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IN SILICO DESIGN AND MOLECULAR DOCKING STUDIES OF CHROMONE DERIVATIVES IN ANTI-DIABETIC, ANTICANCER, ANTI-INFLAMMATORY AND ANTIOXIDANT ACTIVITIES

[1]Dr. S. K. Senthil Kumar, [2*]Mr. S. Venkatraman, [3]V. Swetha, [3]K. Tamizhendhi, [3]K. Thirumalai Selvan, [3]G. Thiruvengadam, [3]K. Thowsif

[1]Principal, Arunai College of Pharmacy, Velu Nagar, Thenmathur, Thiruvannamalai-606 603.

[2]Associate Professor, Department of Pharmaceutical Chemistry, Arunai College of Pharmacy, Velu Nagar, Thenmathur, Thiruvannamalai-606 603.

[3]B. Pharmacy Final Year Students, Arunai College of Pharmacy, Velu Nagar, Thenmathur, Tiruvannamalai-606 603.

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***Corresponding Author**

Mr. S. Venkatraman
Associate Professor, Department of Pharmaceutical Chemistry, Arunai College of Pharmacy, Velu Nagar, Thenmathur, Thiruvannamalai-606 603.

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ABSTRACT

Chromone derivatives are an important class of heterocyclic compounds known for their wide range of pharmacological activities, including anti-diabetic, anticancer, anti-inflammatory, and antioxidant effects. The present study focuses on the in silico design and molecular docking analysis of chromone derivatives to evaluate their potential biological activities against selected therapeutic targets. Ten chromone derivatives were selected from various reported studies and analyzed using computational approaches. The physicochemical and pharmacokinetic properties of the selected compounds were evaluated using SWISSADME software to determine their drug-likeness and compliance with Lipinski's Rule of Five. The toxicity profiles of the compounds were assessed using the PROTOX 3.0 online tool. Molecular docking studies were carried out using SWISSDOCK against target proteins associated with anti-diabetic, anticancer, anti-inflammatory, and antioxidant activities. The docking results demonstrated significant binding affinities of several chromone derivatives with the selected target proteins. Among the tested compounds, C10 showed the best anti- diabetic activity with a docking score of −8.4821 kcal/mol, C4

exhibited the highest anticancer activity with a docking score of −8.4090 kcal/mol, C9 showed potent anti-inflammatory activity with a docking score of −8.3979 kcal/mol, and C6 demonstrated strong antioxidant activity with a docking score of −8.3251 kcal/mol. Most compounds satisfied ADME and drug- likeness criteria, indicating favorable pharmacokinetic properties. The study concludes that chromone derivatives possess promising biological potential and may serve as effective lead molecules for the development of novel therapeutic agents. Further in vitro and in vivo studies are recommended to validate the computational finding.

KEYWORDS: Molecular Docking, Anti-Cancer, Anti-Diabetic, Anti-Inflammatory, Antioxidant, Protox.

INTRODUCTION

MEDICINAL CHEMISTRY

Medicinal chemistry is a Chemistry based discipline, also involving aspects of biological, medical and pharmaceutical science. It is concerned with the invention discovery, design, identification and preparation of biologically active compound, the study of their metabolism, the interpretation of their mode of action at the molecular level and construction of structural activity relationship.

Medicinal chemistry involves the lead molecule potency, selectivity, reduce toxicity, pharmacokinetic and pharmaceutical properties. It is a science the earlier sources of drugs were from plants, animals and minerals. But, due to the lack of potential action, definite cure, dose level, sometime cause more toxicity, the discovery of new drugs that are more potential and less toxic is essential. The synthesis of new derivatives has Being an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% drugs used in practices are synthesized derivatives and day by day the scope of synthetic medicinal chemistry is broadening.

Once the new pharmaceutical lead has been discovered, extensive and costly efforts usually are made to prepare a series of analogue in the hope that even better activity will be found.

Such programs included the branching, lengthening shortening of chain structure, the variation of the kinds and positions of substituents, the replacement of rings by similar cyclic structures and other empirical molecular modifications within the frame work of reasonably

close analogue.

CHROMONE

Chromone ($C_9H_6O_2$) is a bicyclic, naturally occurring heterocyclic compound (benzo-pyrone) that serves as a fundamental structural skeleton in medicinal chemistry and drug discovery. It is widely found in plants and is considered a "privileged scaffold" due to its ability to exhibit diverse biological activities, including anti-inflammatory, antioxidant, anticancer, antimicrobial, and anti-diabetic properties.

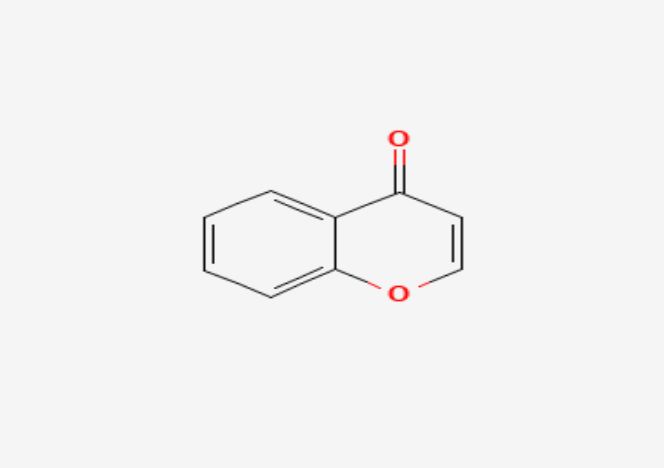
CHARACTERISTICS

- Colourless crystalline solid
- Lipophilic in nature
- Aromatic compound
- Slightly soluble in water
- Soluble in organic solvents

STRUCTURE

- 9 carbon atoms
- 6 hydrogen atoms
- 2 oxygen atoms
- 1 benzene ring
- 1 γ-pyrone ring fused together
- Carbonyl group (C=O) at 4^{th} position[1]

COMMON STRUCTURE



MOLECULAR DOCKING

Molecular Docking is a method which involves orientation and best attempt to find a matching between two molecules it involves binding of one ligand to the active site of protein receptor to form a complex.[2]

It relies on various algorithms and scoring functions to evaluate the binding modes and affinity, making it an essential tool in pharmacology, biochemistry and structural biology.[3]

For example, Protein-ligand docking, more recently, docking is also applied to predict the binding mode between two macromolecules, for instance protein-protein docking.[3]

TYPES OF MOLECULAR DOCKING[4]

There are two distinctive forms of molecular docking.

1. RIGID DOCKING 2. FIXED DOCKING RIGID DOCKING

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameter of a scoring system. The ligand's conformation cab be formed with or without receptor binding activity.[4]

FIXED DOCKING

In conjunction with transformation, we evaluate molecular flexibility to identify confirmation for the receptor and ligand molecule as they exist in the complex.[4]

MODELS OF MOLECULAR DOCKING

THE LOCK AND KEY THEORY

Emil Fischer created a concept termed the "lock-and-key model" in 1890, as seen in figure 4, to describe how biological processes operate. A substrate is inserted into the active site of a macromolecule in the same way as a key is inserted into a lock. In figure 4, biological locks exhibit distinct stereochemical properties that are required for their operation.[4]

THE INDUCED-FIT THEORY

Daniel Koshland proposed the "induced fit theory" in 1958. The fundamental concept is that throughout the character recognition, both the ligand and target, adapt to one another by modest conformational changes until an ideal match is reached.[4]

SOFTWARE AVAILABLE FOR DOCKING[5]

List of some widely used molecular docking software along with their year of introduction

1. Auto Dock 1996
2. Auto Dock Vina – 2010
3. Dock-1989
4. MOE (Molecular Operating Environment) – 1997
5. Schoedinger Glide – 2006
6. Charmm-1983
7. FlexX-2001
8. FRED (Fast Rigid Exhaustive Docking)-2006
9. Rosetta Dock – 2003
10. PIPER-2005
11. ZDOCK – 1999
12. GOLD (Genetic Optimization for Ligand Docking) – 2001
13. SWISSDOCK – 2011

STEPS INVOLVED IN MECHANICS OF MOLECULAR DOCKING[6]

Molecular docking is the process in which the intermolecular interaction between 2 molecules was studied in In-silico. In this process, the macromolecules are the protein receptor. The micro molecule is the Ligand molecules which can be acted as an inhibited.

So, the Docking process involves the following steps.

Step-1 Preparation of Protein

Retrieving the 3D structure of the protein from a Protein Data Bank (PDB) and pre-processing it by removing water molecules, stabilizing charges, and addressing missing residues are side chains.[6]

Step-2 Active site prediction

Identifying the specific active site on the protein receptor that is relevant for docking, often involving the removal of water molecules and heteroatoms.[6]

Step-3 Preparation of ligand

Obtaining from databases or sketching them, and applying Lipinski's Rule of 5 to select suitable drug like candidates.

According to Lipinski's Rule of 5, for the choice of ligand, the following criteria should be

met.

- Less than five hydrogen bond donors.
- Less than 10 hydrogen bond acceptors.
- Molecular mass less than 500 Da
- High Lipophilicity (expressed as Log P not over 5)
- Molar refractivity should be between 40-130.[6]

Step-4 Docking

Docking the prepared ligand against the protein and analyzing the interaction to identify the best docked ligand complex based on scoring.[6]

APPLICATION OF MOLECULAR DOCKING[4]

Applications of molecular docking in drug development

Docking is most often employed for drug discovery, as the majority of medicines are composed of tiny organic compounds. Docking may be used to.

1. **Hit identification**

Docking in conjunction with a score function enables rapid screening of vast databases of possible medications in silicoto find compounds that are capable of binding to a particular target of interest.

2. **Lead optimization**

Docking can be used to anticipate the location and relative position of a ligand's interaction to a protein (also referred to as the binding mode or pose). This data can be utilized to develop more powerful and selective analogues.

3. **Remediation**

Additionally, protein-ligand docking may be utilized to Forecast which contaminants are degradable by enzymes. It can be utilized for the determination of the desired location, collection of the most effective medication. Molecular docking can be used to identify enzymes and their mode of action. It can also be utilized to determine relationships between proteins. Molecules are screened virtually by using the remediation method.

Application of molecular Modeling in modern drug Development[4]

- Molecular docking is used to evaluate potential harmful interactions between compounds and different proteins such as proteases, cytochrome P450 enzymes, and other biological

targets.

- ❖ It helps in predicting unwanted binding of a compound with non-target proteins.
- ❖ Docking studies are useful for determining the **specificity and selectivity** of a proposed drug against homologous proteins.
- ❖ The technique is also commonly applied to identify and study **protein–protein interactions**.
- ❖ Understanding these cellular interactions helps explain various biological processes occurring in living organisms.
- ❖ This knowledge also assists researchers in identifying **potential drug targets for pharmaceutical development**.

DIABETES MELLITUS

- Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria and ketonemia.
- It is a group of metabolic diseases in which there are high blood sugar levels for a prolonged period.
- Insulin is secreted by B-cells of pancreas to control blood sugar levels.
- It is caused due to deficiency of insulin or resistance to insulin or both.[7]

ANTI-DIABETIC ACTIVITY[8]

Anti-diabetic activity refers to the ability of a substance or action to help regulate blood glucose levels in individuals with diabetes. This can involve various mechanisms, such as increasing insulin production, improving insulin sensitivity or reducing glucose absorption from the gut.

PATHOPHYSIOLOGY OF DIABETIC MELLITUS

A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like.

- ➢ Early atherosclerosis
- ➢ Lumen narrowing
- ➢ Retinopathy
- ➢ Neuropathy
- ➢ Peripheral vascular insufficiency.[9]

TYPES OF DIABETIC MELLITUS[7]

Type-1

- Insulin-Dependent Diabetes Mellitus (IDDM)/juvenile onset Diabetes mellitus.
- There is B cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy ß cells are detectable in blood.
- In all type 1 cases circulating insulin levels are low and patients are more prone to ketosis.
- This type is less common and has a low degree of genetic.[7]

Type-2

- Non-Insulin-Dependent Diabetic Mellitus (NIDDM)/ maturity onset diabetes mellitus.
- Most of the patients are obese.
- There is both reduced sensitivity of tissue to insulin and impaired regulation of Insulin secretion. Over 90% cases of diabetes are type 2 DM.[7]

Type-3

- It is secondary is due to causes like pancreatectomy, drugs and non precreatic disease.[7]

Type-4

- It is a gestational diabetes which manifests around 20-24 weeks of pregnancy during which rising placental hormones are responsible for insulin resistance.[7]

INSULIN[7]

- Insulin was discovered by Banting and Best who demonstrated the hypoglycaemia action of an extract of pancreas.
- Insulin is a two-chain polypeptide having 51 amino acids and molecular weight about 6000,
- The A-chain has 21 while B-chain has 30 amino acids.
- There are minor differences between human, pork and beef insulins: pork insulin is more homologous to human insulin that is beef insulin.

MECHANISM OF ACTION[10]

In conditions of hyperglycaemia, excess glucose enters the polyol pathway, where the enzyme aldose reductase (1PWM) converts glucose into sorbitol.

This leads to sorbitol accumulation, causing osmotic and oxidative stress, which contributes

to diabetic complications such as neuropathy, retinopathy, and nephropathy. Administration of 2,4disubstituted furan inhibits aldose reductase activity, reducing sorbitol formation. As a result, cellular damage decreases, helping to prevent diabetic complications.

(Mechanism and action of Diabetes Mellitus)

Hyperglycaemia

↓

Lowering of Glucose enters polyol pathway

↓

Aldose Reductase (1PWM) converts glucose sorbitol

↓

↑ Sorbitol accumulation

↓

Osmotic & oxidative stress

↓

Diabetic complications (neuropathy, retinopathy, nephropathy)

↓

Administration of 2,4-Disubstituted Furan

↓

Inhibits Aldose Reductase activity

↓

Decrease Sorbitol formation

↓

Decrease Cellular damage

↓

Prevention of diabetic complications[11]

ACUTE COMPLICATION OF DIABETES MELLITUS[11]

- Diabetes ketoacidosis
- Hypoglycemic coma

LONG TERM COMPLICATION OF DIABETES MELLITUS[11]

- Cardiovascular disturbance
- Diabetic macroangiopathy
- Diabetic microangiopathy

- Infection
- Renal failure
- Visual impairment and blindness
- Diabetic foot

STANDARD DRUG-ACARBOSE

Acarbose is a complex oligosaccharide which reversibly inhibits a-glucosidases, the final enzymes for the digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose. The stop-NIDDM trial (2002) has shown that long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease. In diabetics, it reduces cardiovascular events. Acarbose is a mild antihyperglycemic and not a hypoglycemic, may be used as an adjuvant to diet in obese diabetics.

CANCER

- Cancer is a highly complicated disease that arises from the uncontrolled growth and division of abnormal cells, which can invade surrounding tissues and spread to other parts of the body. Despite significant progress in medical science, conventional treatments such as chemotherapy and radiotherapy are often associated with several limitations, including severe side effects and resistance. Therefore, the development of new therapeutic agents with improved efficacy and safety has become an important area of scientific investigation.
- Anticancer agents are substances that suppress the proliferation of cancer cells, trigger programmed cell death (apoptosis), or disrupt biological processes involved in tumor growth and metastasis. In recent years, naturally derived phytochemicals have attracted considerable interest due to their potential therapeutic benefits. These compounds are often considered promising because they may exhibit strong biological activity with relatively lower toxicity compared to many synthetic drugs.
- Natural bioactive molecules can exert their anticancer properties through different biological mechanisms. These mechanisms include the regulation of cellular signaling pathways, inhibition of new blood vessel formation (angiogenesis), production of reactive oxygen species (ROS), and control of cell cycle progression.
- Furthermore, a large number of experimental studies, including both in vitro and in vivo investigations, have been carried out to assess the anticancer potential of medicinal plants

and their active constituents. The encouraging findings from these studies suggest that natural products remain an important and valuable source for the discovery and development of new anticancer therapeutic agents.[12]

TYPES[13]

1. **BENIGN TUMOR**

➤ A benign tumor such as a common skin wart, remains confined to its original location, neither invading surrounding normal tissue nor spreading to distant body sites.

➤ Whereas benign tumors can usually we removed surgically.

2. **MALIGNANT TUMOR**

➤ A malignant tumor, however, is capable of both invading surrounding normal tissue and spreading throughout the body via the circulatory or lymphatic system (metastasis).

➤ Only malignant tumors are properly referred to as cancers, and it is the ability to invade and metastasize that makes cancer so dangerous.

➤ The spread of malignant tumors to distant body sites frequently makes them resistant to such localized treatment.

➤ Most cancers fall into one of the main groups.

a. Carcinomas
b. Sarcomas
c. Leukemias and lymphomas

A. CARCINOMAS

Carcinomas, which include approximately 90% of human cancer are malignancies of epithelial cells.

B. SARCOMAS

Sarcomas, which are rare in humans, are solid tumors of connective tissues, such as muscle, bone, cartilage and fibrous tissue.

C. LEUKEMIAS AND LYMPHOMAS

Leukemia and lymphomas, which account for approximately 8% of human's malignancies, arise from the blood-forming cells and from cells of the immune system, respectively.

MECHANISMS OF ACTION[14]

Apigenin

↓

Enters cancer cell

↓

Activates apoptosis pathway

↓

Increases Bcl-2 Associated X Protein Decreases B-cell Lymphoma 2 protein

↓

Damages mitochondrial membrane

↓

Releases cytochrome-c

↓

Activates caspase-9 and caspase-3

↓

Cancer cell death

MANAGEMENT AND TREATMENT[17]

1. **Surgery:** Can remove cancerous tumors that haven't spread.
2. **Chemotherapy:** Destroys cancer cells with powerful drugs in pill form or intravenously (through a needle into a vein).
3. **Radiation therapy:** kills cancer cells with high dosages of radiation.
4. **Immunotherapy:** Engages your immune system to fight the disease.
5. **Targeted therapy:** Targets the genetic mutation (changes) that turn healthy cells into cancer cell.
6. **Hormone therapy:** Blocks cancer-causing hormones.
7. **Hormone therapy:** Replaces damaged blood stem cells with healthy ones.

STANDARD DRUG – PEXIDARTINIB[18]

Pexidartinib selectively inhibits colony-stimulating factor-1 receptor (CSFIR), as wellas KIT and FLT3 kinases. By blocking CSFIR signaling, it prevents the growth and survival of abnormal macrophages involved in tumor formation and progression. Primarily approved for tenosynovial giant cell tumor (TGCT), also known as pigmented villonodular synovitis (PVNS) – a rare tumor involving the joint or tendon sheath. It is also being researched for other

cancers (e.g Leukemia, breast, and prostate cancers) due to its CSFIR pathway inhibition.

INFLAMMATORY

INTRODUCTION

- Inflammation is defined as a protective response involving host cells, blood vessels, and proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair (ROBBINS).
- Term inflammation is derived from Latin word 'inflammare' = 'to burn'.
- Our Principal safeguard against injury.[19]

ANTI-INFLAMMATORY[19]

Anti-inflammatory refers to any drug, substance or mechanism that reduces inflammation by lessening the redness, swelling, fever, or pain and loss of function which are part of bodies inflammatory response.

Anti-inflammatory drugs are agents that inhibit action or production of inflammatory mediators such as cytokines, histamines and prostaglandins. These drugs reduce pain by inhibiting mechanisms of inflammation, as opposed to opioids, which affect the central nervous system to block pain.

TYPES OF INFLAMMATORY

01. Acute inflammation

- This is your immune system's response to a sudden injury or illness. Inflammatory cells travel to the site of injury (like a cut on your finger) or infection and start the healing process.
- Infections in different parts of your body can cause sudden, and usually short-lived, inflammation. For example, bacterial infections like strep throat and viral infections like the flu can cause throat inflammation.
- Other bacterial and viral infections can cause inflammation of your small intestine.

02. Chronic inflammation

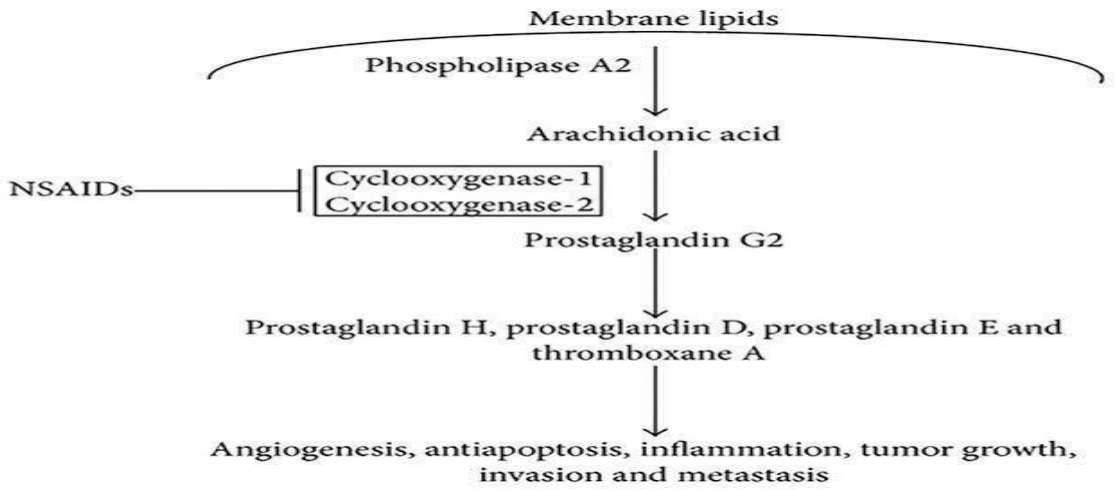
- This is when your body continues sending inflammatory cells even when there's no danger. For example, in rheumatoid arthritis, inflammatory cells and substances attack joint tissues. This leads to inflammation that comes and goes and can cause severe

damage to your joints.

- With chronic inflammation, processes that normally protect your body end up hurting it. Chronic inflammation can last for months or years. You may have periods where it improves and other times when it gets worse.
- Researchers have linked chronic inflammation to a wide range of conditions (inflammatory diseases).

MECHANISM OF ACTION

Membrane lipids are converted into arachidonic acid by the action of the enzyme phospholipase A_2. Arachidonic acid is then metabolized by cyclooxygenase enzymes (COX-1 and COX-2) to form prostaglandin G_2 (PGG_2). This compound is further converted into different mediators such as prostaglandin H, prostaglandin D, prostaglandin E, and thromboxane A. These substances play an important role in biological processes like inflammation, angiogenesis, inhibition of apoptosis, tumor growth, invasion, and metastasis. Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the COX-1 and COX-2 enzymes, thereby reducing the synthesis of prostaglandins and decreasing inflammation.



MANAGEMENT AND TREATMENT

Remove the cause – The main cause such as infection, injury, or allergen should be treated first.

Anti-inflammatory medicines – Medicines are used to reduce pain and swelling (examples: Diclofenac, Naproxen).

Steroid therapy – In severe inflammation, doctors may use steroid medicines (example: Dexamethasone).

Physiotherapy – It helps to improve movement and reduce muscle or joint inflammation.

Hot or cold compress – Ice packs or hot water bags help reduce pain and swelling.

Balanced diet – Eating fruits, vegetables, and healthy foods helps reduce inflammation.

Adequate rest and sleep – Proper rest helps the body recover faster.

Surgery (rare cases) – Surgery may be needed in cases of severe tissue damage.

OXIDANT

- The process of oxidation in the human body damages cell membranes and other structures, including cellular proteins, lipids and DNA. When oxygen is metabolised, it creates unstable molecules called 'free radicals', which steal electrons from other molecules, causing damage to DNA and other cells.
- The body can cope with some free radicals and needs them to function effectively.
- However, the damage caused by an overload of free radicals over time may become irreversible and lead to certain diseases (including heart and liver disease) and some cancers (such as oral, oesophageal, stomach and bowel cancers).[20]

ANTIOXIDANT

Antioxidants are compounds that significantly delay or prevent the oxidation of oxidizable substrates -such as lipids, proteins, or DNA-at low concentrations, often by terminating free radical chain reactions. They function as reducing agents, scavenging reactive oxygen species (ROS) or nitrogen species (RNS) to protect cellular components from oxidative stress.

CAUSES

- Pollution
- Radiation
- Smoking
- Alcohol
- Stress

MANAGEMENT AND TREATMENT

1. Dietary Management

A balanced diet rich in fruits and vegetables is essential. Foods containing antioxidants such as Vitamin C and Vitamin E help neutralize free radicals. Intake of junk and fried foods should be minimized.

2. Lifestyle Modification

Healthy lifestyle practices play a key role. Smoking and alcohol consumption should be avoided. Regular physical activity and adequate sleep help reduce oxidative stress.

1. Antioxidant Therapy

Antioxidant supplements are used to reduce free radical damage. Commonly used antioxidants include Vitamin C, Vitamin E, Beta-carotene, and Glutathione. These agents help in scavenging reactive oxygen species.

2. Management of Underlying Diseases

Proper control of diseases such as Diabetes, Cardiovascular diseases, and Cancer is important to reduce oxidative stress.

3. Reduction of Environmental Exposure

Exposure to environmental pollutants, radiation, and toxic chemicals should be minimized to prevent excessive free radical formation.

4. Stress Management

Mental stress can increase oxidative damage. Techniques such as relaxation, meditation, and yoga are helpful in reducing stress levels.[20]

AIM AND OBJECTIVES

To study the molecular docking of chromone derivatives for multiple biological activities such as anti-diabetic, anti-cancer, anti-inflammatory, antioxidant.

OBJECTIVES

1. Selection of compounds

Synthesized compounds having anti-diabetic, anti-cancer, anti-inflammatory and antioxidant from various schemes and from different articles are selected.

2. Molecular docking studies

- Selection of software
- Selection of protein
- Unfit compounds will be filtered based on the Lipinski's rule
- The fitted compounds are involved in the molecular docking.

PLAN OF WORK

- SELECTION OF DERIVATIVE
- ADME ANALYSIS OF THE SELECTED DERIVATIVES BY COMPUTATIONAL PROCESS
- DETERMINATION OF DRUG-LIKENESS PROPERTIES OF THE SELECTED DERIVATIVE
- MOLECULAR DOCKING ANALYSIS OF SELECTED DERIVATIVE
- THE MOST EFFECTIVE DERIVATIVE HAS BEEN IDENTIFIED.

2. MATERIALS AND METHODS

For SWISSDOCK,

1. PREPARATION OF TARGET (PROTEIN)

Download the 3D structure of the protein from the Protein Data Bank (PDB) Remove water molecules and any co-crystallized ligands not involved in docking. Add hydrogen atoms and optimize geometry. Save the prepared protein as a PDB file.[39]

2. PREPARATION OF LIGAND

Draw or retrieve ligand structure. Optimize its geometry using molecular mechanics.
Save the ligand as MOL2 format.[39]

3. ACCESS SWISSDOCK

Choose between blind docking (entire protein surface) or targeted docking (specific binding site).[39]

4. UPLOAD & SET PARAMETERS

Upload the protein (PDB) and ligand (MOL2). Choose docking type, scoring function, and optional parameters.[39]

5. DOCKING ANALYSIS

The ADME properties of selected lead molecules were calculated using the ADME and molecular properties module of the SWISSADME. The molinspiration tool in the SWISSADME is used to predict the "drug-likeness" features of various compounds from anti-inflammatory, anti-diabetic, anti-cancer, antioxidant activity. The physicochemical properties include formula, molecular weight, No. heavy atoms, No. aromatic heavy atoms, fraction Csp3, No. rotatable bonds. No. H-bond acceptors, No. H-bond donors, molar refractivity, TPSA

[topological polar surface area]. The lipophilicity includes iLOGP, XLOGP3, WLOGP, MLOGP, Silicos-IT Log P, consensus LogP. The predicted water solubility compounds include ESOL log S, ESOL solubility [mg/ml], ESOL solubility[mol/l], ESOL class, Ali log S, Ali solubility[mg/ml], Ali solubility[mol/l], Ali class, Silicos-IT log S, Silicos-IT solubility[mg/ml], Silicos-IT solubility [mol/l], Silicos-IT class.

The pharmacokinetics compounds include Gl absorption, BBB permeant, Pgp substrate, CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, CYP3A4 inhibitor, Log Kp (skin permeation). The predicted drug-likeness compounds include Lipinski, Ghose, Veber, Egan, Muegge, bioavailability, PAINS, Brenk, Lead-likeness, Synthetic accessibility.[6]

3. RESULTS AND DISCUSSION

Table-1: List Of Iupac Name Of Chromone Derivatives.[40]

S.NO	COMPOUNDS NO.	IUPAC NAME
1	C1	3-(4-nitrophenyl)-4H-chromen-4-one
2	C2	2-phenyl-4H-chromen-4-one
3	C3	7-hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one
4	C4	2-[4-(dimethylamino) phenyl]-4H-chromen-4-one
5	C5	6-methyl-2-phenyl-4H-chromene-4-carboxylic acid
6	C6	4-(4-hydroxyphenyl)-6-methyl-2H-chromene-2-carboxylic acid
7	C7	4-chloro-2-(4-methylphenyl)-4H-chromene-3-carboxylic acid
8	C8	8-chloro-2-(4-hydroxyphenyl)-2H-chromene-4-carboxylic acid
9	C9	8-chloro-6-methyl-2-(4-hydroxyphenyl)-4H-chromene-4- carboxylic acid
10	C10	2-(4-chlorophenyl)-6-methyl-3,4-dihydro-2H-1-benzopyran-3-carboxylic acid.

The ADME Study Report of the Compounds of Chromone Derivatives

Captured various compounds were then subjected to ADME testing using SWISSADME software. The forecasted ADME property of various compound based on their structure, functional groups and molecular properties such as Mol/M. W (Molecular weight), BBB permeant (Blood-Brain Barrier parameter of compounds), Gi (Gastrointestinal absorption), H-bond acceptors, H-bond donors, Violation and MLogP (Moriguchi octanol- water partition coefficient). Few compounds transgressed drug-likeness tests were removed as those compounds have poor ability to cross the biological membrane. The ADME report are mentioned under the following table.

Table-2: ADME Study Report.

Compund Number	M.W g/mol	BBB	GI Absorption	H-bond Acceptor	H-bond Donor	Violation	MLogP
1	267.20	Yes	High	4	0	0	1.12
2	222.24	Yes	High	2	0	0	2.27
3	266.29	Yes	High	3	1	0	2.81
4	265.31	Yes	High	2	0	0	2.16
5	266.29	Yes	High	3	1	0	2.81
6	282.29	Yes	High	4	2	0	2.23
7	300.74	Yes	High	3	1	0	3.32
8	302.76	Yes	High	4	2	0	1.50
9	316.74	Yes	High	4	2	0	2.73
10	300.74	Yes	High	3	1	0	3.32
Limit	≤500	Yes	High	≤10	≤5	0	≤4.15

PROTOX 3.0

In-Silico Toxicity Assessment[41]

In silico toxicity assessment for these 10 compounds resulted by using PROTOX 3.0 based on online web tool. The web tool predicts the toxicity effect of chemicals, such as cardiotoxicity, immunotoxicity, androgen receptor, aromatase etc., On PROTOX 3.0, the user needs to specify either the name or canonical SMILES (Simplified Molecular-Input Line Entry System) string of the input compound to run a prediction on the server. The prediction results are also shown as a toxicity radar plot for active class prediction. The results will include a toxicity score and a classification (e.g., active or inactive).

In-Silico Toxicity Assessment Results

The in-silico Toxicity assessment results of the selected 5 ligand molecules were summarized in the Table 3. All the molecules were found to be non-toxic in the terms of cardiotoxicity, Carcinogenicity, Nephrotoxicity, Cytochrome CYP2E1 based on the in-silico.

Table No:3.

Code	Cardiotoxicity	Carcinogenicity	Nephrotoxi City	Cytochrome Cyp2e1
Compound C1	Inactive	Inactive	Inactive	Inactive
Compound C2	Inactive	Inactive	Inactive	Inactive
Compound C3	Inactive	Inactive	Inactive	Inactive
Compound C4	Inactive	Inactive	Inactive	Inactive
Compound C5	Inactive	Inactive	Inactive	Inactive
Compound C6	Inactive	Inactive	Inactive	Inactive
Compound C7	Inactive	Inactive	Inactive	Inactive
Compound C8	Inactive	Inactive	Inactive	Inactive
Compound C9	Inactive	Inactive	Inactive	Inactive
Compound C10	Inactive	Inactive	Inactive	Inactive

FOR SWISSDOCK

In this study, ten Chromone derivatives having anti-diabetic, anti-cancer activity, anti-inflammatory and antioxidant activity, from various schemes and from various articleswere selected. They were examined to recognize the prospects of various compounds that can act as a drug against diabetic and cancer. The Proteinswere downloaded from the protein data bank and then structures were drawn using Molinspiration software. The observed compoundsand their structures.

Cpds. No.	STRUCTURE	DOCKING IMAGE	
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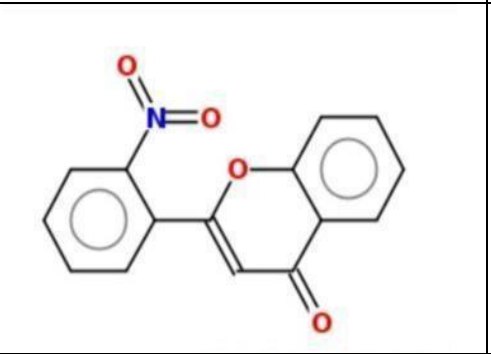
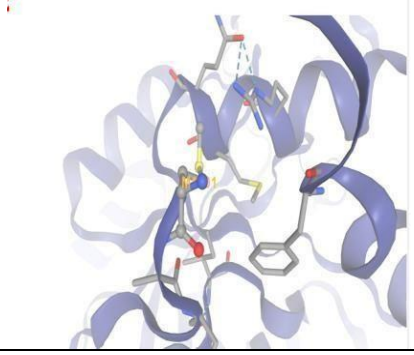
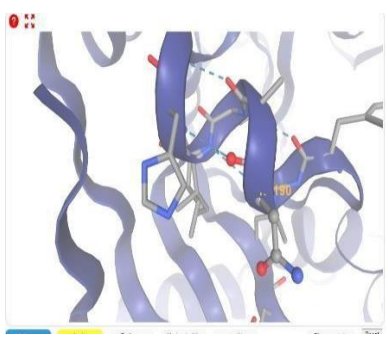
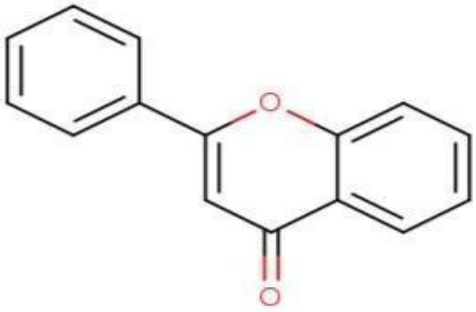
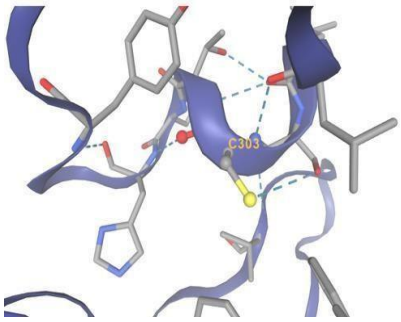
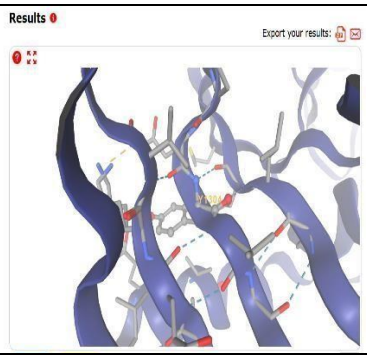
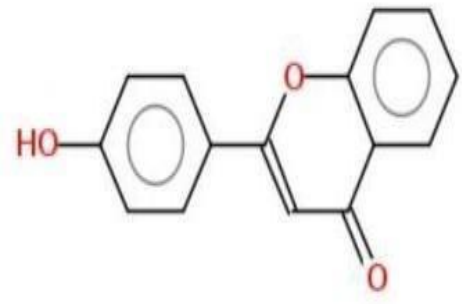
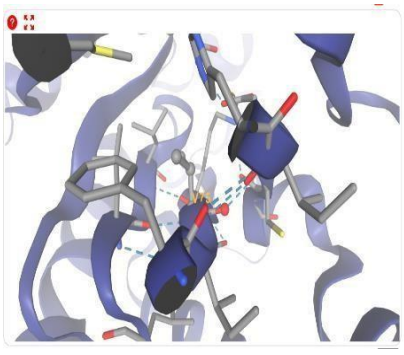
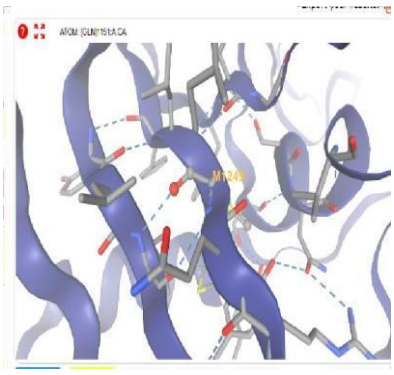
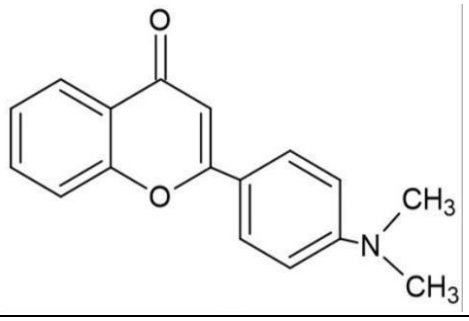
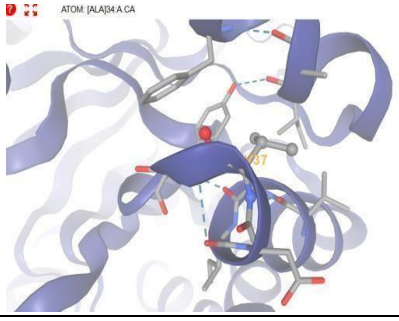
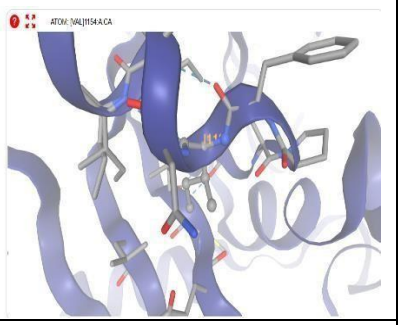
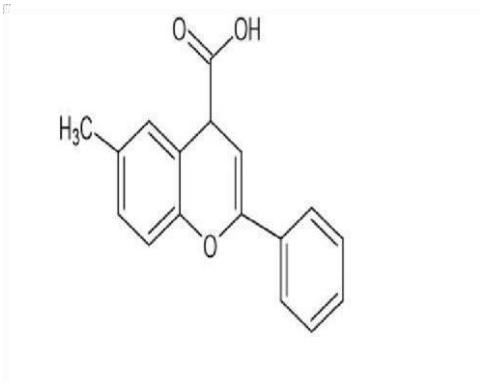
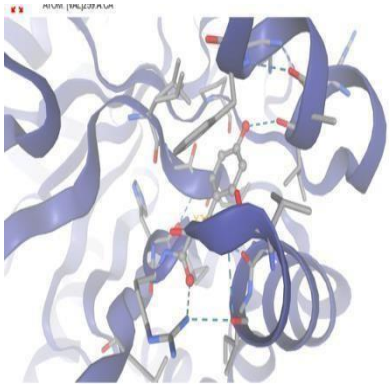
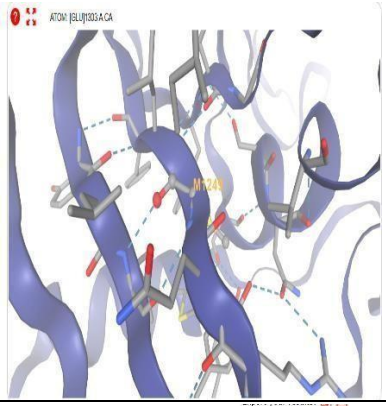
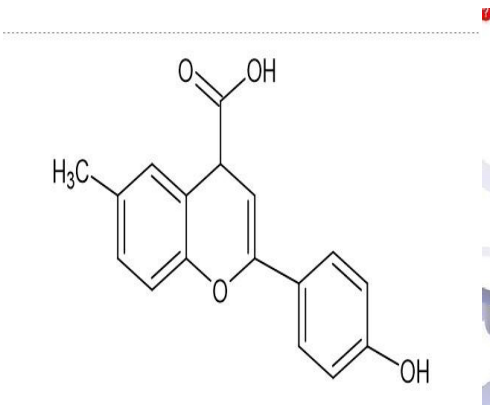
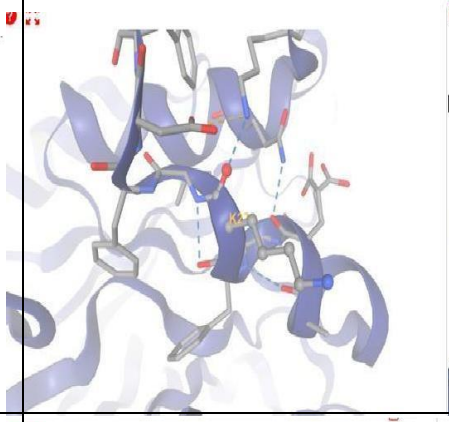
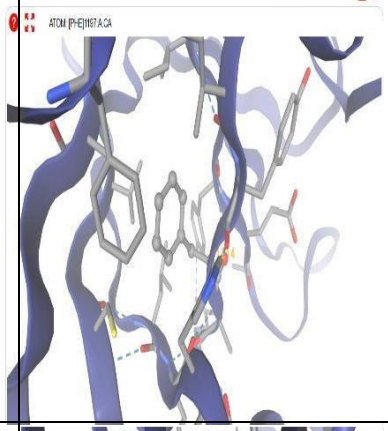
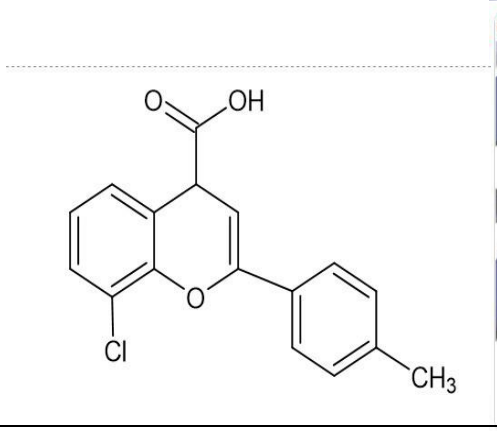
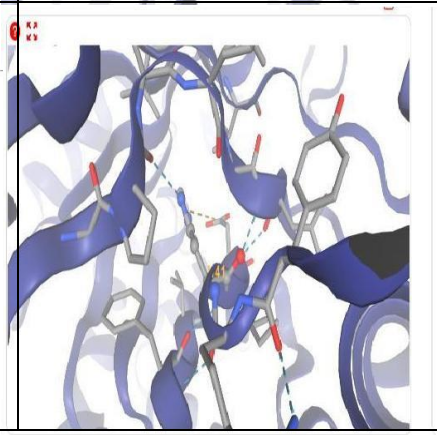
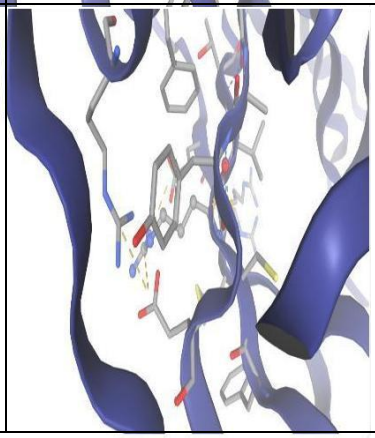
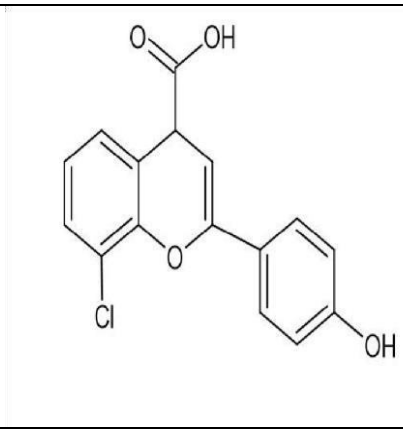
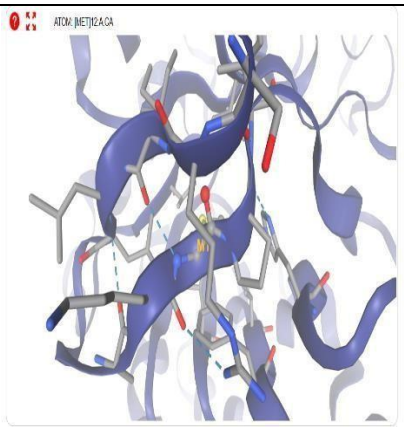
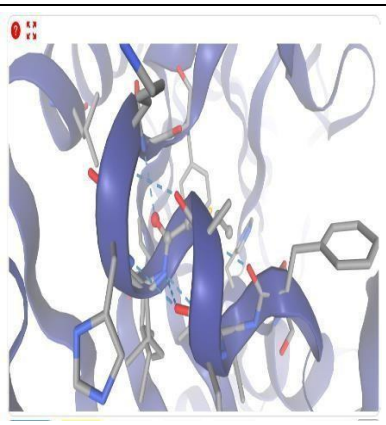
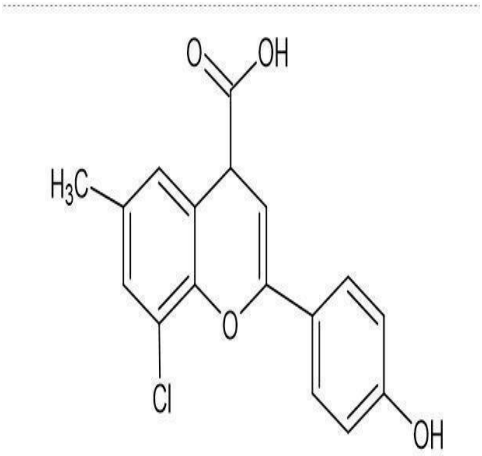
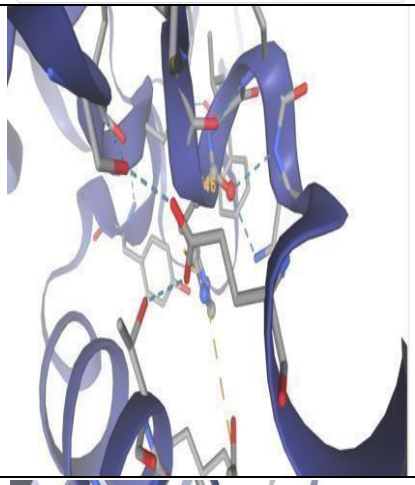
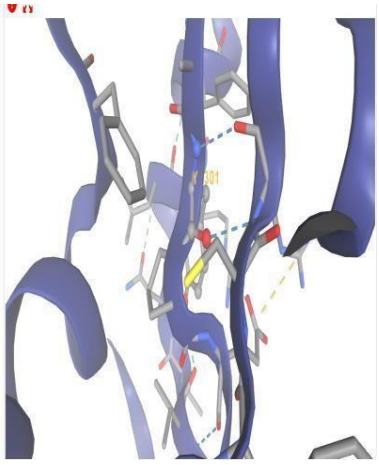
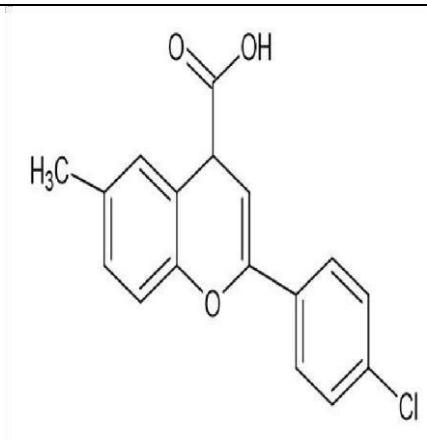
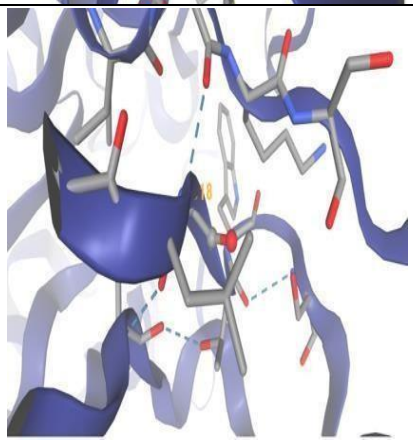
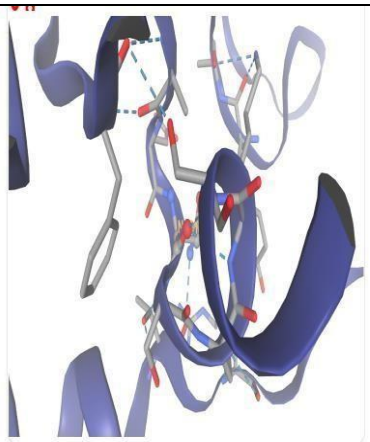
C1			
C2			
C3			

C4			
C5			
C6			
C7			

C8			
C9			
C10			

Cp ds No.	STRUCTURE	DOCKING IMAGE	
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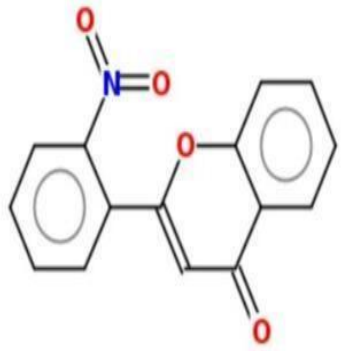
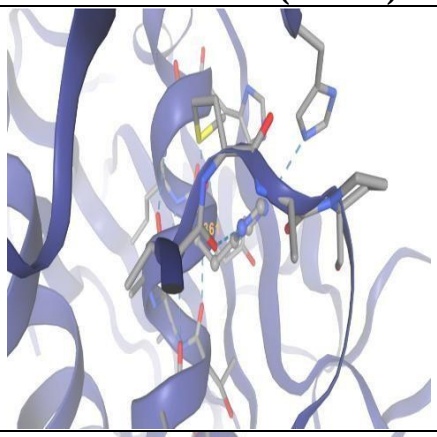
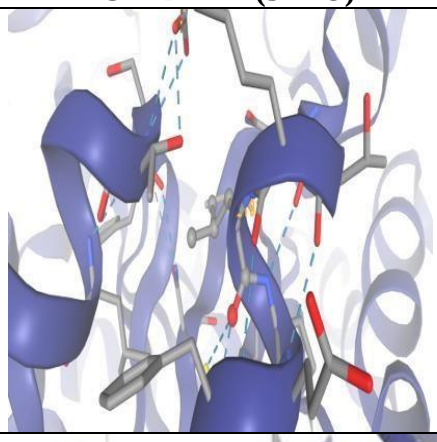
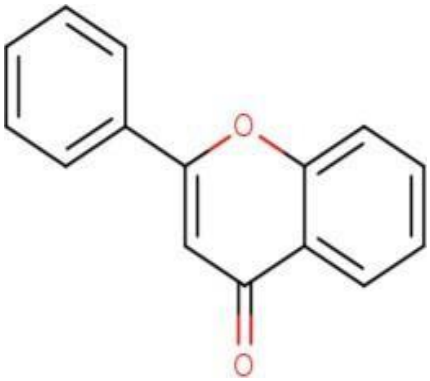
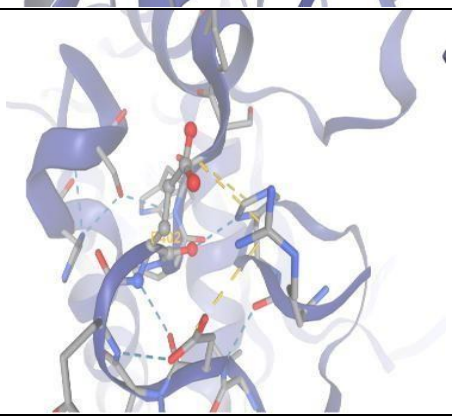
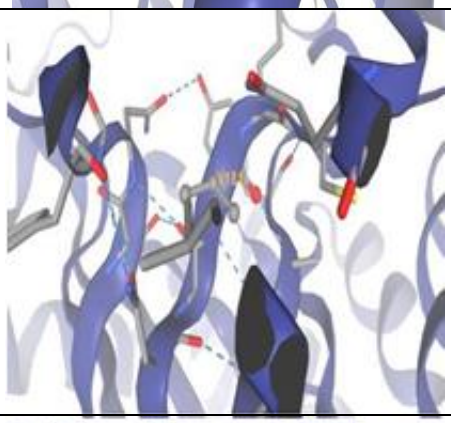
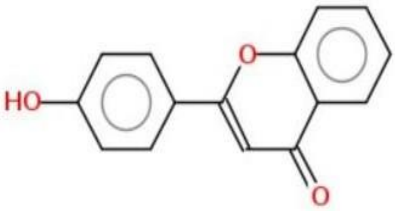
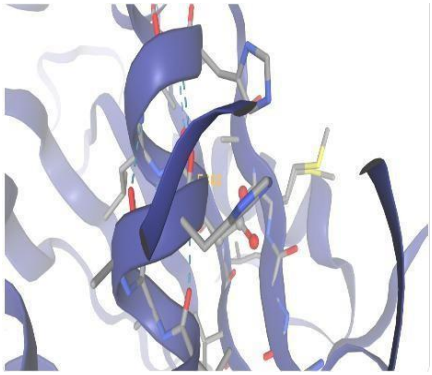
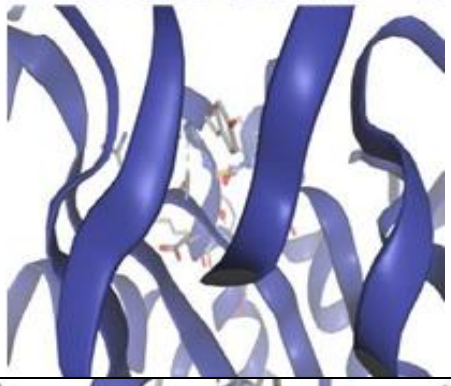
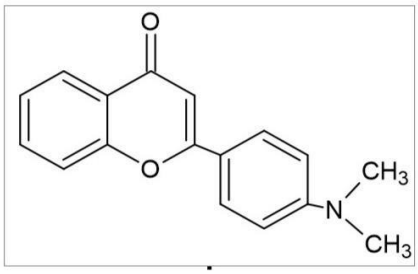
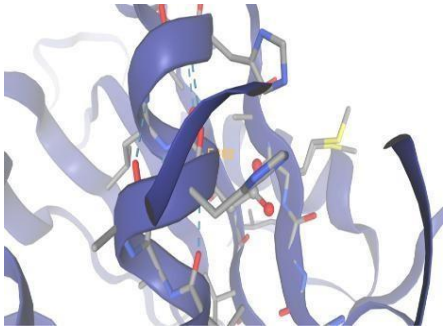
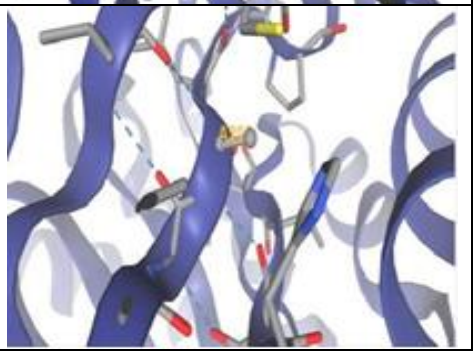
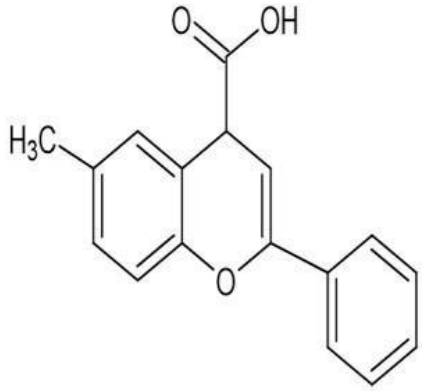
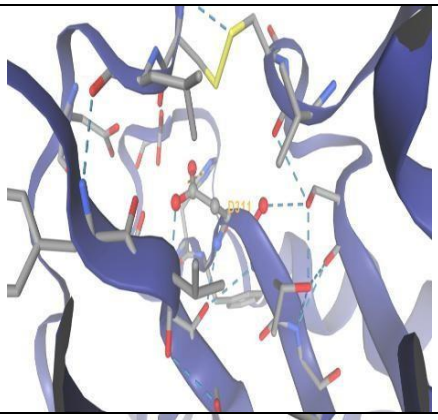
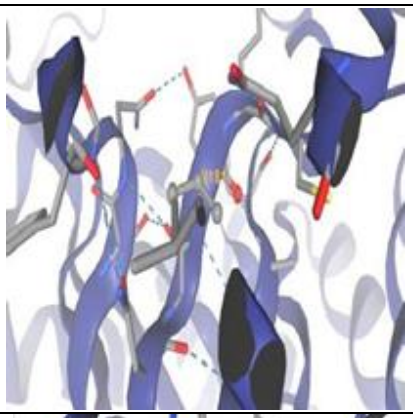
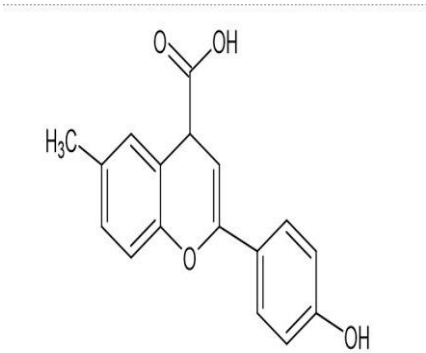
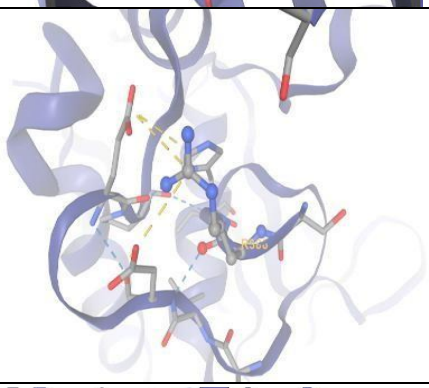
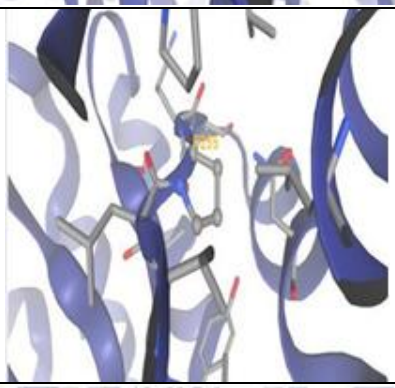
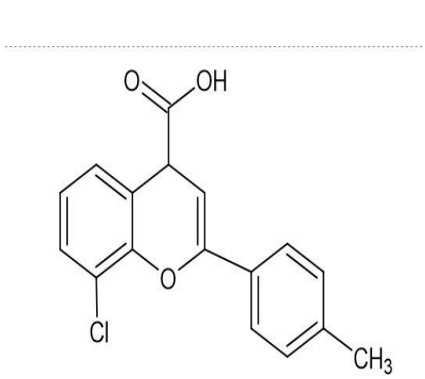
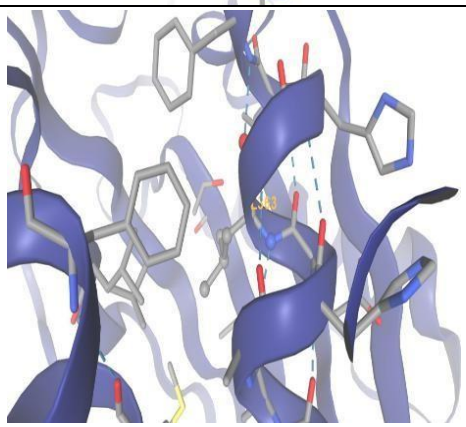
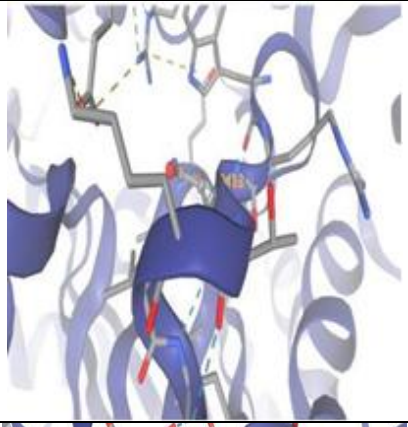
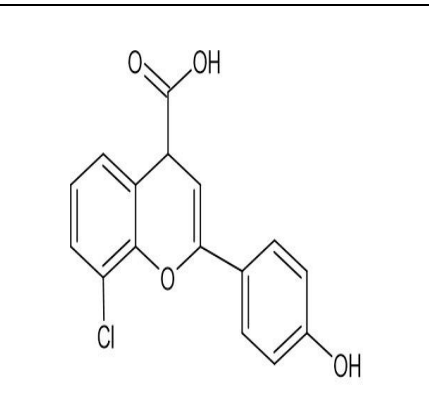
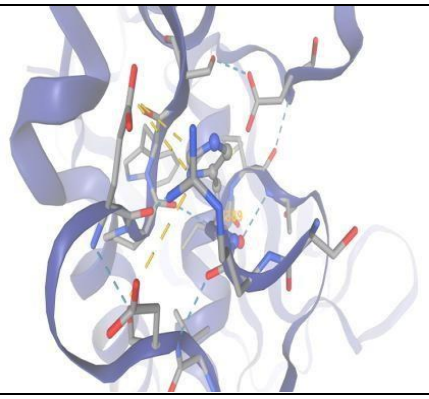
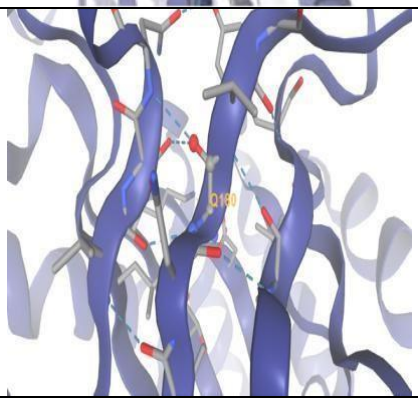
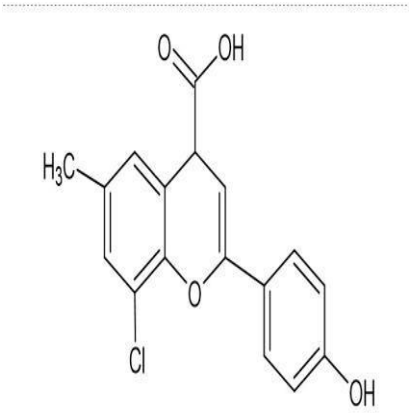
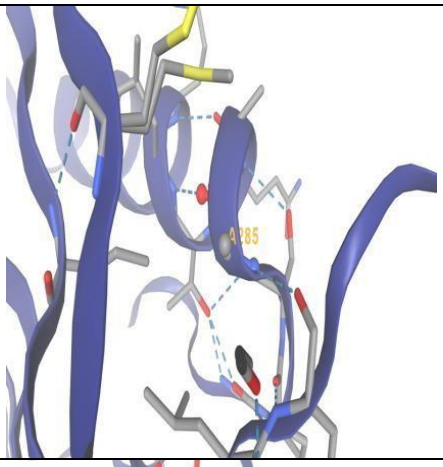
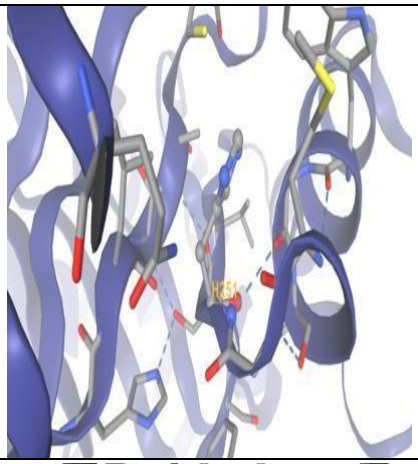
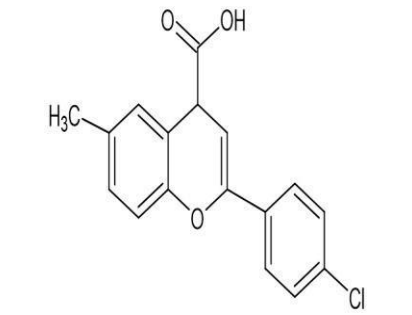
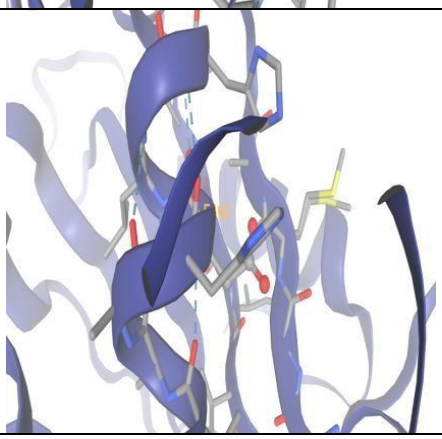
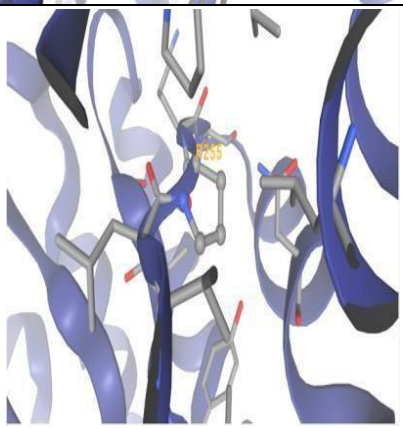
C1			
C2			
C3			
C4			

C5			
C6			
C7			
C8			

C9			
C10			

ANTI-DIABETIC ACTIVITY

TABLE-3: Docking score of SWISSDOCK.

S.NO	Compound Number	Docking score (kcal/mol)
1	C10	-8.4821
2	C6	-8.4799
3	C9	-8.4458
4	C7	-8.3743
5	C3	-8.3533
6	C5	-8.3414
7	C1	-8.3397
8	C8	-8.3317
9	C2	-8.2799
10	C4	-8.2427
11	Acarbose	-8.3670

ANTI-CANCER ACTIVITY

Table-4: Docking score of SWISSDOCK.

S.NO	Compound Number	Docking score (kcal/mol)
1	C4	-8.4090
2	C1	-8.3737
3	C3	-8.1079
4	C2	-8.0234
5	C8	-7.8583
6	C10	-7.8120
7	C9	-7.7022
8	C6	-7.6632
9	C7	-7.5554
10	C5	-7.5478
11	Flavone	-7.4981

ANTI-INFLAMMATORY ACTIVITY

Table-5: Docking score of Swissdock.

S.NO	Compound Number	Docking Score (kcal/mol)
1	C9	-8.3979
2	C7	-8.3392
3	C10	-8.2819
4	C8	-8.2561
5	C6	-8.1086
6	C5	-7.9244
7	C1	-7.9044
8	C4	-7.7113
9	C2	-7.2238
10	C3	-7.2112
11	Diclofenac	-6.8606

ANTIOXIDANT ACTIVITY

Table-6: Docking score of Swissdock.

S.NO	Compound Number	Docking score (kcal/mol)
1	C6	-8.3251
2	C9	-8.3210
3	C10	-8.3143
4	C7	-8.1908
5	C4	-8.1843
6	C5	-8.0938
7	C3	-7.5932
8	C1	-7.4540
9	C2	-7.4398
10	C8	-7.2793
11	Ascorbic acid	-7.9195

4. CONCLUSION

Molecular design

The novel molecules of chromone derivatives are designed using software such as molinspiration, chemSketch and chemDraw.

The designed structural compounds are used to determine important molecular properties such as log P, log S, hydrogen acceptor, hydrogen donar, solubility, molecular weight number of rotatable bonds, etc with the help of swiss ADME.

It is also determined whether the compounds obey Lipinski's Rule of Five.

The proteins for Anti-diabetic, Anticancer, Anti-inflammatory and Antioxidant are identified using the Protein Data Bank [PDB] tool and these docked with ligands and proteins to produce drug -receptor affinity. The suitable affinity highlighted.

The insilico study showed maximum binding affinity for certain compounds and their activities.

Anti-Diabetic = -8.4821 kcal/mol (C10) Anticancer = -8.4090 kcal/mol (C4).

Anti-Inflammatory = -8.3979 kcal/mol (C9) Antioxidant = -8.3251 kcal/mol (C6).

TOXICITY

The chromone derivative structures are subjected to toxicity studies using Pro tox software.

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