2025
12(1), 1251

Chemical Biology
LETTERS

Beyond trial and error: Leveraging advanced software for Therapeutic discovery

Vanshika Rustagi[1#], Shradheya R R Gupta[1#], Archana Singh[2], Indrakant Kumar Singh[1,3*]

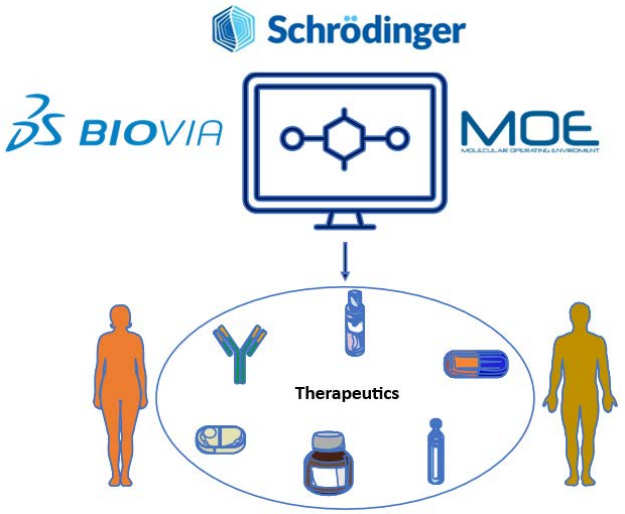
[1]*Molecular Biology Research Lab, Department of Zoology & DBC i4 Centre, Deshbandhu College, University of Delhi, Kalkaji, New Delhi, 110019, India.* [2]*Department of Plant Molecular Biology, University of Delhi South Campus, Benito Juarez Road, Dhaula Kuan, New Delhi 110021, India.* [3]*Delhi School of Public Health, Institute of Eminence, University of Delhi, Delhi, 110007 India*

Submitted on: 28-Jul-2024, Accepted and Published on: 01-Nov-2024

Review

ABSTRACT

In drug discovery, efficiency and precision are crucial elements that play pivotal roles in saving lives, time, and financial resources while pursuing groundbreaking advancements. To aid this, commercial software platforms are explicitly crafted. These platforms leverage the power of classical with quantum mechanics, machine learning and artificial intelligence to predict molecular behaviours and interactions, moving beyond traditional trial-and-error methods. These approaches fundamentally revolutionize identifying, designing, and optimizing potential drug candidates. This review compares commercial tools such as Discovery Studio, Molecular Operating Environment (MOE) and Schrödinger. Our focus is primarily on Schrödinger due to our hands-on experience on it. In addition to the comparison, we highlight Schrödinger's modules, advantages, achievements, and capacity to streamline the discovery of PROTACs, small molecule inhibitors, and antibodies.



Keywords: Schrödinger, Discovery Studio, MOE, Therapeutic, Software

INTRODUCTION

The integration of computers and advanced technologies since the late 20th century has fundamentally reshaped the field of drug discovery. In the 1990s, pharmaceutical research adopted computational tools, ushering in a new era of data analysis and high throughput screening technologies.[1,2] Subsequent advancements in the 2000s propelled machine learning and AI algorithms, enabling faster prediction and modeling of potential drug compounds, thereby moving away from reliance solely on the trial and error approach.[3,4] The 2010 marked a significant increase in data analytics, empowering researchers to extract valuable insights from vast datasets.[5] This surge expedited the identification of drug targets and deepened our comprehension of intricate biological systems. The introduction of the Internet of Things (IoT) in the 2010s revolutionized real-time data collection during experiments, transforming how experiments were monitored and analyzed.[6] These notable advancements have considerably improved the efficiency of drug discovery by reducing timelines and costs, ultimately fostering the development of effective drugs for a wide array of diseases and medical conditions. These tools' ongoing integration and progression continue to shape a future where computational power and advanced technologies drive innovation within pharmaceutical research.

Free academic tools, such as AutoDock, Avogadro, and RDKit, play a significant role in advancing the field of drug discovery.[7–9] These readily accessible platforms empower researchers to engage in molecular modeling, screening, and structure-based drug design. For instance, AutoDock proves invaluable in predicting how potential drug compounds fit within binding pockets and interact with target proteins. Similarly, Avogadro and RDKit greatly assist in visualizing and analyzing structures to identify compounds. These freely available tools democratize drug discovery, enabling researchers from institutions and laboratories to contribute to innovation and accelerate early-stage drug development. Commercial tools often come with precise databases, predictive models, and user-friendly interfaces

# Equal Contribution * Corresponding author: iksingh@db.du.ac.in

URN:NBN:sciencein.cbl.2025.v12.1251
DOI:10.62110/sciencein.cbl.2025.v12.1251

https://pubs.thesciencein.org/cbl

specifically tailored to the needs of companies and funded research institutions. By incorporating these tools, the accuracy and efficiency of drug discovery have seen significant improvements, leading to the development of effective treatments with enhanced efficacy and safety profiles.

Commercial tools like Discovery Studio, Molecular Operating Environment (MOE) and Schrödinger have substantially contributed to the drug discovery landscape by offering advanced suites of tools and features. Discovery Studio stands out for its visualization and simulation modules, revolutionizing how researchers explore structures and understand their interactions, enabling in-depth investigations into the mechanisms of drug-target binding. MOE also has a user-friendly interface with 11 diverse force fields and integrated capabilities for designing small and large molecules. It supports SVL scripting [10]. MOE can connect with programs like ADF, AMBER, ChemDraw, Corina, GAMESS, Gaussian, GOLD, Mogul, MOPAC, NAMD and Omega.[11] In contrast, Schrödinger provides a range of capabilities for molecular modeling, simulation, and structure-based drug design, facilitating comprehensive analysis and optimizing drug candidates.[12]

The review aims to introduce and compare three commercial software packages: Discovery Studio, MOE, and Schrödinger. We emphasise Schrödinger's suite of tools, including Maestro, Glide, Prime, and Desmond, due to our hands-on experience with them. This review is not intended to dictate which tool a reader should prefer but rather to explore Schrödinger's functionalities and applications. We will elucidate the features and capabilities of these packages and their contributions to various stages of the drug discovery process, encompassing molecular modeling, simulations, and both structure- and ligand-based drug design.[13]

Comparison: Discovery Studio v/s Molecular Operating Environment (MOE) v/s Schrödinger

Discovery Studio is compatible with Windows and Linux. It includes tools such as CHARMM and NAMD for molecular dynamics,[14] LibDock for high throughput and CDOCKER for accurate and flexible docking,[15] fragment docking using MCSS program, MODELER for homology modeling,[16] QSAR for quantitative structure-activity relationship analysis, Catalyst for pharmacophore modeling,[17] prediction of protein aggregation site, CNX explorer available for three-dimensional structure determination and analysis of macromolecules using experimental crystallographic diffraction or nuclear magnetic resonance (NMR) data, protein-protein docking using RDock and Zdock, the phylogenetic analysis also available using BLAST, antibody modeling for vaccine design, small molecules filtering via ADMET, Lipinski, TOPKAT, and Pipeline Pilot for workflow automation and data analysis. It provides advanced 3D visualization for molecular modeling. It is known for robust protein modeling, pharmacophore modeling, and QSAR, making it a strong choice for structure-based drug design, ligand-based drug design, and protein-ligand interactions.[18] Despite its comprehensive suite and high-quality visualization, it has a steep learning curve and can be expensive. Discovery Studio is widely used in academia and industry for structural biology and drug discovery.

MOE, supporting Windows, macOS, and Linux, features the MOE Suite with SVL scripting language.[19] It is praised for its versatility, strong cheminformatics and bioinformatics integration, and cost-effective academic licensing.[20] However, its extensive feature set can be challenging, and some may find its interface dated. MOE's primary focus areas include integrated computational chemistry, bioinformatics, and drug discovery.[21] It is respected in academic and industrial settings for its comprehensive tools and customization capabilities.

Schrödinger offers a comprehensive suite of tools, including Prime for protein structure prediction, Glide for molecular docking,[22] and Phase for pharmacophore modeling. These tools are supported by Windows, macOS and Linux. Other tools which require calculations like, Desmond for molecular dynamics, Jaguar for integrating quantum mechanics and FEP+ for free energy perturbation is supported by Linux. It also offers LiveDesign for collaborative online drug discovery.[23] Schrödinger's software is highly regarded in the pharmaceutical industry for its accuracy and user-friendly interface, although it is costly and demands significant computational resources. The primary focus areas of Schrödinger are drug discovery, molecular dynamics, and quantum chemistry. It has been instrumental in establishing collaboration with research institutions to discover drugs like SGR-1505, a clinical-stage MALT1 inhibitor.[24]

Discovery Studio excels in protein modeling, visualization, and structural biology applications. MOE is valued for its versatility and integration with other software. Schrödinger is known for its predictions of binding affinity and user-friendly interface.

Table 1: Comparison of key features and attributes of Schrödinger, Discovery Studio, and MOE software.

Feature/Tool	Schrödinger	Discovery Studio	MOE (Molecular Operating Environment)
Platforms	Windows, macOS, Linux	Windows, Linux	Windows, macOS, Linux
User Interface	GUI-based	GUI-based advanced 3D visualization	Customizable via SVL, less intuitive
Customization	Customizable constraints	Decent range of tools	Extensive customization through scripting
Learning Curve	Moderate	High	High due to scripting requirements
Major Tools	Maestro, Glide, Jaguar, Desmond, Prime, FEP+	CHARMM, LibDock, QSAR,	MOE Suite, Dock, SVL, Pharmacophore Discovery,

		MODELER CDOCKER	Molecular Dynamics
Focus Area	Drug discovery, materials science, molecular dynamics	Protein design, structure and ligand-based drug design	Integrated computational chemistry, Drug discovery, cheminformatics, molecular modeling
Advantages	Comprehensive suite, high accuracy, cloud collaboration, integration	Robust protein modeling, Extensive features, advanced visualization, automation	Versatile, highly customizable
Disadvantages	High-cost, resource-intensive	Steeper learning curve	A steeper learning curve, dated UI
Market Position	Leading in the pharmaceutical industry, widely recognized	Used in academia and industry	Versatile, highly respected in academia

COMPARISON: OPEN V/S PAID DOCKING TOOL:

Open source docking tools like AutoDock,[25] GemDock,[26] AutoDock Vina,[27] and Hex[28] are freely available to use.[29] Amongst them, AutoDock Vina is the most commonly used software. Various factors differentiate tools like AutoDock Vina from Glide.

Glide and AutoDock Vina are powerful molecular docking tools that utilize empirical scoring functions to predict ligand-receptor interactions, but they do so with distinct approaches. Glide employs the Emodel scoring function to select optimal protein-ligand complexes. It uses GlideScore to rank ligands based on binding affinity, focusing on separating active compounds from inactive through detailed physics-based terms, including lipophilic-lipophilic interactions, hydrogen bonds, and hydrophobic enclosure. AutoDock Vina, on the other hand, estimates the free energy of binding by considering intermolecular interactions like van der Waals and Coulombic forces and intramolecular ligand dynamics.[30] Vina's scoring also incorporates Gaussian functions, hydrogen bonding, and torsional strain, coupled with a dual optimization strategy that combines global and local search techniques.[31] While Glide emphasizes maximizing the separation of strong and weak binders, AutoDock Vina focuses on precisely estimating binding affinity through a comprehensive exploration of ligand conformations.

Both employ sophisticated search algorithms for predicting the binding modes of small molecules to their protein targets, but they do so with different strategies. Glide uses a systematic search algorithm that approximates a complete exploration of the ligand's conformational, orientational, and positional space. It starts with a rough positioning and scoring phase, using hierarchical filters to narrow down the search space, followed by torsionally flexible energy optimization on an OPLS-AA grid.[32] The most promising candidates then undergo Monte Carlo sampling for pose refinement, ensuring accurate docking predictions while managing computational costs effectively. In contrast, AutoDock Vina utilizes a global optimization algorithm based on a gradient-based local search genetic algorithm (GA). This process begins with random ligand conformations, followed by iterative refinement through selection, mutation, and crossover to identify the global minimum energy conformations. Vina's GA evaluates binding energies based on ligand-protein interactions, selecting optimal conformations to generate diverse solutions until the best binding modes are identified. While Glide emphasizes a hierarchical and exhaustive search approach with precise energy optimizations, Vina relies on the genetic algorithm's ability to explore a broad conformational space and converge on the most favourable binding solutions.[33]

Glide and AutoDock Vina excel in different aspects of molecular docking, making them suitable for different projects. Glide is highly regarded for its precision, particularly in handling ligands with many rotatable bonds, due to its advanced scoring function and the extra-precision (XP) mode allows it to predict binding affinities and docked poses with remarkable accuracy. However, this level of accuracy comes at the cost of higher computational demands, making Glide ideal for tasks where precision is paramount. In contrast, AutoDock Vina offers a balance between accuracy and computational efficiency. Vina is faster and less resource-intensive, making it a preferred choice for large-scale virtual screenings where speed is crucial.[27] While Vina provides good accuracy for many applications, it may not reach the same level of precision as Glide, especially in complex docking scenarios.

SCHRODINGER DESCRIPTION:

Due to several pivotal factors discussed above and others, like marketing collaboration with academic and commercial institutions, Schrödinger has emerged as a leading entity in the drug discovery field. Its success is rooted in a blend of software solutions, a dedicated focus on innovation, and invaluable collaborations. Schrödinger's software portfolio provides a comprehensive suite of tools that cater to various stages of drug development, offering advanced capabilities for molecular modeling, simulations, and structure- and ligand-based drug design.[34] The company's unwavering commitment to enhancing its algorithms and methodologies ensures that its software remains at the forefront of advancements within this field.[35] Furthermore, strategic partnerships with companies and research institutions have fortified Schrödinger's position by seamlessly integrating its tools into industrial workflows and research pipelines.[20] Further key modules and integrated software in Schrodinger are described below.

1. Maestro:

Maestro is indispensable in the Schrödinger Suite, serving as the primary platform for molecular modeling and computational drug discovery. Its user-friendly graphical interface empowers researchers and scientists to engage in critical tasks crucial for

drug development. The seamless integration of tools and functionalities within Maestro facilitates effortless navigation and utilization, covering diverse aspects of molecular modeling and drug discovery.[36]

Within Maestro, researchers can access an extensive toolkit supporting key stages in drug development, encompassing molecule analysis, manipulation, and visualization.[37] This includes support for docking, molecular dynamics simulations, free energy calculations, quantum mechanics calculations, and ligand- and structure-based drug design.[38–40] Its precision in constructing, modifying, and assessing intricate molecular models allows researchers to explore potential drug candidates efficiently, thereby streamlining early-stage drug discovery through rapid screenings that assess compound libraries for promising candidates.[41]

After the 2020-3 release, the standalone Canvas application key features integrated with Live Design and Maestro. Canvas is a central hub for organizing and managing diverse datasets, encompassing chemical structures, bioactivity data, and computational results.[42] Among its primary features are R-group Analysis, Shape Screening, identification of scaffolds in libraries, selection of diverse compounds, fingerprint calculation, and compound clustering through various methods such as K-Means Clustering, Hierarchical Clustering, Principal Components Analysis, and Maximum Common Substructure.[43] Moreover, the platform facilitates the construction and application of QSAR models using algorithms like Bayes Classification, Multiple Linear Regression, Partial Least Squares Regression, Kernel-Based PLS Regression, and Principal Components Regression.[44] Integrating Canvas with Live Design and Maestro streamlines the user experience and shifts the platform's architecture.

A significant advantage of Maestro lies in its integration with other Schrödinger software such as Glide, Prime, and Desmond. This seamless integration fosters a connected environment, enabling researchers to harness tools that collectively address various facets of molecular modeling. This synergy optimizes and enhances drug development, showcasing Maestro's pivotal role in facilitating comprehensive and efficient drug discovery efforts.

2. Glide:

Glide, a prominent software within Schrödinger's suite, is a robust molecular docking tool crucial for differentiating promising compounds from less favourable ones. They are known for their remarkable precision and rapid performance. Glide was explicitly designed to forecast and explore how small molecules bind to target proteins, a critical phase in the drug design process. Glide adeptly models the fit and interaction of potential drug compounds with specific biological targets using advanced hierarchical clustering algorithms, providing researchers with comprehensive insights into their potential effectiveness.[45]

Glide presents three distinct docking protocols: High-Throughput Virtual Screening (HTVS), Standard Precision (SP) and Extra Precision (XP), along with the inclusion of Covalent Docking.[46,47] HTVS utilizes a faster algorithm with reduced computational demands, enabling swift evaluations of numerous compounds to filter out potential candidates for further investigation (Figure 1). Despite sacrificing some precision for speed, HTVS is an efficient tool for preliminary screenings and broad assessments. Standard Precision (SP) mode balances speed and accuracy. In contrast, the Extra Precision (XP) mode stands out for its emphasis on accuracy, employing a more exhaustive algorithm to ensure higher precision in predictions. Additionally, Covalent Docking within Glide is a specialized mode that specifically considers interactions involving covalent bonds between ligands and target proteins.[48] This mode allows researchers to simulate and analyze compounds that form irreversible covalent bonds with the target protein, offering a unique perspective on drug discovery.

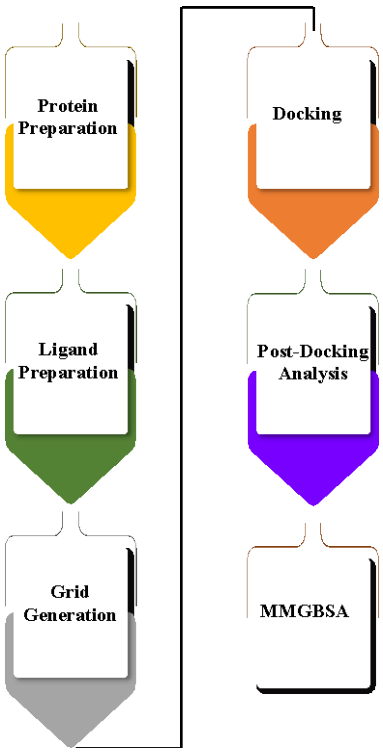


Figure 1: Workflow for performing Docking on Schrodinger software.

This software excels in efficiently screening vast compound libraries against target proteins, employing a parallel computational power to accelerate identifying and ranking potential drug candidates for further investigation. They are primarily used for structure-based drug design. Glide empowers researchers to enhance the efficiency and specificity of compounds by fine-tuning and optimizing them.[49] As an indispensable tool for computational chemists and pharmaceutical researchers, Glide significantly expedites and enhances the drug development process. Its reliability, efficiency, and accuracy establish it as a cornerstone in drug discovery. Further, steps to perform docking has been discussed in the supplementary material. The steps include, protein-ligand preparation, grid generation, docking, and visualization.

3. Prime:

Schrödinger's drug discovery toolkit includes a standout tool called Prime, designed to tackle the challenges of predicting,

refining, and engineering protein structures.[50] Primes' primary purpose is to provide reliable predictions of protein structures.[51] It offers solutions for homology modeling, loop modeling, and ab initio structure prediction.[52,53] These capabilities are crucial for understanding how proteins are arranged in three dimensions, which is vital for designing and optimizing drugs. Prime generates high-quality protein structures when experimental structures are unavailable or existing ones need refinement.[54] This allows researchers to gain insights into the basis of biological processes and interactions.[55]

In addition to its core capabilities in protein structure prediction and refinement, Prime in the Schrödinger toolkit extends its functionalities to include crucial aspects of ligand binding and membrane permeability predictions. One notable feature is the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) calculation, which Prime employs to estimate the binding free energy of ligands to their target proteins.[56] This method combines molecular mechanics calculations with a generalized Born solvation model and surface area terms, providing a more accurate representation of the energetics involved in ligand binding. MM-GBSA calculations in Prime aid researchers in prioritizing and optimizing ligands by assessing their potential binding affinities, contributing valuable insights to the drug discovery process.[57]

However, it's essential to acknowledge these predictions' inherent challenges and limitations. The accuracy of homology modeling is inherently dependent on the availability of closely related template structures, and inaccuracies can arise in the absence of suitable templates. Additionally, loop modeling in regions with high flexibility or extreme conformational changes may present challenges.[58] While MM-GBSA calculations offer a valuable estimate of binding free energy, they are based on certain assumptions and approximations, and their accuracy can vary depending on the system and methodology employed. Similarly, membrane permeability predictions involve complex interactions with biological membranes, and accurate assessments may be influenced by factors such as compound solubility and specific membrane properties.

Recent updates to Prime have focused on refining its algorithms and enhancing its capabilities. Improved template selection methods, incorporation of advanced machine learning techniques and AlphaFold contribute to more accurate predictions.[59] Additionally, updates have addressed challenges related to loop modeling, expanding the applicability of Prime to a broader range of protein structures.

4. Desmond:

Desmond, a program specializing in dynamics simulations, has significantly influenced the domain of computational chemistry, particularly in the context of drug discovery.[60] Its user-friendly interface simplifies both setup and execution compared to academic tools, and its robust, high-performance computing capabilities ensure the accuracy of simulations.[61] Desmond's compatibility with various force fields enhances flexibility, enabling simulations across a spectrum of biological systems. However, certain challenges, such as computational burdens and the necessity for validation against experimental data, need to be addressed. Recent updates in Desmond focus on refining sampling strategies, fine-tuning force fields, and integrating machine learning to enhance the precision of simulations.[62] Steps to perform MD simulation has been discussed in the supplementary material.

Desmond employs cutting-edge techniques to augment its capabilities, including replica exchange, meta-dynamics, binding pose meta-dynamics, and free energy perturbation (FEP).[63,64] Replica exchange involves switching configurations while simulating at different temperatures, improving space exploration to capture critical events in understanding protein dynamics and ligand binding.[65] Meta-dynamics is a sampling method that effectively navigates conformational spaces and overcoming energy barriers, facilitating the study of protein changes and routes of ligand binding in drug discovery. A variant, binding pose meta-dynamics, specifically focuses on identifying appropriate ligand binding positions. Additionally, Desmond utilizes free energy perturbation (FEP) to calculate free energy differences between ligands or states, guiding chemistry efforts in drug design by predicting accurate binding energy changes and understanding the thermodynamics of ligand binding.[63,66]

This versatile tool enables the study of changing behaviours in biological molecules, offering a profound understanding of their interactions, movements, and structural changes at the atomic level over time. It aids in predicting how mutations may impact drug effectiveness and provides insights into the kinetics of ligand binding-critical for designing precise and efficient treatments.

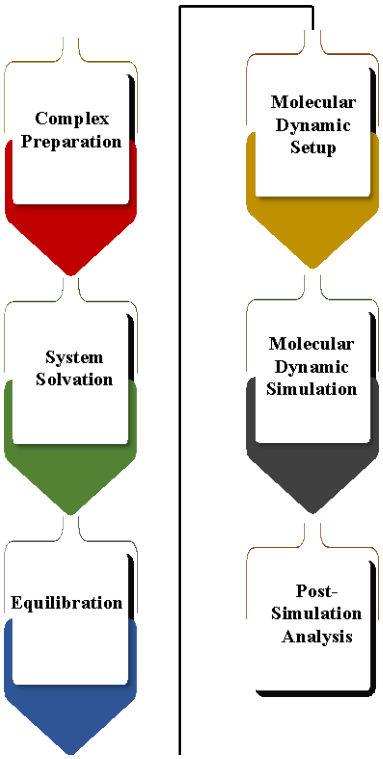


Figure 2: Workflow for performing MD Simulation on Schrodinger software.

5. KNIME integration:

Integrating Schrödinger's drug discovery tools with KNIME, an open-source data analytics platform, establishes a synergistic collaboration that enhances the effectiveness and efficiency of the drug discovery process.[67] Incorporating KNIME into the Schrödinger suite is designed to optimize the workflow for data processing, improving accessibility and compatibility with various resources. This adaptable architecture empowers bench scientists and computational researchers to collaboratively create and refine reproducible workflows spanning tasks such as data preparation, analysis, retrieval, and visualization across teams and projects.[68]

The integration of KNIME with Schrödinger tools offers notable advantages. It provides researchers with an efficient environment to access a spectrum of molecular modeling, computational chemistry, and drug discovery applications. This integration simplifies protocol management and data format handling, resulting in a more streamlined drug discovery process. KNIME's modular and adaptable architecture facilitates incorporating features and tools, ensuring the system's ability to meet evolving research requirements. Moreover, this integration facilitates comprehensive analysis of drug discovery datasets from various perspectives by enabling data integration.[69]

However, challenges accompany the merging of KNIME and Schrödinger tools. Data interoperability and workflow dependencies must be considered to ensure seamless integration across different software platforms. Users unfamiliar with the KNIME interface may encounter a learning curve, though the platform's user-friendly design helps mitigate this challenge. Additionally, the effectiveness of the integration depends on updates and compatibility testing as both KNIME and Schrödinger tools evolve. Recent enhancements in KNIME, including data processing capabilities, workflow automation, and visualization features, have further strengthened its role as an integration partner for Schrödinger tools.

6. Linux and Python integration:

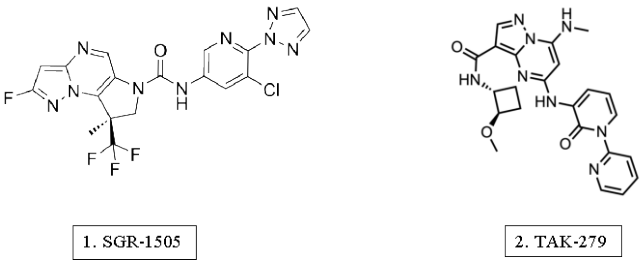
Linux in the Schrödinger drug discovery toolkit provides increased flexibility, scalability and workflow customization options. With its known stability and security, Linux forms a foundation for Schrödinger's toolkit. By integrating Linux, scientists can efficiently execute resource-intensive jobs, like quantum calculations and molecular dynamics simulations, using Linux clusters and high-performance computing (HPC) environments.[70] This integration enables seamless execution of tasks, empowering researchers to tackle the intricacies of drug discovery.

Furthermore, incorporating Python into the Schrödinger toolkit adds a layer of functionality. Python, known for its versatility, acts as a scripting language that allows researchers to create and automate complex workflows. This integration enables the development of customized tools and scripts that cater to research requirements, making data processing, analysis, and visualization more accessible. By leveraging Python libraries like NumPy and Pandas, researchers can easily manipulate datasets generated by Schrödinger tools, thereby enhancing the effectiveness of drug discovery projects. Moreover, Python’s integration promotes collaboration and facilitates reproducibility by simplifying sharing and replication across projects and teams.

Combining Python and Linux in Schrödinger's drug discovery toolkit offers many benefits. Linux's stability and efficiency ensure reliable outcomes for large-scale simulations and computations, providing a consistent and repeatable foundation. Meanwhile, Python's scripting flexibility empowers users to customize workflows, automate repetitive tasks and seamlessly integrate third-party tools. This addresses the evolving needs of drug discovery. Additionally, the collaborative and open nature of Linux and Python fosters the integration of cutting-edge technologies and approaches, enhancing the toolkit's adaptability in drug discovery.

7. Recent Success:

Schrödinger's innovative strides in pharmaceutical research are underscored by the significant achievement of their MALT1 Inhibitor, SGR-1505, which has received clearance for Phase 1 clinical development and is displayed in Figure 2.1.[71] This milestone is complemented by the concurrent development of the Wee1 inhibitor SGR-3515 and the CDC7 inhibitor SGR-2921, illustrating Schrödinger's steadfast commitment to advancing therapeutic solutions.[72,73] Collaborating with Nimbus Therapeutics, Schrödinger scientists have contributed significantly to the field by discovering the selective and potent Tyk2 inhibitor TAK-279, displayed in Figure 2.2.[74] In the domain of antiviral therapeutics, Schrödinger has actively partnered with industry leaders like Takeda, Novartis, Gilead Sciences, and WuXi AppTec, collectively working to develop promising treatments against SARS-CoV-2.



1. SGR-1505 2. TAK-279

Figure 2: Structure for SGR-1505, a MALT-1 inhibitor and TAK-279, a Tyk2 inhibitor**.**

Furthermore, collaborative efforts with Structure Therapeutics have presented preclinical and Phase I dose data for GSBR-1290, an oral GLP-1R targeting Type 2 diabetes and obesity.[75,76] Notably, Morphic Therapeutic's unveiling of new biomarker data for MORF-057 at Digestive Disease Week 2023 signifies progress in developing an orally available α4β7 inhibitor for ulcerative colitis and Crohn's disease.[77] Ajax Therapeutics' positive preclinical data on AJ1-10502, a next-generation Type II JAK2 inhibitor, presented at the ASH Annual Meeting, demonstrates enhanced selectivity and efficacy across multiple disease models of myeloproliferative neoplasms.[78]

Schrödinger's recent introduction of the LRRK2 Inhibitor Program targeting neurodegenerative diseases further solidifies their commitment to addressing unmet medical needs. This commitment is also evident in incorporating new targets into

ongoing collaborations with Bristol Myers Squibb and Eli Lilly and Company, alongside a new collaboration and software agreement with Otsuka Pharmaceutical Co., Ltd.[79] Collectively, these achievements showcase Schrödinger's multifaceted approach to advancing pharmaceutical innovation and fostering impactful collaborations within the industry.

Conclusion

The advancement of various innovative tools and technologies in drug discovery has profoundly transformed the landscape of medical research and development. Commercial tools, encompassing a wide range of applications from high-throughput screening and molecular modeling to advanced computational techniques and laboratory automation, have collectively accelerated the identification and optimization of novel therapeutic compounds. Integrating these diverse methodologies has enhanced the efficiency and precision of drug discovery processes and expanded the potential to address complex diseases with unprecedented accuracy.

Software preference often aligns with familiarity, but assessing the relative accuracy of molecular modeling packages like Discovery Studio, MOE, and Schrödinger requires direct comparison or literature review. No single metric can evaluate a comprehensive suite's overall accuracy; instead, specific aspects with reliable experimental values should be considered. The choice of software depends on particular needs, such as drug discovery, protein modeling, ease of use, or integrated bioinformatics capabilities.

Schrödinger's success is rooted in its comprehensive software portfolio, commitment to innovation, and strategic collaborations. Maestro stands out as a user-friendly platform for molecular modeling, integrating seamlessly with other Schrödinger tools. Glide exemplifies precision in molecular docking, Prime addresses protein structure prediction, and Desmond offers profound insights into molecular dynamics. Integrating Schrödinger's tools with platforms like KNIME, Linux, and Python enhances utility and flexibility, streamlining workflows, providing stability, and allowing customization.

Despite its advancements, challenges remain regarding the price and availability of Schrödinger's software, which may limit its accessibility for small research organizations and academic institutions [80]. Addressing these concerns is essential for promoting inclusivity and fully harnessing the potential of computational tools in drug discovery. Overall, computational tools represent a cornerstone in contemporary drug discovery, and as the pharmaceutical industry evolves, computational methodologies will continue to drive innovation.

Contribution Statement

V.R. and S.R.R.G: conceptualization, data collection, data analysis, and original draft preparation. A.S. and I.K.S.: reviewing, editing, and supervision. All authors contributed to the manuscript revision and approved the submitted version.

Conflict of Interest

The authors declare that they have no conflicts of interest and that all authors have approved the manuscript.

Funding

No funding was obtained.

Acknowledgements

Authors are thankful to Deshbandhu College for providing basic infrastructural support at the DBC i4 centre.

Supplementary Information

Detailed steps to perform MD simulation has been provided in the supplementary material file which can be downloaded freely from article page on journal site.

References

1. R.L. Clark, B.F. Johnston, S.P. Mackay, et al. The Drug Discovery Portal: a resource to enhance drug discovery from academia. *Drug Discov Today* **2010**, 15 (15–16), 679–683.
2. P. Szymański, M. Markowicz, E. Mikiciuk-Olasik. Adaptation of High-Throughput Screening in Drug Discovery—Toxicological Screening Tests. *Int J Mol Sci* **2011**, 13 (1), 427–452.
3. S. Dara, S. Dhamercherla, S.S. Jadav, C.M. Babu, M.J. Ahsan. Machine Learning in Drug Discovery: A Review. *Artif Intell Rev* **2022**, 55 (3), 1947–1999.
4. D. Paul, G. Sanap, S. Shenoy, et al. Artificial intelligence in drug discovery and development. *Drug Discov Today* **2021**, 26 (1), 80–93.
5. N. Elgendy, A. Elragal. Big Data Analytics: A Literature Review Paper; **2014**; pp 214–227.
6. J. Gubbi, R. Buyya, S. Marusic, M. Palaniswami. Internet of Things (IoT): A vision, architectural elements, and future directions. *Future Generation Computer Systems* **2013**, 29 (7), 1645–1660.
7. M.D. Hanwell, D.E. Curtis, D.C. Lonie, et al. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *J Cheminform* **2012**, 4 (1), 17.
8. G.M. Morris, D.S. Goodsell, R. Huey, A.J. Olson. Distributed automated docking of flexible ligands to proteins: parallel applications of AutoDock 2.4. *J Comput Aided Mol Des* **1996**, 10 (4), 293–304.
9. L. Wang, Q. Zhang, Z. Wang, W. Zhu, N. Tan. Design, synthesis, docking, molecular dynamics and bioevaluation studies on novel N-methylpicolinamide and thienopyrimidine derivatives with inhibiting NF-κB and TAK1 activities: Cheminformatics tools RDKit applied in drug design. *Eur J Med Chem* **2021**, 223, 113576.
10. F.H. Allen. The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallogr B* **2002**, 58 (3), 380–388.
11. R.J. Deeth, N. Fey, B. Williams–Hubbard. DommiMOE: An implementation of ligand field molecular mechanics in the molecular operating environment. *J Comput Chem* **2005**, 26 (2), 123–130.
12. T.R. Webb. Improving the Efficiency of the Drug Development by Expanding the Scope of the Role of Medicinal Chemists in Drug Discovery. *ACS Med Chem Lett* **2018**, 9 (12), 1153–1155.
13. R. Kataria, A. Khatkar. Molecular docking, synthesis, kinetics study, structure-activity relationship and ADMET analysis of morin analogous as Helicobacter pylori urease inhibitors. *BMC Chem* **2019**, 13 (1), 45.
14. Biovia. BIOVIA, Dassault Systèmes https://www.3ds.com/products/biovia/reference-center (accessed Aug 1, 2024).
15. C.M. Venkatachalam, X. Jiang, T. Oldfield, M. Waldman. LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites. *J Mol Graph Model* **2003**, 21 (4), 289–307.
16. Biovia. Macromolecule Modeling with Biovia Discovery Studio https://www.3ds.com/fileadmin/PRODUCTS-SERVICES/BIOVIA/PDF/macromolecule-modeling.pdf (accessed Aug 1, 2024).
17. biovia. QSAR, ADMET & Predictive Toxicology https://www.3ds.com/products/biovia/discovery-studio/qsar-admet-predictive-toxicology (accessed Aug 1, 2024).

18. K. Madaan, S. Mehta, R. Singh. Structure-Based Virtual Screening, ADMET prediction and Molecular Dynamics simulation of isoindolin-1-one scaffolds as potential inhibitors of MNK2. *Biomedical and Therapeutics Letters* **2024**, 11 (2), 910.
19. 910-1010 Chemical Computing Group ULC. Molecular Operating Environment (MOE) 2022.02 https://www.chemcomp.com/en/index.htm (accessed Aug 1, 2024).
20. U. Roy, L.A. Luck. Molecular modeling of estrogen receptor using molecular operating environment. *Biochemistry and Molecular Biology Education* **2007**, 35 (4), 238–243.
21. S.I. Khalivulla, U.R.S. Arigala, B.K.K. Althurthi. Molecular Docking Studies of 3a,4-dihydro-3H- [1,3,2] oxazaphospholo [3,4-a]Indole-1-oxide derivatives for Anticancer activity. *Journal of Molecular Chemistry* **2024**, 4 (2), 697.
22. N. Azad, R. Kakkar. Computational molecular docking analysis of Doxifluridine and its metabolites to identify potential hits for PDHK1. *Journal of Molecular Chemistry* **2024**, 4 (2).
23. P. McMeekin, D.W. Lendrem, B.C. Lendrem, et al. Schrödinger's pipeline and the outsourcing of pharmaceutical innovation. *Drug Discov Today* **2020**, 25 (3), 480–484.
24. Schrodinger. Schrödinger announces FDA clearance of investigational new drug application for SGR-1505, a MALT1 inhibitor https://ir.schrodinger.com/node/8621/pdf (accessed Aug 2, 2024).
25. G.M. Morris, R. Huey, W. Lindstrom, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J Comput Chem* **2009**, 30 (16), 2785–2791.
26. J. Yang, C. Chen. GEMDOCK: A generic evolutionary method for molecular docking. *Proteins: Structure, Function, and Bioinformatics* **2004**, 55 (2), 288–304.
27. O. Trott, A.J. Olson. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem* **2010**, 31 (2), 455–461.
28. G. Macindoe, L. Mavridis, V. Venkatraman, M.-D. Devignes, D.W. Ritchie. HexServer: an FFT-based protein docking server powered by graphics processors. *Nucleic Acids Res* **2010**, 38 (Web Server), W445–W449.
29. A. Sharma, R.M. Yennamalli. Docking strategies. In *Basic Biotechniques for Bioprocess and Bioentrepreneurship*; Elsevier, **2023**; pp 243–258.
30. V.Y. Tanchuk, V.O. Tanin, A.I. Vovk, G. Poda. A New, Improved Hybrid Scoring Function for Molecular Docking and Scoring Based on AutoDock and AutoDock Vina. *Chem Biol Drug Des* **2016**, 87 (4), 618–625.
31. D.T.-H. Chang, Y.-J. Oyang, J.-H. Lin. MEDock: a web server for efficient prediction of ligand binding sites based on a novel optimization algorithm. *Nucleic Acids Res* **2005**, 33 (Web Server), W233–W238.
32. G.A. Kaminski, R.A. Friesner, J. Tirado-Rives, W.L. Jorgensen. Evaluation and Reparametrization of the OPLS-AA Force Field for Proteins via Comparison with Accurate Quantum Chemical Calculations on Peptides. *J Phys Chem B* **2001**, 105 (28), 6474–6487.
33. S. Murlidaran, G. Brannigan. Physical Accuracy Leads to Biological Relevance: Best Practices For Simulating Ligand-Gated Ion Channels Interacting With General Anesthetics. *Methods Enzymol* **2018**, 602, 3–24.
34. P. Aparoy, K.K. Reddy, P. Reddanna. Structure and ligand based drug design strategies in the development of novel 5- LOX inhibitors. *Curr Med Chem* **2012**, 19 (22), 3763–3778.
35. B. Sever, K. Kucukoglu, H. Nadaroglu, M.D. Altıntop. In silico Molecular Docking and ADME Studies of 1,3,4-Thiadiazole Derivatives in Relation to in vitro PON1 Activity. *Curr Comput Aided Drug Des* **2019**, 15 (2), 136–144.
36. B. Ramachandran, S. Kesavan, T. Rajkumar. Molecular modeling and docking of small molecule inhibitors against NEK2. *Bioinformation* **2016**, 12 (2), 62–68.
37. S.P. Gandhi, K.B. Lokhande, V.K. Swamy, R.K. Nanda, S.S. Chitlange. Computational data of phytoconstituents from Hibiscus rosa-sinensis on various anti-obesity targets. *Data Brief* **2019**, 24, 103994.
38. S. Mehta, S. Kumar, R.K. Marwaha, et al. Synthesis, molecular docking and biological potentials of new 2-(4-(2-chloroacetyl) piperazin-1-yl)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)acetamide derivatives. *BMC Chem* **2019**, 13 (1), 113.
39. C. Huang, J. Chen, F. Ding, et al. Related parameters of affinity and stability prediction of HLA-A*2402 restricted antigen peptides based on molecular docking. *Ann Transl Med* **2021**, 9 (8), 673–673.
40. N. Ipinloju, A. Ibrahim, R.A. da Costa, et al. Quantum evaluation and therapeutic activity of (E)-N-(4-methoxyphenyl)-2-(4-(3-oxo-3-phenylprop-1-en-1-yl) phenoxy)acetamide and its modified derivatives against EGFR and VEGFR-2 in the treatment of triple-negative cancer via in silico approach. *J Mol Model* **2023**, 29 (5), 159.
41. J. Liu, H. Zhao, L. He, R. Yu, C. Kang. Discovery and design of dual inhibitors targeting Sphk1 and Sirt1. *J Mol Model* **2023**, 29 (5), 141.
42. A.S. de Souza, L.L.G. Ferreira, A.S. de Oliveira, A.D. Andricopulo. Quantitative Structure–Activity Relationships for Structurally Diverse Chemotypes Having Anti-Trypanosoma cruzi Activity. *Int J Mol Sci* **2019**, 20 (11), 2801.
43. J. Duan, S.L. Dixon, J.F. Lowrie, W. Sherman. Analysis and comparison of 2D fingerprints: Insights into database screening performance using eight fingerprint methods. *J Mol Graph Model* **2010**, 29 (2), 157–170.
44. M.F. Khan, G. Verma, W. Akhtar, et al. Pharmacophore modeling, 3D-QSAR, docking study and ADME prediction of acyl 1,3,4-thiadiazole amides and sulfonamides as antitubulin agents. *Arabian Journal of Chemistry* **2019**, 12 (8), 5000–5018.
45. M. Kaur, A. Kumari, M.S. Bahia, O. Silakari. Designing of new multi-targeted inhibitors of spleen tyrosine kinase (Syk) and zeta-associated protein of 70kDa (ZAP-70) using hierarchical virtual screening protocol. *J Mol Graph Model* **2013**, 39, 165–175.
46. R.A. Friesner, R.B. Murphy, M.P. Repasky, et al. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein−Ligand Complexes. *J Med Chem* **2006**, 49 (21), 6177–6196.
47. K. Zhu, K.W. Borrelli, J.R. Greenwood, et al. Docking Covalent Inhibitors: A Parameter Free Approach To Pose Prediction and Scoring. *J Chem Inf Model* **2014**, 54 (7), 1932–1940.
48. T.A. Rants'o, C. Johan van der Westhuizen, R.L. van Zyl. Optimization of covalent docking for organophosphates interaction with Anopheles acetylcholinesterase. *J Mol Graph Model* **2022**, 110, 108054.
49. G. Rakshit, S. Murtuja, B.K. Kumar, S. Murugesan, V. Jayaprakash. Structure-based drug design (SBDD). In *Computer Aided Drug Design (CADD): From Ligand-Based Methods to Structure-Based Approaches*; Elsevier, **2022**; pp 181–229.
50. D. Sindhikara, S.A. Spronk, T. Day, et al. Improving Accuracy, Diversity, and Speed with Prime Macrocycle Conformational Sampling. *J Chem Inf Model* **2017**, 57 (8), 1881–1894.
51. D. Sindhikara, K. Borrelli. High throughput evaluation of macrocyclization strategies for conformer stabilization. *Sci Rep* **2018**, 8 (1), 6585.
52. K. Zhu, T. Day. *Ab initio* structure prediction of the antibody hypervariable H3 loop. *Proteins: Structure, Function, and Bioinformatics* **2013**, 81 (6), 1081–1089.
53. C. Rummey, G. Metz. Homology models of dipeptidyl peptidases 8 and 9 with a focus on loop predictions near the active site. *Proteins: Structure, Function, and Bioinformatics* **2007**, 66 (1), 160–171.
54. X. Li, M.P. Jacobson, K. Zhu, S. Zhao, R.A. Friesner. Assignment of polar states for protein amino acid residues using an interaction cluster decomposition algorithm and its application to high resolution protein structure modeling. *Proteins: Structure, Function, and Bioinformatics* **2007**, 66 (4), 824–837.
55. S. Pugazhendhi, T. Murugesan, A.R. Dhanapal, et al. Inhibition of *mecA* and *bla* $_{CTX-M}$ from MRSA and ESBL strains of diabetic foot infection by screening antibiotics compound library: an *in silico* analysis. *J Biomol Struct Dyn* **2023**, 41 (21), 11431–11436.
56. P.D. Lyne, M.L. Lamb, J.C. Saeh. Accurate Prediction of the Relative Potencies of Members of a Series of Kinase Inhibitors Using Molecular

Docking and MM-GBSA Scoring. *J Med Chem* **2006**, 49 (16), 4805–4808.
57. J. Li, R. Abel, K. Zhu, et al. The VSGB 2.0 model: A next generation energy model for high resolution protein structure modeling. *Proteins: Structure, Function, and Bioinformatics* **2011**, 79 (10), 2794–2812.
58. K.A. Rossi, A. Nayeem, C.A. Weigelt, S.R. Krystek. Closing the side-chain gap in protein loop modeling. *J Comput Aided Mol Des* **2009**, 23 (7), 411–418.
59. H.R. Pearce, B.W. Purse, A.L. Cooksy. Explicit solvation modeling in the accurate TD-DFT prediction of absorption spectra for natural nucleobases and fluorescent nucleobase analogues. *ChemRxiv* **2024**.
60. Z.L. Watson, I.J. Knudson, F.R. Ward, et al. Atomistic simulations of the Escherichia coli ribosome provide selection criteria for translationally active substrates. *Nat Chem* **2023**, 15 (7), 913–921.
61. M.J. Robertson, G.C.P. van Zundert, K. Borrelli, G. Skiniotis. GemSpot: A Pipeline for Robust Modeling of Ligands into Cryo-EM Maps. *Structure* **2020**, 28 (6), 707-716.e3.
62. F. Li, Y. Du, Y. Liang, et al. Redesigning an (*R*)-Selective Transaminase for the Efficient Synthesis of Pharmaceutical *N* -Heterocyclic Amines. *ACS Catal* **2023**, 13 (1), 422–432.
63. D. Cappel, M.L. Hall, E.B. Lenselink, et al. Relative Binding Free Energy Calculations Applied to Protein Homology Models. *J Chem Inf Model* **2016**, 56 (12), 2388–2400.
64. D. Lukauskis, M.L. Samways, S. Aureli, et al. Open Binding Pose Metadynamics: An Effective Approach for the Ranking of Protein–Ligand Binding Poses. *J Chem Inf Model* **2022**, 62 (23), 6209–6216.
65. L. Wang, R.A. Friesner, B.J. Berne. Replica Exchange with Solute Scaling: A More Efficient Version of Replica Exchange with Solute Tempering (REST2). *J Phys Chem B* **2011**, 115 (30), 9431–9438.
66. M.C. Ford, K. Babaoglu. Examining the Feasibility of Using Free Energy Perturbation (FEP+) in Predicting Protein Stability. *J Chem Inf Model* **2017**, 57 (6), 1276–1285.
67. M.P. Mazanetz, C.H.F. Goode, E.I. Chudyk. Ligand- and Structure-Based Drug Design and Optimization using KNIME. *Curr Med Chem* **2020**, 27 (38), 6458–6479.
68. B. Füzi, R.S. Malik-Sheriff, E.J. Manners, H. Hermjakob, G.F. Ecker. KNIME workflow for retrieving causal drug and protein interactions, building networks, and performing topological enrichment analysis demonstrated by a DILI case study. *J Cheminform* **2022**, 14 (1), 37.
69. J. Gally, S. Bourg, Q. Do, S. Aci-Sèche, P. Bonnet. VSPrep: A General KNIME Workflow for the Preparation of Molecules for Virtual Screening. *Mol Inform* **2017**, 36 (10).
70. M.T. Lusk, A.E. Mattsson. High-performance computing for materials design to advance energy science. *MRS Bull* **2011**, 36 (3), 169–174.
71. A. Olszewski, D. Kahn, B. Yoo, et al. PB2349: A Phase 1, open-label, multicenter, dose-escalation study of SGR-1505 as monotherapy in subjects with mature b-cell malignancies. *Hemasphere* **2023**, 7 (S3), e40906a2.
72. S. Guler, M.C. DiPoto, A. Crespo, et al. Selective Wee1 Inhibitors Led to Antitumor Activity *In Vitro* and Correlated with Myelosuppression. *ACS Med Chem Lett* **2023**, 14 (5), 566–576.
73. Inc. Schrödinger. SGR-2921 is a cell division cycle 7-related protein kinase (CDC7) inhibitor https://www.schrodinger.com/pipeline/cdc7/#:~:text=SGR%2D2921%20is%20a%20cell,cancers%20with%20high%20cell%20proliferation (accessed Aug 1, 2024).
74. S. Leit, J. Greenwood, S. Carriero, et al. Discovery of a Potent and Selective Tyrosine Kinase 2 Inhibitor: TAK-279. *J Med Chem* **2023**, 66 (15), 10473–10496.
75. Z. Cong, Q. Zhou, Y. Li, et al. Structural basis of peptidomimetic agonism revealed by small-molecule GLP-1R agonists Boc5 and WB4-24. *Proceedings of the National Academy of Sciences* **2022**, 119 (20).
76. Structure Therapeutics. Structure Therapeutics Announces Positive Results from Phase 1b Clinical Study of Oral GLP-1 Receptor Agonist GSBR-1290 and Provides Program Update https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-announces-positive-results-phase-1b (accessed Aug 1, 2024).
77. Inc. Schrödinger. Schrödinger Expands Discovery Efforts for COVID-19 Alliance with Advanced Molecular Simulation Leveraging High-Powered Parallel Computing on Google Cloud.
78. Ajax Therapeutics. Ajax Therapeutics Presents Preclinical Data on AJ1-10502, a Next Generation Type II JAK2 Inhibitor, at the American Society of Hematology Annual Meeting. *Ajax Therapeutics*. December 11, 2022.
79. Inc. Schrödinger. Schrödinger Provides Update on Progress Across the Business and Outlines 2023 Company Strategic Priorities. *Schrödinger, Inc.* January 9, 2023.
80. G. Kawakita, S. Kamiya, S. Sasai, J. Kitazono, M. Oizumi. Quantifying brain state transition cost via Schrödinger Bridge. *Netw Neurosci* **2022**, 6 (1), 118–134.

AUTHORS BIOGRAPHIES

Vanshika Rustagi is SRF at Dr I.K Singh's lab, and her research interests include drug design, AI/ML models, and computational tool development.

Shradheya R R Gupta is a Research Scientist II at Dr I. K. Singh's lab and his research interests include bioinformatics and computational biology.

Dr. Archana Singh is currently working as an Associate Professor, Department of Plant Molecular Biology, University of Delhi South Campus and IoE Fellow, Delhi School of Climate Change and Sustainability, University of Delhi. Dr. Singh has worked as Raman Fellow at University of Kentucky, Lexington, USA and EMBO Fellow at Max Planck Institute of Chemical Ecology, Jena, Germany. Dr. Singh serves as editorial board member of the journals, Scientific Reports and Frontiers in Plant Sciences. Her research mainly focuses on "Plant Protection and Human Health".

Prof. Indrakant K. Singh is presently working as a Professor at Department of Zoology, Deshbandhu College & Fellow at the Delhi School of Public Health, Institute of Eminence, University of Delhi. Prof. Singh has worked as Visiting Professor & ICMR-DHR International Fellow at Keck School of Medicine, University of Southern California, Los Angeles, USA and UGC-Raman Fellow at University of Kentucky, Lexington, USA, his research interests revolve around therapeutic targeting of Cancer (Breast cancer and Neuroblastoma) and Fibrodysplasia Ossificans Progressiva (FOP). Besides this, Dr Singh's lab has a special inclination towards bioinformatics, machine learning, development of web servers and bioinformatics tools.