EXECUTIVE SUMMARY OF THE PROJECT REPORT

U.G.C.

Minor Research Project

(2014-2016)

PROJECT TITLE

"SYNTHESIS AND PHYSICOCHEMICAL STUDIES OF 3-ACETYL COUMARINE DERIVATIVES OF MEDICINAL INTEREST"

SUBMITTED TO

UNIVERSITY GRANT COMMISSION
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UGC Minor Research Project**:**

F.NO. 47-609/13 (WRO) (2014-2016)

Name of the Principal Investigator: **Dr. G. J. Kher**

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Introduction:

Medicinal or pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacy involved with designing, synthesizing and developing pharmaceutical drugs. It deals with identification, synthesis and development of new chemical entities suitable for therapeutic use. In recent years, many researchers have been work on medicinal chemistry which involves various aromatic compounds including heterocyclic ring systems(Acetyl coumarine). Coumarine compounds are biologically active and they have a large number of applications in medicine and pharmacy.

Coumarin derivatives (CDs) are often discussed because of their diverse biological properties. CDs have attracted considerable attention from organic and medicinal chemists, as they are widely used as fragrances, pharmaceuticals and agrochemicals. Their antioxidant, bacteriostatic and anti-cancer activities make these compounds attractive for investigators for further backbone derivatization and screening as novel therapeutic agents and other foremost topics of this field of research. Some reports have emphasized the efficacies of pure coumarins against Gram-positive and Gram-negative bacteria as well as fungi. In addition CDs have been shown to inhibit cell proliferation in a cancerous cell line. Experimental investigations as well as clinical and epidemiological findings have provided evidence supporting the role of reactive oxygen metabolites or free radicals in the etiology of cancer. Certain aldehydes such as malonyldialdehyde, the end product of lipid peroxidation arising from free radical degeneration of polyunsaturated fatty acids, can cause cross-linking in lipids, proteins and nucleic acids leading to cellular damage. The human body is equipped with certain enzymatic and non-

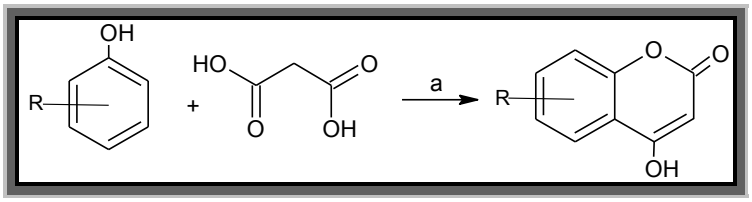
enzymatic antioxidants which can counteract the deleterious actions of free radicals and radical-induced cellular and molecular.

Taking in view of the applicability of coumarine compounds, the present work was undertaken to synthesize some new 3-Acetyl coumarine derivatives.

The detailed summary of project is as bellow.

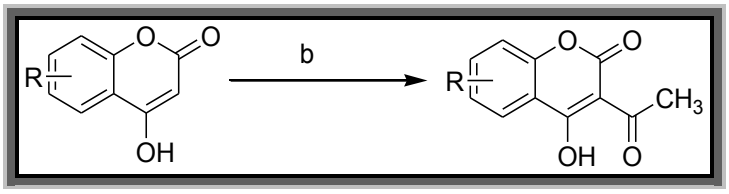
➢ Synthesis and characterization of 3-Acetyl-4-Hydroxy Coumarine Derivatives

❖ Step-1: Synthesis of **4-Hydroxy Coumarine** is given bellow**:**



Reagents / Reaction Condition (A): Anhydrous $ZnCl_2$, $POCl_3$ / 70°C, 36 hours.

❖ Step-2: Synthesis **of 3-Acetyl-4-Hydroxy Coumarine**



Reagents / Reaction Condition (b) : POCl3, Glacial acetic acid / Reflux, 2-3 hrs.

Ten Derivatives were prepared are as follow.

- ❖ 3-acetyl-4-hydroxy-2H-chromen-2-one (GK-01)
- ❖ 3-acetyl-6-chloro-4-hydroxy-2H-chromen-2-one (GK-02)
- ❖ 3-acetyl-7-chloro-4-hydroxy-2H-chromen-2-one (GK-03)
- ❖ 3-acetyl-4-hydroxy-6-methyl-2H-chromen-2-one (GK-04)
- ❖ 3-acetyl-6-fluoro-4-hydroxy-2H-chromen-2-one9 GK-05)
- ❖ 3-acetyl-7-fluoro-4-hydroxy-2H-chromen-2-one (GK-06)
- ❖ 3-acetyl-4-hydroxy-6-nitro-2H-chromen-2-one (GK-07)
- ❖ 3-acetyl-6-bromo-4-hydroxy-2H-chromen-2-one (GK-08)
- ❖ 3-acetyl-7-Bromo-4-hydroxy-2H-chromen-2-one (GK-09)
- ❖ 3-acetyl-4,7-dihydroxy-2H-chromen-2-one (GK-10)

All the derivatives were characterized by elemental analysis, Infrared, ^{1}H NMR and Mass spectroscopy. In addition to this thermo gravimetric and DSC study were performed for compound 3-acetyl-4-hydroxy-2H-chromen-2-one.

➢ Synthesis and physicochemical studies :

❖ Section-I : Acoustical properties:

- **Density and Sound velocity measurements:**

The densities and ultrasonic velocities of pure solvents and solutions of studied compounds of different concentrations (0.01M to 0.10M) were measured at different temperatures (298.15 - 318.15 K).

- **Viscosity measurement:**

Ubbelohde viscometer was of 25 ml capacity was used for the measurement of viscosity. The pore size of capillary of viscometer was 0.5 mm. The measured quantity of the distilled water/solvent/solution was placed in the viscometer, which was suspended in a thermostat at 298.15 K to 318.15 K. Using the flow times (t) and known viscosity of water, the viscosity of solvents and solutions were determined.

Overall, in all the studied solutions both compound-solvent and compound-compound interactions exist. However, most of the acoustic and apparent properties indicate predominance of compound-solvent interactions.

❖ Section-II : Density and Refractive index:

The density and refractive index of solutions were measured by using pyknometer and Abbe refractometer respectively. Study of refractive index and density was completed at constant temperature viz. 303.15 K, which is maintained by circulating water through jacket around the prisms of refracto meter from an electronically controlled thermostatic water bath.

In every solution molecular interactions exist which differ with different solvents. This is further confirmed by acoustical parameter which is already discussed. Generally, intermolecular interactions do not affect the density but due to the presence of different substituted groups in solutes, interactions differ in different solvents which may cause change in volume thereby affecting the density of solute in a particular solvent. Each solvent interacts differently with different functional groups, so that refractive index of compounds is different in each solvent.

❖ Section – III: Conductance :

In present work, conductance of 3-acetyl-4-hydroxycoumarin derivatives in different solutions have measured by using N, N-dimethylformamide and DMSO as a solvent at 303.15 K. Conductivities of all studied compounds are observed to be less in DMF than those in DMSO. Further, for all the systems studied, conductance increases with concentration. There is sharp

increase in conductance with concentration. However, at higher concentration, the values increase very slowly.

- **Section – IV: Solubility:**

In the present Study solubility of 3-acetyl 4- hydroxy coumarin derivatives Compounds have been done in methanol, ethanol and chloroform at various temperatures (293.15 to 313.15 K). It is obvious from the data that there is an increase in solubility with temperature for all the compounds in the studied solvents. Comparison between the experimental solubility and calculated solubility (x_{ci}) has been made which gives similar behavior as reported in literature.

- **Section –V: Thermal Properties:**

In the present section, thermal properties of 3-acetyl-4-hydroxycoumarins have been studied by TGA and DSC methods. The thermal stability cannot be decided by weight loss for 3-acetyl-4-hydroxy-2H-chromen-2-one, because degradation is multi step process (From TGA Graph). Further, the variation in the trend of thermal decomposition might be interpreted by taking into account some interactions (structural as well as electronic) and also because of several experimental factors. For multi step degradation compounds, in first and second steps, energy of activation is found to be maximum for 3-acetyl-4-hydroxy-2H-chromen-2-one in second step. Weight loss continuously decreases by increase the temperature. This suggests that position of functional groups also affect the stability. Further, From DSC we knew that melting points of the compounds are determined along with melting points determined by open capillary method. And check agreement between the values evaluated from DSC and those determined by open capillary method.

- **Section –VI : Dissociation Constants :**

In the present section the dissociation constant of 3-Acetyl 4-hydroxy Coumarin have studied in dimethyl formamide – water system at 303.15K. The titration curves obtained in the above two titrations are designated as the acid titration curve and ligand or reagent titration curve respectively. Comparison of pK_1^H values of all compounds shows that, 3-acetyl-7-chloro-4-hydroxy-2H-chromen-2-one is more acidic which contains 6-chloro group. However, From these results, it is concluded that different compounds exhibit different dissociation constant which also depends upon the type and position of substituent groups. This is due to inductive or mesomeric effect of functional groups.

➢ Biological Activities:

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.

The inhibition depends upon three S: strain, solvent and structure. All the compounds have the same central moiety but different functional groups. So, presence of different functional groups affects inhibition in the studied compounds. GK02, GK05, GK06 and GK10 show good result against Gram-positive bacteria Staphylococcus aureus contains hydroxy group as well as Flouro group which is most effective in comparison to other groups. While compounds GK04 and GK09 show good result against Gram-negative bacteria Pseudomonas aeruginosa.