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A review on Drug Design
Running title:Chemical Representation of Montelukast in ChemSketch

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ABSTRACT :- The review aims to have a fundamental information on drug design and discovery, their purpose, their aspects and their importance. In this review, topics such as Quantitative Structure-Activity Relationship (QSAR), Computer- Aided Drug design (CADD), High throughput screening (HTS), Molecular Docking will be covered.

KEYWORDS :-Quantitative Structure-Activity Relationship (QSAR), Computer- Aided Drug design (CADD), High throughput screening (HTS), Molecular Docking.

I. INTRODUCTION :-

Drug design, an essential field at the convergence of chemistry, biology, and pharmacology, serves as a beacon of hope in healthcare advancement. With evolving diseases, drug resistance, and complex medical conditions, the call for innovative therapies grows louder. Central to this pursuit is drug design, an intricate discipline aimed at crafting molecules capable of influencing biological processes to alleviate suffering and restore health.

At its core, drug design relies on a deep understanding of molecular interactions, biochemical pathways, and the inner workings of living organisms. It thrives on curiosity and responds to the urgent need for novel medical solutions. Thus, it draws extensively from a wealth of published research, spanning from fundamental insights into cellular functions to clinical observations guiding therapeutic target identification.

A rich tapestry of scientific literature underpins the objectives of drug design studies. From foundational discoveries revealing the structures of vital biological molecules to large-scale screenings uncovering promising drug candidates, existing knowledge both inspires and directs the creation of new therapies. Each study contributes to our grasp of disease mechanisms and informs the strategic design of tailored treatments.

In this context, our study aims to elucidate the rationale behind developing innovative therapeutic agents by synthesizing insights from existing literature and employing state-of-the-art methodologies. By integrating molecular interactions and computational modeling, we strive to tackle pressing medical issues and improve treatment efficacy. Our goal is to design molecules with superior pharmacological properties and enhanced therapeutic benefits, leveraging the latest advancements in drug design.

Ultimately, the significance of drug design lies in its potential to reshape healthcare and improve patient outcomes. As we embark on this journey, we honor past achievements while embracing future challenges, confident in our ability to make a positive impact on global health.

The following is the history of drug discovery:

- Sir David Jack created chemical analogues of known active ingredients at Allen and Hanbury.
- Ranitidine, which replaced cimetidine as the first inhaled steroid for asthma, was developed by GlaxoSmithKline. It was also the first inhaled selective beta-2-adrenergic agonist for asthma.
- Gertrude Elion played a part in the development of azathioprine, the first immunosuppressant and antiviral that permitted the transplantation of human organs.
- The ability to clone human proteins allowed for the screening of vast chemical libraries against particular targets.

The use of quantum computers to speedup drug research began in 2020s.

Many forms of drug design :-

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1. Drug design based on structure:-

It is predicated on the understanding of the biological target's three-dimensional structure, which is acquired by techniques like NMR spectroscopy or X-ray crystallography. Making use of the framework of Candidate medications that are anticipated to bind to the biological target with high affinity and selectivity are created utilizing interactive visuals and a medicinal chemist's intuition in conjunction with the target's structure.

2. Designing drugs based on loops:-

It is dependent on the existence of other molecules that bind to the target biological. These other molecules can be utilized to create a pharmacophore model, which outlines the minimal structural requirements that a molecule must meet in order to bind to the target.

Quantitative Structure-Activity Relationship (QSAR) :-

Quantitative Structure-Activity Relationship (QSAR) is a quantitative method that establishes a connection between measurable or computable chemical characteristics and a specific biological effect. It identifies a reliable link between molecular attributes and biological responses, enabling the application of these principles in assessing the efficacy of new compounds. Essentially, QSAR examines the quantitative aspects of structural features to predict the biological effects of chemical substances.

The variations observed in structure due to substitution can be partially explained through the utilization of the computational statistical method known as QSAR modeling. This concept suggests that distinct physicochemical analyses contribute to the observed biological effects exhibited by a group of related chemicals.

A QSAR takes the form of a mathematical model:
Activity = f(structural and/or physicochemical characteristics) + error.

The aim of QSAR is to establish a mathematical relationship between the biological effect or property being studied and one or more descriptive parameters or descriptors associated with the molecular structure

Molecular descriptors in QSAR:-

These are mathematical representations of molecule properties generated through algorithms. They represent the outcome of a logical and mathematical process that converts chemical information encoded within a symbolic representation of a molecule into a meaningful numerical value or the result of a standardized experiment. These descriptors serve as fundamental, feature-independent parameters used to predict the biological effects or molecular properties of compounds.

S.No.	Descriptor	Name of Descriptor	Symbol
1	Hydrophobic descriptors	Partition coefficient Substation coefficient	Log p, clogp, ∏
2	Electronic descriptors	Hammett constant Taft constant Ionization constant	σ (σm, σp) Σs pka
3	Theoretical descriptors	Energy of highest occupied molecular orbital energy Energy of lowest unoccupied molecular orbital energy	E_{HOMO} E_{LOMO}
4	Steric descriptors	Taft steric constant Molar refractivity	E_S MR
5	Topological	Vander Waal's volume	V1

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	descriptors	Length parameter Molar refractivity index	B1-B5 Ci

Parameters of QSAR :-

1. Hydrophobicity (π)
2. Hammet's electronic parameter (σ)
3. Taft's steric parameter (Es)
4. Hansch's analysis

Parameter	Equation	Given by
Hydrophobicity (π)	Log (1/C)= -k1 (LogP)2 + k2LogP + k3	-----
Electronic σ	$\sigma_X = \log K_X/K_H$	Hammet
Steric E_s	E_s= logKX - logKO	Taft
Hansch equation	1) Log(1/C) = K1logP + k2σ + K3Es +K4 (when data points have a small range) 2) Log(1/C) = -K1(logP)2 + K2logP + K3σ + K4Es + K5 (When data points have large scale)	Hansch

Computer-Aided Drug Design (CADD) :-

Computer-Aided Drug Design (CADD) refers to the application of computer-based techniques in the discovery, development, and analysis of pharmaceuticals and other biologically active substances. In the realm of drug discovery, CADD plays a pivotal role in sifting through vast compound libraries to pinpoint potential active compounds, thereby facilitating the refinement of lead compounds by enhancing their biological properties. The utilization of CADD methodologies expedites the initial stages of drug development.

Historical Evolution of CADD:

- Early 19th century: Extraction of compounds from plants (e.g., morphine, cocaine).
- Late 19th century: Increased utilization of synthetic substances over natural products, with dye and chemical companies establishing research labs that discovered medical applications.
- 1905: Introduction of John Langley's theory of receptive substances, laying the foundation for the concept of specific receptors binding drug or transmitter substances to cells, either initiating biological effects or inhibiting cellular function.
- 1909: Emergence of the first Rational Drug Design.
- 1960: First successful attempt to quantitatively correlate chemical structure with biological action.
- Mid to late 20th century: Advancements in understanding disease states, biological structures and processes, drug transport, distribution, and metabolism.

Various Approaches in Computer-Aided Drug Design:

i. Structure-based drug design (SBDD): SBDD involves the design and refinement of a drug's chemical structure based on its biological target. This approach employs computational chemistry tools to identify or create new chemical compounds capable of binding to the target protein's binding site.

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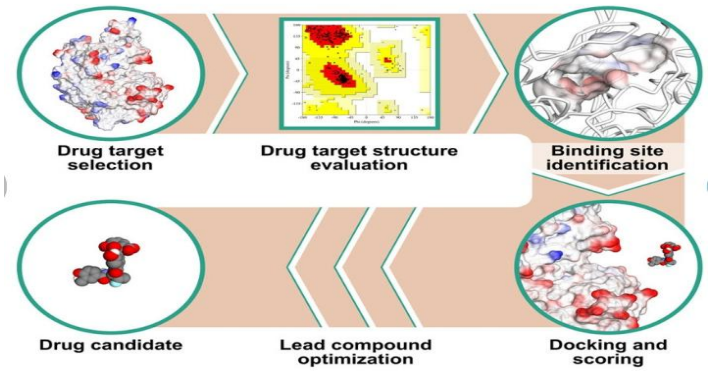
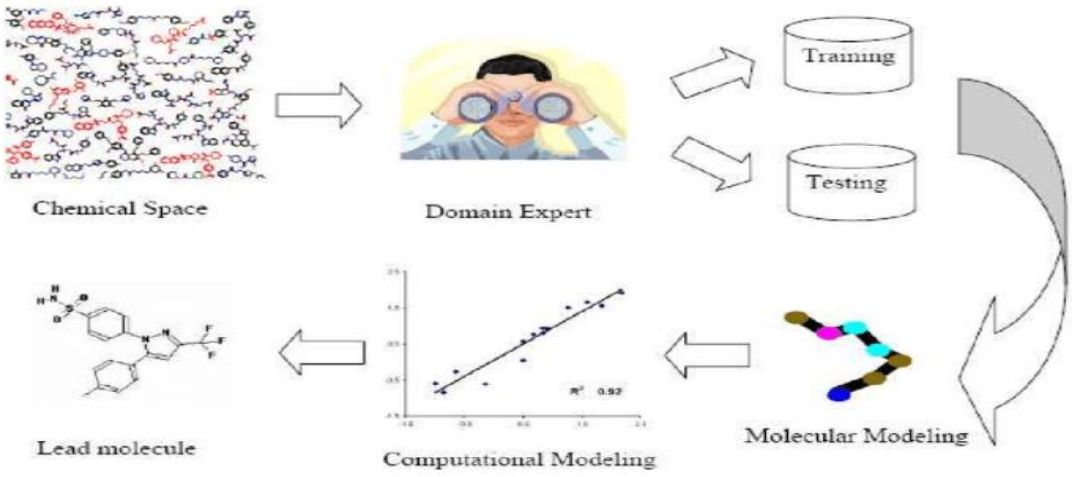


ii. Ligand-based Drug Design (LBDD): LBDD is a strategy for drug discovery that relies on knowledge of molecules with biological activity, irrespective of specific information about the molecular target. It utilizes the chemical information of active and inactive compounds in a test series to establish a correlation between biological activity and chemical structure. LBDD encompasses a cycle of chemical synthesis and bioactivity screening to develop compounds optimized for a desired biological effect.



Molecular Docking :-

Molecular Docking is a technique that forecasts the preferred positioning of one molecule in relation to another when a ligand and a target form a stable complex. Understanding this preferred orientation can help anticipate the strength of association or binding affinity between the two molecules based on key details. Interactions between biologically significant molecules like proteins, peptides, nucleic acids, carbohydrates,lipids are crucial in signal transduction processes. The alignment of the interacting molecules can impact the type of signal generated, such as agonism or antagonism. Therefore, docking is valuable for predicting both the intensity and nature of the signal produced. This method can be applied to simulate the interaction between a small molecule and a protein at the atomic level, enabling the characterization of small molecule behavior in the target protein's binding site and the clarification of essential biochemical processes.

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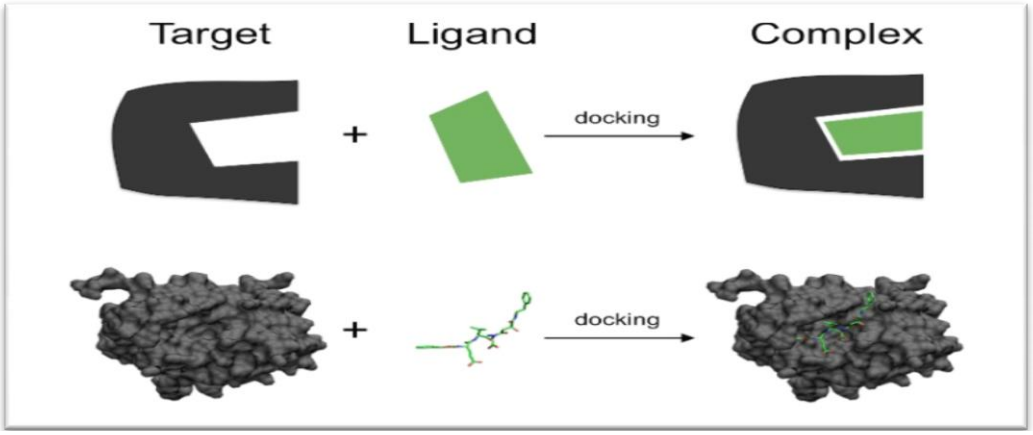

The docking process involves the following stages:
Step 1: Ligand Preparation:

- Create your ligand using a Java applet, upload a single ligand file, or multiple ligand files.
- Utilize MarvinSketch to draw chemical structures, offering a wide range of editing features and templates for simplified molecule drawing.
- Upload the ligand in various formats such as MDL, MOL, SYBYL, MOL2, PDB, HYPERCHEM HIN, or SMILES.
- Automatically set up rotatable bonds and atom types, or manually modify them.
- Download the ligand files in multiple formats.
- Organize ligands into user-defined folders.

Step 2: Protein Preparation:

- Upload protein structures from files or retrieve them from the Protein Data Bank using a docking server.
- Choose specific protein chains, heteroatoms, ligands, and water molecules present in the protein PDB file.
- Configure the simulation box using one of the following methods:

i. Select a known binding site using a co-crystallized ligand.
ii. Choose the center of mass of the protein.
iii. Specify the coordinates of the box center.
iv. Define amino acid residues that delineate the binding site.

Step 3: Setup Ligand-Protein Docking Calculations:

- Choose a protein and a ligand from your library.

Step 4: Results Evaluation:

- Select an image from the image gallery or render it using the molecular docking server.
- Analyze the secondary interactions between the protein and ligand.

Docking Analysis:
Search Algorithms:

- These are techniques employed to forecast potential conformations of a binary complex.
- The search algorithms utilized to anticipate credible conformations of the complex are determined by a defined set of rules and parameters.

Rigid Docking	Flexible docking
• Ligand and protein are treated as a rigid structure during docking.	• Here, conformations of each molecule are generated on-the-fly by the search algorithm during the docking process.
• No conformation modification of the molecules.	• Conformational modifications for both the ligand and protein.
• Not that expensive as the flexible docking.	• Exhaustive(systematic) searching is computationally too expensive.

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List of major available molecular docking webs :-

Sr. no.	Program	Availability	Search method
1	AutoDock	Freely available	Genetic Algorithm/Monte Carlo
2	Gold	Paid	Genetic Algorithm
3	Glide	Paid	Monte Carlo
4	FlexX	Paid	Incremental construction
5	Dock	Freely available	Shape fitting(sphere sets)
6	LigandFit	Paid	Monte Carlo
7	FRED	Freely available	Shape fitting(Gaussian)

Analysis steps done in AutoDockvina software are as follows:-

- Autodock docking log file analysis.
- Save best docking confirmation to PDBQT – in autodock.
- PDBQT to PDB is done using Babel GUI.
- 2D and 3D images – PLP, Protein Plus, LigPlot and Pymol.

High Throughput Screening (HTS) :-

• High Throughput Screening (HTS) is a method in drug discovery that automates the testing of large numbers of chemical or biological compounds against specific biological targets.

• Widely adopted in the pharmaceutical industry, HTS methods utilize robotics and automation to rapidly assess the biological or biochemical activity of numerous molecules, expediting target analysis by screening extensive compound libraries cost-effectively.

• The primary aim of HTS is to pinpoint potential candidates that interact with the target in the desired manner through compound library screening.

• HTS employs liquid handling services, robotics, plate readers as detectors, and dedicated software for instrument control and data processing.

• HTS processes do not identify drugs as they cannot evaluate critical properties such as toxicity and bioavailability.

• Instead, the main role of HTS assays is to identify "leads" and offer suggestions for their optimization.

• Consequently, the results of HTS assays provide a starting point for subsequent stages in the drug discovery pipeline.

Basic steps of HTS :-

A.Preparation of samples and compound libraries :

•Samples are prepared in arrayed format. The key platform or sample carrier used is microplate. Typical formats include 384-, 1536- or 3456- well plates.

•Screening facilities keep their compound library collections in stock plates.

B.Establishment of a method suitable for automation :

• Automation is used to convert a benchtop to an automated HTS screening assay and enforces specific constraints affecting practical assay design.

•HTS assay is performed in a single well, with a low amount of reagents and minimal or no further manipulation than injection of the sample to be tested.

•Accordingly the choice of optimal detection mode and assay has to be subordinated to automation issues.

C.Configuration of robotic workstation :

•Robotic platforms for HTS screenings range from simple automated liquid handling machines to multidimensional workstations performing multiple functions.

•Robotic system manages microplates from station to station for several steps such as reagent addition, mixing, incubation, detection.

D.Acquisition and handling of data

•Data acquisition is performed by an optical measurement, quantifying the amount of light produced by the sample.

•Different readouts such as fluorescent or luminescent detection, colourimetry or turbidity are available.

II. MATERIAL AND METHODS :-

Chemical Database:

I. A chemical database is a specialized database designed to store chemical information. Typically, these databases contain data on stable molecules and are expected to manage and search through information on millions of molecules, requiring terabytes of physical memory.

Representation of Chemical Structures in Chemical Databases:

II. Chemical structures are represented in digital databases using two main techniques:

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a) Connection tables, adjacency matrices, or lists, which include additional information on bond and atom attributes (e.g., MDL Molfile, PDV, CML).
b) Linear string notation based on depth-first or breadth-first traversal. These approaches enable the representation of stereochemical differences, charges, and special bonding seen in organometallic compounds. Computer representations offer increased storage capacity and fast, flexible searching capabilities.

Search:

III. Databases are searched using parts of structures, portions of their IUPAC names, and constraints on their properties. This type of search involves seeking subgraph isomorphism and is a widely studied application of graph theory. Atom-by-atom searching (ABAS) is an intensive component of search, aiming to map the search substructure atoms and bonds with the target molecule, often utilizing Ullman's Algorithm or its variations.

Descriptors:

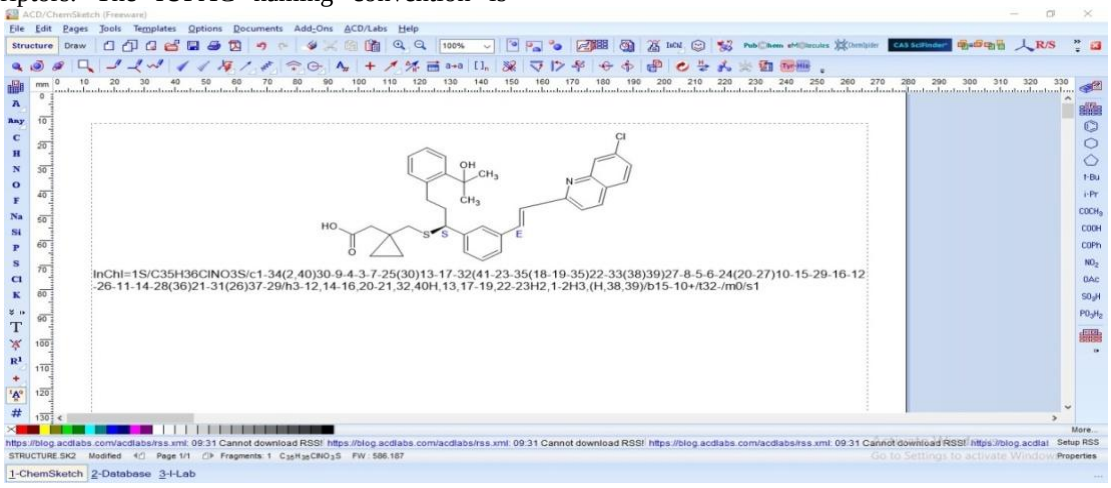
IV. Properties of molecules beyond their structure are categorized into physicochemical or pharmacological attributes, also known as descriptors. The IUPAC naming convention is commonly used to represent a molecule's structure in a human-readable and unique string format. Physicochemical descriptors such as molecular weight, charge, and solubility can be computed directly from the molecule's structure, while pharmacological descriptors are derived indirectly using complex multivariate statistics or experimental results.

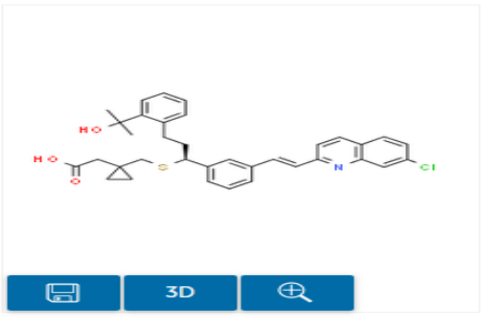
Registration Systems:

V. Database systems that maintain unique records of chemical compounds are referred to as registration systems. These systems are utilized for chemical indexing, patent systems, and industrial databases. They ensure uniqueness through unique representations, with some systems, such as the CAS system, employing algorithms to generate unique hash codes.

Tools:

VI. Graphical display of data makes computational representations transparent to chemists. Chemical structure editors simplify data entry by allowing for the graphical representation of chemical structures.
Chemical database generated using ACD/ChemSketch of montelukast :-





(S)-montelukast

Molecular Formula $C_{35}H_{36}ClNO_3S$

Average mass 586.183 Da

Monoisotopic mass 585.210449 Da

ChemSpider ID 5022835

- Double-bond stereo
- 1 of 1 defined stereocentres

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More details:	
Systematic name	{1-[(((1S)-1-{3-[(E)-2-(7-Chloro-2-quinolinyl)vinyl]phenyl}-3-[2-(2-hydroxy-2-propanyl)phenyl]propyl}sulfanyl)methyl]cyclopropyl}acetic acid
SMILES	CC(C)(c1ccccc1CC[C@@H](c2cccc(c2)/C=C/c3ccc4ccc(cc4n3)Cl)SCC5(CC5)CC(=O)O)O
Std. InChI	InChI=1S/C35H36ClNO3S/c1-34(2,40)30-9-4-3-7-25(30)13-17-32(41-23-35(18-19-35)22-33(38)39)27-8-5-6-24(20-27)10-15-29-16-12-26-11-14-28(36)21-31(26)37-29/h3-12,14-16,20-21,32,40H,13,17-19,22-23H2,1-2H3,(H,38,39)/b15-10+/t32-/m0/s1
Std. InChIKey	UCHDWCPVSPXUMX-OYLFJNDKSA-N
Cite this record	CSID:5022835, http://www.chemspider.com/Chemical-Structure.5022835.html (accessed 08:34, Nov 16, 2023)

Montelukast :-

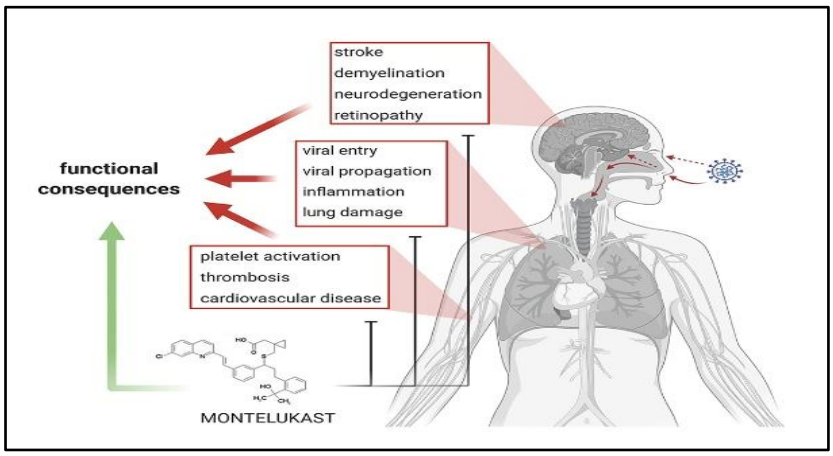
- Montelukast , sold under the brand name Singulair, is a medication used in the maintenance treatment of Asthma.
- It was approved for medical use in the US in 1998and was available as a generic medication.
- In 2020, it was the 14th most commonly prescribed medication in US.
- Montelukast comes as a tablet, a chewable tablet and granules.

Medical uses:-

- Asthma
- Exercise induced Bronchospasm
- Urticaria (Skin rashes)
- Mainly used as a complimentary therapy in adults in addition to inhaled corticosteroids.
- Also used to prevent allergic reaction and Asthma flare-ups during the administration of IV immunoglobuliln.
- It may also used as an adjunct therapy in symptomatic treatment of mastocytosis (a type of mast cell disease affecting both children and adults caused by accumulation of functionally defective mast cells and CD34+ mast cell precursors)

Pharmacology :-

- Montelukast is the leukotriene receptor antagonist.
- It works by blocking the action of leukotriene D4 in the lung which leads to decreased inflammation and relaxation of smooth muscle.
- Leukotrienes are the inflammatory mediator that are produced by immune system and serve to promote bronchoconstriction, inflammation, microvascular permeability, mucus secretion in asthma and COPD



Drug Interactions:-

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- Montelukast inhibits the drug metabolizing enzyme CYP2C8.
- Therefore the combination of montelukast with a CYP2C8 substrate i.e. amodiaquine (antimalarial drug) increase the plasma concentrations of that substrate.

Adverse effects:-

I. Common side effects :Diarrhoea , Nausea, vomiting , mild rashes, asymptomatic elevations in liver enzymes, fever.

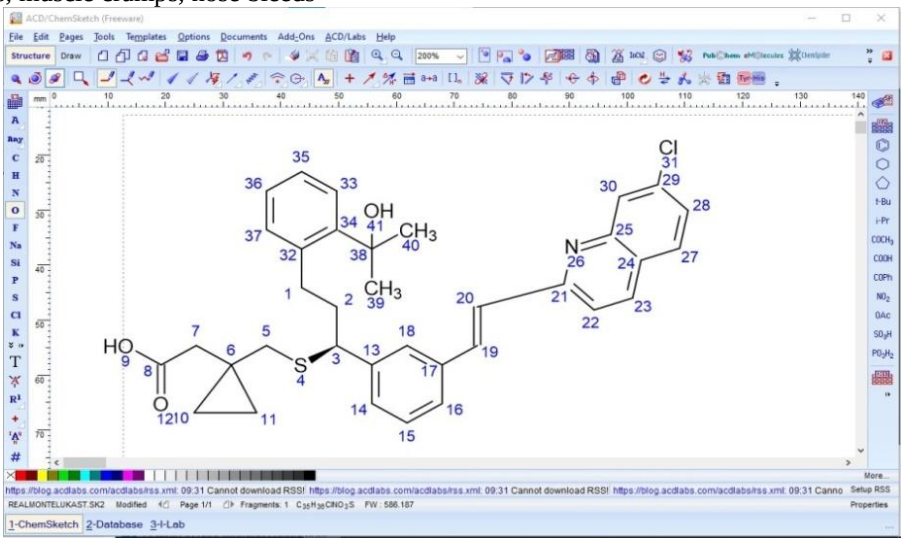
II. Uncommon side effects : Fatigue , malaise, seizures, muscle cramps, nose bleeds

III. Rare side effects (1 in 10,000 people): Suicidal thoughts, Angio edema and liver problems.

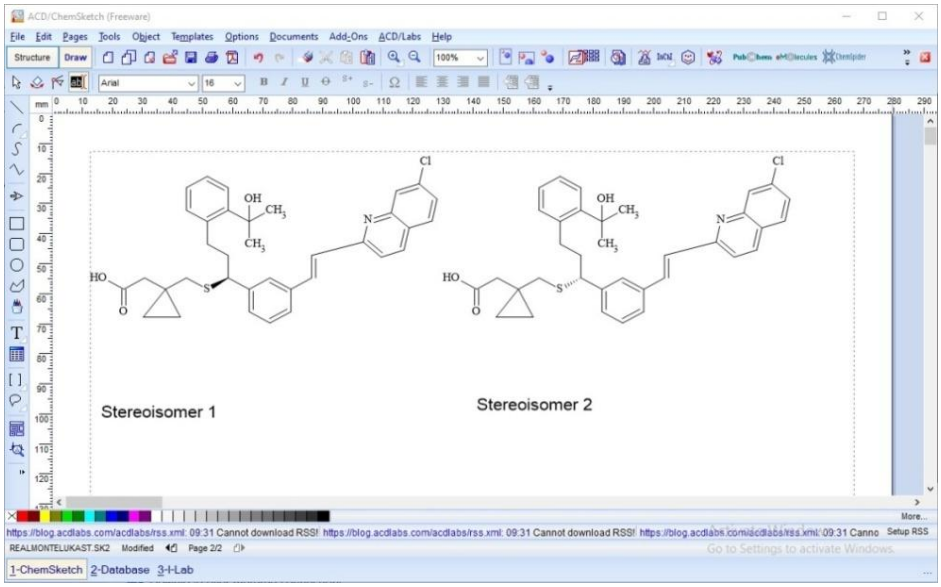
Clinical Data:-

- Trade name :Singulair
- Route of administration : Oral
- Drug Class: LT receptor antagonist

Number of atoms present in Montelukast:-
Montelukast has a total of 40 atoms present in it.



Stereoisomers of Montelukast:-



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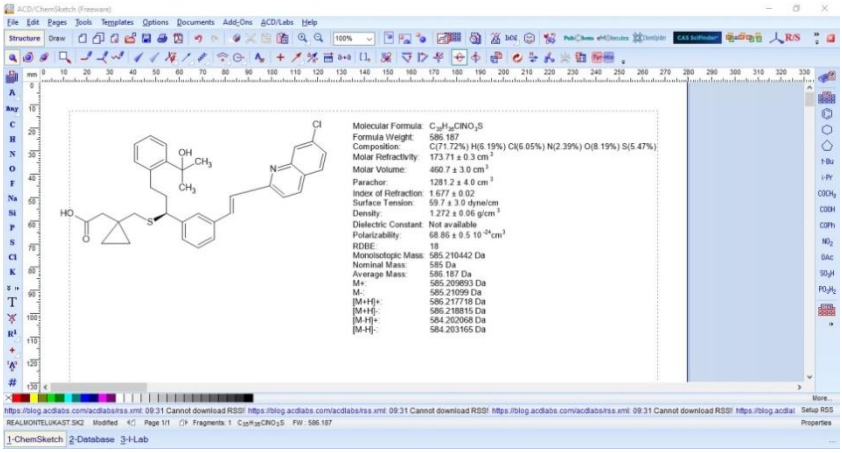
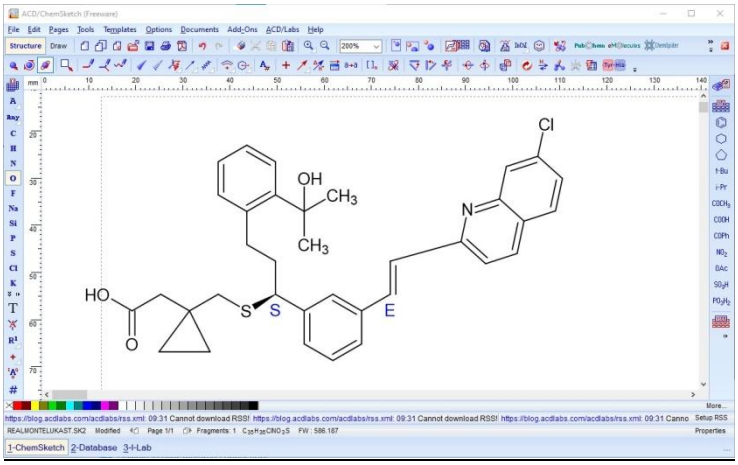
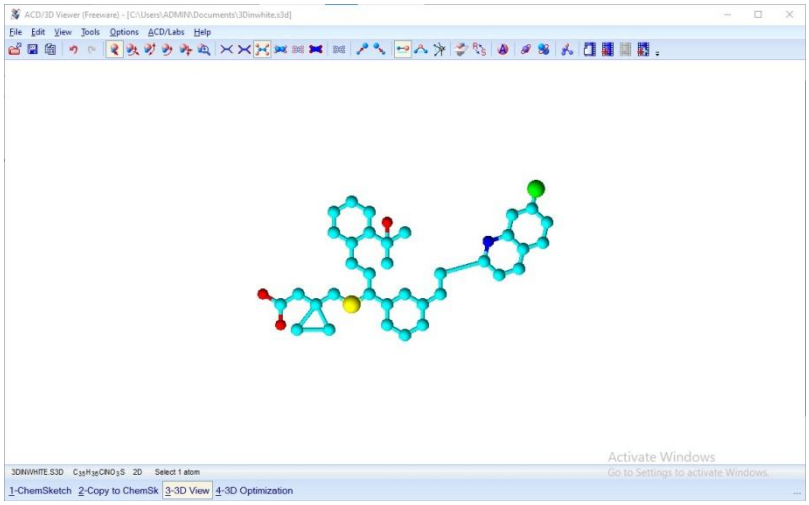
Properties of Montelukast:-



Configurations of Montelukast :-



3D structure of Montelukast :-



III. CONCLUSION :-

In conclusion, this review has provided a comprehensive overview of drug design, encompassing various methodologies and techniques employed in the pursuit of novel therapeutic agents. From the historical evolution of

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drug design to contemporary approaches such as computer-aided drug design (CADD) and high throughput screening (HTS), the journey towards discovering new drugs is marked by innovation and collaboration across disciplines.The chemical representation of Montelukast in ChemSketch serves as a tangible example of the intricacies involved in drug design. Through molecular modeling and computational techniques, researchers can explore the structural features and interactions of potential drug candidates, laying the groundwork for rational drug designAs we continue to unravel the complexities of disease mechanisms and harness the power of technology, the future of drug design holds great promise. By leveraging cutting-edge tools and interdisciplinary approaches, we can accelerate the discovery and development of therapeutics that address unmet medical needs and improve patient outcomes.In essence, drug design is a dynamic and multifaceted field that bridges the gap between theory and practice, science and innovation. It is through the collective efforts of researchers, scientists, and clinicians that we can unlock the potential of drug design to transform healthcare and enhance the quality of life for individuals worldwide.

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