

DRUG-TARGET INTERACTION PREDICTION

Submitted in partial fulfilment of the required for the award of
Master of Science Degree in Bioinformatics and Data Science

By

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**DEPARTMENT OF BIOINFORMATICS AND DATA
SCIENCE**

SCHOOL OF BIO AND CHEMICAL ENGINEERING

SATHYABAMA

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BONAFIDE CERTIFICATE

I, Ancy Preshifa.X (43739021) who carried out the project entitled “Drug-Target Interaction Prediction” under my / our supervision from January 2024 to April 2024

Internal Guide

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Head of the Department

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DECLARATION

I, **ANCY PRESHIFA.X (43739021)**, hereby declare that the Project Report entitled “**DRUG-TARGET INTERACTION PREDICTION**” done by me under the guidance of **Dr.JEMMY CHRISTY** is submitted in partial fulfilment of the requirements for the award of Master of Science degree in Bioinformatics and Data Science

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ACKNOWLEDGEMENT

I am pleased to acknowledge my sincere thanks to **Board of Management of SATHYABAMA** for their kind encouragement in doing this project and for completing it successfully. I am grateful to them.

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I wish to express my thanks to all Teaching and Non-teaching staff members of the **Department of Bioinformatics and Data Science** who were helpful in many ways for the completion of the project.

(ANCY PRESHIFA.X)

ABSTRACT:

One of the most important steps in drug development is figuring out how medicines interact with target proteins. This helps detect unanticipated therapeutic action or unfavorable drug side effects in addition to helping to understand the illness mechanism. Thus, in the field of therapeutic repurposing, drug-target interaction prediction becomes a crucial technique. Numerous researchers have developed a variety of computational strategies to understand unknown drug-target interactions thanks to the availability of heterogeneous biological data on known drug-target interactions. Additionally, a description of how lead compound identification can be aided by drug-target interactions in a variety of disorders has been provided. The current study presents the interaction between Mitogen-activated protein kinase 1 (MAPK1) of Kidney cancer and pazopanib. Bioinformatics tools and databases like Cytoscape, Swiss Target, Discovery studio, Uniprot and PDB were used to study the interactions.

Keywords: Mitogen-activated protein kinase 1; Docking; Therapeutic repurposing; Drug-target interaction

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INTRODUCTION:

Over the past ten years, there have been significant advancements in the treatment of individuals with advanced renal cell carcinoma. These have included new understandings of the disease's molecular pathophysiology, which have led to paradigm-shifting therapeutic approaches. Among these accomplishments, one of note is the clarification of the significance of signalling pathways associated with angiogenesis. Pazopanib is a newly developed small molecule tyrosine kinase inhibitor that specifically targets VEGFR -2. The pharmacokinetic and toxicity profiles of this medication differ from those of other medicines in the class of VEGF signalling pathway inhibitors. The scientific basis for pazopanib's development as well as the preclinical and clinical studies that resulted in its approval for use in patients with advanced renal cell carcinoma. Members of the transmembrane tyrosine kinase receptor family, which includes VEGF receptors, mediate the transmission of signals from extracellular signalling ligands to intracellular signalling cascades. VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4) are receptors that belong to this family. Pazopanib is an orally administered, small molecule inhibitor of c-kit tyrosine kinases, PDGFR- α , PDGFR- β , and VEGFR-1, -2, and -3 that is both potent and selective. The substance specifically prevents endothelial cell proliferation when stimulated with VEGF, but not when stimulated with basic fibroblast growth factor. In preclinical angiogenesis models, pazopanib suppressed VEGF-dependent angiogenesis in a dose-dependent manner. Swiss Target Prediction: This web-based application forecasts the macromolecular targets (human, mouse, and rat protein targets) of bioactive small compounds. This is helpful in predicting off-targets, understanding the molecular pathways driving a certain phenotypic or bioactivity, rationalizing potential side effects, and determining whether therapeutically relevant molecules can be repurposed. The 'similarity principle', which essentially says that two similar molecules are likely to have comparable properties, is the foundation of SwissTargetPrediction. We have statistically quantified the likelihood that two similar bioactive compounds will share their protein targets in the context of SwissTargetPrediction. As a result, we find the compounds that are most comparable to a query molecule from a set of over 370'000 actives on known targets. The targets with the most actives exhibiting are the ones that are forecasted.

AIM AND SCOPE:

To predict drug-target interaction specific to patient treatment and drug design ultimately to aid drug repurposing. Identifying the interactions between drugs and target proteins is a key step in drug discovery. This not only aids to understand the disease mechanism but, also helps to identify unexpected therapeutic activity or adverse side effect of drugs.

MATERIALS:

- Uniprot.
- PDB.
- Cytoscape.
- Swiss Target.
- Discovery Studio.

METHODS:

1. Pazopanib, an FDA approved drug associated with renal cell carcinoma was chosen and smiles notation was retrieved from PubChem using following link <https://pubchem.ncbi.nlm.nih.gov/>.
2. Swiss target home page was accessed using following link <http://www.swisstargetprediction.ch/index.php>.
3. Predicted the targets (Top five) and drug interaction was analyzed using discovery studio Receptor ligand interaction module.

RESULTS:



Figure 1: Swiss Target Result.

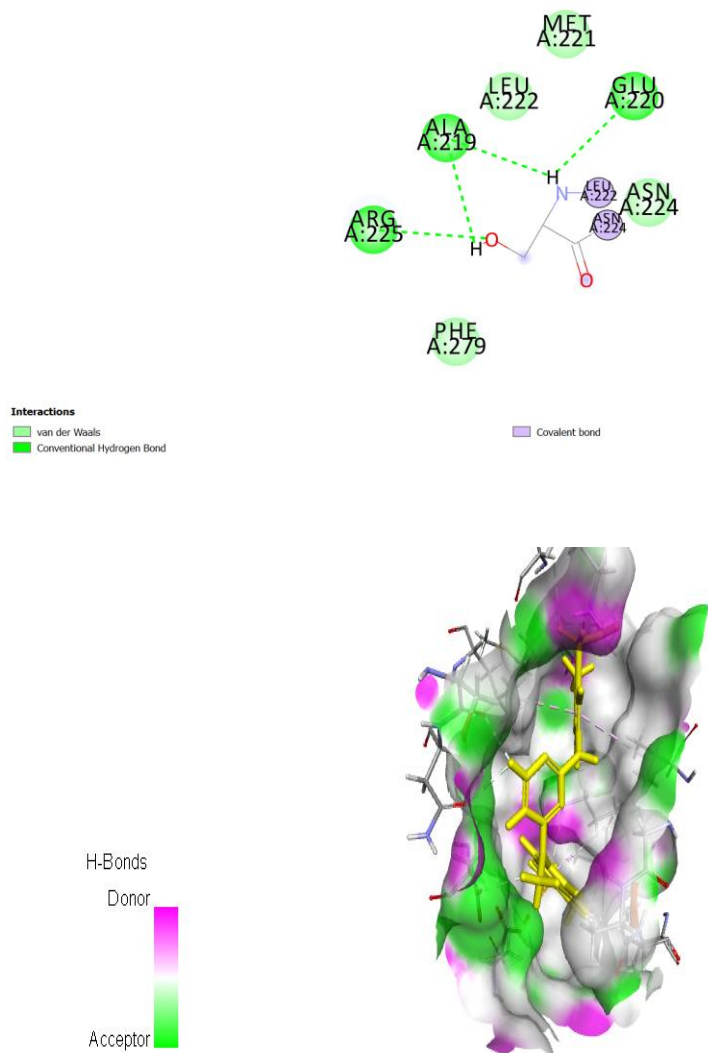


Figure 2: Docking of MAPK-1's protein structure i.e. 5WP1 with the drug Pazopanib.

Name	Distance	Category	Types	From	To
A:LYS114:	1.5467	Hydrogen	Conventic	A:LYS114:HZ	10113978:O3
10113978	2.96654	Hydrogen	Conventic	10113978:H5	A:MET108:O
A:THR110:	3.05454	Hydrogen	Carbon H	A:THR110:HA	10113978:O2
10113978	2.28445	Hydrogen	Carbon H	10113978:HA	A:ASP167:OD2
10113978	2.42307	Hydrogen	Carbon H	10113978:H5	A:SER153:O
10113978	2.83968	Hydrogen	Carbon H	10113978:H5	A:ASN154:OD1
A:GLU71:	3.44245	Electrosta	Pi-Anion	A:GLU71:OE2	10113978
A:GLU71:	3.40083	Electrosta	Pi-Anion	A:GLU71:OE2	10113978
A:LYS54:H	2.70334	Hydrogen	Pi-Donor	A:LYS54:HZ1	10113978
10113978	4.2779	Hydropho	Alkyl	10113978:C1	A:ILE56
10113978	4.83133	Hydropho	Alkyl	10113978:C1	A:ILE103
10113978	5.38537	Hydropho	Pi-Alkyl	10113978	A:LYS54
10113978	5.10919	Hydropho	Pi-Alkyl	10113978	A:VAL39
10113978	5.06009	Hydropho	Pi-Alkyl	10113978	A:LEU156
Name	PLP1	PLP2	Jain	PMF	Dock Score
5WP1					
10113978	69.41	60.62	1.38	98.72	65.387
10113978	66.16	57.25	1.39	86.39	64.089
10113978	74.76	66.51	1.94	86.6	63.617
10113978	79.75	66.59	1.28	84.04	63.447
10113978	75.62	63.27	0.54	63.7	63.358
10113978	70.52	63.88	2.32	91.08	63.287
10113978	73.96	60.91	0.72	84.49	63.206
10113978	72.38	60.75	1.39	57.36	62.748
10113978	71.12	60.4	0.91	55.47	62.745
10113978	66.32	56.94	0.27	96.18	62.586

Figure 3: Non-Bond and Molecule table showing the number of interactions, Type of interactions and the residues involved.

DISCUSSION:

The protein MAPK1 consisting of 360 residues was docked with the drug Pazopanib. The domain of this protein, Protein Kinase lies within the region 25-313. The interactions indicate various bonds or contacts between the residues of MAPK1 and atoms/groups within pazopanib. These interactions could involve hydrogen bonds, van der Waals interactions, or other types of chemical interactions.

- Lys114 - Lysine 114 is part of the catalytic core of MAPK1, where ATP and substrate binding occur during kinase activity. Drug designers often aim to develop small molecules that can bind tightly to this active site, effectively competing with ATP or substrates and inhibiting the kinase activity of MAPK1.
- Met108 - Methionine residues participate in protein-protein interactions and contribute to the overall folding and stability of the protein structure. It contributes to the binding affinity and specificity of inhibitors targeting MAPK1. Inhibitors designed to interact with residues near MET108, such as those within the ATP-binding site, may exploit its presence to enhance binding affinity and inhibit MAPK1 activity more effectively.
- Thr110 - The position of threonine (THR) 110 in MAPK1 (also known as ERK2) is significant in the context of drug design, particularly for understanding the structural features of the protein and designing inhibitors that target specific regions, such as the ATP-binding site. Changes in the conformation of THR110 or its surrounding residues can impact the accessibility and affinity of the active site for inhibitors. Drug designers may leverage computational modelling and molecular dynamics simulations to explore the structural dynamics of THR110 and its role in ligand binding.
- ASN154 - ASN154 may be situated close to the active site of MAPK1, where ATP binds and undergoes phosphorylation, or near other functionally important regions. In drug design, understanding the position and interactions of ASN154 within the active site can guide the development of inhibitors that target this region. Inhibitors that interact with ASN154 may disrupt the function of MAPK1 by interfering with ATP binding or substrate recognition.
- Val39 - Involves in allosteric modulation of protein function. In drug design, targeting allosteric sites near VAL39 may provide opportunities to develop inhibitors that modulate MAPK1 activity indirectly by altering its conformation

or dynamics. Understanding the position and role of VAL39 in allosteric regulation can inform the design of allosteric inhibitors with therapeutic potential.

Overall, Pazopanib interacts with the residues to mask its functions in the following manner:

- Binding to active site residue.
- Allosteric inhibition.
- Disruption of protein-protein interactions.

CONCLUSION:

In conclusion, the endeavour to predict drug-target interactions is paramount for advancing patient-specific treatment and optimizing drug design. Through the exploration of various approaches, including computational modelling, machine learning algorithms, and biological assays, researchers can enhance our understanding of molecular interactions underlying disease mechanisms. By harnessing these predictive methods, tailored therapies can be developed, maximizing efficacy while minimizing adverse effects. As we continue to refine these techniques and integrate multidisciplinary insights, the potential for personalized medicine and innovative drug discovery becomes increasingly promising, heralding a new era in healthcare where treatments are precisely tailored to individual patients' needs.

“DECODING CELLULAR SIGNALLING PATHWAYS: UNRAVELING INTRICATE COMMUNICATION NETWORKS”

ABSTRACT:

Cellular signalling pathways constitute a complex network of molecular interactions essential for coordinating cellular responses to various stimuli. This review delves into the intricate mechanisms underlying cellular signalling, highlighting the significance of molecular messengers, signal transduction, cross talk among pathways, and the implications of dysregulation in disease states. By elucidating these fundamental aspects, we aim to provide insights into the dynamic nature of cellular communication and its implications for biomedical research and therapeutic interventions.

KEYWORDS:

Cellular signalling, molecular messengers, signal transduction, cross talk, dysregulation, disease.

INTRODUCTION:

Cellular signalling pathways govern essential biological processes by relaying extracellular signals to intracellular effectors, thereby regulating gene expression, cell proliferation, differentiation, and apoptosis. Understanding the intricacies of these pathways is crucial for deciphering the molecular basis of physiological and pathological phenomena.

MOLECULAR MESSENGERS:

Signalling molecules, including hormones, growth factors, cytokines, and neurotransmitters, serve as molecular messengers that initiate cellular responses upon binding to their respective receptors. These molecules convey information across cellular compartments and orchestrate diverse physiological functions.

SIGNAL TRANSDUCTION:

Signal transduction encompasses a series of molecular events triggered by receptor activation, leading to the propagation and amplification of signals within the cell. Key players in this process include protein kinases, second messengers, and adaptor proteins, which mediate signal transmission from the cell membrane to the nucleus, ultimately modulating gene expression.

CROSS TALK AMONG PATHWAYS:

Cellular signalling pathways often exhibit extensive cross talk, wherein signals from distinct pathways converge and intersect, influencing each other's activity and outcome. This phenomenon allows for integration of diverse signalling inputs and facilitates fine-tuning of cellular responses to dynamic environmental cues.

DYSREGULATION AND DISEASE:

Dysregulation of signalling pathways is implicated in various pathological conditions, including cancer, metabolic disorders, and autoimmune diseases. Aberrant activation or inhibition of key signalling components can disrupt cellular homeostasis, leading to uncontrolled proliferation, inflammation, and tissue damage.

CONCLUSION:

Deciphering the intricate communication networks underlying cellular signalling is essential for elucidating physiological processes and disease mechanisms. By unravelling the complexities of molecular messengers, signal transduction, cross talk among pathways, and the consequences of dysregulation, researchers can identify novel therapeutic targets and develop strategies for combating human diseases.

REFERENCES:

1. Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 6th edition. New York: Garland Science; 2014. Chapter 15, Cell signalling.
2. Kholodenko BN. Cell-signalling dynamics in time and space. Nat Rev Mol Cell Biol. 2006;7(3):165-176.
3. Pawson T, Warner N. Oncogenic re-wiring of cellular signalling pathways. Oncogene. 2007;26(9):1268-1275.
4. Roskoski Jr R. Vascular endothelial growth factor (VEGF) signalling in tumour progression. Crit Rev Oncol Hematol. 2007;62(3):179-213.
5. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 2006;7(2):85-96.

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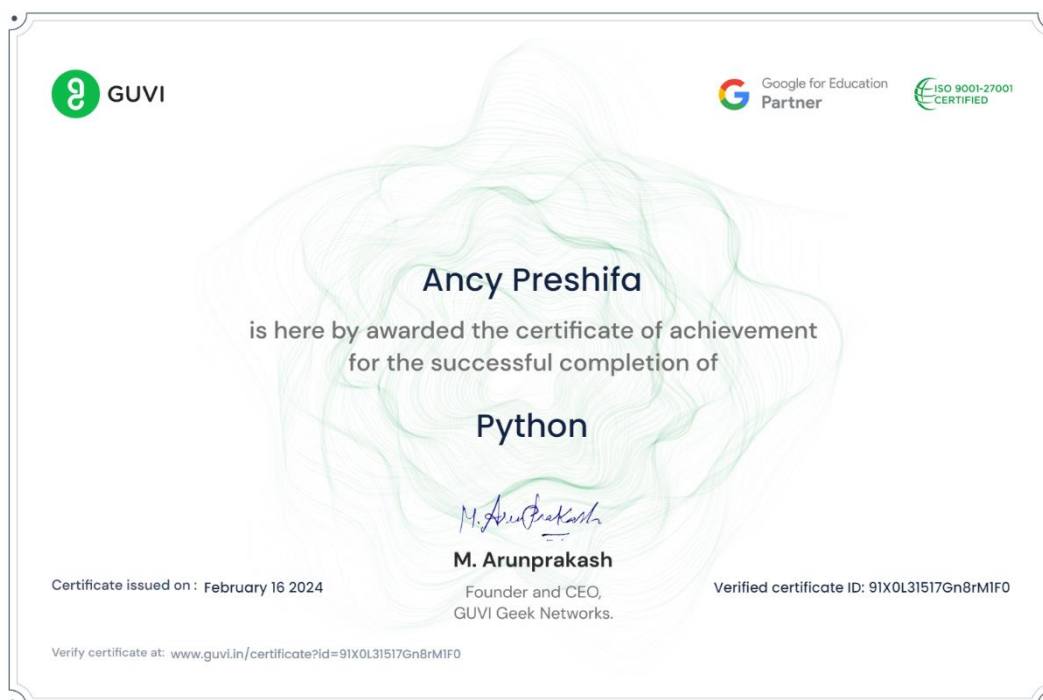
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