



CODEN [USA]: IAJPBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.7327002>Available online at: <http://www.iajps.com>

Research Article

**NOVEL COUMARIN DERIVATIVES: SYNTHESIS,
CHARACTERIZATION AND ITS BIOLOGICAL VALUATIONS**Shaikh Sameena*¹, Sameer Shafi¹, Dhumal P.B.¹, Dharashive V.M.¹Address: - 1. Shivlingeshwar College of Pharmacy, Almala-Latur (413520) Maharashtra (MH),
India.**Article Received:** September 2022 **Accepted:** September 2022 **Published:** October 2022**Abstract: -**

Compounds containing coumarin backbone are unit an awfully necessary cluster of compounds as a result of their usage in pharmacy and drugs. Properties and biological activities of coumarin derivatives have a giant role inside the event of recent drugs. Therefore, many alternative ways and techniques area unit developed thus on synthesize coumarin derivatives. Coumarin derivatives could also be obtained from whole totally different starting materials with varied ways but with vast variations in yield. Coumarins possesses different kinds of biological activities like medicine, antimicrobial medication, analgesic, inhibitor, anticancer, antiviral etc. Coumarin belongs to a bunch as Benzopyrones that consists of a benzene nucleus joined to a pyrone nucleus. These freshly designed Coumarin derivatives were screened for medication activity by gum induced rat paw hydrops model, medication and antifungal activity. Coumarin is of the benzopyrone thus, it is the essential particle which can be synthesis from them additional sophisticated for the Coumarin derivatives that containing alkyl groups or radical or unit as imitative totals. In vitro toxicity studies and in vivo acute oral toxicity examination additionally counsel that the synthesized compounds are unit non-toxic in nature. Coumarin and their derivatives have attracted vital attention within the scientific world due to their unbounded applications in knowledge domain areas. This work incontestable a simple and economical approach to developing coumarin derivatives as outstanding compounds.

Key words: - Coumarin, Benzopyrones, Analgesic, Antifungal, Anticancer activity etc.

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Please cite this article in Shaikh Sameena Ibrahim et al, Novel Coumarin Derivatives: Synthesis, Characterization And Its Biological Evaluations., Indo Am. J. P. Sci, 2022; 09(10).

1. INTRODUCTION:

Many drug-resistant human infective microbes are determined within the past few decades and this can be turning into a heavy public pathological state in an exceedingly wide selection of infectious diseases. In spite of an oversized range of antibiotics and chemotherapeutics offered for medical use, antimicrobial resistance has created a considerable medical would like for brand spanking new categories of antimicrobial agents as these resistant infective germ strains cause antimicrobial treatment failure and enhance the mortality risks and generally contribute to complications. To beat this drawback the event of latest bioactive compounds effective against resistant strains is extremely required and also the style and synthesis of newer antimicrobials can forever stay a neighborhood of large significance. One approach to the invention of novel and potent antimicrobial agents is by modifying the structure of a well-known antimicrobial agent whereas the second strategy is to mix along 2 or additional totally different antimicrobial pharmacophores into one molecule. Coumarin or 2H-chromen-2-one Figure 1, the study of coumarin dates back to 1820 once coumarin was 1st extracted from Tonka bean by Vogel. It is Associate in nursing aromatic organic compound with formula $C_9H_6O_2$. Its molecule will be delineating as an aromatic hydrocarbon molecule with 2 adjacent H atoms replaced by a lactone-like chain $-(CH) = (CH) - (C=O) - O-$, forming a second membered heterocycles that shares 2 carbons with the benzene. Coumarin could be a colorless crystalline solid with a sweet odor resembling the scent of vanilla and a bitter style. It's found in several plants, wherever it's going to function a defense against predators. By inhibiting synthesis of antihemorrhagic factor, a connected

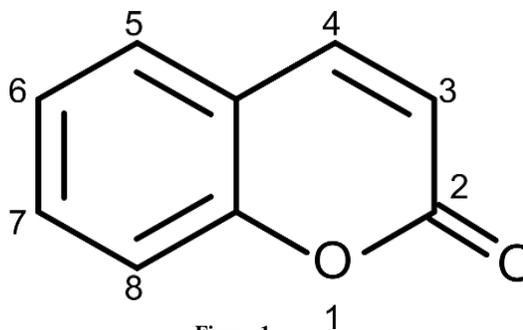


Figure 1

compound is employed because the medicinal drug Coumarin – Associate in nursing anticoagulant medication – to inhibit formation of blood clots, deep vein occlusion, and embolism. Coumarin is of the benzopyrone thus it's the essential particle that may be synthesis from them more advanced for the Coumarin derivatives that containing group teams or chemical group or radical as imitative totals. Coumarin is among the necessary organic compounds and among the numerous uses of terms among the cosmetics, dyes and food acquisitions. These compounds became indispensable structural units that square measure helpful in healthful chemistry, displaying metastatic tumor, inhibitor, and anti-plasmodial, anti-malarial, anti-rhinovirus, antifungal and medicine activity medicament, antiproliferative, antitumor, antiviral, anticoagulant medication, metastatic tumor and anti-HIV activities. Natural coumarins will be divided into six basic teams as follows: easy Coumarins, Funaro Coumarins, Pyrano Coumarins (Linear kind and Angular type), Dihydrofurano Coumarins, Phenyl Coumarins and Bicoumarins Figure 2.

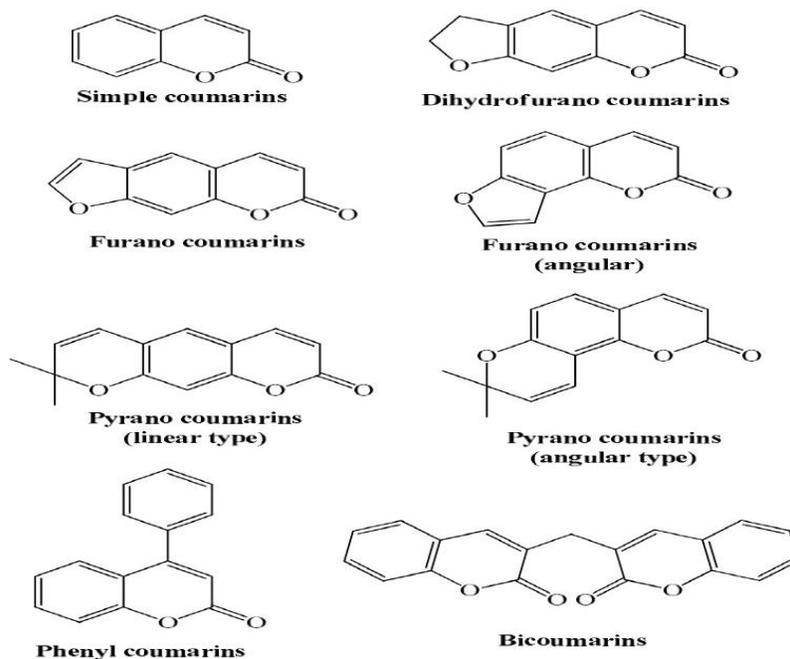


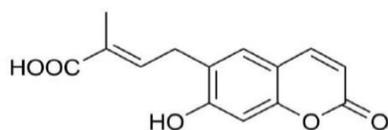
Figure 2: - Six Basic groups Natural Coumarins

The synthesis of coumarin and its derivatives have attracted wide attention from organic and healthful chemists for several years, as giant numbers of natural merchandise contain this heterocyclic nucleus. So, the synthesis of this heterocyclic nucleus is of abundant interest. Most of the extracted coumarins have biological activity and so coumarin derivatives square measure more and more being synthesized, since their extraction from plants is time-consuming and unprofitable (too several operation steps to the ultimate product). Coumarins might be synthesized

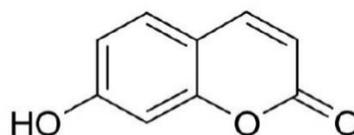
2. NATURALLY OCCURRING COUMARINS: -

2.1 7-Oxygenated coumarins: -

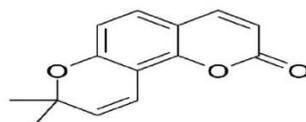
Ex.



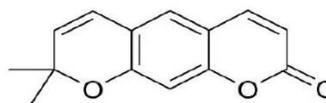
6-(3-carboxybut-2-enyl)-7-hydroxycoumarin



Umbelliferone



Xanthyletin

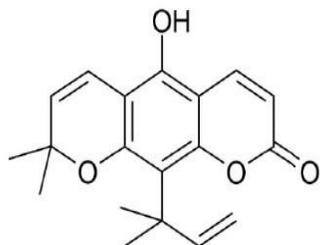


Seseline

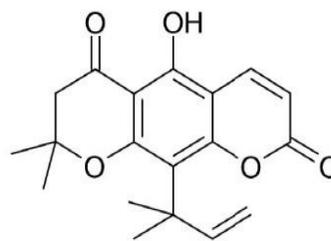
2.2 Dioxygenated coumarins: -

2.2.1. 5, 7- Dioxygenated coumarins:-

Ex.



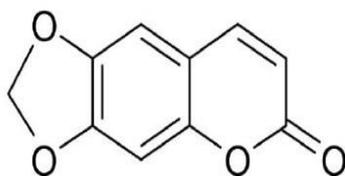
Nordentatin



Claucavatin

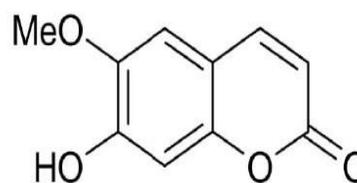
2.2.2. 6, 7- Dioxygenated coumarins:-

Ex.



Ayapin

6, 7-methylenedioxy coumarin

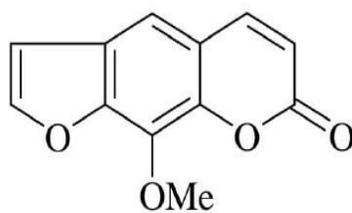


Scopoletin

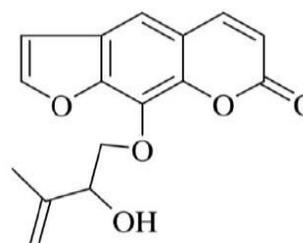
6-methoxy-7-hydroxy-coumarin

2.2.3. 7, 8- Deoxygenated coumarins: -

Ex.



8-methoxypsoralen

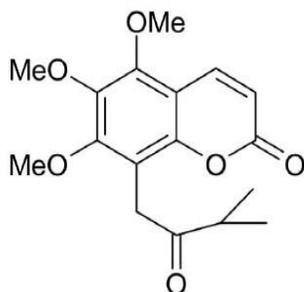


Isogospherol

2.3 Trioxxygenated coumarins: -

2.3.1. 5, 6, 7- Trioxxygenated coumarins:-

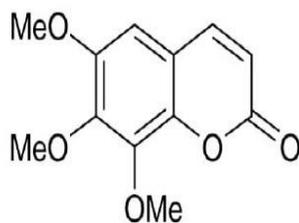
Ex.



Murrayanone

2.3.2. 6, 7, 8- Trioxxygenated coumarins:-

Ex.



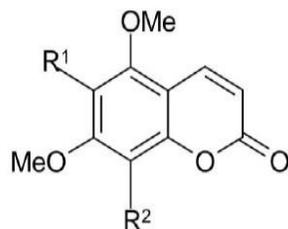
6, 7, 8- Trimethoxycoumarine

2.3.3. 5, 7, 8- Trioxxygenated coumarins:-

Ex. Umbelliferone family.

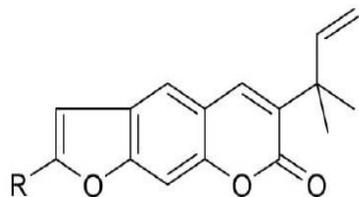
2.4 Tetraoxxygenated coumarins: -

Ex.



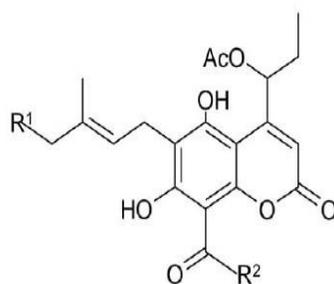
Sr. No.	R ¹	R ²	Name
A	OH	OH	6, 8-dihydroxy-5, 7- dimethoxycoumarine
B	OCH ₃	OCH ₃	5, 6, 7, 8- tetramethoxycoumarine

2.5 3-Substituted coumarin: -
Ex.



Sr. No.	R	Name
A	H	Chalepensis
B	C(CH ₃)-OH	Chalepin

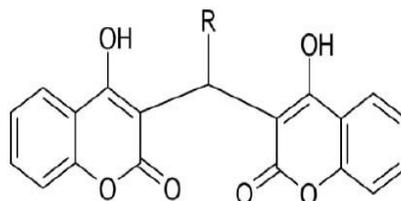
2.6 4-Substituted coumarin: -
Ex.



Sr. No.	R ₁	R ₂
A	H	CH ₂ CH ₂ CH ₃
B	H	CH(CH ₃)CH ₂ CH ₃
C	H	CH ₂ CH ₂ CH ₂ CH ₃
D	H	CH(CH ₃) ₂
E	CH ₂ CH=C(CH ₃) ₂	CH(CH ₃)CH ₂ CH ₃

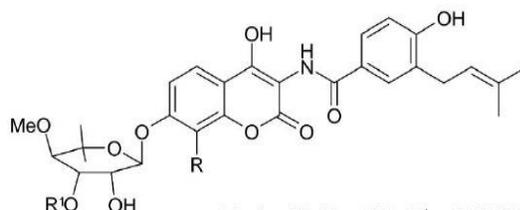
3. BIOLOGICALLY ACTIVE COUMARINS: -

3.1 Anticoagulant compounds: -
Ex.



Sr. No.	R	Chemical Name
A	H	Dicoumarol
B	CH ₃	Pentrombon
C	COOC ₂ H ₅	Tromexan

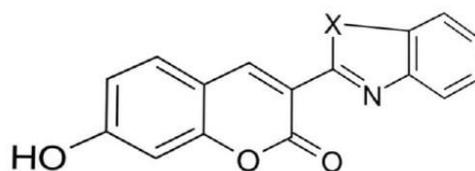
3.2 Antibiotic and Antibacterial coumarins: -
Ex.



Sr. No.	R	R ¹	Name
A	CH ₃	H ₂ NCO	Novobiocin
B	Cl	C ₆ H ₅ N	Chlorobiocin

3.3 Biologically Active Fluorescent and Photostable coumarins: -

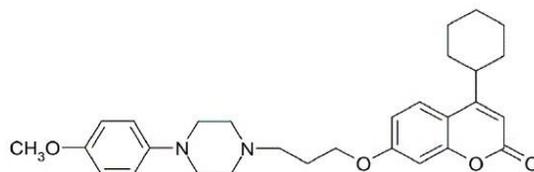
Ex. 3-substituted 7-hydroxycoumarins



X= S, NH, O

3.4 Potential Antipsychotic compounds: -

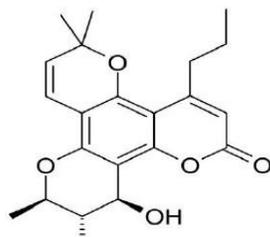
Ex. Aryl piperazine coumarin derivatives



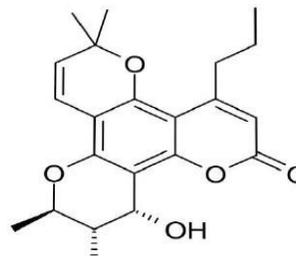
Arylpiperazinopropyloxycoumarin

3.5 Anti-HIV compounds: -

Ex.



Calanolides-A



Calanolides-B

4. EXPERIMENTAL DESIGNS: -

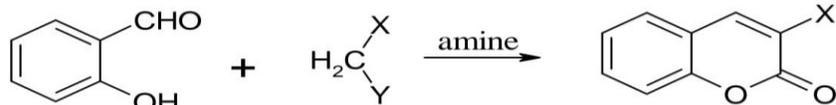
4.1 Materials and Methods: -

The chemicals area unit used as of analytical grade i.e. Resorcinol, alkyl acetoacetate, Conc. H₂SO₄, 7-hydroxy-4-methyl Coumarin, Conc. HNO₃, Benzene, Iron powder, Ethanol, Conc. HCl, Pyridine, NaOH, Dil. HCl, acetic/ maleic/ succinic/ anhydride, Glacial acid, Benzaldehyde, P-nitro-benzaldehyde, 4-bromo benzaldehyde, 3,4-dichloro benzaldehyde, Dichloroacetic chloride, anhydrous carbonate, Chloroacetyl chloride, anhydrous carbonate and dimethyl ketone etc. All the melting points were determined in open capillaries, victimization Boitus temperature instrumentality, expressed in °C. The IR spectra of the compounds were recorded on Shimadzu IR Affinity FTIR photometer victimization KBr discs and conjointly the values square measure expressed in cm⁻¹. The 1H proton magnetic resonance spectra of

compounds were recorded on Bruker Avance Ii 400 rate nucleon resonance photometer victimization acceptable solvents as an interior traditional and conjointly the values area unit expressed in δ ppm. The structures of synthesized compounds were confirmed by spectral and elemental analysis. Several manmade routes to the coumarins area unit developed. These embrace use of Pechmann, Claisen, Perkin, Knoevenagel, and Wittig reactions, to mention but several.

4.2 Knoevenagel condensation: -

The Knoevenagel reaction involves the condensation of benzaldehyde with activated methylene compounds within the presence of Associate in nursing alkane series, and is employed to beat the inherent difficulties related to the synthesis of coumarins via the Perkin reaction. So as to get coumarin instead of the standard



for the Knoevenagel reaction are less severe than those needed for the Perkin reaction.

cinnamic acid, a 2-hydroxy substituent should be gift within the aromatic aldehyde and also the conditions

$X = \text{CO}_2\text{H}, \text{CO}_2\text{Et}, \text{CONH}_2, \text{CN}.$

$Y = \text{CO}_2\text{H}, \text{CO}_2\text{Et}, \text{CN}.$

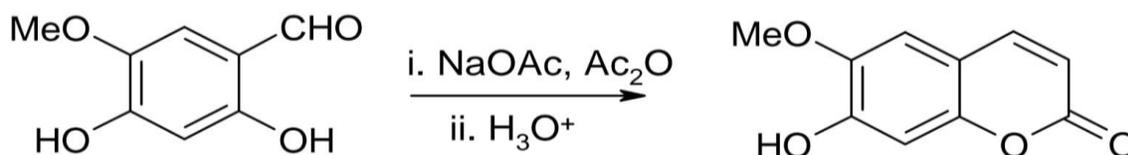
Benzaldehyde

Activated methylene

Coumarin derivatives

4.3 Perkin's reaction: -

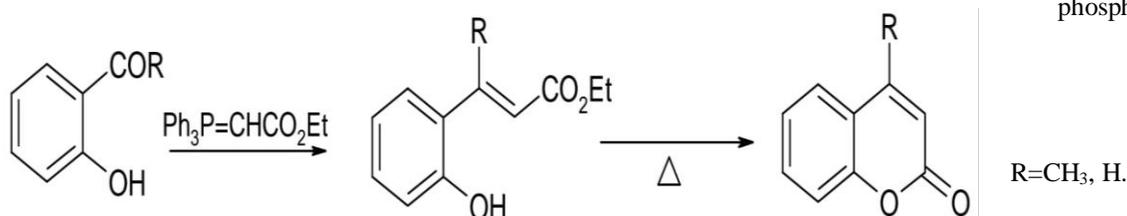
Perkin reaction, a reaction that involves heating Associate in Nursing O-hydroxybenzaldehyde with anhydride within



the presence of Na-acetate at a warmth (ca. 200°C) to afford a trans-cinnamic acid. Optimum yields of coumarins area unit obtained once a 1:2 molar quantitative relation of aldehyde to anhydride is employed. Transition of the trans-cinnamic acid by irradiation or treatment with iodine followed by cyclization affords the coumarin.

4.4 Wittig reaction: -

The synthesis of coumarins by condensing *o*-hydroxybenzaldehyde or *o*-hydroxy acetophenones with the stable phosphorane,



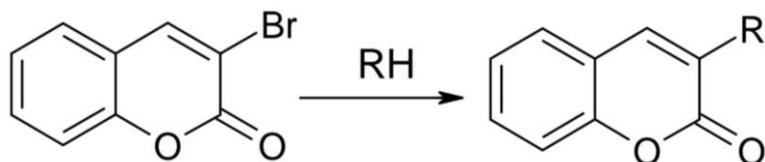
(ethoxycarbonylmethylene) - triphenyl phosphorane has been done. It is used in the synthesis of potential antipsychotic compounds containing the coumarin moiety by subjecting keto diphenols to a Wittig reaction with (ethoxy carbonyl methylene) triphenyl phosphorane to give the expected 7ethoxycoumarin in rather poor yield (24%) and 7-hydroxycoumarin in 70% yield.

4.5 Michael Reaction:-

The simplest synthetic approach to 4-arylchroman-2-ones (useful precursors for 4aryl coumarins) might be expected to involve the condensation of phenols with cinnamic acids (or alkyl cinnamates) in strongly acidic media. It is a novel, mild procedure for the synthesis of 4-arylchroman-2-ones (and 1arylbenzo-chroman-3-ones) *via* a Michael-type reaction of dihydric or trihydric phenols with *p*-substituted *N*-cinnamoyl azoles in the presence of DBU.

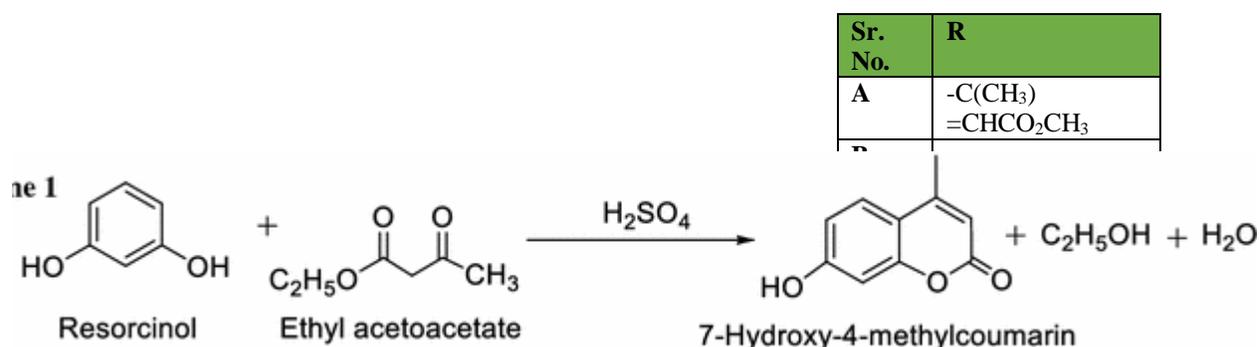
X = OCH₃, CH₃, H, F, Cl, Br, NO₂

Y =



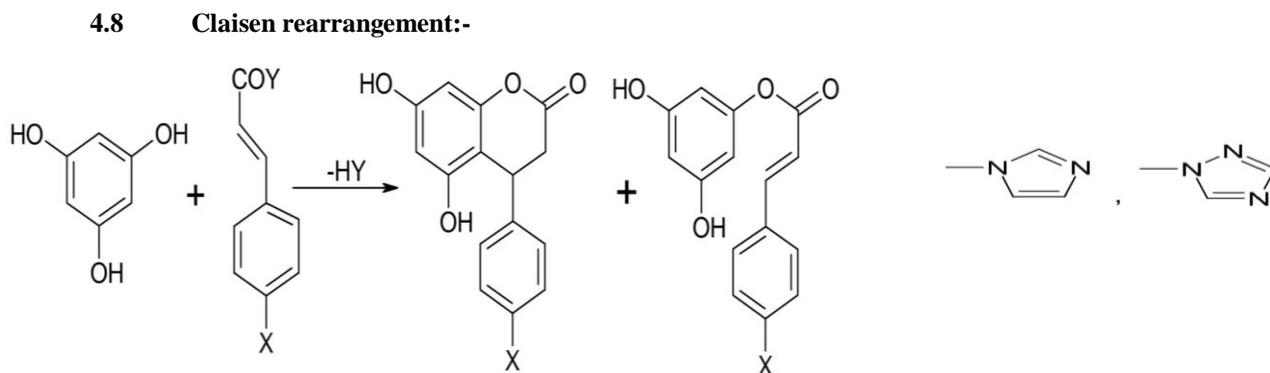
4.6 Palladium-catalyzed addition:-

Heck reaction to synthesize 3-substituted coumarins. They reported the palladium catalyzed insertion of 3-bromocoumarin into a number of alkenes and alkynes to form the 3-substituted coumarins in yields ranging from 48% to 91%.



4.7 Pechmann reaction: -

The Pechmann reaction may be a wide used methodology for getting ready coumarins in sensible yield, it involves reacting a phenol with a β -Oxo ester within the presence of a catalyst. The Pechmann reaction has been distributed victimization each homogeneous acid catalysts [such as sulphuric, hydrochloric, phosphoric and tri-fluoroacetic acids and with Lewis acids, such as zinc chloride, iron (III) chloride, tin(IV) chloride, titanium chloride and aluminium chloride] and heterogeneous catalysts [such as ion exchange resins, Nafion-H, zeolite-HBEA and alternative solid acids]. The reaction is taken into account to involve the subsequent steps: - (i) addition across the covalent bond of the enolic form of the β -keto ester; (ii) ring closure; and (iii) dehydration.



The synthesis of 3-methylenecoumarin was reported, which involves Lewis-acid catalyzed Claisen rearrangement of a α -aryloxymethylacrylate ester. A small amount of a dimer is also produced, which is assumed to form *via* an ENE reaction of the highly reactive Methylene coumarin.

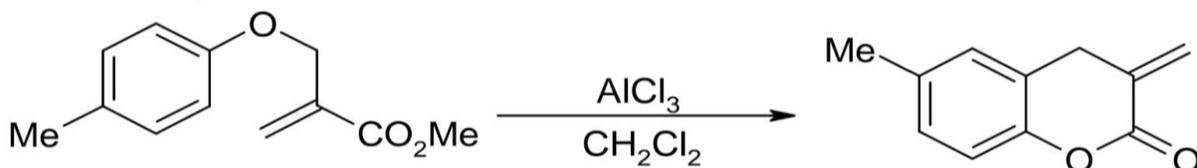
5. BIOLOGICAL EVALUATION / BIOLOGICAL ACTIVITY:

All the α -aryloxymethylacrylate ester

synthesized compounds were screened for their *in vitro* antifungal and antibacterial activity. The bactericidal activity was evaluated against 3 human pathogenic bacterial strains: *Escherichia coli* (NCIM-2256), *Bacillus subtilis* (NCIM-2063) and *Staphylococcus aureus* (NCIM-2901). The antifungal activity was evaluated against seven human pathogenic fungal strains: *Candida albicans* (NCIM-3471), *Candida glabrata* (NCYC-388), *Fusarium oxysporum* (NCIM-1332), fungus genus *fumigates* (NCIM-902), fungus genus *flavus* (NCIM-539), fungus genus *Niger* (NCIM-1196) and *Cryptococcus neoformans* (NCIM-576), that are usually encountered clinically. Antimycotic agent was used as customary drug. Minimum repressive concentration (MIC) values were determined as per CLSI tips [20–23]. Dimethyl sulfoxide (DMSO) was used as solvent management.

5.1 *In Vitro* Antifungal Activity:

Antifungal activity decided as per CLSI (formerly, NCCLS) guidelines. The synthesized compounds and also the standard drug Miconazole were dissolved in



DMSO solvent. The medium yeast nitrogen base was dissolved in phosphate buffer pH 7 and it had been autoclaved at a 110°C for 10 min. With every set a growth management while not the antifungal and solvent management DMSO were enclosed. The fungus strains were freshly sub genteil on to Sabouraud dextrose agar (SDA) and incubated at 25°C for 72 hr. The fungus cells were suspended in sterile water and diluted to urge 105 cells/mL. 10 μL of the standardized suspension was inoculated onto the management plates and also the media incorporated with the antifungal agents. The inoculated plates were incubated at 25°C for 48 hr. The readings were taken at the tip of 48 h and 72 hr. The MIC was all-time lowest concentration of drug preventing growth of macroscopically visible colonies on drug containing

plates once there was visible growth on the drug free management plates.

5.2. *In Vitro* Methylene coumarin Antibacterial Activity:-

All the synthesized compounds were screened for their *in vitro* antibacterial drug activity. Minimum Inhibitory Concentration (MIC) values were determined victimization technique counseled by National Committee for Clinical Laboratory Standards (NCCLS). *In vitro* antibacterial drug activities of the synthesized compounds were tested in Nutrient Broth (NB) for bacteria by the 2 fold serial dilution technique. Seeded broth (broth containing microbic spores) was ready in NB from 24 h recent microorganism cultures on nutrient agar (Hi-media) at $37 \pm 1^\circ\text{C}$. The bacterial suspension was adjusted with sterile saline to an amount of 1×10^4 – 10^5 C.F.U. The synthesized compounds and standard drug Ampicillin were ready by 2 fold serial dilutions to get the specified concentrations of 400, 200, 100, 50, 25, 12.5, 6.25 and 3.13 $\mu\text{g/mL}$. The tubes were incubated in BOD incubators at $37 \pm 1^\circ\text{C}$ for microorganism. The MICs were recorded by visual observations once 24 h (for bacteria) of incubation.

5.3 Anti-inflammatory activity

The compounds were tested for medicine activity by Carrageenan evoked rat paw oedema model. Inflammation was evoked by injecting 0.05 ml unit of 1% carrageenan suspension subcutaneously into the sub plantar region of the left hind paw and 0.05 ml of saline was injected into the sub plantar region of the left hind paw for all teams. Albino rats of either sex were divided into 15 teams of six animals every. 1 hr. before carrageenan injection, the teams III to XV treated with new Coumarin derivative administered 10 mg/kg, DMSO was given to group-I used as gum treated management and customary drug NSAID (5mg/kg) was administered to group-II. All the doses were administered orally. Anti-inflammatory activity was evaluated by measuring carrageenan evoked rat

paw oedema before carrageenan gum injected and once carrageenan injection of your time intervals 1st, 2nd and 3rd hour exploitation Plethysmometer. The percentage increase of paw oedema volume make up my mind 1st, 2nd and 3rd hrs. Once induction of inflammation.

5.4 Ergosterol Extraction and Quantitation

Assay:-

A single candida (NCIM-3471) colony from a nightlong Sabouraud dextrose agar plate culture was accustomed inoculate 50 mL of Sabouraud dextrose broth for management and for numerous concentrations of the molecules. The cultures were incubated for 16 h and harvested by centrifugation at 2700 revolutions per minute (856× g) for 5 min. Net weight of the cell pellet make up my mind. 3 milliliters of 25% potassium hydroxide solution answer was added to every pellet and vortex mixed for 1 min. Cell suspensions were transferred to sterile salt glass screw-cap tubes and were incubated in an 85^oC water bath for 1 hour. Following incubation, the tubes were allowed to chill. Sterols were then extracted by addition of a mix of 1 mL of sterile water 3mL of n-heptane followed by vigorous vortex commixture for 3 min. The heptane layer was transferred to a clean salt glass screw-cap tube and hold on at -20^oC. before analysis, 0.6 mL aliquot of sterol extract was diluted fivefold in 100% ethanol and scanned spectrophotometrically between 240 nm and 300 nm with a spectrophotometer (UV-Visible spectrophotometer 2100 Thermo Fischer Scientific, Waltham, MA, USA). The presence of ergosterol and therefore the late sterol intermediate 24(28) dehydroergosterol (DHE) within the extracted sample resulted during a characteristic four-peaked curve. The absence of detectable sterol alcohol in extracts was indicated by a flat line. A dose-dependent decrease within the height of the absorbance peaks was evident and corresponded to remittent ergosterol concentration.

6. TOXICITY STUDY:-

6.1 *In Vitro* Cytotoxicity Study:-

To study the safety profile and to explore the selective antimicrobial activity of the most active compounds, *in vitro* cytoxocity study was performed. This study proves that the synthesized compounds show only antimicrobial activity at their MIC values and do not kill the human cell lines indicating their safety profile and selectivity towards antimicrobial activity. *In vitro* cytotoxicity study of the synthesized compounds was performed against HeLa (Human cervical cancer cell line) by Sulforhodamine B (SRB) assay using Adriamycin as positive control.

6.2 *In Vivo* Acute Oral Toxicity Study and Behavioral Study

The *in vivo* acute oral toxicity study for the foremost active compounds was applied by the subsequent OECD guideline no. 425 victimization Swiss albino mice (18–22 gm. weight) segregated at animal house. Every cluster consists of 6 mice (overnight fasted) and kept in colony cage at 25 ± 2^oC with 55% relative humidity and 12 h of light and dark cycle. A specific dose of a 100, 250, 500, 750, 1000, 1500 and 2000 mg/kg weight of mice was administered orally as one dose. The acute noxious symptoms and therefore the behavioral changes made by the synthesized compounds were determined unceasingly for 4 hrs. Periods at 8th, 12th and 24th onset of noxious symptoms conjointly the gross behavioral changes were also recorded. These animals were maintained for any 10 days with observation created daily.

7. CONCLUSION:

A series of novel bioactive coumarin derivatives are synthesized, pure and characterized. Several routes area unit out there for the synthesis of coumarins in wonderful yields while not forming environmentally harmful waste. All of those syntheses have totally different reaction conditions. Totally different techniques like heating, microwave and ultrasound irradiation were utilized in coumarin synthesis. Additionally, varied solvents and catalysts were utilized in order to get coumarin derivatives in high yields. A number of catalysts and solvents area unit harmful and a few have green character. Throughout synthesis, it's necessary to cut back energy consumption, to avoid harmful substances and to get pure compounds in high yields. This work demonstrates an easy and economical approach to develop coumarin derivatives. The artificial approach has concerned the coupling of coumarin derivatives with totally different merchandise. Coumarin derivatives area unit essential scaffolds in healthful and artificial chemistry. Compounds of this category have shown necessary activities, like metastatic tumor and antiparasitic, besides the commercially out there medicine. These properties junction rectifier to the event of economical and greener artificial ways to attain the 2H -chromen-2-one core. Variety of innovative artificial techniques, together with the classic Pechmann, Claisen, Perkin, Knoevenagel, and Wittig reactions, are represented within the synthesis of coumarin. Coumarin derivatives area unit acknowledged for their wide range of biological activities. The world of the assembly of coumarin rings endures to grow, and also the chemical science can afford a lot of and higher ways for the synthesis of

this attractive heterocycles, willing the invention of recent drug candidates a lot of active, a lot of specific and benign.

8. ACKNOWLEDGEMENTS: -

The Authors are thankful to Principal, Dharashive V. M. for providing the laboratory facility and his persistent creative encouragement and valuable guidance throughout the research work. Also, I would like to thank my supervisor, for all his help, guidance and assistance throughout the course of the work. It has been a great pleasure and wonderful learning experience to work under his supervision.

9. CONFLICT OF INTEREST: -

The Authors declare no conflict of interest.

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