

RESEARCH ARTICLE

Discovery of Mitogen-Activated Protein Kinase for Melanoma Using Melphalan Based Hybrid Classic 3-Point Pharmacophore Virtual Screening and Molecular Docking Approach

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ABSTRACT

Melanoma, a highly aggressive type of skin cancer, poses a significant health risk due to its proclivity for metastasis and poor response to conventional treatments. Mutations in the MEK are one of the key molecular alterations driving melanoma progression, resulting in constitutive activation of the MAP2K signaling pathway. Targeting this pathway, specifically the MAP2K, has emerged as a promising approach to melanoma treatment. This study investigates the therapeutic potential of Mitogen-activated protein kinase, which are compounds designed to inhibit the abnormal activity of mutated MEK, disrupting the oncogenic signaling cascade and stopping melanoma progression. The ChEMBL 2D database was used to conduct a comprehensive pharmacophore-based screening to identify potential mitogen-activated protein kinase with the desired molecular properties. Afterwards the initial screening, selected compounds underwent rigorous molecular docking studies to verify their binding affinity and interaction patterns with the MAP2K substance. Among the compounds tested, ChEMBL852 (Melphalan), ChEMBL250892(R)-Melphalan and ChEMBL1200863 (Metyrosine) had particularly high binding affinities, indicating potential efficacy as mitogen-activated protein kinase. Toxicity tests were carried out to assess the safety profiles of these compounds. Notably, metyrosine had a favorable toxicity profile across multiple endpoints, including hepatotoxicity, carcinogenicity, immunotoxicity, and cytotoxicity, indicating its potential as a safer therapeutic candidate. Metyrosine pharmacokinetics were further evaluated using ADME studies, which demonstrated its high water solubility and moderate lipophilicity, indicating favorable drug-like properties. These findings suggest that metyrosine may have higher bioavailability and fewer side effects than other potential inhibitors. Subsequently, this study identifies promising lead compounds, specifically metyrosine, potential candidates for the research and development of novel mitogen-activated protein kinase for melanoma therapy. These compounds require additional experimental validation, optimization, and preclinical research to determine their therapeutic efficacy, safety, and potential for clinical application. This study highlights the importance of targeted therapies in the growing melanoma treatment landscape, paving the way for the development of novel strategies to combat this devastating disease.

Keywords: Melanoma, Virtual screening, Molecular docking, Metyrosine.

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INTRODUCTION

Melanoma, a cancer originating from melanocytes, is a substantial global health challenge due to its tendency to spread to other parts of the body and its resistance to conventional treatments.¹ Despite advancements in treatment modalities,

including immunotherapy and targeted therapy, challenges persist in achieving durable responses and overcoming acquired resistance.² Among the targeted therapeutic strategies, inhibitors targeting protein have shown remarkable efficacy, particularly in melanomas harboring activating

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mitogen-activated protein kinase (MAP2K) mutations.³ The identification of mitogen-activating protein kinase in a significant portion of melanoma patients has opened up possibilities for precision medicine strategies, in which the specific suppression of the altered protein presents a hopeful opportunity for therapeutic intervention.⁴ The MAP2K protein is a key component of the mitogen-activated protein kinase signaling system, which controls the proliferation of cells, survival, and differentiation. A mutation in MAP2K results in the continuous activation by the MAP2K pathway, which promotes the advancement of melanoma and makes tumor cells rely heavily on this abnormal signaling system.⁵ Inhibition of mutated MAP2K with small molecule inhibitors has demonstrated substantial clinical benefit, resulting in improved progression-free survival and overall response rates in MAP2K-mutant melanoma patients.⁶ However, the emergence of resistance mechanisms, including secondary mutations in MAP2K and activation of alternative signaling pathways, limits the long-term efficacy of MAP2K inhibitors.⁷ To address these challenges and further optimize targeted therapy for melanoma, the exploration of novel mitogen-activated protein kinase holds great promise.⁸ Mitogen-activated protein kinase aims to disrupt the oncogenic signaling driven by mutated MAP2K, thereby exerting potent antitumor effects while potentially mitigating acquired resistance mechanisms.⁹ By specifically targeting the dysregulated MAPK pathway, mitogen-activated protein kinase offers a precision therapeutic approach tailored to the molecular characteristics of individual tumors.¹⁰ This research involves the therapeutic potential of mitogen-activated protein kinase in melanoma treatment, aiming to elucidate their mechanisms of action, efficacy, and safety profiles. Leveraging both preclinical models and clinical data, this study aims to assess the efficacy of Mitogen-Activated protein kinase alone or in combination with other treatment modalities, such as immunotherapy or MEK inhibitors, to overcome resistance and improve patient outcomes.

MATERIALS AND METHODS

The molecular structure of the chosen compound, as shown in Figure 1, was inputted in SMILES format. This format is a simplified molecular input line entry system utilized for chemical representation. For our pool of bioactive compounds, we utilized the ChEMBL 2D database as our primary source. This database is rich in bioactivity data and encompasses a diverse array of chemicals with documented biological effects.

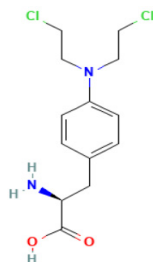


Figure 1: 2D structure and SMILES of melphalan

Cl=CC(=CC=C1C[C@@H](C(=O)O)N)N(CCCl)CCCl

Pharmacophore-Based Screening

In this study, we employed a pharmacophore-based virtual screening method to discover candidate compounds that share structural similarities with melphalan, a bioactive chemical of interest.¹¹ First, a 3-point pharmacophore model for melphalan was created using molecular modeling software, capturing its key pharmacophoric features, such as hydrogen bond acceptors, donors, and hydrophobic regions based on its known bioactive conformation and molecular structure.¹² Consequently, we utilized the comprehensive ChEMBL database, which consisted of 29 bioactive chemicals with well-established biological activity, as an initial screening library to detect prospective hits.¹³ The generated pharmacophore model was used as a query to search the ChEMBL database, evaluating the database compounds' ability to match the essential pharmacophoric features of the Melphalan model. Swiss Similarities, a well-known virtual screening tool, was utilized to assist in the screening process. This algorithm computes similarity scores for the pharmacophore query and database compounds, ranking them based on their similarity to the reference model. Afterwards the virtual screening, compounds with high similarity scores and pharmacophore features consistent with the melphalan model were chosen as potential hits.¹⁴ These hits were then examined further for their relevance to the study's objectives, such as known biological activities and potential therapeutic uses. Compounds identified as potential hits were cataloged and annotated with relevant data such as ChEMBL IDs, chemical structures, and known biological activities.¹⁵ In addition, the structural similarities and differences between the selected hits and melphalan were visually reviewed and analyzed. Finally, the virtual screening procedure successfully identified potential compounds with structural similarities to melphalan in the ChEMBL database. These identified compounds are promising candidates for further experimental validation and study into their pharmacological activities, potentially paving the way for the development of novel therapeutic agents.

Protein Structure and its Pre-processing

The complete crystal structure of the kinase subdomain of mitogen-activated protein kinase (Figure 2), with a PDB ID of 3enm, was acquired from the website <https://www.rcsb.org/>. It was then pre-processed using the online server PDB-



Figure 2: Structure of the MAP2K (PDB ID: 3enm)

REDO version 8.01, which can be found at <https://pdb-redo.eu/eb/3enm>.¹⁶

Molecular Docking

The procedure for molecular docking of mitogen-activated protein kinase begins with the preparation of the receptor structure, which includes retrieving a 3D model of the MAP2K protein or relevant receptor from a reputable database such as the protein data bank.¹⁷ The receptor structure is then pre-processed to remove water molecules, heteroatoms, and any co-crystallized ligands, leading to a clean and relevant environment for docking experiments.¹⁸ The next step after the preparation is to prepare the ligands. This entails searching the ChEMBL 2D database for an array of compounds known to inhibit MAP2K activity. The 2D chemical structures of these compounds are then converted to 3D and optimized for geometry using molecular modeling software, ensuring that their conformations are accurately represented during docking. Afterward, the prepared receptor structure and ligand are submitted to Cb-dock server platform for molecular docking.^{19, 20}

ADMETox Filtering and Property Assessment

The ADMETox filtering and property assessment procedure includes several critical steps in the assessment of chemical compounds for drug discovery.²¹ The process begins with dataset preparation, which involves compiling a list of compounds of interest, such as potential drug candidates or hits from screening tests.²² Subsequently, using molecular modeling software with ADMETox prediction modules allows for the evaluation of compound absorption, distribution, metabolism, excretion, and toxicity.²³ Filters based on established guidelines such as Lipinski's Rule of Five, Veber's rules, Ghose's rule, and Muegge's rule, as well as specific ADMETox parameters such as molecular weight, lipophilicity (logP), and predicted solubility, help to prioritize compounds with desirable physicochemical properties.²⁴ Toxicity prediction then becomes crucial, utilizing computational toxicity prediction models within the software to assess endpoints such as mutagenicity, carcinogenicity, and hepatotoxicity.²⁵

RESULTS

ChEMBL Compound Screening

A pharmacophore-based screening was performed and substances that demonstrated a strong degree of conformity with the recognized pharmacophore characteristics were chosen for additional examination (Table 1).

In our virtual screening study, we utilized a pharmacophore-based approach to identify several compounds from the ChEMBL database as potential hits with high similarity scores to the Melphalan pharmacophore model. Notably, compounds like CHEMBL852, CHEMBL250892, CHEMBL3247494, CHEMBL3185250, CHEMBL429405, CHEMBL1885615, CHEMBL143441, and CHEMBL4525324 had a catching score of 1.000, indicating a strong structural resemblance to the reference model. These compounds share essential

Table 1: Screening results using 3-point pharmacophore 2D database

<i>CHEMBL ID</i>	<i>Catching score</i>	<i>2D Structure</i>
CHEMBL852	1.000	
CHEMBL250892	1.000	
CHEMBL3247494,	1.000	
CHEMBL3185250,	1.000	
CHEMBL429405,	1.000	
CHEMBL1885615,	1.000	
CHEMBL143441,	1.000	
CHEMBL1200863,C[C@]	1.000	
CHEMBL925,	0.793	
CHEMBL4525324,	1.000	

structural motifs like aromatic rings, amino groups, and carbonyl groups which must be present for binding to the target protein. Although CHEMBL925 had a slightly lower catching score of 0.793, it still shares structural similarities with the Melphalan pharmacophore model, implying potential binding interactions that might need further optimization for increased binding affinity. One standout compound, CHEMBL1200863 (Metyrosine), has a high catching score of 1.000 and a strong

structural resemblance to melphalan. Metyrosine, also known as a tyrosine analog, has been studied in the past for its therapeutic potential and given its low toxicity profile, appears to be a promising candidate for future experimental validation. Overall, our findings point to these identified compounds as potential starting points for the development of novel therapeutic agents targeting the identified biological pathways, which requires further investigation in experimental studies.

Screening Using Pharmacophores

A refined set of candidates was obtained by filtering the ChEMBL compounds based on specific pharmacophoric features that are essential for MAP2K inhibition. An enhanced crystallographic model of MAP2K has been produced because of PDB-REDO refinement. Lower R and R-free values indicate improved agreement between the refined structure and the experimental data. A more trustworthy and precise illustration of the protein structure is also indicated by several model quality metrics an overall improvement in structural quality (Table 2).

The original structure's quality metrics improved significantly after crystallographic refinement with PDB-REDO. The R-values, which are indicators of data fitting and model quality, decreased from 0.2210 to 0.1992 for R and 0.2638 to 0.2336 for R-free, indicating improved overall structure refinement. Furthermore, the RMS Z-scores for bond lengths improved from 0.767 to 0.645 and bond angles from 0.926 to 0.897, indicating improved stereochemical accuracy and bond geometry (Figure 3).

Further evaluation of model quality revealed significant improvements. The Ramachandran plot normality increased from 17 to 51%, while rotamer normality increased from 23 to 65%, indicating improved backbone and side-chain conformations. The packing scores also improved, with coarse packing rising from 4 to 6% and fine packing increasing.

Molecular Docking and Lead Compound Analysis

In our molecular docking analysis, compounds such as CHEMBL852, CHEMBL250892, and CHEMBL1200863 (Metyrosine) had high binding affinities to the target protein, indicating their potential as lead compounds. These compounds interacted firmly with the target, indicating their ability to effectively inhibit the protein's function. Metyrosine stood out among them, with both high similarity scores and strong binding affinities, indicating that it could be a promising lead candidate for therapeutic development. These findings provide useful information for prioritizing compounds for further experimental validation and improvement (Table 3).

Several compounds from the ChEMBL database showed high binding affinities to the target protein in our molecular docking study, as evidenced by negative Cb-Dock scores. Notably, compounds such as CHEMBL852, CHEMBL250892, CHEMBL429405, and CHEMBL1200863 (Metyrosine) had the best binding scores, ranging from -7.0 to -7.2, indicating strong interactions with the target site. These compounds have a catching score of 1.000 and significant Cb-Dock

Table 2: Protein structure of the MEK (3enm) after refinement

<i>Parameters</i>	<i>Before refinement</i>	<i>After refinement</i>
R	0.2210	0.1992
R-free	0.2638	0.2336
Bond length RMS Z-score	0.767	0.645
Bond angle RMS Z-score	0.926	0.897
<i>Model quality</i>	<i>Raw scores</i>	<i>Percentiles</i>
Ramachandran plot normality	17	51
Rotamer normality	23	65
Coarse packing	4	6
Fine packing	15	45
Bump severity	6	35
Hydrogen bond satisfaction	41	38

scores, indicating their potential as lead candidates for further experimental validation in drug development. On the other hand, CHEMBL925 had a slightly lower Cb-Dock score of -6.0 despite a catching score of 0.793, indicating a moderate binding affinity to the target protein. This variation could be attributed to structural differences between it and other compounds, which could impact its binding mode or affinity. Nonetheless, the overall docking results show that several compounds, particularly metyrosine, are promising lead candidates for therapeutic research. These findings provide helpful insight for prioritizing compounds for further investigation and optimization in the search for novel therapeutic agents.

ADME Analysis Using Swiss ADME Server

Metyrosine (CHEMBL1200863) demonstrated promising properties in our absorption, distribution, metabolism, and excretion (ADME) assessment using SwissADME, with high water solubility and moderate lipophilicity, indicating the potential for good bioavailability. These favorable ADME profiles indicate that metyrosine may be easily absorbed and distributed in the body, potentially leading to effective therapeutic concentrations. Such characteristics highlight its potential as a candidate for future drug development and experimental validation.

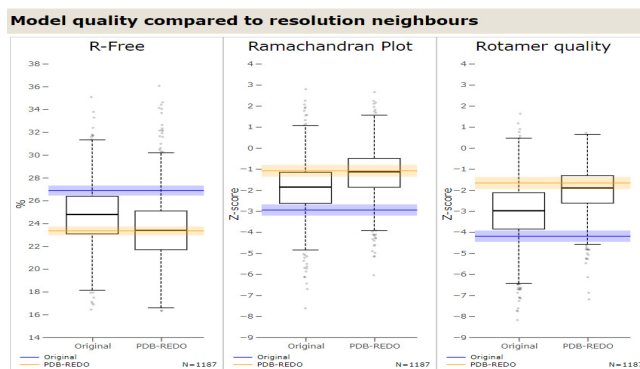
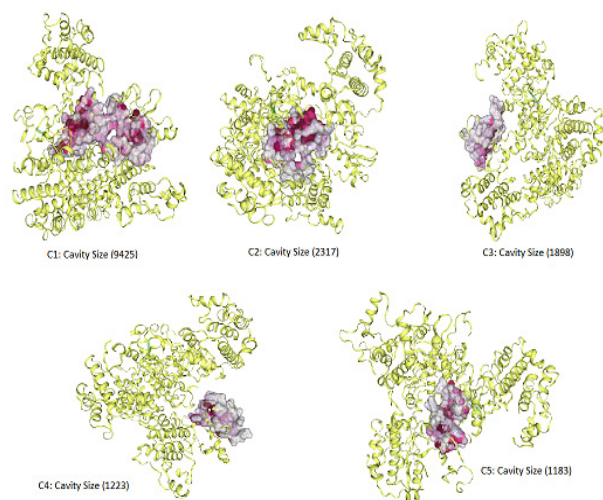
The physicochemical properties of the compound include its water solubility, molecular weight, and various molecular descriptors. The compound has a molecular formula of C₁₀H₁₃NO₃ and a molecular weight of 195.22 g/mol. It exhibits high water solubility, with a Log S (ESOL) value of 0.02 and a solubility of 2.05e+02 mg/mL; 1.05e+00 mol/l. The compound contains 14 heavy atoms, with 6 of them being aromatic, contributing to its highly soluble nature. It has three rotatable bonds and four hydrogen bond acceptors. The molar refractivity is 52.37, indicating its solubility. Lipophilicity assessments show a Log Po/w (iLOGP) of 0.97 and Log Po/w (XLOGP3) of -1.89. The compound demonstrates high gastrointestinal absorption but is not a blood-brain barrier permeant. It is not a substrate for P-glycoprotein and does not

Table 3: Results of docking experiments

CHEMBL ID,	2D structure	Cb-dock score	Cavities
CHEMBL852,		-7.0	8332
CHEMBL250892,		-7.1	9135
CHEMBL3247494		-6.7	1775
CHEMBL3185250,		-6.8	1645
CHEMBL429405,		-7.1	9135
CHEMBL1885615		-6.8	2734
CHEMBL143441		-7.0	8235
CHEMBL1200863		-7.2	9224
CHEMBL925,		-6.0	1473
CHEMBL4525324		-6.9	3124

inhibit various cytochrome P450 enzymes. Moreover, it passes Lipinski, Ghose, and Veber rules, indicating good drug-like properties. However, it violates the lead likeness criterion due to its molecular weight being less than 250. The compound shows synthetic accessibility and a bioavailability score of 0.55.

Metyrosine (CHEMBL1200863) demonstrated offering ADME properties throughout our evaluation with the SwissADME server. The compound had a high water solubility,

**Figure 3:** Model quality compared to resolution neighbours**Figure 4:** Cavities detected in 3nm by structure-based cavity detection

with a Log S (ESOL) value of 0.02 and a solubility of $2.05e + 02$ mg/mL, making it highly soluble. This property shows that metyrosine has a high potential for effective absorption in the body, which facilitates its distribution to target sites. In addition, the substance's moderate lipophilicity, as evidenced by a Log Po/w (iLOGP) of 0.97, contributes to its potential for high bioavailability, which is critical for achieving therapeutic levels. Likewise, metyrosine's physicochemical properties highlight its drug-like nature and potential to be a viable drug candidate. The compound follows Lipinski's, Ghose's, and Veber's rules without exception, indicating a favorable profile in terms of molecular weight, lipophilicity, and polar surface area. Furthermore, the absence of significant structural alerts, as demonstrated by the lack of PAINS alerts and adherence to medicinal chemistry guidelines, improves its safety profile and suitability for future drug development. In brief, metyrosine's favorable ADME and physicochemical properties, such as high-water solubility, moderate lipophilicity, and adherence to drug-likeness rules, highlight its potential as a promising candidate for future drug development and validation through experiments (Figures 4-6). These findings necessitate further investigation into its therapeutic potential and efficacy in specific applications.

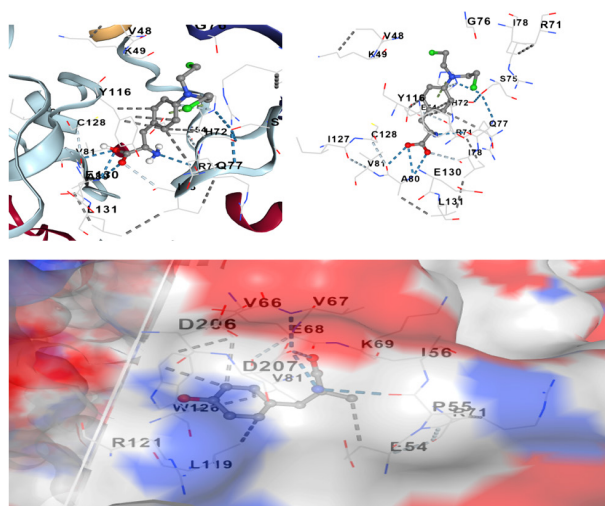


Figure 5: Interaction of CHEMBL1200863 (Metyrosine)

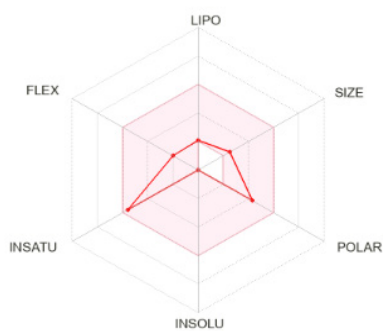


Figure 6: Bioavailability radar of CHEMBL1200863 (Metyrosine)

ADME Tox Filtering

Metyrosine (CHEMBL1200863) exhibited favorable ADME properties in our ADMETox assessment, such as high water solubility and moderate lipophilicity, indicating potential for effective absorption and distribution. The compound also adhered to important drug-likeness rules, which improved its safety as well as suitability for drug discovery. These promising characteristics emphasize metyrosine's potential as a viable candidate for future experimental validation and therapeutic investigation.

The compound was subjected to classification regarding various toxicity endpoints, nuclear receptor signaling pathways, stress response pathways, molecular initiating events, and metabolic processes. It was found to be inactive in terms of hepatotoxicity, carcinogenicity, immunotoxicity, cytotoxicity, and the activation of several nuclear receptor signaling pathways, including aryl hydrocarbon receptor (AhR), androgen receptor (AR), aromatase, peroxisome proliferator-activated receptor gamma (PPAR-Gamma), and others. Additionally, it showed inactivity in stress response pathways such as nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE), heat shock factor response element (HSE), and mitochondrial membrane potential (MMP), among others. Furthermore, the compound

did not initiate molecular events related to thyroid hormone receptors (THR α and THR β). In terms of metabolism, it exhibited inactivity towards cytochrome CYP2C19, CYP2C9, and CYP3A4 enzymes.

Metyrosine (CHEMBL1200863) demonstrated a particularly positive safety profile in our comprehensive ADMETox evaluation, demonstrating that it has the potential to be a safe and well-tolerated therapeutic candidate. The compound had a high likelihood of inactivity across an array of toxicity endpoints, including hepatotoxicity (0.93), carcinogenicity (0.77), and immunotoxicity (0.99). These findings highlight metyrosine's reduced risk of causing liver damage, carcinogenic effects, or immune system-wide adverse reactions, which improves its safety profile. Also, our findings revealed that metyrosine had inactive interactions with a variety of critical molecular targets that influence nuclear receptor signaling pathways, stress-related mechanisms, and metabolic enzyme activities. It was specifically found to be inactive with the aryl hydrocarbon receptor (AhR), androgen receptor (AR), peroxisome proliferator activated receptor gamma (PPAR-Gamma), and several other key proteins. Such interactions indicate a lower risk of unintended pharmacological effects and off-target interactions, bolstering its potential safety and therapeutic specificity. Finally, these comprehensive ADMETox profiling results provide compelling evidence for metyrosine's promising safety profile. Given its favorable characteristics, metyrosine emerges as a promising candidate for further preclinical research and clinical trials, paving the way for its potential development as an effective and safe therapy.

CONCLUSION

This study used a pharmacophore-based screening approach to identify potential mitogen-activated protein kinase from the ChEMBL 2D database. The refined candidates demonstrated significant adherence to pharmacophoric features required for MAP2K inhibition. Crystallographic refinement with PDB-REDO resulted in improved structural quality of the mitogen-activated protein kinase (MAP2K) model, as evidenced by lower R-values, higher RMS Z-scores for bond lengths and angles, and better model quality metrics. These modifications resulted in a more accurate representation of the protein structure. Molecular docking analysis with the CB-Dock server demonstrated several compounds with high affinity for binding to the MAP2K protein. Notably, CHEMBL852, CHEMBL250892, and CHEMBL1200863 (Metyrosine) showed promising Cb-Dock scores, indicating that they could be effective mitogen-activated protein kinase. Toxicity assessments of CHEMBL1200863 revealed inactivity across multiple toxicity endpoints, indicating a potentially favorable safety profile. Furthermore, ADME studies on metyrosine revealed high water solubility and moderate lipophilicity, indicating beneficial pharmacokinetic characteristics such as high gastrointestinal absorption and metabolic stability. However, the compound demonstrated low permeability across the blood-brain barrier, implying that it had little

effect on the central nervous system. In general, the findings identify several principal substances with promising MAP2K inhibitory activities and favorable pharmacological profiles, requiring additional experimental validation and optimization for potential therapeutic uses in melanoma treatment.

REFERENCES

1. Wagstaff W, Mwamba RN, Grullon K, Armstrong M, Zhao P, Hendren-Santiago B, Qin KH, Li AJ, Hu DA, Youssef A, Reid RR. Melanoma: Molecular genetics, metastasis, targeted therapies, immunotherapies, and therapeutic resistance. *Genes & diseases*. 2022 Nov 1;9(6):1608-23. <https://doi.org/10.1016/j.gendis.2022.04.004>
2. Yu C, Liu X, Yang J, Zhang M, Jin H, Ma X, Shi H. Combination of immunotherapy with targeted therapy: theory and practice in metastatic melanoma. *Frontiers in immunology*. 2019 May 7; 10:431246. Volume 10 - 2019 | <https://doi.org/10.3389/fimmu.2019.00990>
3. Tojjari A, Saeed A, Sadeghipour A, Kurzrock R, Cavalcante L. Overcoming Immune Checkpoint Therapy Resistance with SHP2 Inhibition in Cancer and Immune Cells: A Review of the Literature and Novel Combinatorial Approaches. *Cancers*. 2023 Nov 13;15(22):5384. <https://doi.org/10.3390/cancers15225384>
4. Florent L, Saby C, Slimano F, Morjani H. BRAF V600-mutated metastatic melanoma and targeted therapy resistance: an update of the current knowledge. *Cancers*. 2023 May 4;15(9): 2607. <https://doi.org/10.3390/cancers15092607>
5. Poulidakos PI, Sullivan RJ, Yaeger R. Molecular pathways and mechanisms of BRAF in cancer therapy. *Clinical Cancer Research*. 2022 Nov 1;28(21):4618-28. <https://doi.org/10.1158/1078-0432.CCR-21-2138>
6. Zhao JH, Xu QL, Ma S, Li CY, Zhang HC, Zhao LJ, Zhang ZY. Recent advance of small-molecule drugs for clinical treatment of multiple myeloma. *European Journal of Medicinal Chemistry*. 2023 May 16;115492. <https://doi.org/10.1016/j.ejmech.2023.115492>
7. Yuan J, Guo Y. Targeted therapy for anaplastic thyroid carcinoma: advances and management. *Cancers*. 2022 Dec 28;15(1):179. <https://doi.org/10.3390/cancers15010179>
8. Letsoalo K, Nortje E, Patrick S, Nyakudya T, Hlophe Y. Decoding the synergistic potential of MAZ-51 and zingerone as therapy for melanoma treatment in alignment with sustainable development goals. *Cell Biochemistry and Function*. 2024 Mar;42(2): e3950. <https://doi.org/10.1002/cbf.3950>
9. Manikkam R, Periyasamy V, Sabapathy I. Repurposing of phytocompounds-derived novel bioactive compounds possessing promising anticancer and cancer therapeutic efficacy through molecular docking, MD simulation, and drug-likeness/ADMET studies. In *Computational Methods in Drug Discovery and Repurposing for Cancer Therapy* 2023 Jan 1 (pp. 201-222). Academic Press. <https://doi.org/10.1016/B978-0-443-15280-1.00020-0>
10. Dain Md Opo FA, Alsaiani AA, Rahman Molla MH, Ahmed Sumon MA, Yaghmour KA, Ahammad F, Mohammad F, Simal-Gandara J. Identification of novel natural drug candidates against BRAF mutated carcinoma; An integrative in-silico structure-based pharmacophore modeling and virtual screening process. *Frontiers in Chemistry*. 2022 Oct 4; 10:986376. <https://doi.org/10.3389/fchem.2022.986376>
11. Hekmat A, Saboury AA. Protein kinase inhibitors and cancer targeted therapy. In *Protein Kinase Inhibitors* 2022 Jan 1 (pp. 23-70). Academic Press. <https://doi.org/10.1016/B978-0-323-91287-7.00022-3> Get rights and content
12. Banegas-Luna AJ, Cerón-Carrasco JP, Pérez-Sánchez H. A review of ligand-based virtual screening web tools and screening algorithms in large molecular databases in the age of big data. *Future medicinal chemistry*. 2018 Nov;10(22):2641-58. <https://doi.org/10.4155/fmc-2018-0076>
13. Younis MK, Elakkad YE, Fakhr Eldeen RR, Ali IH, Khalil IA. Propranolol-Loaded trehalosome as antiproliferative agent for treating skin cancer: Optimization, cytotoxicity, and in silico studies. *Pharmaceutics*. 2023 Jul 28;15(8):2033. <https://doi.org/10.3390/pharmaceutics15082033>
14. Chaudhary M, Kumar N, Baldi A, Chandra R, Babu MA, Madan J. 4-Bromo-4'-chloro pyrazoline analog of curcumin augmented anticancer activity against human cervical cancer, HeLa cells: in silico-guided analysis, synthesis, and in vitro cytotoxicity. *Journal of Biomolecular Structure and Dynamics*. 2019 Apr 17. <https://doi.org/10.1080/07391102.2019.1604266>
15. Padalino G, Coghlan A, Pagliuca G, Forde-Thomas JE, Berriman M, Hoffmann KF. Using ChEMBL to complement schistosome drug discovery. *Pharmaceutics*. 2023 Apr 28;15(5):1359. <https://doi.org/10.3390/pharmaceutics15051359>
16. Rai M, Singh AV, Paudel N, Kanase A, Falletta E, Kerkar P, Heyda J, Barghash RF, Singh SP, Soos M. Herbal concoction unveiled: a computational analysis of phytochemicals' pharmacokinetic and toxicological profiles using novel approach methodologies (NAMs). *Current Research in Toxicology*. 2023 Jan 1; 5:100118. <https://doi.org/10.1016/j.crttox.2023.100118>
17. Patil K, Nemade M, Bedse A, Chandra P, Ranjan R, Tare H, Bhise M. Virtual Screening, Molecular Docking, and ADMET Analysis of Flavonoids as a Potential Pi3k Inhibitor for Cancer Treatment. *International Journal of Drug Delivery Technology*. 2023;13(3):966-970.
18. Mujawar T, Kayande N, Thube U, Belhekar S, Deshmukh N, Tare H. Unlocking Therapeutic Potential: A Comprehensive Exploration of FDA-Approved Sirolimus similars for Perivascular Epithelioid Cell Tumor Treatment through Transcriptomic Insight, Structural Integration, and Drug-Drug Similarity Analysis with Cavity-Guided Blind Docking. *International Journal of Drug Delivery Technology*. 2023;13(4):1194-1198.
19. Gaikwad A, Kayande N, Tare H, Udugade B, Kachave R. In-silico Design and Development of Multi-Target Agents Targeting Glycogen Synthase Kinase-3 Beta (GSK-3 β) and Vascular Endothelial Growth Factor Receptor 2 for Acute Myeloid Leukemia. *International Journal of Drug Delivery Technology*. 2023;13(4):1428-1434.
20. Patil K, Nemade M, Bedse A, Chandra P, Ranjan R, Tare H, Patil S. In-silico Exploration for Novel CDK8 Inhibitors: A Virtual Study by Pharmacophore Screening. *International Journal of Drug Delivery Technology*. 2023;13(3):904-907.
21. Mujawar T, Tare H, Deshmukh N, Udugade B, Thube U. Repurposing FDA-Approved Anastrozole-based Drugs for Breast Cancer through Drug-Drug Transcriptomic Similarity and Cavity Detection Guided Blind Docking. *International Journal of Drug Delivery Technology*. 2023;13(4):1172-1177.
22. Tare H, Bedse A, Thube U, Kachave R, Wagh V. Eriodictyol Flavonones Based Virtual Screening of Bioactive Compounds from ChEMBL 2D Database with Classic 3-point Pharmacophore Screening Method for HER2 Inhibitors for Breast Cancer. *International Journal of Drug Delivery Technology*.

- 2023;13(4):1161-1166.
23. Tare H, Thube U, Kachave R, Wagh V, Udugade B. Catechins as Catalase Modulators: A Comprehensive In-silico Analysis Unveiling their Potential Antioxidant Effects. *International Journal of Drug Delivery Technology*. 2023;13(4):1156-1160.
24. Nemade M, Patil K, Bedse A, Chandra P, Ranjan R, Tare H, Bhise M. Phenol Glucosides as Potential Inhibitors of SGLT1 for Enhanced Diabetes Mellitus Treatment in Patients with Declining Renal Function. *International Journal of Drug Delivery Technology*. 2023;13(3):948-954.
25. Nemade M, Patil K, Bedse A, Chandra P, Ranjan R, Tare H, Patil S. Computational Exploration of Anti-Alzheimer Potential of Flavonoids against Inducible Nitric Oxide Synthetase: An In-silico Molecular Docking and ADMET Analysis Approach. *International Journal of Drug Delivery Technology*. 2023;13(3):899-903.