SYNTHESIS,CHARACTERIZATION,DOCKING, BIOLOGICAL EVALUATION AND APPLICATION OF COUMARIN DERIVATIVES

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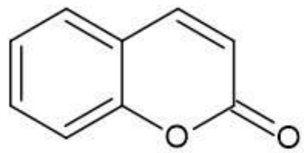
ABSTRACT:

Coumarins are part of the benzopyrone family, consisting of a benzene ring and a pyrone ring. They are primarily found in the benzo-alfa-pyrones and benzo-gama-pyrones, with flavonoids being the principal members. The most common coumarins are umbelliferone, esculetin, and scopoletin. Synthesis of these compounds involves ortho-hydroxylation on p-coumaric, caffeic, and ferulic acid. Coumarins are highly valuable due to their pharmacological properties, including physiological, bacteriostatic, and anti-tumor activity.
Coumarin derivatives have garnered significant attention due to their broad spectrum of biological activities and synthetic versatility. In this study, a series of novel coumarin-based compounds were synthesized via a multi-step reaction pathway involving Pechmann condensation and subsequent functionalization. The synthesized compounds were thoroughly characterized using spectral techniques including FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry to confirm their structures and purity.

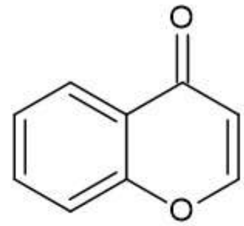
KEYWORDS: Synthesis, characterization, docking, biological evalution.

INTRODUCTION:

Coumarins, also known as benzopyrones, are a class of cinnamic acidderived phenolic compounds found in fungi, bacteria, and various plant species, especially edible, medicinal, and spice plants from different botanical families [1]. These secondary plant metabolites consist of fused benzene and α-pyrone rings and occur in different plant parts such as roots, seeds, nuts, flowers, and fruits, either in free form or as heterosides(2) . The name "coumarin" originates from "cumaru," the local name for the Brazilian teak plant (Dipteryx odorata Wild.) from the Fabaceae family, used in traditional medicine in the Brazilian Amazon rainforest. Dipteryx odorata, an endemic plant of Central and South America, was the first known natural source of coumarin, which was isolated by Vogel in 1820 . Its seeds, known as tonka beans, are widely used in the perfume industry as a vanilla substitute, particularly as a fixative and enhancing agent in fragrances. Additionally, coumarin is found in various consumer products, including toilet soap, detergents, toothpaste, tobacco, and alcoholic beverages . (3)



Alpha-Benzo pyrone



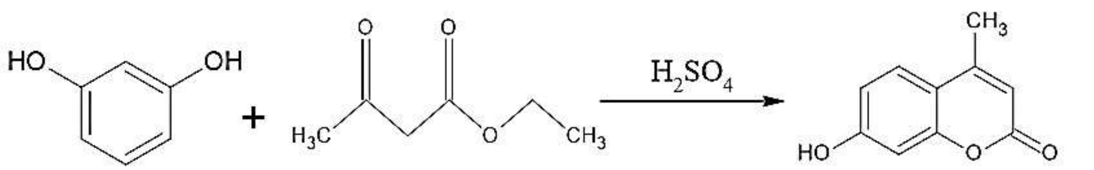
Gamma-Benzo pyrone

SYNTHESIS:

SYNTHESIS OF 7-HYDROXY-4-METHYL COUMARIN :

PROCEDURE :

- About 150 ml. of conc. H_2SO_4 in a 500 ml beaker was stirred with external ice water cooling until the temperature of acid become about 5 ^{0}C – 10^{0}C.
- 37 gm of powdered resorcinol was added to 45 ml. of ethyl acetoacetate until a complete solution was obtained.
- Then this solution was added slowly to H_2SO_4. In such a way that the temperature does not rise above 100C and the stirring was continued for ½ an hour.
- The mixture is poured into the ice/cold water & the solid product is separated, filtered out and dried. Then the crude product was recrystallized from ethan.



Resorcinol Ethyl acetoacetate 7-Hydroxy-4-methyl Coumarin

Yield : 85 %

Melting Point : 192 ^{0}C

Solublity :

Methanol,

Ethanol,

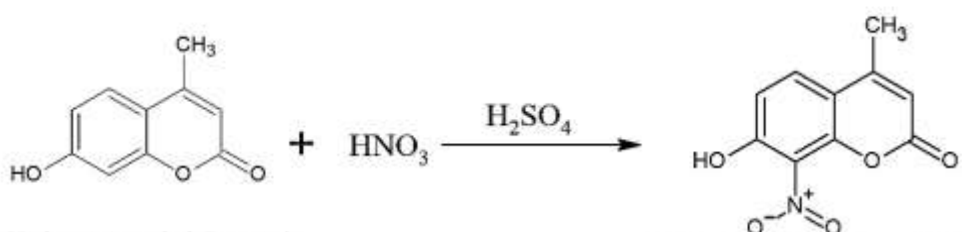
Pyridine,

H_2SO_4 etc.

SYNTHESIS OF 8-NITRO-7-HYDROXY-4-METHYL

PROCEDURE

- In a conical flask 7-hydroxy-4-methyl Coumarin (12 gm) was dissolved in conc. H2SO4 acid (100 ml.) and then keep the flask in an ice bath.
- When the temperature inside the flask is below 10C, 20 ml of nitrating mixture (5ml of concentrated nitric acid and 15 ml of concentrated sulphuric acid) taking care that the temperature does not rise above 10 ^{0}C.
- After the addition was completed, removed the flask from the ice bath and keep it at room temperature for an hour.
- The flask shaked occasionally during this period and then poured with stirring in a beaker containing crushed ice.
- The crude product filtered which is a mixture of 6 and 8 nitro derivatives and washed with cold water.
- Transfer the crude mixture in a conical flask containing ethanol and boiled.
- Concentrated the filtrate, and cooled in an ice bath, 8-nitro derivative soon crystallized out. The crude product filtered which is a mixture of 6 and 8 nitro derivatives and washed with Cold waterTransfer the crude mixture in a conical flask containing ethanol and boiled.
- Concentrated the filtrate, and cooled in an ice bath, 8-nitro derivative soon crystallized out.
- Recrystallized from ethanol and collect 8-nitro-4-methyl-7-hydroxy coumarin



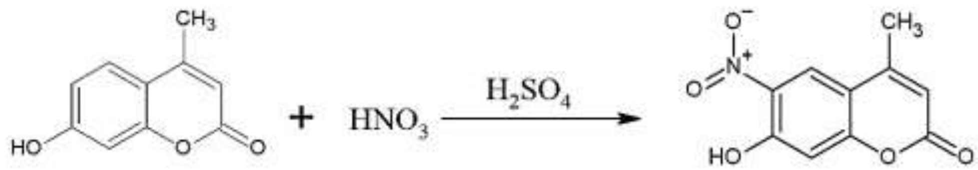
7-Hydroxy-4-methyl Coumarin   8-Nitro 7-Hydroxy-4-methyl Coumarin

SYNTHESIS OF 6-NITRO-7-HYDROXY-4-METHYL COUMARIN :

PROCEDURE :

- In a conical flask 7-hydroxy-4-methyl Coumarin (12 gm) was dissolved in conc. H_2SO_4 acid (100 ml.) and then keep the flask in an ice bath.
- When the temperature inside the flask is below 10C, 20 ml of nitrating mixture (5ml of concentrated nitric acid and 15 ml of concentrated sulphuric acid) taking care that the temperature does not rise above 10 ^{0}C.
- After the addition was completed, removed the flask from the ice bath and keep it at room temperature for an hour.
- The flask shaked occasionally during this period and then poured with stirring in a beaker containing crushed ice.

- The crude product filtered which is a mixture of 6 and 8 nitro derivatives and washed with cold water.
- Transfer the crude mixture in a conical flask containing ethanol and boiled.
- The residue 6-nitro-4-methyl-7- hydroxy coumarin is filtered and dried.

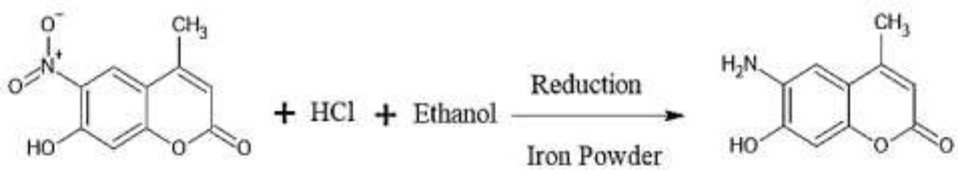


7-Hydroxy-4-methyl Coumarin 6-Nitro 7-Hydroxy-4-methyl Coumarin

SYNTHESIS OF 6-AMINO-7-HYDROXY-4-METHYL COUMARIN :

PROCEDURE:

- Iron powder (8 gm) was added portion wise with stirring to a hot mixture of 6nitro-7-hydroxy-4- methyl Coumarin (4.4 gm, 0.02 moles) in ethyl alcohol (20 ml) and concentrated hydrochloric acid (30 ml) at reflux temperature.
- After completion of the addition, the refluxing was continued for 6 hours. Upon cooling a Black precipitate formed, which was filtered off, washed with water, dried and recrystallized



6-Nitro 7-Hydroxy-4-methyl Coumarin 6-Amino 7-Hydroxy-4-methyl Coumarin

Yield : 50 %

Melting Point : 280 ^{0}C

Solublity :

Pyridine,

10% aq NaOH,

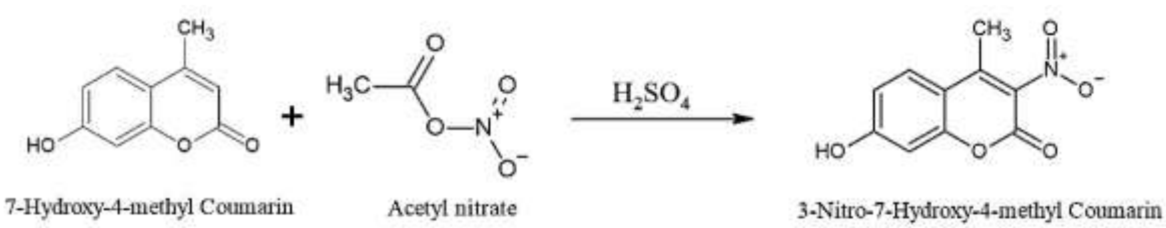
DMF,

DMSO etc.

SYNTHESIS OF 3-NITRO-7-HYDROXY-4-METHYL COUMARIN :

PROCEDURE :

- In a conical flask 7-hydroxy-4-methyl Coumarin (12 gm) was dissolved in conc. H2SO4 acid (100 ml.) and then keep the flask in an ice bath.
- When the temperature inside the flask is below 10C, 20 ml of nitrating mixture (5ml of acetyl nitrate and 15 ml of concentrated sulphuric acid) taking care that the temperature does not rise above 10 ^{0}C.
- After the addition was completed, removed the flask from the ice bath and keep it at room temperature for an hour.
- The flask shaked occasionally during this period and then poured with stirring in a beaker containing crushed ice.
- The crude product filtered which is a mixture of 6 and 8 nitro derivatives and washed with cold water.
- Transfer the crude mixture in a conical flask containing ethanol and boiled.
- The residue 3-nitro-4-methyl-7- hydroxy coumarin is filtered and dried.



Yield : 42 %

Melting Point : 125 ^{0}C

Solublity : Ethanol,

Methanol.

DOCKING:

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex[4].

Information gained from the preferred orientation of bound molecules may be employed to predict the energy profiling (such as binding free energy), strength and stability (like binding affinity and binding constant) of complexes. This can be done using scoring function of molecular docking. Now days, molecular docking is often utilized to forecast the binding orientation of small molecules (drug candidates) to their biomolecular target (such as protein carbohydrate and nucleic acid) with the aim to determine their tentative binding parameters. This establishes raw data for the rational drug designing (structure based-drug development) of new agents with better efficacy and more specificity [5].

The main objective of molecular docking is to attain an optimized docked conformer of both the interacting molecules in furtherance of achieving lessen free energy of the whole system. Final predicted binding free energy (ΔGbind) is modeled in terms of dispersion & repulsion (ΔGvdw), hydrogen bond (ΔGhbond), desolvation (ΔGdesolv), electrostatic (ΔGelec), torsional free energy (ΔGtor), final total internal energy (ΔGtotal) and unbound system's energy (ΔGunb). Therefore, detailed understanding of the general principles that govern predicted binding free energy (ΔGbind)provides auxiliary information about the nature of various kinds of interactions driving the docking of molecules [6].

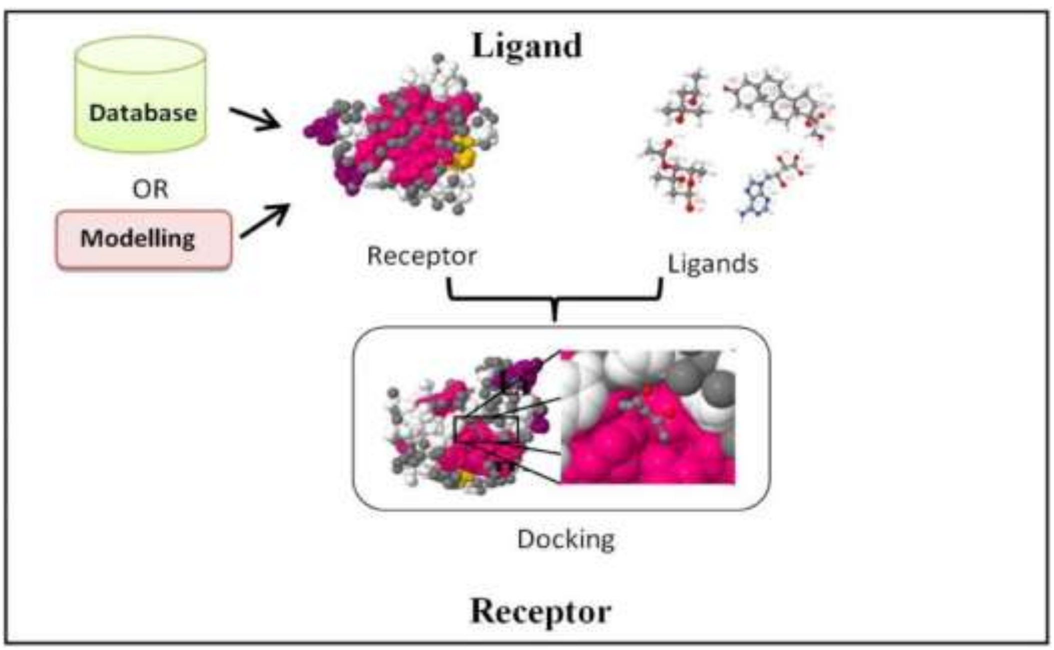


Figure 1

DOCKING FOR ANTIFUNGAL ACTIVITY

TARGET PROTEIN (1) : Candida Albicans Dihydrofolate reductase

PROTEIN ID : 1AI9

Dihydrofolate reductase (DHFR) is a crucial enzyme in Candida albicans, a pathogenic fungus responsible for opportunistic infections in humans. Here's some detailed information: Dihydrofolate Reductase (DHFR) in Candida albicans

FUNCTION :

DHFR is an essential enzyme involved in the folate biosynthesis pathway.
It catalyzes the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF) using NADPH as a cofactor. THF is necessary for DNA synthesis, repair, and methylation processes. Inhibition of DHFR disrupts thymidylate and purine synthesis, ultimately affecting fungal growth and survival.

STRUCTURE & CHARACTERISTICS :

C. albicans DHFR is structurally similar to human DHFR but has distinct differences that make it a potential antifungal target. It consists of a single polypeptide chain with an active site that binds dihydrofolate and NADPH. The enzyme has conserved amino acid residues essential for its catalytic function.

CLINICAL RELEVANCE & ANTIFUNGAL TARGETING :

DHFR is a key target for antifungal drugs, particularly antifolates. Trimethoprim and methotrexate inhibit DHFR but are more selective for bacterial and human enzymes, respectively. Pyrimethamine and some experimental antifolates have been studied for their potential antifungal activity against C. albicans. Targeting C. albicans DHFR selectively (without affecting human DHFR) is an ongoing challenge in antifungal drug development.

RESEARCH & DRUG DEVELOPMENT :

Structural studies (via X-ray crystallography and computational modeling) help design selective DHFR inhibitors. DHFR inhibitors are explored in combination therapy with other antifungals like fluconazole to enhance efficacy.

MOLECULAR INTERACTION OF SYNTHESIZED COMPOUNDS WITH TARGET PROTEIN DIHYDROFOLATE REDUCTASE OF CANDIDA ALBICANS(1AI9) :

S. No	CODE	H-BOND INTERACTION	H-BOND DISTANCE(A)	AUTODOCK SCORE
1	C1	LYS B:57 ARG B:56	1.87 2.98	-7.18
2	C2	GLU A:107 VAL A:109 ALA A:7	2.54 2.62 2.88	-6.52
3	C3	LYS A:14 ALA A:16	2.14 2.23	-5.06
4	C4	LYS A:31 TYR A:186 VAL A:172	2.83 2.12 2.06	-5.71
5	C5	VAL A:109 HIS A:129	2.80 3.09	-6.9

Table 1

S.NO	CODE	LIGAND EFFICIANCY	INHIBITORY CONSTANT	Vdw SOLVED ENERGY	BINDING ENERGY
1	C1	-0.45	5.45	-7.78	-7.18
2	C2	-0.43	16.53	-7.12	-6.52
3	C3	-0.32	194.41	-5.67	-5.06
4	C4	-0.44	65.38	-6.01	-5.71
5	C5	-0.43	8.82	-7.49	-6.9

Table 2

Based on binding energy of the docked compounds, we conclude that the compound C1 is more potent among all the synthesized compounds

Binding mode of compound C1in the active site of DIHYDROFOLATE REDUCTASE along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C1

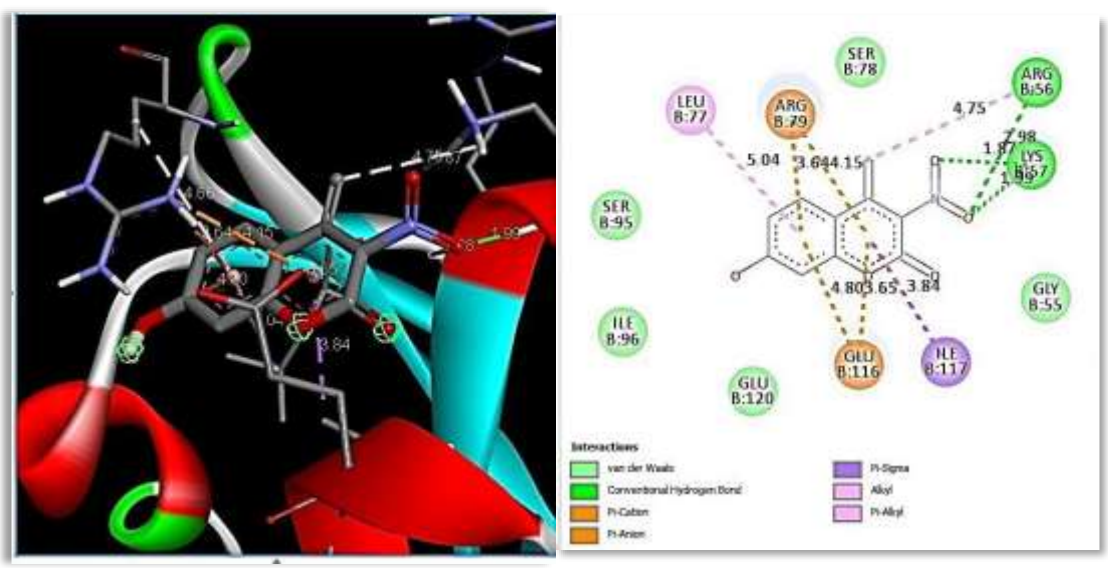


Figure 2

Binding mode of compound C2 in the active site of DIHYDROFOLATE REDUCTASE along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C2

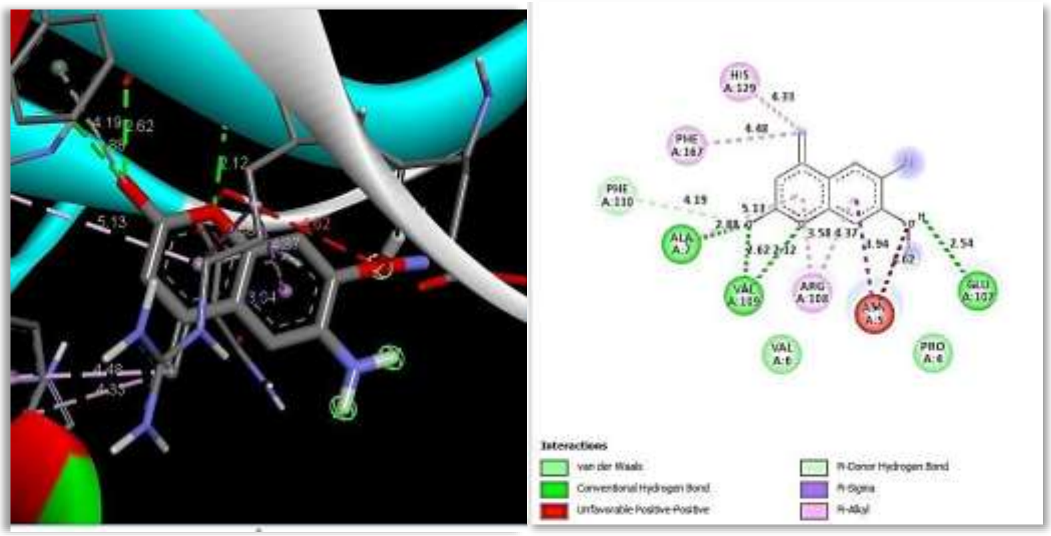


Figure 3

Binding mode of compound C3 in the active site of DIHYDROFOLATE REDUCTASE along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C3

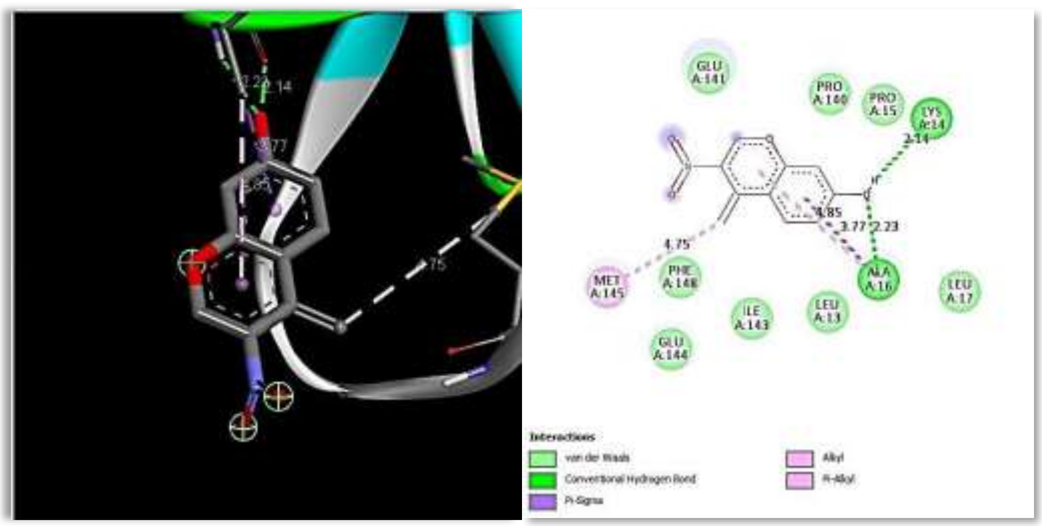


Figure 4

Binding mode of compound C4 in the active site of DIHYDROFOLATE REDUCTASE along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C4

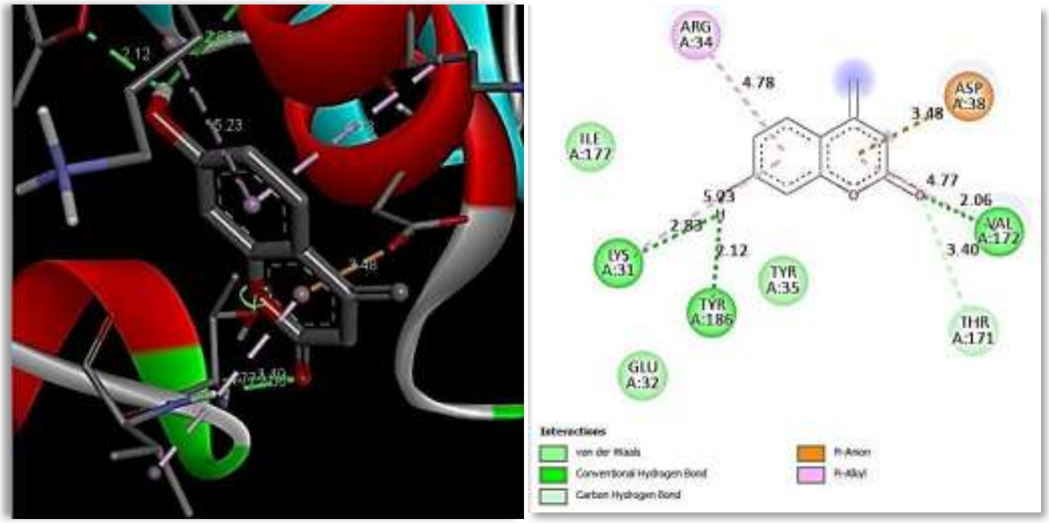


Figure 5

Binding mode of compound C5 in the active site of DIHYDROFOLATE REDUCTASE along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C5

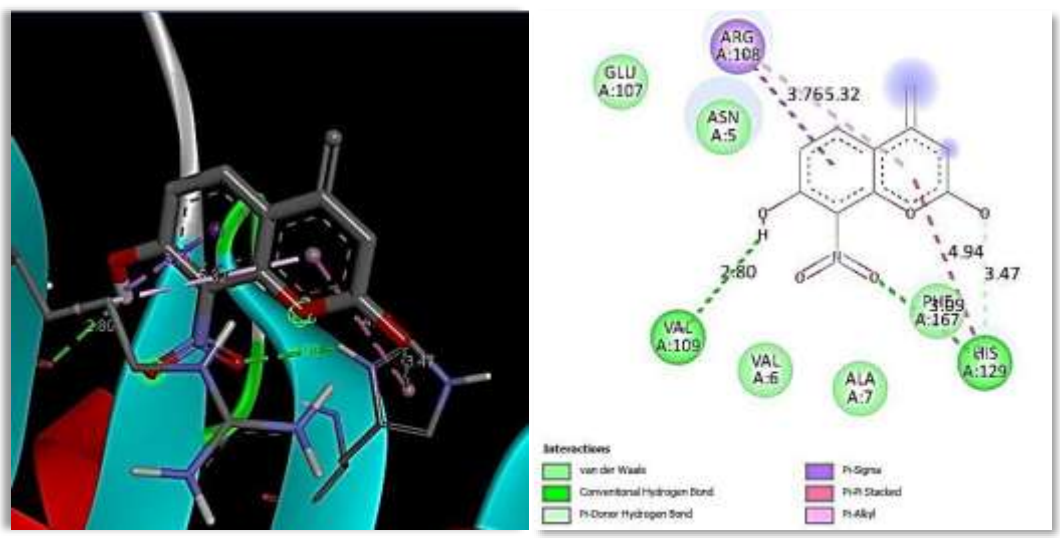


Figure 6

DOCKING FOR ANTHILMINNTIC ACTIVITY

DOCKIING WITH 3VR9 (TARGET PROTEIN) :

Information about the protein :

Rhodoquinol-fumarate reductase is a key enzyme in the anaerobic respiratory chain of adult A.*suum* mitochondria[76].

In Ascaris suum, fumarate reductase plays a crucial role in anaerobic energy metabolism by converting fumarate to succinate within the mitochondrial membrane, functioning as a reversed succinate dehydrogenase.

Catalytic activity, This enzyme, also known as NADH-fumarate reductase, catalyzes the reduction of fumarate to succinate.

The unique nature of the mitochondrial NADH-fumarate reductase system in Ascaris suum has made it target for anthelmintic drug development. Inhibitinng this enzyme can impair the parsiste's anaerobic energy metabolism, leading to its death.

MOLECULAR INTERACTION OF SYNTHESIZED COMPOUNDS WITH TARGET PROTEIN (3VR9) :

S. No	CODE	H-BOND INTERACTION	H-BOND DISTANCE(A)	AUTODOCK SCORE
1	C1	SER A:437 ALA A:435	2.99 3.45	-7.53
2	C2	HIS A:79 LEU A:438 SER A:437 GLY A:86	2.82 2.43 2.85 2.26	-6.53
3	C3	THR A:71 SER A:78	2.40 2.70	-7.82
4	C4	THR A:328 VAL A:386 THR A:385	2.32 2.28 3.55	-6.19
5	C5	ASN A:565 LYS A:605	1.92 2.31	-5.79

Table 3

S.NO	CODE	LIGAND EFFICIANCY	INHIBITORY CONSTANT	Vdw SOLVED ENERGY	BINDING ENERGY
1	C1	-0.47	3.01	-8.13	-7.53
2	C2	-0.47	16.24	-7.13	-6.53
3	C3	-0.49	1.86	-8.41	-7.82
4	C4	-0.48	29.09	-6.49	-6.19
5	C5	-0.36	56.09	-6.39	-5.79

Table 4

Binding mode of compound C1 in the active site of 3VR9 along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C1

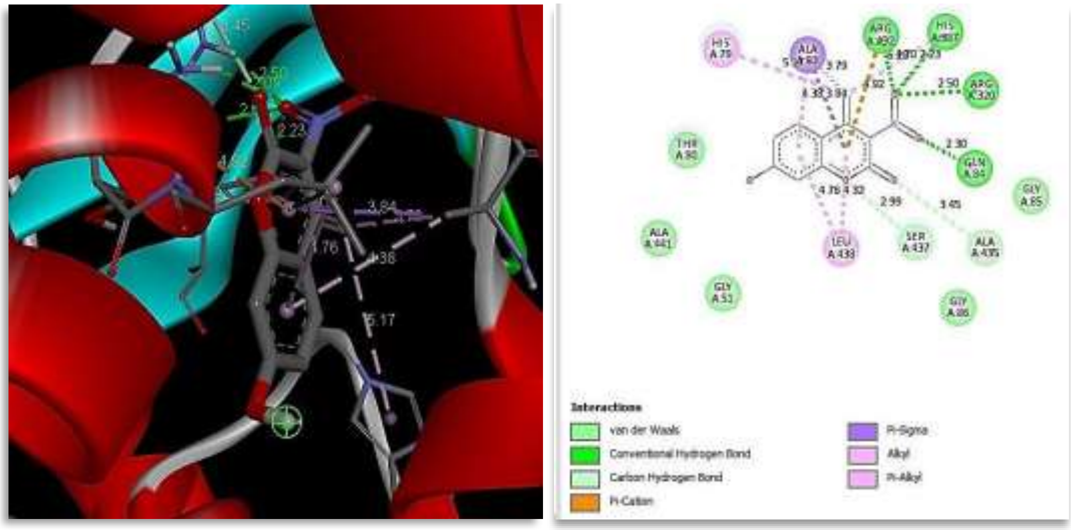


Figure 7

Binding mode of compound C2 in the active site of 3VR9 along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C2

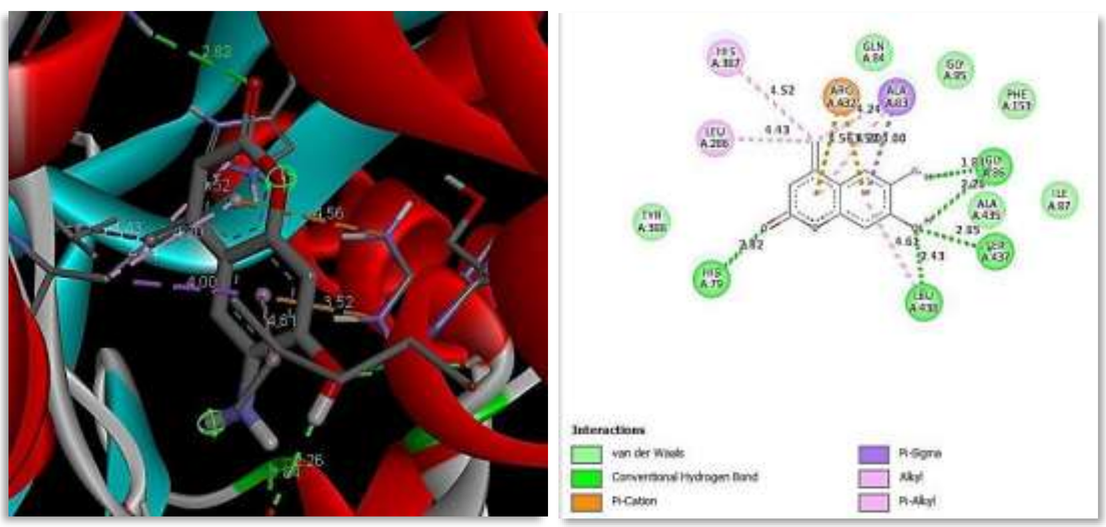


Figure 8

Binding mode of compound C3 in the active site of 3VR9 along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C3

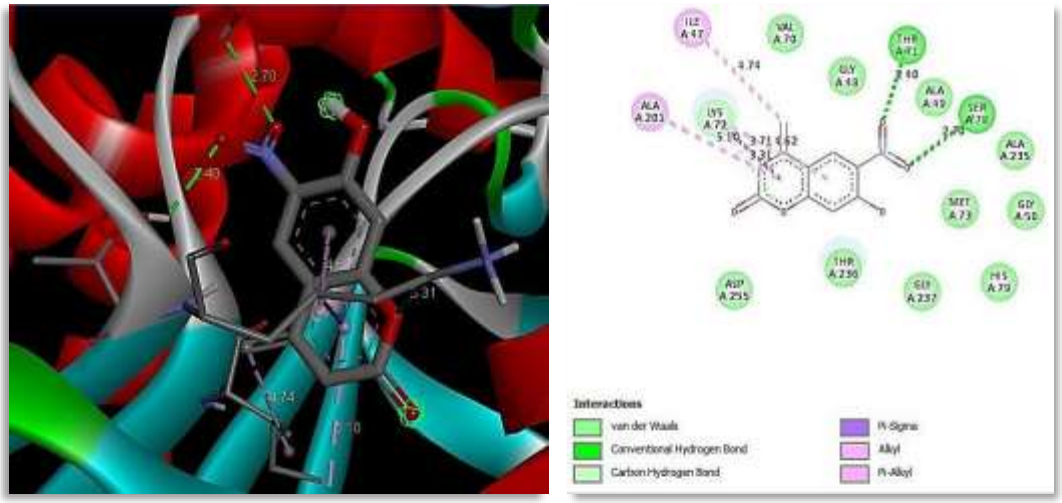


Figure 9

Binding mode of compound C4 in the active site of 3VR9 along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C4

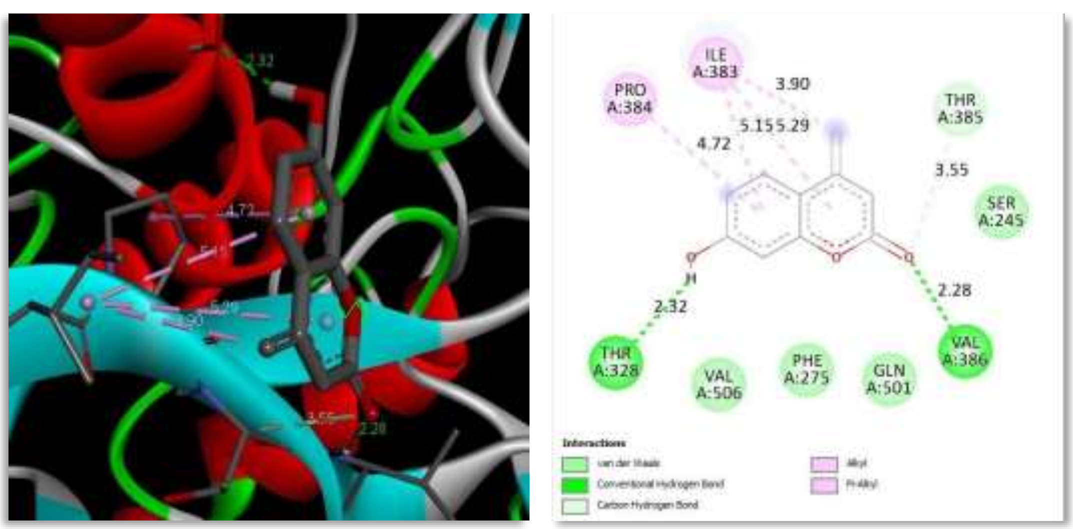


Figure 10

Binding mode of compound C5 in the active site of 3VR9 along with interacting amino acid viewed through biovia discovery studio software.

COMPOUND C5

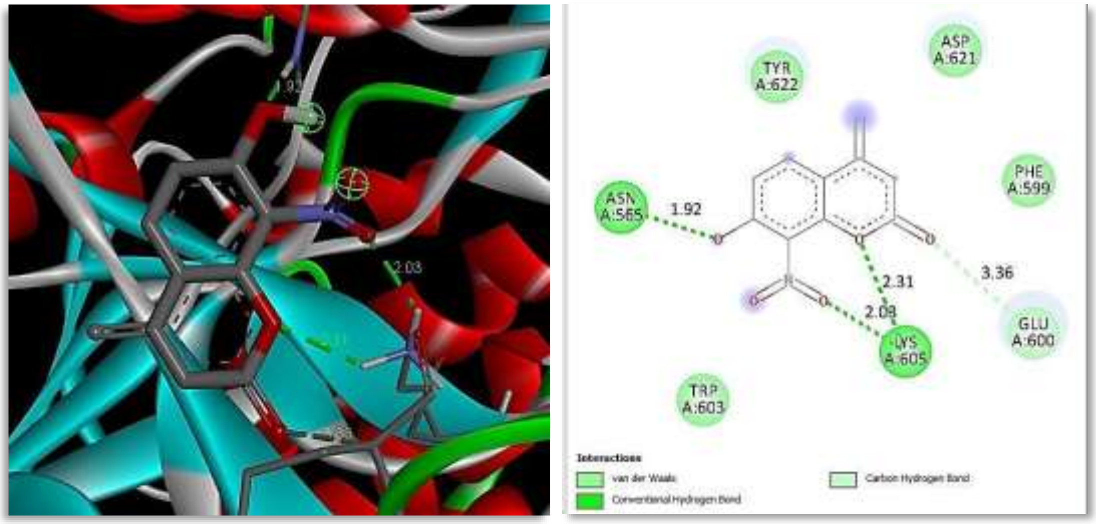


Figure 11

EVALUATION OF ANTHELMINTIC ACTIVITY OF THE SYNTHESIZED COMPOUNDS INTRODUCTION :

Anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths. The anthelmintic drugs show their effects on the human body and their regular activities by causing helminthiasis which is a very severe parasitic disease. Mostly population and the livestock parasites produce the resistance against the helminths parasites which causes morbidity and mortality. This revive deals with the activities of the anthelmintic drugs on the different types of species on human body also. The prevalence of parasitics worms, anthelmintic drug discovery is more important in the pharmaceutical industry. When the efficacy of available anthelmintic drugs produces the better results over the discovery of new drugs it is hindered by the lack of high-throughput screening methods and drug effect is assessed by observing motility or mortality of parasites using laborious, subjective and low-throughput by using the different genes and mutants. The purpose of review is to focus on drugs which are used in human and verterinary medicine to treat parasitic nematode infection.

Figure 12

Anthelmintics are drugs used for the treatment of infections caused by the worms , flukes, nematodes, round worm, tapeworms.

ANTHELMINTICS DRUGS:

Helminthes infections are the most common infections in man which affects the large proportions of the world's population, In the treatment of paracitic diseses, the anthelmintics drugs are used indiscriminately. Various plants were used in veneral disease, to promote healing of wounds, swelling, abscesses, rheumatism and trating pain in lower extremities, skin disease, leucorrhoea, dysentery, dysuria and fever [73,74].Natural anthelmintic includes the following list of compounds :

- Tobacco
- Walnut
- Wormwood
- Clove
- Kalonji seeds
- Garlic
- Pineapple
- Soya and other legumes
- Malefern
- Honey ,water and vinegar are mixed with warm water act as vermifuges

SYNTHETIC DRUGS :

- Diethylcarbamazine
- Albendazole
- Ivermectin
- Praziquantel
- Mebendazole
- Levamisole

ANTHELMINTIC ACTIVITY :

Species used	:	*Pheretima posthuma*
Standard used	:	ALBENDAZOLE
Control	:	Water
Test concentration	:	100 mg/ml
Method	:	Mathew *et al*

PROCEDURE :

The anthelmintic activity was evaluated on adult Indian earthworm Pheretima posthuma due to its anatomical resemblance with intestinal roundworm parasites of human beings. The activity was carried out using Mathew et al method. Six groups of earthworms each containing two earthworms approximately of equal size was uses for the study. Each group was treated with vehicle, synthesized compounds and albendazole.

Observations were made for the time taken for paralysis and death of individual worms.

Paralysis was said to occur when the worms do not revivie even in normal saline. Death was concluded when the worms lost their motility followed with fading of their body colour.

Code	Paralysis		Death	
	50 mg/ml	100 mg/ml	50 mg/ml	100 mg/ml
STD	2.5 min	1.4 min	17.1 min	11.5 min
C1	4.0 min	2.1 min	23.2 min	17.3 min
C2	5.2 min	3.1 min	24.1 min	19.2 min
C3	5.5 min	3.3 min	25.6 min	20.2 min
C4	4.4 min	2.4 min	24.0 min	19.1 min
C5	5.3 min	3.0 min	24.4 min	19.5 min

Table 5

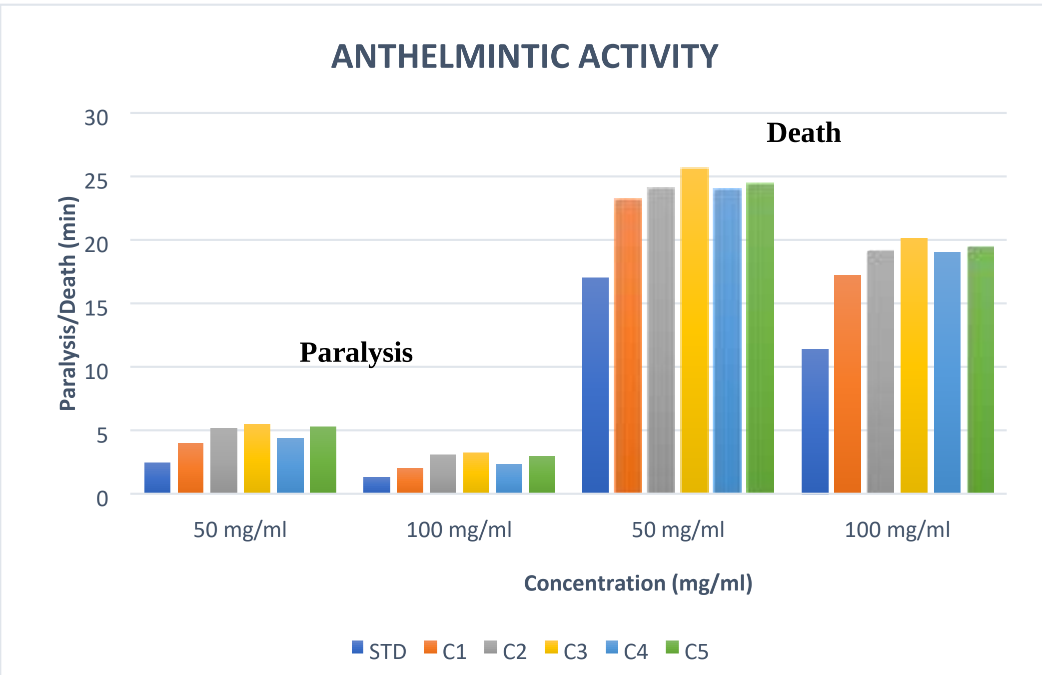


Figure 13

CHARACTERISATION:

IR SPECTRAL DATA

CHARACTERIZATION OF SYNTHESIZED COMPOUND COMPOUND C1 :

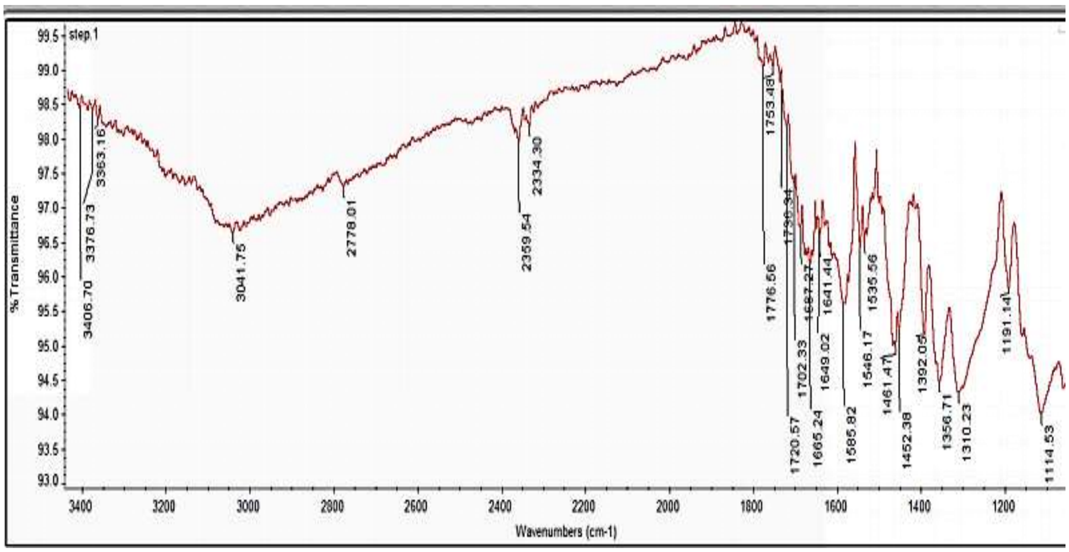
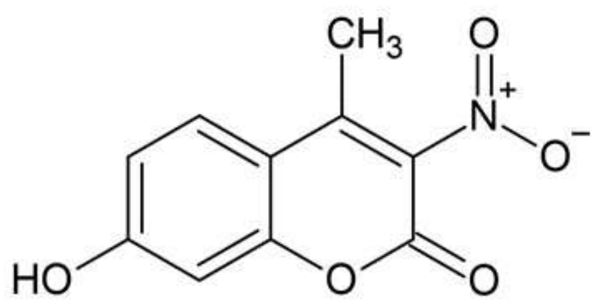


Figure 14

COMPOUND STRUCTURE :



N – H stretching - 3238.14 cm^{-1}

N - H Vibration - 1460. 47cm^{-1}

COMPOUND C2 :

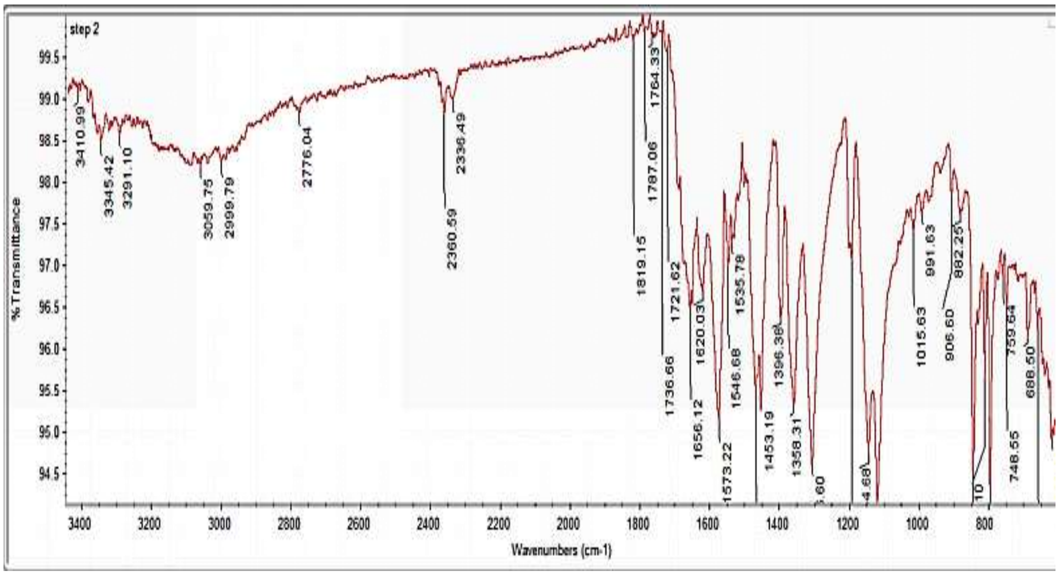
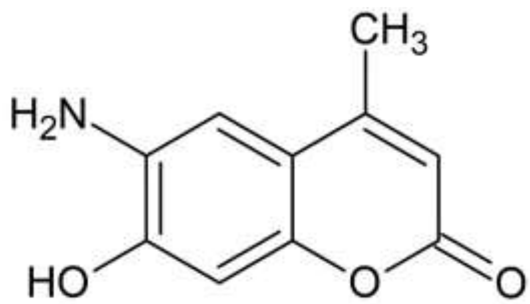


Figure 15

COMPOUND STRUCTURE :



C-O stretching - 1015.63 cm-1

COMPOUND C3 :

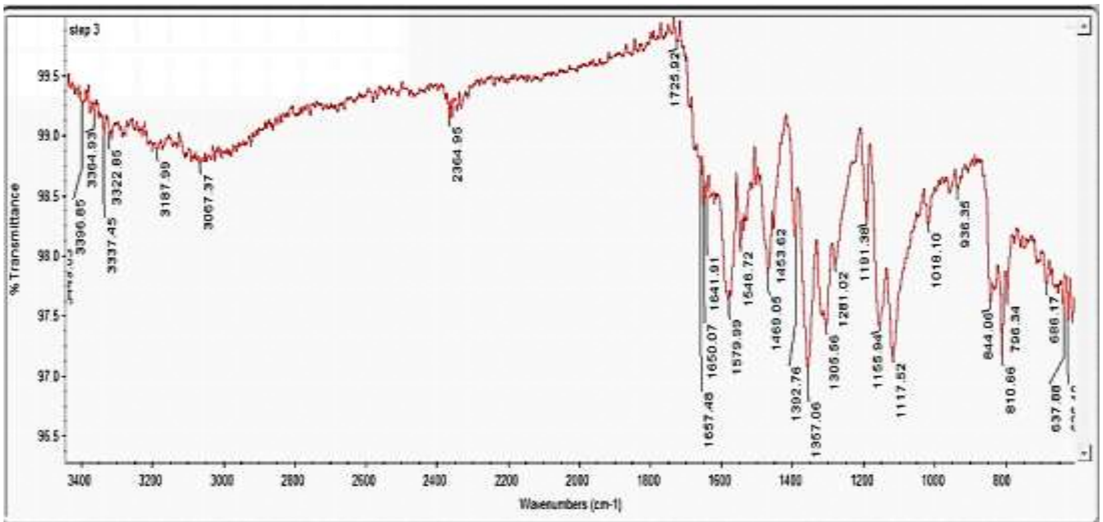
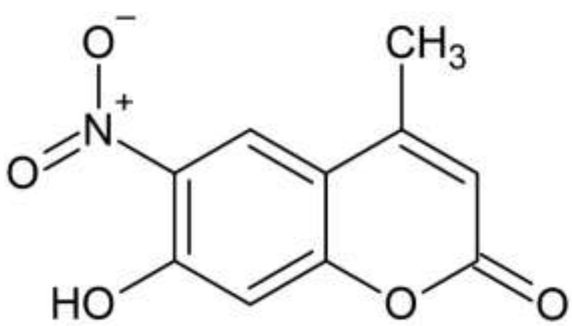


Figure 15

COMPOUND STRUCTURE :



Ar- stretching	-	3187.99
C=N, stretching	-	1579.99
N-H-Stretching	-	3398.85
C-O-C	-	1392.78
C=O	-	1641.97
C=C	-	1657.48
C-N	-	1281.02

COMPOUND C4 :

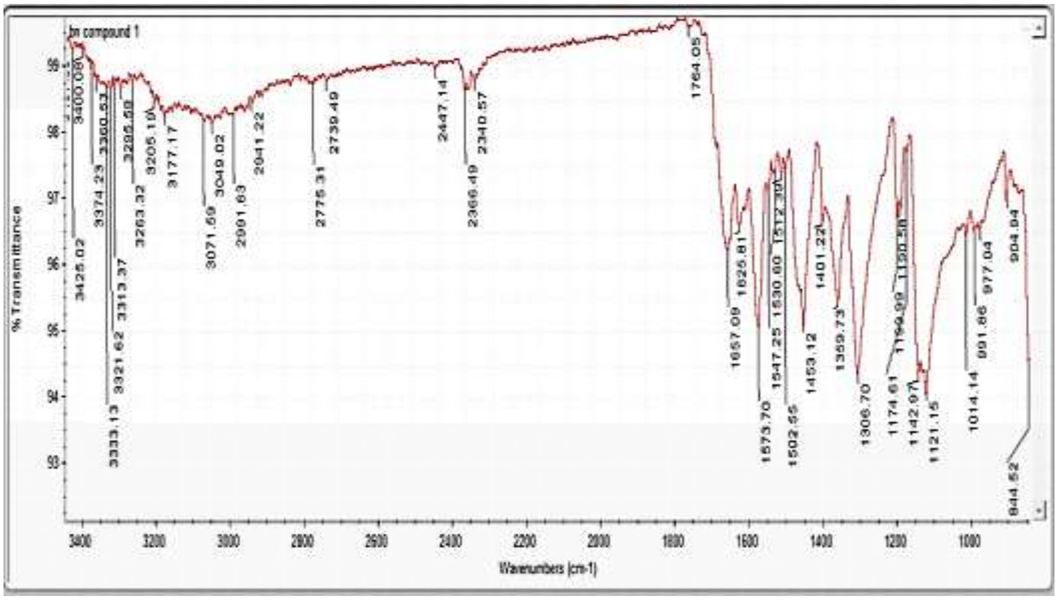
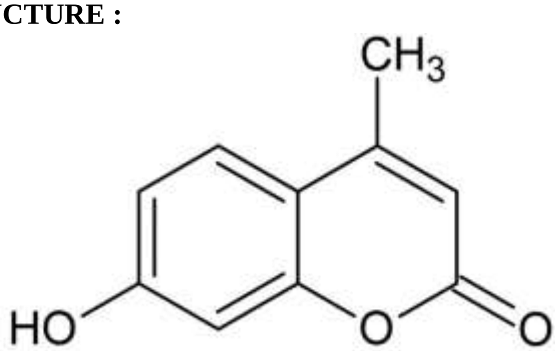


Figure 16

COMPOUND STRUCTURE :



Ar- stretching - 3177.17

NH2, Pyrimidine moitey - 3400.08

C=N, Primidine moity - 1573.70

N-H-Stretching - 3400.08

C-O-C - 1358.73

C=O - 1625.81

C=C - 1657.09

COMPOUND C5 :

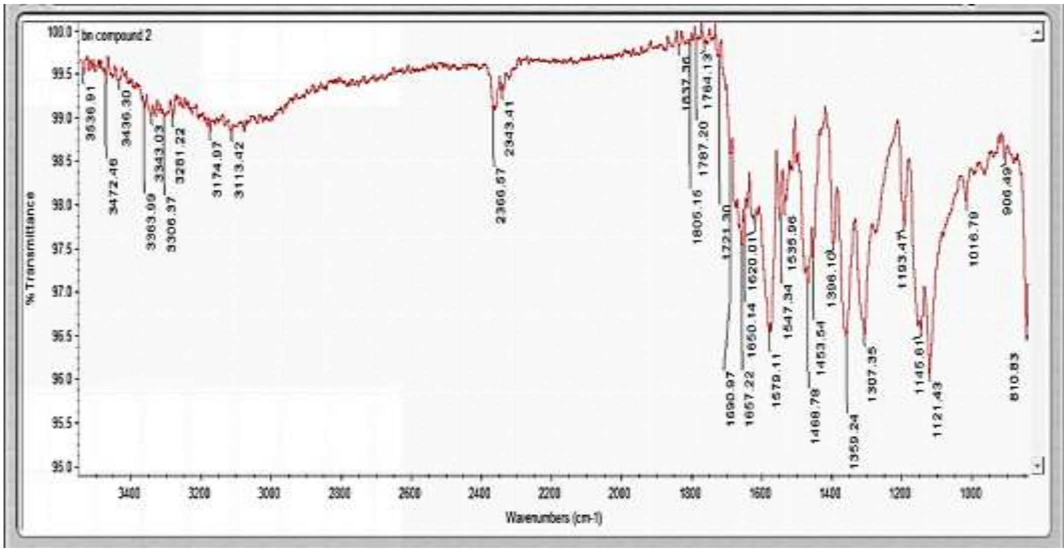
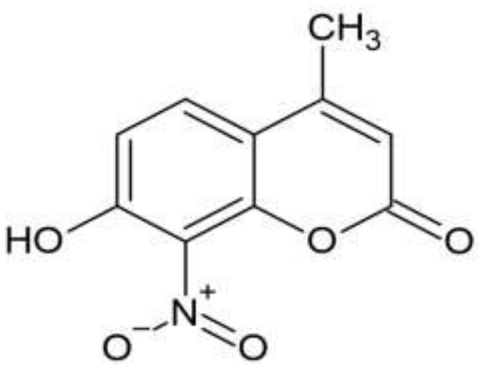


Figure 17

COMPOUND STRUCTURE :



Ar stretching	-	3174.97
NH_2, Pyrimidine moiety	-	3472.46
C=N Pyrimidine moiety	-	1579.11
N-H-Stretching	-	3363.97
C-O-C	-	1396.10
C=O	-	1625.81
C=C	-	1657.09
C-N	-	1174.61

APPLICATIONS:

ANTIMICROBIAL ACTIVITY:

Coumarin derivatives demonstrate significant antibacterial and antifungal properties. Studies reveal that 7-hydroxy-4- methylcoumarin derivatives containing triazole moieties exhibit potent activity against Staphylococcus aureus and Escherichia coli, with MIC values ranging from 0.5-4 μg/mL. The incorporation of pyrazole substituents enhances activity against fungal pathogens, particularly Candida albicans and Aspergillus niger. The mechanism involves disruption of cell membrane integrity and interference with cell wall synthesis [7].

ANTICANCER PROPERTIES :

Cytotoxic Effects :

Coumarin derivatives induce apoptosis through multiple mechanisms in various cancer cell lines. The compound 7,8-dihydroxy-4- methylcoumarin shows remarkable cytotoxicity against MCF-7 breast cancer cells with an IC50 value of
2.4 µM. The mechanism involves activation of mitochondrial-mediated apoptotic pathways, leading to enhanced caspase activity and DNA fragmentation [8].

Anti-proliferative Activity :

The 4-substituted coumarins effectively inhibit tumor cell growth through targeting tubulin polymerization. Compounds featuring electron-withdrawing groups at the C-4 position demonstrate superior activity with IC50 values below 1 µM against HeLa cells. These derivatives interfere with microtubule dynamics, leading to cell cycle arrest in G2/M phase [9].

ANTI-INFLAMMATORY ACTIVITY :

Coumarin derivatives exhibit significant anti-inflammatory properties through multiple mechanisms. The 3-phenylcoumarin derivatives effectively reduce carrageenan-induced paw edema by 65-78% at 10 mg/kg dosage. These compounds modulate inflammatory responses through COX-2 inhibition with IC50 values ranging from 0.8-2.5 µM. Furthermore, they suppress TNF-α production and regulate the NF-κB signaling pathway, contributing to their overall anti-inflammatory effect [10].

Antioxidant Properties :

Hydroxylated coumarins demonstrate remarkable free radical scavenging capabilities. The compound 7,8-dihydroxycoumarin exhibits the strongest antioxidant effects, comparable to ascorbic acid. These derivatives show significant DPPH radical scavenging activity with IC50 values ranging from 4.212.6 µM. The antioxidant mechanism involves electron donation and stabilization of free radicals, leading to reduced oxidative stress in biological systems [11].

Anticoagulant Activity :

Modified warfarin derivatives demonstrate enhanced therapeutic profiles compared to traditional anticoagulants. Structure modifications at the C-3 position optimize anticoagulant properties while maintaining safety. These compounds show improved vitamin K antagonism with enhanced therapeutic indices and reduced bleeding risk. The optimization of substituents has led to compounds with better pharmacokinetic profiles and more predictable dose-response relationships
[12].

Antiviral Effects :

Coumarin derivatives demonstrate significant activity against various viral pathogens. Studies indicate potent activity against HIV-1 with EC50 values ranging from 0.1-1.2 µM. The compounds exhibit dual mechanisms through viral protease inhibition and reverse transcriptase suppression. Structural modifications incorporating heterocyclic rings enhance antiviral potency against influenza and hepatitis viruses. The 4-hydroxycoumarin derivatives show particular promise in targeting viral replication mechanisms while maintaining low cytotoxicity profiles in host cells [13].

Anti-diabetic Properties :

Coumarin-based compounds demonstrate significant potential in diabetes management through multiple pathways. Pyrancoumarin derivatives exhibit remarkable α-glucosidase inhibition with IC50 values between 2.8-15.6 μM. These compounds stimulate insulin secretion from pancreatic β-cells and enhance glucose uptake in peripheral tissues. In vivo studies demonstrate significant reduction in blood glucose levels, accompanied by improved insulin sensitivity. The incorporation of specific substituents at the C-7 position enhances their antidiabetic properties through increased interaction with target enzymes [14].

Neuroprotective Activity :

Coumarin derivatives display significant neuroprotective properties through various mechanisms. The 7-methoxycoumarin derivatives effectively reduce β-amyloid aggregation, a key pathological feature in Alzheimer's disease. These compounds demonstrate potent acetylcholinesterase and monoamine oxidase inhibition, contributing to improved cognitive function. The neuroprotective effects extend to oxidative stress reduction in neuronal cells, with evidence suggesting enhanced survival of hippocampal neurons under stress conditions [15].

Antiplatelet Activity :

Novel coumarin derivatives demonstrate significant antiplatelet properties through multiple mechanisms. Structure-activity relationship studies reveal optimal substitution patterns for enhanced activity. These compounds effectively inhibit platelet aggregation through thromboxane A2 synthesis reduction and P2Y12 receptor antagonism. The incorporation of specific functional groups at key positions modulates their interaction with platelet receptors, leading to improved antiplatelet efficacy while maintaining favorable bleeding risk profiles [16].

Anti-tuberculosis Activity :

Mycobacterium tuberculosis, with MIC values ranging from 0.5-4 μg/mL. These derivatives act through InhA enzyme inhibition, a critical target in mycobacterial cell wall synthesis. Heterocyclic hybrid molecules demonstrate enhanced bioavailability and improved tissue penetration. The incorporation of specific substituents at the C-6 and C-7 positions correlates with increased anti-tuberculosis activity. Recent developments focus on optimizing both potency and pharmacokinetic properties through rational design approaches [17].

Some of the coumarin derivatives with its activity, compounds and key structural features are mentioned below.

ACTIVITY TYPE	REPRESENTATIVE COMPOUNDS	IC50/EC50 RANGE	KEY STRUCTURAL FEATURES
Anticoagulant	Warfarin, Acenocoumarol	0.5-2.0 μM	4-hydroxy substitution
Anticancer	7,8-dihydroxycoumarin	1.2-15 μM	C-7,8 hydroxylation
Anti-inflammatory	3-phenylcoumarin	0.8-5.5 μM	C-3 phenyl substitution
Antimicrobial	Novobiocin derivatives	2.0-25 μM	Glycosidic linkages
Antiviral	Hybrid coumarins	0.1-1.2 μM	Heterocyclic fusion
Antidiabetic	Pyranocoumarins	2.8-15.6 μM	Pyran ring fusion
Neuroprotective	7-methoxycoumarin	5.0-30 μM	C-7 methoxy group

Table 6

RESULT:

In this study, coumarin derivatives were successfully synthesized and characterized using IR spectroscopy. The compounds were evaluated through molecular docking studies against fungal protein (1AI9) for antifungal potential and Ascaris protein (3VR9) for anthelmintic activity. The docking results indicated significant binding affinities, suggesting their potential biological relevance.

Further, in vitro anthelmintic studies against Pheretima posthuma demonstrated moderate to good activity, with some compounds showing promising results compared to the standard drug. These findings indicate that the synthesized coumarin derivatives could serve as potential lead molecules for future pharmaceutical development.

BIBILOGRAPHY:

1. 1. Hoult, J.R.S.; Paya, M. Pharmacological and biochemical actions of simple coumarins: Natural products with therapeutic potential. Gen. Pharmacol. Vasc. Syst. 1996, 27, 713–722.
2. Lake, B.G. Coumarin metabolism, toxicity and carcinogenicity: Relevance for human risk assessment. Food Chem. Toxicol. 1999, 37, 423–453.
3. Jain, P.K.; Joshi, H. Coumarin: Chemical and pharmacological profile. J. Appl. Pharm. Sci. 2012, 2, 236–240.
4. B Mukesh, K Rakesh. Molecular docking: a review. IJRAP. 2011; 2: 17461751.
5. IA Guedes, CS de Magalhães, LE Dardenne. Receptor–ligand molecular docking, Biophysical Reviews. 2014; 6: 75-87.
6. S Agarwal, D Chadha, R Mehrotra. Molecular modeling and spectroscopic studies of semustine binding with DNA and its comparison with lomustine– DNA adduct formation. J Biomol Struct Dyn. 2015; 33: 1653-1668.
7. Cao D, Liu Y, Yan W, Wang C, Bai P, Wang T, et al. Design, synthesis and evaluation of coumarin-based molecular probes for imaging of cancer cells. Bioorg Med Chem. 2016;24(7):1495-502.
8. Zhang JY, Wang YZ, Zhang C, Li Y. Synthesis and biological evaluation of coumarin derivatives containing isoxazole moieties as potential antibacterial agents. Bioorg Med Chem Lett. 2020;30(7):127055.
9. Al-Majedy Y, Al-Amiery A, Kadhum AA, Bakar Mohamad A. Antioxidant activity of coumarins. Sys Rev Pharm. 2017;8(1):24-30.
10. Vekariya RH, Patel HD. Recent advances in the synthesis of coumarin derivatives via Knoevenagel condensation: A review. Syn Commun. 2014;44(19):2756-88.
11. Keri RS, Sasidhar BS, Nagaraja BM, Santos MA. Recent progress in the drug development of coumarin derivatives as potent antituberculosis agents. Eur J Med Chem. 2015;100:257-69.
12. Najmanová I, Doseděl M, Hrdina R, Anzenbacher P, Filipský T, Říha M, et al. Cardiovascular effects of coumarins besides their antioxidant activity. Curr Top Med Chem. 2015;15(9):830-49.
13. Ribeiro CV, Kaplan MA. Tendências evolutivas de famílias produtoras de cumarinas em Angiospermae. Quím Nova. 2002;25(4):533-38.
14. Tian X, Song HS, Cho YM, Park B, Song YJ, Jang S, et al. Anticancer effect of coumarins via overexpression of AMPK in NSCLC. Arch Pharm Res. 2019;42(2):180-191.
15. Wu L, Wang X, Xu W, Farzaneh F, Xu R. The structure and pharmacological functions of coumarins and their derivatives. Curr Med Chem. 2009;16(32):4236-60.
16. Zhang L, Xu Z. Coumarin-containing hybrids and their anticancer activities. Eur J Med Chem. 2019;181:111587.
17. Sashidhara KV, Kumar A, Kumar M, Sarkar J, Sinha S. Synthesis and in vitro evaluation of novel coumarin-chalcone hybrids as potential anticancer agents. Bioorg Med Chem Lett. 2010;20(24):7205-11.