

# **SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES**

*Affiliated To The Tamil Nadu Dr. MGR Medical University, Chennai*

*Approved by Pharmacy Council of India, New Delhi.*

**Coimbatore -641035**



**COURSE NAME : COMPUTER AIDED DRUG DESIGN(BP 807 ET)**

**VIII SEM / IV YEAR**

**TOPIC : DOCKING BASED SCREENING & DE NOVO DRUG DESIGN**

# WHAT IS MOLECULAR DOCKING ..?

What is molecular docking?

It's a computational method to predict how a ligand and receptor will orient themselves when bound together, forming a stable complex.

What can this knowledge be used for?

It can predict the binding affinity or strength between the ligand and receptor.

How is it used in drug discovery?

It's frequently used to predict the binding orientation of small molecule drug candidates to their protein targets, which in turn helps predict their binding affinity and activity.



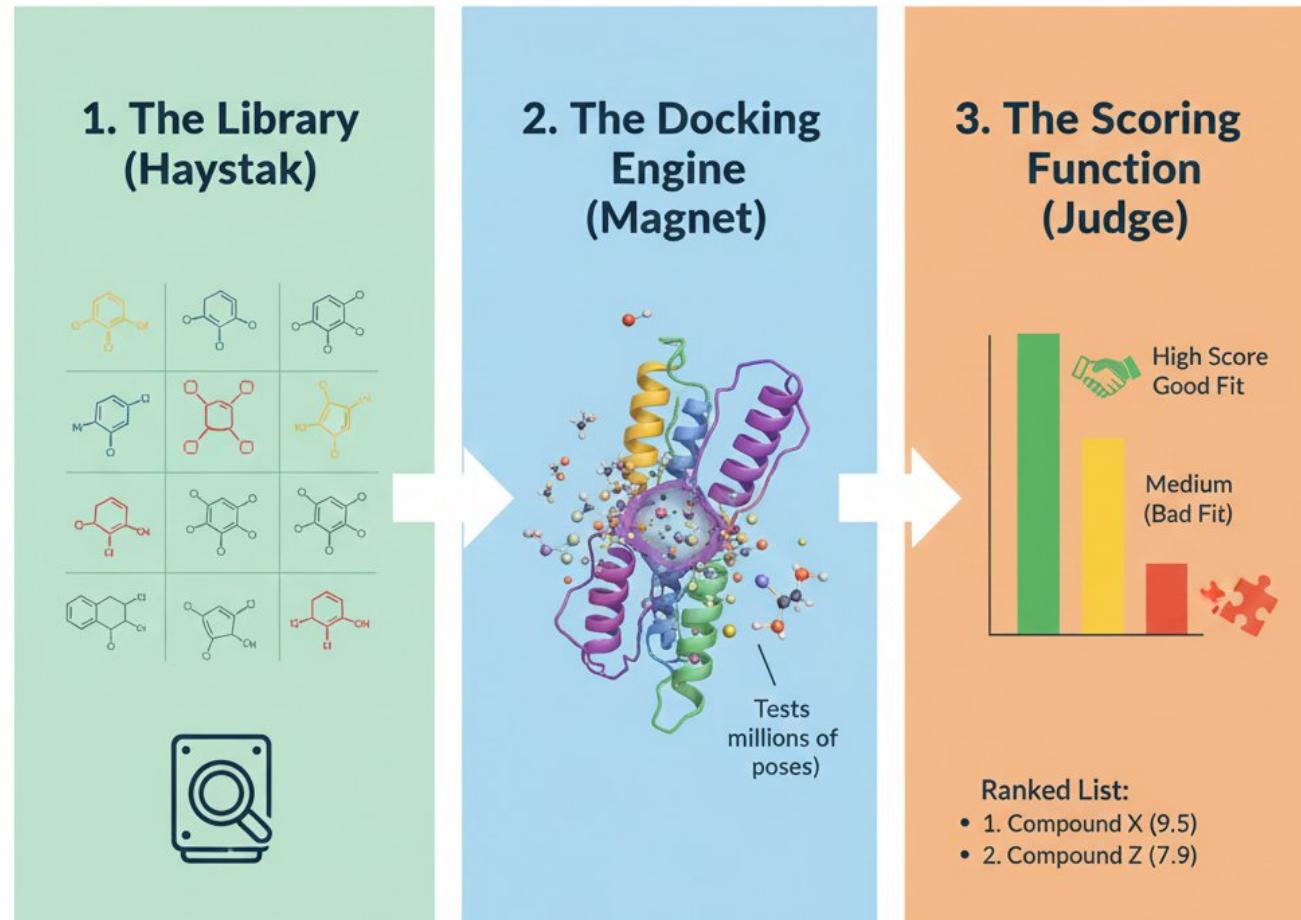
# THE CORE VOCABULARY

## (THE LANGUAGE OF DOCKING)

Term	Simple Definition	The Analogy
<b>Receptor</b>	The target protein structure that acts as "host" for travels to molecule.	 The Lock Key
<b>Ligand</b>	The specific "pocket" or hollow area where the chemical reaction happens.	 The Keyhole
<b>Binding Site</b>	A specific 3D orientation or "posture" of ligantiod happens.	 A specific "turn" of of the key
<b>Pose</b>	A mathemtical value (Energy) tells us how stable inside bon site.	 The "Click" sound
<b>Affinity</b>	A mathemtical value (Energy) that atraction the attraction becepore the receptor and the ligand.	 How hard of is pull pull the key out

# WHAT IS DOCKING BASED SCREENING..?

## Docking-Based Screening: The Digital Filter

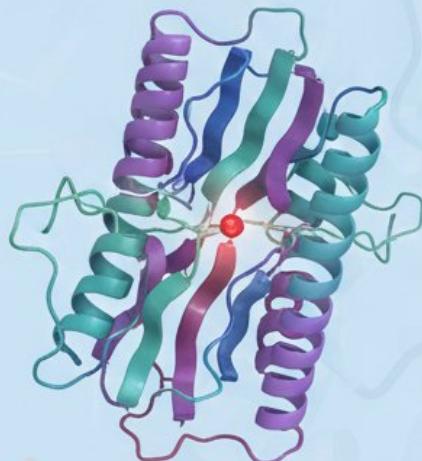


# THE WORKFLOW OF DOCKINGBASED SCREENING



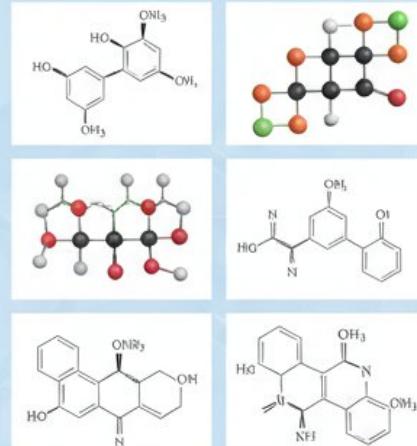
# THE COMPONENTS OF DOCKING BASED SCREENING SYSTEM

## The Receptor (Target)



A high-resolution 3D structure (-Xray or Cryo-EM).

## The Library (Ligands)



A digital database of 3D chemical structures.

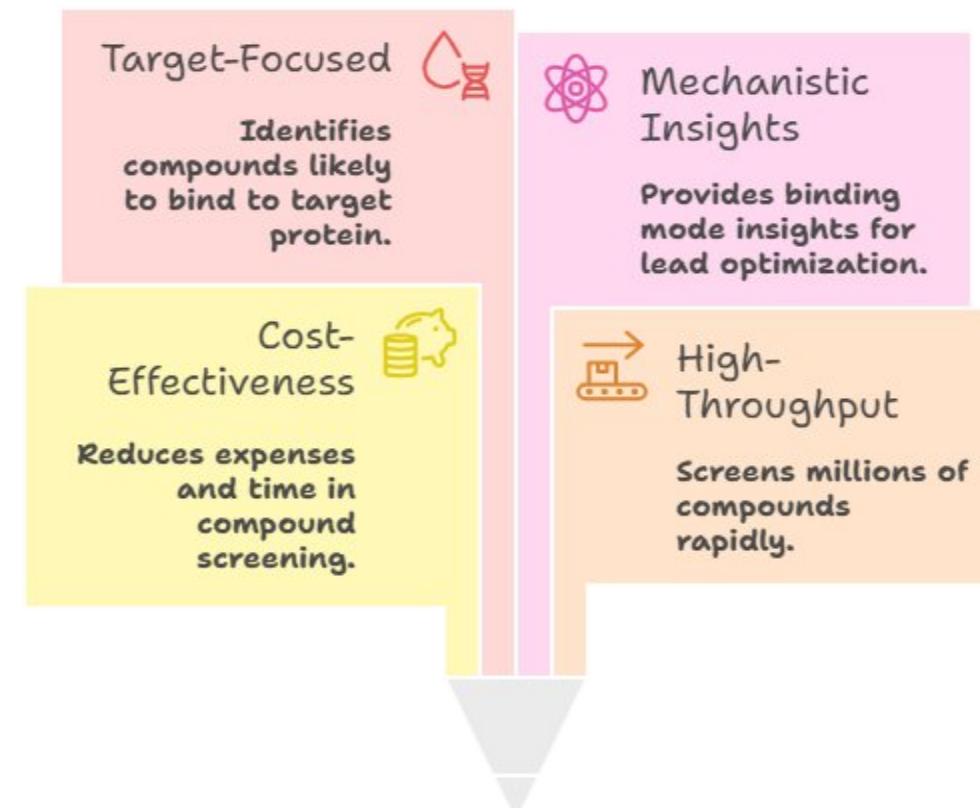
## The Engine (Software)



An algorithm that explores & evaluates.

# ADVANTAGES OF DOCKING BASED SCREENING

## Docking-Based Screening Advantages



# DISADVANTAGES OF DOCKING BASED SCREENING

## 1. Scoring Function



- Not always accurate.
- May mispredict bind 'false positives'.

## 2. Receptor Flexibility



- Proteins are dynamic.
- Most programs use rigid models.
- Miss "induced fit".

## 3. Water Molecules



- Often ignored or simplified.
- Can mediate interactions.
- Affects binding affinity.

## 4. Entropic Effects



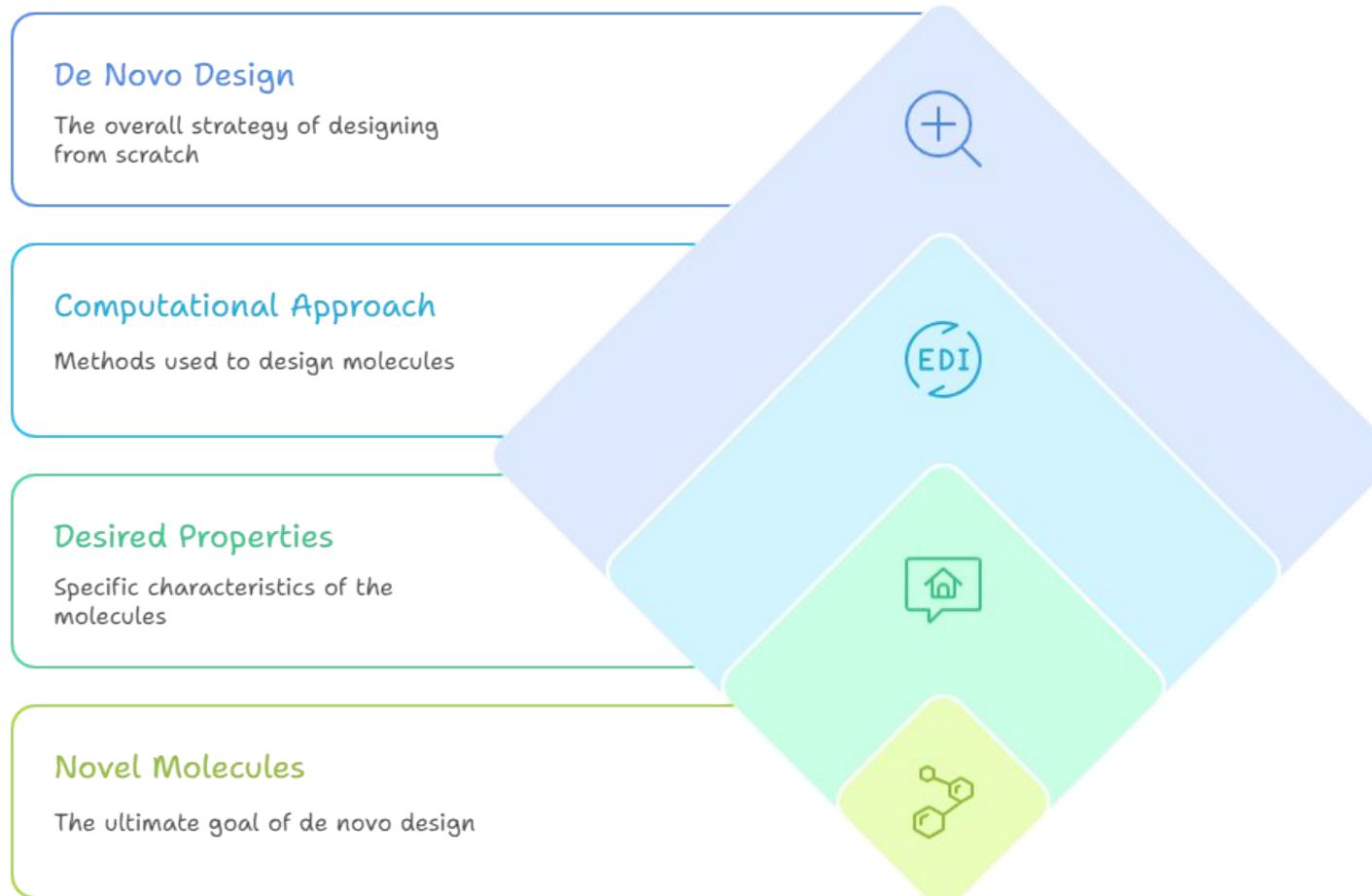
- Hard to calculate.
- Relates to molecular motion.
- Impacts binding free energy.

## 5. Solvent Effects



- Simplified solvent models.
- Bulk water properties.
- Less accurate for local effects.

# DE NOVO DRUG DESIGN PROCESS

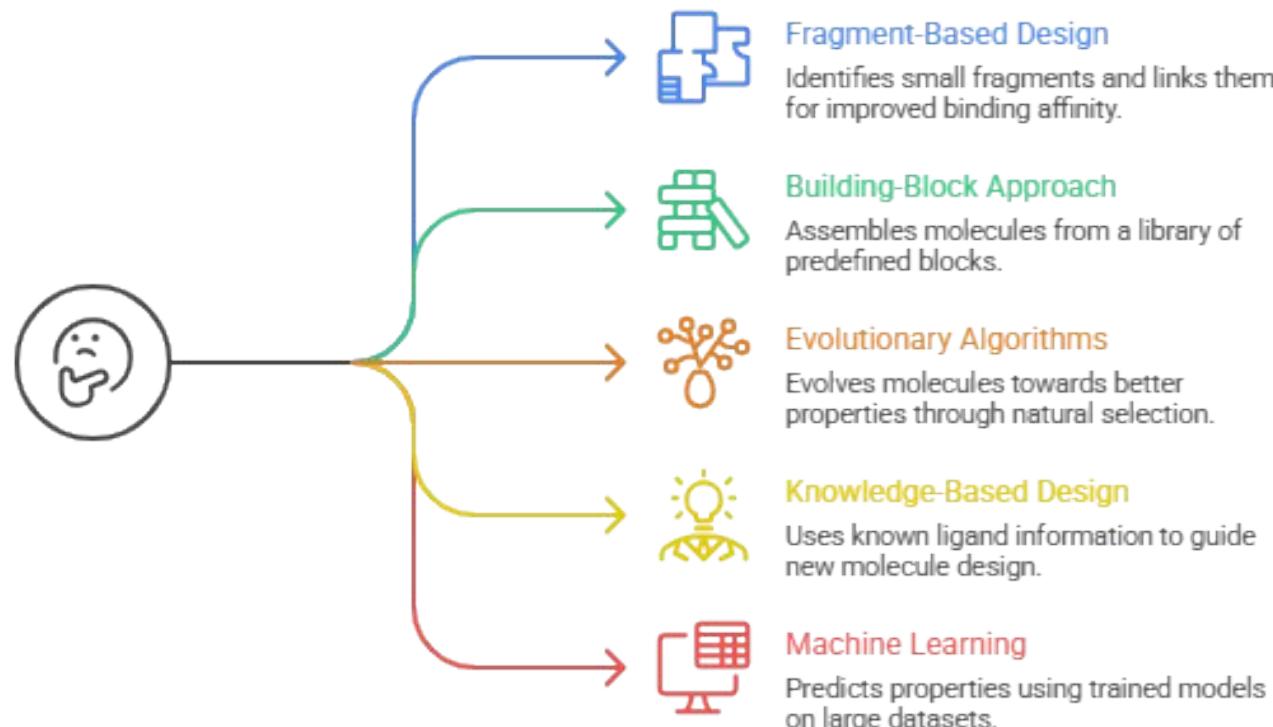


# PRINCIPLES OF DE NOVO DRUG DESIGN APPROACHES



# METHODOLOGIES IN DE NOVO DRUG DESIGN

Which de novo drug design methodology should be used?



# ADVANTAGES OF DE NOVO DRUG DESIGN

## 1. Novel Chemical Space



- Explore beyond existing molecules.
- Create unique structures.
- Avoid "me-too drugs."

## 2. Tailored to Target



- Designed for specific pocket.
- Optimize interactions.
- Maximize potency.

## 3. Intellectual Property



- Generates patentable molecules.
- Stronger market position.
- Avoidance of prior art.

## 4. Overcome Resistance



- New mechanisms of action.
- Effective against mutated targets.
- Addresses drug resistance.

# DISADVANTAGES OF DE NOVO DRUGDESIGN



## 1. Synthesizability

- May design impossible molecules.
- Complex, multi-step synthesis.
- Low success rate for bench chemists.



## Computational Cost

- Very CPU-intensive.
- Requires advanced algorithms.
- Much slower than screening.



## Limited Chemical Space

- Builds from small fragments.
- May miss large, complex drugs.
- Depends on fragment library quality.



## 4. Experimental Validation

- Novelty means no prior data.
- Requires full biological testing.
- Higher risk of late-stage failure.

# KEY APPLICATIONS OF DE NOVO DRUG DESIGN



## 1. Novel Lead Discovery

- Creates entirely new molecules.
- Complex, multi-step synthesis.
- Not limited to existing chemical libraries.
- Addresses unmet medical needs.



## Targeted Therapies

- Designs molecules specific to targets.
- Reduces off-target effects and toxicity.
- Promotes personalized medicine potential.



## Overcoming Resistance

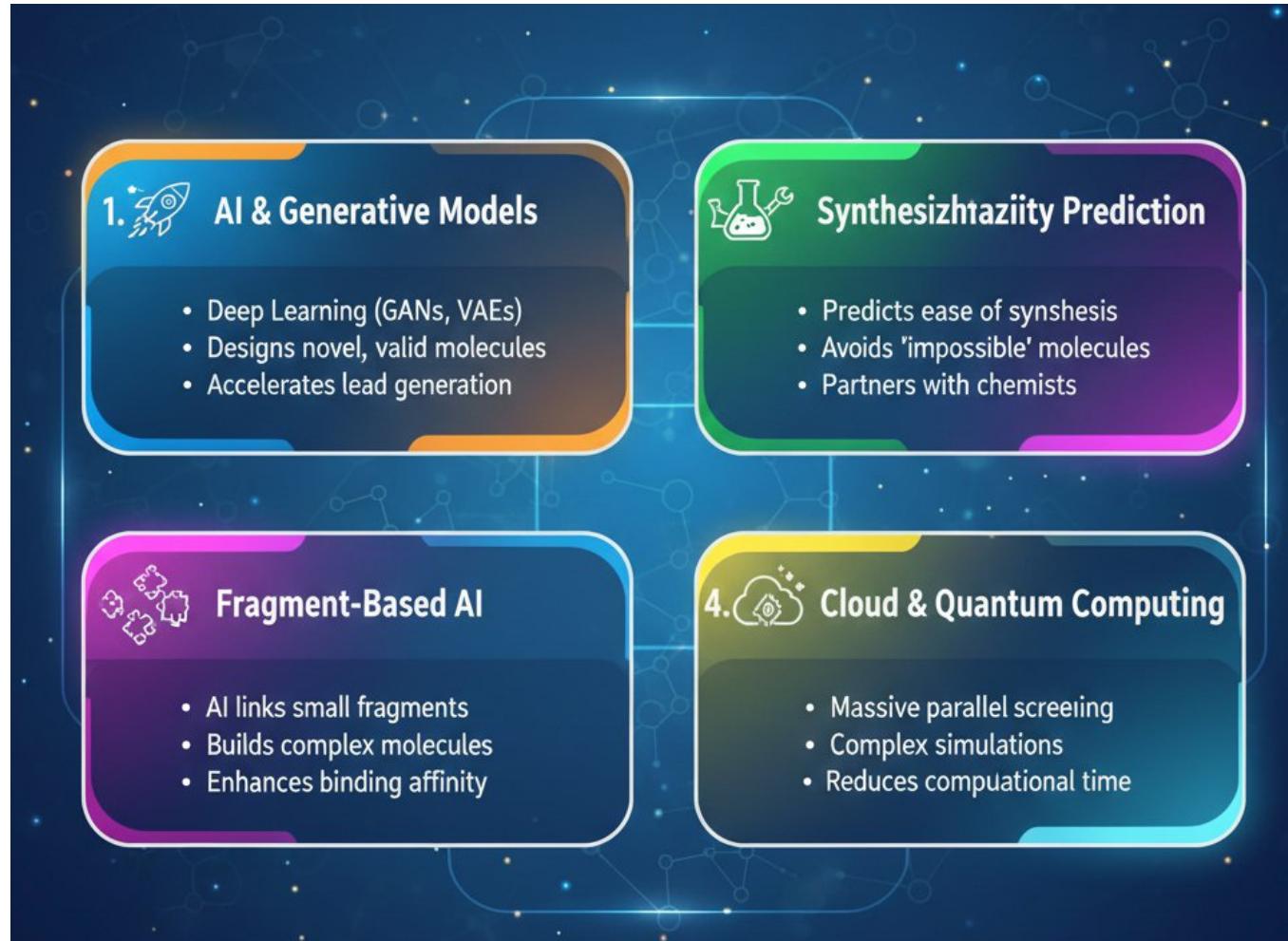
- Designs drugs against mutated proteins.
- May require drug resistance.
- Critical for antivirals & antibiotics.
- Critical for some antibiotics.



## 3. Optimizing Drug Properties

- Improves potency, selectivity, & pharmacokinetic (ADMET) properties.
- Enhances solubility and half-life.

# RECENT ADVANCEMENTS IN DE NOVO DRUG DESIGN



**1. AI & Generative Models**

- Deep Learning (GANs, VAEs)
- Designs novel, valid molecules
- Accelerates lead generation

**2. Synthesizability Prediction**

- Predicts ease of synthesis
- Avoids 'impossible' molecules
- Partners with chemists

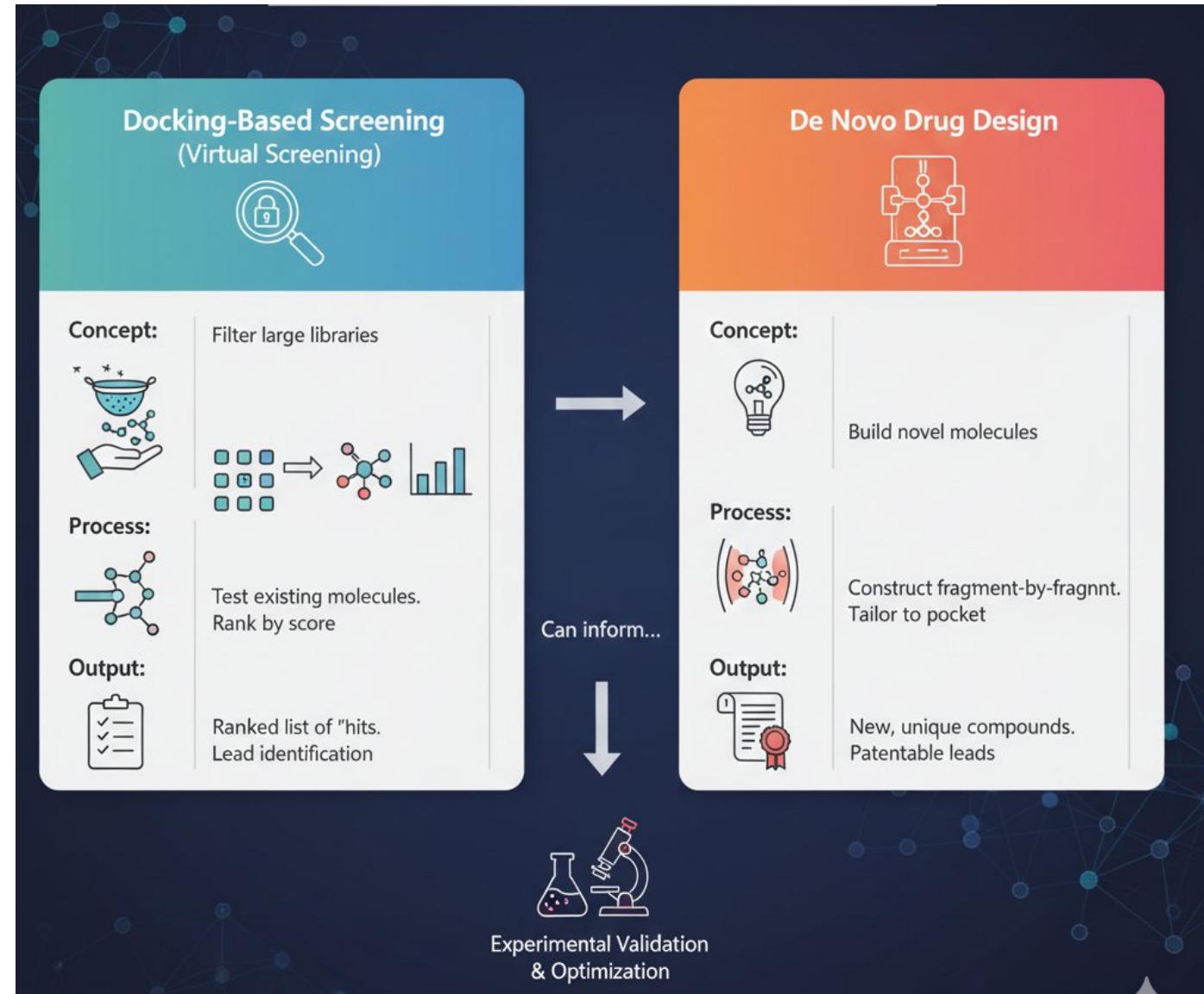
**3. Fragment-Based AI**

- AI links small fragments
- Builds complex molecules
- Enhances binding affinity

**4. Cloud & Quantum Computing**

- Massive parallel screening
- Complex simulations
- Reduces computational time

# SUMMARY



# ASSESSMENTS

Question 1 : In Virtual Screening, what is the primary purpose of the "Scoring Function"?

- A) To synthesize the drug molecule in the lab.
- B) To rank molecules based on their predicted binding affinity.
- C) To determine the 3D structure of the protein.
- D) To name the chemical compound.



Question 2: Which of the following best describes "De Novo" drug design?

- A) Searching the ZINC database for existing drugs.
- B) Testing drugs on animal models.
- C) Building a new molecule fragment-by-fragment inside a target site.
- D) Using X-ray crystallography to see a protein.



## REFERENCES

1. Molecular Docking for Computer-Aided Drug Design by Mohane Selvaraj Coumar, 1st Edition, pg. no: 120 – 145 (chapter 6 ).
2. Molecular Modeling: Principles and Applications by Andrew R. Leach, 2<sup>nd</sup> edition , pg.no :618–625.
3. Computer-Aided Drug Design by Aman Thakur, Vineet Mehta, Priyanka Nagu , 1st edition pg.no: 92/105.

