

**Original Review Article**

**DOI - 10.26479/2018.0402.16**

**COMPREHENSIVE REVIEW ON THE APPLICATIONS OF COUMARIN FUSED WITH FIVE MEMBERED HETEROCYCLICS IN THE FIELD OF MATERIAL CHEMISTRY, AGROCHEMISTRY AND PHORMOCOLGY**

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**ABSTRACT:** Coumarin and its compounds are well known in chemistry. Due to their abundant availability, low toxicity, ease of extraction from the plants and from micro organisms, readily synthesized in the laboratory and significantly, a widespread application in all the branches of Science and Technology, most of the research work is carried on this scaffold. Recent studies and previous literature survey on coumarin and their fused compounds dragged the attention to focus on the review of the title compound. Coumarin fused with five membered heterocyclic compounds such as thiazole, pyrazole, imidazole, oxazole, thiophene, pyrrole, furan, triazole are the important skeletal compounds in the synthesis of new pharmacophore drugs and other synthetic intermediates with improved activity than their individual compounds. The dominant theme of this review article is synergic effect of coumarin when it is in combination with five membered heterocyclic compounds.

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**KEYWORDS:** Five membered hetero cyclic compounds, Science and Technology, Material Chemistry, Agro Chemistry, Pharmacology.

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## **1.INTRODUCTION**

Coumarin is abundantly available phytochemical, the most common raw materials for the extraction of Coumarin are woodruff, sweet clover and Tonka beans. Large number of Coumarin moiety containing plants belongs to Umbelliferae family. In 1960s extensive work is carried on naturally

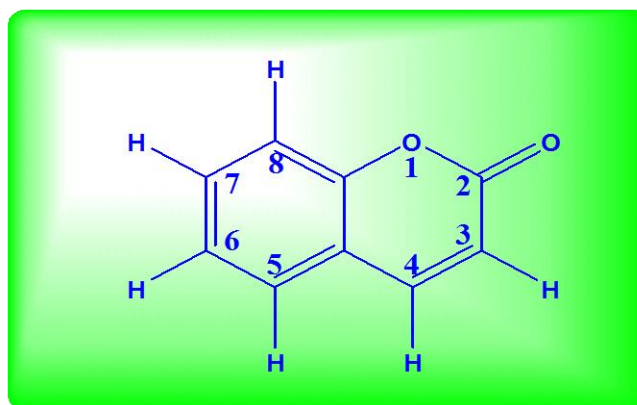
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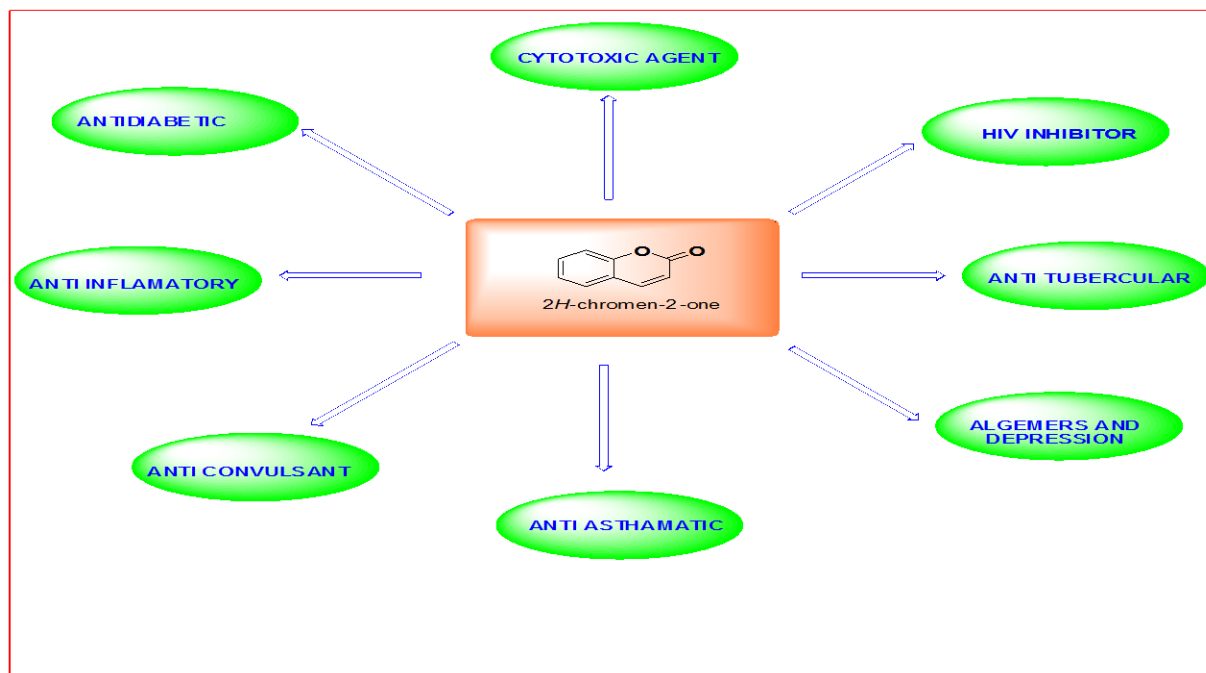
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occurring Coumarins. Coumarin has two major biosynthetic pathways one is shikimic acid pathway and second is Birch Donovan acetate pathway [1] for its biochemical synthesis. Because of its pleasant smell, it is most commonly applied as food additive. It is the major constituent in the oil of Cassia (Cinnamon) and lavender. It is also used in soap manufacturing, perfumes, cosmetics due to its aroma smell. 0.2 % of Coumarin is present in soaps, 0.02 % present in detergents, 0.8 % in perfumes, 0.1 % in creams and loations[2]. When Coumarin and their derivatives administrated orally they get readily absorbed by gastrointestinal track. Because of this nature so many synthetic drugs containing Coumarin nucleus were invented and they show potential therapeutic activity on receptoric site. Coumarin exhibit synergic effect when it is in combination with endotoxin interleukin[3] effect in the human beings i. e, enhancing the immunity power.

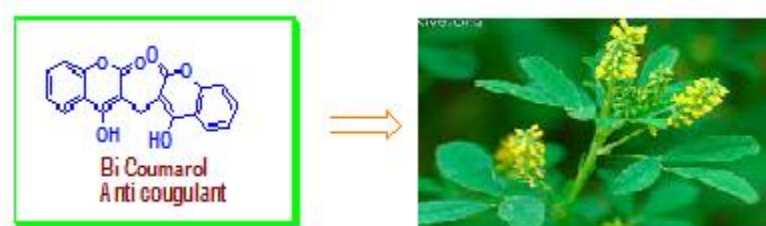


**Molecular structure of Coumarin with appropriate atom numbering**

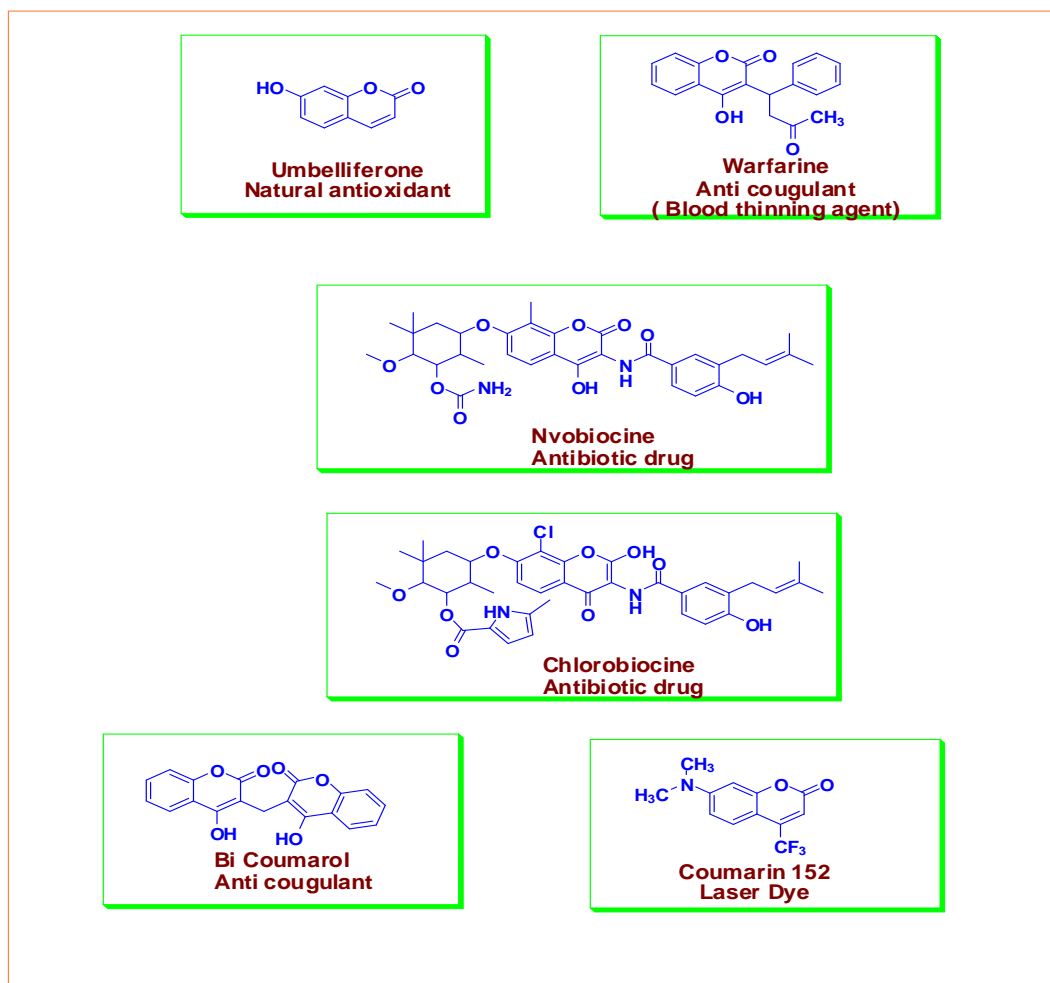


**Figure I: Pharmacological activity of Coumarin and its derivatives.**

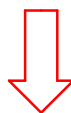
According to Ryan Ketcham and Wexler (1968) Coumarin nucleus is effective in inhibiting metastases (avoiding the growth of secondary tumor cells). Di-Coumarol is the natural extract of the



**Image I: Sweet clover plant which secrets Bi Coumarol.**



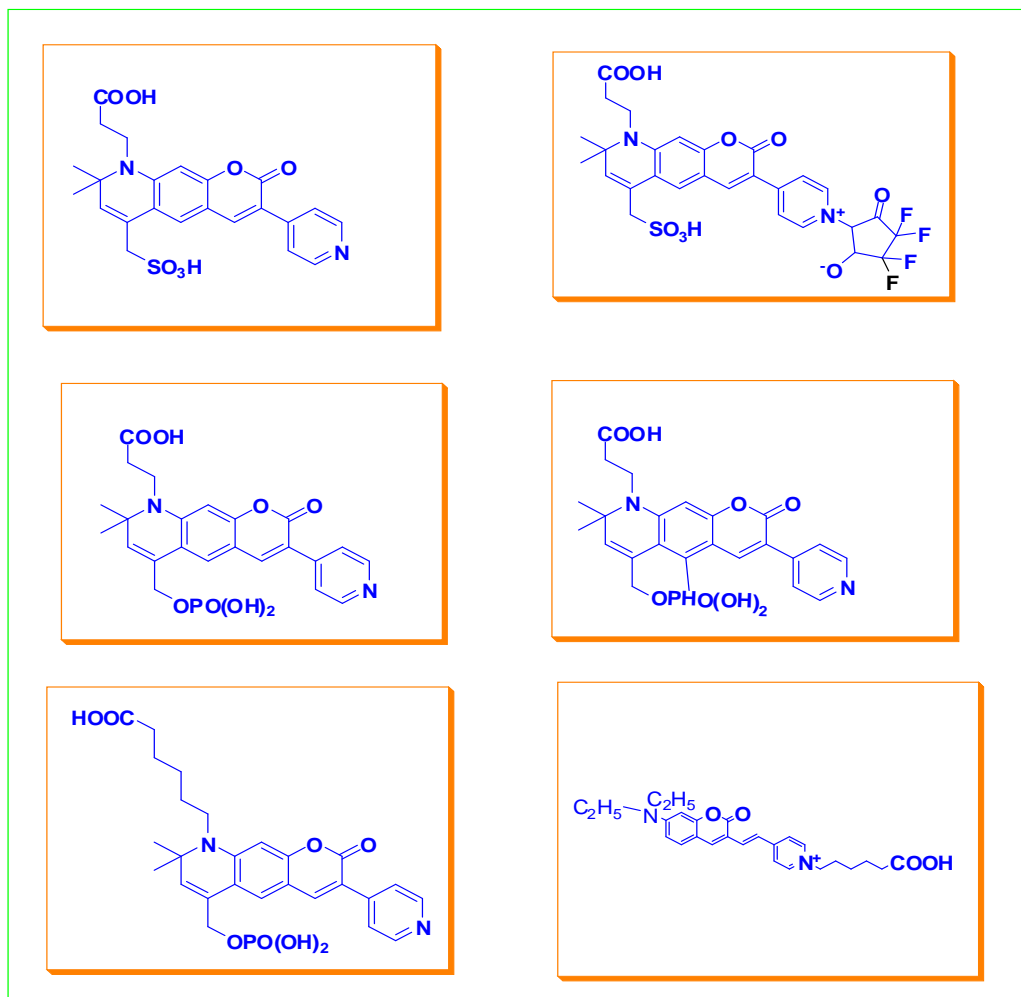
**Structure I: Some of the commercially available Coumarin compounds.**



**Image II: Coumarin used as medicine and laser dyes.**

**Material Chemistry applications of Coumarin nucleus:**

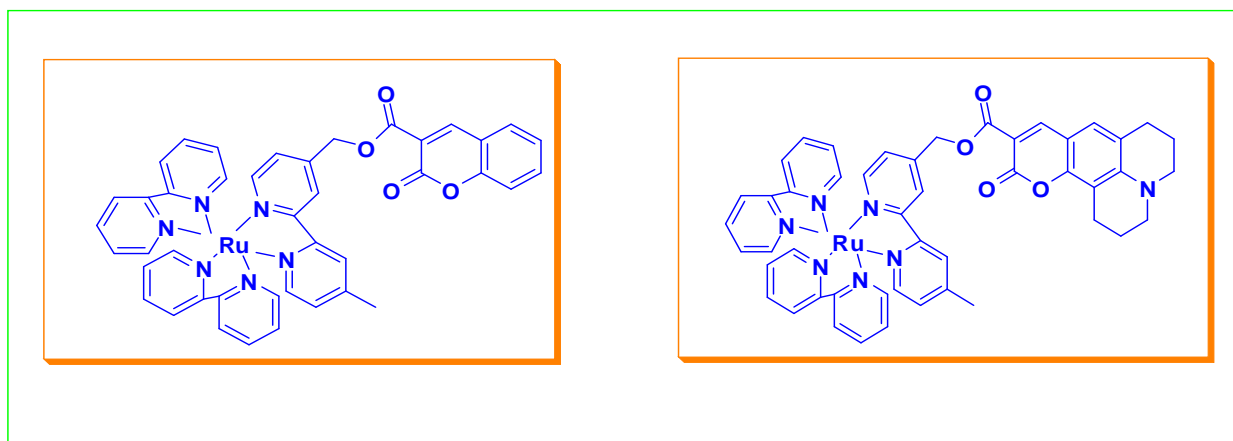
Coumarin compounds are generally used as dyes due to their light emitting properties[4-9]. Coumarin nucleus is the fluorophore (Fluorescent chemical compound reemit the light upon excitation) which is used in laser dyes[10] having brightness, photo stability, greater stock difference which have significant commercial applications in the field of electronics. Some of the examples for commercially available laser dyes are listed below.

**Structure II: List of commercially available laser dyes with Coumarin ring.**

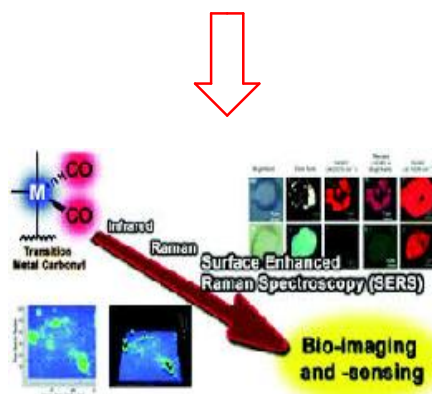
Ruthenium II di imine complex fused with coumarin moiety used in bio imaging studies[11] with high FRET studies (Fluorescent resonance energy transfer). These are significant in molecular and supra molecular physics. These fused compounds also used as DNA intercalators (the material used to insert the nitrogen bases at required place in living organisms), oxygen sensors[12]. Coumarin compounds are also used in thermal transformations such as polyphotonic, disproportionation, thermal ionization[13-15]. Coumarin containing compounds are used as neutralizers in rubber and plastic industry. It is also used to reduce unpleasant smell in paints and sprays, due to the aroma smell[16]of coumarin. It is well known that the scent smell of Sweet vernal plant, scientifically called as *Anthoxanthum odoratum* (Odoratum for its pleasant smell) is due to the presence of Coumarin nucleolus[17].



**Image III: Sweet vernal plant, which gives perfumery material having coumarin ring.**

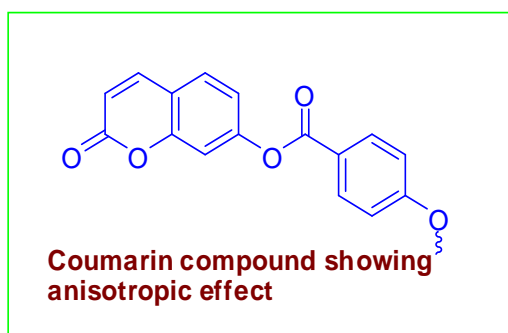


**Structure III: Ruthenium pyridine complex clubbed with Coumarin used in bio-imaging studies.**



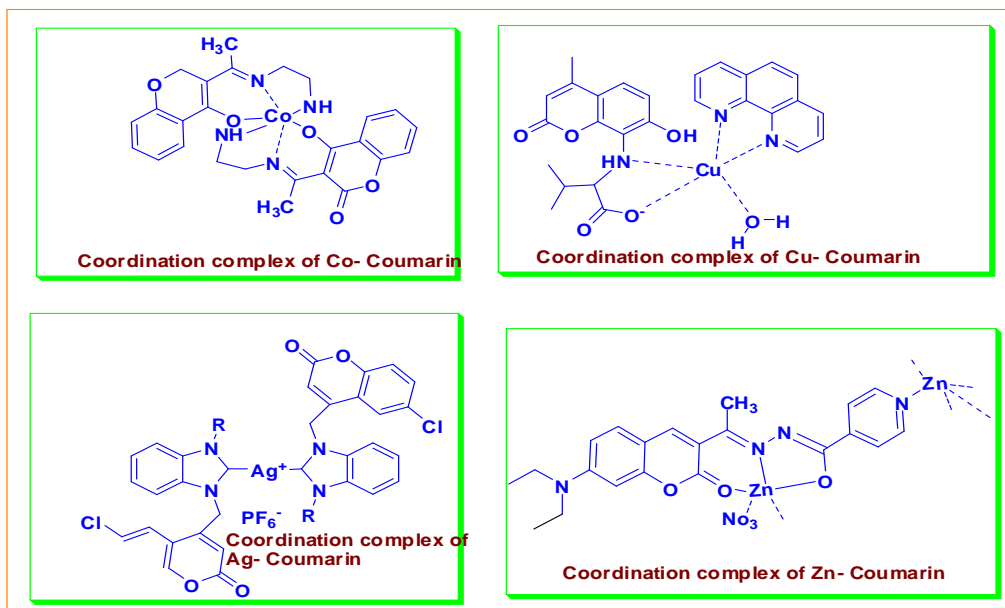
**Image IV: Bio-Imaging application of Coumarin.**

Coumarin nucleus due to its distinct orientations in the molecule it exhibit anisotropic effect[18].



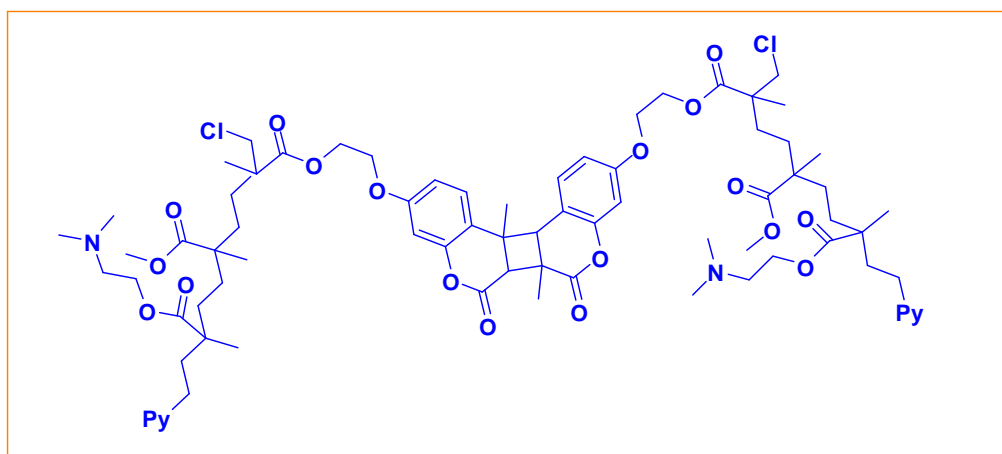
**Structure IV: Coumarin resin exhibiting anisotropic effect.**

Coumarin and their fused compounds are working as poly dentate ligands in the preparation of wide range of coordination complexes[19-20]. Coumarin based Copper complexes are showing potential free radical scavenger activity and anti oxidant property[21].



### Structure V: Some of the Coumarin ring containing Coordination complexes.

Photodegradable Coumarin based nano particles have applications in the field of biomedicine, biotechnology, and nano science. These polymers are used as hydrogels (gel made up of water) in tissue engineering and photo labile polymers for biopatterning applications[22].



**Structure VI: Polymer of Coumarin nano material finds the applications in biotechnology, biomedicine, nano science.**

### Pharmacological applications of coumarin:

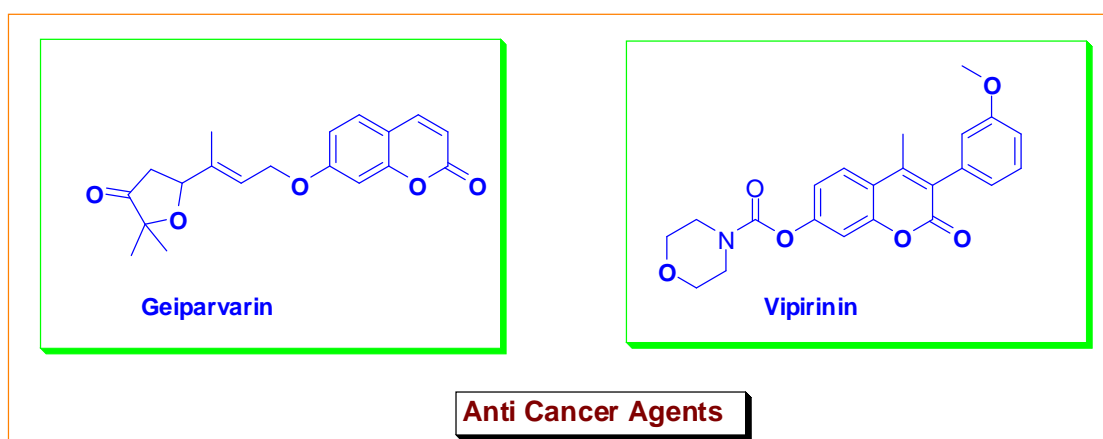
Wattenberg et. al, in 1976 synthesized and evaluated the cytotoxic activity[23] of Benzo coumarin compound. Coumarin is the key intermediate in the synthesis of cannabinioids, which are potent pain relievers and shows antiemetic action[24]. Natural products with coumarin nucleus such as fraxetin, esculetin, daphnيتين are known to exhibit anti inflammatory and anti oxidant activities[25],[26]. Coumarin 7-Xyloside is used as oral thrombotic agent[27] (reduces blood clots). Geiparvarin,



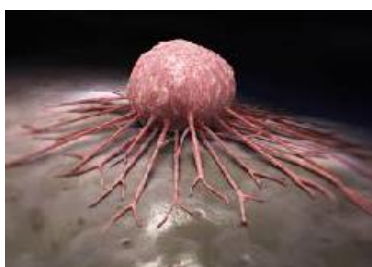
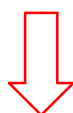
Vipirinin are commercially available anti cancer agents[28]. Coumarin is used as HIV Inhibitor. Warfarin extracted from woodruff as well as from lavender is used to avoid the blood clots in veins, lungs, heart[29],[30].



**Image V: Warfarin, which is extracted from woodruff and lavender.**



**Structure VII: Coumarin compounds showing anticancer activity.**



**Image VI: Cancer cell**

General pharmacological applications of coumarin include Anti tumor agent[31], anti HIV agent [32], antidepressant[33], anti inflammatory[34], anti fungal[35], anti bacterial[36]. Novabiocin is the antibiotic, which is extracted from Streptomycin bacteria, Aflatoxin extracted from Aspergillus.

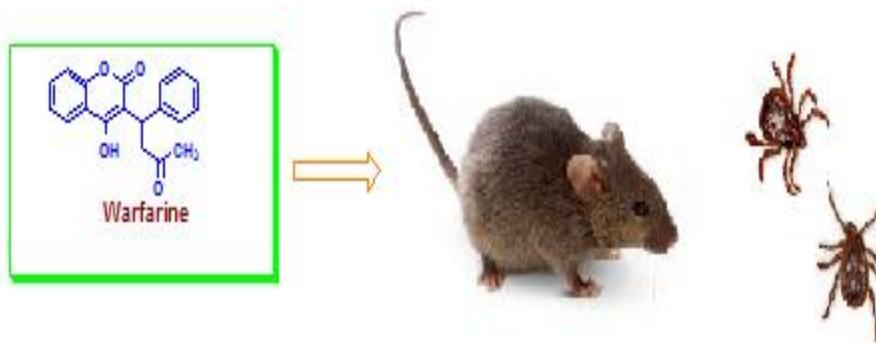
#### **Agrochemical applications of Coumarin:**

Development of novel synthetic compounds which should exert potent activity against the pests and other targeted organisms without effecting non targeted organisms and production of crop yield. They should be non toxic towards the surrounding environment and ground water is the prominent requirement in the agricultural based countries. It is the burning issue that, for rapidly growing

population we need to provide sufficient food with limited amount of available resources. Many countries are focusing on the improvement of the crop yielding and food production. But recent studies reveals that around 60 % of food products produced are damaged due to the attack of pests and insects. That is the reason why we need to concentrate on pest control programs along with food production. Some of the Coumarin derivatives which are naturally occurring phytochemicals working as environmental friendly agrochemicals applied in this field are discussed here. Coumarin and their derivatives are effective in the field of agricultural science showing fungicidal and fungistatic activity[37-41], insecticidal and insectistatic activity[42], anti bacterial activity[43], inhibits mites, weeds and works as Allelochemical[44],[45]( chemical that extracted from living organisms and works on individual organisms present in its surroundings). Warfarin is the potential first generation Coumarin rodenticide[46],[47], and used as a medicine for heart patients due to its anticoagulating activity. This is also a pesticide not only kills the rats but also mice, woodchucks, chipmunks, squirrels, porcupines, beavers and nutria. Warfarin is widely used to control the rodents population which causes big threats to plants, animals, crops, public health, damage to the furniture, farmlands and forest since fifty years[48].

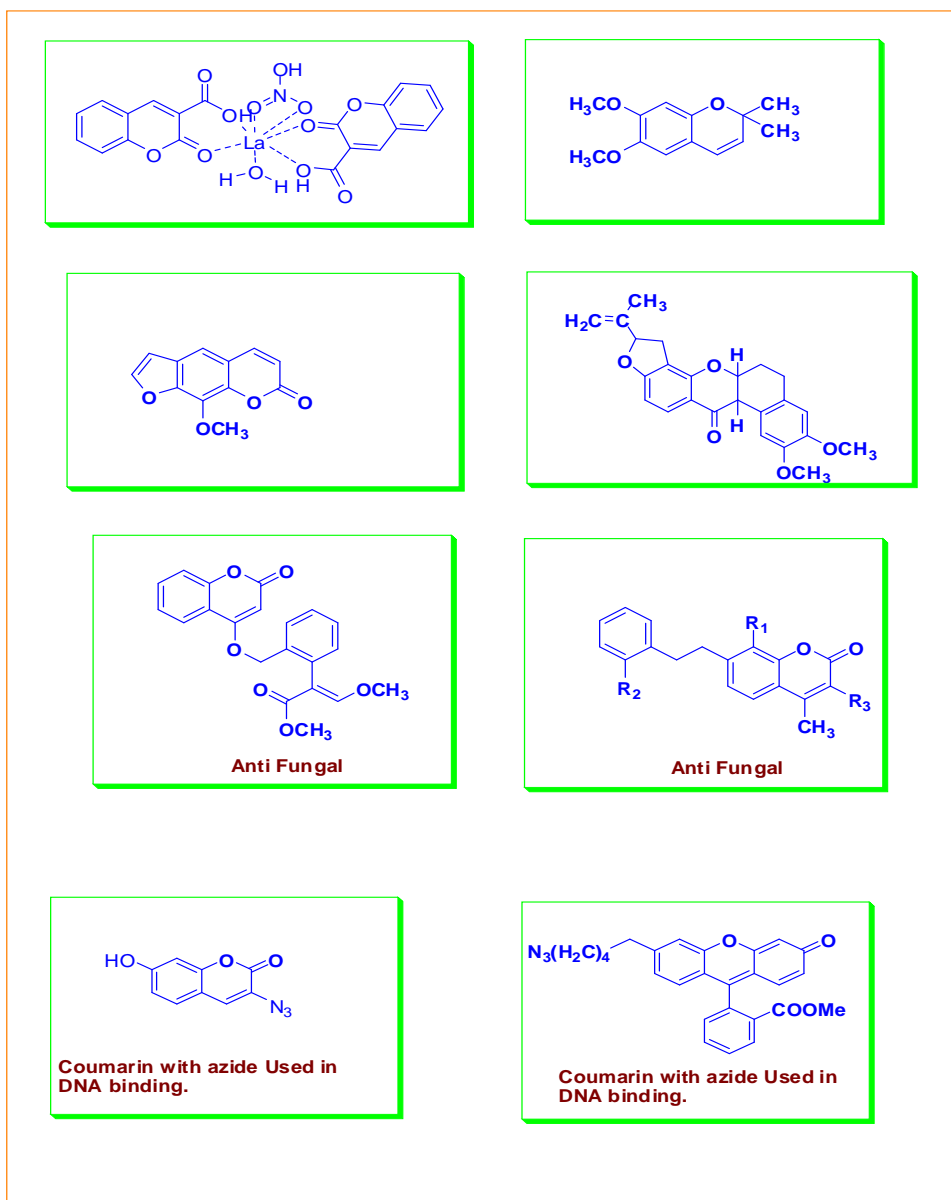


**Image VII: Some of the pests in the crop lands**



**Image VIII: Warfarin acting as potent rodenticide.**





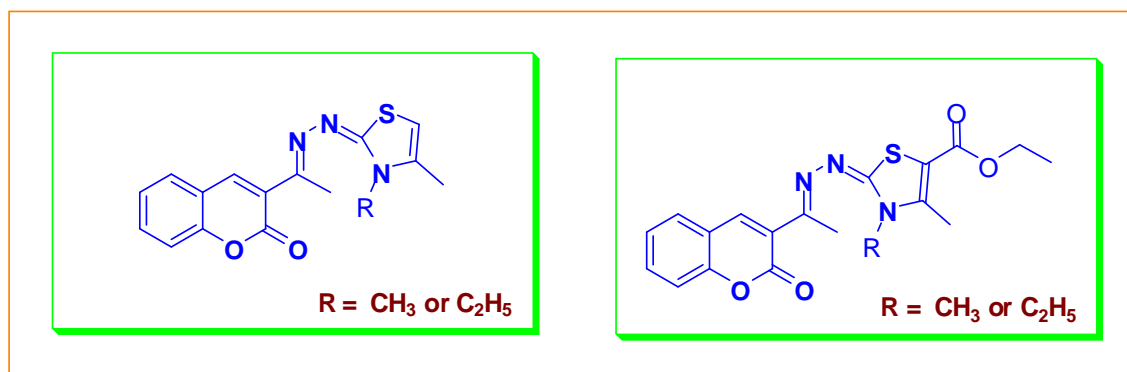
**Structure VIII: Few Insecticides and pesticides of Coumarin, used in crop lands for pest control.**



**Image IX: Applying pesticides in cropland.**

## Pharmacological applications of Coumarin with five membered heterocyclic fused compounds:

Coumarin – imidazole fused compounds are effective in CYP19 inhibition[49](C19 steroidal aromatase inhibition) which is further used in the treatment of malignant tumors. Ningalin B is the marine alkaloid which is exhibiting multiple activities such as immunomodulatory activity (the substance which alters the function of immune system), anticancer activity and HIV inhibition activity[50],[51]. Coumarin clubbed with triazoles working as anti fungal[52],anti Alzheimer[53], anticancer[54],antivirus[55],antibacterial[56],antitubercular[57],antimalarial[58],antiinflammatory [59]drugs. Triazole may be 1, 2, 3 or 1, 2, 4 tri aza positions. Generally non steroidal anti-inflammatory drugs (NSAID) are commonly used in swellings, inflammations but recently it is observed that these are adversely influencing by their side effects on kidneys and heart. Hence alternative methods are needed to overcome these side effects. Coumarin and their derivatives when they are in combination with thiazole ring are exhibiting reduction of inflammations by inhibiting the secretion of Cyclooxygenase (COX) with lower toxicity. Cyclooxygenase promotes the release of prostaglandins which causes inflammations in the body [60-63].

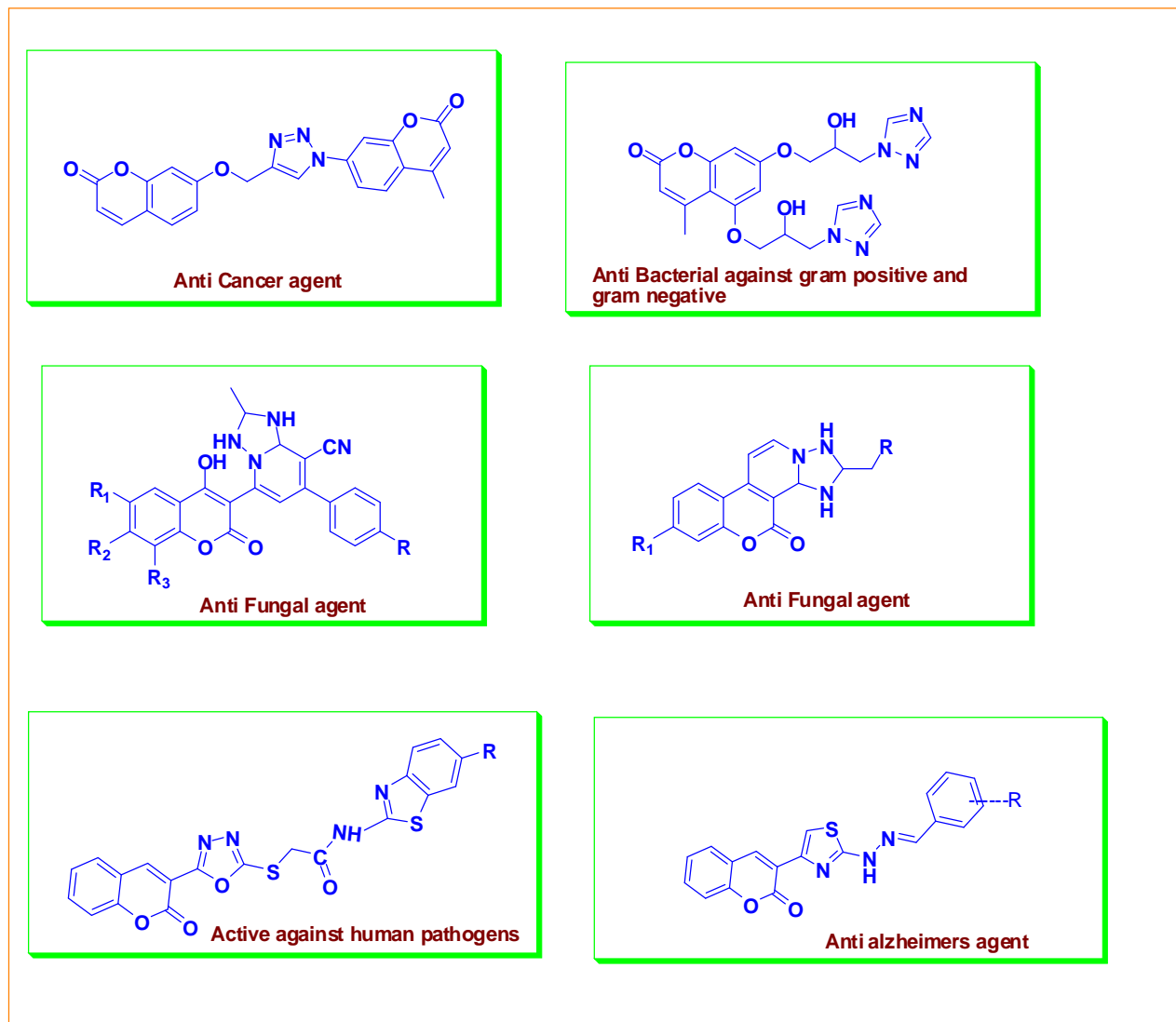


**Structure IX: Coumarin- Thiazole hybrid compounds acting as anti-inflammatory agent.**



**Image X: Inflammation symptoms.**

Coumarin ring connected with oxa-diazole incorporated with Benzo-thiazole ring is potent against broad spectrum human pathogenic organisms[64]. 3- Thiazolo Coumaryl derivatives are identified as potential in treatment of Alzheimer by inhibiting the action of acetyl cholinesterase as well as buteryl cholinesterase enzyme[65-67].



**Structure X: Some of the Coumarin-five membered heterocyclics having pharmacophore centers.**



### Diseases Caused by Bacteria

- Lyme disease
- Tetanus
- Tuberculosis
- Diphtheria
- Bacterial meningitis
- Strep throat
- Tooth decay

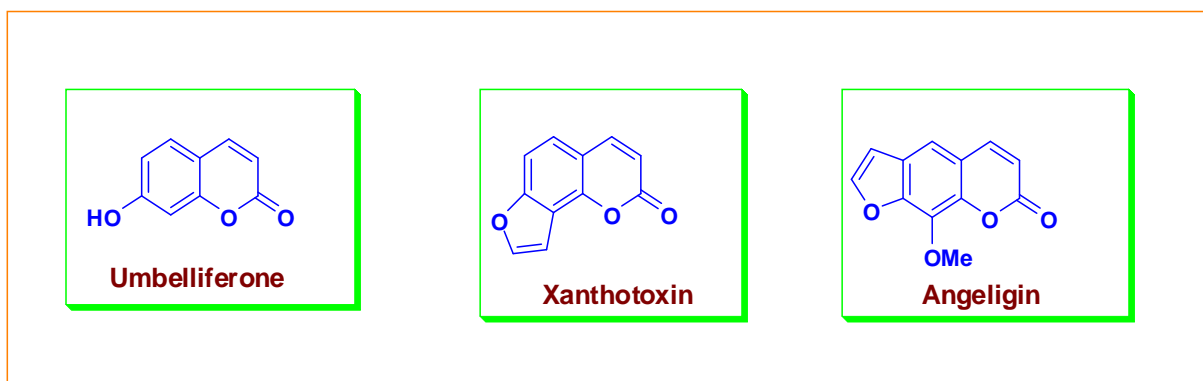


### Diseases Caused by Viruses

- Common cold
- Influenza
- Small pox
- Warts
- AIDS
- Chickenpox
- Measles
- Hepatitis A, B and C
- West Nile Virus
- Polio



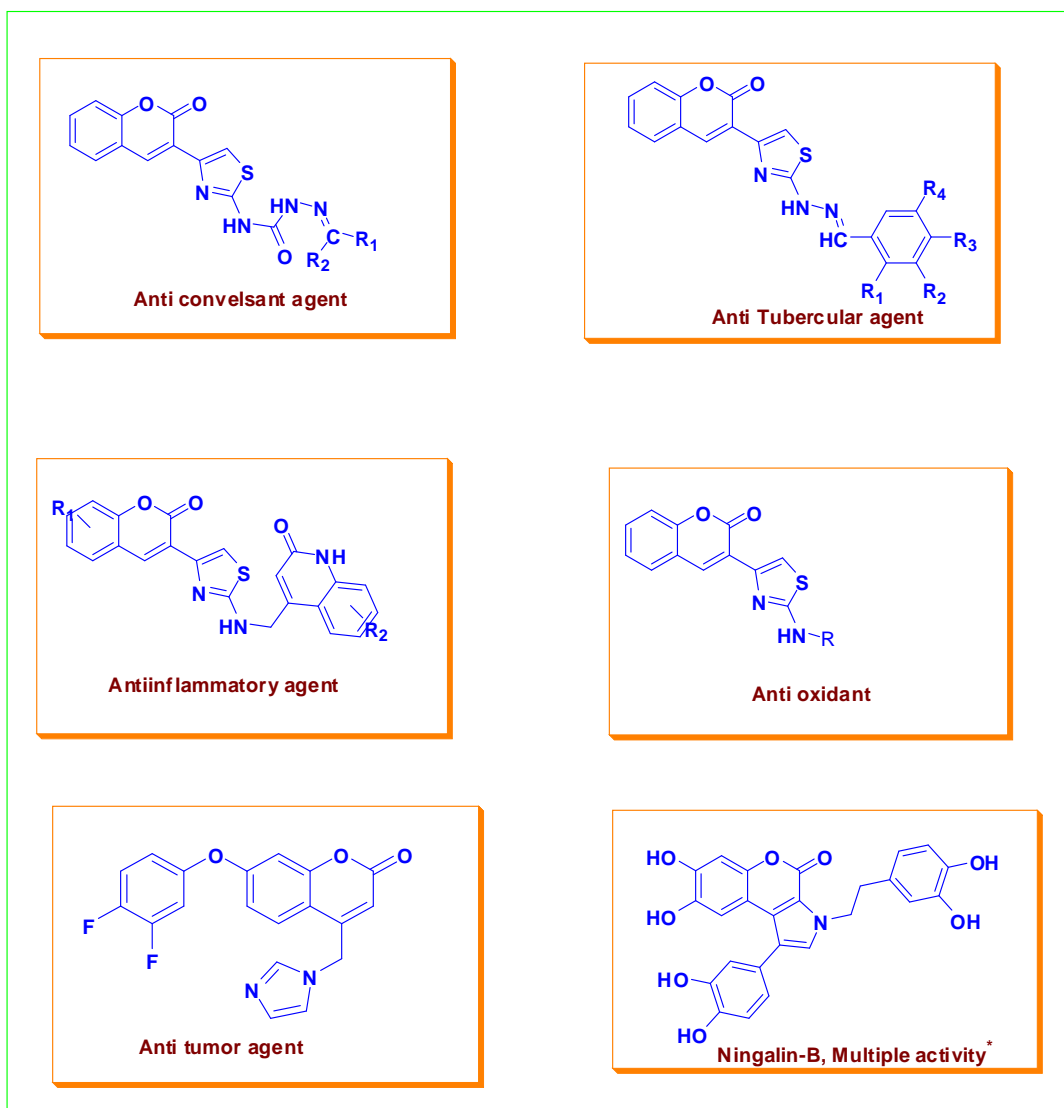
**Image XI: Different types of diseases, which are caused by the various pathogens in human beings. Coumarin fused with one more heterocyclic ring (Tricyclic ring) is proved to show the activity against psoriasis, vitiligo diseases[68],[69].**



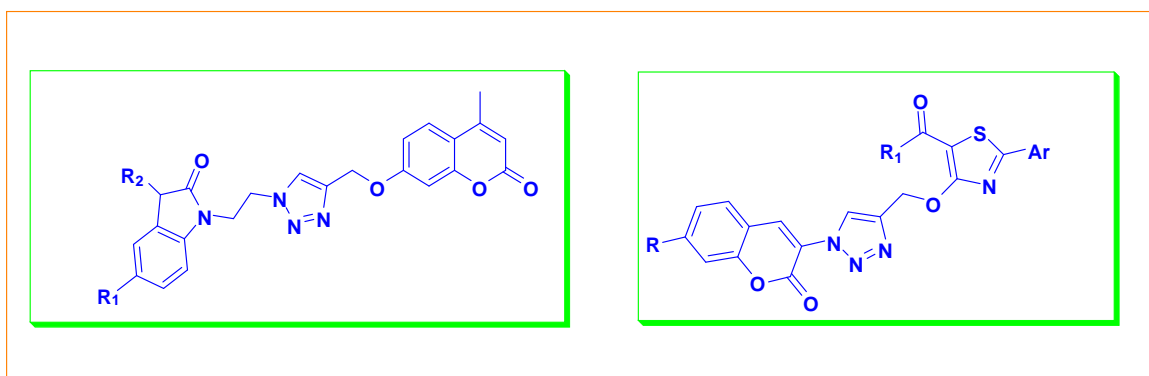
**Structure XI: Naturally extracted coumarin compounds having medicinal value**



**Images XII: Plants, from which generally coumarin compounds are extracted.**



**Structure XII: Some of the Coumarin fused with five membered ring heterocyclic drugs.**



**Structure XIII: Coumarin - Triazole with antimycobacterial activity (Anti - tubercular)**



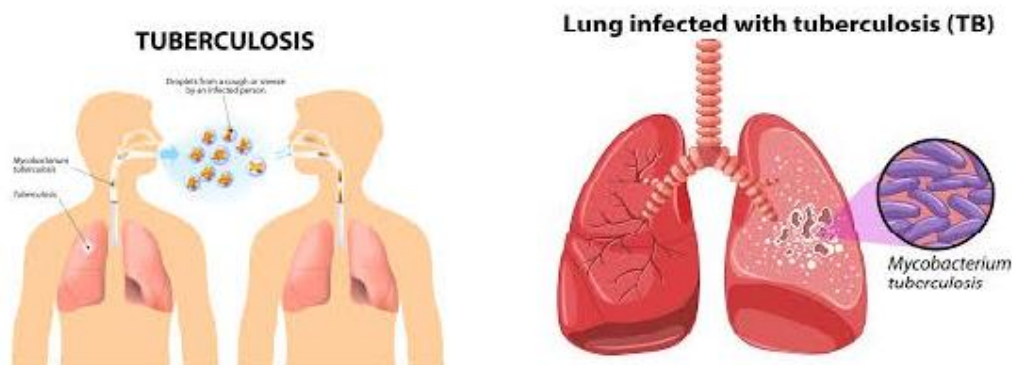
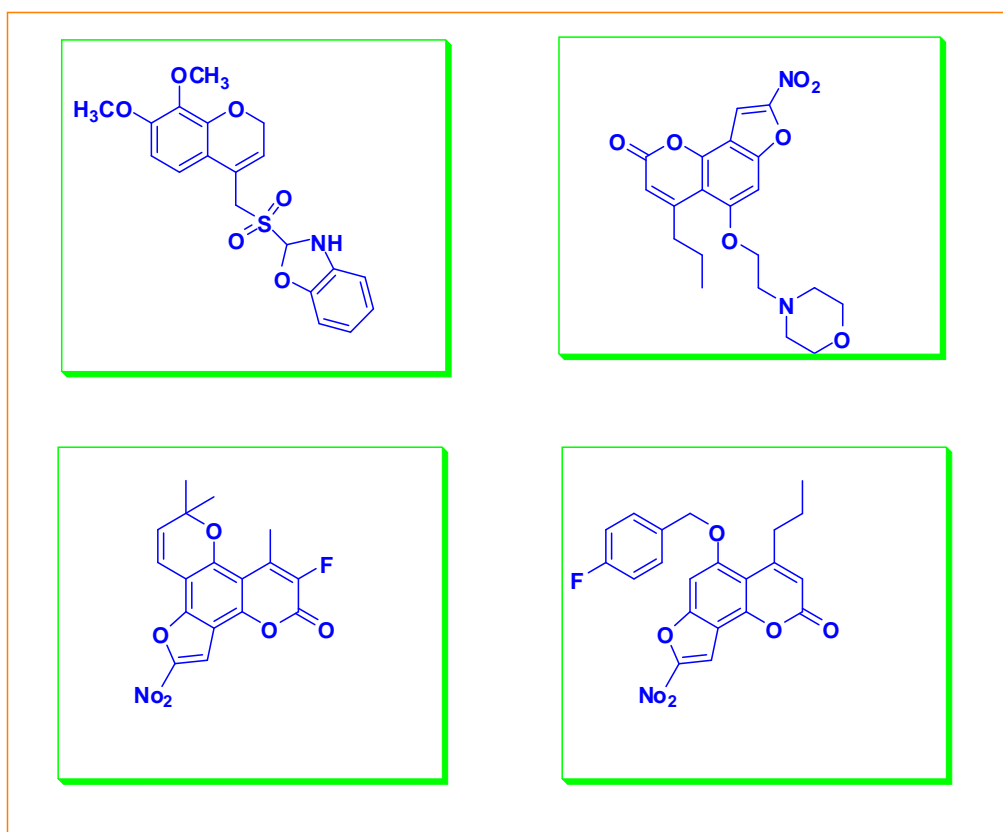


Image XIII: Tuberculosis infected lungs



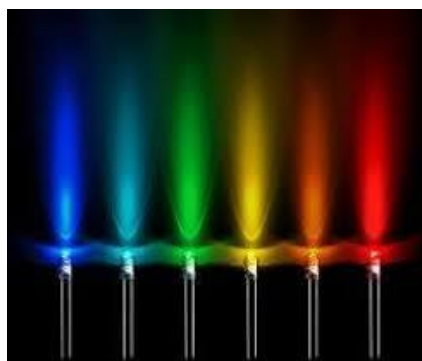
**Structure XIV: Coumarin clubbed with five membered ring as potential anti tubercular agents.**

**Material Chemistry applications of Coumarin with five membered heterocyclic fused compounds:**

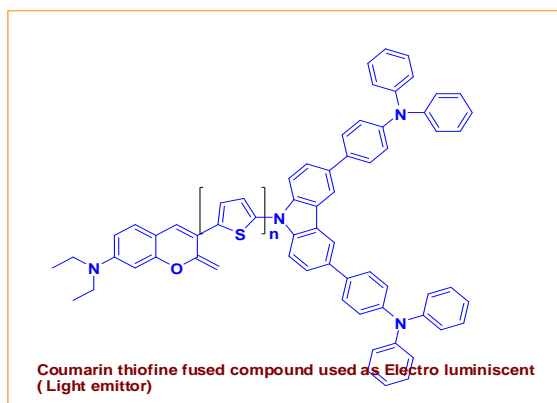
Coumarin – Thiazole hybrid compounds are widely used as photochrom , it is the process of converting colored images from black and white negatives[70]. N- Coumaryl compounds commercially called as CThnT and CThnCT with polymeric thiophene ring exhibit optical, electroluminescence properties. Hence they are used in OLED lights. By studying their physical properties it is observed that they are showing high morphological and thermal stability[71]. Coumarin compounds are well known as dyes due to their light emitting property, but only the



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drawback is instability of simple Coumarins in the presence of visible light. This can be overcome by combining the molecule with five membered rings such as pyrrole or furan[72-74].



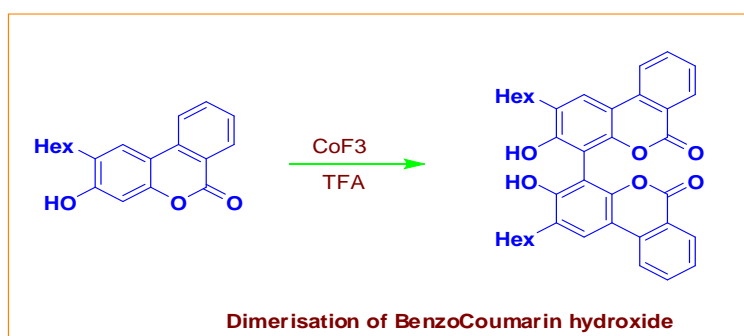
**Image XIV: Light emission in visible region.**



**Structure XV: Coumarin- Thiophene polymer as light emitter.**

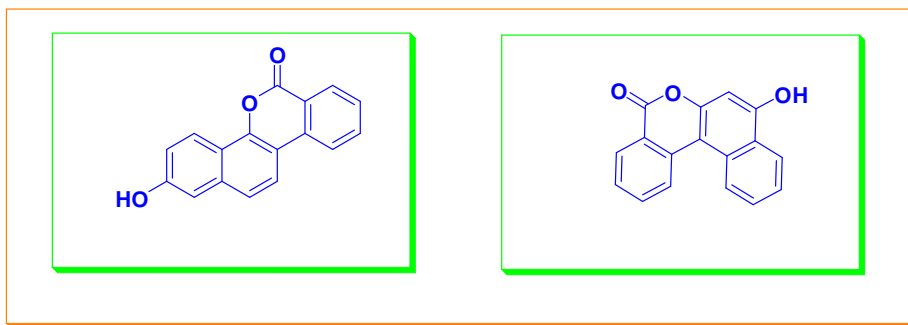


**Image XV: Electro luminescence.**



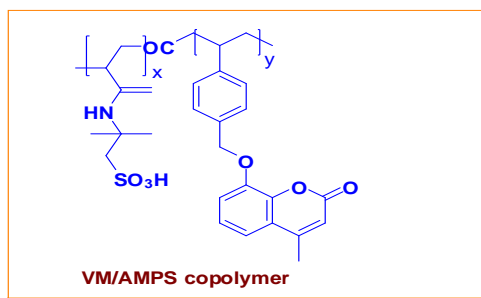
**Scheme I: Electron rich dimer of benzo-coumarin have photo physical property.**

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Coumarin extended with conjugation is more efficient in the light emission property having architecture value[75-77].



**Structure XVI: Dyes absorbing UV radiation and emitting violet blue light.**

Polyaniline nanoparticles are well known in the conduction of current, copolymerization of these photosensitive compounds with Vinyl Coumarin and 2-Acryl amido- 2- methyl-1- propane sulphonic acid exerting enhanced activity and applied as conducting polymer[78].



**Structure XVII: Coumarin based nano -sized copolymer working as conducting polymer.**

#### 4. CONCLUSION

Heterocyclic compounds play a vital role in every field of science. Around 80% of pharmaceutical medicines are composed of N, S, O atom containing heterocyclic compounds. Although much more literature is there on the review of synthetic organic chemistry especially on heterocyclic compounds and their applications, we tried to contribute in this field by collecting few of them. However there is a rapid expansion of the synthesis of new scaffolds in different routes, wide applications in the everyday life, the review of these compounds are endless. Hence we are inviting our co-researchers to continue the process of reviewing the synthetic organic chemistry of heterocyclic compounds.

**Main objective of this review:**

In current days there is a great advancement in the synthetic organic chemistry, many more new methods have been invented to carry the reactions in safe manner and to avoid the toxic effects of solvents and reagents. At the same time those compounds are characterized by various technical methods to know their properties extensively. These synthesized compounds are tested for their activity to introduce their applications in industrial, domestic and agricultural fields which are helpful for our current life style. Hence we tried to gather some of the new synthetically prepared

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heterocyclics connected with Coumarin and quoted their applications. Coumarin and its compounds  
have many practical applications, so this family of compounds is subject of intensive research.

## 5. ACKNOWLEDGEMENT

Authors are sincerely thankful to Department of Chemistry, JNTU College of Engineering, JNTU  
Hyderabad for valuable laboratory facilities, financial and technical support. And also thankful to  
the people who supported and encouraged to write this article.

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