Uttar Pradesh Journal of Zoology

Volume 45, Issue 17, Page 619-632, 2024; Article no.UPJOZ.3849
ISSN: 0256-971X (P)

Identification of Novel Drug Compound for the Mutated Protein (PKBB-Protein Kinase B, Beta) Responsible for Endometrial Cancer Using Advanced *Insilico* Drug Designing Technique

S. Rekha [a++*] and Arivoli.S [a#]

[a] *Department of Zoology, Thiruvalluvar University, Vellore-632 115, India.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.56557/upjoz/2024/v45i174407

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.mbimph.com/review-history/3849

Review Article

Received: 23/06/2024
Accepted: 25/08/2024
Published: 31/08/2024

ABSTRACT

Currently, one of the most important health problems affecting individuals worldwide is endometrial cancer. Numerous studies have been conducted by oncologists in an effort to create preventive medications that will lower the cancer's death rate. Using 3D Insilico drug docking techniques, we investigate the potential interactions between the mutant target protein, PKBB-Protein Kinase B, Beta, and the anti-cancer pharmaceutical (control drug), Mercaptopurine, and the proposed de novo drug derivative. To perform drug docking procedures, the translated amino acid sequence and

[++] *Research Scholar;*
[#] *Associate Professor;*
**Corresponding author: Email: rekhasrini1981@gmail.com;*

Cite as: *Rekha, S., and Arivoli. S. 2024. "Identification of Novel Drug Compound for the Mutated Protein (PKBB-Protein Kinase B, Beta) Responsible for Endometrial Cancer Using Advanced Insilico Drug Designing Technique". UTTAR PRADESH JOURNAL OF ZOOLOGY 45 (17):619-32. https://doi.org/10.56557/upjoz/2024/v45i174407.*

three-dimensional chemical compound were acquired from the NCBI database. The most sophisticated 3D molecular imaging instruments were used to conduct post-docking studies. The de novo medicine directly blocks amino acid mutational sites, as the results of the docking investigation clearly showed (PKBB). The suggested de novo drug has a higher binding score than the control medication, mercaptopurine. Using molecular dynamics techniques, a three-dimensional image of the H-bond contact force between PKBB and the de novo drug is produced. Therefore, we deduce that the suggested anti-cancer de novo drug may aid in the treatment of endometrial cancer. Thus, we suggest the de novo medicine, which lessens discomfort while reducing the signs and symptoms of malignancy.

Keywords: PKBB-protein kinase B; beta drug designing; docking.

1. INTRODUCTION

Over the past 30 years, there has been a noticeable increase in the prevalence of endometrial cancer and a substantial rise in the complexity of patients affected by the disease. Over 417,000 new cases of endometrial cancer were reported globally in 2020, and 97,370 people died from the disease, making it a significant health burden [1]. With the world's population getting older and the prevalence of diabetes and obesity rising, these figures are expected to rise even higher. With the goal of stopping this rise, a deeper comprehension of the processes by which these risk factors promote the development of endometrial carcinogenesis has made it possible to design focused primary disease preventive treatments. “Despite the nearly twofold increase in endometrial cancer deaths since 1990, the age-standardized mortality rate has declined dramatically in nearly every geographical region due to advancements in early diagnosis and treatment” [2]. “Although the majority of women receive an early-stage diagnosis and are expected to fully recover from their endometrial cancer, 20% of women still have extra-uterine disease at the time of presentation, and only 15% of women with stage IV illness are still living five years after their diagnosis. Thus, early detection is still crucial. Non-invasive diagnostics that aim to rule out endometrial cancer in most postmenopausal bleeding women are becoming more and more common, and women are probably going to find them more acceptable than endometrial biopsies. The growing discrepancy in survival between White, Black, Asian, and Hispanic women is concerning, as it could be caused by variations in tumor biology as much as a lack of access to endometrial cancer therapies” [3,4]. “Hopefully, a deeper comprehension of the genetic alterations causing endometrial carcinogenesis will close this knowledge gap. However, this knowledge is already being applied to tailor treatments and identify women with Lynch syndrome, for whom endometrial cancer is a sentinel malignancy” [5]. “The goal of this review is to identify the unanswered research concerns that need to be addressed over the next thirty years while also summarizing the most recent developments in the prevention, diagnosis, and treatment of endometrial cancer. Endometrial cancer is highly amenable to primary disease prevention due to its significant correlation with modifiable risk factors. Models indicate that up to 60% of instances of endometrial cancer may be averted” [6,7]. “Many interventions to lower the incidence of endometrial cancer have been proposed as a result of a better understanding of the mechanisms underlying endometrial carcinogenesis, specifically unopposed oestrogen, insulin resistance, and chronic inflammation. However, the majority of the data regarding these interventions' efficacy comes from retrospective observational studies” [8]. Designing an anti-cancer medicine without side effects is one of the major issues faced by pharma industries. Our research work focuses on resolving this problem.

1.1 Objectives of the Project Work

- To use digital literature databases and clinical literature to identify putative genes linked to endometrial cancer.
- To examine and visualize the target protein's molecular mechanics.
- To choose and create drugs in order to forecast drug docking and binding scores and to visualize the results.

2. METHODOLOGY

Insilico 3D Modelling:

- **Sequence Retrieval System:** We selected the PKBB (Protein Kinase B -

Beta) gene, which is directly linked to endometrial cancer in humans, based on a variety of clinical and molecular genetics literature research. OMIM can be found at https://omim.org/entry/118505. The UniProt database provided the gene-coded protein sequence in FASTA format. Proteomics database UniProt (https://www.uniprot.org/uniprot/P30532).

- **Protein 3D Structure Prediction:** Using an automated homology modeling server called CPH 3.0 model server (http://www.cbs.dtu.dk/services/CPHmodels/), the amino acid sequence of the PKBB (PROTEIN KINASE B -BETA) protein was transformed into a 3D structure. The structure was then verified using Procheck server (https://www.ebi.ac.uk/thornton-srv/software/PROCHECK/).

Insilico Drug Designing:

- **Drug compound selection:** To construct the medicine, the endometrial cancer drug chemical that was already on the market was obtained from the NCBI PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/). With the use of Discovery Studio software, the chemical 2D structure was recovered and transformed into a 3D structure.
- **Drug designing and validation:** Using the Molinspiration software (https://www.molinspiration.com/), the preexisting drug molecule and an antioxidant molecule were joined, and the qualities of the drug likeness score were verified.

.

Molecular Drug Docking:

- Using an automated molecular protein-drug docking service called PatchDock (https://bioinfo3d.cs.tau.ac.il/PatchDock/), the developed chemical compounds were inserted into the modeled endometrial cancer target protein, PKBB (Protein Kinase B -Beta). Discovery Studio Software was used to verify the docking data and view the affinities for drug-protein binding and the H-bond interaction.

3. RESULTS AND DISCUSSION

Table 1. Protein target summary

Gene name	Gene ID	Chr Loc	OMIM ID	UniProt ID	Gene length	Protein Length
PKBB -Protein Kinase B -Beta	208,	19	164731	P31751	1446 nt	481 aa

The above table gives information on the target protein retrieved from NCBI and UniProt databases.

10	20	30	40	50
MNEVSVIKEG 60	WLHKRGEYIK 70	TWRPRYFLLK 80	SDGSFIGYKE 90	RPEAPDQTLP 100
PLNNFSVAEC 110	QLMKTERPRP 120	NTFVIRCLQW 130	TTVIERTFHV 140	DSPDEREEWM 150
RAIQMVANSL 160	KQRAPGEDPM 170	DYKCGSPSDS 180	STTEEMEVAV 190	SKARAKVTMN 200
DFDYLKLLGK 210	GTFGKVILVR 220	EKATGRYYAM 230	KILRKEVIIA 240	KDEVAHTVTE 250
SRVLQNTRHP 260	FLTALKYAFQ 270	THDRLCFVME 280	YANGGELFFH 290	LSRERVFTEE 300
RARFYGAEIV 310	SALEYLHSRD 320	VVYRDIKLEN 330	LMLDKDGHIK 340	ITDFGLCKEG 350
ISDGATMKTF 360	CGTPEYLAPE 370	VLEDNDYGRA 380	VDWWGLGVVM 390	YEMMCGRLPF 400
YNQDHERLFE 410	LILMEEIRFP 420	RTLSPEAKSL 430	LAGLLKKDPK 440	QRLGGGPSDA 450
KEVMEHRFFL 460	SINWQDVVQK 470	KLLPPFKPQV 480	TSEVDTRYFD	DEFTAQSITI

Fig. 1. Sequence of PKBB protein (Normal) - UniProt Database

The above picture shows the sequence format of Normal amino acids content of PKBB with amino acid position (Asp: 399) highlighted in yellow.

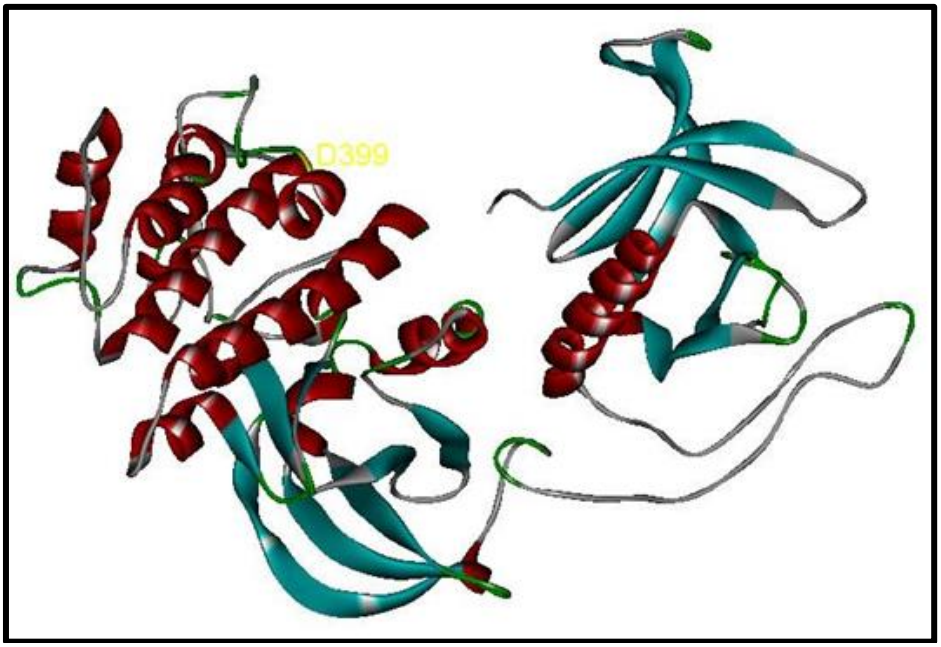


Fig. 2. Protein Modelling: 3D structure of PKBB (Normal)

The above picture shows the 3D view of the normal protein structure of PKBB shown in secondary structure colour model with amino acid label (Asp: 399,), visualized using Discovery Studio Software.

10	20	30	40	50
MNEVSVIKEG	WLHKRGEYIK	TWRPRYFLLK	SDGSFIGYKE	RPEAPDQTLP
60	70	80	90	100
PLNNFSVAEC	QLMKTERPRP	NTFVIRCLQW	TTVIERTFHV	DSPDEREEWM
110	120	130	140	150
RAIQMVANSL	KQRAPGEDPM	DYKCGSPSDS	STTEEMEVAV	SKARAKVTMN
160	170	180	190	200
DFDYLKLLGK	GTFGKVILVR	EKATGRYYAM	KILRKEVIIA	KDEVAHTVTE
210	220	230	240	250
SRVLQNTRHP	FLTALKYAFQ	THDRLCFVME	YANGGELFFH	LSRERVFTEE
260	270	280	290	300
RARFYGAEIV	SALEYLHSRD	VVYRDIKLEN	LMLDKDGHIK	ITDFGLCKEG
310	320	330	340	350
ISDGATMKTF	CGTPEYLAPE	VLEDNDYGRA	VDWWGLGVVM	YEMMCGRLPF
360	370	380	390	400
YNQDHERLFE	LILMEEIRFP	RTLSPEAKSL	LAGLLKKDPK	QRLGGGPSNA
410	420	430	440	450
KEVMEHRFFL	SINWQDVVQK	KLLPPFKPQV	TSEVDTRYFD	DEFTAQSITI
460	470	480		

Fig. 3. Sequence of PKBB protein (Mutated) - UniProt Database

The above picture shows the FASTA format of Normal amino acids content of PKBB with amino acid position (Asn : 399) highlighted in yellow [9].

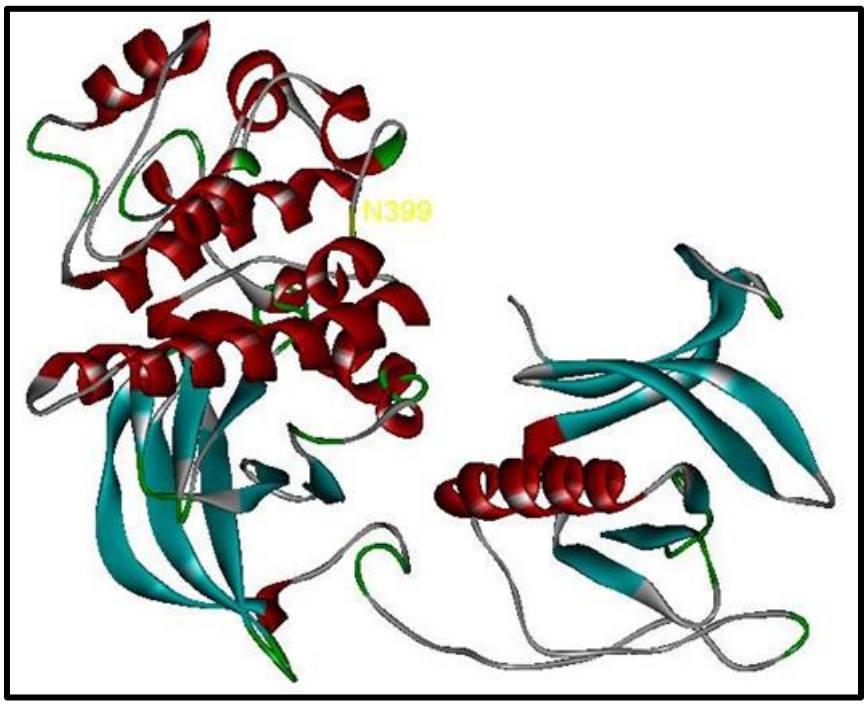
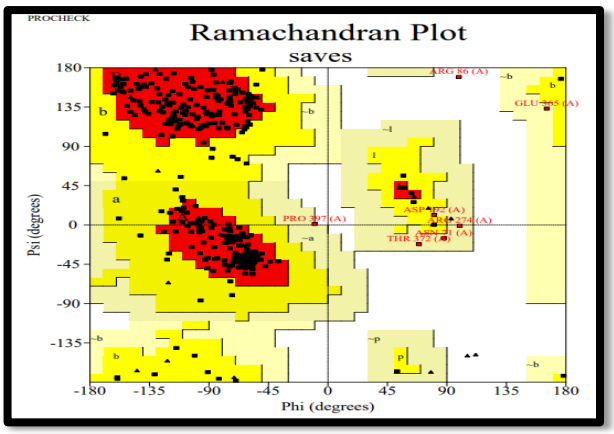


Fig. 4. Protein Modelling: 3D structure of PKBB (Mutated)

The above picture shows the 3D view of the Mutated protein structure of PKBB shown in Space-filling model with the mutated amino acid label (Asn: 399,), visualized using Discovery Studio Software.



Plot statistics

Residues in most favoured regions [A,B,L]	314	88.2%
Residues in additional allowed regions [a,b,l,p]	36	10.1%
Residues in generously allowed regions [~a,~b,~l,~p]	5	1.4%
Residues in disallowed regions	1	0.3%
Number of non-glycine and non-proline residues	356	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	26	
Number of proline residues	19	
Total number of residues	403	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig 5 Assessment of Ramachandran plot for the predicted mutated protein sequence of the modeled PKBB

Cheminformatics

Table 2. Drug compound summary

Drug name	CID :	Mol.Weigh t	Mol.Formula	Smiles	Summary
Mercapto purine	667490	152.180 g/mol	C5H4N4S	C1=NC2=C(N1)C(=S)N=CN2	Anti- neoplastic Properties
2-acetyloxybenzoic acid	2244	180.160 g/mol	C9H8O4	CC(=O)OC1=CC=CC=C1C(=O) O	Anti- Oxidant

The above table provides information on the drug compounds retrieved from NCBI PubChem Compound database.

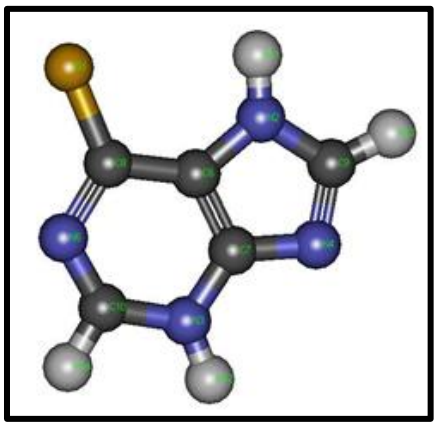


Fig. 6. Cheminformatics -3D Structure of Mercaptopurine

The above picture shows the 3D structure of Mercaptopurine with coloured atoms: Grey-Carbon, Blue-Nitrogen, Yellow-Sulphur and White –Hydrogen using Discovery Studio Software

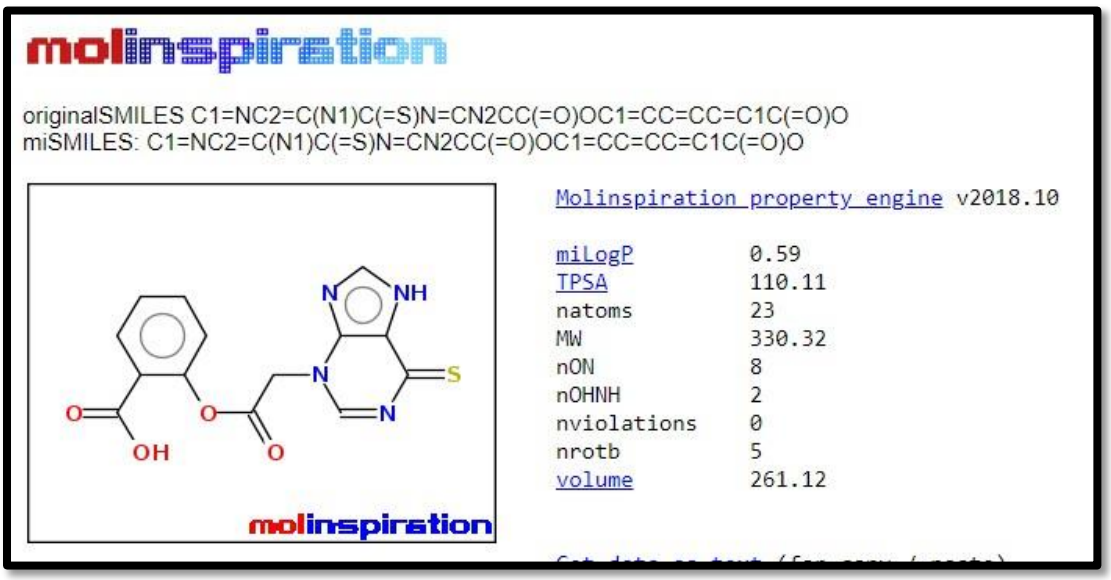


Fig. 7. Cheminformatics -2D Structure of *de novo* Drug

Calculation of the Molecular Properties of the combined structure of Mercaptopurine with 2-acetyloxybenzoic acid using Molinspiration Cheminformatics Software.

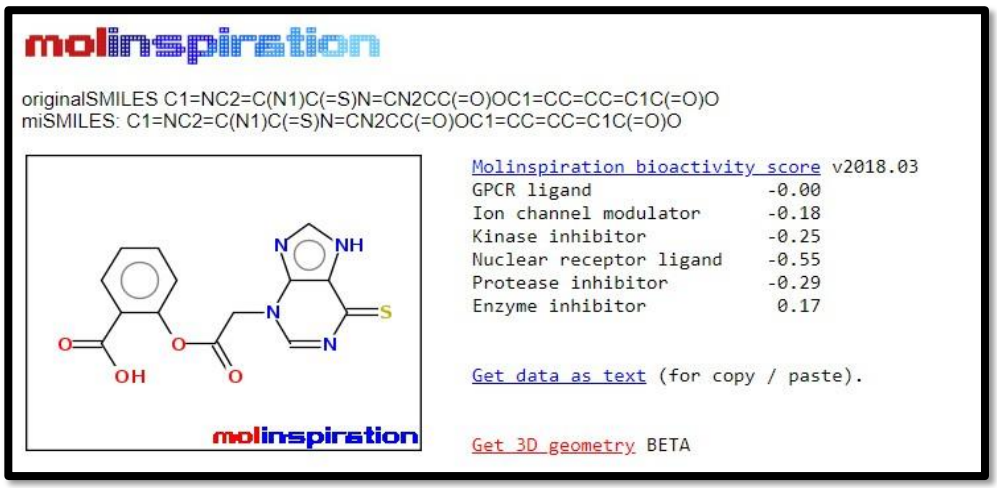


Fig. 8. Cheminformatics -2D Structure of Mercaptopurine Drug

Calculation of the Bioactivity Scores of the combined structure of Mercaptopurine with 2-acetyloxybenzoic acid using Molinspiration Cheminformatics Software.

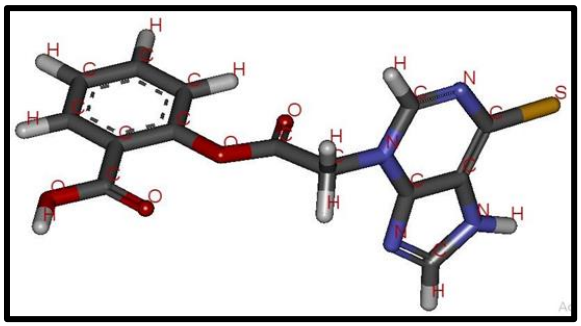


Fig. 9. Cheminformatics - 3D Structure of *de novo* Drug

*The above picture shows the 3D structure of the **de novo** compound with atom colours: Grey-Carbon, Red-Oxygen, Yellow-Sulphur, Blue-Nitrogen and White – Hydrogen using Discovery Studio Software.*

Receptor	Ligand	Complex Type	C
AKT2_mut.pdb	Mercaptopurine.pdb	drug	4

Solution No	Score	Area	ACE
1	2522	311.30	-127.70
2	2412	281.00	-110.00
3	2394	263.50	-83.82
4	2382	238.90	-127.25
5	2334	268.30	-160.33
6	2332	246.80	-64.44
7	2320	263.70	-1.53
8	2320	259.00	-166.52
9	2314	255.40	-133.85
10	2292	286.70	-128.89
11	2274	261.50	-160.48
12	2262	288.40	-161.64
13	2254	261.00	-133.23
14	2228	256.10	-97.24
15	2222	253.70	-115.88
16	2206	264.30	-72.90
17	2188	228.20	-97.63
18	2180	256.20	-73.08
19	2156	249.80	-171.92
20	2154	241.30	-186.66

Fig. 10 Molecular drug docking

The above picture is the PatchDock result page showing the drug docking score of the existing drug, Mercaptopurine with the modelled mutated protein target, PKBB. The negatively high ACE (Atomic Contact Energy) value is -186.66

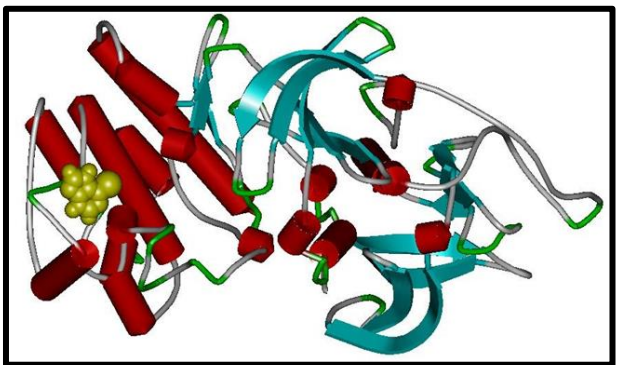


Fig. 11. Molecular drug docking

The above picture represents the existing drug molecule (Mercaptopurine) docked with PKBB protein structure. Yellow colour indicates Mercaptopurine in space- filling model using Discovery Studio Software.

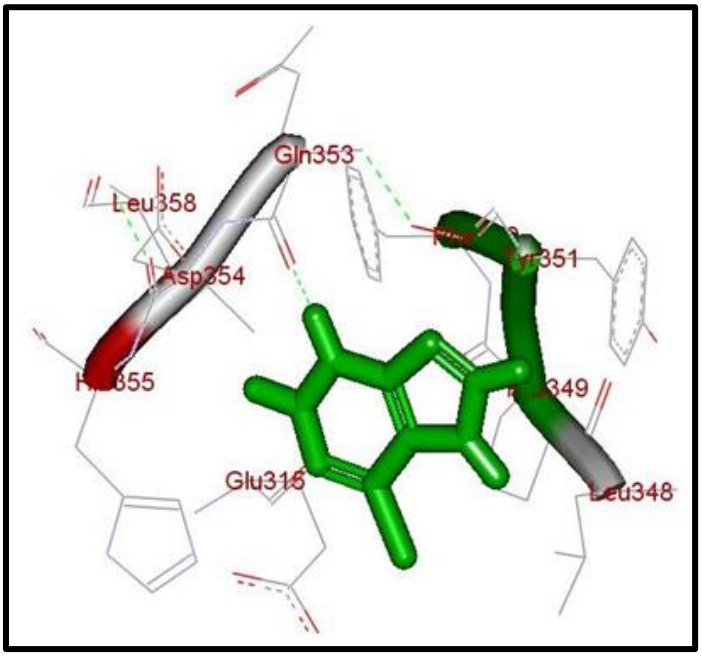


Fig. 12. Ligand –protein binding prediction

The above picture represents the existing drug molecule docked with PKBB protein structure with drug binding amino acids labels. Green colour indicates Mercaptopurine in Stick model using Discovery Studio Software

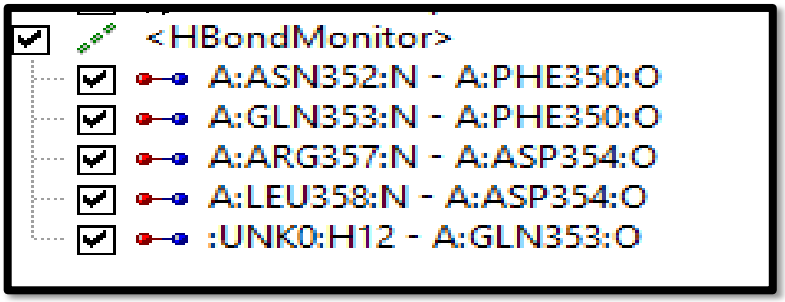


Fig: 13. H-bond interaction (Mercaptopurine + PKBB)

The above table shows the H-bond interaction between Mercaptopurine and the endometrial cancer protein, PKBB

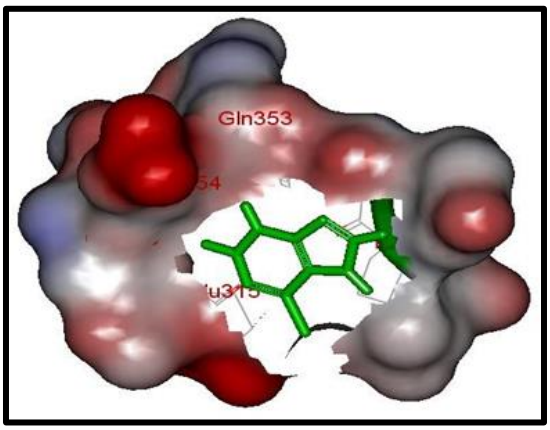


Fig 14. Van Der Waals Interaction Prediction 3D structure of PKBB with Existing Drug

The above picture represents the existing drug molecule (Mercaptopurine) docked with PKBB protein structure in Van Der Waals model view with drug binding amino acids labels. Green colour indicates Mercaptopurine in Stick model using Discovery Studio Software

Receptor	Ligand	Complex Type	Clusterin
AKT2_mut.pdb	denovo.pdb	drug	4.0

Solution No	Score	Area	ACE
1	4724	564.90	-128.60
2	4472	564.20	-305.25
3	4468	540.30	-209.31
4	4450	546.00	-45.88
5	4386	520.20	-90.75
6	4170	522.90	-202.25
7	4150	540.10	-253.49
8	4146	518.40	-34.27
9	4018	455.70	-158.30
10	4006	437.70	-145.33
11	3982	492.70	-94.91
12	3948	458.30	-108.74
13	3912	488.50	-154.06
14	3888	452.10	-151.93
15	3852	450.40	-228.59
16	3826	483.40	-73.46
17	3822	554.30	-248.26
18	3820	473.80	-159.05
19	3816	481.70	-112.03
20	3806	493.20	-149.04

Fig. 15. Molecular Drug Docking- PatchDock results PKBB with *de novo* (Mercaptopurine + 2-acetyloxybenzoic acid)

*The above picture is the PatchDock result page – drug docking score of de novo (Mercaptopurine + **2-acetyloxybenzoic acid)** drug with the modelled mutated protein target, PKBB. The negatively high ACE (Atomic Contact Energy) value is -305.25*

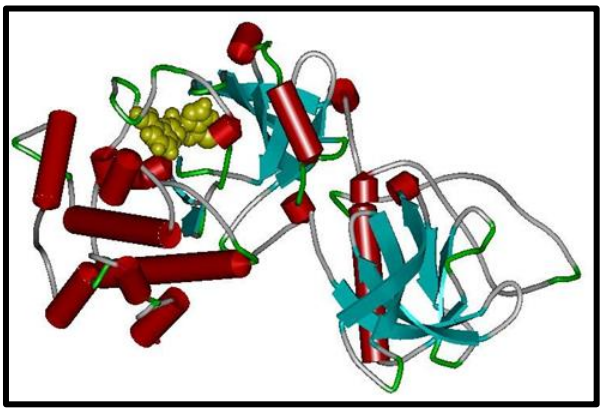


Fig. 16. Molecular drug docking

The above picture represents the de novo drug molecule docked with PKBB protein structure. Yellow colour indicates the de novo molecule in space-filling model viewed using Discovery Studio Software

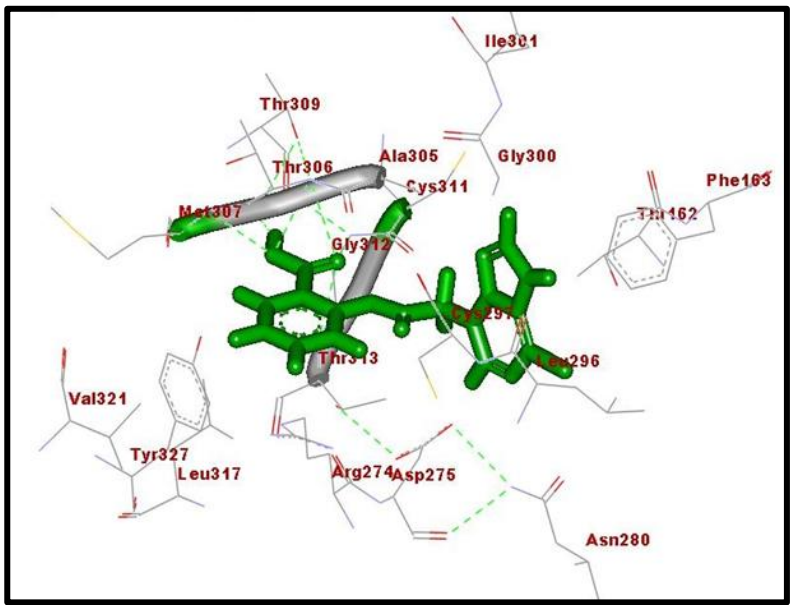


Fig. 17. Molecular drug docking

The above picture represents the de novo drug molecule docked with PKBB protein structure with drug binding amino acids labels. Green colour indicates denovo molecule in Stick model viewed using Discovery Studio Software

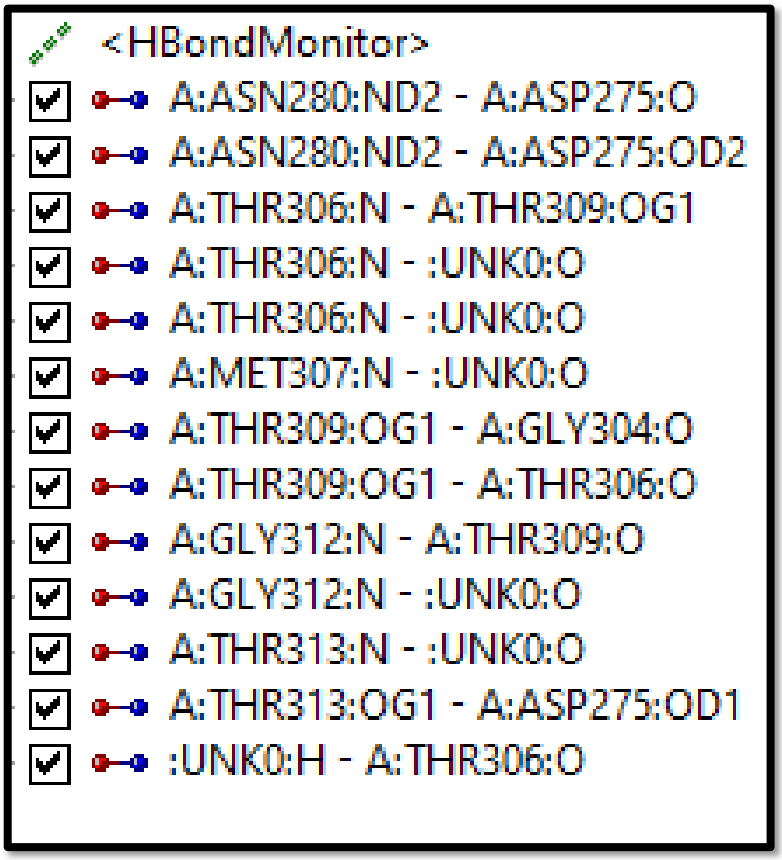


Fig. 18. H-bond interaction (Mercaptopurine+ 2-acetyloxybenzoic acid + PKBB)

The above table shows the H-bond interaction between Mercaptopurine+2- acetyloxybenzoic acid and the endometrial cancer protein, PKBB.

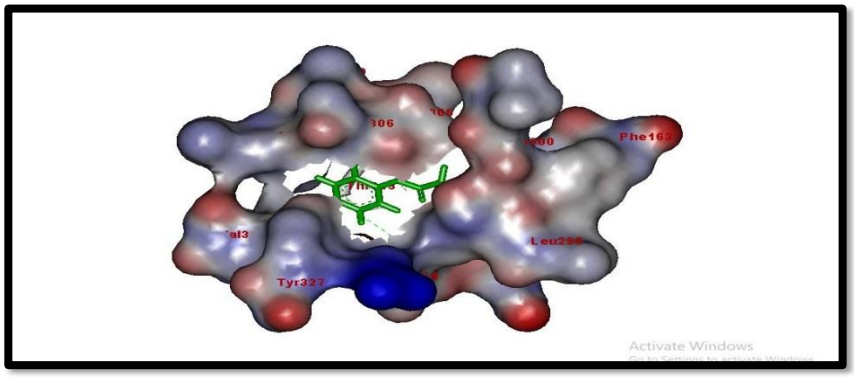


Fig. 19. Molecular drug docking

The above picture represents the de novo drug molecule docked with PKBB protein structure in Van Der Waals model view with drug binding amino acids labels. Green colour indicates De Novo drug in Stick model viewed using Discovery Studio Software

Table 3. Molecular Drug Docking Summary

	Existing Drug (667490)	***De Novo* compound**
Protein target	Mercaptopurine	Mercaptopurine + 2- Acetoxybenzoic acid (*de novo*)
PKBB (Protein Kinase B -Beta)	-186.66	-305.25

The above table represents the molecular drug docking results of the control molecule, Mercaptopurine and the designed molecule docked with PKBB protein. The *de novo* drug value when docked with PKBB is high when compared to the value of the existing molecule interacting with PKBB protein.

The target protein for endometrial cancer in this study is PKBB, or protein kinase B-beta (UniProt: P31751). Its gene sequence is 1446 nt long, while its protein sequence is 481 aa long. It is located on the 19th chromosome. Our first step in the research was to do motif and domain analysis. The amino acid FASTA sequence in PKBB is displayed in Fig. 1 (OMIM ID: 164731). Figs. 1 and 3. Table 1

(PKBB-Protein Kinase B -Beta) One of the three closely related serine/threonine-protein kinases known as the AKT kinase, AKT2, AKT1, and AKT3, regulates a number of biological processes, including angiogenesis, growth, metabolism, and cell survival. A variety of downstream substrates are phosphorylated either serine or threonine to facilitate this process. Kinases of eukaryotic proteins [10] are enzymes that belong to a large family of proteins that includes both tyrosine and serine/threonine protein kinases, which have a shared catalytic core. The catalytic domain of protein kinases contains multiple conserved areas. Two of these regions have been chosen by us to create signature patterns. The first area is a stretch of residues near a lysine residue that is rich in glycine and is situated at the N-terminal end of the catalytic domain. It has been shown that ATP binding implies this. The conserved aspartic acid residue in the second region, which is located in the middle of the catalytic domain, has been demonstrated to be important for the enzyme's catalytic activity. Two signature patterns—one particular to tyrosine kinases and the other to serine/threonine kinases—have been identified for that location. Additionally, we created a profile that spans the whole catalytic domain and is connected to the alignment [11]. Oral contraceptives have been shown to reduce the risk of endometrial cancer by 24% after five years of use, a benefit that has been demonstrated over the past 20 years.

In this research study, SWISS-MODEL was used to convert the amino acid sequence of PKBB into 3D structure. To facilitate docking, a detailed molecular and structural analysis of TSHR was conducted using SWISS-MODEL [12]. A service called SWISS-MODEL is used to automatically compare three-dimensional (3D) protein structures. The SWISS-MODEL server homology

modeling pipeline, which is built on ProMod3, an internal comparative modeling engine based on Open Structure, is used by Waterhouse et al. to calculate models. Ramachandran Plot evaluation of the modelled 3D protein was conducted using ProCheck server [13] in a comprehensive manner. Following modeling, ProCheck server was used to validate the altered protein's 3D structure. The Ramachandran Plot evaluation in Fig. 12 verifies that the simulated protein has no errors (88.2%). Fig. 5.

Discovery studio software, a molecular visualization tool, was used to explore the anticipated structure. The 3D structure of the normal PKBB protein is displayed in Fig. 2 with the use of Discovery studio software, an advanced molecular visualization tool. Using Discovery Studio software, the 3D structure of the mutant PKBB protein is displayed in Fig. 4.

In order to create the innovative drug candidate based on the existing molecule, the possible existing drug candidate was chosen utilizing the NCBI PubChem compound database. Here, we select Mercaptopurine (CID: 667490), a possible culprit for a number of cancers, including endometrial cancer. Our plan is to use Cheminformatics procedures to increase this molecule's efficiency. 2-Acetoxybenzoic acid (CID: 2244) also known as acetylsalicylic acid is a pharmaceutical product that has been used for more than a century in clinical and therapeutic settings. It is arguably the most widely used analgesic sold worldwide: Table 2. Fig. 6.

Mercaptopurine (CID: 667490) is a purine analogue used to treat leukemia, autoimmune diseases, and several types of cancer. It is also useful as an immunosuppressive and anticancer agent. Molinspiration software was used to mix the two molecules and validate them in drug-designing studies. Our goal is to add the antioxidant 2-Acetoxybenzoic acid to the current medication, Mercaptopurine. There are no errors in the created molecule, as indicated by the computation of their molecular properties and the expected bioactivity 7 and 8. It follows the scores for drug likeness. Mercaptopurine coupled with 2-Acetoxybenzoic acid is shown in Fig. 9

3.9 Drug Docking

An innovative and incredibly effective approach for docking two molecules was presented by [14]. Although the algorithm's results for the docking of two protein molecules are displayed here, receptor-drug scenarios can also benefit from its application. We introduced the De Novo drug with PKBB protein and the existing medicine, Mercaptopurine, with PKBB protein in molecular docking investigations. The amino acids that interact with H bonds and have binding affinity scores were found in this investigation. The drug-docking outcome scores are displayed in Table 3. Fig. 10,11,12,13 and 14 displays the 3D structure of H-bond interactions with the corresponding drug-binding amino acid pockets and the PatchDock result scores of the PKBB protein with Mercaptopurine (an existent medication) (His:591,Cys : 589,Lys:602,Pro:590,Cys:621,and Lys:622) . Our study's conclusions are in agreement with those of several earlier docking investigations. [15,16,17]. Comparably, PKBB protein PatchDock result scores with Mercaptopurine + 2-Acetoxybenzoic acid (de novo drug) are displayed in Figs. 15, 16, 17, 18 and 19. Fig. 18 illustrates the three-dimensional structure of H-bond interactions with the corresponding drug-binding amino acid pockets (Gly:31, Met:60, Gly:284,Thr:282, Cys:301, Gln:281,Val:302, and Val:295) Table 3.

The De Novo medication's PatchDock results with the PKBB protein indicate an atomic contact energy value of -305.25. In contrast, Mercaptopurine, the pharmacological compound now in use, has a PKBB protein of -186.66 (Table 3). Thus, it's interesting to note that the de novo drug candidate in the study had a good binding to the PKBB protein. A larger negative number, in theory, denotes a greater affinity for binding between the medication and the target. Here, we have demonstrated that the PKBB protein, which causes endometrial cancer, may be effectively targeted by our therapeutic candidate. In the end, the developed De Novo drug candidate exhibits anti-inflammatory and possible inhibitory effects on cancer cell proliferation. Remarkably, our docking study's results unequivocally demonstrate that the 282 (Rouse M.B et al., 2009) binding areas are the locations of H-bond interactions between the PKBB protein and the proposed de novo medication.

4. CONCLUSION

We draw the conclusion that the newly developed therapeutic candidates would be effective molecules for the treatment of endometrial cancer based on the Insilico results. For the created compounds, we have completed

the pharmacokinetics profiling investigations. All things considered, the drug docking data provide a clear explanation for the possible binding affinities between the PKBB protein and the intended candidates. This chemical would lessen its carcinogenic qualities and boost its inhibitory effect, which would slow the proliferation of cancer cells in endometrial cancer.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

ACKNOWLEDGEMENT

The authors acknowledge the help extended by Dr.Balaji Munivelan, PhD., CEO and Senior Bioinformatician (bioinfobalaji@gmail.com) , ABS Geno-informatics, Chennai, for his contribution towards *Insilico* drug docking studies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021;71:209–249.
2. Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, Zhang C. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990–2019. Gynecol. Oncol. 2021;161:573–580.
3. Moss EL, Teece L, Darko N. Uterine cancer mortality and Black women: Time to act. Lancet Oncol. 2023;24:586–588.
4. Clarke MA, Devesa SS, Hammer A, Wentzensen N. Racial and ethnic differences in hysterectomy-corrected uterine corpus cancer mortality by stage and histologic subtype. JAMA Oncol. 2022;8:895–903.
5. Ryan NAJ, Glaire MA, Blake D, Cabrera-Dandy M, Evans DG, Crosbie EJ. The proportion of endometrial cancers associated with Lynch syndrome: A systematic review of the literature and meta-analysis. Genet. Med. 2019; 21:2167–2180.
6. Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, Deas A, Elliss-Brookes L, Gavin A, Hounsome L, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br. J. Cancer. 2018;118:1130–1141.
7. Fortner RT, Hüsing A, Dossus L, Tjønneland A, Overvad K, Dahm CC, Arveux P, Fournier A, Kvaskoff M, Schulze MB, et al. Theoretical potential for endometrial cancer prevention through primary risk factor modification: Estimates from the EPIC cohort. Int. J. Cancer. 2020;147:1325–1333.
8. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022; 399:1412–1428.
9. Pavithra S, Nithya G, Balaji Munivelan. 3D molecular dynamics and drug docking studies on the gene (ESR1 – Estrogens Receptor 1) involved in breast cancer. Peer Reviewed and Refereed Journal. 2021;10:8(7).
10. Chen XR, Igumenova TI. Regulation of eukaryotic protein kinases by Pin1, a peptidyl-prolyl isomerase. Adv Biol Regul. 2023;87:100938.
    DOI: 10.1016/j.jbior.2022.100938.
    Epub 2022 Nov 30.
    PMID: 36496344;
    PMCID: PMC9992314.
11. Yin Z, Shen D, Zhao Y, Peng H, Liu J, Dou D. Cross-kingdom analyses of transmembrane protein kinases show their functional diversity and distinct origins in protists. Comput Struct Biotechnol J. 2023;21:4070-4078.
    DOI: 10.1016/j.csbj.2023.08.007
12. Waterhouse AM, Studer G, Robin X, Bienert S, Tauriello G, Schwede T, The structure assessment web server: for proteins, complexes and more. Nucleic Acids Res, gkae270 Epub ahead of print; 2024.
    DOI: logo10.1093/nar/gkae270
13. Carlus FH, Sujatha LB, Kumar AG, Loganathan L, Muthusamy K, Carlus SJ. *In*

silico prediction, molecular modeling, and dynamics studies on the targeted next-generation sequencing identified genes underlying congenital heart disease in Down syndrome patients. Ann Pediatr Cardiol. 2023;16(4):266-275.

14. Pinzi L, Rastelli G. Molecular docking: Shifting paradigms in drug discovery. Int J Mol Sci. 2019;20(18):4331.
DOI: 10.3390/ijms20184331
PMID: 31487867;
PMCID: PMC6769923.
15. Zashumo KJ, Mathivanan V, Grace H, Leelavathi D. *In silico* toxicity prediction on novel antiobesity drug using cheminformatics approaches. International Journal of Pharmaceutical Investigation. 2022;12(4).
16. Grace H, Mathivanan V, Zashumo KJ, Leelavathi D. Plant derived compound-luteolin promising role against SARS-CoV-2 Protein; 2022.
17. Zashumo KJ, Leelavathi D, Grace H. Anti-obesity property of indian tulsi plant (*Ocimum sanctum*) using in silico docking techniques. biological forum. An International Journal. 2023;15(2): 09-14.

Peer-review history:
The peer review history for this paper can be accessed here:
https://prh.mbimph.com/review-history/3849