactonization, and generates the umbelliferone. The biosynthesis of coumarins, catalyzed through the various cluster of P450 enzymes, with the rate limiting indication. Various P450 enzymes are also used in furanocoumarins

synthesis. Biosynthesis of coumarin and its derivatives is illustrated in fig. 2. (Mishra et al., 2009; Sauvain et al. 1999; Oketch-Rabah et al. 1997)

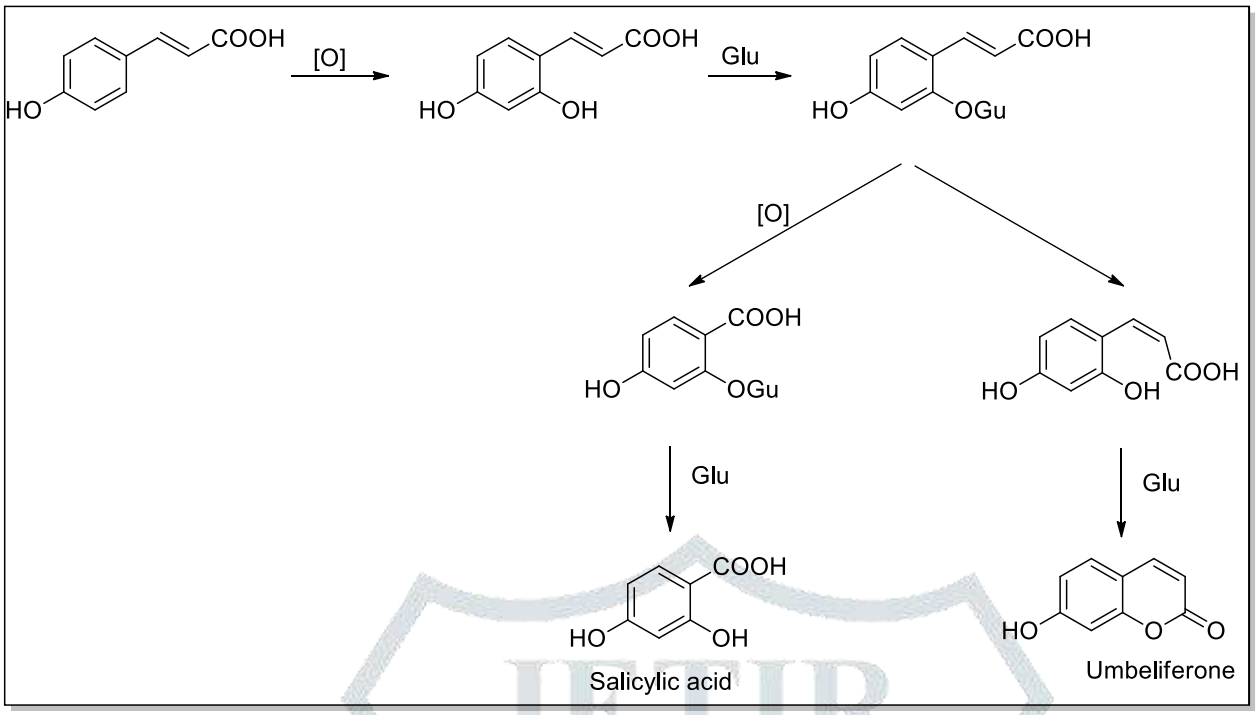


Figure 2 Biosynthesis of coumarin and its derivatives

1.2 Pharmacological activities:

1. Coumarin and its derivatives as anti-microbial

Coumarin derivates broadly used for the purpose of synthesis and pharmacological screening. It shows a strong reaction for nucleophile which seems beneficial in terms of preparing numerous products. Antimicrobial properties were found in various coumarin derivatives (both natural and synthetic). Coumarins derivatives are as an antimicrobial agent works by inhibiting effect against C. *Albicans*, for treating vaginal candidiasis. Other effects are enhancing macrophages, shows beneficial to treat bacterial infections. Coumarin compounds are rich in multiple biological properties, due to which taking attention for treating various diseases, related to bacteria, fungus, virus and many more (Venugopala et al., 2013; Hirsch et al., 2002; Fournet and Muñoz, 2002; Mishra et al., 2009; Sauvain et al. 1999; Oketch-Rabah et al. 1997; Brenzan et al. 2008).

2. Coumarin as anti-leishmania

Every year, between 0.7 and 1.3 million people are affected by cutaneous leishmaniasis. due to a lack of effective treatments and the rising issue of drug resistance, treating this condition is challenging. natural substances like coumarins function as therapeutic agents that are used in conjunction with the current treatment procedures. in alkaloids, phenolic compounds, terpenes, and saponins are a few examples of natural substances with anti-leishmanial capabilities (Tenover, 2006; Adelia et al., 2016) additionally, recent research has revealed that coumarins contain anti-leishmanial properties (Naithani et al., 2008). The roots from vernoniabrachycalyx were used to isolate two novel coumarins, specifically 5-methylcoumarins, as their structures were clarified by ms and nmr spectra (Tataringa, Zbancioc, 2019). The discovery by Brenzan and his colleagues in 2008 for coumarin (-) mammae a/bb demonstrates its effectiveness against l.amazonensis including an ic50 value of 10 µm (Al-Majedy et al.,2017). More recently, substances that have been demonstrated to be effective against by the promastigote form of leishmania major have been isolated, including auraptene (ld50 = 30 µm), osthole (ic50 = 14.95 µg/ml), coumarin-triazolothiadiazine hybrids (ic50 = 0.8 µm), antibiotic cultivars (ec50 = 9.4; 10.2; 13.5 and 27.5 µg/ml) (Hassan et al., 2016; Prusty et al., 2019; Venugopala et al., 2013; Hirsch et al., 2002; Fournet and Muñoz, 2002; Mishra et al., 2009).

3. Coumarin as appetite suppressing property

Coumarin has appetite-suppressing properties, though it has a pleasant sweety odor but has pungent taste. Coumarins are used in anti-psoriatic and anticoagulant therapy. Various skin diseases like atopic dermatitis, alopecia areata, urticaria pigmentosa and lichen planus are treated with furanocoumarins. Bergapten is taken as a alternative for chemotherapy of psoriasis. Warfarin, a oral anticoagulant and vitamin K antagonist, has coumarin a parent molecule used as an rodenticide. In small-cell lung cancer, warfarin is used in conjugation with standard chemotherapy. Coumarin has strong fragrant odor for which broadly used in industries. Coumarin derivatives used as a sweeting agent and fixative of perfumes. It is broadly used as a food additive with vanillin and odor stabilizer in tobaccos. 6-methylcoumarin is widely used as a enhancing the flavor and 7-hydroxycoumarin is used in sunscreens. Coumarins can inhibit aromatase enzyme therefore used in osteoporosis and cardiovascular disease.

4. Coumarins as antiviral

Viruses pose a worldwide hazard and upload many scientific and social issues to mankind. They are the primary contributors for minor and main outbreaks like epidemics and pandemics all over the world, like Avian Influenza, Swine Influenza or Dengue fever, although numerous methods for the remedies of viral diseases are available in the market, like chemotherapy. But due to their potential of mutation causation and emergence of new strains and growing of resistance toward these tablets is quite big

concern. Viruses are now a day's evolving rapidly. This increase the necessity of searching for modified antiviral drugs which can be stronger and powerful against viruses with least or without detrimental adverse effects (Kermani et al., 2016; Sangshetti et al., 2016; Bashir et al., 2014).

Recent all these years have recognized great development in research field and improvement of the antiviral agents, inspired by lot of advancement in the field of virology, in return it has given many new hopes for several therapeutic interventions. Various virus-particular proteins or the approaches have been also finding as objectives for targeted chemotherapeutic intervention. Mostly antiviral drugs usually inhibit the intracellular occasions and specifically affect synthesis and also the dynamics of viral proteins and nucleic acids. The viral polymerases usually taken as primary goal for number of antiviral drugs already present in market. The cycle of viral replication generally includes virus adsorption, reverse transcription, translation, integration, virus-cellular fusion, proteolytic cleavage, assembly, glycosylation or launch. In addition to these unique activities of virus there are also some of host present with enzymes and the innately approaches viral DNA, glycoprotein syntheses and RNA. So many natural compounds consist some natural constituents in the plant extracts has been isolated and checked for their exclusive antiviral activities for numerous of viruses. One of the herbal compounds that is noticeable is coumarin, and the component which makes it an amazing candidate is the for an anti-viral type of drug, are also its role in targeting numerous biological pathways, inhibiting the growth and replication of viruses. Antiviral action of coumarin and also its derivatives, were determined for huge number of viruses comprises of influenza viruses, Enterovirus seventy-one (EV71), coxsackievirusA16 (CVA16), HIV, chikungunya virus and dengue virus. This write up will elaborate anti-microbial characteristics of the coumarins along with the mechanisms covering its inhibitory actions and it will also elucidate its potential and relevance in the treatment of diseases and healing procedures (Sauvain , 1999; Oketch-Rabah et al., 1997; Brenzan et al., 2008; Napolitano et al., 2004).

5. Coumarin analogues as antifungal

Numbers of the serious fungal infections in the human body are usually resulting from 3 fundamental fungal species, i.e., Cryptococcus, Aspergillus and Candida. To set up fungal infection in the host, there are commonly 4 distinctive criteria that has been studied i.e., pathogen

(a) Sought to be able to reproduce at or above the temperature of 37°C,
(b) Should be capable to enter into the particular host tissue by diffusing through
(c) Need to be capable to identify and also can engulf the substances present in human tissue
(d) Should be successfully stand by human defense system of immunity.
Mostly those coumarin compounds with prominent anti-fungal activity, they are dispersed in plant kingdom and microorganism vastly. Almost 1300 coumarin derivatives have been determined, and numbers of similar compounds have been synthesized as they provide six extraordinary transposition sites to play with. Coumarins, as well its derivatives have ability to be developed and emerged as potential anti-viral, anti-fungal or antimicrobial drugs. For example, Cyperusincompletus contains unique coumarin forms that have been isolated and purified for their antifungal activity. With the aid of assays, it was established that these coumarin compounds' crucial actions against fungi are caused by an additionally oxygenated functional group and an aromatic hydroxyl group in the 7 and 6 positions.

6. Coumarin as anticancer property

Because of their numerous pharmacological effects, coumarins have garnered a lot of attention recently. The anticancer effect of these traits has received the greatest attention. This review discusses the wide spectrum of effects they have on tumors, as demonstrated by numerous in vitro & in vivo tests as well as medical studies. According to studies, coumarins have inhibitory effects on the growth of a variety of carcinoma cell lines & could be used to treat cancer. These organic substances have been useful starting points for further methods for the synthesis of more potent analogues. Given the relative ease of coumarin molecules and their mode of action, the coumarin drug molecule might be a useful paradigm for creating novel chemotherapeutic regimens for cancer patients. In-depth analysis of the title compounds' anticancer characteristics is the goal of this review. Due to their relative low toxicity, affordability, prevalence in the diet, and use in a variety of herbal medicines (Kostova, 2005; Lacy and O'kennedy , 2004).

7. Coumarin as antioxidant

The heterocyclic compounds known as coumarins have been linked to favorable impacts on human health, including lowering the risk of diseases like cancer, diabetes, cardiovascular, and brain disorders. Due to its antioxidant properties, these effects are assumed to be connected to the free radical - scavenging effect. Since a few years ago, coumarins have been synthesized in several of their derivatives; this substance is a key source of interest for so many medicinal chemists as they investigate its many pharmacological potentials, including anticoagulant action. In this article, we examine current coumarin derivatives that have been synthesized along with their pharmacological properties, such as antioxidant activity. This review's primary goal is to outline recent chemical and structural developments related to coumarin and its derivatives, which are of interest because of their distinctive entangled molecular structures and biological activity (Al-Azawi et al., 2016).

1.3 SIMPLE COUMARINS ARE SYNTHESIZED BY CLASSICAL AND NONCLASSICAL METHODS

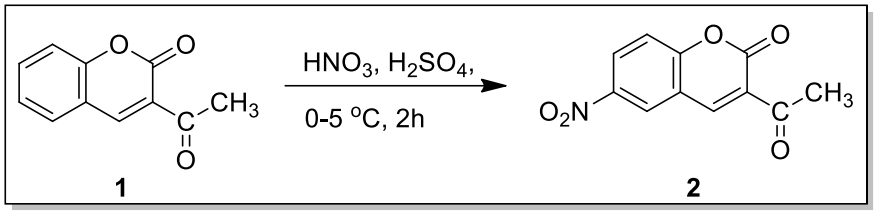
The Perkin, Pechmann, or Knoevenagel reactions can be used to conventionally synthesize coumarins. Wittig, Kostanecki-Robinson, and Reformatsky recently.

Figure 3 Structures of dimeric and trimeric simple coumarins

SCHEME 1:

Series 1: 3-acetyl-6-(substituted amino)-2H-chromen-2-one derivatives

Step- 1



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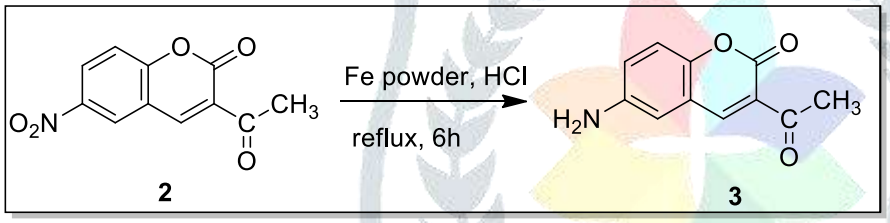
Synthesis of 3-acetyl-6-nitro-2H-chromen-2-one (2): 3-acetyl coumarin1 (0.188 gm, 1 mmole) and sulphuric acid in concentrated form, i.e., 1.10 ml was taken together, mix and stir for 15 minutes at 0 ˚C. Further addition of a mixture of concentrated nitric acid, i.e. 0.06ml, 1.4 and sulphuric acid 0.2 ml, 98%), by maintaining temperature between 0-5 ˚C at that time. The continuous stirring of the mixture at 5 ˚C for a time period of two hours. Pour the above mixture in a conical flask having 25 ml of ice water, formed solid precipitate from water layer, then dried the precipitate after filtration. Purifying with the help of silica gel column chromatography (petroleum ether/benzene 1:1 v/v) to separate the component 3-acetyl-6-Nitro-2H-Chromen-2-one 2.

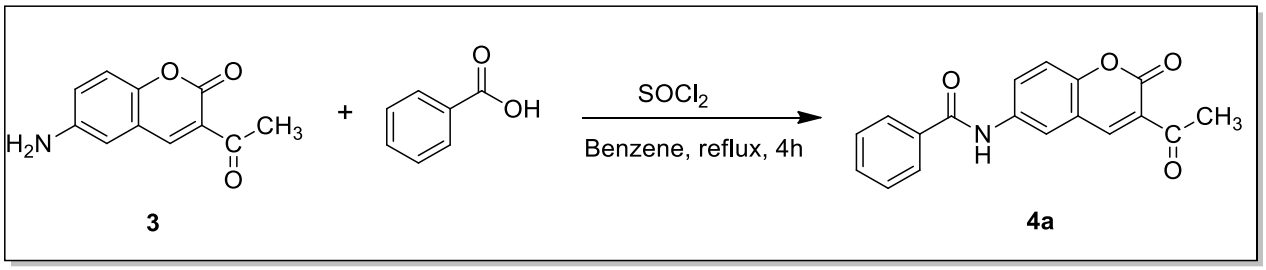
Step-2



Synthesis of 3-acetyl-6-amino-2H-chromen-2-one (3): To a solution of compound 2 3-acetyl-6-nitro-2H-chromen-2-one (0.233 g, 1 mmol 3.14 gm, 0.01 mole) with Iron powder (0.296 g), Conc. HCl (1.11 ml) and ethanol (10 ml) reflux timing is 6 hours. Then cool the reaction mixture, the precipitate obtained was filter and washing done with a abundant amount of water and dry that. Purification of untreated product done by recrystallization with ethanol and compound 3-acetyl-6-amino-2H-chromen-2-one 3 formed.

Step- 3 Synthesis of Coumarin derivatives through the various benzoic acids

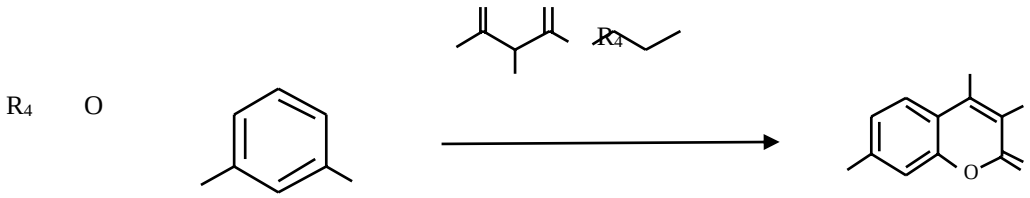
Synthesis of Compound- 4a



Synthesis of *N*-(3-acetyl-2-oxo-2H-chromen-6-yl) benzamide (4a): Synthesis takes place by taking 3-acetyl-6-aminocoumarin (0.203 g, 1 mmol) and benzoic acid (0.122 g, 1 mmol) in combination and was poured into thionyl chloride (0.141 g, 1.2 mmol, 1.2 equiv) and benzene (1.5 ml) and 2 hours reflux was done. Above solution obtained was put into a conical flask having ice water (25 ml). Formation of solid precipitates from the layer of water, filter the mixture and pour in 1.25 ml of 2N NaOH solution and filter the mixture. Then acidification done with the help of 2NHCl, filter by Buchner funnel and washed with a abundant quantity of cold water to afford the re-crystallization from form ethanol and compound, which was obtained *N*-(3-acetyl-2-oxo-2H-chromen-6-yl)benzamide(4a) with yield of 65%.

SCHEME 2:

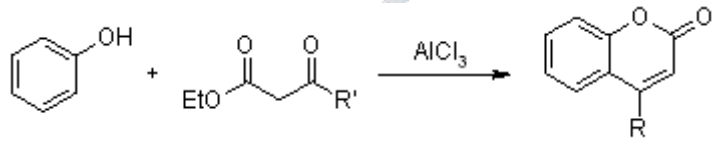
In the Perkin reaction, aromatic ortho-hydroxybenzaldehyde and acid anhydrides are combined to create coumarin in the addition of the alkali salt of the acid (Scheme 1). Several studies on the synthesizing of coumarins using this technique have been reported (Mallick et al., 2015; Oketch-Rabah, 1997; Naithani et al., 2008).



Montmorillonite clay has been used to increase the yield of the reactions (Hirsch et al., 2002) and has been discovered to be a successful condenses material for the synthesis of 7-hydroxy-4- alkylcoumarins (Naithani et al., 2008). Amberlyst 15 and Nafion resin/silica nanocomposites were both successful in facilitating the synthesis of 7-hydroxycoumarins (Fournet and Muñoz, 2002). A different method for creating 4-substituted 7-aminocoumarins on solid supports utilizing microwave irradiation was also disclosed (Mallick et al., 2015).

SCHEME 3

By reacting phenols with -keto esters, the Pechmann Condensation enables the production of coumarins.

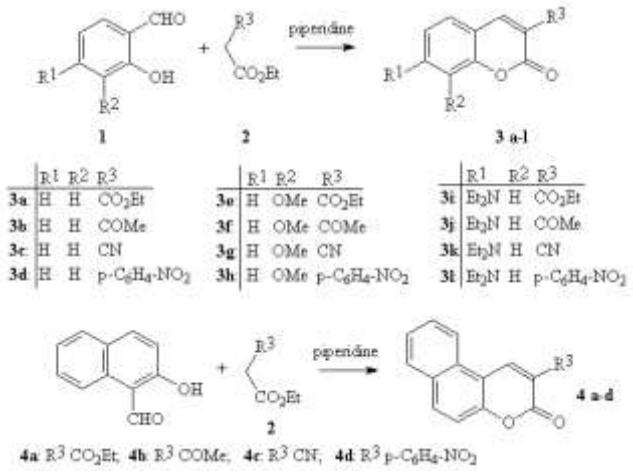


7-Alkynyl-substituted A Sonogashira reaction between 6-substituted-7-(trifluoromethylsulfonyloxy) coumarins 7 and terminal acetylenes 8 produced coumarins 9. Additionally, the corresponding 7-[(1-carboxyphenyl)-1H-1,2,3-triazol-4-yl] coumarins with azidobenzoic acids were created by reacting them with azidobenzoic acids and 7-ethynyl-substituted coumarins in the presence of copper (II) sulphate and sodium ascorbate. 12 Coumarins.

R = H, 4-F, 2-Cl, 2-F, 4-Cl, 2,4-di-F, 4-OMe, 2,4-di-OMe, 2-NO_2, 3-F, 3,5-di-Me, 4-$NHCOCH_3$

SCHEME 4:

By microwave irradiating the chemicals in a standard microwave oven, the Pechman reaction might be quickly accomplished (Harvey et al., 2013). We are presenting our findings on the synthesis of coumarins by the Knoevenagel condensation under this kind of conditions because the major issue of our lab is the solvent free phase-transfer catalytic processes under microwave irradiation (Tenover, 2006). However, in the past, microwave-induced reactions have been used to study the Knoevenagel reaction (Adelia et al., 2016) and the synthesis of coumarin by the Knoevenagel condensation (Naithani et al., 2008). For coumarins, the only example that has consistently been reported is indeed the manufacture of 3-ethoxycarbonylcoumarin (i.e., ethyl 2H-1-benzopyran-2-oxo-3-carboxylate). Numerous coumarins can be designed and synthesized using the Knoevenagel condensation with microwave radiation, and the method's use is much more extensive. According to a published method, coumarin is produced by condensing salicylaldehyde or a derivative of it with different ethyl acetate derivatives (e.g., R3, CO2Et, COMe,R3CH2COEt; CN, or p-C6H4-NO2) inside the addition of piperidine in a solvent-free environment.



	R1	R2	R3
3a	H	H	CO_2Et
3b	H	H	COMe
3c	H	H	CN
3d	H	H	p-C_6H_4-NO_2
3e	H	OMe	CO_2Et
3f	H	OMe	COMe
3g	H	OMe	CN
3h	H	OMe	p-C_6H_4-NO_2
3i	Et_2N	H	CO_2Et
3j	Et_2N	H	COMe
3k	Et_2N	H	CN
3l	Et_2N	H	p-C_6H_4-NO_2

II. CONCLUSION

Coumarin is showing very diverse group of pharmacological activity in this present study we have studied about the activities as coumarin and its derivatives showing antimicrobial activity, coumarins as antilesihmania, coumarin exhibit the property of antifungal as well as antiviral activity. Coumarin is synthesized by various reaction mechanism some of them are studies in this review.

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