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A BRIEF REVIEW ON MOLINSPIRATION AND PASS STUDY

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ABSTRACT

Calculation of molecular properties and bioactivity of the simple drug molecules like aspirin, paracetamol, and the drugs of your choices using the online server molinspiration.

ABOUT MOLINSPIRATION; Molinspiration is a privately owned company focused on development and application of modern cheminformatics techniques, especially in connection with the web. Molinspiration was founded in 1986 as a spin-off of Bratislava University.

ABOUT PASS STUDY: Post-authorisation safety studies (PASS) are essential in monitoring the safety and effectiveness of pharmaceutical products after they have been approved for public use. While pre-marketing clinical trials provide vital information on a drug's efficacy and safety, they are often limited by sample size, duration, and patient population diversity. PASS are conducted to gather real-world data on the long-term safety and effectiveness of medicines once they are widely used. This review aims to explore the role of PASS in pharmacovigilance, including study designs, methodologies, regulatory requirements, and challenges associated with their implementation.

KEYWORDS: *Molinspiration, Post-authorisation safety studies, Bioactivity Score, Drug likeness, Mol. Properties.*

1. 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.

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.

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.

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.

post-authorisation safety study (PASS) included by the pharmaceutical company in the Risk Management Plan (RMP) of the product at the time of its marketing authorisation application. The authors point out the limitations of the clinical trials to genuinely reflect real-world settings and concerns, and post-authorisation safety studies are particularly important for regulatory authorities to further evaluate the safety of medicines as used in clinical practice.

PASS may inform regulators in taking measures for the protection of patients and the safe use of the medicine. Examples of (risk minimisation) measures that may be taken include an amendment of the product information or a restriction of the use of the product to some indications or some categories of patients. The regulatory oversight of PASSs by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) includes an in-depth review of the study protocol and its results in order to assess the possible impact of the outcomes.

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The ETNA VTA study is a good illustration of a PASS conducted voluntarily. It aimed to gain further insight into the use of edoxaban in routine clinical practice, including compliance to the summary of product characteristics (SmPC), the use of a heparin lead-in, dosing patterns and the consideration of concomitant diseases.

2. MOLECULAR PROPERTIES PREDICTION AND DRUG LIKENESS BY MOLINSPIRATION

2.1 Molecular Properties Prediction

Physicochemical parameter such as TPSA, MW, Drug Likeness & MiLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration software. These parameters play a vital role in generation and determination of bioactivity of chemical entity.

2.2 Drug Likeness

Drug likeliness is a qualitative means of analysis to check whether the given molecule is a drug or not and it is defined as a complex balance of various molecular properties and structural features which determine whether a particular molecule is similar to the known drugs. Activity of all test compounds and standard drug (Ampicillin) were analyzed under six criteria of known successful drug activity in areas of GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor by the molinspiration software.

2.3 Antibacterial Activity

All the compounds synthesized were screened in vitro for anti-bacterial activity against Staphylococcus Gram aureus positive bacteria and Staphylococcus epidermidis and Gram negative bacteria- Escherichia coli and Pseudomonas aeruginosa using disc diffusion method at 30 µg/ml concentration, ampicillin (30 µg/ml) was taken as standard. Dimethyl sulphoxide was used a control.

2.4 Evaluation of drug likeliness based on Lipinski's rule of five

Lipinski's rule of five is helpful in describing molecular properties of drug compounds required for estimation of important pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion. The rule is helpful in drug design and development.

Table 1: Molecular property of Phytochemical Compounds

S.No	Phytochemical compounds	MiLogP	TPSA	natoms	nON	nOHNH	nviolations	nrotb	volume	MW
1	Dodecanoic acid	5.038	37.299	14.0	2	1	1	10	224.215	200.322
2	Ethyl caprylate	3.701	26.305	12.0	2	0	0	8	191.338	172.268
3	Glycine (trifluoroacetyl)-methyl butyl ester	2.007	55.405	16.0	4	1	0	7	208.642	241.209
4	Capric acid ethyl ester	4.711	26.305	14.0	2	0	0	10	224.941	200.322
5	α - Tocopherol	8.847	29.462	30.0	2	1	1	11	457.697	416.690
6	n- Hexadecanoic acid	7.059	37.299	18.0	2	1	1	14	291.422	256.430

3. BIOACTIVITY SCORE

Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www.molinspiration.com). Calculated drug likeness score of each compound and compared with the specific activity of each compound, and the results were compared with standard drug. For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive.

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Drug score values indicate overall potential of a compound to be a drug candidate. Mol inspiration is a web-based tool used to predict the bioactivity score of the synthesized compounds against regular human receptors such as GPCRs, ion channels, kinases, nuclear receptors, proteases and enzymes.

Table 2: Bioactivity score of Phytochemical Compounds

S.No	Phytochemical compounds	GPCR ligand	Ion Channel Modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Dodecanoic acid	-0.27	-0.04	-0.75	-0.24	-0.36	0.04
2	Ethyl caprylate	-0.85	-0.34	-1.25	-0.84	-0.86	-0.40
3	Glycine (trifluoroacetyl)-methyl butyl ester	-0.38	-0.38	-0.88	-0.31	-0.18	-0.12
4	Capric acid ethyl ester	-0.60	-0.21	-0.93	-0.57	-0.62	-0.23
5	α - Tocopherol	**0.25**	**0.15**	-0.22	-0.22	**0.29**	**0.25**
6	n- Hexadecanoic acid	0.02	0.06	-0.33	-0.33	-0.04	0.18

4. MOLINSPIRATION ANALYSIS

In Molinspiration Log p measures the totality of fragment-based aids and correction factors. This method processes all organic and organometallic molecules. Topological polar surface area (TPSA) is the sum of fragment contributions, O and N centred polar fragments are considered. It is a good descriptor containing drug absorption plus intestinal absorption, bioavailability, and blood-brain barrier penetration. Molecular volume is based on group contributions. mostly drug-like molecules. Several bonds are rotatable, it is a measure of molecular flexibility. it is a fine descriptor of the oral bioavailability of drugs. Rotatable bond is distinct for any single non-ring bond, limited to a non-terminal heavy atom. The Lipinski rule of five affirms, that most drug-like molecules have log P ≤ than or equal to 5, molecular weight ≤ than or equivalent to 500, number of hydrogen bond acceptors ≤ than or equivalent to 10 and number of hydrogen bond donors less than or equal to 5. Molecules crossing more than one of these rules may have encountered the problems of bioavailability. The rule is known as the Lipinski Rule of five. Molinspiration software is written in java software, it is a molecular properties computation toolkit, Molinspiration is applied in the process of a large number of molecules in batch mode and can process data of about 10000 molecules per 60sec, it is way in through web interface directly on the internet.

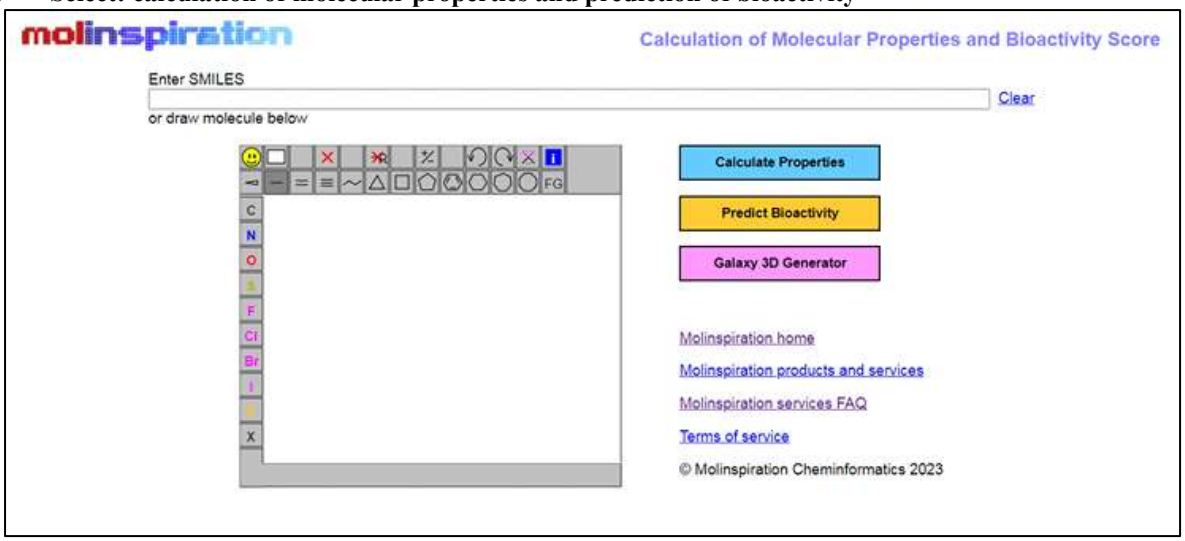
5. PROCEDURE

i. Molinspiration link

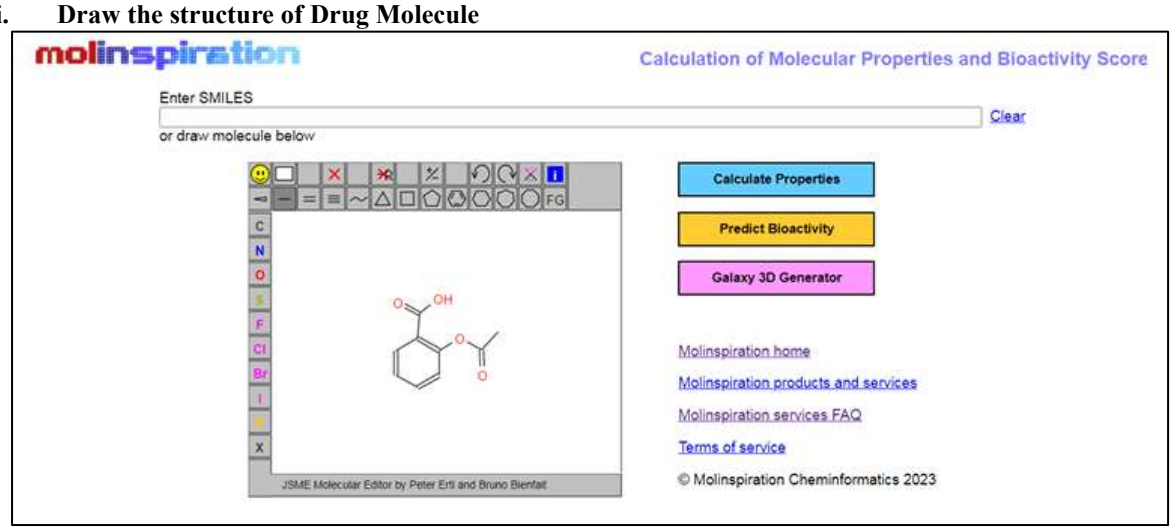
https://www.molinspiration.com

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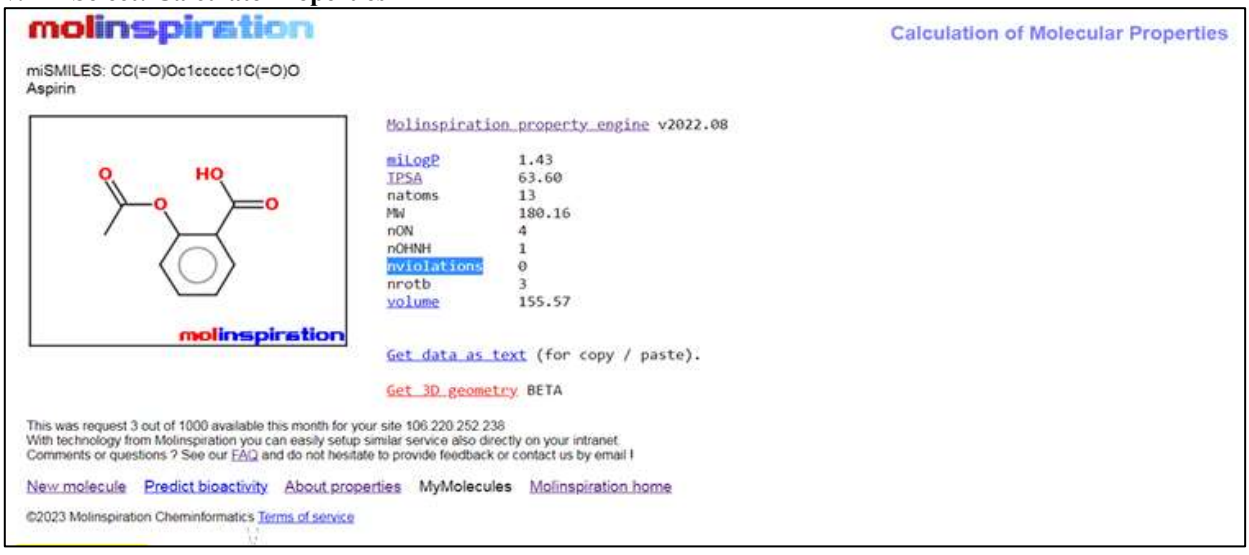
ii. Select: calculation of molecular properties and prediction of bioactivity



iii. Draw the structure of Drug Molecule

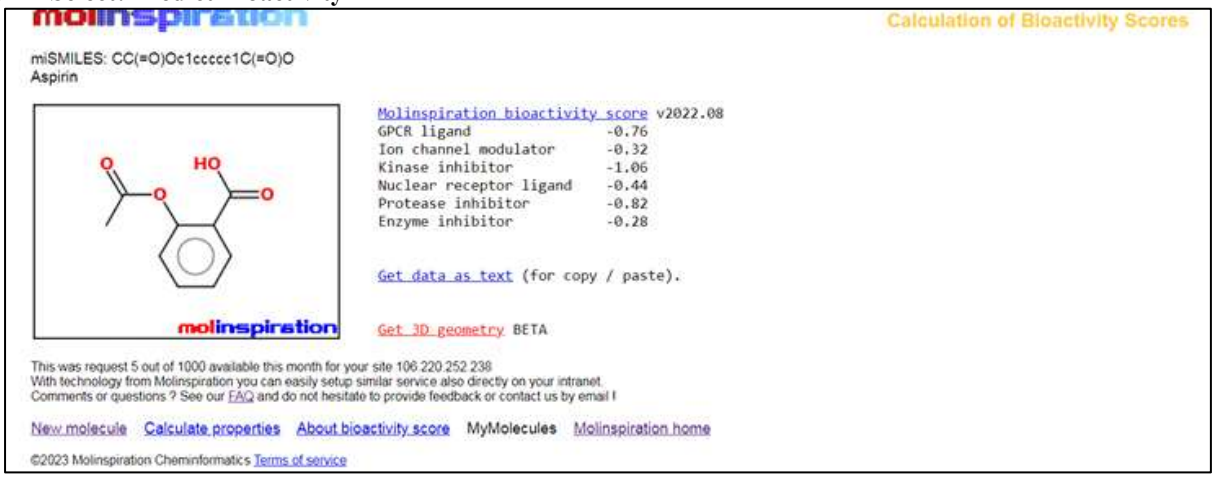


iv. Select: Calculate Properties



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v. **Select: Predict Bioactivity**

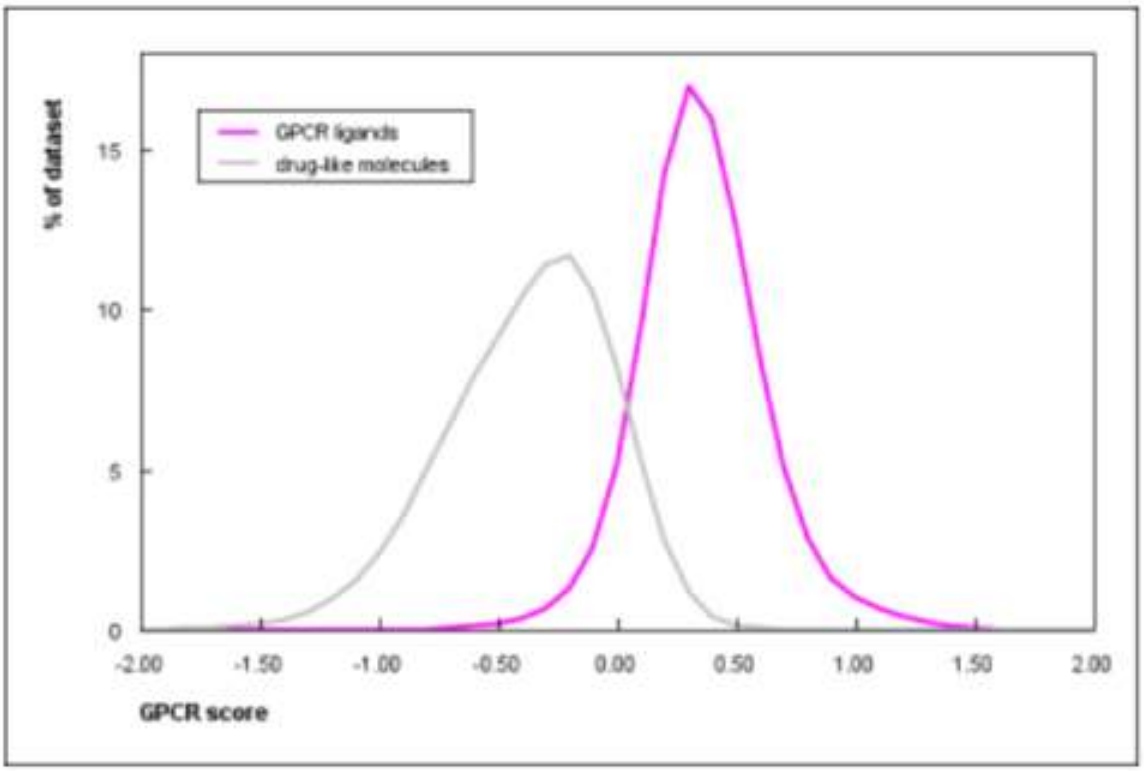


6. DRUG LIKENESS

Drug likeliness is a qualitative means of analysis to check whether the given molecule is a drug or not and it is defined as a complex balance of various molecular properties and structural features which determine whether a particular molecule is similar to the known drugs. Activity of all test compounds and standard drug (Ampicillin) were analyzed under six criteria of known successful drug activity in areas of GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor by the molinspiration software.

i. GPCR Ligand

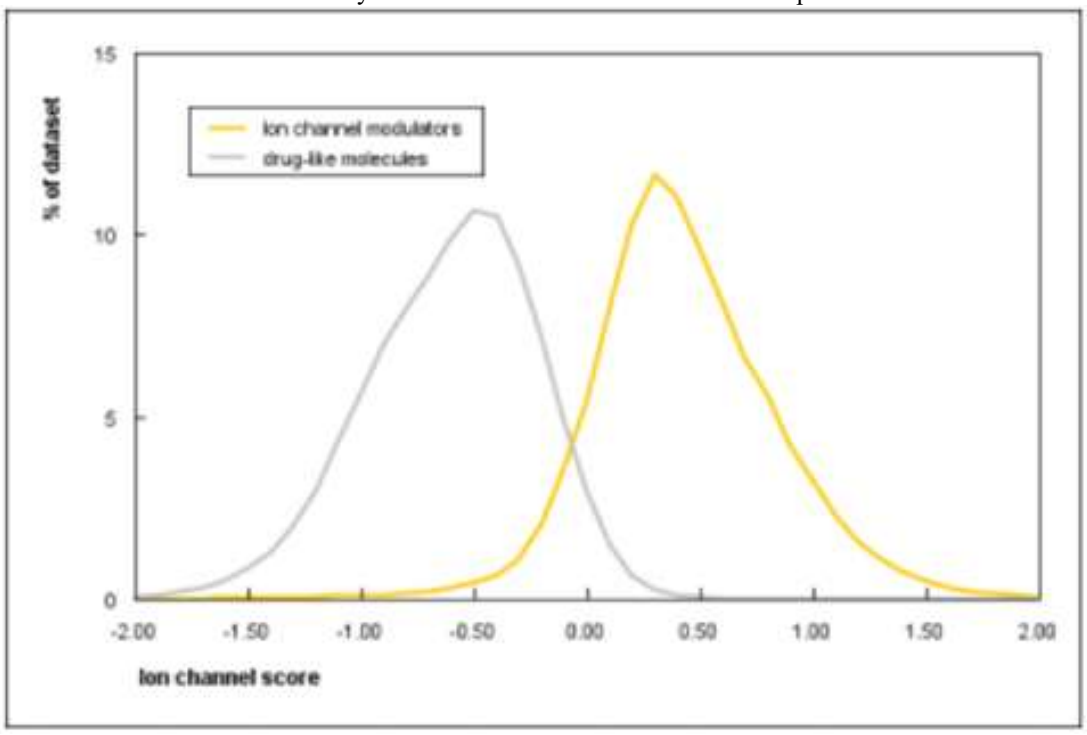
G Protein-Coupled Receptors (GPCRs) represent one of the largest and most important integral membrane protein families. These receptors serve as increasingly attractive drug targets due to their relevance in the treatment of various diseases, such as inflammatory disorders, metabolic imbalances, cardiac disorders, cancer, monogenic disorders, etc.



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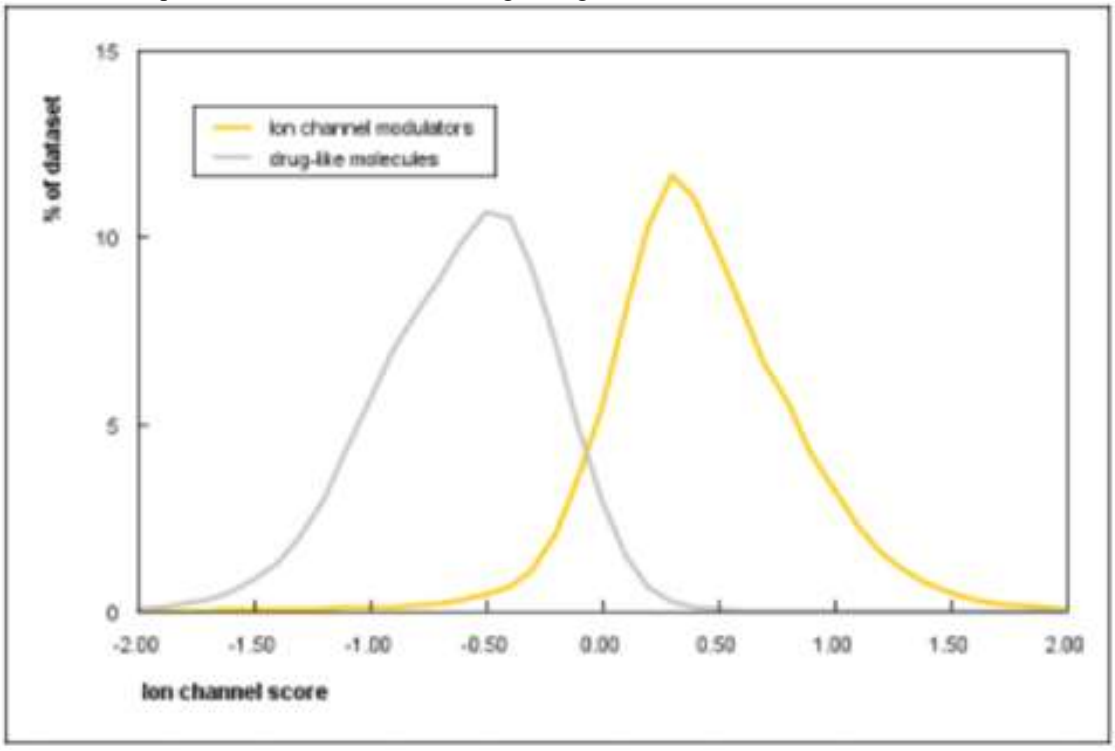
ii. Ion Channel Modulator

Ion channels are essentially pore-forming membrane proteins where some drugs may directly or indirectly interact leading to a change in action potentials and other electrical signals across the membrane. A channel modulator, or ion channel modulator, is a type of drug which modulates ion channels. They include channel blockers and channel openers.



iii. Kinase Inhibitor

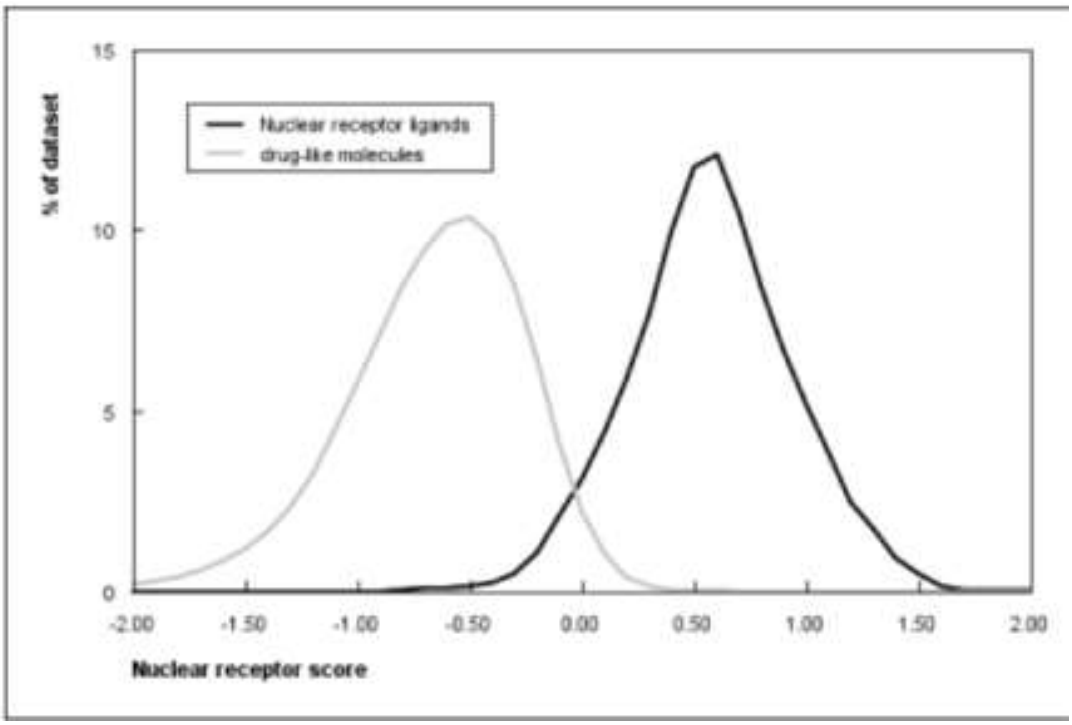
A substance that blocks a type of enzyme called a kinase. Human cells have many different kinases, and they help control important functions, such as cell signalling, metabolism, division, and survival.



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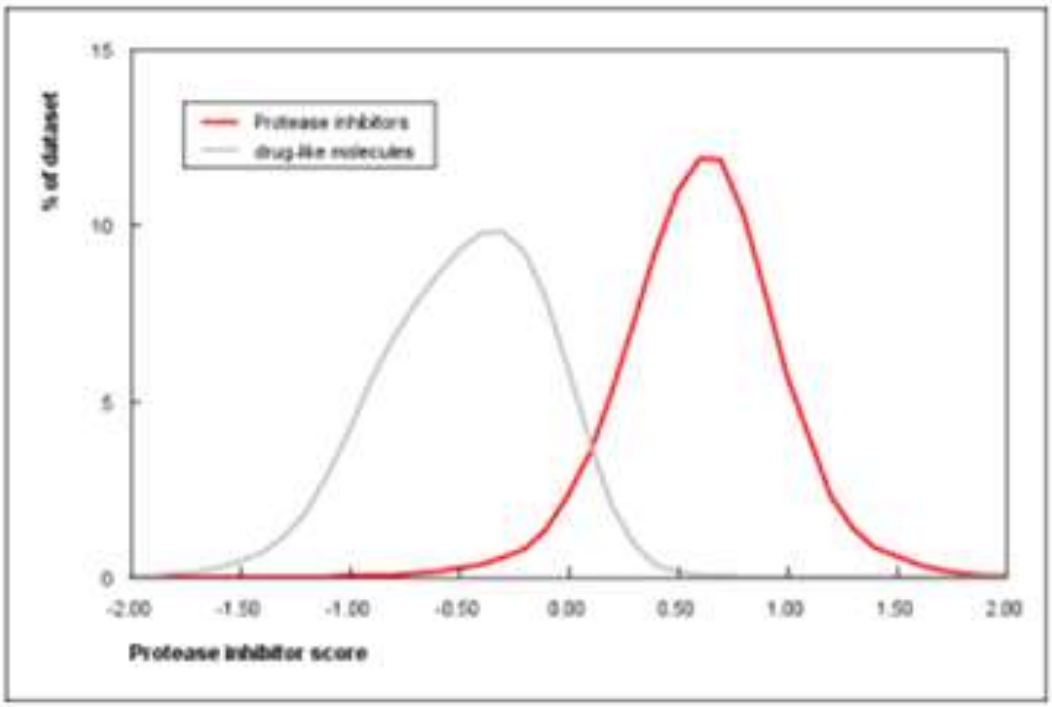
iv. Nuclear Receptor Ligand

Nuclear receptors are a family of ligand-regulated transcription factors that are activated by steroid hormones, such as estrogen and progesterone, and various other lipid-soluble signals, including retinoic acid, oxysterols, and thyroid hormone.



v. Protease Inhibitor

Medications that inhibit the cleavage of the polyprotein into functional proteins are called protease inhibitors. Protease is a protein-based enzyme that normally breaks the polyprotein into functional proteins, so blocking, or inhibiting, protease prevents this essential step of viral reproduction. Some protease inhibitors can keep a virus from making copies of itself (for example, AIDS virus protease inhibitors), and some can prevent cancer cells from spreading.



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7. PASS – A CRITICAL TOOL IN SEARCHING FOR 'MISSING INFORMATION'

New Definition of a post-authorisation safety study is "any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effective ness of risk management measures". However, previously, a post-authorisation safety study was defined as "a pharmaco epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product". One may therefore conclude that the amended definition of PASS aims to cover not only on-label, but also off-label studies, thus implying that any new safety information, based on the studies conducted outside the scope of the MA, ought to be communicated to the CAs and will be taken into account in the risk/benefit analysis of the product.

Depending on the type of the study, the medical objective and the size of the patient population to be observed, PASS can be conducted either as clinical trials of phase or as non-interventional (observational) studies. Unlike clinical trials, observational research provides data on how marketed products are actually being used in the real world without the restrictions of a controlled environment. In accordance with legal requirements, PASS may be requested by CAs either as a commitment at the time of authorisation or in the post-authorisation phase, for identifying previously unrecognized safety concerns. For certain medicinal products, applicants may receive a MA under the condition that they perform additional monitoring. In such cases the MA will be compulsorily varied to include the obligation as a condition of the MA and the risk management system has to be updated accordingly.

"Principally those non interventional post-authorisation safety studies where there is a known safety issue under investigation and/or when the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s)", creating ambiguity in further defining of what does and what does not constitute PASS. Inconsistent interpretation of the PASS definition within and between companies resulted in various outcomes, varying from under- to over-reporting, including inadequate company oversight and tracking of PASS, non-inclusion of relevant study updates and reports in RMPs/Peri odic Safety Update Reports (PSURs) and the FDA annual reports, or the opposite - MAHs taking the conservative approach and including every post-marketing study in RMPs/ PSURs or generation/reporting of data irrelevant to safety. These misconceptions of PASS resulted in significant unnecessary work for MAH and CAs. In order to address the request of CAs in the most competent and efficient manner, careful analysis and definition of the study objectives, typically requiring a pharmacoepidemiology expertise, is of utmost importance.

8. ADVANTAGES AND DISADVANTAGES

❖ ADVANTAGES

- **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

- **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.

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- **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.

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