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Delivery of Novel Anti-Microbial Chemical Compound Using *In silico* Chemical Repurposing Techniques

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A B S T R A C T

The objective of the present study will focus on increasing the efficiency of the existing antibiotic drugs with no toxic effect in the human biological system. *1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid* and *2-Acetoxybenzoic acid* antibiotics were focused for this study. Canonical SMILES (Simplified Molecular-Input Line-Entry System) of the selected antibiotic were retrieved from NCBI PubChem and converted to 3D structure using online SMILES translator tool. The designed 3D structure was visualized using advanced molecular visualization tool - *Discovery Studio*. Drug Designing and Validation studies were done using automated Cheminformatics drug designing software - *Molinspiration*. The predicted chemical compound was validated using an advanced *In silico* toxicity prediction server-SwissADME to analyze the Physicochemical Properties, Lipophilicity, Water Solubility, Pharmacokinetics, Druglikeness and Medicinal Chemistry. The results obtained from Pharmacokinetic tests showed that the designed compound is devoid of lethal effects. Furthermore, the *de novo* compound has the potential to be employed as an antibacterial agent.

***Key words*:** Discovery studio, *In silico*, Molinspiration, SwissADME, NCBI PubChem

Drug repurposing—finding new uses for existing drugs—is an intriguing use of computational pharmacology. This technique, which has already produced a number of intriguing candidates, has the potential to increase medication development efficiency and reach patient populations with previously unmet needs, such as those with rare disorders [1]. Drug repositioning has emerged as a potential substitute for conventional drug development, with the goal of finding new indications for authorised or investigational medications. While developing a totally new drug for treating diseases, medication repositioning offers the capability to minimize development time and boost success rates because it uses de-risked therapeutic molecules [2-3].

Antibiotics are currently the most important weapons in the fight against infectious diseases. However, the emergence of antimicrobial resistance, along with a shortage of newly produced antimicrobial medications, poses a serious threat to human and animal health [4-5]. Biological and chemical data has been generated at an ever-increasing rate throughout the years, ushering in the so-called "big data" age. Drug repurposing requires a deeper understanding of the interactions between medications and their targets, as well as between targets and diseases [6-7].

The United States Food and Drug Administration (FDA) have approved 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid for the control and diagnosis of bacterial infections such as urinary tract infection, lower respiratory tract infection and skin infection [8]. It has been found to be effective *in vitro* and *in vivo* against a number of Gram-positive and Gram-negative bacteria isolates [9-10]. Bayer A.G. patented *1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid* in 1983, and the US Food and Drug Administration (USFDA) authorized it in 1987 [11-12].

2-Acetoxybenzoic acid is the world's most widely used analgesic and antipyretic medication, with nearly a century of clinical use. *2-Acetoxybenzoic acid* is a non-steroidal anti-inflammatory drug that is taken orally [13]. It has a significant impact on the management of cancer, heart attack, strokes and cardiovascular diseases. Long-term use of 2-Acetoxybenzoic acid has been demonstrated in studies to lower the risk of a variety of cancers, including colorectal, esophageal, breast, lung, prostate, liver, and skin cancer [14].

Despite Antimicrobial overall success, the establishment and spread of Antimicrobial Resistance (AMR) among microorganisms has significantly affected their efficacy and reliability in recent years [15-16]. Antimicrobial resistance (AMR) is a global threat to human health and development [17]. Data in the biological, chemical, and clinical domains is rapidly growing, with the potential to speed up and inform drug

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development in novel ways. This is the goal of computational pharmacology, which use *in silico* approaches to better understand and anticipate how medications affect biological systems, hence improving therapeutic use, avoiding undesired side effects, and guiding treatment selection and development [1].

MATERIALS AND METHODS

Drug selection

The study focused on the antibiotics *1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid* and *2-Acetoxybenzoic acid*. Using an online SMILES translator tool, canonical SMILES of the chosen antibiotics that were obtained from NCBI PubChem [18] were converted to 3D structure. Then, a sophisticated molecular visualization application called Discovery Studio was used to visualize the 3D structure (Fig 2). An important phase in the creation of antibodies is typically the construction of three-dimensional (3D) models using protein sequences, which enables researchers to investigate antibody characteristics including stability, antigenicity, propensity for aggregation, solubility, viscosity and more [19].

Drug designing and validatio

The use of computer-aided drug design has been acknowledged as a potent tool in the drug discovery pipeline due to the high costs and length of time involved in bringing a commercial medicine to market [20]. For this approach, we used Molinspiration, an automated cheminformatics drug design tool. Molinspiration software is used to determine the bioactivity score for the most significant drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors) as well as to calculate significant molecular parameters (such as log P, polar surface area, number of hydrogen bond donors and acceptors) [21].

In siclico toxicity prediction

High-throughput computer toxicity predictions must be carried out in order to decrease the costs and uncertainty associated with animal research. Quantitative Structure-Activity Relationships (QSAR), based on chemical structural characteristics, is one of the most widely used and advanced toxicity prediction techniques [22]. The predicted chemical compound was validated using an advanced *In silico* toxicity prediction server- SwissADME. SwissADME is a free web application that predicts physicochemical qualities, absorption, distribution, metabolism, elimination, and pharmacokinetic properties of molecules, which are all critical elements in the clinical trial process. Flexibility, lipophilicity, saturation, size, polarity, and solubility are among the six important physicochemical properties considered [23].

RESULTS AND DISCUSSION

Canonical SMILES of *1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid* and *2-Acetoxybenzoic acid* were retrieved from NCBI PubChem and validation of molecular properties and the bioactivity of the designed structure were carried out using Molinspiration software (Fig 1) which illustrated the following properties- Molecular weight: 509.49g/mol, LogP:0.41, TPSA (Topological Polar Surface Area): 127.18.

The SwissADME drug design study was then run and *Toxicity studies* were carried out to analyze the Physicochemical Properties, Lipophilicity, Water Solubility, Pharmacokinetics, Druglikeness and Medicinal Chemistry Toxicity tests were then conducted to examine the Physicochemical Properties, Lipophilicity, Water Solubility, Pharmacokinetics, Druglikeness, and Medicinal Chemistry, all of these are important tasks to complete as clinical trials advance, see (Table 1). The correlation between pharmacokinetic and physicochemical characteristics was defined by the so-called Rule-of-five [24-25]. The Lipinski rule of five stipulates that the molecular weight should be less than 500 daltons, the hydrogen bond acceptor should be less than 10, the hydrogen bond donor should be more than 5, the log P value should be less than 5, and biological transporters shouldn't be part of drug [25].

Lipophilic property of a drug must be considerable for it to pass through the cell membrane and have biological activity. With a consensus Log Po/w of 1.84, it can be stated that the proposed chemical has good Lipophilic character based on the Log P values. A drug's water solubility is important for oral bioavailability and absorption. In our investigation, we employed three techniques to measure water solubility: Log S (ESOL), Log S (Ali), and Log S (SILICOS-IT), with values of -2.75 (soluble), -2.15 (soluble), and -5.39 (Moderately soluble) accordingly, demonstrating that the molecule has good water solubility qualities. The log S scale ranges from -10 (insoluble), -6 (poorly soluble), -4 (soluble), -2 (very soluble), and 0 (highly soluble) [26].

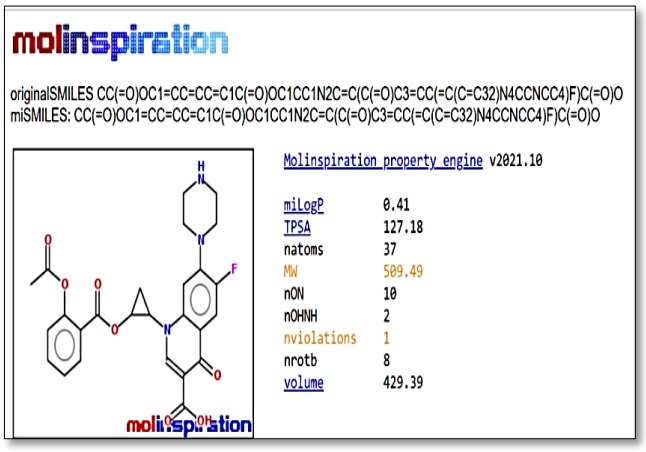

Fig 1 The above figure is the interface of *Molinspiration* which determine Molecular weight, LogP, TPSA (Topological Polar Surface Area) of a designed compound

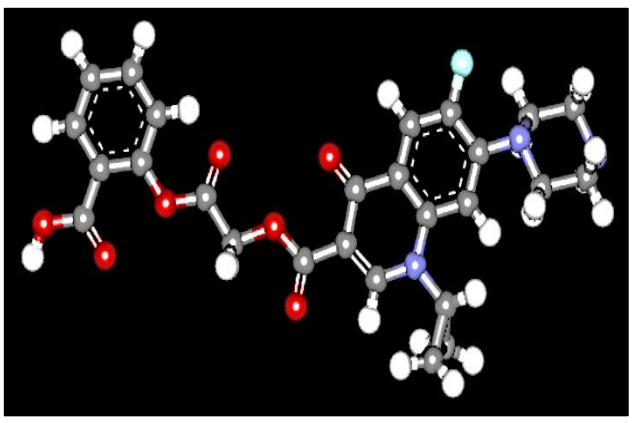

Fig 2 3D structure of a designed compound visualized using advanced molecular visualization tool *Discovery studio*. Red represents oxygen, grey represents carbon, white represents hydrogen and blue represents nitrogen

Table 1 The table illustrates the physicochemical properties, lipophilicity, water solubility, phsarmacokinetics, druglikeness and medicinal chemistry of a designed chemical compound using SwissADME tool

Physicochemical properties		Water solubility		Pharmacokinetics	
Molecular weight	509.48 g/mol	Log *S* (ESOL)	-2.75	GI absorption	High
Num. heavy atoms	37	Solubility	9.13e-01 mg/ml; 1.79e-03 mol/l	BBB permeant	No
Num. arom. heavy atoms	16	Class	Soluble	P-gp substrate	Yes
Fraction Csp3	0.31	Log *S* (Ali)	-2.15	CYP1A2 inhibitor	No
Num. rotatable bonds	8	Solubility	3.61e+00 mg/ml; 7.09e-03 mol/l	CYP2C19 inhibitor	No
Num. H-bond acceptors	9	Class	Soluble	CYP2C9 inhibitor	No
Num. H-bond donors	2	Log *S* (SILICOS-IT)	-5.39	CYP2D6 inhibitor	No
Molar Refractivity	137.55	Solubility	2.05e-03 mg/ml; 4.03e-06 mol/l	CYP3A4 inhibitor	No
TPSA	127.17 Å²	Class	Moderately soluble	Log K_p (skin permeation)	-9.46 m/s
Lipophilicity		**Druglikeness**		**Medicinal chemistry**	
Log $P_{o/w}$ (iLOGP)	2.88	Lipinski	Yes; 1 violation: MW>500	PAINS	0 alert
Log $P_{o/w}$ (XLOGP3)	-0.07	Ghose	No; 2 violations: MW>480, MR>130	Brenk	1 alert: phenol_ester
Log $P_{o/w}$ (WLOGP)	2.00	Veber	Yes	Leadlikeness	No; 2 violations: MW>350, Rotors>7
Log $P_{o/w}$ (MLOGP)	1.90	Egan	Yes	Synthetic accessibility	4.28
Log $P_{o/w}$ (SILICOS-IT)	2.51	Muegge	Yes		
Consensus Log $P_{o/w}$	1.84	Bioavailability score	0.55		

[Description of table i: TPSA: Topological Polar Surface Area, Å² (Square Angstrom) - a unit of measurement of area, Log $P_{o/w}$: octanol/water partition coefficient, MW: Molecular weight, GI absorption: Gastrointestinal absorption, BBB: Blood Brain Barrier, P-gp: P-glycoprotein, CYP1A2: Cytochrome P450 1A2, PAINS- Pan Assay Interference Compounds, (-) indicates negative, > indicates Greater than]

Pharmacokinetic data revealed good Gastrointestinal absorption and a Log Kp (skin permeation) of -9.46 cm/s; the lower the Log Kp (in cm/s), the less permeant the molecule to the skin [26]. The models respond "Yes" or "No" if the molecule under examination has a higher probability of being a P-gp substrate or non-substrate (respectively inhibitor or non-inhibitor of a given CYP) [24]. The ability to assess active efflux through biological membranes requires knowledge of chemicals that are substrate or non-substrate of the permeability glycoprotein (P-gp). Understanding how chemicals interact with cytochromes P450 (CYP) is also crucial. This isoenzyme superfamily plays an important role in drug clearance via metabolic biotransformation. Inhibition of these isoenzymes can result in toxic or other undesirable side effects due to decreased clearance and buildup of the drug or its metabolites [26]. With a Bioavailability Score of 0.55, the drug likeness parameter is high, as it follows the Lipinski, Verber, Egan, and Muegge guideline.

Synthetic accessibility was 4.28 according to medical chemistry parameters, indicating that synthesizing the chemical would not be difficult. Synthetic accessibility is a method for estimating the ease of synthesis of drug-like compounds that is important in many aspects of the drug development process. The creation and validation of such a method assigns a score to molecular synthetic accessibility ranging from 1 (easy to produce) to 10 (very difficult to make) [27]. In high-throughput screens, chemical substances known as pan assay interference compounds (PAINS) frequently give false positive results. It has a predisposition for reacting to a range of biological targets in a non-specific manner rather than affecting a single target [26]. There is no indication for PAINS in our data, suggesting that it is a very specific molecule. Thus, the results obtained from this study clearly showed that the predicted designed compound does not directly or indirectly induce any toxic effect in the human biological system.

Drug designing and *in silico* toxicity prediction studies were done using Cheminformatics drug designing software-Molinspiration and Swiss ADME respectively. Early absorption, distribution, metabolism, and excretion (ADME) screening has significantly decreased the number of drugs that fail clinical trials [28]. The present study will help understand how SwissADME will be useful in the design and development of novel therapeutic agents. According to Toxicity prediction studies the designed compound has significant lipophilic nature, good water solubility properties, high Gastrointestinal absorption, Substrate for P-gp, exceptional Log Kp (*skin permeation*) value, follow regulations of Lipinski, Verber, Egan and Muegge rule, have great Synthetic accessibility value and no indication for PAINS suggesting that it is a very specific molecule. During the early stages of drug development, drug-likeness is a key criterion for evaluating drug candidates. This measure can be defined as a technique to link a compound's physicochemical features to its biopharmaceutical properties in the human body, with a focus on the impact on bioavailability via each oral route [29]. As a result, the findings of this investigation clearly demonstrated that the predicted designed molecule does not have any hazardous effects in the human biological system, either directly or indirectly.

CONCLUSION

In the context of modern clinical pharmacological research, identifying toxicity effects and validating drug likeness scores of novel chemical compounds is a major challenge. The predicted *de novo* molecule is beneficial in the realm of antimicrobial research on Microbial targets. As a result, it can be determined that the predicted *de novo* drug has no harmful effects, which is useful in drug docking and clinical pharmacology research.

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