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In – Silico Biological Evaluation of Antifungal Drugs - Molinspiration

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Abstract

The aim of this research work is to evaluate *In – Silico* Antifungal Drugs, in this work Molinspiration is used to provide predictive tools for essential molecular properties, such as lipophilicity, aqueous solubility and pKa, which are critical in drug discovery and cheminformatics. It operates based on a comprehensive database of chemical structures and employs algorithms to calculate these properties. Molinspiration is a renowned software and informatics company that plays a pivotal role in the pharmaceutical and biotechnology industries. With a primary focus on providing cutting-edge cheminformatics tools and software solutions, Molinspiration has significantly contributed to the field of drug discovery and medicinal chemistry. Molinspiration's software is an indispensable resource for the pharmaceutical and biotechnology sectors.

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INTRODUCTION

Molinspiration is a renowned software and informatics company that plays a pivotal role in the pharmaceutical and biotechnology industries. With a primary focus on providing cutting-edge cheminformatics tools and software solutions, Molinspiration has significantly contributed to the field of drug discovery and medicinal chemistry. Its suite of software applications and predictive models has proven invaluable to researchers and scientists in their quest to design and develop novel pharmaceutical compounds [1].

Molinspiration's software offerings are diverse and cater to a wide range of tasks crucial in the drug development process. One of its core functionalities is property prediction, where its tools can accurately estimate various molecular properties such as lipophilicity, solubility, and bioavailability. These predictions are pivotal in selecting and optimizing potential drug candidates, saving time and resources in the drug development pipeline [2].

Virtual screening is another key aspect of Molinspiration's software suite. It enables researchers to virtually assess the potential of thousands of compounds for their biological activity against a specific target. This high-throughput screening approach helps identify

promising lead compounds, expediting the early stages of drug discovery [3].

Molinspiration's commitment to innovation and user-friendly design has made it a goto choice for chemists and scientists engaged in drug development. Its molecular visualization tools provide a clear and intuitive representation of complex chemical structures, facilitating the analysis and design of new molecules with enhanced pharmacological properties [4]. The software also aids in the interpretation of molecular descriptors and structural alerts, which are crucial for understanding the relationships between chemical structures and their biological activities. This knowledge is essential for making informed decisions throughout the drug development process [5].

Molinspiration's software is an indispensable resource for the pharmaceutical and biotechnology sectors. It empowers researchers to make data-driven decisions, accelerates drug discovery, and ultimately contributes to the development of safer and more effective medications. The company's dedication to advancing cheminformatics and computational chemistry tools has positioned it as a leader in the field, driving progress in the quest for new and improved drugs [6].

Molinspiration, headquartered in Slovakia, has a notable reputation in the scientific community for its continuous commitment to advancing the field of cheminformatics. The company's software offerings are designed to address the complex challenges faced by pharmaceutical and biotechnology researchers in their pursuit of innovative drug candidates[16].One of the distinguishing features of Molinspiration is its focus on predicting various molecular properties [7]. This includes essential parameters like lipophilicity, which influences how a drug is distributed in the body, as well as solubility, which impacts the drug's bioavailability and, consequently, its effectiveness. By accurately predicting these properties, Molinspiration aids in the selection and prioritization of compounds, allowing researchers to concentrate their efforts on the most promising candidates [8].

Moreover, Molinspiration's software is particularly beneficial in dealing with issues of toxicity and safety. Through the analysis of structural alerts and toxicophores, it helps identify potential toxic liabilities in candidate molecules early in the drug discovery process. This proactive approach can prevent costly and time-consuming setbacks later on, ensuring the safety and well-being of patients [9].

PRINCIPLE

The principal of Molinspiration is to provide predictive tools for essential molecular properties, such as lipophilicity (LogP), aqueous solubility (LogS), and pKa, which are critical in drug discovery and cheminformatic [10]. It operates based on a comprehensive database of chemical structures and employs algorithms to calculate these properties. Molinspiration aids researchers in making informed decisions, optimizing drug design, and performing virtual screening by offering user-friendly interfaces and visualization tools. Its core principle is to simplify the assessment of molecular properties to support pharmaceutical and chemical research [11].

FUNCTIONS

Molinspiration Software Products

Molinspiration specialises on developing Java-based cheminformatics tools. Molinspiration tools are consequently platform independent and may be used on any PC, Mac, UNIX, or LINUX machine. The software is distributed in the form of engines that can be used as standalone computational engines, to power web-based tools, or to easily integrate into bigger in-house Java programmes [12].

The following software is currently available:

Mib engine - calculation of important molecular properties, molecular processing (SMILES canonicalization, charge normalisation), conversion between SMILES and SD files, SMILES depiction, production of molecular images (see also an online property calculation service powered by the mib engine). [13].

The misearch engine is a versatile molecular database that supports substructure, similarity, and pharmacophore similarity searches (see also the misearch engine-powered web molecular database).

miscreen engine is a virtual screening engine that allows for the generation of pharmacophore

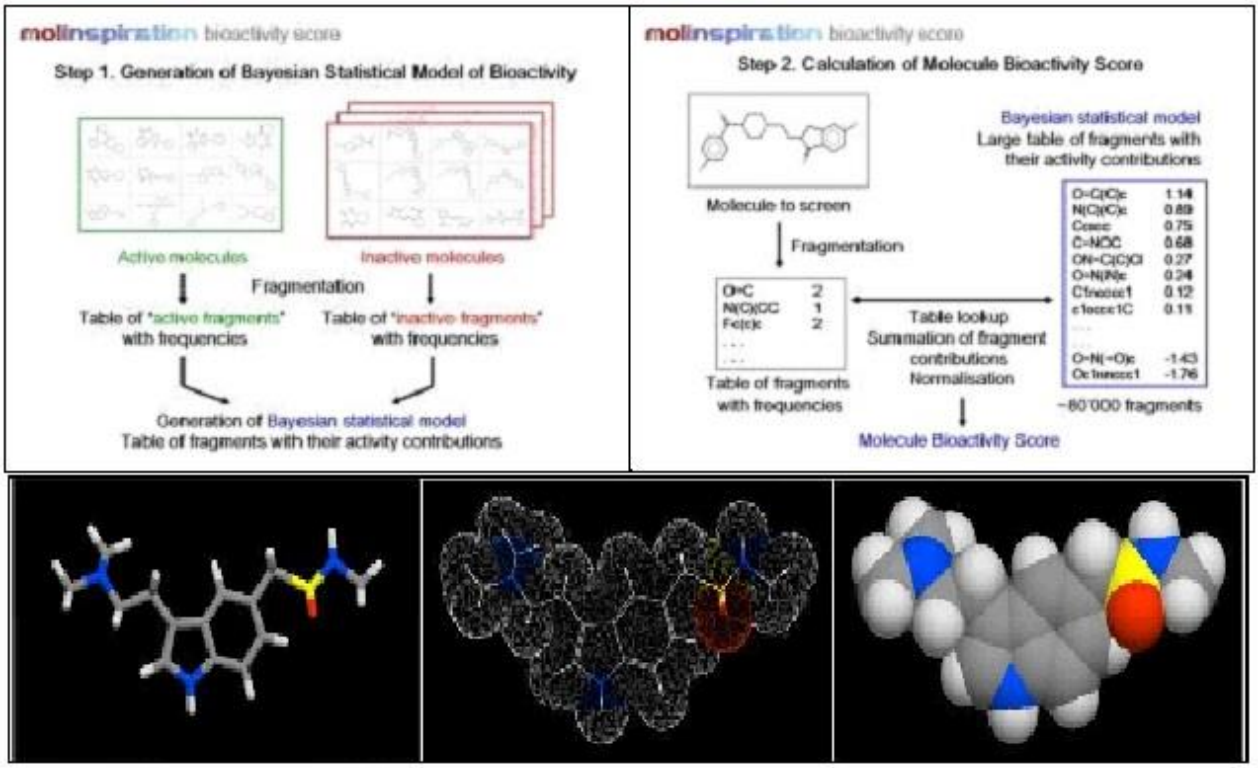


Figure 1 Galaxy - 3D structure generator. Generates 3D structures from SMILES. Currently in beta. Try Galaxy

models, validation, and screening of huge molecular libraries (see some examples or an interactive calculation of bioactivity scores driven by the miscreen engine - select option [Predict Bioactivity] [14].

Molinspiration Property Calculator: Easy interactive calculation of molecular characteristics, including the creation of QSAR tables. Molinspiration provides software tools to calculate various molecular properties essential for drug design and development. These properties include molecular weight, logP (partition coefficient), polar surface area, hydrogen bond donors and acceptors, and many others. These calculations help researchers assess the physicochemical characteristics of molecules, guiding decisions in the drug discovery process [15].

Example: Calculating the molecular weight of Aspirin (acetylsalicylic acid) using Molinspiration's software. The molecular weight of Aspirin is 180.16 g/mol.

Molinspiration Molecule Viewer - Visualising enormous groups of molecules

Molinspiration Data Viewer - Visualisation of QSAR datasets using an interactive molecular display.

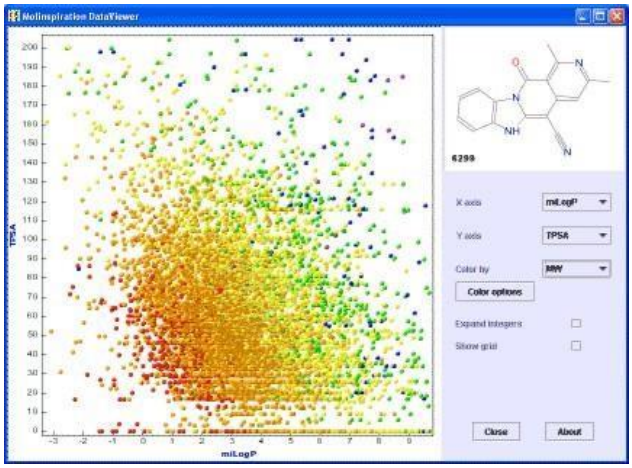


Figure 2 Visualization of QSAR datasets with interactive molecule display

Molinspiration Depiction - High-quality representation of molecules stored as SMILES in MDL Molfile.

Database of Bioactive Substituents and Linkers: Database includes 21 thousand substituents and 49 thousand linkers taken from

bioactive compounds, with computed characteristics [16].

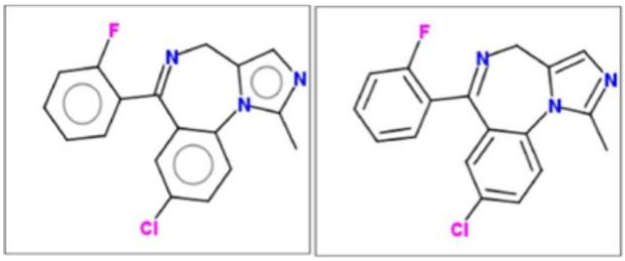


Figure 3 Default depiction of aromatic rings (inner circle) and depiction with alternation

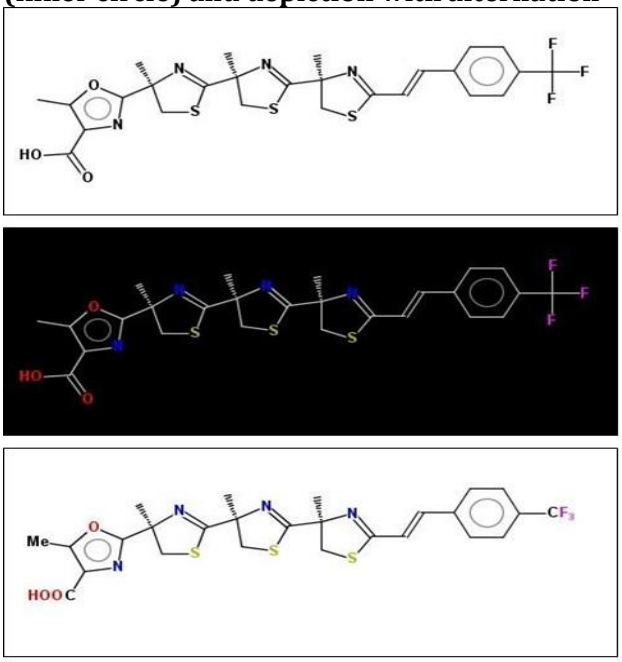


Figure 4 Chemical structures and depiction with alternation single and double bonds

Lipinski's Rule of Five: Molinspiration tools allow users to evaluate adherence to Lipinski's Rule of Five, a set of guidelines for identifying drug-like compounds. By checking whether a molecule meets these criteria, researchers can assess its potential for oral bioavailability and suitability for drug development.

Example: Analyzing a compound to see if it adheres to Lipinski's Rule of Five. If a molecule has a calculated logP value below 5, it meets this guideline for drug-likeness.

Chemical Space Exploration - Molinspiration helps researchers explore chemical space by providing tools to visualize and analyze the chemical diversity of compound libraries. This is crucial for creating diverse screening libraries and selecting compounds for synthesis or testing.

Example: Visualizing the chemical diversity of a library of potential drug candidates. Molinspiration can generate 2D and 3D scatterplots to help researchers select compounds that cover a broad area of chemical space [17].

ADME prediction: Absorption, Distribution, Metabolism, and Excretion (ADME) properties are crucial in drug development. Molinspiration offers predictions and calculations for ADME parameters, enabling researchers to assess the pharmacokinetic and pharmacodynamic properties of compounds.

Example: Predicting the solubility of a compound by calculating its logS (solubility) value. This information can be used to assess a molecule's likelihood of being absorbed in the body.

Drug-Likeness Assessment: Molinspiration tools assist in evaluating the drug likeness of compounds, helping researchers identify molecules with a higher likelihood of becoming successful drugs. This involves considering factors like molecular size, lipophilicity, and the presence of specific functional groups.

Example: Evaluating the drug-likeness of a newly synthesized compound by checking if it meets specific criteria, such as having a molecular weight below 500 Daltons, a logP value below 5, and fewer than 5 hydrogen bond donors.

Molecular Fragment Analysis: Molinspiration allows the dissection of molecules into fragments, aiding in the identification of important substructures and functional groups that can impact a compound's biological activity or toxicity.

Example: Breaking down a complex molecule, like a protein inhibitor, into its constituent fragments. Molinspiration can identify key structural motifs or pharmacophores that are crucial for its bioactivity.

Custom Software Development: Molinspiration offers custom software development services to meet specific research and project needs. This enables organizations to create tailored solutions for their unique requirements in drug discovery and cheminformatics.

Example: Collaborating with Molinspiration to develop a custom software solution for managing a large chemical compound database or

automating specific cheminformatics workflows tailored to a pharmaceutical company's needs [18].

Consultancy Services: Molinspiration provides consultancy services to support clients in optimizing their research and drug discovery processes. These services include expert advice on cheminformatics, molecular modeling, and data analysis.

Example: Seeking Molinspiration's consultancy services to assess the ADME properties of a series of drug candidates and receiving expert advice on how to optimize the compounds for better pharmacokinetics [19].

Integration with Other Tools: Molinspiration software can be integrated with other cheminformatics and molecular modeling software, allowing for a comprehensive approach to drug discovery and research.

Example: Integrating Molinspiration's property calculation toolkit with a molecular modeling software like Schrödinger's Maestro to perform structure-activity relationship (SAR) analyses and optimize lead compounds.

Educational Resources: Molinspiration offers educational resources and training materials to help researchers and students learn how to use their tools effectively. This promotes the broader adoption of their software within the scientific community.

Example: Accessing Molinspiration's online tutorials and training materials to learn how to use their software effectively, such as using their chemical property prediction tools for virtual screening of compound libraries [20].

APPLICATIONS [21-22]

Chemical Property Prediction:

Molinspiration provides tools for predicting various chemical properties, such as logP (lipophilicity), solubility, polar surface area, and more.

Example: Medicinal chemists can use this to estimate the solubility of a new drug candidate, which is crucial for its bioavailability.

Chemical Space Exploration:

Researchers can use Molinspiration to explore chemical space, which involves analyzing the diversity and distribution of chemical compounds.

Example: Chemists can identify regions in chemical space where existing drugs are located and find opportunities for designing novel compounds.

Molecule Filtering and Selection:

Molinspiration helps in filtering and selecting molecules based on specific criteria, such as drug-likeness, bioavailability, or toxicity.

Example: During the drug discovery process, researchers can filter out compounds with undesirable properties and focus on those with potential therapeutic value.

Chemical Similarity Analysis:

Molinspiration allows for comparing the similarity of molecules, which is valuable for scaffold hopping and lead optimization.

Example: Chemists can identify molecules with similar structures to known drugs and make modifications to improve their efficacy.

Virtual Screening:

Virtual screening involves using computational methods to identify potential drug candidates from large chemical libraries.

Example: Molinspiration tools can be used to virtually screen compound databases to discover new hits for a specific target.

Chemical Drawing and Visualization:

Molinspiration offers tools for drawing and visualizing chemical structures.

Example: Chemists can create and edit chemical structures, which is essential for documenting and sharing research findings.

Structure-Activity Relationship (SAR) Analysis:

Researchers can use Molinspiration to analyze the link between a compound's chemical structure and biological action.

Example: SAR analysis can guide the optimization of lead compounds to enhance their effectiveness.

Toxicity Prediction:

Molinspiration provides models for predicting the toxicity of chemicals, which is crucial for safety assessments.

Example: This can be used to identify potential toxicities of new compounds before conducting expensive and time-consuming in vitro or in vivo studies.

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) Prediction: Molinspiration helps in assessing the ADMET properties of compounds, which is essential in drug development.

Example: Predicting how a drug candidate will be absorbed, distributed, metabolized, and excreted in the body is critical for its success in the clinic.

ADVANTAGES AND DISADVANTAGES

Advantages [23]

Rapid Property Prediction: Molinspiration allows for the quick and efficient prediction of various molecular properties, such as logP, logS, pKa, and more, which is essential in drug design and other chemistry-related applications.

User-Friendly Interface: Its user-friendly interface is both intuitive and accessible to a broad spectrum of users, including those without extensive computational or programming knowledge.

Large Molecular Database: Molinspiration is based on a comprehensive database of chemical compounds, enabling users to work with a broad range of chemical structures. Versatility: It can be used for a variety of tasks, including virtual screening, lead optimization, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction. Visualization Tools: The software provides visualization tools for molecular structures and properties, making it easier for users to interpret and communicate their results. Compatibility: Molinspiration is compatible with various chemical file formats, facilitating data import and export. Predictive Accuracy: It has been widely used and validated in scientific research, demonstrating good predictive accuracy for many molecular properties. Customization: Users can customize and adapt the software to their specific needs and research goals.

Disadvantages [24]

Data Accuracy: The accuracy of predictions heavily depends on the quality and relevance of the underlying data in its database. In some cases, the database may not include specific compounds or have limited representation for certain chemical classes.

Predictive Variability: Prediction accuracy can vary for different properties and compounds. Some properties may be predicted with higher accuracy than others.

Sensitivity to Input Data: The quality of input molecular structures and data can significantly impact the accuracy of predictions. Small errors or discrepancies in input data can lead to inaccurate results.

Cost: Molinspiration may require a paid license or subscription, which can be a disadvantage for users with budget constraints, especially in academic or small research settings.

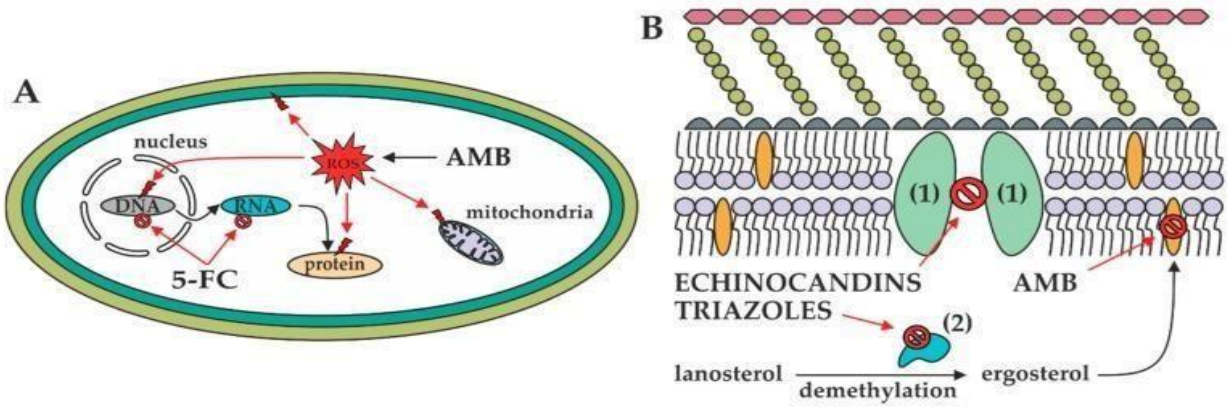


Figure 5 (A): fungal cytoplasm (B): In the fungal biomembrane, 1,3-β-D-glucan synthase (1) and 14-α-demethylase (2) are inhibited by echinocandins and triazoles, respectively

Table 1 Structures with IUPAC names and smile notations

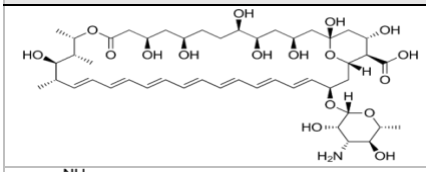
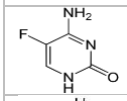
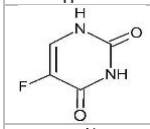
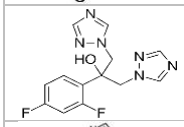
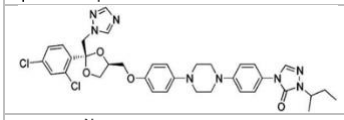
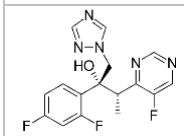
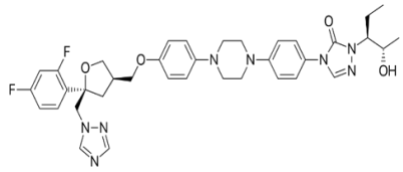
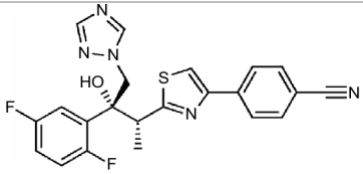
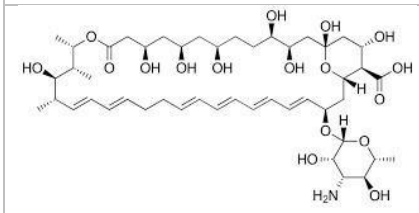
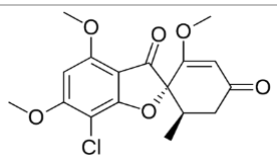
Structure	IUPAC Name	Smile Notation
	Amphotericin- B	CC3CCCCCCCCCCCCCC (OC1OC(C) C(O)C(O)C1O) C(CC(O) C2C(=O) O)C(O)C(O) CC(O)C(O) CCC(O) CC(O)CC(=O)OC(C)C(C)C3O
	4-amino-5-fluoropyrimidin-2(1H)-one Flucytosine	Nc1nc(=O)[nH]cc1F
	5-fluoropyrimidine-2,4(1H,3H)done 5-flurouracil	O=c1[nH]cc(F)c(=O) [nH]1
	2-(2,4-difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)propan-2-ol Fluconazole	OC(Cn1cncn1) (Cn2cncn2)c3ccc (F)cc3F
	Itraconazole	CCC(C)n7ncn(c6ccc(N5CCN(c4ccc (OCC3COC(C(Cn1cncn1)c2ccc(Cl) cc2Cl)O3)cc4)CC5)cc6)c7=O
	2-(2,4-difluorophenyl)-3-(5fluoropyrimidin-4-yl)-1-(1H1,2,4triazol-1-yl)butan-2-ol voriconazole	CC(c1ncncc1F)C(O) (Cn2cncn2) c3ccc(F) cc3F
	Posaconazole	CC(O)C(C)n7ncn (c6ccc(N5CCN (c4ccc (OCC3COC(C(Cn1cn cn 1)c2ccc(Cl)cc2Cl) O3)cc4)CC5)c c6)c7=O
	4-12-13-(2,5-difluorophenyl)- 3hydroxy-4- (1H-1,2,4- triazol-1-yl)butan-2-yl]- 1,3-thiazol-4-yl)benzonitrile Isavuconazole	CC(c2nc(c1ccc(C#N)cc1) cs2)C(O)(Cn3cncn3)c4cc(F) ccc4F
	Nystatin	[H][C@]23C[C@@H(O[C@11 ([H])[C@H](C)[C@H](O)[C@H] (N)[C@@H] 1O)C=CC=cc=cc= ccc =CC=C[C@H](C)[C@H](O) [C@@H](C)[C@H](C)OC(=O)CC (O)CC(O)CC(O)CC[C@@H](O) C(O)C[C@KO) (C[C@H](O) [C@H]2C (=O)O) 03
	(5'R)-7-chloro 3,4,6-trimethoxy5'methylspiro[1-benzofuran-2,4'- cyclohex-2-ene]- 1,3-dione Griseofulvin	COC1=CC(=O)C[C@@H](C)C13 0c2c(Cl)c(OC)cc(O) C)c2C3=0

Table 2 Calculation of Molecular Properties using molinspiration

Code	Mi LogP	TPSA	No. of atomes	M.W	nON	nOHNH	N violation	No. of rotatable bonds	volume
Amphotericie B	3.23	313.81	65	939.19	18	12	3	3	905.87
Flucytosine	-0.43	71.78	9	129.09	4	3	0	0	100.08
5-Flurouracil	-0.59	65.72	9	103.08	4	2	0	0	96.91
Fluconazole	-0.15	81.66	23	320.30	7	1	0	6	265.76
Itraconazole	5.25	104.73	50	719.67	12	0	3	12	625.05
Voriconazole	1.49	76.73	25	349.32	6	1	0	5	285.11
Posaconazole	4.11	124.95	51	735.67	13	1	2	12	633.09
Isavuconazol	2.96	87.63	31	437.48	6	1	0	6	363.31
Nystatin	-1.99	319.61	65	926.11	18	13	3	3	871.66
Griseofulvin	1.57	71.08	24	352.77	6	0	0	3	293.60

Table 3 Calculation of bioactivity scores using Mol insoiration v2022.08 [30]

Code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Amphotericie B	-3.06	-3.51	-3.54	-3.45	-2.45	-2.95
Flucytosine	-1.91	-2.21	-1.44	-3.55	-2.36	-0.97
5-Flurouracil	-2.60	-1.95	-2.62	-3.04	-3.15	-1.56
Fluconazole	0.05	-0.02	-0.11	-0.26	-0.08	-0.00
Itraconazole	-0.38	-1.40	-1.24	-1.26	-0.62	-0.90
Voriconazole	0.18	0.11	0.06	-0.29	-0.04	0.19
Posaconazole	-0.80	-1.86	1.66	1.82	-0.73	1.35
Isavuconazol	-0.02	0.19	-0.08	-0.34	-0.14	-0.14
Nystatin	-3.04	-3.51	-3.54	-3.44	-2.45	-2.93
Griseofulvin	-0.34	-0.30	-0.72	-0.04	-0.26	-0.03

BIOACTIVITY OF ANTIFUNGAL AGENTS

While over 200 polyenes with antifungal properties have been identified since the 1950s, amphotericin B continues to be the only polyene medication of choice for treating invasive fungal infections. The original purpose of flucytosine was as an antimetabolite in the treatment of cancer. 5-FC now functions in combination with antifungal therapy due to its modest antineoplastic efficacy. While voriconazole (VOR), posaconazole (POS), and isavuconazole (ISV) have better pharmacological profiles than first-generation triazoles like fluconazole (FLC) and itraconazole (ITC), second-generation triazoles are different. Echinocandins are the newest class of peptide antifungals. They include capsofungin (CSF), micafungin (MCF), and anidulafungin (ANF). The timeline for the use and advancement of antifungals. A recent summary [25] provided insight into the effectiveness of combination therapy in treating invasive fungal infections.

The cyclic heptaene amphotericin B is generated by the Gram-positive bacterium Streptomyces nodosus. It acts via two different methods. Initially, a number of AMB molecules attach to ergosterol by integrating into the fungal lipid bilayer. Pores are created by ergosterol sequestration, releasing the electrolyte glucose together with the ions K+, Mg2+, Ca2+, and Cl−. Fungi die when their internal ions are rapidly depleted. Second, AMB causes reactive oxygen species (ROS) to build up, which damages proteins, DNA, mitochondria, and membranes. For the biological activity of AMB, the structural components mycosamine and the hydroxyl groups at positions C8, C9, and C35 are essential [26].

Mechanisms of antifungal drug action within the fungal cell. (A): AMB causes the production of ROS in the cytoplasm of the fungal fungus, which damages the DNA, proteins, mitochondria, and biomembranes. Moreover, 5-FC inhibits the formation of proteins, RNA, and DNA. (B):

Echinocandins and triazoles block 1,3-β-D-glucan synthase (1) and 14-α-demethylase in the fungal biomembrane, respectively. Furthermore, AMB sequesters ergosterol from the biomembrane, causing pore development.

An artificial counterpart of cytosine is called flucytosine. Following injection, 5-FC is absorbed by the fungal cell via cytosine permease and converted to 5-fluorouracil by cytosine deaminase. Next, 5-fluorouracil is changed into 5-fluorouridine triphosphate. This substance inhibits the synthesis of proteins because, in contrast to uridylic acid, it is integrated into the RNA of fungal ribonucleic acids. Uridine monophosphate pyrophosphorylase is also capable of metabolising 5-fluorouracil into 5-fluorodeoxyuridine monophosphate. The main enzyme responsible for producing thymidine in DNA biosynthesis, thymidylate synthetase, is inhibited by this compound because it cannot eliminate the fluorine atom [27].

Triazoles work by inhibiting 14-α-demethylase, which is dependent on microsomal cytochrome P450 (CYP450) monooxygenase. The reduced form of nicotinamide dinucleotide phosphate (NADPH) and oxygen are required for the two-step demethylation of fungal lanosterol. The heme iron is bound by nitrogen from the triazole ring, preventing the methyl group from oxidising. The fungistatic effect is caused by both the reduction of ergosterol and the buildup of harmful 14α-methylsterols. Pneumocandins' modified counterparts, echicocandins, are fermentation byproducts of a range of microbes. Specifically, micafungin comes from pneumocandin A0 (Coleophoma empetri), caspofungin from pneumocandin B0 (Glarea lozoyensis), and anidulafungin from echinocandin B0 (Aspergillus nidulans). Echinocandins are directed against the enzyme complex known as 1,3-β-D-glucan synthase, which is made up of intracellular regulatory Rho1 subunits and transmembrane catalytic Fks [28]. Because the former is non-competitively inhibited, the fungal cell wall becomes very porous and 1,3-β-D-glucan synthase is unable to convert uridine diphosphate glucose to a β-D-glucan 123. Cyclic hexapeptides with particular lipophilic N-acetylated side chains are known as echinocandins. Their physicochemical features are determined by their core: proline residues increase antifungal potency; homotyrosine inhibits 1,3-β-D-glucan synthase; and replacement with a hydroxyl group, ethylenediamine, and sulphated moieties improves water solubility. Echinocandin B0's linoleoyl side chain has been changed to an alkoxytriphenyl, dimethylmyristoyl, and diphenyl substituted isoxazole chain since it shows hemolytic activity [29].

CONCLUSION

Molinspiration is to provide as a predictive tools for essential molecular properties, such as lipophilicity (LogP), aqueous solubility (LogS), and pKa, which are critical in drug discovery and cheminformatic. It operates based on a comprehensive database of chemical structures and employs algorithms to calculate these properties. Molinspiration's software is particularly beneficial in dealing with issues of toxicity and safety. Through the analysis of structural alerts and toxicophores, it helps identify potential toxic liabilities in candidate molecules early in the drug discovery process. This proactive approach can prevent costly and time-consuming setbacks later on, ensuring the safety and well-being of patients.

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