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Synthesis and Antimicrobial Study of Coumarinyl Derivatives

N. A. Kalambe[1] and N. R. Thakare[2],
Department of Chemistry, Shri Shivaji Science College,

Shivaji Nagar, Amravati. (MS) INDIA.

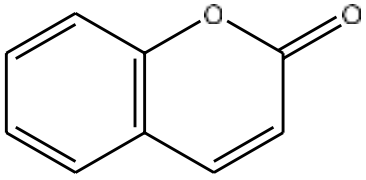
Abstract:
The Synthesis of Coumarin and Coumarinyl derivatives (Pyrazole) is done in greener way. Further their Antimicrobial study of various Coumarinyl derivatives of Compound 1-pyridoyl-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole (5a), 1-H-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole (5b), 1-carboxamido-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole (5c), 7-hydroxy-4-methyl-8-(5-phenylisoxazol-3-yl)-2H-chromen-2-one (5d), has been done with the gram negative bacteria, Salmonella typhi and Escherichia coli has been studied.

Index Term- *Coumarin, Pyrazoles,* Isoxazole *Antimicrobial study.*

INTRODUCTION

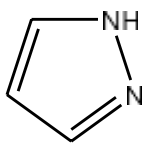
Coumarins are the best known aromatic lactones[1]. The isolation of coumarin was first reported by *Vogel*[2] in Munich in 1820. He associated the pleasant odour of the tonka bean from Guiana with that of clover, *Melilotous officinalis*, which gives rise to the characteristic aroma of new-mown hay. *Vogel* then concluded that the long colorless crystals which he discovered on slicing open tonka beans and which crystallized as glistening needles from aqueous alcohol were identical with similar crystals he obtained, albeit in much lower yield, by extracting fresh clover blossoms[3]. The name coumarin originated[4] from a Caribbean word *'coumarou'* for the tonka tree, which was known botanically at one time as *Coumarouna odorata Aubl*. Coumarin is now well accepted trivial name. The IUPAC nomenclature of the coumarin ring system is 2H-1-benzopyran-2-one. The coumarin ring system has an easy acceptability in the biological system compared to its isomeric chromones and flavones nucleus[5] and is widely distributed in nature[6-8]. An excellent account of these naturally occurring coumarins is presented by *R D H Murray* and *S A Brown*[9].

Coumarins can be synthesized by various methods such as, Pechmann, Perkin, Knoevenagel and Reformatsky reactions. Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives. This method involves the reactions between a phenol and a α-keto ester in the presence of an acid catalyst. Simple starting materials are required here to produce various substituted coumarins in good yields[10].

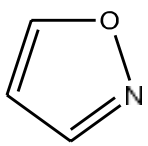


Coumarin

Pyrazole (A) is the given name to organic compounds by Knorr,[11] which is consist of a five membered ring containing adjacent nitrogen atoms. It can also be assumed as an isoxazole nucleus (B) in which -O- is replaced by –NH- group[12].



(A) Pyrazole



(B) Isoxazole

In medicine, derivatives of pyrazoles are used for:

- Analgesics
- Anti-Inflammatory Drugs
- Antipyretics
- Treating Erectile Dysfunction
- Antidiabetic (Anti-Hyperglycemic)
- Cancer Treating Medicine
- Antifungals
- Antibacterials
- Antivirals

The pyrazole ring is found within a variety of pesticides as fungicides, insecticides & herbicides, including chlorfenapyrl, fenpyroximate, fipronil, tebufenpyrad, tolfenpyrad& tralopyril.

The characterization of given synthesize compound were known. From survey of literature it was clearedthat Interferometric study of various Pyrazoles synthesized (5a-d) are not yet studied. It was therefore, thought of interest to study ultrasonic Interferrometric study of synthesized Pyrazoles (5a-d).

The Measurement of physiochemical properties such as density and ultrasonic velocity of pure components and their binary mixtures are being increasable used as tools for investigations of the properties of pure components and the nature of intermolecular interactions between the components of liquid solutions[13]. The significance reasons for the study of thermo-physical and thermodynamic properties of multi-component liquid solutions are as follows:

- They provide way for studying the physical forces acting between molecules of different species.
- The study of liquid solutions provides appearance of new phenomena, which are absent in pure liquids. The most interesting of these are the new types of phase equilibria, which are introduced by the variation in the promotion of the pure components.
- The study of thermo-physical and thermodynamic properties of liquid solutions helps in obtaining in depth knowledge about molecular interactions.

EXPERIMENTAL SECTION

O-Hydroxy acetyl coumarin (3):
4-Methyl-7-hydroxy-8-acetyl coumarin (3), m. p. 165˚C, was used as starting material which was obtained by Fries migration of 4-methyl-7-acetoxy coumarin (2) m. p. 150˚C.

7-Benzoyloxy-8-acetyl coumarin (4):
4-Methyl-7-benzoyloxy-8-acetyl coumarin (4), m. p. 198˚C, was obtained by treatment of 4-methyl-7- hydroxy-8-acetyl coumarin with benzoic acid in pyridine medium.

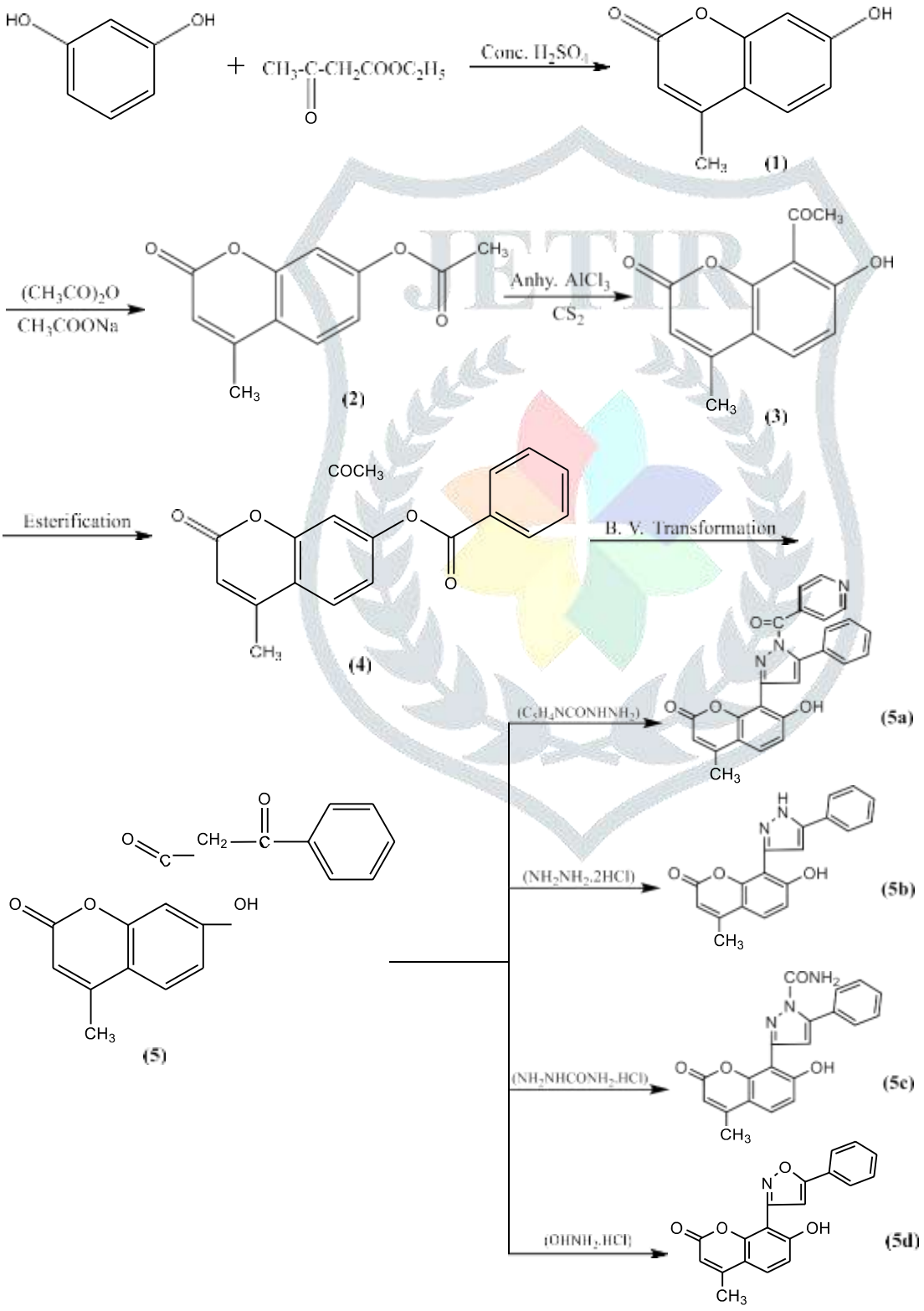
1-Coumaryl-3-phenylpropane-1,3-dione (5):
1-Coumaryl-3-phenylpropane-1,3-dione (5), m. p. 158˚C, was obtained by Baker-Venkatraman transformation of 4-methyl-7-benzoyloxy-8-acetyl coumarin.

1- Pyridoyl/H/Carboxamido-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazoles (5a-c) & Isoxazole (5d):
1-Pyridoyl/H/Carboxamido-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazoles (5a-c) &Isoxazole (5d) were synthesized on refluxing 1-coumaryl-3-phenylpropane-1,3-dione (5) with isoniazide/hydrazine dihydrochloride/semicarbazide hydrochloride/hydroxylamine hydrochloride

respectively, using pyridine as a medium for 4 hrs. Thus, following Coumarinyl pyrazoles & Isoxazole weresynthesized.

1. (5a)1-pyridoyl-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole, **m. p.** 238˚C
2. (5b) 1-H-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole, **m. p.** 275˚C
3. (5c)1-carboxamido-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole, **m. p.** 267˚C
4. (5d) 7-hydroxy-4-methyl-8-(5-phenylisoxazol-3-yl)-2H-chromen-2-one, **m. p.** 440˚C

SCHEME



The all above synthesized compounds were known and their structures are confirmed by spectralanalysis.

Antimicrobial activity

Antimicrobial activity refers to the ability of a substance to kill or inhibit the growth of microorganisms such as bacteria, fungi, viruses, or protozoa. This information is crucial in variousfields, including medicine, agriculture, and food production. Synthesis and Biological Activity of Antimicrobial Agents.[13] Synthesis of Antimicrobial Benzimidazole–Pyrazole Compounds and Their Biological Activities.[14] Antioxidant, antimicrobial, and theoretical studies of the thiosemicarbazone derivative Schiff base 2-(2-imino-1-methylimidazolidin-4-ylidene) hydrazine carbothioamide (IMHC).[15] Design, synthesis and antimycobacterial activity of hybrid molecules combining pyrazinamide with a 4-phenylthiazol-2-amine scaffold.[16] Synthesis, characterization, antimicrobial activity and DFT study of some novel Schiff bases.[17] Synthesis and antimicrobial activity of azo compounds containing drug moiety.[18] Synthesis, Characterization and Antimicrobial screening of some Azo compounds derived from Ethyl vanillin. [19]

Several methods are used to assess antimicrobial activity, including:

Disk Diffusion Method: This involves placing paper disks impregnated with a substance onto an agar plate inoculated with the microorganism of interest. The zone of inhibition around the disk indicates the extent of antimicrobial activity.

Minimum Inhibitory Concentration (MIC): This method determines the lowest concentration of a substance that inhibits visible growth of the microorganism. MIC values are important for determining the potency of antimicrobial agents. **Minimum Bactericidal (Fungicidal, Virucidal) Concentration (MBC, MFC, MVC):** This is the lowest concentration of an antimicrobial agent that kills the microorganism rather than just inhibiting its growth.

Time-Kill Kinetics: This measures the rate at which a substance kills microorganisms over time. It provides information on the speed and efficacy of antimicrobial action.

Bioassay-guided Fractionation: Used in natural product research, this method involves fractionating crude extracts and testing each fraction for antimicrobial activity to isolate and identify active compounds.

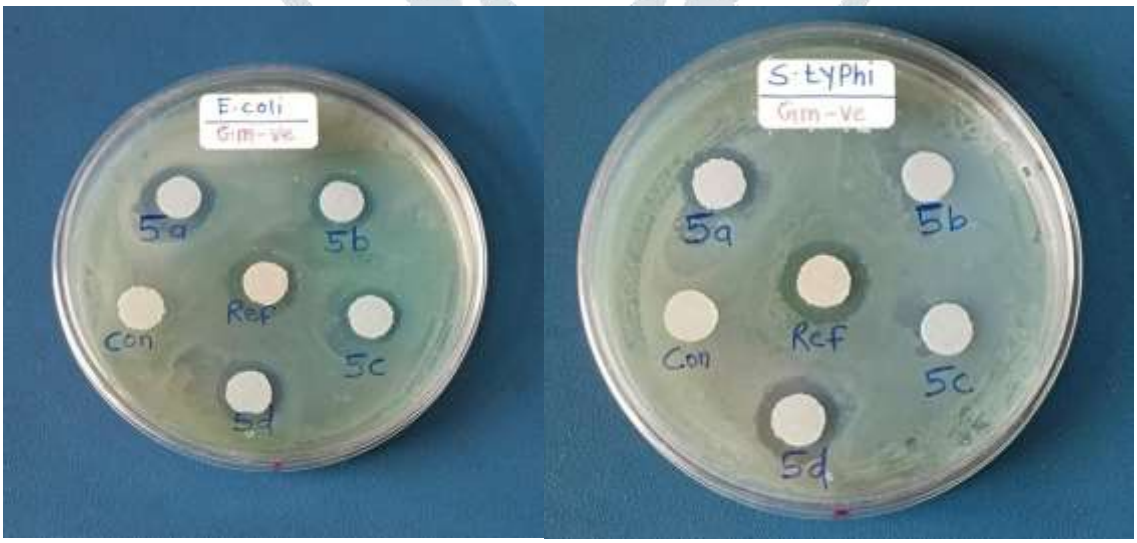
Synergism and Antagonism Studies: These assess the interaction between multiple antimicrobialagents to determine whether their combined effect is greater or lesser than the sum of their individual effects.

In vivo Studies: These involve testing the antimicrobial activity of a substance in living organisms, such as animals or humans, to assess its efficacy and safety for therapeutic use.

The results of antimicrobial activity assays are crucial for determining the potential of substancesas antimicrobial agents, guiding drug development, and informing clinical practice. Additionally,they contribute to the development of new antimicrobial strategies to combat the growing threat of antimicrobial resistance

RESULT AND DISCUSSION

Antimicrobial activity of Coumarinyl derivatives determined by using the disk diffusion methodagainst the gram negative bacterial strains. Antimicrobial activity was investigated against the various bacterial organisms included gram negative stains Escherichia coli and Salmonella typhi.In this activity Dise size is 10 MM .Whattman filter paper No 40, sterile. Solvent used is DMSO. The disc was place at the Muller Hinton Agar plates for Bacterial sensitivity standard Antibiotics used for Bacteria is OFLOXACIN (2mcg). Antimicrobial sensitivity test against bacteria after 24 hours At 37°C temperature



Observation Table

Sr. No	Test Compound Code	Antimicrobial sensitivity test against bacteria after 24 Hrs at 37^0 C temp (zone of inhibition in MM)	
		Gram –ve Bacteria	
		Salmonella typhi	Escherichia Coli
1	1-pyridoyl-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole **(5a)**	**12 mm**	**14 mm**
2	1-H-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole **(5b)**	--------	**12mm**
3	1-carboxamido-3-(4-methyl-7-hydroxy-8-coumarinyl)-5-phenylpyrazole **(5c)**	--------	**12mm**
4	7-hydroxy-4-methyl-8-(5-phenylisoxazol-3-yl)-2H-chromen-2-one **(5d)**	**12 mm**	**12mm**
5	Control	----	------
6	Reference (ofloxacin)	**14mm**	**14mm**

Conclusion

We have Successfully synthesized the coumarinyl derivatives and Antimicrobial study of various coumarinyl derivatives of compound (5a),(5b),(5c),(5d).In this we have used gram negative bacteria, Salmonella typhi and Escherichia coli from which we seen that bacterial zone is obtained.

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