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A BRIEF REVIEW OF SYNTHESIS AND APPLICATIONS OF INDIVIDUAL COUMARIN, THIAZOLE SCAFFOLDS AS WELL AS COUMARIN-THIAZOLE HYBRID COMPOUNDS IN THE FIELD OF SCIENCE AND TECHNOLOGY

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Main objective of this research topic

Heterocyclic compounds play a vital role in every field of science. Around 80 % of pharmaceutical medicines are composed of these compounds. However, there is a rapid expansion of the synthesis of new scaffolds, wide applications, the review of these compounds are endless. 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, to avoid the toxic effects during the synthesis, storage, transportation and usage. 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 for our current life style, industrial, domestic and agricultural purpose. Hence, there is a thrust for the compounds of wide applicability and safe to use. Coumarin and its compounds have many practical applications; this family of compounds is the subject of intensive research.

SCOPE AND STUDY OF THE COUMARINS AND THIAZOLES IN THE FIELD OF SYNTHETIC-ORGANIC CHEMISTRY AND MEDICINAL CHEMISTRY

1.1.1. Scope and sudy to coumarins

Coumarin is a phytochemical belongs to benzopyrone group of family with cyclic lactone ring (figure.1.1.1). Coumarin was first extracted from the tonka beans and sweet clover in 1820 by A. Vogel, which has been further named as coumarin by the scientist Guibourt. It was first synthesized in the laboratory by Perkin in 1868. The familiar natural sources of coumarin are Tonka bean (Dipteryx odorata), sweet woodruff (Galium odoratum), vanilla grass (Anthoxanthum odoratum), mullein (Verbascum Thapsus), cassia (little coumarin), sweet clover (Melilotus), Justica pectoralis, etc. Large number of coumarin containing plants belongs to Umbelliferae family. In 1960's extensive work has carried out on naturally occurring coumarins. The two major pathways for biochemical synthesis of coumarin are shikimic acid pathway and Birch Donovan acetate pathway.[1] Coumarin and its derivatives occur abundantly in umbellifereae, rutaceae, leguminaceae, asteraceae, guttifereae, thymelaceae, orchidaceae and solanaceae, etc. the gist of some of the coumarin structures that were isolated from the natural source listed in the figure 1.1.2.

Chemical name: 2-*H*-Chromen-2-one.

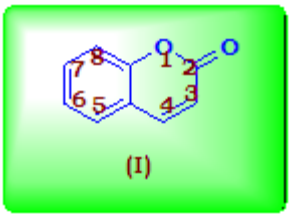


Figure 1.1.1: Molecular structure of coumarin with appropriate atom numbering.

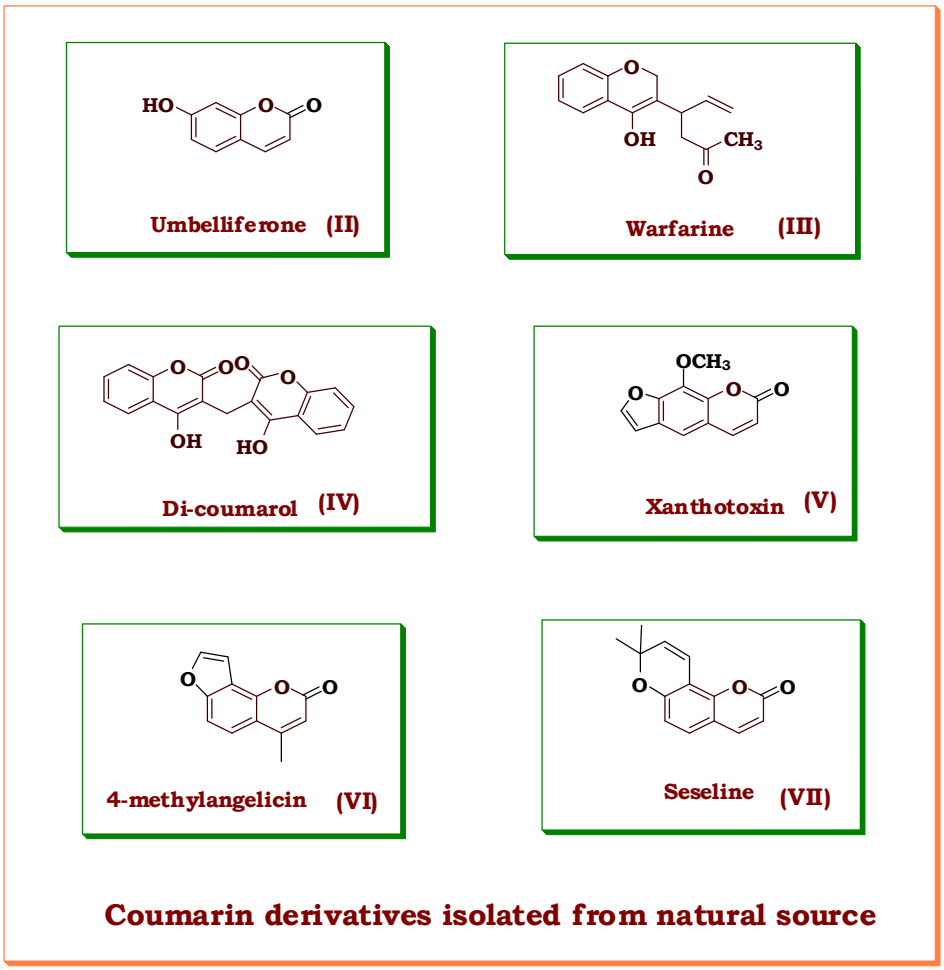


Figure 1.1.2: Naturally occurring coumarin derivatives.

1.1.2. Classification of benzopyrone compounds

Pyrone ring can be fused to the benzene ring in either of the position α or γ giving two distinct types of isomers, 1. Alpha-benzo-pyrones which are commonly known as coumarins. 2. Gamma-benzo-pyrones known as chromones. Both isomers are differentiated by the change in the position of their carbonyl group as shown in the figure 1.1.3 below.

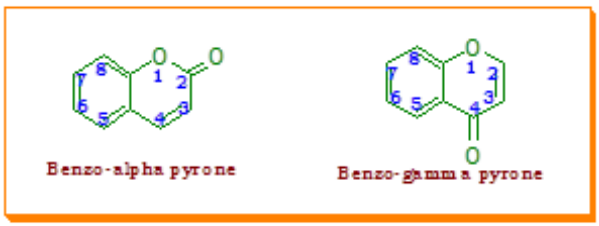
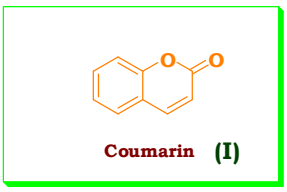


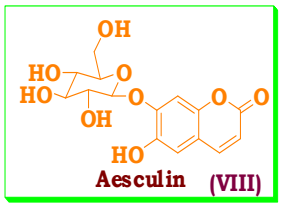
Figure 1.1.3: Positional isomerism in benzopyrone.

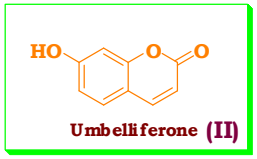
Further, coumarins are classified based on the substitution on benzene and pyrone ring figure 1.1.4.

1.1.2.1 Simple coumarins

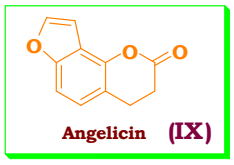


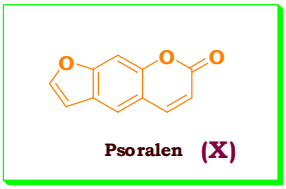
1.1.2.2. Hydroxyl, di hydroxyl coumarin



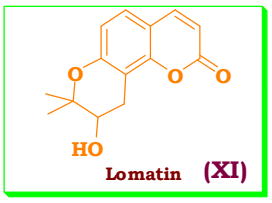


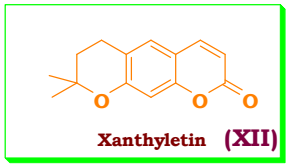
1.1.2.3. Furocoumarins



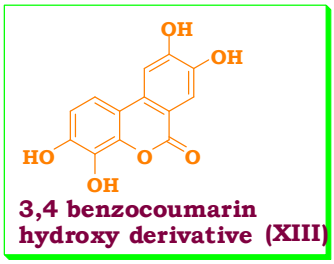


1.1.2.4. Pyrano coumarins





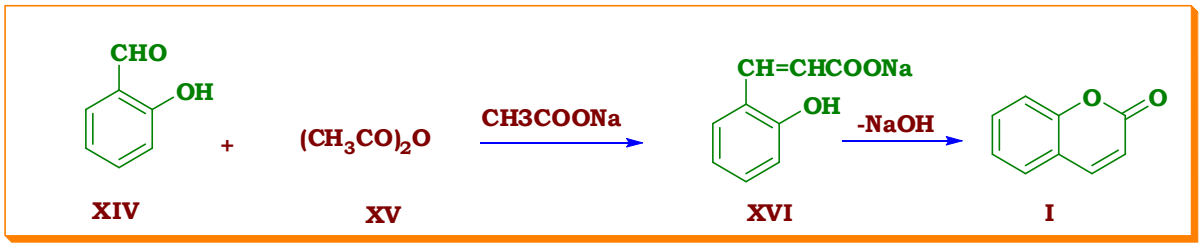
1.1.2.5. Benzocoumarins



1.1.3. Named reactions on coumarin synthesis

1.1.3.1. Perkin reaction

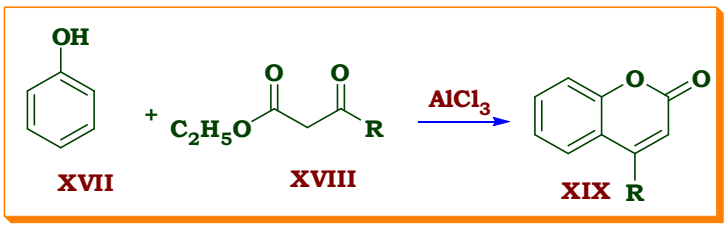
Perkin[2] reaction is well known for the synthesis of coumarin from salicylaldehyde (XIV) by reaction with acetic anhydride (XV) and anhydrous sodium acetate. It generates the o-hydroxycinnamic acid derivative (XVI), and converted in to lactone ring (I) spontaneously. The limitation of this method is to introduce the substitution on pyrone ring. The schematic representation of Perkin synthesis of coumarin is shown below in scheme 1.1.1.



Scheme 1.1.1: Synthesis of simple coumarin by Perkin reaction.

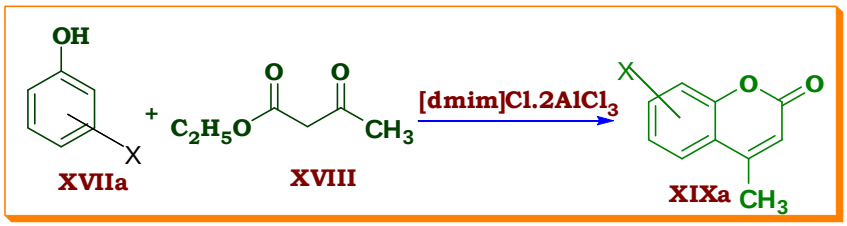
1.1.3.2. Pechmann condensation reaction

Pechmann condensation[3] is the widely applied method for the synthesis of coumarin from phenol and β-keto ester gives high yield of the product with either the substitution on pyrone ring or benzene ring or both. 7-hydroxy-4-methyl coumarin is obtained in high yield when the reaction takes place between ethyl acetoacetate with 1,3-dihydroxy benzene (resorcinol). Phenol (XVII) when treated with ethyl aceto acetate (XVIII) in the presence of Lewis acid $AlCl_3$ generates 4-substituted coumarin ring (XIX) as shown in scheme 1.1.2.1.



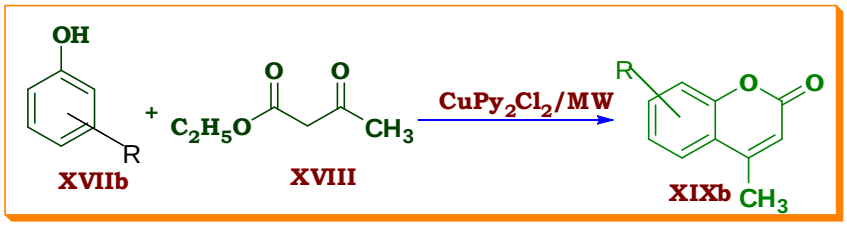
Scheme 1.1.2.1: Synthesis of 4-substituted coumarin by Pechmann condensation.

Recently, several modifications were reported in literature where Lewis acid replaced by other green catalysts. Use of liquid 1-butyl-3-methylimidazolium chloroaluminate is reported for coumarin syntheses via Pechmann condensation[4] as shown in the scheme 1.1.2.2.



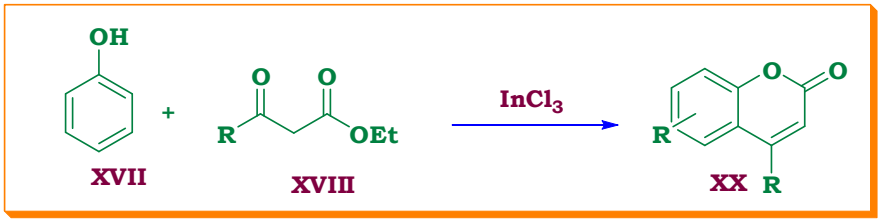
Scheme 1.1.2.2: Synthesis of 4-substituted coumarin in the presence of ionic liquid.

Rajitha et al. reported[5] the synthesis of coumarin nucleus XIXb by dipyridine copper chloride catalyzed Pechmann condensation reaction of phenol XVIIb under microwave irradiation conditions as shown in the scheme 1.1.2.3.



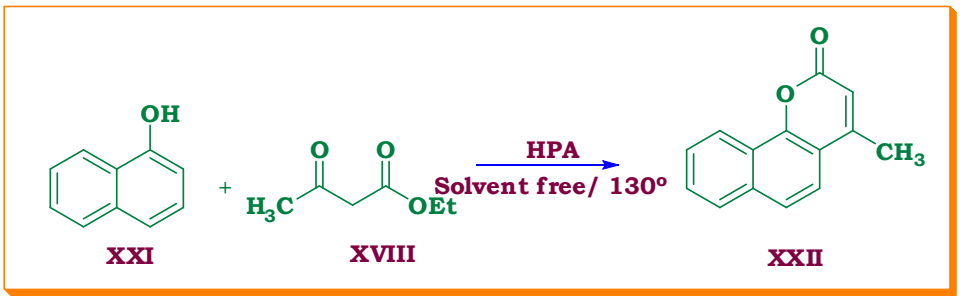
Scheme 1.1.2.3: Synthesis of coumarin by Pechmann condensation in the presence of dipyridine copper chloride.

Bose et al. synthesized[6] the coumarin scaffold by Indium (III) chloride catalyzed Van-Pechmann reaction to give 4-substituted coumarin compounds (XX) as shown in the scheme 1.1.2.4.



Scheme 1.1.2.4: Synthesis of substituted coumarin by Pechmann Condensation in the presence of $InCl_3$.

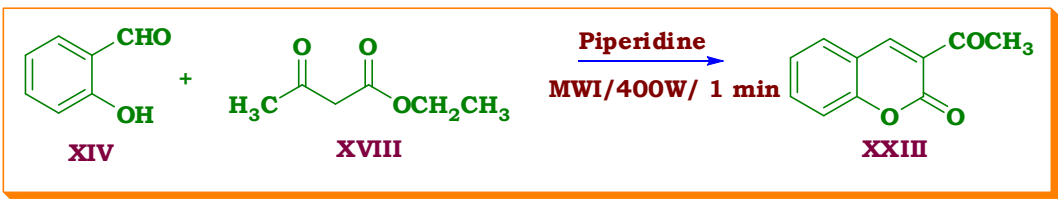
Heravi[7] et al. reported the synthesis of coumarin derivatives (XXII) in the presence of sodium 30-tingsto pentaphosphate, $[NaP_5W_{30}O_{110}]^{-14}$ called Preyssler's anion as shown in the scheme 1.1.2.5.



Scheme 1.1.2.5: Synthesis of coumarin by pechmann condensation, in the presence of hetero poly acids.

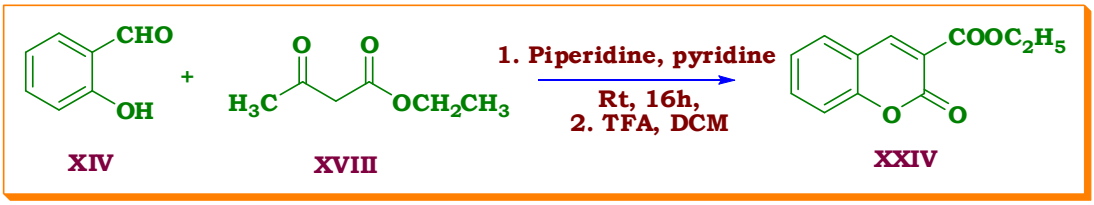
1.1.3.3. Knoevenagel condensation

Ajani et al.[8] have reported the synthesis of 3-acetyl coumarin (XXIII) using o-hydroxy benzaldehydes (XIV) and ethyl aceto acetate (XVIII) in the presence of piperidine base under microwave irradiation conditions as shown in scheme 1.1.3.1.



Scheme 1.1.3.1: Synthesis of coumarin derivative by Knoevenagel Condensation.

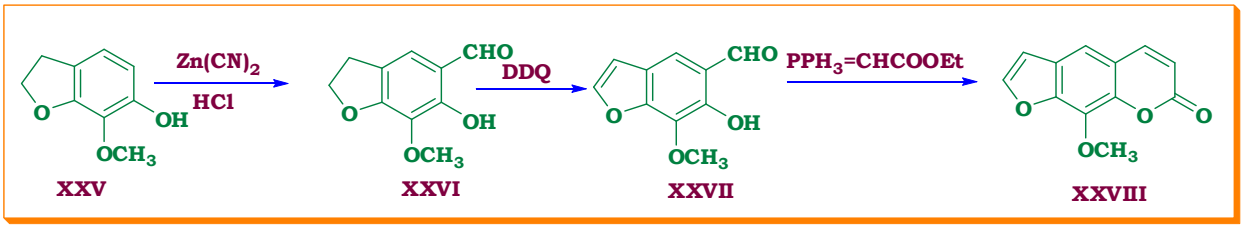
Watson et al. reported[9] the solid phase synthesis of 3-substituted coumarin (XXIV) using Knoevenagel condensation reaction between o-hydroxy benzaldehyde (XIV) and ethyl aceto acetate (XVIII) in the presence of pyridine and piperidine at room temperature conditions as shown in the scheme 1.1.3.2.



Scheme 1.1.3.2: Synthesis of coumarin derivative, in the presence of piperidine and pyridine.

1.1.3.4. Wittig reaction

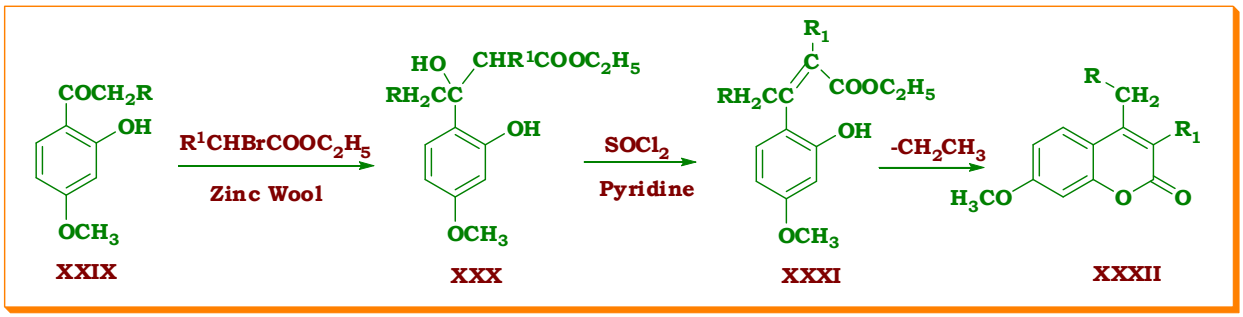
Liu et al. reported[10] the synthesis of coumarin derivatives (XXVIII) via Wittig reaction of substituted anisole (XXV) as shown in the scheme 1.1.4.



Scheme 1.1.4: Synthesis of furo-coumarin via Wittig reaction in the presence of triphenyl phosphene.

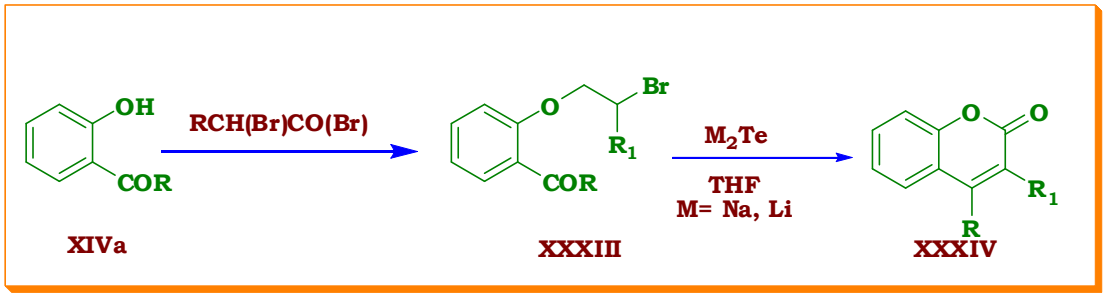
1.1.3.5. Reformatsky reaction

Reformatsky reaction[11] involves the condensation of aldehydes or ketones (XXIX) with α-halo esters in the presence of Zinc metal to give β-hydroxyesters (XXX). Reaction route was discovered by Sergei Nikolaevich Reformatsky. It is the most useful method for the formation of new carbon-carbon bond formation. It is very difficult to synthesize 3,4-dialkyl substituted coumarins by usual coumarin synthetic routes may be synthesized by Reformatsky reaction (XXXII) as shown in the scheme 1.1.5.



Scheme 1.1.5.1: Synthesis of coumarin derivative by Reformatsky reaction in the presence of thionyl chloride and pyridine catalyst.

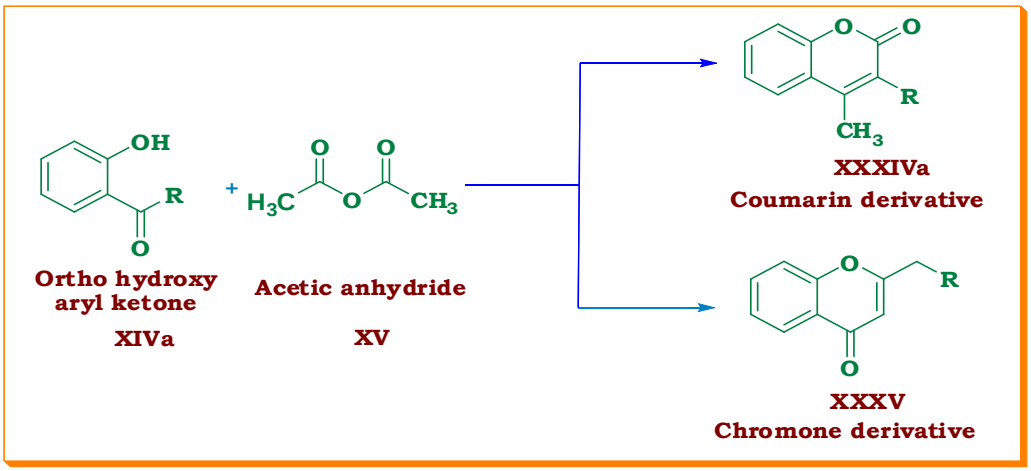
Donald et al. reported[12] the synthesis of 4-hydroxy substituted coumarin (XXXIV) from Salicylaldehyde (XIVa) in the presence of M_2Te alloy where M= Na or Li as shown in the scheme 1.1.5.2.



Scheme 1.1.5.2.: Synthesis of coumarin derivative in the presence of Na/Li-Te alloy.

1.1.3.6. Kostanecki acylation

Ortho hydroxyl aryl ketones (XIVa) when acylated with aliphatic anhydrides (XV) followed by intra molecular aldol condensation involves cyclization reaction generates coumarin (XXXIVa) and chromone (XXXV) as represented in the below scheme 1.1.6.



Scheme 1.1.6: Synthesis of mixture of coumarin and chromone by the Kostanecki acylation.

1.1.4. Applications of coumarin

Coumarin is a well known compound due to its substantial applications in various fields of science and technology.

1.1.4.1. Synthetic Chemistry applications of coumarin

Coumarin is the widely used valuable starting material for the synthesis of large number of heterocyclic compounds due to ease of synthesis, non toxic nature, easy workup procedures and high purity of the final product. Compounds like furano-coumarins, pyrido-coumarins, thiophene-coumarins, thiazole-coumarins, oxazole-coumarins, pyrazolo-coumarins are synthesized from coumarin as shown in the figure 1.1.5.

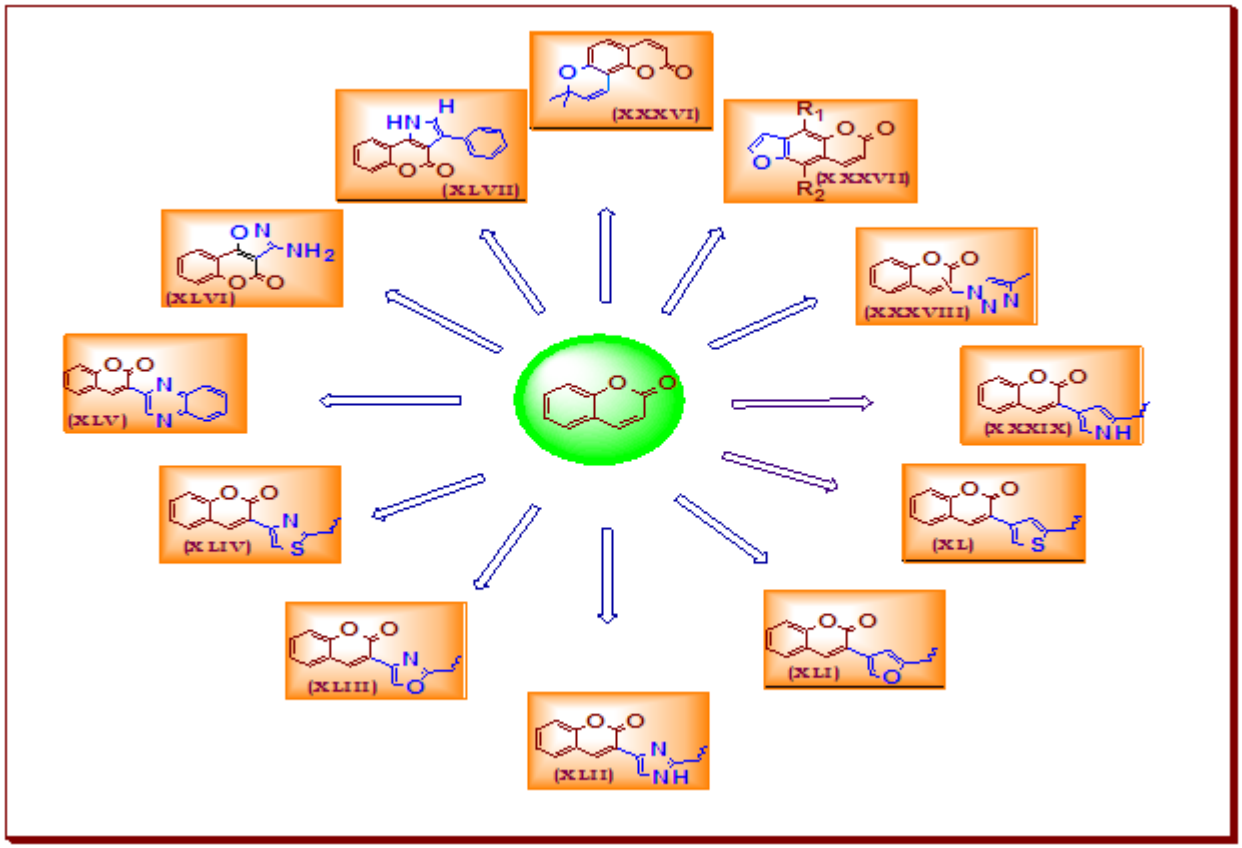


Figure 1.1.5: Synthetic importance of coumarin in heterocyclic Chemistry.

1.1.4.2. Material chemistry applications of coumarin

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 fragrant aroma smell. 0.2 % of coumarin is present in soaps, 0.02 % present in detergents, 0.8 % is present in perfumes, 0.1 % in creams and loations.[13] Coumarin and its combined compounds have light emitting property, hence they applied in optical studies. Coumarin compounds are generally used as dyes due to their light emitting properties.[14-19] Coumarin nucleus is the flourophore which is used in laser dyes having brightness, photo stability, greater stock difference which has significant commercial applications in the field of electronics.[20] Few of the coumarin scaffolds used as laser dyes is listed in the figure 1.1.6.

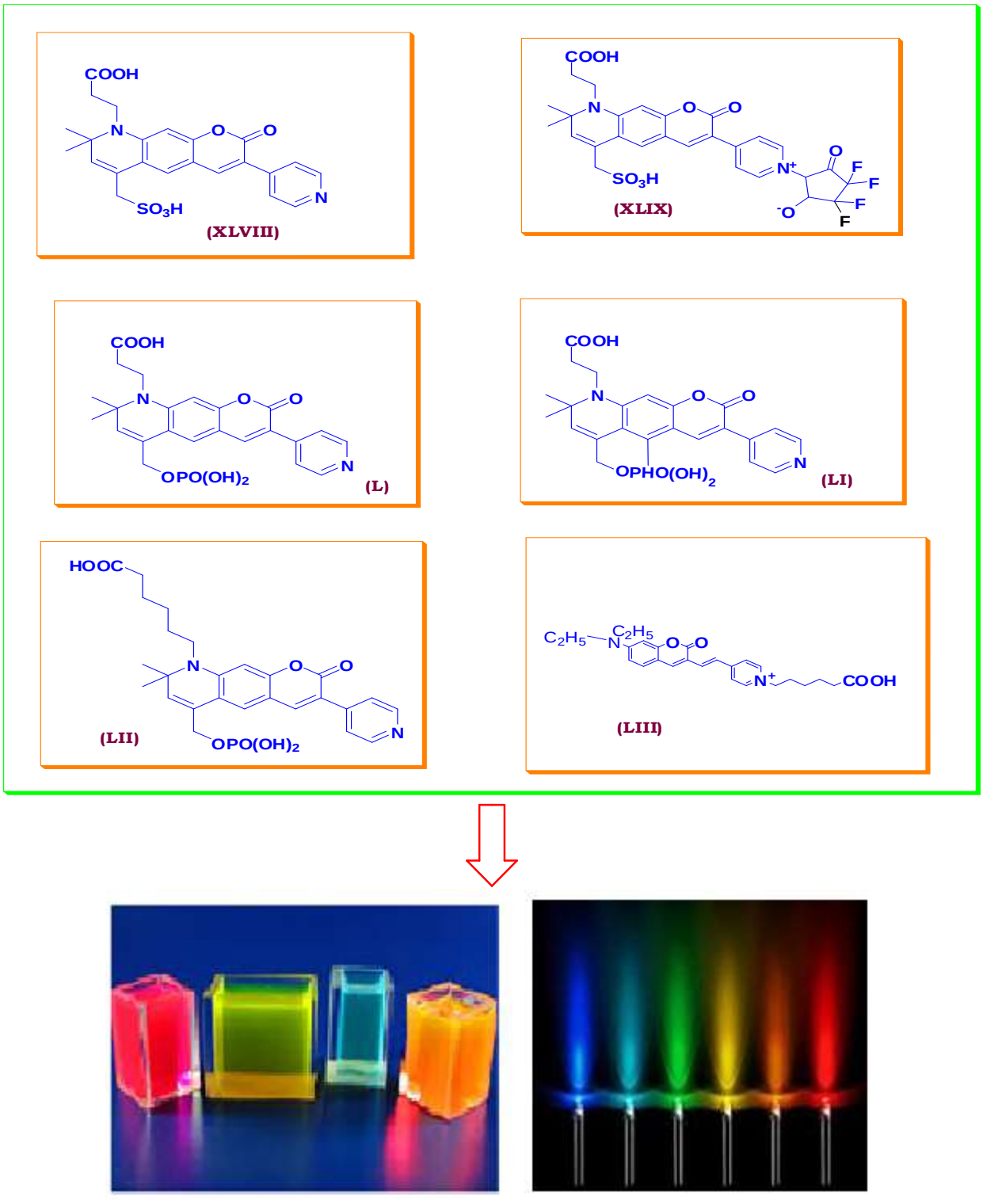


Figure 1.1.6: New class of coumarin compounds used as laser dyes.

Ruthenium II di imine complex fused with coumarin moiety shows used in bio imaging studies[21] with high FRET studies (Fluorescent resonance energy transfer) These are significant in molecular and supra molecular physics (Figure 1.1.7).

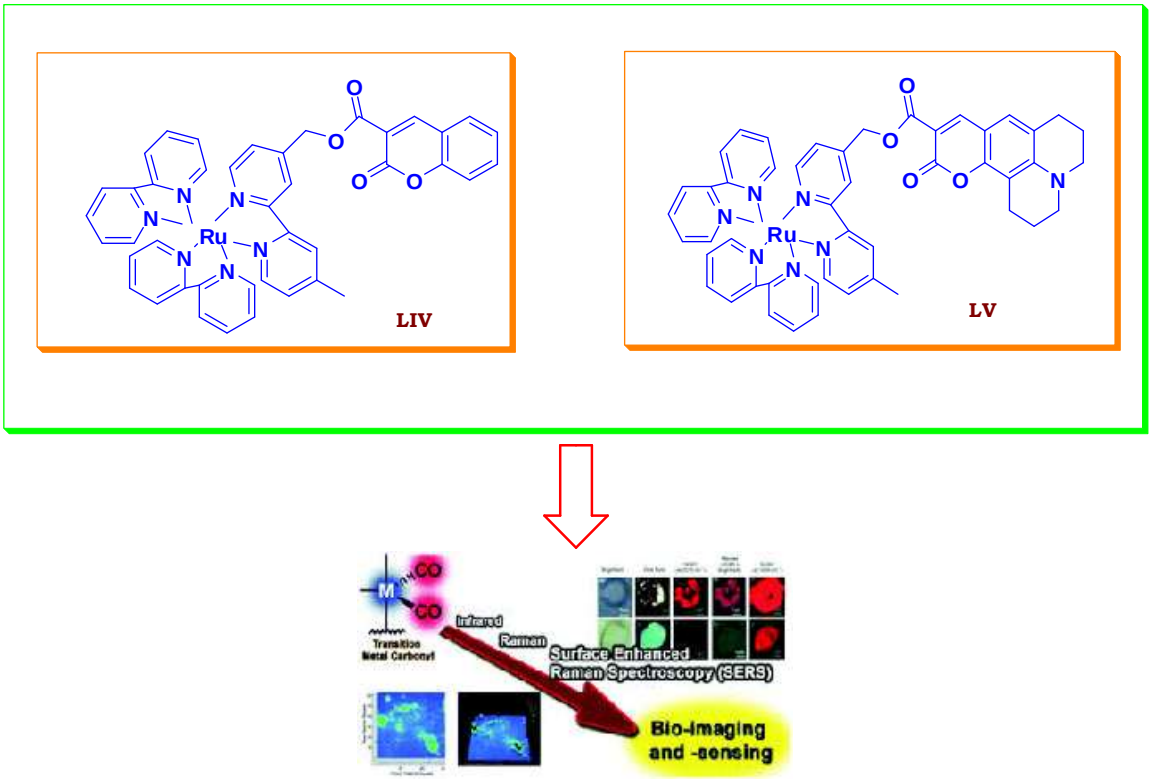


Figure 1.1.7: Ruthenium pyridine complex clubbed with coumarin used in bioimaging studies.

Coumarins also used as DNA intercalators (the material used to insert the nitrogen bases at required place), oxygen sensors[22]. Coumarins are also used in thermal transformations such as polyphotonic, disproportionational, thermal ionization[23-25]. Coumarin and its derivatives are used as neutralizers in rubber and plastic industry, they are also used to reduce unpleasant smell in paints and sprays due to their aroma smell[26]. 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. Coumarin and its fused compounds are working as poly dentate ligands in the preparation of wide range of coordination complexes[27,28]. Coumarin based copper complexes are showing potential free radical scavenger activity and anti oxidant property[29]. 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[30]. Other material chemistry applications of coumarin includes tissue engineering applications[31], cell imaging[32], chromogenic and ratiometric probe[33], photo sensitisers[34]. Light emission property of coumarin-thiophene hybrid compounds was shown in the figure 1.1.8.

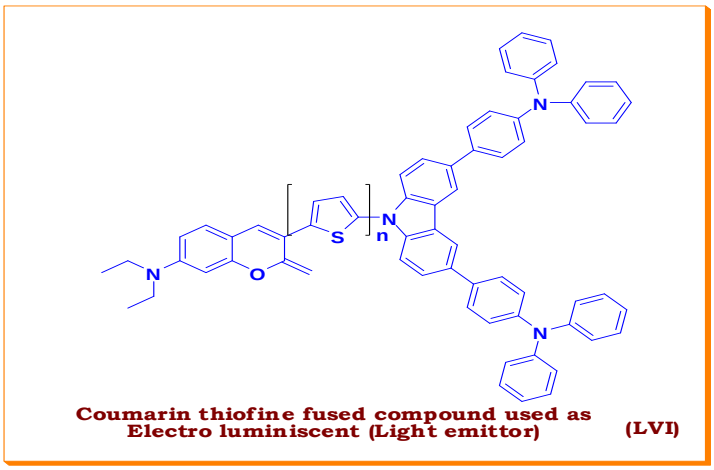


Figure 1.1.8: Coumarin- thiophene polymer used as light emitter.

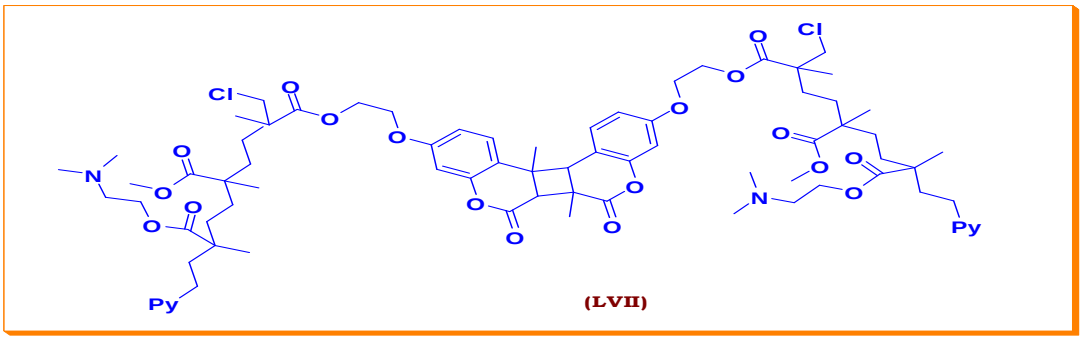


Figure 1.1.9: Polymer of Coumarin nano material finds the applications in biotechnology, biomedicine, nano science.

1.1.4.3. Medicinal chemistry applications of coumarin

Coumarin and their derivatives when administrated orally, they get readily absorbed by gastrointestinal tract. Because of this nature so many synthetic drugs with coumarin nucleus were invented having potential therapeutic activity. According to Ryan Ketcham and Wexler (1968) coumarin nucleus is effective in inhibiting metastases (avoiding the growth of secondary tumor cells). Pharmacological applications of coumarin were shown in figure 1.1.12. Coumarin exhibit synergic effect when it is in combination with endotoxin interleukin[35] effect in the human beings i. e, enhancing the immunity power. Keri et al. evaluated the progress of anti-tubercular activity[36] of coumarin derivatives. Coumarin is the key intermediate in the synthesis of cannabiniods which are potent pain relievers and posses antiemetic action[37]. Natural products with coumarin nucleus such as fraxetin, esculetin, daphnitin are known to exhibit anti inflammatory and anti oxidant activities[38,39]. Coumarin 7-Xyloside are used as oral thrombotic agents[40] (reduces blood clots). Geiparvarin, Vipirinin are commercially available anti cancer agents[41]. Coumarin is used as HIV inhibitor[42]. Warfarin extracted from woodruff as well as from lavender is used to avoid the blood clots in veins, lungs, heart[43-44]. The coumarin skeletal moiety is at the core of important antibiotics, such as coumermycin, Novabiocin, chlorobiocin[45,46], and remains a valuable source of lead compounds for the design and development of effective antifungal and antimicrobial therapy drugs[47,48]. Additionally, these compounds involved in the actions of plant growth hormones, growth regulators, the control of respiration, photosynthesis, as well as defense against infection[49]. Natural source of Warfarin used as anti-coagulant was shown in the figure 1.1.10. General diseases caused by various pathogens are shown in the figure 1.1.11.

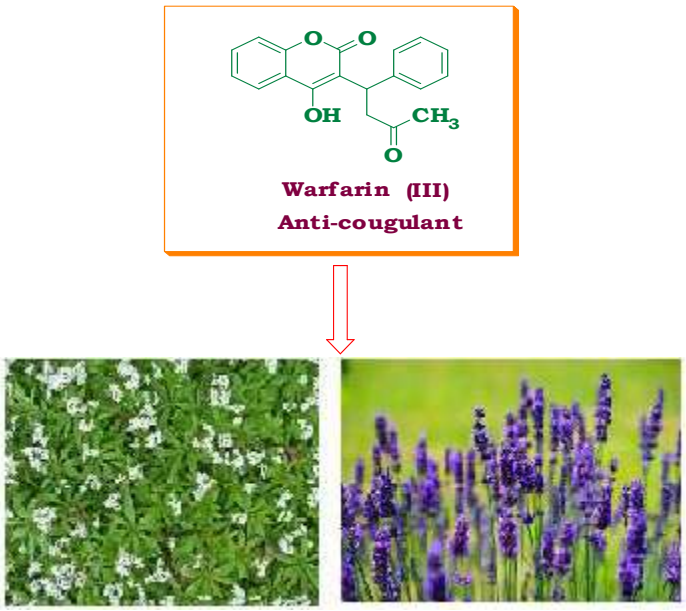


Figure 1.1.10: Warfarin (4-hydroxy coumarin) extracted from woodruff and lavender.

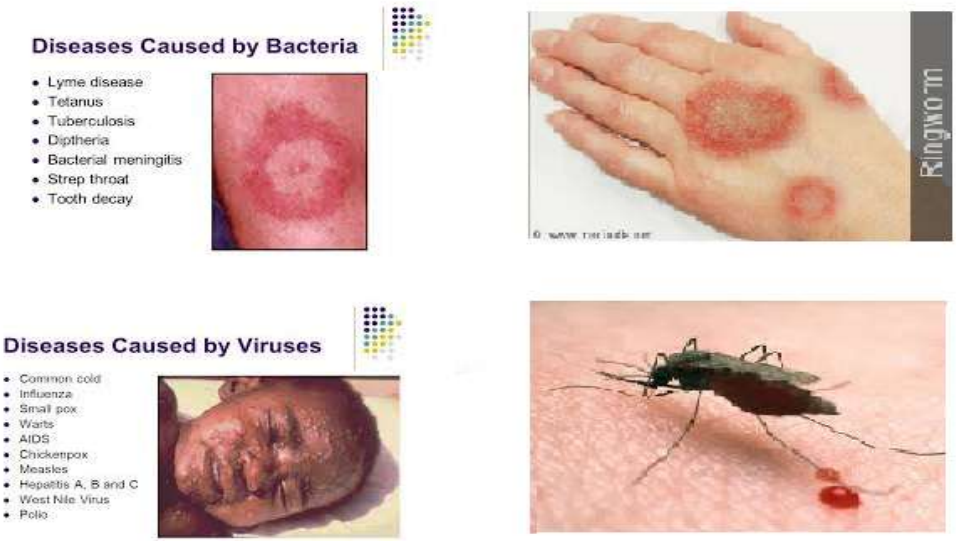


Figure 1.1.11: Different types of diseases, which are caused by the various pathogens in human beings.

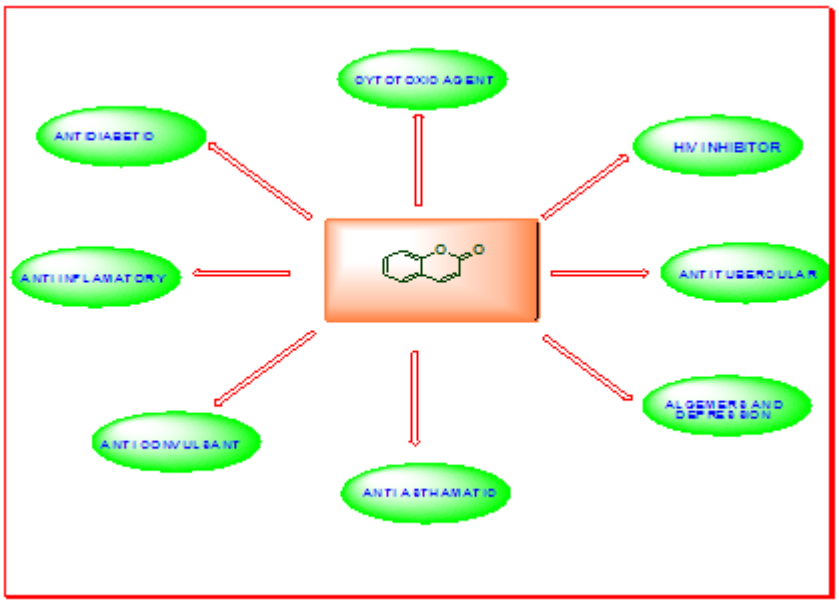


Figure 1.1.12: Various pharmacological activities of coumarin and its derivatives.

Commercially available drugs containing coumarin skeletal structure were shown in the figure 1.1.13.

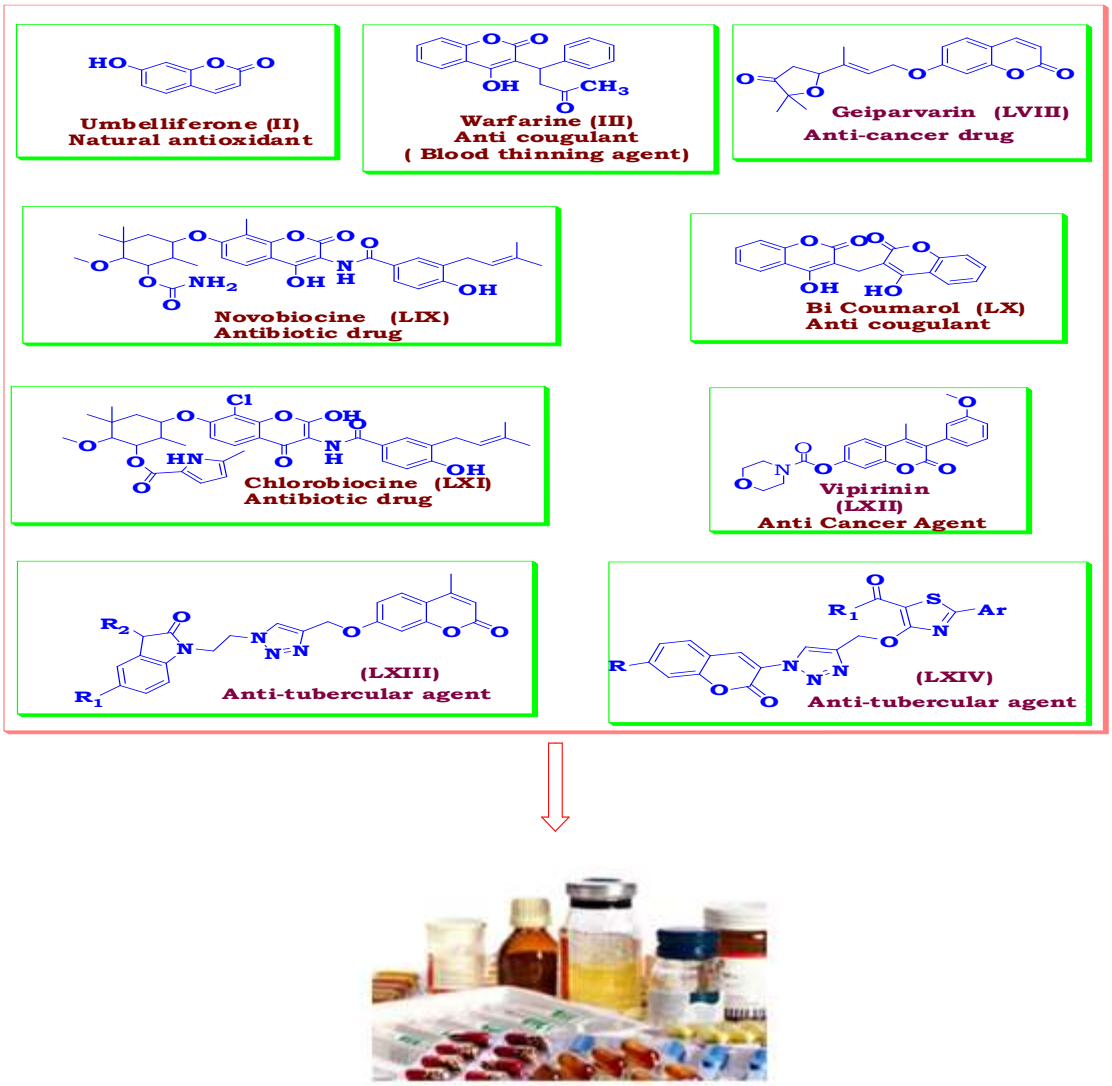


Figure 1.1.13: Commercially available coumarin based drugs.

Generally fused heterocyclic compounds and compounds containing two or more heterocyclic rings have potential therapeutic activity compared to the individual molecules. Hence few of the coumarins incorporated with other heterocyclics having medicinal value were listed in the figure 1.1.14.

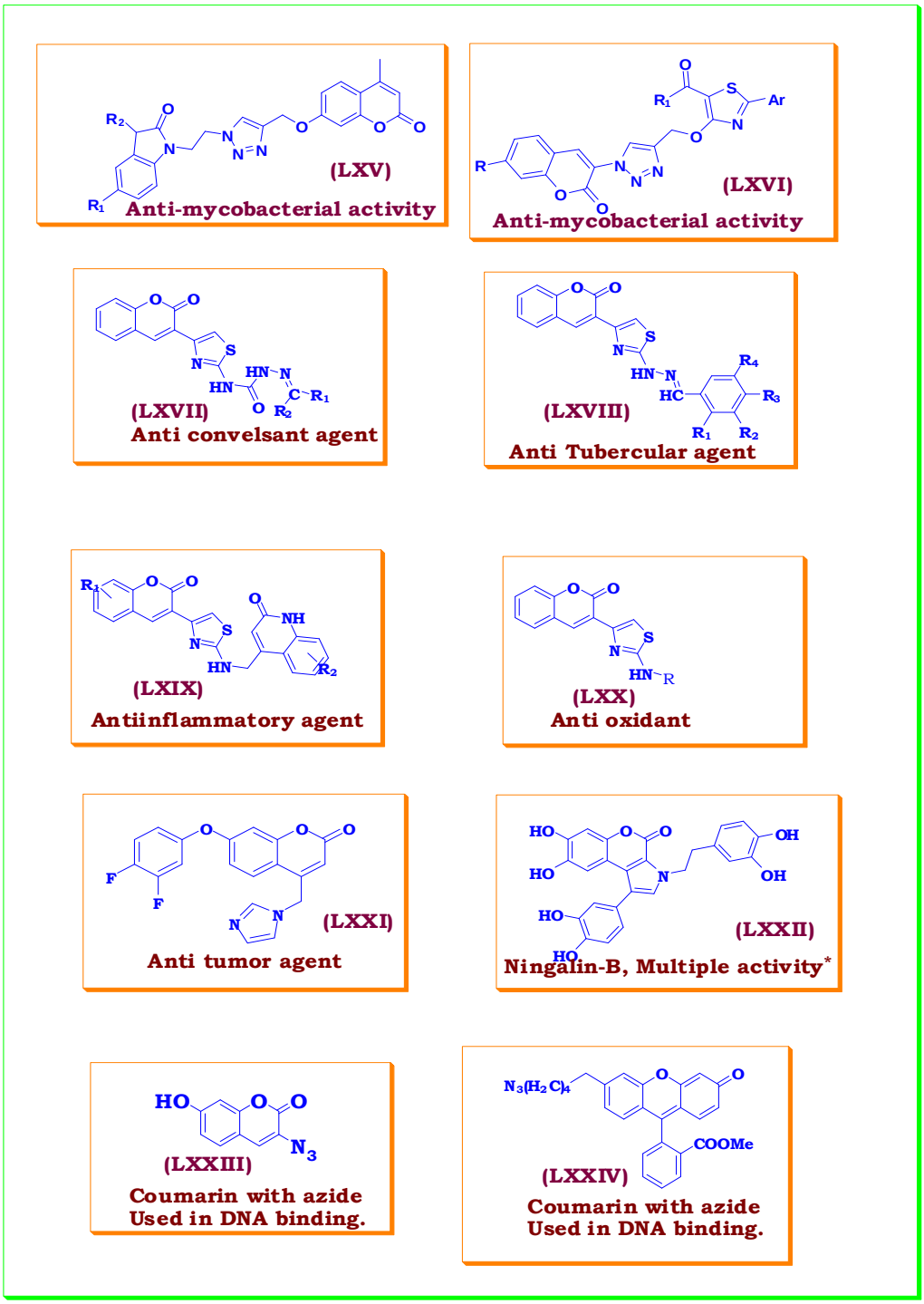


Figure 1.1.14: Compounds having coumarin moiety incorporated with other heterocyclics showing medicinal value.

Coumarin–imidazole fused compounds are effective in CYP19 inhibition[50] (C19 steriodal 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[51-52].

1.1.4.4. Agro-chemical 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[53-57], insecticidal and insectistatic activity[58], anti bacterial activity[59], inhibits mites, weeds and works as Allelochemical[60,61] (chemical that extracted from living organisms and works on individual organisms present in its surroundings). Warfarin is the potential first generation coumarin rodenticide[62,63], 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 a naturally occurring compound containing the 4-hydroxy coumarin moiety. It has been isolated from woodruff as well as from lavender and is widely used to control the rodents population which causes big threat to plants, animals, crops, public health, damage to the furniture, farmlands and forests[64]. Damage to the croplands by the pests and rodents shown in the figure 1.1.15. Some of the coumarins having pest control activity are shown in the figure 1.1.16.

Figure 1.1.15: Some of the pests damaging the crop lands.

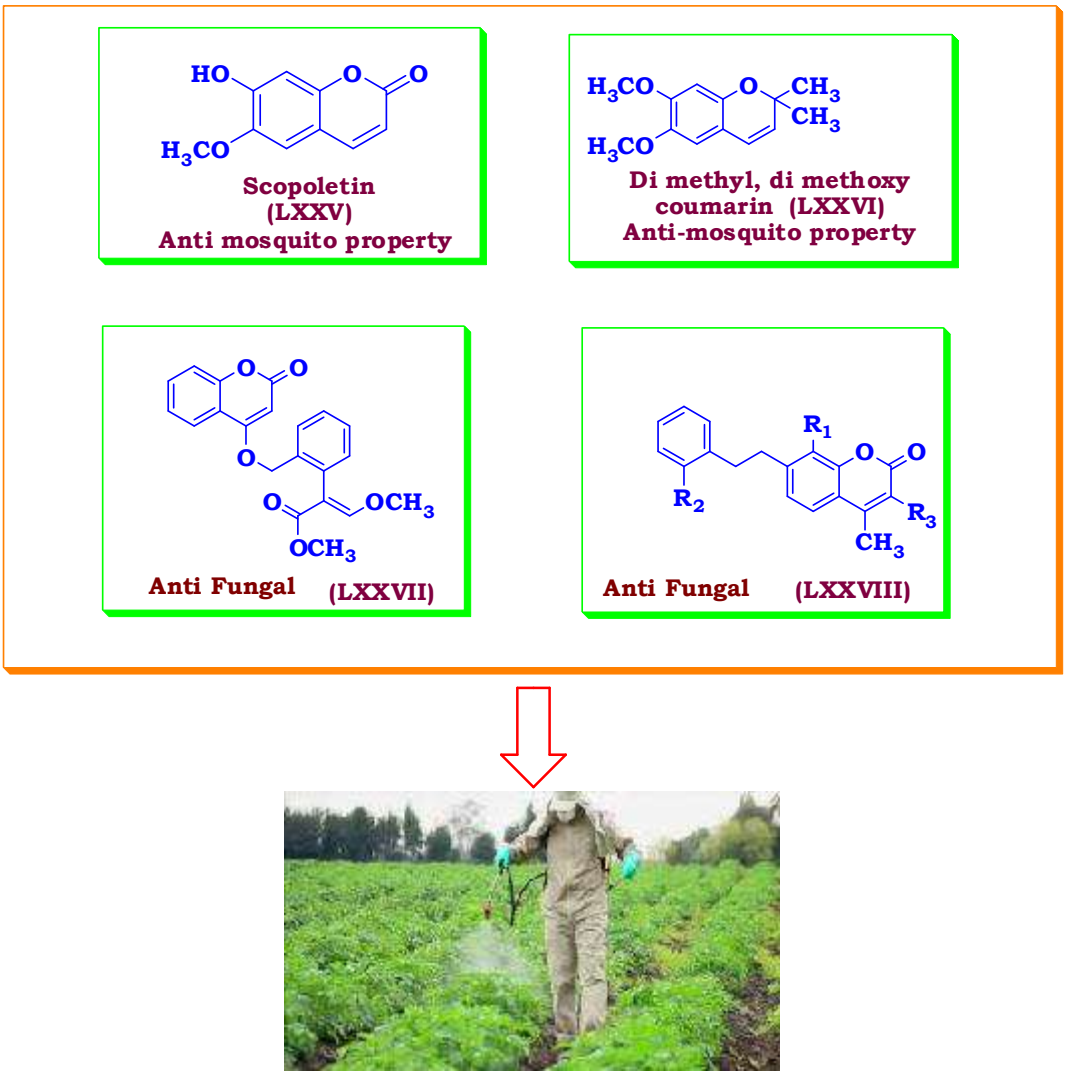


Figure 1.1.16: Coumarin compounds used in the pest control.

1.2.1. Scope and study of thiazoles

In addition to coumarin, 1,3 thiazoles are five membered heterocyclic compound with sulphur and nitrogen as hetero atoms. It is the pale yellow colored liquid. They are well known for their broad spectrum applications. It is the major constituent in vitamin B_1 essential for higher animals in carbohydrate metabolism. Epothilone is the anti cancer agent with thiazole nucleus. Penicillin is the wonder drug which is constituted by thiazole ring.

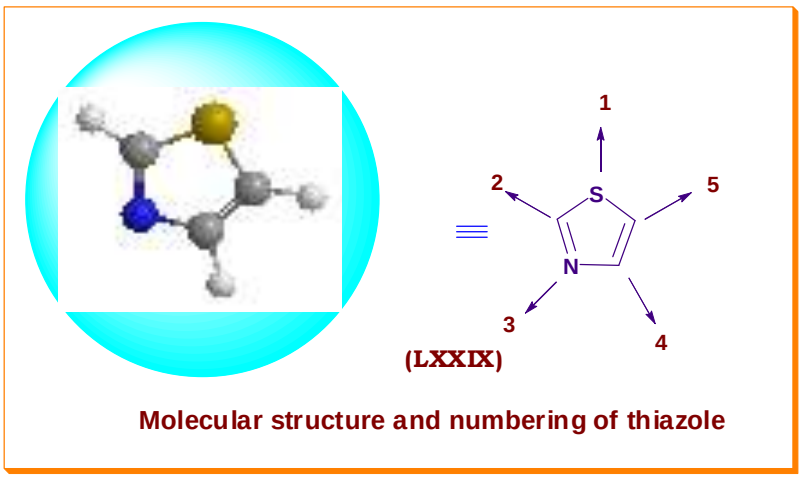
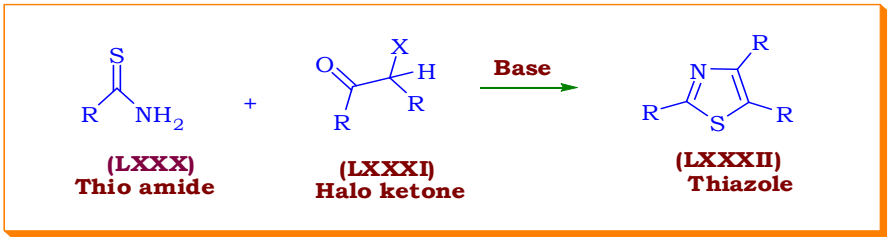


Figure 1.2.1: Molecular structure and numbering of thiazole.

1.2.2. Synthesis of thiazole ring

1.2.2.1. Hantzsch thiazole synthesis

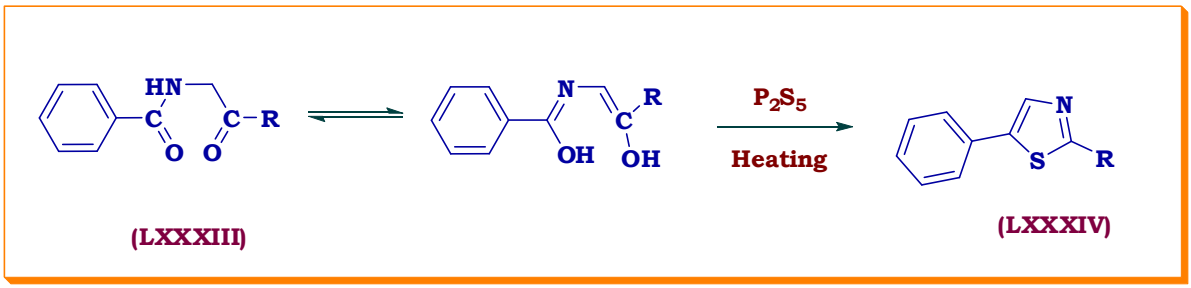
Cyclo condensation between halo ketones (LXXXI) with thioamide (LXXX) gives substituted thiazole ring[65] (LXXXII) as shown in the scheme 1.2.1.



Scheme 1.2.1: Synthesis of thiazole, from thio amide by Hantzsch method.

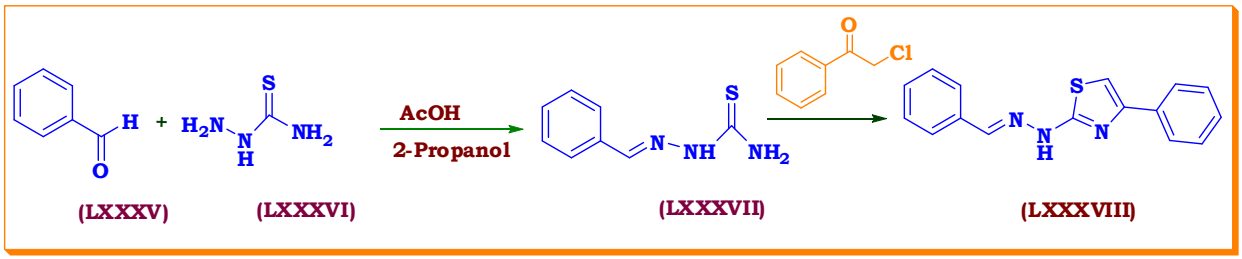
1.2.2.2. Gabriel's synthesis

Gabriel treated acylaminoketone (LXXXIII) with equal ratio of phosphorus penta sufide gives 2-phenyl 5-alkyl thiazole (LXXXIV).



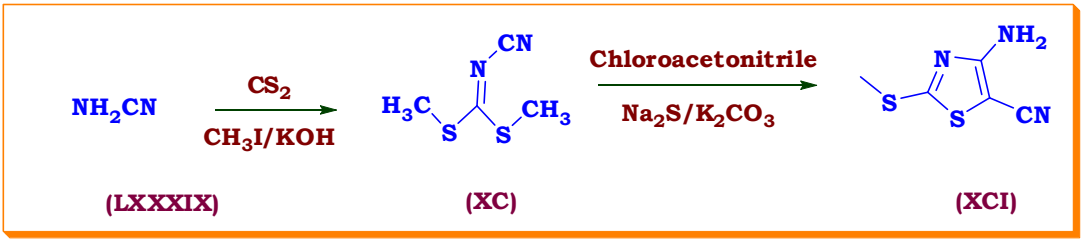
Scheme 1.2.2: Synthesis of thiazole by the Gabriel method.

1.2.2.3. Peng-Cheng et al. reported the synthesis of 2,4-disubstituted thiazole derivative (LXXXVIII) by the reaction between substituted aldehydes (LXXXV) with thiosemicarbazide (LXXXVI) followed by 2-haloacetophenone[66] as shown in the scheme 1.2.3 .



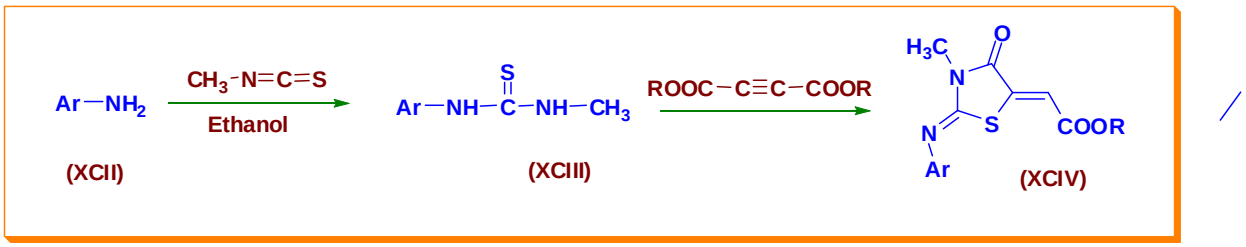
Scheme 1.2.3: Synthesis of thiazole derivative from benzaldehyde.

1.2.2.4. Thomae et al. synthesized[67] substituted thiazole derivative (XCI) by developing a new condition for the preparation of di methyl cyanodithioimidocarbonate. This further reacted with sodium sulfide, chloroacetonitrile and potassium carbonate as shown in scheme 1.2.4.



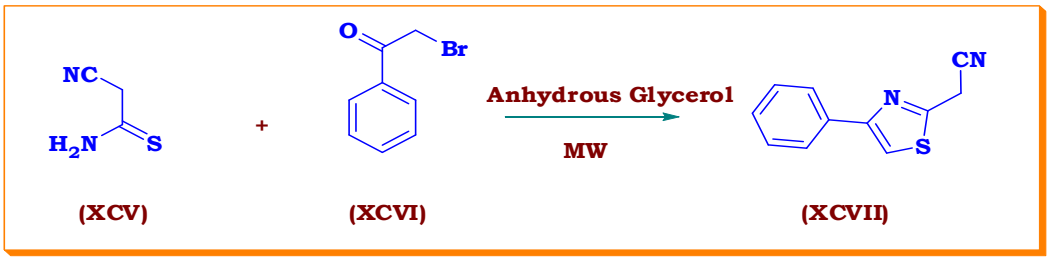
Scheme 1.2.4: Synthesis of thiazole derivative from compound (LXXXIX) reaction with carbon di sulfide.

1.2.2.5. Ali et al. proposed the synthesis[68] of substituted thiazole (XCIV) compounds by reacting activated acetylinic compound with thiourea derivatives (XCIII) as shown in scheme 1.2.5.



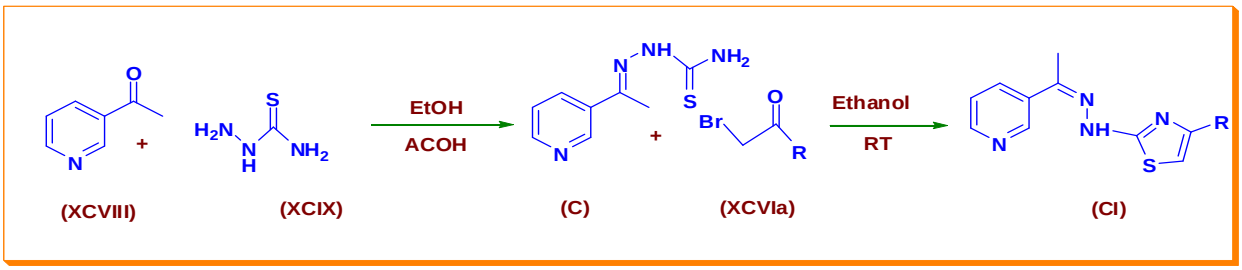
Scheme 1.2.5: Synthesis of thiazole derivative from aromatic amines.

1.2.2.6. Todor et al. synthesized[69] the thiazole compound (XCVII) by microwave irradiation method by treating 2-cyanothio acetamide (XCV) with various 2-bromo acetophenone derivatives (XCVI) in glycerol solvent as shown in the scheme 1.2.6.



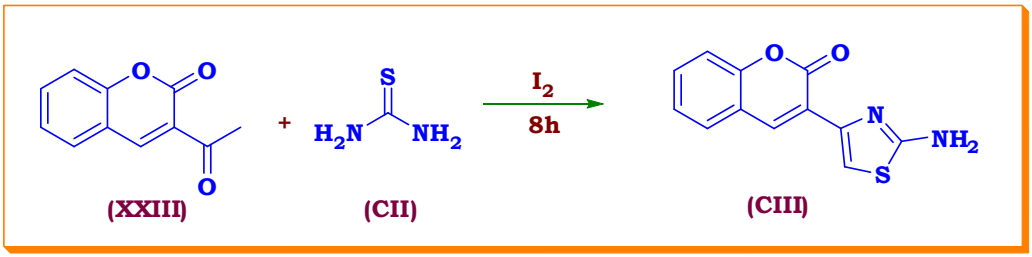
Scheme 1.2.6: Synthesis of thiazole derivative from thiocyano acetamide and 2-bromo-1-phenylethanone.

1.2.2.7. Melissa et al. synthesized[70] thiazole hydrazone derivatives (CI) from thiosemicarbazone derivative of pyridine (C), followed by reaction with aromatic alpha halo acetyl derivative (XCVIa) in the presence of acetic acid in ethanol solvent media at room temperature conditions as shown in the scheme 1.2.7.



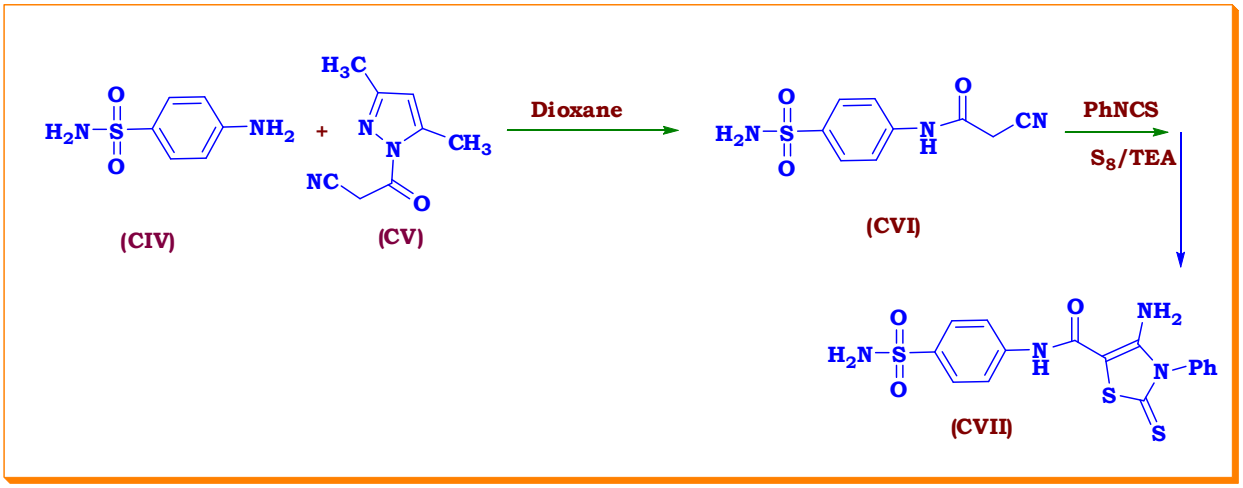
Scheme 1.2.7: Synthesis of thiazole derivative, from 3-acetyl pyridine and thiosemi carbazone.

1.2.2.8. Moustafa et al. synthesized[71] thiazole incorporated on coumarin ring (CIII) by treating 3-acetyl coumarin (XXIII) on treating with thiourea (CII) in the presence of Iodine as shown in the scheme 1.2.8.



Scheme 1.2.8: Synthesis of coumarin-thiazole hybrid compound from 3-acetyl coumarin.

1.2.2.9. Darwich et al. reported[72] the synthesis of thiazole ring (CVII) by reacting cyano acetamide (CV) with sulphanilamide (CIV) will give intermediate (CVI). Further reaction with phenylisothiocyanate and elemental sulfur gave thiazole-2-thione derivative as described in the below scheme 1.2.9.



Scheme 1.2.9: Synthesis of thiazole derivative from pyrazole derivative with phenyl isothiocyanate.

1.2.3. Applications of thiazole

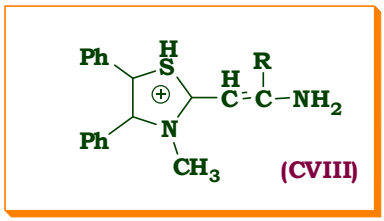
1.2.3.1. Material Chemistry applications of thiazoles

Thiazoles are widely used as optical instruments and also used to enhance molecular second order optical susceptibilities[73]. Some of the thiazole dyes are classified as below. They are also main constituents in direct, vat and disperse dyes[74]. Thiazolothiazole derivatives are used in n-type organic field effective transistors[75].

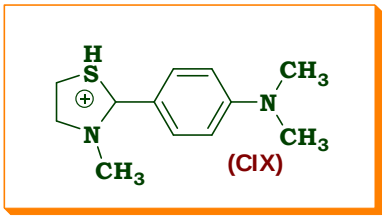
Classification of thiazole based dyes

There are large number of thiazole based dyes are available. Few are described here.

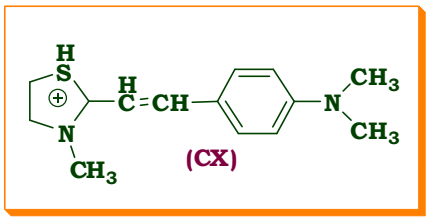
1. **Amino vinyl thiazole dye**



2. **Amino phenyl thiazole dye**



3. **Styryl thiazole dye**



1.2.3.2. Pharmacological applications of thiazoles

They found applications in pharmacology which includes treatment of allergies[76], Schezophrenia[77], hypertension[78], anti HIV[79], anti-bacterial[80], anti thrombotic activity[81], hypnotics[82], anti-protozoal[83], anti-helmentic[84], anti-microbial[85], anti-cancer[86]. Additionally 2-aminothiazoles are exhibiting potential activity against human cancer cell lines such as leukemia, lung, breast, melanoma, ovarian, renal, CNS, prostate and colon[87-90]. Dasatinib SPRYCEL is a multi-targeted kinase inhibitor which is used in the treatment of chronic myelogenous leukemia as well as Philadelphia chromosome-positive acute lymphocytic leukemia. It is more potent than imatinib and inhibits the SRC family kinases[91-94].

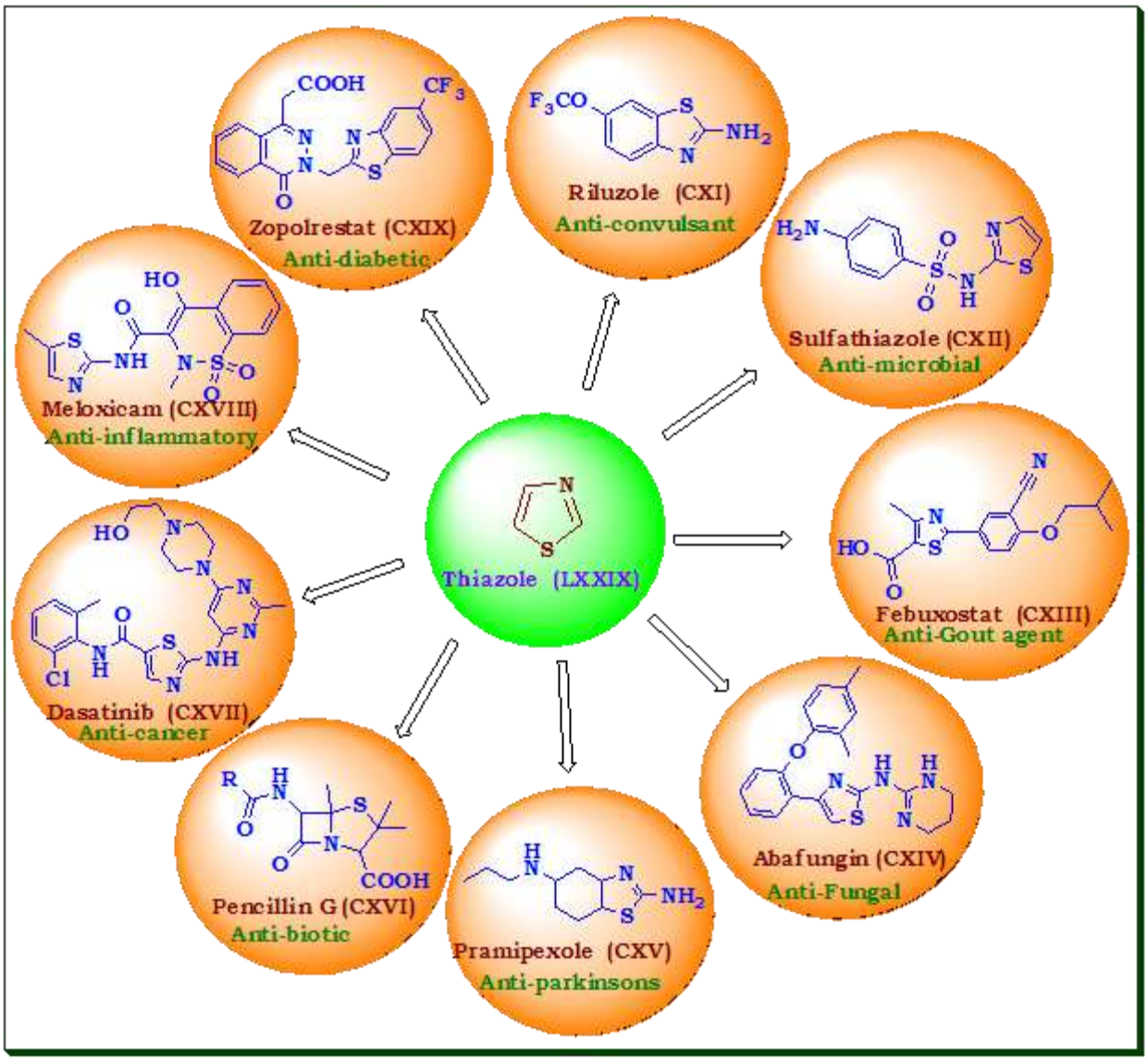
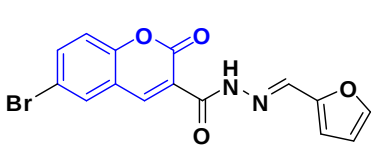


Figure 1.2.2: Pharmacological applications of thiazole ring.

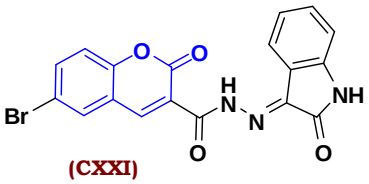
Coumarin as potential anti cancer agent

Biological investigations of coumarins revealed the engrossment of innumerable pathways by which coumarins act as anticancer agents. Coumarins target a number of pathways in cancer such as kinase inhibition, cell cycle arrest, angiogenesis inhibition, heat shock protein (HSP90) inhibition, telomerase inhibition, anti-mitotic activity, carbonic anhydrase inhibition, monocarboxylate transporters inhibition, aromatase inhibition and sulfatase inhibition. Furthermore, such research helped in derivation of structure activity relationship studies (SARs) which lead to the discovery of diverse substitution of coumarin nucleus, thereby enhancement/broadening of activity. Investigators studied/developed their SAR as well as conformation and configurational requirements for binding site through docking simulation studies. There is still a lot to explore about the coumarin and its various interaction networks toward diverse targets. Thus, such similar derivatives can be explored which may lead to the development of a potent anticancer pharmacophore.

In recent years, various researchers have reported the anti-cancer activity of coumarins. Some of the active anti-cancer compounds are shown below[95-97].

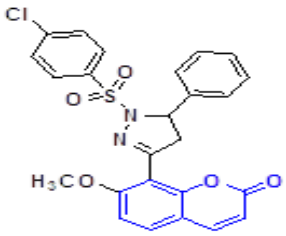


(CXX)

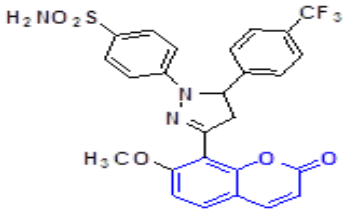


(CXXI)

Nasr et al., 2014, Eur. J. Med. Chem., 76, 539.

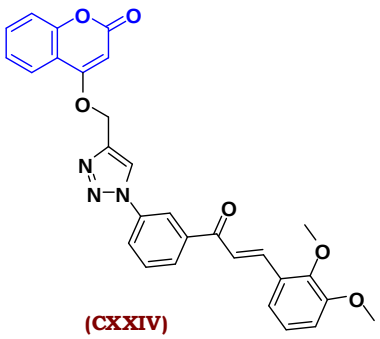


(CXXII)

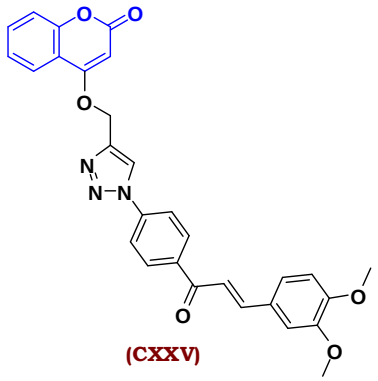


(CXXIII)

Amin et al., 2013, Eur. J. Med. Chem. 60, 187.



(CXXIV)

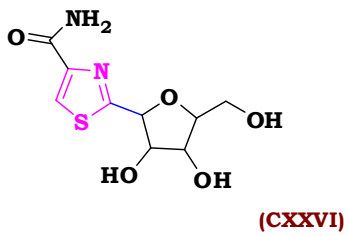


(CXXV)

Pingaew, et al, 2014, Eur. J. Med. Chem. 85, 65

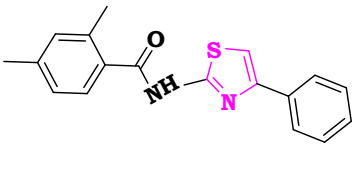
Thiazole ring as potential anti cancer agent

1,3-thiazole is an important and versatile structural analogue possessing a diverse spectrum of biological activities. Moreover, several **1,3-thiazole** scaffolds were documented to contribute to a variety of antineoplastic potentials being employed as **anticancer**. Recently, it was reported that the chemotherapeutic activity of **1,3-thiazoles** derivatives are augmented by the discovery of tiazofurin (natural antineoplastic antibiotic) (**CXXVI**) and S3U937 (**CXXVII**), which exhibited potential antitumor activity against various cancer types. In an initial antitumour assay, 2-(b-D-xylofuranosyl)thiazole-4-carboxamide (**A**) was shown to be non-cytotoxic to murine lymphoma P388 cells. Subsequent studies revealed that this molecule devoid of any significant cytotoxicity toward K562 and HL-60 cell lines.



(CXXVI)

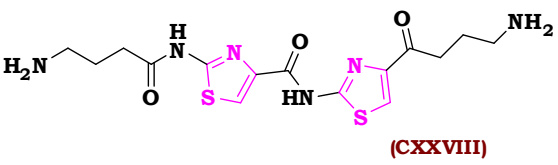
A. Tiozofurin



(CXXVII)

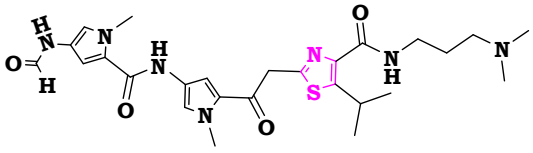
B. S3U937

The documented DNA minor groove binding property of **1,3-thiazole**-netropsin, and thiazotropsin A (**CXXVIII and CXXIX**) are also played attention.



(CXXVIII)

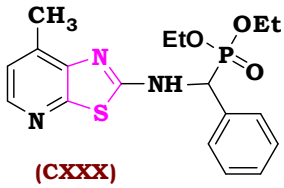
C. Thia-netropsin



(CXXIX)

D. Thiazotropsin

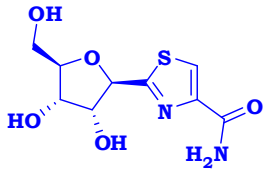
Thiazole[5,4-b]- pyridine (CXXX) belong to an important class of compounds which show a wide range of biological activities such as anticancer, antiviral, anti-bacterial properties. The antitumor activities of these compounds were evaluated against three human cancer cell lines (PC-3, Bcap-37 and H460). Most of the target compounds displayed from moderate to excellent antitumor activities against one or two cancer cell lines.



(CXXX)

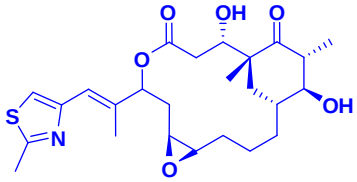
Thiazole(5,4,b) pyridine derivative

There are several mechanisms which are working on tumor cells, such as ionosin monophospate dehydrogenase (IMPDH)[98], tumor necrosis factor TNS-α[99], Apoptosis inducers[100]. Tiazofurin is potential anti-tumor agent which is ionosin monophospate dehydrogenase, used in treatment of lung cancer, metastasis, leukaemia[101].



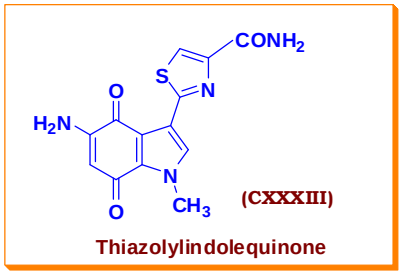
Tiazofurin (CXXXI)

Epothilonesis[102] a recent class of natural product, which has been reported to exhibit excellent cytotoxicity in a broad range of human cancer cell lines. Epothilones are apoptosis inducers through one of two pathways, namely a receptor mediated and a non receptor-mediated or chemical-induced pathway[103]. Thus epothilones have much greater activity against multi-drug resistant cell lines.



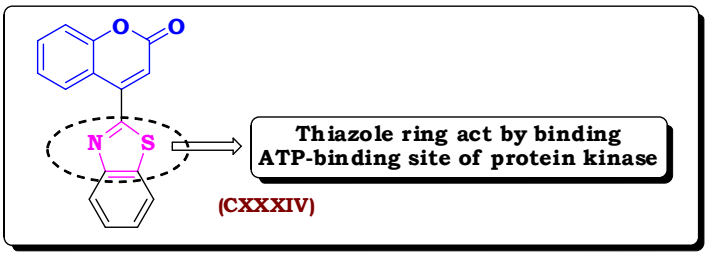
Epothilone (CXXXII)

The thiazolylindolequinone was shown to inhibit topoisomerase II with marked cytotoxic activities towards human cancer cell lines. The indolequinone antibiotic does not covalently binds to DNA but triggers double stranded cleavage of DNA through the inhibition of the enzyme topoisomerase II[104].



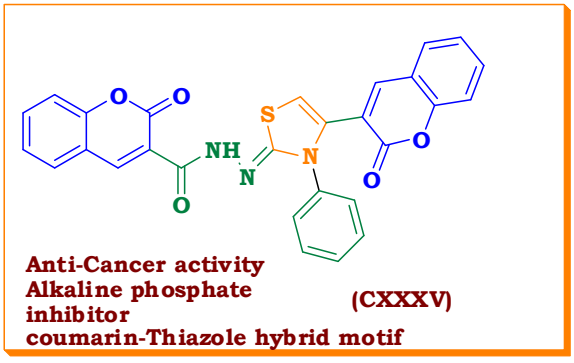
Anti-cancer activity of coumarin thiazole hybrid compounds

Further, docking study and synthesis of coumarin substituted benzothiazole derivatives were accomplished in 2012 by Kini[105] et al. They selected receptor tyrosine kinase as a target for anticancer activity for docking study. It was evaluated by SAR study and this compound was most active compound. It was investigated by docking simulation that coumarin substituted benzothiazole has not shown hydrogen bonding with the receptor but has found to form hydrophobic bonding by C-atom of allyloxy methylene group.

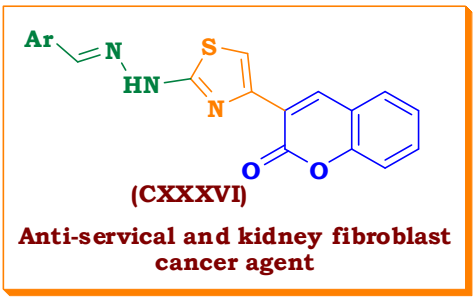


The incorporation of another heterocyclic moiety, either as a substituent group or as a fused component into coumarin, alters the properties of the parent material, and the resulting compounds may generally exhibit promising or even unprecedented properties. For example, neo-tanshinlactone, a minor component isolated from an ethanolic extract of Salvia miltiorrhiza, was 10-fold more potent and 20-foldmore selective against breast cancer cells than tamoxifen.

Alia et al. reported[106] the synthesis of coumarin thiazole hybrid compounds and evaluated their alkaline phosphate inhibition and anti-cancer activity.



Moustafa et al. reported[107] the synthesis and found anti-cancer activity of the synthesized compound with various substituents on aromatic ring.



(CXXXVI)

Anti-servical and kidney fibroblast cancer agent

Anti-liver cancer activity

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes. Over 100 cancers affect humans. Next to cardiovascular diseases cancer is the biggest killer disease.

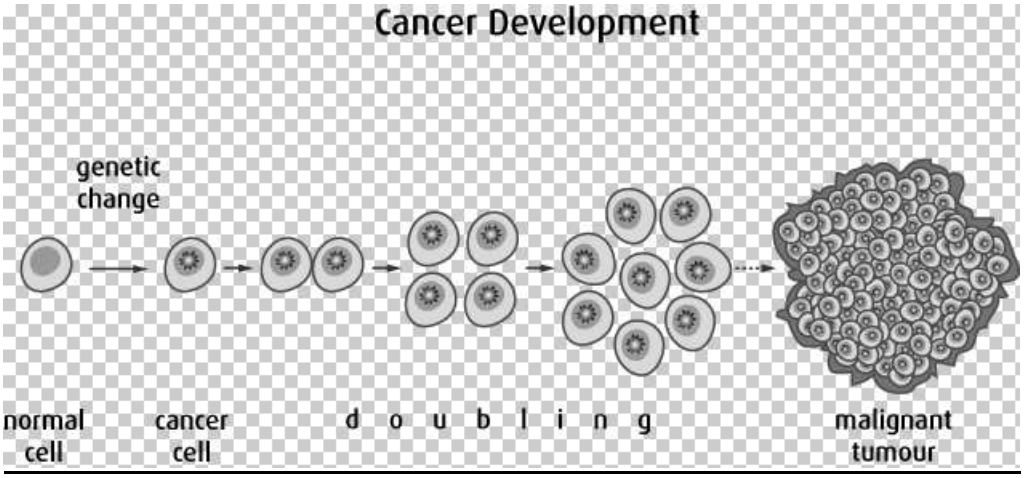


Figure 1.2.3: Development of cancer cells.

Hepato cellular carcinoma (HCC) is the fifth most common cancer in the world and incidence is increasing due to increased rate if liver cirrhosis, hepatitis B and C infections. The majority of HCC patients are diagnosed at their advanced stage[108-114]. General symptoms of HCC are pain in upper right part of the stomach, loss of weight, heaviness in the right side part of stomach and loss of appetite. Medical diagnosis is carried with blood test, CT scan, Ultra sound scan, MRI scan and liver biopsy. Treatment of HCC includes surgery or liver transplantation.

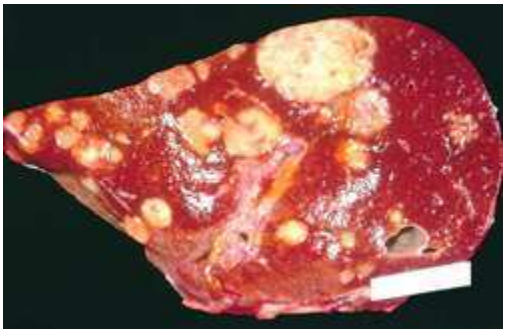


Figure 1.2.4: Tumor affected liver.

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CONCLUSION

In the design of new drugs, the hybridization approach might allow obtaining molecules with improved biological activity with respect to the corresponding lead compounds. Many of biologically active agents are hybrid molecules, which are designed through concept of

molecular hybridization and have shown multiple pharmacological activities. This multifunctional attribute of these hybrid compounds makes them potential drug candidates for the treatment of multi-factorial diseases such as cancer, Alzheimer's disease, metabolic syndromes, AIDS, malaria and cardiovascular diseases.

After the careful observation of scope and applicability of coumarin and thiazole scaffolds these two moieties incorporated in to the single skeletal framework and hybrid compounds are synthesized to intensify their activity. Based on the careful literature survey on the hepato cellular carcinoma it was chosen as the research object and synthesized compounds were tested for the anti-hepato cellular carcinoma studies with the help of molecular docking studies.

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