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AI-ENABLED MOLECULAR MODELLING OF MACROCYCLIC COMPOUNDS IN DRUG DISCOVERY – USAGE AND CHALLENGES

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ABSTRACT

Despite macrocyclic compounds having great potential in drug discovery, their designs still very challenging both synthetically and computationally. Molecular modelling of macrocycles poses significant challenges due to the flexibility of their ring structure, necessitating advantage beyond standard small-molecule Docking approaches to adequately address conformational variability. To manage this complexity, researchers often generate conformers before Docking or employ flexible Docking methods to explore bioactive conformations and predict interactions with protein targets comprehensively. Although these challenges persist, such methodology remains essential for structure-based drug development because it enhances stability, permeability and binding affinity in the design of new therapeutic agents. Software like AutoDock, Glide, and GOLD effectively simulate most organic molecules, whether rigid or flexible. Here we are generating a basic roadmap for the docking of macrocyclic compounds.

Keywords: macrocycles, docking, protein-ligand binding, simulation, AutoDock Vina

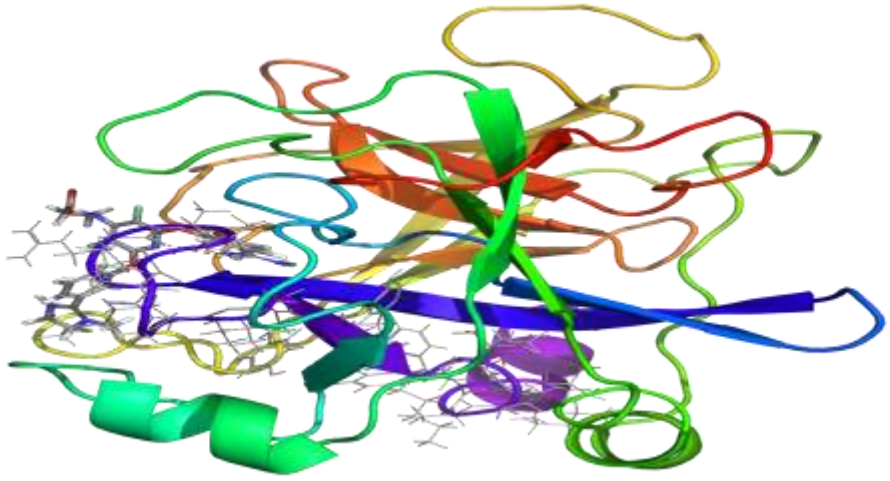

Fig.1- 3-D molecular docking visualization illustrating protein-ligand binding.
https://www.schrodinger.com/platform/products/maestro/

INTRODUCTION

Macrocyclic compounds are highly versatile due to their unique structural and chemical properties. Their multidisciplinary use spans across chemistry, biology, materials science, medicine, and environmental science, fitting them into various fields. Some fields like supramolecular chemistry, catalysis, signal transduction, protein and peptide stabilization, drug delivery, enzyme mimics, antimicrobials, cancer therapy, molecular machines, organic electric sensors, ion/molecule capture, gas storage, and many more are having a high emergence of macrocycles [1-4]. Their pre-organized, conformationally rigid structure makes them more selective in binding to biomolecules such as enzymes, receptors, and proteins. This quality of macrocyclic compounds makes them suitable candidates for targeting specific proteins and other receptors. These compounds have better potency and can possess high levels of metabolic and proteolytic

stability. At present, many macrocyclic compounds are actively used in biology, medicine and pharmaceuticals [5,6].

Generally, small-molecule medicine, having a molecular weight of less than 500 Daltons, has been the focus of drug discovery [7]. Though macrocycles are much larger compounds, they often deviate from Lipinski's "Rule of Five" guidelines for oral administration. Exceptionally, macrocycles, rings of more than 12 atoms, reside in "beyond rule-of-five" and can be administered orally [8-10]. They bind selectively to their target with greater affinity than non-macrocyclic medicines because of stronger interactions through a larger surface area. This speciality of macrocycles makes them future candidates in drug discovery for targets having "difficult" binding sites [11-13].

Alongside these synthetic initiatives, computational techniques have arisen as powerful complementary tools that are significantly enhancing the discovery of macrocycles. These methods utilize advanced algorithms and machine learning to estimate and define macrocycle structures, characteristics and their interactions with biological targets. Modern *de novo* design algorithms can construct novel virtual compounds with drug-likeness using various methodologies [14,15]. High-throughput virtual screening, molecular dynamics simulations, and structure-based design allow researchers to quickly access millions of macrocycle candidates in silico, significantly minimizing the time and resources needed for experimental synthesis and evaluation [16,17]. The integration of artificial intelligence (AI), especially deep learning models, has further accelerated the design of macrocycles by adding intricate structure activity relationships and the construction of innovative scaffolds [18,19].

Molecular Modelling of Macrocyclic Compounds

Molecular modelling of macrocyclic compounds requires a specialized work flow as standard methods often fail to sample their full conformational space. A step-by-step computational chemistry approach is needed for molecular modelling of macrocycles [20].

The recommended sequence:

1) 2D Structure designing of macrocyclic compound
2) Generation of their all-3D conformers
3) Optimization of Molecular mechanics
4) DFT refinement of the molecule for more accurate structure
5) Ensemble analysis of the molecule
6) Flexible docking or rigid docking of compound
7) MD simulation tools for molecular stability
8) Free energy calculations to quantify binding affinity

Macrocycles are computationally designed typically in a way that begins with 2D sketching with ChemDraw or MarvinSketch of the designed macrocycle, followed by conversion of 2D to 3D structure using Avogadro or RDKit. Avogadro can provide semantic chemical data editing and conversion. It also provides an integrated environment in cheminformatics [21]. For high-level conformational sampling, algorithms like RDKit ETKDG (macrocycle mode), OMEGA's macrocycle engine, are used. CREST software is a chemical space exploration software that delivers mechanized algorithms for conformational sampling and energy calculations [22]. Molecular mechanics of conformers are optimized with MMFF94, AMBER, OPLS, or CHARMM force field like software that reduces structural strain and recognizes low-energy geometries [23]. DFT enhancement improves accuracy of hydrogen bonding, intramolecular interactions, and torsional energies [24]. PCA clustering and CREST ensembles are used to determine Global minima and biologically relevant confirmations [25]. Macrocycle Docking required special handling because the ring adapts multiple torsional states. Tools like AutoDock, CrankPep, and GOLD support advanced macrocycle sampling and post-docking rescoring improves ranking accuracy [26,27]. MD simulations validate Complex stability and reveal conformational transitions. GROMACS, AMBER, and Desmond are effective tools for molecular simulation [28]. Advanced free energy methods such as FEP, Umbrella sampling, and Metadynamics quantify binding affinity and conformational barriers [29,30].

Why are macrocycles difficult to Dock?

Macrocycles are flexible and can adopt many conformations, and it is difficult to find the correct binding pose in their large ring structure. Unlike small molecules, they target less defined or difficult proteins for binding [31,32].

Important Methods in Macrocyclic Docking

Despite the difficulty in macrocycle docking, they can be docked with some extended methods discussed here-

1. Conformer Ensemble Docking – by generating multiple low-energy conformations i.e. ensembles of the macrocycle, techniques like molecular dynamics (MD) or specialised sampling are able to dock these conformers rigidly against the protein, treating each conformer as a separate ligand [33].

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2. Integrated Flexible Docking- some advanced Software like AutoDock Vina or Glide has built-in protocols to predict model bond flexibility during the docking process itself, saving time. This allows for on-the-fly conformational sampling within the binding site [34].
3. Hybrid Methods- another method is to combine MD simulations for initial sampling, followed by docking and scoring, optimising both ligand and receptor flexibility [35].

Use of AutoDock Vina in Macrocyclic Docking

The most popular open-source molecular docking application, AutoDock Vina, makes it easier and faster to dock molecules. However, docking of macrocycles is found to be difficult work because of their flexible ring shape and torsional changes in various conformations, which makes their sampling more challenging. The current version of AutoDock Vina offers Python binding, simpler scripting for virtual screenings, and other advanced applications. Currently, AutoDock Vina facilitates the creation and execution of both simple and complicated simulations. Combining with many of the features included in the AutoDock software, AutoDock Vina gives users the power to access local search [36].

Conclusion

Recent advancements in computational chemistry provide powerful tools to synthesise macrocycles virtually. The properties of macrocyclic compounds can be predicted with emerging tools and ML approaches. Their rigidity, flexibility, drug-likeness, conformational preference, specificity, toxicity, and permeability can be studied computationally. Costly synthesis methodologies and high failure rates of the synthesised drugs can be avoided by implementing these methods. These methods can provide a path to future in rational designing of macrocyclic compounds with high-binding affinities. The prospect for macrocycles in therapeutics is bright, and the near future in which rational designing of macrocycles eliminates reserved laboratories and exhaustive failures of clinical trials, is plausible.

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