Rational Drug Design and *In-Silico* Evaluation of Sulfonyl Hydrazone Derivatives for Potential Therapeutic Applications

Qazi Syed Iftikhar Hayat[1],Sohail Hassan[1], Khwaja Ali Hasan[3], Shereen[1,4], Yashra Shakeel[4], Yusra khan[2,4], Syeda Rafia Zahra Rizvi[2, 4], Iffat Sultana[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan

[2]Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan

[3]Department of Biochemistry, University of Karachi, Karachi, 75280, Pakistan

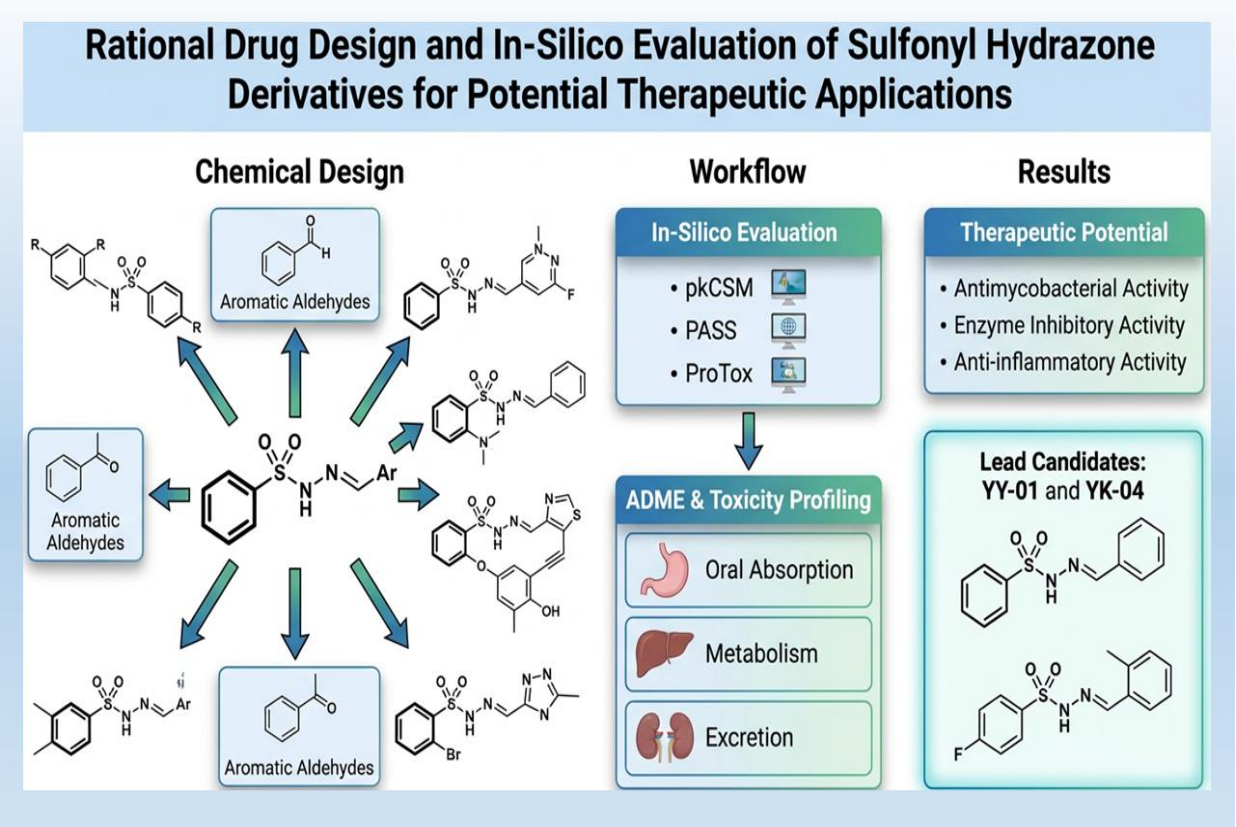
[4]Department of Pharmacy, Nazeer Hussain University, Karachi, Pakistan

Abstract

The rise of drug-resistant and emerging illness shows how important it is to find new ways for innovative therapeutic interventions. By Using existing drugs in new ways and computer-based methods, it can help speed up the process of finding and developing new medicines. This study uses these methods to create and evaluating derivatives of a drug that are already approved by the FDA, called Sulfonyl hydrazone, to see how altering its structure affects its ability to treat diseases. The derivatives have been created using of a group of small molecules with imine groups, based totally on a sulfonyl hydrazone scaffolds (YY-01, YU-02, YH-03, YK-04, YR-05) with substituted aromatic aldehydes and evaluated in silico for physicochemical properties, drug-likeness, expected bioactivity, ADME, and toxicity. Computational tools like stoptox, protox, way2drug, PASS and pkCSM platform (website) had been used to check the physical and chemical properties, drug-likeness, potential biological results of every derivative of sulfonyl hydrazone, and how far it's absorbed, distributed, metabolized, and excreted (ADME profiles) in the body. All the five derivatives complied with Lipinski's Rule of five, which relatively shows molecular weights present in low-to-mid 300 Da range, YY-01 displayed the finest steric bulk due to an indane fragment while YR-05 and YU-02 had been the least bulky. ADME predictions indicated favourable oral absorption potential and acceptable permeability and distribution metrics for small-molecule leads, with limited predicted BBB/CNS penetration; metabolic profiling revealed substituent-dependent interactions with cytochrome P_{450} enzymes, notably enhanced CYP-related interactions for the 2-chloro bearing YK-04 and altered clearance patterns for the bulky YY-01. Pass and cheminformatics bioactivity scoring returned high possibilities for several therapeutic events, with core predictions inclusive of antimycobacterial and enzyme inhibitory actions and secondary symptoms spanning antibacterial, antiviral, anti-inflammatory, and anticancer outcomes; All derivatives except YU-02 showed the most powerful multi category activity profiles.YK 04 and YY 01 benefit potency optimization however require centred metabolic and safety comply with up; usual, the in silico evaluation supports the sulfonyl hydrazone derivatives as promising candidates for synthesis and experimental validation, with recommended subsequent steps consisting of in vitro ADME assays, CYP inhibition testing, and targeted toxicity studies. These Schiff base

derivatives display exceptional ability for future drug improvement, highlighting how computational strategies play a key role in enhancing discovery and design of the drug and its derivatives.

Keywords: Rational drug design; drug repositioning or rediscovery; in-silico study; and ADME properties



Introduction

A drug, in medicinal terminology, is a chemical or biological substance designed to work with the biological processes to treat, diagnose, or stop a disease. These drugs can develop from one or another different sources inclusive of natural, semi-synthetic, or man-made. The continuous need for new drugs comes from many factors, together with the harmful effects and side effects of current drugs, the emergence of latest diseases, the way some diseases become resistant to drugs, and higher expertise of health issues. These factors can drive any pharmaceutical studies and development to pursue new molecules, enhance therapeutic effectiveness, and meet clinical needs that stay unaddressed. The most common way of finding new drugs followed by a well-established procedure, that starts with identifying and validating the right molecular targets. This is done by high-throughput screening of large chemical libraries, potentially to find therapeutic lead compounds. Conventional drug discovery techniques depend upon trial-and-error techniques, which includes in vitro and in vivo testing on animals to assess the compounds efficacy, pharmacokinetics (ADME) and its toxic levels. Despite the fact that this technique has helped create many successful treatments, it is more expensive, longer time taking, and often need more than ten years and over $2.5 billion to get a new drug to the marketplace. To address these challenges, other methods

such as drug repurposing, or drug repositioning, have become more popular. Drug repositioning means finding new ways to use existing drugs, whether they are already approved by the FDA, taken off the market, or no longer used. This method uses the known safety of these drugs, which speeds up and lowers the cost of developing new treatments and also involve using an existing drug as a base to make new analogues that work against different diseases. Compared to other conventional methods, this approach has clear benefits, like shorter development time period, lower costs, and better chances of success. As the fact which stated that 33% of drugs were approved in recent years and developed through drug repositioning, showing how effective this method is in modern drug discovery.

Advanced computational technologies such as, bioinformatics, and proteomics have greatly sped up the drug discovery process by using in-silico methods. One of the common Computational approaches, often called as computer-aided drafting and design of the drug (CADD), are now essential tools to use at every stage of drug development. This helps to transform biological target information into computer models, and allows for data analysis, computation, and the prediction of how compounds might work. Techniques like molecular docking, virtual screening, and machine learning help reduce large chemical libraries to smaller groups of more promising compounds that can be tested in experiments. Also, CADD provides important guidance for improving lead compounds by enhancing their binding strength, how well they work in the body, their safety, and by designing new compounds through structural changes.

The advantages of CADD includes, less time-consuming and inexpensive, and scope of experimental work usually needed in rational drug discovery. By predicting and optimizing compound properties using computer models, CADD can reduce research time and development costs by up to 50%. As computational accuracy keeps improving gradually, these predictions are becoming more reliable and align better with real-world experimental results, increasing the trust in in silico methods. Now a days, CADD is widely used in searching for treatments for various diseases, as cancer, diabetes and infectious diseases caused by viruses and bacteria.

Sulfonyl hydrazone which constitutes a flexible subclass of hydrazone compounds characterized by a sulfonyl group bonded to the hydrazone nitrogen, serving as a scaffold for drug discovery. Biological activities which are reported for these compounds include properties such as antimicrobial, anticancer, antioxidant, enzyme-inhibitory, and anti-inflammatory properties. The linkage of sulfonyl-hydrazone influences key molecular attributes such as polarity, hydrogen-bonding potential, and lipophilicity which affects the target recognition and pharmacokinetic behavior. The core structure, shown in Figure 1, readily accommodates modification at the hydrazone N–H (for example with alkyl, aryl, acyl, or heteroatom substituents) and by altering the sulfonyl or carbonyl partners, enabling systematic tuning of polarity, hydrophobicity, hydrogen-bonding patterns, and three-dimensional shape. This chemical adaptability has led to too many derivatives including, broadened therapeutic profiles, spanning anti-inflammatory, antimicrobial, anticancer, enzyme-modulating, and central nervous system activities. Additionally, the sulfonyl group often enhances metabolic resilience and can engage in noncovalent interactions with

protein targets to improve affinity and selectivity, while also serving as a convenient synthetic handle (for example, for sulfonamide formation or cross-coupling) to further expand chemical diversity during lead optimization.

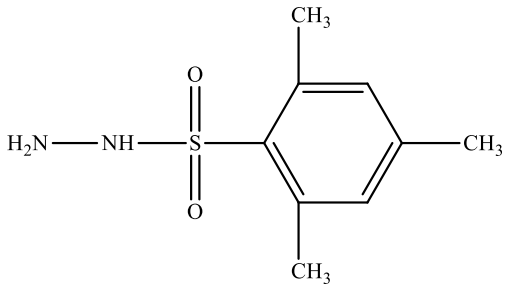


Figure 1: Generalized Chemical Structure of Sulfonyl Hydrazone

According to these advancements, this study seeks to create and evaluate a collection of small molecules that include imine groups and sulfonyl hydrazone structures. by Using computer-based techniques, we will forecast the physical and chemical properties, drug-like qualities, biological activity, and how well these compounds are absorbed, distributed, metabolized, and excreted in the body before actually making them and testing them. This strategy is meant to reduce the wasted resources and prevent spending time and money on compounds that are unlikely to show any useful effects. With the help of this active approach, identification of new drugs will be easy and more efficient, which lowers the chances of failure in later stages of development.

Materials and Methods

Design Strategy

In this study, Schiff bases compounds were created by using an FDA-approved drug known as sulfonyl hydrazone and combines it with substituted aldehydes. Five different compounds were developed and given the names YY-01, YU-02, YH-03, YK-04, and YR-05.

In silico Study

This study was carried out by using a high-performance computer which consists of Windows 10 operating system, an Intel(R) Core (TM) i5-2520M, CPU running at 2.50 GHz, and 4 Gigabytes of RAM. By using Chem Draw software, the chemical structures of five compounds (YY-01, YU-02, YH-03, YK-04, and YR-05) were created as shown in Table 1A. This in-silico process started with preparing the molecular structures of these compounds. First, they were developed in two-dimensional (2D) format by using Chem3D Ultra software and saved in Structure Data File (SDF) format. The above mentioned 2D molecular models were then converted into SMILES (Simplified Molecular Input Line Entry System) format, using through an online tool. To make sure the SMILES strings were accurate, they were carefully compared with their original chemical structures, as outlined in Table 1B. After validation, the SMILES data was carefully used as input for further predictive analysis. The data was sent to various online platforms, which helped to calculate important molecular properties and predict possible biological activities of the designed-derivative compounds. This computational process gave important information about the physicochemical properties, drug-likeness, bioactivity, and pharmacokinetics of the sulfonyl hydrazone derivatives being studied. The specific platforms used and the details of the predictions are discussed in later sections.

Physicochemical, Drug-likeness, and bioactivity Properties predictions

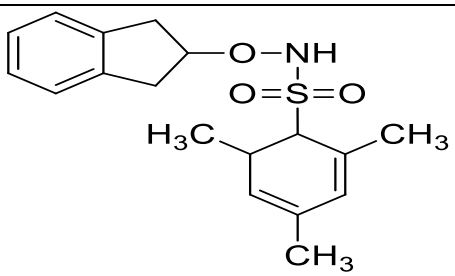
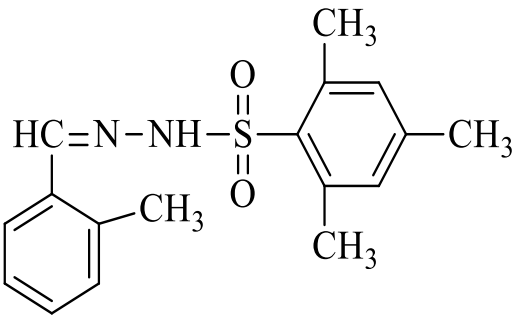
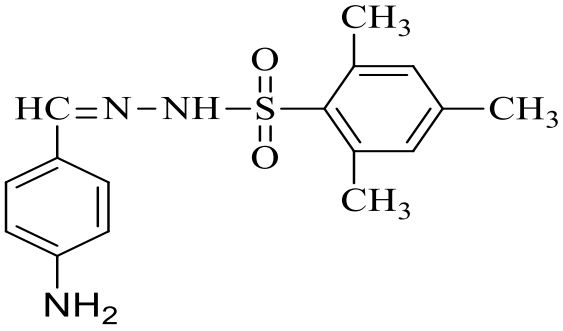
The physicochemical properties, and drug-like characteristics, were assessed by using the pkCSM platform and bioactivity of the compounds through stoptox. Drug-likeness was determined based on Lipinski's Rule of Five.

Prediction of Activity Spectra for Substances (PASS)

The PASS online tool was used for the better understanding of the biological activity of sulfonyl derivatives. (https://www.way2drug.com/passonline/)

ADME Prediction

The ADME properties of the derivatives of sulfonyl hydrazine were predicted using the pkCSM-Pharmacokinetics software (https://biosig.lab.uq.edu.au/pkcsm/). These predictions were based on established methodologies that are well-documented in scientific literature.

Codes	Chemical Structure
YK-01	
YK-02	
YK-03	

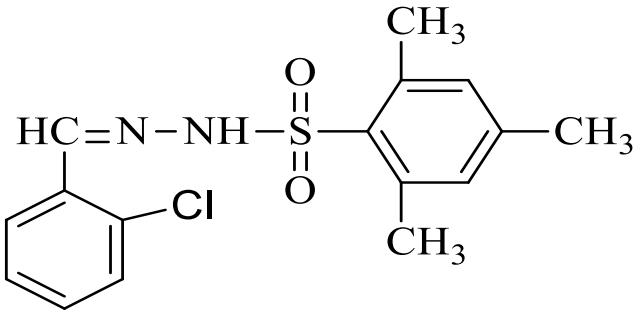
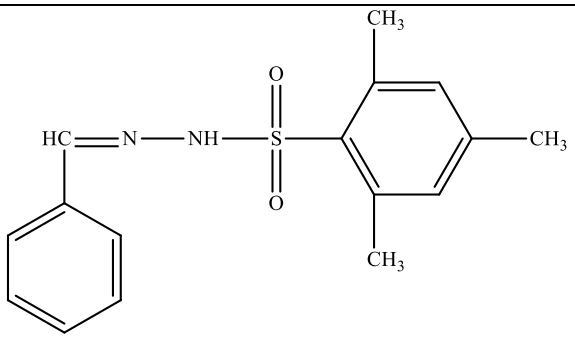
YK-04	
YR-05	

Table 1A: Codes and chemical Structure of the designed derivative compounds of sulfonyl hydrazone.

Codes	Character	
YY-01	IUPAC name	N-((2,3-dihydro-1H-inden-2-yl) oxy)-2,4,6-trimethylcyclohexa-2,4-diene-1-sulfonamide
	SMILES	O=S(NOC1CC2=CC=CC=C2C1) (C3C(C)C=C(C)C=C3C) =O
YU-02	IUPAC name	2,4,6-trimethyl-N'-(2-methylbenzylidene) benzenesulfonohydrazide
	SMILES	O=S(NN=CC1=CC=CC=C1C) (C2=C(C)C=C(C)C=C2C) =O
YH-03	IUPAC name	N'-(4-aminobenzylidene)-2,4,6-trimethylbenzenesulfonohydrazide:
	SMILES	O=S(NN=CC1=CC=C(N)C=C1) (C2=C(C)C=C(C)C=C2C) =O
YK-04	IUPAC name	N'-(2-chlorobenzylidene)-2,4,6-trimethylbenzenesulfonohydrazide:
	SMILES	O=S(NN=CC1=CC=CC=C1Cl) (C2=C(C)C=C(C)C=C2C) =O
YR-05	IUPAC name	N'-benzylidene-2,4,6-trimethylbenzenesulfonohydrazide
	SMILES	O=S(NN=CC1=CC=CC=C1) (C2=C(C)C=C(C)C=C2C) =O

Table 1B: IUPAC names and SMILES of the predicted compounds of Sulfonyl hydrazone.

Parameter	Predictor	Unit	Required value
Physiochemical and drug-likeness properties			
Rule	Molecular weight (MW)	g/mol	Less than 500
	Partition coefficient (LogP)	-	Less than 5
	Number of hydrogen bond acceptors	-	Less than 10
	Number of hydrogen bond donors	-	Less than 5
Pharmacokinetic properties			
Absorption	Water solubility	LogS	-
	Intestinal absorption (HIA)	% Absorbed	High absorption (%Abs) should be **greater than 30%** Poorly absorption (%Abs) involves **Less than 30%**
	Caco-2 permeability (Caco-2)	log Papp in 10^{-6} cm/s	High permeability is greater than 0.90
	Skin permeability (SP)	log Kp	Log kp greater than -2.5
	P-glycoprotein substrate (P-gp)	Yes / No	-
	P-glycoprotein I inhibitor	Yes / No	-
	P-glycoprotein II inhibitor	Yes / No	-

Parameter	Predictor	Unit	Requirement value
Distribution	The volume of distribution (VD_{ss})	log L/kg	Low: VDss: Less than -0.15 and High: VDss: Greater than 0.45
	Fraction unbound (FU)	-	High greater than 0.45
	BBB permeability (BBB)	log BB	Log BB Value constitutes Less than -1 (poorly). Log BB Value constitutes greater than 0.3 crosses the BBB.
	CNS permeability	log PS	Log PS Value Less than -3 unable to penetrate. Log PS Value: Greater than -2 penetrates CNS.
Metabolism	CYP1A2 inhibitor	Yes / No	-
	CYP3A4 substrate/inhibitor	Yes / No	-
	CYP2C8 inhibitor	Yes / No	-
	CYP2C9 substrate/inhibitor	Yes / No	-
	CYP2C19 inhibitor	Yes / No	-

	CYP2D6 substrate/inhibitor	Yes / No	-
Excretion	Total clearance (CL_{tot})	log mL/min/kg	Higher is better
	Renal OCT2 substrate	Yes / No	-

Table 1C: Summary of Computational models and Predictor variables used in the *in-Silico* Study.

Results and discussion

Design strategy

This study introduces a method for the discovery of sulfonyl hydrazone derivatives by making changes into the terminal NH2 group. This approach combines sulfonyl hydrazone with different types of aromatic or heteroaromatic aldehydes or ketones. But as Aromatic aldehydes were chosen as partners for this combination because of their specific structure. As compared to longer chains, aromatic aldehydes, having less flexibility, which can improve how well the compound binds to its target by reducing the energy loss due to movement. This could make the compound more effective, and make them have maximum potency.

Physiochemical and drug-likeness properties predictions

Prediction of the physicochemical properties of the drug derivatives is essential for efficient drug development and understanding their biological and medicinal actions. Properties such as molecular weight, and the number of heavy atoms is used for evaluating drug likeness, that helps to identify oral drug candidates of drug discovery and its design in the early stages. Drug-like compounds are molecules that have functional groups or physical properties similar to those of most known drugs, suggesting they may have biological activity or therapeutic effects. These drug-like characteristics are used as a parameter to choose a more promising compound as a lead from large combinatorial libraries. One of the basic methods for assessing drug-like properties is Lipinski's Rule of Five (Ro5), which was developed and stated by Pfizer's medicinal chemist, Christopher Lipinski. The Ro5 was based on an analysis of orally available drugs and clinical candidates, although it does not include certain classes such as antibiotics, antifungals, vitamins, and cardiac glycosides.

The Rule of Five (RO5) stated that a compound require certain conditions to more likely pass through cell membranes and be absorbed well in the human intestine. These conditions involve a molecular weight below 500, hydrogen bond donors fewer than 5, which are all the NH and OH groups, a partition coefficient value below 5, and fewer than 10 hydrogen bond acceptors, which are all the N and O atoms. The numbers in this rule are chosen as the multiple of five, which is why it's called the Rule of Five. Several researches indicate that if a compound doesn't meet two or more of the Rule of Five criteria, it is usually not good for drug development or for being taken orally. Lipinski's Rules helps scientists quickly decide which compounds might not be worth studying further.

Pk-CSM web-based software is important for assessing physicochemical properties and drug-like characteristics. This tool uses

machine learning models that rely on graph-based signatures. It combines structural and property data from both active and inactive compounds to detect sub-structural features commonly found in biologically active molecules. This software computes key physicochemical parameters that helps to predict the oral bioavailability of the compounds being studied. These parameters include molecular weight, partition coefficient (logP), and the number of hydrogen bond acceptors and donors. This tool also helps to predict ADMET properties, covering absorption, distribution, metabolism, excretion, and toxicity, As outlined in Table 4A.

Number of heavy atoms (N atoms):

The number of heavy atoms in a molecule plays an important role in drug design, and used to affect factors like molecular size, complexity, drug-likeness, and how well the drug works in the body (ADME). Although larger molecules may have a greater ability to bind to the targets, they can also create problems such as reducing aqueous solubility, passive cell membrane permeability, and synthetic complexity. These changes can improve target binding but usually worsen pharmacokinetic and developability metrics. During the process of improving a lead compound, reducing the number of heavy atoms can help lower the overall weight of the molecule and improve its solubility, which makes it more likely to behave like a potent drug without greatly reducing its effectiveness. Sulfonyl hydrazone derivatives fall in the 7–30 heavy-atom range depending on substituents, with aromatic examples commonly having 15–25 heavy atoms, but with sulfonyl hydrazone, having the lowest count at just 3 atoms. This increase in heavy atoms in the derivatives of sulfonyl hydrazone is usually because they include larger aromatic rings or extra chemical groups, as seen in YY-01, which has the highest number of heavy atoms due to the presence of an indane (fused bicyclic) fragment linked via an ether, making it more bulkier sulfonyl derivative

Molecular weight (MW)

Molecular weight defined as the total sum of the weights of all the atoms present in a molecule, which measured in Daltons (Da) or grams per mole. The main role of Molecular weight includes drug pharmacokinetic behavior (ADME) in the body. As molecular weight increases, the drug's ability to pass through cell membranes and be absorbed generally decreases, especially when it comes to crossing the blood-brain barrier (BBB), being inversely proportional to the molecular weight. The molecular weights of the designed compounds fall between 302.39 and 336.844 Da, which is all below the 500 Da limit. This suggests that these molecules are probably easy to absorb and have good ability to pass through cell membranes.

Partition coefficient (LogP):

The partition coefficient is important for determining lipophilicity or hydrophobicity of a substance or drug. It is calculated as the logarithm of the ratio of a compound's concentration between an organic phase, n-octanol, and an aqueous phase. A positive partition coefficient showed that the compound prefers a lipophilic or hydrophobic environment, whereas a negative value suggests lipophobic or hydrophilic environment. LogP values, plays a significant role in various aspects of drug pharmacokinetic behavior, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), as well as how the drug interacts with receptors and its overall effectiveness. Compounds with

very high or very low LogP values are affected by its permeability and solubility. Thus, highly hydrophilic compounds often have trouble passing through cell membranes due to the inability to penetrate the hydrophobic part of the lipid layer. On the other hand, increased lipophilic compounds are unable to penetrate through membranes as they tend to stay trapped inside the lipid bilayer, making it hard for them to move more effectively. Researchers have also found that a compound's partition coefficient value is related to drugs ability to cross the blood-brain barrier (BBB), as it is important for the drugs targeting the central nervous system (CNS). Generally, Log P value ranges from 4 to 5, considered ideal for CNS-active drugs.

Whereas, the Log P values of the designed compounds of sulfonyl hydrazine (YY-01, YU-02, YH-03, YK-04, and YR-05) fall within the acceptable range according to Lipinski's Rule and shows moderate to highly lipophilicity (YH-03 and YR-05). This increased lipophilicity, indicates the better absorption through biological membranes and add hydrophobic surface area and reducing polarity relative to a more polar parent scaffold.

Hydrogen bond acceptor and hydrogen bond donor groups:

Hydrogen bonds used to play major role by determining how molecules recognize each other, and thus maintains stability in their structures, helping enzymes to work efficiently, and affecting how drugs move through the body. Drugs consists of groups which can form hydrogen bonds, and enhance their solubility and their ability to interact more effectively with their biomolecular targets, and improves their affinity for binding and its selectivity. However, drugs consist of several hydrogen bond donors or acceptors which can make it harder for drugs to pass through cell membranes and move properly. To help to predict whether a compound is likely to be a potent drug or not, tools like Lipinski Rule of Five (Ro5) are used for determining the number of hydrogen bond donors and acceptors as a part of their analysis. The derivatives of compound which are designed contain the number of hydrogen bond acceptors ranges from 3 to 5, and the number of HB donor which ranges from 1 to 2. These numbers stay within the limits set by the Rule of Five and make sure that the compounds still have good drug-like qualities even with their hydrogen bonding ability.

Toxicity Prediction:

Toxicity is the ability of a compound to produce harmful biological effects (adverse effects) in living organisms. Every substance can be a potential poison; whereas its toxicity levels determine by its dose. It can be acute which occurs rapidly after single high-dose exposure (e.g., an overdose) or chronic toxicity which develops over a longer period from repeated low-level exposure, where damage accumulates over time (e.g., lead poisoning).

To determine the below toxicity of predicted compounds (YY-01, YU-02, YH-03, YK-04, YR-05) shown in TABLE 4C, we use stop tox which finalize the results that except YY-01 (oral toxicity) and YK-04 (dermal toxicity) all derivatives are non-toxic in acute toxicity. Whereas, YU-02, YH-03, YK-04, and YR-05 are listed as sensitizers, and skin irritation is negative for all.

PASS Prediction:

The Prediction of Activity Spectra for Substances (PASS) website used as a strong computational method for predicting the biological activities of chemical substances.

It was created by the V. N. Orechovich Institute of Biomedical Chemistry. This uses structural similarities of the known active compounds to forecast pharmacological effects. This model is built on a large dataset, mainly from the MDL Drug Data Report (MDDR), and is regularly updated with new findings in medicinal chemistry.

Interpreting the results from PASS predictions needs some flexibility, and can be done by determining Pa values. When Pa value is above 0.7, it denotes that there's a high chance that the predicted biological activity can be tested in experiments, which suggests that the compound has a structure similar to known active drugs, making it a potentially potent for further study. Whereas, the probability of experimental confirmation is lower, when Pa values are between 0.5 and 0.7. However, these compounds might contain new structural features that are different from existing drugs. These unique features could help in understanding new or rare ways through which drugs can work. If the Pa value is below 0.5, the chance of experimental validation is low. Even so, these compounds might still have new structures which could lead to discoveries in areas of biological activity that haven't been explored much before. PASS predictions for a group of sulfonyl hydrazone derivatives which are designed (YY-01, YU-02, YH-03, YK-04, YR-05), can be shown in TABLE 5 which focuses on those which have highest Pa values (greater than 0.7). These predictions help in exploring the possible therapeutic uses of these compounds, with sulfonyl hydrazone acting as the base structure. From the data, each compound has several potential activities, which can be grouped into different categories.

Core Activities: These activities appear consistently across multiple INH compounds and represent the primary mechanisms of action which includes antimycobacterial, inhibitor of Glutamyl endopeptidase II, PfA-M1 aminopeptidase inhibitor, or Mucomembranous protector.

Secondary Activities: These are the activities that appear in multiple sulfonul hydrazone compounds, and have less frequency or probability than the core activities. This includes HMGCS2 expression enhancer (cholesterol metabolism), inhibitor of Aminobutyraldehyde dehydrogenase, phosphatidylserine decarboxylase inhibitor (cell signaling), inhibitor of glutamine phenylpyruvate transaminase (amino acid metabolism), Acetylcholine neuromuscular blocking agent, antiviral (picornavirus and poxvirus), Antineoplastic (melanoma), Nicotinic alpha4beta4 receptor agonist, beta-adrenergic receptor kinase inhibitor (hormonal signaling).

Tertiary Activities: These are the less common activities and often have probabilities lower than secondary and core activities including Acetylcholine neuromuscular blocking agent, Anaphylatoxin receptor antagonist, Para amino benzoic acid antagonist, Thromboxane B2 antagonist, Creatininase inhibitor, Nicotine dehydrogenase inhibitor, Anti-infective, Acetylgalactosaminyl O glycosyl glycoprotein β 1,3 N acetylglucosaminyltransferase inhibitor, Calcium channel N-type blocker, Aldosterone antagonist, Prostaglandin E2 agonist, Thiamine pyridinylase inhibitor, Erythropoiesis stimulant, Falcipain 3 inhibitor; N hydroxyarylamine O acetyltransferase inhibitor; Anti-inflammatory, intestinal, 3 Hydroxybenzoate 6 monooxygenase

inhibitor; Oligopeptidase B inhibitor; Endothelial growth factor antagonist, Thioredoxin inhibitor, IgA specific serine endopeptidase inhibitor, Lysyl oxidase inhibitor, Diuretic, ATPase stimulant; Arylesterase inhibitor, Gamma guanidinobutyraldehyde dehydrogenase inhibitor; Cyclooxygenase 2 inhibitor, Angiotensin II receptor antagonist, anti-leprosy.

Additionally, the predicted potency levels of the designed derivatives of sulfonyl hydrazone had shown clear pattern from their structure and produces antibacterial effects, which is important because the basic framework is relevant for targeting Mycobacterium tuberculosis and Gram-positive bacteria like Staphylococcus aureus and Bacillus subtilis. Changes made to the imine-linked aromatic ring greatly affected how well the compounds worked. For example, adding groups at the para position on the benzylidene ring often improved antimycobacterial activity. The para-amino derivative YH-03 had higher predicted activity compared to the unsubstituted YR-05. Electron-donating groups, like para-NH_2 or methoxy groups, generally increased predicted antibacterial strength. However, electron-withdrawing groups could also boost activity, depending on where they were placed and the overall context. In contrast, substituents at the ortho or meta positions, as seen in the 2-methyl YU-02 and 2-chloro YK-04 derivatives, tended to lower predicted activity compared to para-substituted versions. This is probably because the extra bulk and changes in the ring's electronic properties made it harder for the molecules to bind effectively. Larger, fused, or bulky parts, like the indane-containing YY-01, changed the compounds' lipophilicity and three-dimensional shape. This will be led to the mixed effects on antibacterial predictions, but in some cases, the improved hydrophobic interactions helped increase potency. Overall, these computer-based structure-activity trends suggest that para-substituted, electron-rich benzylidene groups are promising starting points for further work to improve effectiveness against mycobacterial and Gram-positive bacteria.

According to the in-silico antiviral screening, the original sulfonyl hydrazone structure showed very low or no expected activity against different viruses. However, some of the designed Schiff base derivatives, like YH-03 and YK-04, showed better antiviral effects against Picornavirus, showing how specific changes to the structure can make a big difference. The strength of the antiviral effect depends on the type of substitution, when the benzylidene part had substituents in the para position, the effect was generally better. Electron-donating groups, such as para-amino or methoxy, usually improved activity, while electron-withdrawing groups like chloro or nitro could also boost activity in certain cases. Heteroaromatic rings like furan or thiophene didn't show much antiviral activity. Also, substitutions in the ortho or meta positions usually made the effect weaker compared to para substitution. Overall, these findings suggest that para-substituted, electron-rich benzylidene derivatives are the most promising for further testing in lab and animal studies.

In contrast, sulfonyl hydrazone demonstrated predicted activity of enhancing HMGCS2 expression, a key enzyme in lipid metabolism. However, many derivatives had shown increased activity in this area (YH-03, YK-04), and indicates that structural modifications improved the HMGCS2 expression-enhancing properties. Whereas, Para-

substitution on the phenyl ring was again play important role for enhancing HMGCS2 expression. Compounds such as (YH-03, YK-04) had shown increased activity, if electron donating groups are present (e.g., -OCH3, -NH2). Electron-withdrawing groups (e.g., NH, -Cl) which contain a furan substituent, also proved beneficial, as seen in (YY-01, YK-04), and exhibited the highest activity for HMGCS2 expression enhancement as well. As with antibacterial and antiviral activities, ortho- and meta-substitutions resulted in reduced activity, while naphthyl substituents (YH-03, YK-04) did not significantly improve activity over phenyl groups. Derivatives are particularly promising for further exploration in pathways which were regulated by HMGCS2.

ADME prediction

As Pharmacodynamics defined as how the drug affects the body, pharmacokinetics (PK) refers to how the body processes the drug. The following four key factors that determine how a drug behaves in the body, known as ADME properties are absorption, distribution, metabolism, and excretion. These pharmacokinetic properties are essential in assessing the drug's effectiveness, safety and therapeutic activities. The mechanism of ADME process involves the dissolution of drug in the GIT, which then gets absorbed through the gut wall, and enters the bloodstream, often passing through the liver. The drug then spreads into different parts of the body depending on its chemical structure and physical properties. As it is distributed, the drug then gets metabolized and changed into different forms, with the help of enzymes in the body. Whereas, elimination refers to how the drug is removed from the body, through excretion. For a drug to work properly, it needs to reach its intended site in the body in enough amount and stay active long enough to produce its desired effect. This section examines the absorption, distribution, metabolism, and excretion features of sulfonyl hydrazone derivatives (YY-01, YU-02, YH-03, YK-04, YR-05).

(A) Absorption

Absorption defined as the process by which drug travels from the site of administration and reaches into the bloodstream. Following several factors that are considered to assess how well a drug can be absorbed involves, water solubility (LogS), how well it is absorbed in the human intestine (HIA), permeability across the Caco-2 cell line (LogPapp), skin permeability (LogKp), and their interactions with P-glycoprotein (P-gp I, II (LogS). These factors play a key role in determining how much of the drug actually reaches the bloodstream, especially when taken by mouth (orally). The outcomes of these factors are listed in Table 6A

Water solubility (logS):

Water solubility play main role to determine how drugs are made and how well they are absorbed, especially when given orally. Low solubility can cause poor bioavailability and impaired absorption, whereas high solubility increases drug dissolution and plasma concentration. The ability of a substance to dissolve in water is usually measured using log units of molar solubility (mol/L), called logS. Sulfonyl hydrazone derivatives consists of different levels of water solubility, which ranges from -2.892 to -4.59. A negative value shows that the substance is not very soluble in water. For example, YU-02 and YR-05 are expected to have high solubility in water as compared to the basic sulfonyl hydrazone compound. This is because they contain simpler aromatic groups, such as methyl or unsubstituted benzylidene, that

reduces the overall hydrophobic surface area and do not greatly increase the drug's fat-like properties, and helps to maintain absorption. additionally, YY-01, which has a large indane group connected through an ether, and YK-04, which has a chlorine group that is electron withdrawing group, are expected to be less soluble. The added bulk and the presence of more hydrophobic or electron-withdrawing groups makes difficult for these derivatives to dissolve in water. Predictions of lower solubility indicates that these derivatives might have a difficulty with absorption in the body's mostly water-based environments.

Human intestinal absorption (HIA):

HIA determines how well a compound is taken up or absorbs by the intestines. However, 80% suggests good absorption. The highest HIA values for the sulfonyl hydrazone derivatives involve YY-01 (92.884%) and YU-02 (92.365%), which indicates strong predicted intestinal absorption. This is probably because YY-01 consists of a bulky indane group connected to an ether, whereas YU-02 has a 2-methylbenzylidene group, which increases the compound lipophilicity and help it pass through cell membranes more easily. On the other hand, YH-03 and YK-04 consists of lower HIA values due to YH-03 having a polar 4-amino group and YK-04 having a chloro group that pulls electrons away, both of which make it harder for the compounds to cross cell membranes. The parent sulfonyl hydrazone has a lower HIA of about 75.65%, which matches its simpler, less lipophilic structure that lacks features that help with passive absorption. Thus, the HIA values for the compounds range from 89.818% to 92.884%, meaning all the compounds have good predicted absorption and are likely to be well absorbed when taken by mouth.

The Caco-2 cell line (Caco-2):

The Caco-2 cell line is commonly used to study intestinal permeability. Derivative compound with the value higher than 0.90 cm/s is generally classified as high permeability compounds. The sulfonyl hydrazone derivatives have different permeability values, which ranges from -1.328 to 1.36. Some compounds, such as YY-01, YU-02, and Yk-04, shows high permeability, while others such as YH-03 and YR-05 have lower permeability. The lower permeability of these compounds might be due to the presence of polar substituents, like the 4-amino group in YH-03, bulky groups, or electron-withdrawing groups, which can slow down their movement across the intestinal membranes.

Skin permeability (LogKp):

Skin permeability shows how well a drug can pass through the skin barrier, which is very important for drugs that are delivered through the skin. Drugs with value above -2.5 cm/h, generally indicates low skin permeability. The Log Kp values for the sulfonyl hydrazone derivatives range from -3.228 to -2.735, which indicates relatively poor/low skin permeability. But the compound, YH-03, consists of a Log Kp value of -2.735, which indicates the highest skin permeability among the derivatives, suggesting it might work well for transdermal drug delivery.

Permeability glycoprotein (P-gp) interaction:

A type of protein called P-gp is attached to cell membranes and helps to move substances out of cells. This reduces the amount of a drug that reaches the bloodstream by actively pushing it out of cells, especially in areas like the intestines, liver, and brain. Drugs that are recognized by P-gp might not reach highly enough levels in the body to be effective, since the transporter removes them before they can

build up to a therapeutic level. These drugs can be divided into two groups including those that are not broken down by the body's enzymes and those that are handled by both P-gp and certain enzymes which are involved in the drug metabolism, like CYP3A4. Since many drugs that are affected by P-gp are also processed by CYP3A4. Due to which P-gp inhibitors often also affect CYP3A4, and many drug interactions can occur when either of these processes is slowed down or sped up. Several compounds mentioned in this study (YH-03, YY-01, YK-04, YR-05, YU-02) are predicted to be the substrates for P-gp, which could lead to lowering the bioavailability because they might be released out of cells by this protein. This also make them more likely to be broken down by CYP3A4. On the other hand, the parent sulfonyl hydrazone and its derivatives are not expected to interact with P-gp, which may help them to stay in the body longer and improve their bioavailability. The data shows that none of the compounds have P-gp inhibitory activity.

(D) Distribution

Drug distribution involves the movement of a substance reversibly from the circulatory system to different organs and tissues, having a pivotal role in the ADME process as it affects the drug's concentration at target sites, and impacts both the efficacy and the potential toxicity. Distribution properties of derivative compounds has been studied and evaluated. This involves four significant parameters which is volume of distribution, fraction unbound, blood-brain barrier permeability, and central nervous system permeability, as detailed in Table 6B.

The Volume of Distribution (VD)

The Volume of Distribution measures the extent to which a drug is distributed throughout the body tissues compared to its concentration in the bloodstream. Increased values of volume of distribution suggest a more extensive tissue distribution. A compound seems to exhibit favorable tissue distribution when its Vd value surpasses 2.81 L/kg (log VD greater than 0.45), and poor distribution when it falls below 0.71 liters per kilogram (log Vd -0. 15). The VD values for the derivatives vary from -0. 295 to 0. 162 L/kg. This increased VD values indicates more extensive tissue distribution. Derivative compounds as labeled YY-01, YU-02, YH-03, YK-04, and YR-05 show moderate tissue penetration, due to their aromatic structures, which improve their lipophilicity.

Fraction Unbound (FU)

Fraction Unbound (FU) is important for determining the percentage of a drug that are unbounded to proteins and present in the bloodstream, but is pharmacologically effective. A higher value of FU suggests a larger proportion of the drug capable of delivering therapeutic benefits. The FU values for the derivatives vary from 0.087 to 0.254, indicates that the lower FU values are associated with higher protein binding.

Derivative compounds like YY-01 and YR-05 (N'-benzylidene-2,4,6 trimethylbenzenesulfonohydrazide) along with other derivatives YU-02, YH-03, and YK-04, have lower fraction unbound values (YY-01 Fu = 0. 134; YR-05 Fu = 0. 108), and suggested enhanced protein binding.

Blood-Brain Barrier (BBB) Permeability

Blood-brain Barrier (BBB) Permeability suggests a drug's ability to cross the BBB, which is a selective barrier that regulates the entry of substances into the brain. Compounds with a LogBB value greater than 0.3 are taken into consideration of

capable of crossing the BBB easily, while LogBB value less than -1.0 face significant barriers. Most sulfonyl hydrazone derivatives demonstrate low BBB permeability, suggesting limited brain penetration. However, none of the reported derivatives exceed the 0.3 threshold. For example, YY-01 has LogBB = −0.10 (limited CNS access) and YR-05 (N′-benzylidene-2,4,6-trimethylbenzenesulfonohydrazide) has LogBB = 0.025, both indicating only modest or negligible brain exposure compared with the > 0.3 benchmark.

CNS Permeability (Log PS)

CNS Permeability used to evaluate the potential of these compounds for penetrating into the central nervous system. Compounds which consists of Log PS value greater than -2 are considered to be capable of CNS penetration, even with a Log PS value less than -3 are not able to cross the CNS barrier. For the derivatives, YY-01, YH-03 and YR-05 have Log PS value lower than -2, which indicates that these compounds are used to poorly penetrate into the CNS. Whereas, the derivatives remaining as YU-02 and YK-04, shows off slightly moderate CNS permeability with Log PS value more -2.

3.5.3 | (M) Metabolism

The drug metabolism is the process by which drug molecules are transformed by body's enzymes through chemical modifications. This serves as a crucial protective function against possible toxins which frequently have lipid solubility and can accumulate in the body. Those toxins then transformed into more water-soluble compounds to facilitate elimination. However, in liver the majority of drug metabolism takes place where hepatic microsomal enzymes act and help to breakdown the process. The metabolic characteristics of sulfonyl hydrazone derivatives were then investigated when examine their ability to act as substrates or inhibitors for key enzymes called as cytochrome P450 (CYP), that are crucial for detoxifying enzymes. All these enzymes predominantly found in the liver. As of now, 57 different isoforms of these enzymes have been identified in humans, including five important isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) that are being crucial for drug metabolism.

The properties of the compounds regarding their metabolic and pharmacokinetic characteristics have been described (**Table 6C)**. Due to the particular involvement of CYP 3A4 and CYP 2D6 among those isoforms within the metabolism of several drugs, they constitute unique significance clinically. Inhibiting these enzymes can cause reduction in drug clearance, enhances drug plasma concentrations, and have ability for potential adverse effects. When a compound serves as a substrate for these enzymes, it is possibly to be metabolized efficiently, and lowers the risk of side effects which are related to the drug accumulation. Derivatives of sulfonyl hydrazone, which includes YY-01, YU-02 and YR-05, act as substrates for CYP3A4, and indicates their probability of increasing metabolic processing by means of this enzyme, lowering the risk of accumulation-related side effects. Furthermore, most derivatives show no substantial inhibition of CYP2D6, and CYP3A4, which indicates its high-quality, as it shows a lower capability for drug-drug interactions and decreased threat of hepatotoxicity in liver. All derivatives except YY-01 inhibit CYP1A2, isoform, causing increased plasma concentrations of co-administered drugs which is metabolized by means of CYP1A2 and increase the risk of drug-drug interactions. The inhibition of CYP1A2 can

be connected to the electron-withdrawing substituents, along with nitro and halogen groups, present at the aromatic rings of those compounds, which likely facilitate interaction with the enzyme's active site. This inhibition determined that other derivatives can be attributed to structural features, inclusive of bulky substituents, that may obstruct the enzyme's binding affinity. Only YU-02 and YK-04 shows inhibitory activity for CYP2C9 isoform, which can be attributed to the presence of a dimethylaminonaphthyl which interacts with the active site of CYP2C9.

(E) Excretion

Excretion is the elimination of the drugs from the body, and is closely related to the rate of elimination and concentration of the drug in the bloodstream. The excretion of sulfonyl hydrazone derivatives (YY-01, YU-02, YH-03, YK-04, YR-05) were studied and evaluated based on their total clearance values (unit: Log ml/min/kg), and their potential interactions with the renal Organic Cation Transporter 2 (OCT2). This was presented in Table 6D. The total clearance values for the derivatives ranged from -0.028 to 1.522 Log ml/min/kg. Several derivatives showed clearance values close to this value and suggests that despite structural modifications, the sulfonyl hydrazone core structure contributes to a baseline level of metabolic stability. Derivative with higher clearance rates which is greater than 0.800) is YY-01 having 1.522 of total clearance value, indicating rapid elimination from the body, consist of shorter half-lives and a possible need for more frequent dosing. Structural modifications such as electron-withdrawing groups present in YK-04 (2-chloro substituent) or bulky aromatic substituents present in YY-01 derivative compound (indane moiety) enhances the interaction of the compound with the metabolic enzymes, that leads to the increased clearance. In contrast, a derivative compound YU-02 having 0.711 total clearance value exhibited moderate clearance rate (0.700–0.800), generally indicates less complex aromatic substitutions, which may reduce to metabolic enzyme interactions, causing in slower clearance rates. These compounds with moderate clearance rates should remain in the body for an extended duration, which may also increase their ability to attain and preserve therapeutic ranges at target sites. The lowest clearance rates lesser than 0.700, have been discovered in YH-03, YK-04 and YR-05 derivative compound. However, YK-04 consists of a chlorine atom which decreases the derivative compounds' susceptibility for metabolic breakdown and its excretion. This leads to the decrease in clearance. Derivatives with low to moderate clearance can also have extended half-lives, which increases the chance of accumulation, and providing the advantage of being less frequent dosing. The role of OCT2 in renal clearance were also assessed. OCT2 is a key renal uptake transporter which helps in the active secretion of drugs and endogenous compounds. Predicting whether a compound interacts with OCT2 or not is important for the knowledge of excretion pathway and the risk of contraindications. The result based on pkCSM predictions has shown that none of the derivatives of sulfonyl hydrazone have been recognized as OCT2 substrates. This suggests that all derivative compounds which have been designed are not going to be actively transported through OCT2. This lowers the chance of their involvement in renal secretion. So, their clearance is much more likely to be mediated through hepatic pathways rather than renal pathways. This implies that renal toxicity or drug-drug interactions which are related to the OCT2

inhibition aren't classified as a first-rate problem for those derivatives.

Conclusion

In rational drug discovery and its design, to optimize the pharmacokinetic profiles of the compounds, its knowledge and predicting the physicochemical characteristic of compounds is necessary. In this study, sulfonyl hydrazone derivatives were examined and studied, showing a clear trend of improved physicochemical characteristics. These are due to the structural adjustments which involves diverse aromatic substituents, resulting in derivatives with varied molecular weight, its quantity, hydrophobicity and its hydrogen bonding potential. The results were shown that all tested compounds meet the criteria of Lipinski's Rule of 5, which suggests that they own favourable drug-likeness characteristics, high permeability and organic availability. No matter of what their extended molecular complexity is, those compounds hold drug-likeness without causing any violations, and reinforcing their potential as potent drug derivatives.

The predictions of the sulfonyl hydrazone derivatives which were obtained through PASS platform, provides clear insights into how structural changes have an impact on pharmacological ability. Derivative compounds which includes YY-01, YH-03, YK-04, and YR-05 display high expected activity for more than one therapeutic classes. This makes them as promising candidates in addition to the further experimental assessment. The results shown that derivatives have potential for antimycobacterial, antibacterial, antiviral, anti-inflammatory, and anticancer properties. The observed substitutions on the benzylidene and indane/aryl fragments create possibilities to discover novel bioactive compounds for developing new therapeutic interventions across various scientific fields. The pharmacokinetic properties of the sulfonyl hydrazone derivatives were also affected by structural modifications. Some of the derivatives display progressed absorption and permeability profiles, mainly those derivative compounds which consists of electron-withdrawing or hydrophobic substituents but a few derivatives also face challenges consisting of constrained solubility or interactions with P-glycoprotein (P-gp), which are necessary to conquer these absorption boundaries. In terms of distribution, bulky and lipophilic derivatives exhibit extra tissue penetration and blood-brain barrier permeability. This suggests their potential for treating CNS-associated conditions.

However, these changes may increase the risk of CNS-related outcomes that requires balanced approach for designing new compound. The effect of unique substituents for its interaction with cytochrome P450 enzymes highlighted by the metabolic profile. Derivative compound as YK-04 which bears a 2-chloro benzylidene, and indicates stronger CYP450 inhibitory activity. This requires the recollection of structural modifications carefully to decrease the risks of drug-drug interaction. Excretion rates also ranges, with derivatives displaying exclusive clearance values. In excretion, results were shown that compounds having higher clearance rates require more common dosing, while others with lower clearance risks the accumulation. The absence of renal OCT2 interactions shows hepatic clearance pathways, and reduces the renal toxicity risks. These derivatives had shown promising pharmacological and pharmacokinetic profiles, and further optimization and experimental validation of these compounds can be vital to achieve their therapeutic potential.

Designed Derivative compounds	Number of atoms	Lipinski's Rule of five			
		Molecular weight expressed in Da	Partition coefficient (Log P value)	N-ON	N-OHNH
YY-01	23	333.453	2.9157	4	1
YU-02	28	316.426	3.23268	3	1
YH-03	22	317.41	2.506	4	2
YK-04	22	336.844	3.57766	3	1
YR-05	21	302.39	4.4	4	1

TABLE 4A: Physicochemical Properties and Drug-Likeness Scores for the Designed Derivative Compounds.

Abbreviations: Number of hydrogen atoms or N atoms; Molecular weights; octanol/water partition coefficient indicate as Log P; Number of hydrogen bond acceptors or N-ON; Number of Hydrogen Bond Donors or N-OHNH.

CODES	Acute Inhalation Toxicity	Acute Oral Toxicity	Acute Dermal Toxicity	Eye Irritation and Corrosion	Skin Sensitization	Skin Irritation and Corrosion
YY-01	Non-Toxic	Toxic	Non-Toxic	Toxic	Non-Sensitizer	Negative
YU-02	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	Sensitizer	Negative
YH-03	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	Sensitizer	Negative
YK-04	Non-Toxic	Non-Toxic	Toxic	Toxic	Sensitizer	Negative
YR-05	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	Sensitizer	Negative

Table 4B: Toxicity (-) and non-toxicity (+) of newly Designed Derivative Compounds.

Codes	Probability of Activity (Pa)	Therapeutic Activity
YY-01	0.666	Antieczematic

	0.705	Mucomembranous protector
	0.704	Glutamyl endopeptidase II inhibitor
	0.628	Nicotinic alpha4beta4 receptor agonist
	0.610	Omptin inhibitor
	0.557	Polyporopepsin inhibitor
	0.594	CYP3A2 substrate
	0.573	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.297	Acetylcholine neuromuscular blocking agent
	0.513	Antianginal
	0.534	Vasoprotector
	0.379	Antibacterial
	0.292	Anaphylatoxin receptor antagonist
	0.295	Para amino benzoic acid antagonist
	0.288	Calcium channel N-type blocker
	0.278	Aldosterone antagonist
	0.064	Prostaglandin E2 agonist

YU-02	0.669	Omptin inhibitor
	0.612	HMGCS2 expression enhancer
	0.573	Antineoplastic (melanoma)
	0.558	Insulysin inhibitor
	0.516	Chloride peroxidase inhibitor
	0.509	Phospholipid translocating ATPase inhibitor
	0.429	Thioredoxin inhibitor
	0.417	Aminobutyraldehyde dehydrogenase inhibitor
	0.399	Aspergillopepsin II inhibitor
	0.303	Falcipain 2 inhibitor
	0.303	Aspartate-phenylpyruvate transaminase inhibitor
	0.302	Feruloyl esterase inhibitor
	0.279	Thromboxane B2 antagonist
	0.277	Creatininase inhibitor
	0.290	Nicotine dehydrogenase inhibitor (Pa 0.290)
	0.272-0.273	Antiinfective
	0.274	Acetylgalactosaminyl O glycosyl glycoprotein β 1,3 N acetylglucosaminyltransferase inhibitor
	0.561	Omptin inhibitor
	0.537	HMGCS2 expression enhancer
	0.472	Antiprotozoal (Coccidial)
	0.461	Phospholipid-translocating ATPase inhibitor

YH-03	0.435	Antineoplastic (melanoma)
	0.426	Antiinfective
	0.425	Phthalate 4,5 dioxygenase inhibitor
	0.401	Antiviral (Picornavirus)
	0.397	Para amino benzoic acid antagonist
	0.373	Antituberculosic
	0.346	Antileprosy
	0.305	Antimycobacterial; CYP3A2 substrate
	0.328	Acetylcholine neuromuscular blocking agent
	0.322	CYP2C9 inducer
	0.287	Thiamine pyridinylase inhibitor
	0.283–0.281	Erythropoiesis stimulant;
	0.243–0.240	Falcipain 3 inhibitor; N hydroxyarylamine O acetyltransferase inhibitor; Antiinflammatory, intestinal
	0.230–0.220	3-Hydroxybenzoate 6-monooxygenase inhibitor; Oligopeptidase B inhibitor; Endothelial growth factor antagonist (Pa ≈ 0.230–0.222)
	0.215–0.200	Prostaglandin E1 antagonist; Saluretic; Pyruvate decarboxylase inhibitor; other lower-Pa enzyme targets (Pa ≈ 0.215–0.200)
	0.199 and below	Many additional tertiary items (heat-shock agonists, various enzyme inhibitors, receptor antagonists, substrates and therapeutic indications) with Pa values down to ~0.025.
YK-04	0.735	PfA-M1 aminopeptidase inhibitor
	0.696	Glutamyl endopeptidase II inhibitor
	0.674	HMGCS2 expression enhancer
	0.587	Omptin inhibitor
	0.419	Glycosylphosphatidylinositol phospholipase D inhibitor
	0.404	CYP2C3 substrate
	0.452	5-O-(4-coumaroyl) -D-quinate 3'-monooxygenase inhibitor
	0.438	Complement factor D inhibitor
	0.531	Chloride peroxidase inhibitor
	0.522	Phthalate 4,5-dioxygenase inhibitor
	0.512	Phospholipid-translocating ATPase inhibitor
	0.507	Insulysin inhibitor
	0.305	Sphingosine 1-phosphate receptor antagonist
	0.300	Nicotine dehydrogenase inhibitor
	0.296	Thioredoxin inhibitor
	0.294	IgA-specific serine endopeptidase inhibitor
	0.275	Prostaglandin E1 antagonist
	0.265	Creatininase inhibitor
	0.256	Lysyl oxidase inhibitor
	0.246	Diuretic
	0.225–0.223	ATPase stimulant; Arylesterase inhibitor (Pa range)
	0.220	Viral entry inhibitor

	0.215–0.209	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor; Myeloblastin inhibitor (Pa range)
	0.197 and below	Multiple lower-probability tertiary items (heat-shock agonists, enzyme inhibitors, receptor modulators).
YR-05	0.786	PfA-M1 aminopeptidase inhibitor
	0.791	Glutamyl endopeptidase II inhibitor
	0.696	Omptin inhibitor
	0.637	HMGCS2 expression enhancer
	0.673	Venombin AB inhibitor
	0.565	Aspulvinone dimethylallyltransferase inhibitor
	0.655	Polyporopepsin inhibitor
	0.549	Chloride peroxidase inhibitor
	0.549	Chloride peroxidase inhibitor
	0.540	**Phthalate 4,5-dioxygenase inhibitor**
	0.525	**2-Hydroxymuconate-semialdehyde hydrolase inhibitor**
	0.466	Thioredoxin inhibitor
	0.487	Antineoplastic (melanoma)
	0.456	N-benzyloxycarbonylglycine hydrolase inhibitor
	0.465; 0.425	Aspergillopepsin I / II inhibitors
	0.464	Adenomatous polyposis treatment
	0.450	Phosphatidylcholine-retinol O-acyltransferase inhibitor
	0.374	Limulus clotting factor B inhibitor
	0.384	Pancreatic elastase inhibitor
	0.129	Cyclooxygenase 2 inhibitor
	0.071;	Angiotensin II receptor antagonist
	0.370	Kidney function stimulant
	0.289	Chenodeoxycholoyltaurine hydrolase inhibitor
	0.280	Antituberculosic
	0.246	Antileprosy
	0.211	Heat shock protein 70 agonist
	0.273	Age-related macular degeneration treatment
	0.201	Posttraumatic stress disorder treatment

Table 5: Properties of PASS prediction of the newly derivative Compounds.

Codes	LogS (log mol/L)	HIA (%)	Caco-2 or Log Papp; (log cm/s)	LogKp (cm/h)	P-gp subs	Inhibitor of P-gp I	Inhibitor of P-gp II
YY-01	-3.779	92.884	1.369	-3.228	Yes	No	No
YU-02	-3.941	92.365	1.324	-2.796	Yes	No	No
YH-03	-3.597	89.393	1.139	-2.937	Yes	No	No
YK-04	-4.329	90.906	1.35	-2.793	Yes	No	No
YR-05	-3.538	91.237	1.328	-2.774	Yes	No	No

Table 6A: Properties related to the Absorption of Newly Designed Derivative Compounds.

Abbreviations: Log S indicates Water solubility, Human Intestinal Absorption (HIA), Human colon epithelial cancer cell line (Caco-2), Skin permeability (LogKp), Permeability glycoprotein I, II (P-gp I, II).

Codes	VD (Log L/kg)	FU	LogBB	Log PS
YY-01	0.162	0.134	-2.184	-2.184
YU-02	-0.088	0.103	-0.026	-1.962
YH-03	-0.295	0.254	-0.171	-2.193
YK-04	-0.138	0.087	-0.039	-1.922
YR-05	-0.232	0.108	0.025	-2.03

Table 6B: Properties related to the Distribution of Newly Designed Derivative Compounds.

Abbreviations: VD indicates distribution Volume in Humans, FU indicates Fraction Unbound, Log BB shows Permeability of blood blood-brain barrier, and Central Nervous System Permeability is expressed as Log PS.

Code names	Cytochrome 1A2	CYP3A4		Cytochrome 2C9	CYP 2C19	CYP 2D6	
	Inhibitor	Inhibitor	Substrate	Inhibitor	Inhibitor	Inhibitor	Substrate
YY-01	Not possible	Not possible	Yes	Not possible	Yes	Not possible	Not possible
YU-02	Yes	Not	Yes	Yes	Yes	No	Not

		possible				possible	possible
YH-03	Yes	Not possible	Not possible	Not possible	Yes	Not possible	Not possible
YK-04	Yes	Yes	Not possible	Yes	Yes	Not possible	Not possible
YR-05	Yes	Not possible	Yes	Not possible	Yes	Not possible	Not possible

Table 6C: Properties for Metabolism of newly Predicted derivative Compounds.

Abbreviations: CYP (Cytochrome P450)

Codes	**Excretion**	
	Total Clearance Value (CL_{tot}) Log ml/min/kg	**Renal OCT2 substrate (Yes/ No)**
YY-01	1.522	No
YU-02	0.711	No
YH-03	0.551	No
YK-04	-0.028	No
YR-05	0.698	No

Table 6D: Properties of Excretion for the newly Predicted Derivative Compounds.

Abbreviations OCT2 stands for Organic cation transporter 2.

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