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PREDICTION OF MEK2 INHIBITORS USING VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION METHODS

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Abstract:

MEK2 (MAP2K2) is a protein within the MAPK pathway which can cause cancer and also be targeted using drugs in an attempt. However, knowing the full length structure of the protein is crucial when developing drugs against the proteins using computational methods. Hence we modelled the protein using I-TASSER server and performed molecular dynamics simulations using GROMACS. Since Selumetinib is a MEK inhibitor drug used in Neurofibromatosis Type 1 disease, its structural analogues were put through virtual screening in order to find comparatively less toxic MEK inhibitors to treat cancer. By performing MD simulation of Protein-Ligand complexes we report ligands similar to Selumetinib which can be potentially used for the treatment and management of cancer.

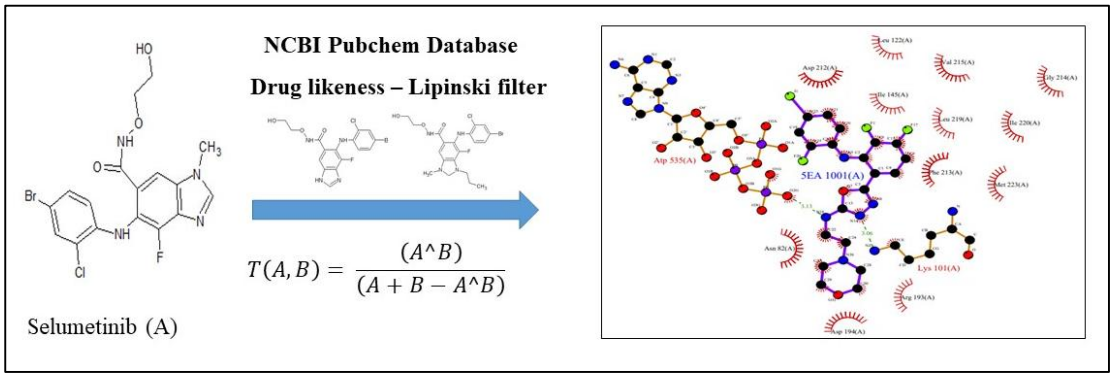


Figure 1.0 Graphical Abstract

Keywords: MEK2, Molecular Docking, MD simulations, Toxicity, ADME

Introduction:

Proteins are one of the most important biomolecules due to the fact that they carry out a wide range of functions. This is determined by their sequence, structure, localization, etc. The sequence of amino acids that make up a protein determines the structure and folding of proteins. The role that proteins play in the functioning of various biochemical pathways makes them an interesting point of study, since the malfunction of pathways like the MAPK pathway may lead to failure of cell cycle control and subsequent diseases like cancer. The relentless contributions by the scientific fraternity to the study of the disease has resulted in steady decline of cancer incidences [I]. This gives us all the more reasons to pry into the inner workings of the disease down to the molecular level and come up with innovative approaches that improve the provision of treatment for the patients and ensures we make the numbers fall steadily. Simulating the molecular dynamics of proteins gives us great insight into their properties [Ii]. MAP2K2, also referred to as MEK2 is a protein kinase within the MAPK pathway. It is dual specificity tyrosine/threonine protein kinase. The MAPK pathway is constitutively amplified in an overwhelming number of human cancers [Iii]. This opens possibility of designing drug candidates which might be able to inhibit the activity of these proteins and thus causing the amelioration of the signal transduction, leading to subsequent management of the disease. MEK2 is highly homologous to MEK1 and both the proteins have 2 adjacent non-competitive binding pockets to accommodate an inhibitor in one and ATP in another [Iv]. Elucidating the probable structure of the protein also gives us information of the residues that form the cavity region of the binding sites. Ligands react differently to each residue and form hydrogen bonds with them leading to the inhibition of the protein and thus mitigating its activity. Knowing this information allows us to perform virtual screening of many ligands in order to pick up the one that has the highest stability and lowest binding energy.

Results:

Target mining:

Owing to the fact that the MEK2 protein is a disease causing protein which can be targeted with drugs. The role of MEK2 in Acute Myeloid Leukemia, Chronic Myeloid Leukemia, and Breast Cancer is clearly mentioned in the KEGG metabolic pathway database. In the protein pathway annotation process by DAVID, and EnrichR analysis MEK2 involvement was identified Table 1.0 and table 2.0.

Table 1.0: David Annotation data

Protein	**Biocarta**	**DISGENET**	**KEGG Pathway**
MEK2	Anthrax Toxin Mechanism of Action, Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling, Role of ?-arrestins in the activation and targeting of	Non-Small Cell Lung Carcinoma, Adenoid Cystic Carcinoma, melanoma, Noonan Syndrome, Turner Syndrome, Male, Cutaneous Melanoma, LEOPARD Syndrome, Cafe-au-lait macules with pulmonary stenosis, Costello syndrome (disorder), Cardiomyopathies, Cardio-facio-cutaneous syndrome, Female Pseudo-Turner Syndrome, Noonan	EGFR tyrosine kinase inhibitor resistance, Endocrine resistance, MAPK signaling pathway, ErbB signaling pathway, Ras signaling pathway, Rap1 signaling pathway, cGMP-PKG signaling pathway, cAMP signaling pathway, HIF-1 signaling pathway, FoxO signaling pathway, Sphingolipid signaling pathway, Phospholipase D signaling pathway, Autophagy - animal, Efferocytosis, mTOR signaling pathway, PI3K-Akt signaling pathway, Apoptosis,

	MAP kinases, Roles of ?-arrestin-dependent Recruitment of Src Kinases in GPCR Signaling, Bioactive Peptide Induced Signaling Pathway, Phosphorylation of MEK1 by cdk5/p35 down regulates the MAP kinase pathway, Erk1/Erk2 Mapk Signaling pathway, fMLP induced chemokine gene expression in HMC-1 cells, Human Cytomegalovirus and Map Kinase Pathways, Integrin Signaling Pathway, Role of MAL in Rho-Mediated Activation of SRF, MAPKinase Signaling Pathway, Signaling of Hepatocyte Growth Factor Receptor, Links between	syndrome-like disorder with loose anagen hair, Neurofibromatosis-Noonan syndrome, Noonan-Like Syndrome With Loose Anagen Hair, CARDIOFACIOCUTANEOUS SYNDROME 4, Noonan Syndrome 1,	Cellular senescence, Vascular smooth muscle contraction, VEGF signaling pathway, Apelin signaling pathway, Gap junction, Signaling pathways regulating pluripotency of stem cells, Neutrophil extracellular trap formation, Toll-like receptor signaling pathway, Natural killer cell mediated cytotoxicity, T cell receptor signaling pathway, B cell receptor signaling pathway, Fc epsilon RI signaling pathway, Long-term potentiation, Neurotrophin signaling pathway, Long-term depression, Regulation of actin cytoskeleton, Insulin signaling pathway, GnRH signaling pathway, Estrogen signaling pathway, Melanogenesis, Prolactin signaling pathway, Thyroid hormone signaling pathway, Oxytocin signaling pathway, Relaxin signaling pathway, GnRH secretion, Cushing syndrome, Growth hormone synthesis, secretion and action, Alzheimer disease, Pathways of neurodegeneration - multiple diseases, Salmonella infection, Yersinia infection, Hepatitis C, Hepatitis B, Human cytomegalovirus infection, Influenza A, Human papillomavirus infection, Human T-cell leukemia virus 1 infection, Kaposi sarcoma-associated herpesvirus infection, Human immunodeficiency virus 1 infection, Pathways in cancer, Proteoglycans in cancer, MicroRNAs in cancer, Chemical carcinogenesis - receptor activation, Chemical carcinogenesis - reactive oxygen species, Colorectal cancer, Renal cell carcinoma, Endometrial cancer, Glioma, Prostate cancer,

	Pyk2 and Map Kinases,		Thyroid cancer, Melanoma, Bladder cancer, Chronic myeloid leukemia, Acute myeloid leukemia, Non-small cell lung cancer, Breast cancer, Hepatocellular carcinoma, Gastric cancer, Central carbon metabolism in cancer, Choline metabolism in cancer, PD-L1 expression and PD-1 checkpoint pathway in cancer.

Table 2.0: EnrichR Annotation data with statistical significant value p-value <0.05.

Sr no	Reactome Pathways 2024	Wiki Pathways 2024	Elsevier Pathway Collection
1	Negative Feedback Regulation of MAPK Pathway	Ethanol Metabolism Production Of ROS By CYP2E1 WP4269	non-Genomic Rapid Actions of Vitamin D in Vitamin D Biology
2	MAPK1 (ERK2) Activation	MAPK Pathway In Congenital Thyroid Cancer WP4928	HCAR1/HCAR2 -> MAPK Signaling
3	Frs2-mediated Activation	IL9 Signaling WP22	HTR4/6/7 -> Cation Channels
4	Uptake and Function of Anthrax Toxins	ERK Pathway In Huntington 39 S Disease WP3853	ADRB1 -> Prostaglandin Generation
5	Prolonged ERK Activation Events	Serotonin Receptor 4 6 7 And NR3C Signaling WP734	PECAM -> SP1 Signaling
6	Signal Transduction by L1	IL7 Signaling WP205	Mast-Cell Activation without Degranulation through CYSLTR1/CYSLTR2 Signaling
7	RAF-independent MAPK1 3 Activation	Serotonin Receptor 2 And ELK SRF GATA4 Signaling WP732	VEGFA High Expression Level in Pulmonary Emphysema
8	Signalling to ERKs	GNAQ Pathways In Port Wine Stain WP5437	OR1A1 -> GNAS Signaling
9	RAF Activation	Kallmann Syndrome WP5074	HMGB1/RAGE Signaling in Middle Ear Cholesteatoma
10	Signaling by High-Kinase Activity BRAF Mutants	4 Hydroxytamoxifen DEX And Retinoic Acids Regulation Of P27 WP3879	VEGFA Low Expression Level in Chronic Bronchitis

11	MAP2K and MAPK Activation	Thyroxine Thyroid Hormone Production WP1981	Protein Kinase C in Diabetic Microangiopathy
12	Signaling by RAF1 Mutants	EPO Receptor Signaling WP581	Melatonin in Cell Survival and Antioxidant Response
13	Negative Regulation of MAPK Pathway	FGFR3 Signal Chondrocyte Proliferation Terminal Differentiation WP4767	GLP1R -> ARRB1 Signaling
14	Uptake and Actions of Bacterial Toxins	Nanoparticle Mediated Activation Of Receptor Signaling WP2643	MTNR1 Signaling
15	Paradoxical Activation of RAF Signaling by Kinase Inactive BRAF	miRNA Regulation Of Prostate Cancer Signaling WP3981	NCAM1 -> CREB/ELK/SRF/MYC Signaling
16	Signaling by RAS Mutants	Cardiomyocyte Signaling Converging On Titin WP5344	TNFRSF6 -> HSF1 Signaling
17	Signaling by Moderate Kinase Activity BRAF Mutants	MAPK Cascade WP422	TRPM8 Effects in Prostate Cancer (Hypothesis)
18	Signaling Downstream of RAS Mutants	Hepatocyte Growth Factor Receptor Signaling WP313	CHRNA7 -> CREB Signaling
19	Signaling by BRAF and RAF1 Fusions	Host Pathogen Interaction Of Human Coronaviruses MAPK Signaling WP4877	DRD2 Pharmacological Inhibition in Hyperprolactinemia
20	Oncogenic MAPK Signaling	Serotonin HTR1 Group And FOS Pathway WP722	WHIM Syndrome
21	Signaling by NTRK1 (TRKA)	IL5 Signaling WP127	Hypothyrodism Associated Hyperprolactinemia
22	L1CAM Interactions	IL2 Signaling WP49	CHRNA7 -> NOS1 Production
23	Signaling by NTRKs	Thymic Stromal Lymphopoietin TSLP Signaling WP2203	IL6R -> CEBP/ELK/SRF Signaling
24	Bacterial Infection Pathways	Amyotrophic Lateral Sclerosis ALS WP2447	PTPRC -> BCL6 Signaling
25	RAF MAP Kinase Cascade	Relevant Molecular Pathways And Targeted Agents In TNBC WP5215	SELE -> ELK-SRF Signaling

The outcomes from DAVID annotation and EnrichR (top 25 pathways) table 1.0 and 2.0 with significant p-values <0.05, supported that the MEK2 is highly involved in several important processes and pathways in human. Working with such multiple dimensional protein will help us to design new therapy or in diagnosis as a biomarker.

The full length protein MEK2 3D structure 400 aa model generated by I-TASSER with C-score of 1.60 was selected for further processing. The Ramachandran plot of this model was calculated which showed that 98.2% of residues fell under allowed regions and 1.8% under disallowed regions. After energy minimization, the Ramachandran plot placed 98.8% residues in allowed regions and 1.2% residues in disallowed regions. The overall model quality Z-Score was found to be -7.8 when submitted to ProSA server fig 2.0. The protein MEK2 3D structure is deposited in public database, Protein Model Data Base and can be accessed with accession id: PM0084086 (Author name: Aravind Venkatasubramanian and Pramodkumar P Gupta).

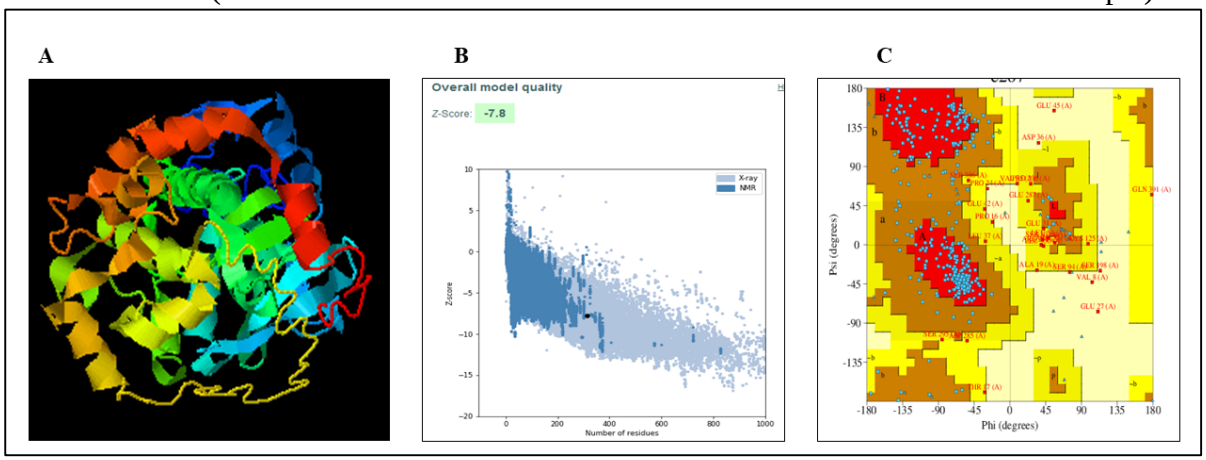


Fig 2.0: A 3D structure model from I-Tasser., B: Overall Model Quality generated by ProSA server., C: Ramachandran Plot of the Model.

The simulation of protein model in water optimized with potential energy of -9.55204e+05 kJ/mol and total energy -7.95459 e+05 kJ/mol and checked for their bond, angle, and Proper-dihedral parameters fig 3.0 . The RMSD and Radius of Gyration plots show a stable graph without a lot of wild fluctuations fig 4.0, Protein energy minimization results:

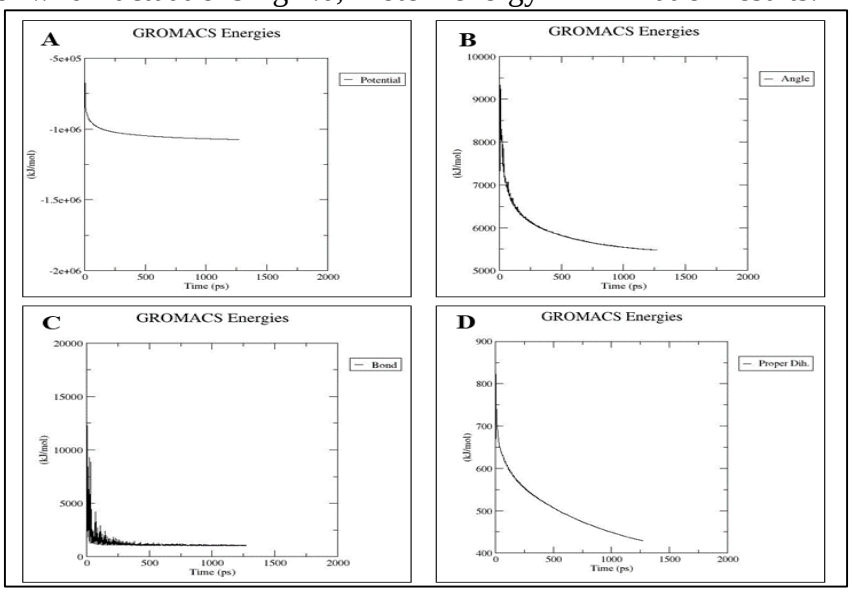


Fig 3.0: A – potential energy. B – Angle. C – Bond and D – Proper-Dihedral

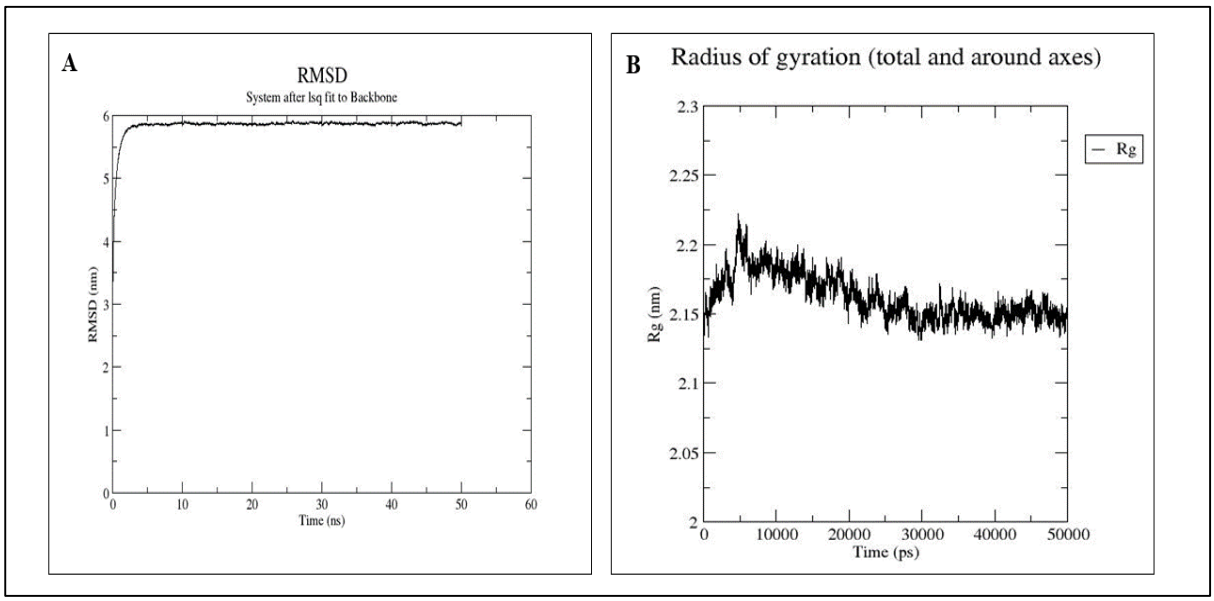
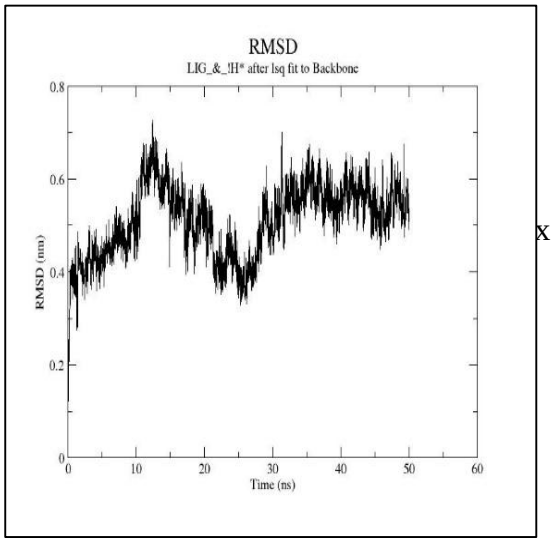


Fig 4.0: A-MD simulation results RMSD and B-Radius of gyration

In comparison to the approved drug compounds Selumetinib, Binimetimib, and Trametinib binding affinity of -7.5, -7.7,nd -8.6 kcal/mol the molecule 41 (PMCID 69106642) , 42 (PMCID 69916053), 21, 55, 116, 127, and 103, exhibited a more stable binding affinity energy of -9.2, -9.0, -8.8, -8.7, -8.7, -8.7, and -8.7 kcal/mol. All the above listed compounds predicted with high GI-absorption, No Blood Brain Barrier (BBB) permeability means does not crossing the CNS system in the human. Considering the Efflux out function, the approved drugs including the molecule 21, 55, 116, and 103 are predicted to be non-substrate to the P-glycoprotein (Pgp), whereas molecules 41, 42 and 127 are predicted to be the substrate of P-glycoprotein (Pgp) and may be efluxed out from the system. Comparing the metabolising factor and excretion part, The Cyp class of enzymes, Where Selumetinib predicted as an inhibitor to the CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 and may be difficult in metabolising and excreting out from the body and hence ay disturb the metabolism acivity, as well may affect some off-target toxicity. Whereas similar predictions were observed with other two approved drugs, where Binimetimib was predicted to be an inhibitor to CYP1A2, CYP2C9, CYP2D6, and CYP3A4and may be difficult in metabolising and excreting out from the body and hence ay disturb the metabolism acivity. Drug Trametinib was predicted to be an inhibitor to CYP2C19, CYP2C9, and CYP3A4 and may be difficult in metabolising and excreting out from the body and hence ay disturb the metabolism acivity. Considering molecule 41 was predicted to be an inhibitor to CYP2D6, and CYP3A4 and may be less difficult in metabolising and excreteing out from the body. In case of molecule 42 was predicted to be an inhibitor to CYP2C9, CYP2D6, and CYP3A4 and may be difficult in metabolising and excreteing out from the body. Ligands molecule 41 (PMCID 69106642) and molecule 42 (PMCID 69916053) returned the best docking pose with a binding energy of -9.2 kcal/mol and -9 kcal/mol, which is lower than that of Selumetinib and also had lower toxicity too Table 3.0.

Table 3.0 : Results of Docking and ADMET Properties

Molecule	Binding Energy (kcal/mol)	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Selumetinib	-7.5	High	No	No	Yes	Yes	Yes	Yes	Yes
Binimetinib	-7.7	High	No	No	Yes	No	Yes	Yes	Yes
Trametinib	-8.6	High	No	No	No	Yes	Yes	No	Yes
Molecule 41	-9.2	High	No	Yes	No	No	No	Yes	Yes
Molecule 42	-9	High	No	Yes	No	No	Yes	Yes	Yes
Molecule 21	-8.8	High	No	No	Yes	Yes	Yes	Yes	No
Molecule 55	-8.8	High	No	No	No	Yes	Yes	Yes	Yes
Molecule 116	-8.7	High	No	No	Yes	Yes	Yes	No	No
Molecule 127	-8.7	High	No	Yes	No	Yes	No	Yes	Yes
Molecule 103	-8.7	High	No	No	Yes	No	Yes	Yes	Yes



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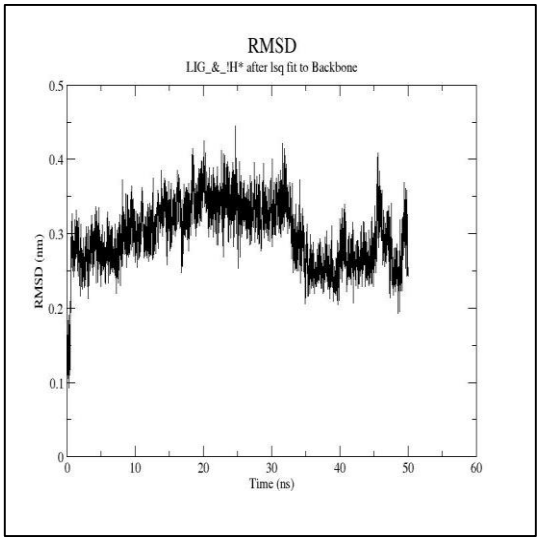

Fig 6.0: Molecule 42 and Protein complex RMSD RMSD

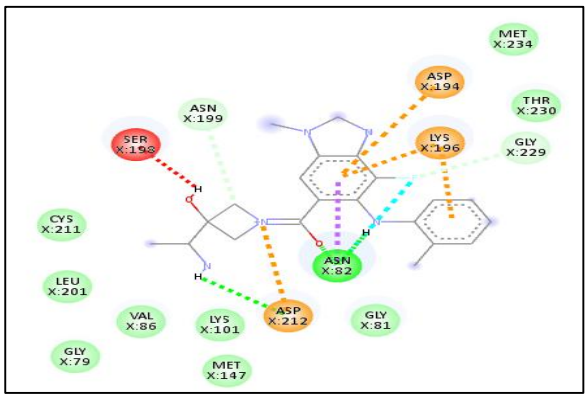

Fig 7.0: Molecule 41 in complex with MEK before MD Simulations

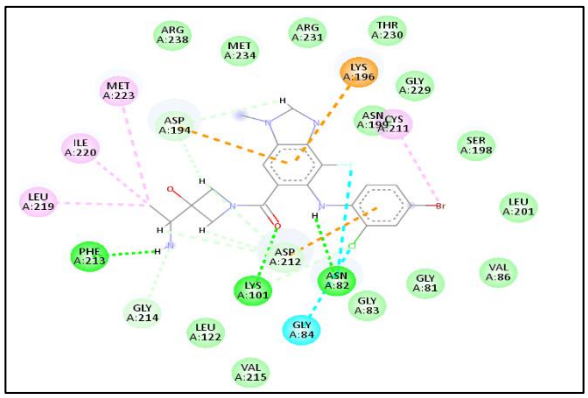

Fig 8.0: : Molecule 41 in complex with MEK after MD Simulations

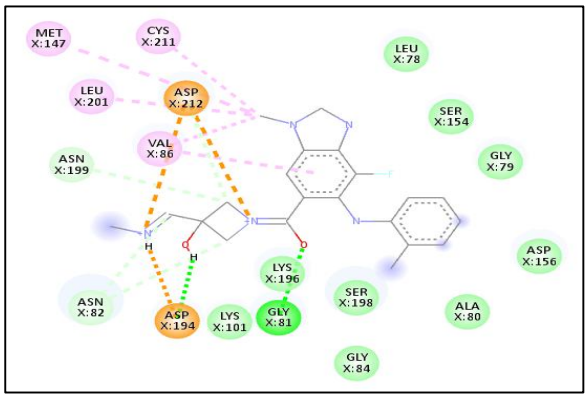

Fig 9.0: Molecule 42 in complex with MEK2 MD Simulations

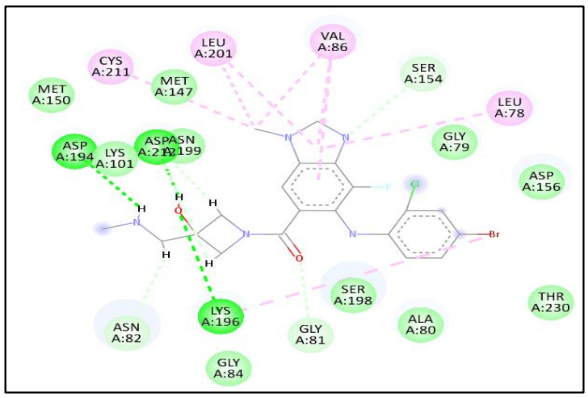

Fig 10.0 : Molecule 42 in complex with before MEK2 after MD Simulations

3.1 MD Simulation of docked complex results

Lys 101 is the residue of interest here since that is the only residue that is interacting with standard ligand 5EA on PDBsum database. Hence it is expected that drug candidates must interact with Lys 101 after MD Simulation of Protein-Ligand Interactions. After simulation Ligand 41, which showed the best binding energy of -9.2 kcal/mol, formed 3 h-bond, with ASN 82, Lys 101, and Phe 213. Lys 101 changed from being Van der Waal to h-bond. Apart from this, Van der Waals interactions increased from 8 to 13 (GLY 81 & 83, VAL 86, LEU 122, SER 198, ASN 199, LEU 201, VAL 215, GLY 229, THR 230, ARG 231, MET 234, ARG238), C-H bonds also increased to 3 from 2 (ASP 194 &212, GLY 214), one Halogen bond was newly observed (GLY 84), there were 4 Alkyl interactions (CYS 211, LEU 219, ILE 220, MET 223) fig 5.0, 7.0 and 9.0.

Ligand 42, which showed the best binding energy of -9 kcal/mol, formed 3 h-bond, with ASP 194 &212, and LYS 196. Lys 101 continued forming Van der Waal interaction. Apart from this, Van der Waals interactions increased from 8 to 10 (GLY 79, ALA 80, GLY 84, LYS 101, MET 147 and 150, ASP 156, SER 198, ASN 199, THR 230), C-H bonds also increased to 3 from 2 (ASP 194 &212, GLY 214), There were 3 C-H bonds (GLY 81, ASN 82, SER154) there were 4 Alkyl interactions (LEU 78, VAL 86, LEU 201, CYS 211), fig 6.0, 8.0, and 10.0.

4.0 Discussion:

MEK2 is a significant player in cancer pathways and thus it becomes imperative to study it and formulate treatments that will attenuate and modulate its function in cancer cells with minimum off-target activity to ensure that we bring the best therapeutic care to the ailing patients without jeopardizing their well-being and quality of life. In this piece of academic work, we have

attempted to introduce alternatives to the drugs that are currently being as treatments for cancer, especially concerning the inhibition of MEK2 protein. Ligands 41 and 42 with PubChem CID 69106642 & 69916053 are very good drug candidates as they have better binding efficiency and comparatively lower toxicity when put against the drugs in current use such as Binimetinib, Selumetinib, and Trametinib. It is no surprise that these proposed analogues also have certain toxicity, but since drug discovery is not always a trial and error science, we are often left with drugs that are marginally better than current forerunners, thus it is natural for us to adopt them and put them through the test in pre-clinical and clinical trials and pave the way for the drugs' eventual approval and common use for the purpose of treating cancer. This also opens to many opportunities after wide-spread approval like the repurposing of these approved drugs to combat other ailments. The onus is upon the scientific and medical communities to take into cognizance the availability of such drugs that usually fly under the radar and use them for treating patients in case the other drugs don't work or have portentous side-effects and complications due to any of the million possible reasons that have been studied. This project also reiterates the demonstration of tremendous potential of employing the use of computational techniques for the purpose of drug discovery that has been voiced by the scientists of the past and henceforth, will continue to be demonstrated by the scientists of the future.

Methodology:

Target mining

Owing to the fact that the MEK2 protein is a disease causing protein which can be targeted with drugs. The role of MEK2 in Acute Myeloid Leukemia, Chronic Myeloid Leukemia, and Breast Cancer is clearly mentioned in the KEGG metabolic pathway database [V]. Protein pathway annotation process is carried out by various bioinformatics based analysis using DAVID [Vi], and EnrichR [Vii] to identify the involvement of MEK2 in various cancer and disease.

Protein Modelling

The protein 3D structure 1S9I.pdb was obtained from RCSB-Protein Data Bank. Deep analysis of protein 3D structure revealed with several missing residues in the crystallized data. As the molecular interactions are dependent on the complete 3D structure of the target, the missing region in the protein 3D structure might give a biased results. The protein sequence in FASTA format is retrieved from Uniprot database : P36507 (MP2K2_HUMAN), owing to poor homology in homology modelling using SWISS_MODEL server we have adopted to I-TASSER online server for modelling the complete length of protein by fold recognition and threading based approach [Viii].

Molecular Dynamics Simulation

The model generated by I-TASSER was used to perform the molecular dynamics simulations. The Groningen Machine for Chemical Simulation (GROMACS) was used to simulate the protein model. The energy minimization was conducted with maximum 50000 steps which is terminated when the maximum force is less than 1000 kJ/mol/nm, and then fed to the PDBsum server for the Ramachandran plot. The results of the Ramachandran plot and the E_{pot} scores after energy minimization were noted down and then the model was subjected to MD simulation at 50ns using OPLS-AA force field within GROMACS [Ix]. The results were visualized using VMD software, using the same the water molecules from the solvated simulation file was and only protein structure was saved in pdb format.

Selection and Processing of Ligands

Selumetinib drug was chosen as a reference ligand since the drug has been used in MEK2 related cancer treatments in the past [X]. The drug was searched on PubChem database and 90% Tanimoto based similarity search was implemented to find similar ligand molecules and additional drug likeness Lipinski's rule of five [Xi] too considered. About 130 ligands were

retrieved from the pubchem database that are supposed to be similar to Selumetinib in structure and predictively in function too fig 11.0. The SMILES of each of the ligands were used to construct the ligand files on ChemSketch and the drawn molecules were cleaned [Xii] **Supplementary table 1.0** . The cleaned structures were then loaded on to Argus lab [Xiii] software and energy minimization was carried out using UFF force field [Xiv] with maximum number of steps set at 1500. Upon attaining geometric convergence, the molecule was saved in pdb format.

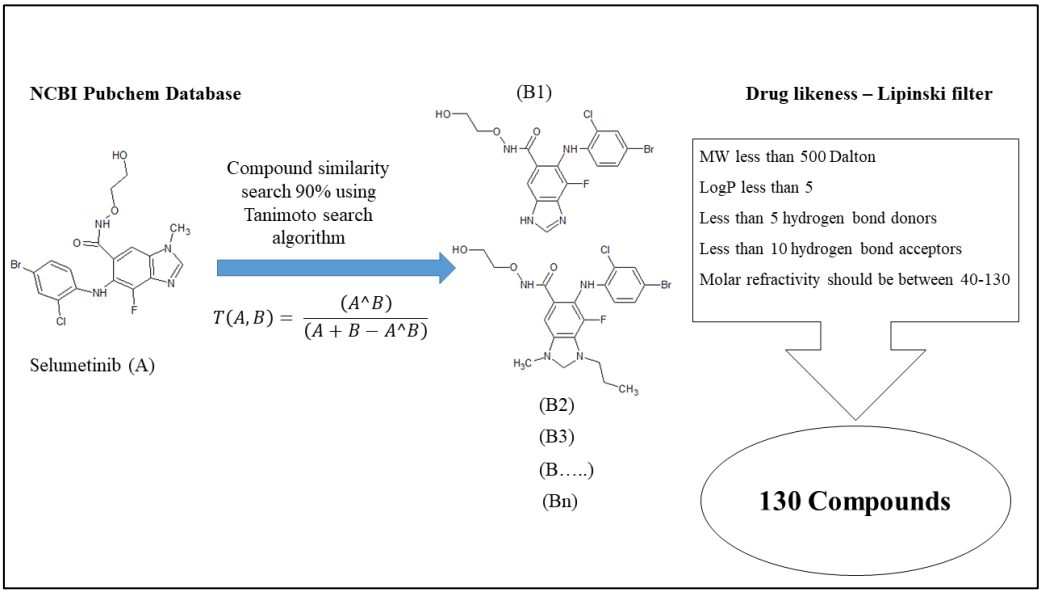

Fig: 11.0 Ligand selection and screening

Molecular docking

AutoDockTools was used to determine the grid docking parameters for the energy minimized protein by selecting the residues that comprise the cavity region of ATP and Ligand Binding sites and then positioning the grid box to enclose the region fig 12.0. Upon obtaining the grid coordinates, the ligand 5EA and ATP were separately docked using Autodock Vina [Xv]. The docked poses with lowest energy were then examined for their interactions with protein residues using Biovia Discovery Studio [Xvi]. Upon optimizing the grid box coordinates, a python script was written to automate the docking process in Autodock Vina , which was used to carry out the virtual screening of the ligands. After completion, the ligand with the lowest binding energy and highest stability was then exported and analysed for residue interactions using Biovia Discovery Studio and then saved in pdb format.

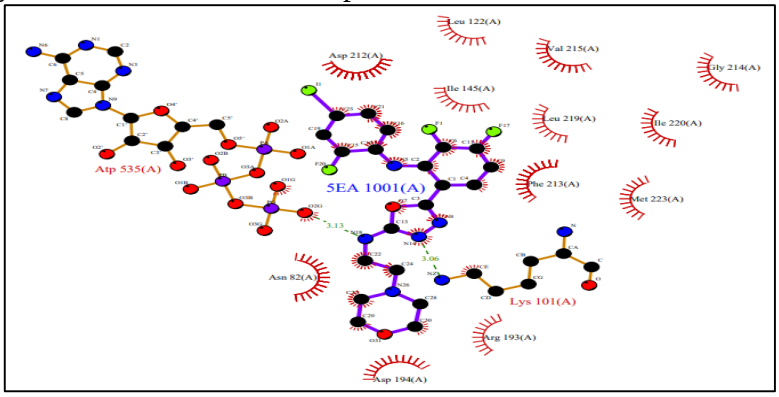

Fig 12.0:1S9I.pdb the crystallized of MEK2 Protein with ATP and Inhibitor

ADME calculations

The ligands were then uploaded to SwissADME server for generation of ADMET properties [Xvii].

Molecular Dynamic Simulation of Protein-Ligand Complex

The ligand with the best pose generated after docking was complexed with the MEK2 energy minimized model and the 2D diagram of interactions was checked before generation using Biovia Discovery Studio . Then the P-L simulation was carried out using CHARMM force field at 50ns resolution using GROMACS [Ix]. After simulation was completed, the resulting complex was analysed by generating the 2D diagram of interactions using Biovia Discovery Studio.

Conclusion:

The full length model generated by I-TASSER server showed a definite improvement after energy minimization, thus it can be taken as a reliable model to conduct further study. Ligands 41(PMCID 69106642) and 42 (PMCID 69916053) are good potential drug candidates which can be further investigated in clinical trials to check for their safety and efficacy.

Acknowledgement: NA

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