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AN *IN-SILICO* APPROACH FOR DESIGNING POTENTIAL ANTAGONISTIC MOLECULES TARGETING CYCLIN-DEPENDENT KINASE HAVING THERAPEUTIC SIGNIFICANCE IN CANCER

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ABSTRACT: Cancer is a preminent cause of death worldwide after heart disease. Although there are many types of cancer treatments, depending on the type of cancer and its stages, due to their complexity and adverse cytotoxic effects, some novel targets at the molecular level that are cancer-specific have become the area of research for more than a decade. Some targets have been identified, and CDKs are among them. They play a pivotal role in the cell cycle. This has directed to developing of novel Cyclin-Dependent Kinase Inhibitors with a major emphasis on designing compounds that can effectively inhibit the cell cycle progression in cancer by inhibiting the CDKs selectively, such as abemaciclib. In this study, we have generated and evaluated some CDKIs. These compounds were designed to target CDK6 (PDB ID: 5L2S). The bio-affinity values and binding modes of all designed analogs were evaluated and the pharmacokinetic profile (Caco-permeability, efflux, fdp, vdss, bbb parameters) was also examined. The study exhibited significant findings and analogs 10c, 20a and 34b with docking scores -12.11, -14.91, and -12.41 kcal/mol, respectively, were found to be more potent inhibitors of the CDK6 than abemaciclib (docking score -6.54) and also possess good pharmacokinetic profile. These findings proved them a good candidate for future research.

INTRODUCTION: The unconstrained growth of cells characterizes cancer. Different factors may be responsible for cancer *e.g.*, chemical, environmental, mutagenic and viral that leads to an abrasion in the expression of proto-oncogenes, the product of which control normal cell life. The mutation of these genes leads to the formation of oncogenes through a sequential multistep process that results in the development of cancer [1].

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Cancer is a predominant health problem and the second most significant cause of death worldwide after heart disease. The "International Agency for Research on Cancer" (IARC) estimates that there will be approximately 19.3 million new cancer cases and close to 10.0 million cancer-related deaths globally in 2020.

The most commonly diagnosed cancers worldwide were female breast cancer (2.26 million cases), lung (2.21 million cases), and prostate cancers (1.41 million cases) [2]. Although there are a lot of chemotherapeutic agents for the treatment of cancer they have various cytotoxic effects because these drugs target rapidly dividing cancer cells as well as certain normal tissues, which results in other complexities in patients, thereby targeted therapy

have become area of cancer research [3, 4, 5]. The term 'targeted therapy' confers to a new group of anticancer agents contrived to interfere with a distinguished molecular target (generally a protein or enzyme) that is postulated to have a pivotal role in tumor development. The appropriate target can be identified by detailed understanding and analyzing the molecular changes underlying particular kind of cancer [6]. These drugs are expected to have less severe side effects than standard chemotherapeutic agents [7, 8, 9].

CDKs and CDKIs: As the name suggests, the activation of cyclin-dependent kinases requires interaction with another group of proteins known as 'cyclins' [10]. Different complexes of CDKs and their cyclin co-partners are responsible for the timely occurrence of each cell cycle 11, 12 phase. Human cells contain '20 CDKs' and '29 cyclins' [13]. Mitogenic signals and these complexes trigger Cyclin-CDK complexes then phosphorylates the retinoblastoma (RB) protein and promote the cell progression from G1 to S-phase. RB hyper-phosphorylation also activates the E2F family of transcription factors. Endogenous Cyclin-dependent kinase inhibitors (CDKIs) of the 'CIP/KIP' (CDK-interacting protein/Kinase-inhibitory protein) and 'INK4' families produce growth-inhibitory signals and antagonize G1–S progression through checkpoint kinases (CHK1 and CHK2) [14, 15].

In cancer, the cell-cycle machinery is debilitated and various mechanisms can be accountable for this debilitation. In some cancers, specific tumor-harbor exacerbation of genes encrypting particular 'cyclins' and 'CDKs', elevates their levels. In further cases, genes encrypting endogenous CDKIs have been deleted, resulting in unconstrained CDK activity and proliferation of cells. Consequently, CDKs have been considered appealing targets for cancer treatment [16, 17]. Several CDK inhibitors have been developed; some are under clinical investigations [18, 19], and [20]. CDK inhibitors can be ATP-competitive (interacting with CDKs in their catalytic ATP-site) or non-competitive (interacting with CDKs on allosteric sites) and inhibits the phosphorylation of substrates, appropriate for simultaneous blockade of cell-cycle progression and transcription and facilitates the induction of apoptosis [21]. The clinical-trial results of CDK4/6 inhibitors and hormone therapy have demonstrated a remarkable improvement in PFS rates in patients with advanced HR+, HER2-negative breast cancer compared to hormone therapy alone [22, 23]. Based on the encouraging clinical trial results palbociclib, abemaciclib and ribociclib have been approved by USFDA [24, 25, 26].

MATERIALS AND METHODS: CADD can be used in diversified ways in lead discovery processes. The most significant methods are QSAR and structure-based drug design. These approaches show escalating adequacy for lead compounds discovery, especially for their straining and for re-engineering drugs to overcome certain resistance. The structure-based approaches are getting prominent due to the expeditious expansion in structural data and particularly high speed by which structures can be persistent as part of an engrossed drug-discovery endeavor with a well-analyzed target [27, 28]. The present study aims to design CDK6 inhibitors by utilizing a structure-based drug design approach and molecular modeling technique that could offer the potential of simultaneous blockade of cell cycle progression by inhibiting CDKs to target cancer.

Overview of the Process: We have designed the CDKIs using processes ranging from 'graphical visualization' of the ligand in the different binding pockets to calculation and analysis of comparative binding affinities, docking score, and Pharmacokinetic parameters using molecular mechanics in 'Inventus V 1.1' software. Apart from understanding the ligand's bio-active conformation, we have examined the 3D structure of target protein in complex with the ligand and thoroughly studied their various interaction patterns. Subsequently, we modified the ligand to achieve more explicit interaction with the target that could result in superior potency and selectivity.

Target Selection and Assessment: Among different CDKs, CDK6 was selected as a target for the present study, and the X-ray co-crystal structure of human CDK6 and abemaciclib was acquired from RCSB-PDB having PDB ID- 5L2S **Fig. 1**. The structure 5L2S has 1 chain, Resolution 2.27 Å and consists of 307 residues [29]. Subsequently, using the structural information available in RCSB PDB, the 3D structure of the target protein was prepared.

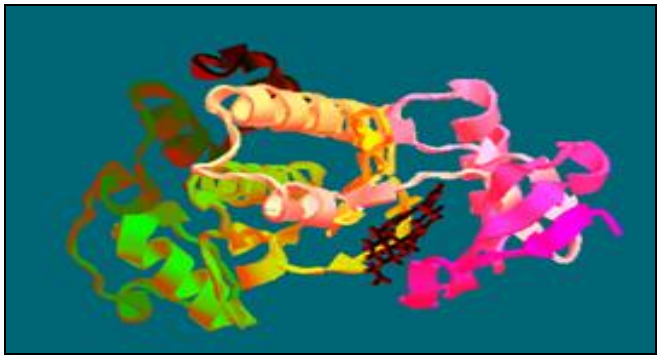

FIG. 1: THE X-RAY CO-CRYSTAL STRUCTURE OF HUMAN CDK6 AND ABEMACICLIB (PDB ID: 5L2S)

Protein Preparation: of Protein structure's *In-silico* processing involves the foremost step *i.e.* energy minimization, by utilizing SD (steepest descent) and CG (conjugate gradient) algorithms to diminish the potential energy of the target. In our target molecule, the initial energy was found to be 6.868E+06 kcal/mol, and the final energy was minimized to -6.175E+03 kcal/mol. Clash optimization as per' Monte Carlo technique' was used to eliminate all the steric clatters from protein structure which may cause anomaly in results during the docking of target ligand and protein or inhibitor molecule. We fixed the number of cycles 25-30 for the clash optimization process.

Selection of Binding Site: The target protein (PDB ID 5L2S) that we have selected for this study was a co-crystallized structure; therefore, we have taken the binding site of abemaciclib as an active site for further process. The active site residues of reference ligand were compared with all bonding cavities, and it was observed that each residue of dynamic site was found in cavity 1. So, cavity 1 was taken as an active binding site. Following were the active site residues within the distance of 5 Å- ALA 7, GLU 8, ILE 9, GLY 10, GLU 11, GLY 12, TYR 14, VAL 17, LYS 19, ALA 31, LYS 33, HIS 71, VAL 72, ASP 73, GLN 74, ASP 75, THR 78, ASP 116, LYS 118, GLN 120, ASN 121, LEU 123, ALA 133, ASP 134 and THR 139.

Molecular Modeling and Docking: In the very first step, the reference molecule (Abemaciclib, CDK4/6 Inhibitor) was docked into the active site of a prepared protein, and its docking score was found to be -6.54 kcal/mol, and then the analogues were designed based on maximizing complementary interactions in the active site of the target protein with the help of the data collected after high throughput screening and SAR information of pyrido [2, 3-*d*] pyrimidin-7-one [30]. Total 70 analogues were designed and all analogues were subjected to docking with the target protein using the Novo-Docker module to carry out the protein-analog interaction patterns in detail [31]. Genetic algorithm parameters were used for docking that involves a conformational search to discover the prime commendatory binding pose of analogue with the active site of the target. The interactions between protein and analogs were then analyzed. Electrostatic and hydrophobic interactions determining the fitness of docked analogues were also studied.

Pharmacokinetic Modeling: Pharmacokinetic simulations were developed retrospectively and used to predict the behavior of designed molecules under specific conditions. Structure-based algorithms were used to predict pharmacokinetic profile, which is extremely important in early drug discovery. All the pharmacokinetic parameters were calculated by correlating the structure of compounds to a dataset for a particular pharmacokinetic endpoint [32]. In this study, all the pharmacokinetic properties were calculated by Pharmopredicta module, including the Caco-permeability, efflux, fdp, vdss, bbb parameters [32].

RESULTS AND DISCUSSION: We have analyzed all the designed analogues and the influence of different groups and ring substitution in different positions on the inhibitor activity. Docking was performed to study the protein-ligand interactions in different patterns using the NovoDocker module of Inventus v 1.1 software **Table 1**, **Fig. 2**. Subsequently, we have examined the structural ADME profile of the entiremap out analogues by employing Pharmo Predicta module **Table 4, 5** & **Fig. 3**. The key highlights of this module are described below:

TABLE 1: ANALOGUES STRUCTURE WITH BIOAFF VALUES

Analogue	Structure	BioAff (kcal/mol)
7d	F[C@@H]1N(CC2=CC(NC3=NC=NC4=C3NC=N4)=NC=C2)C[C@H](NC1)C5=NCC=C5	-11.99
8a	FC1=CC(C2=NC(NC3=NC=CC(CN4CCNCC4)=C3)=NC=C2F)=CC(C5=NCC=N5)=C1	-11.89
10c	CC1=NC(N)=NC(N)=C1NC2=NC=C(C=C2)N3[C@@H](CNCC3)F	-12.11
12a	C12=NC(NC3=NC=CC(CN4CCNCC4)=C3)=NC=C1N=CN2C5CCCC5	-11.52
18b	FC1=CC2=CN=C(N=C2N1C3CCCC3)NC4=NC=C(C=C4)CN5CCNCC5	-11.44
19c	FC1=CC2=CN=C(NC3=NC=C(N4CCNCC4)C=C3)N=C2N1C5CCCC5	-11.17
20a	FC1=C(C2=C(N=CS2)N(C)C)N=C(NC3=NC=C(C=C3)CN4CCNCC4)N=C1	-14.91
34b	FC(NC1=NC=N2)=NC1=C2NC3=NC=CC(CN4CCN(CC4)C5CCCC5)=C3	-12.41
36b	F[C@@H]1CNCCN1C2=CC=C(NC3=NC=NC4=C3NC=N4)N=C2	-11.92
50c	F[C@@H]1C[C@@H](C2=CN=C(N=C2C1)NC3=NC=CC(N4CCNC4)=C3)OC(C)=O	-11.91

ADME (Structure Based)

Parameters	Range
Human Absorption, FDp (%) binned Results are classified as	
Low	0-33% absorbed
Medium	33-64% absorbed
High	67-100% absorbed
Caco-2 Permeability P_{eff}at pH 7.4(cm/s)	A→ B or apical to basolateral
Caco-2 Permeability P_{eff}at pH 7.4 (cm/s)	B→ A or basolateral to apical
Efflux at pH 7.4	0 if ≤ 5.3,1 if >5.3
Blood brain barrier permeability	0 if no penetration,1 if penetration
Protein binding	0 if ≤ 85%, 1 if > 85%
Volume of Distribution at steady state (liters)	Low; if < 0, High; if > 0

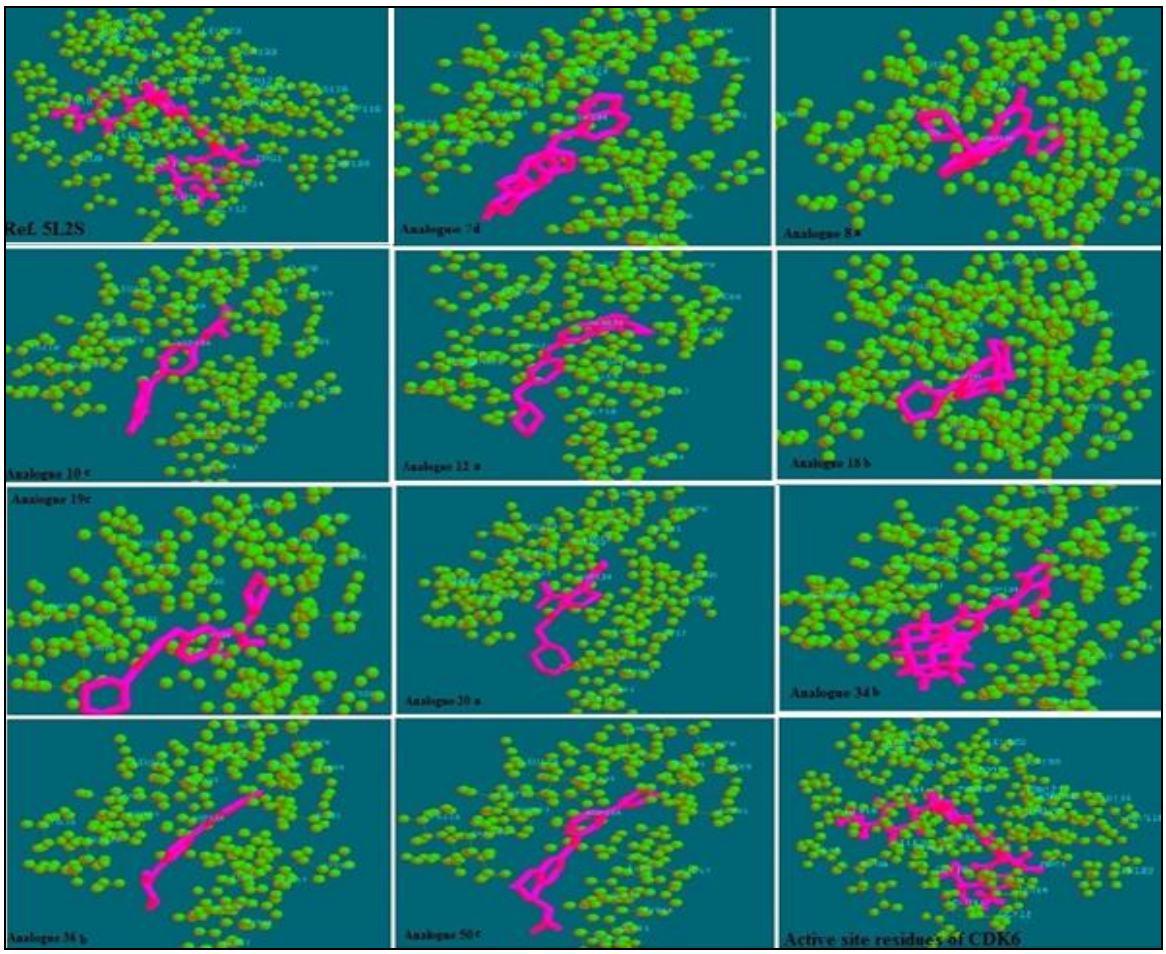

FIG. 2: BINDING INTERACTIONS OF REFERENCE DRUG AND DESIGNED ANALOGUES

A huge proportion of the designed analogues were eliminated, someon the basis of Lipinski rule of 5 and others by contemplating their physicochemical profile, binding affinities/docking score and ADME profile **Table 2**.

Compounds 7, 8, 10, 12, 18, 19, 20, 34, 36 and 50 have been found as potent analogues with good pharmacokinetic properties and high docking scores.

Where the docking score of the reference drug abemaciclib was -6.54, the docking scores of the top leads were found as follows:

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF ANALOGUES

Analogues	HBD	HBA	M.W.	LogP
7d	3	9	393.42	2.84
8a	2	8	448.47	4.22
10c	4	8	318.35	1.93
12a	2	8	378.47	3.62
18b	2	7	395.48	4.37
19c	2	7	381.45	4.37
20a	2	8	414.50	3.49
34b	2	8	396.46	3.96
36b	3	8	314.32	2.18
50c	2	8	372.40	2.73

TABLE 3: DOCKING SCORE OF ANALOGUES AND DIFFERENT RESIDUES INVOLVED IN DRUG-RECEPTOR INTERACTION

Name	Docking score (kcal / mol)	Residues involved in Electrostatic interactions	Residues involved in Hydrophobic interactions
Reference	-6.54	ILE9, VAL17, TYR14, LYS33, LEU123, GLN120, GLY10, GLU11, ASP75, LYS118, GLN120, ASP 134, VAL 72, ASP 73	TYR 14, VAL 17, GLN 12, ASP 134, ILU 9, GLN 74
Analog7d	–11.99	ILE 9, GLY 10, TYR 14, VAL 17, ALA 31, HIS 71, VAL 72, ASN 121, LEU 123	ILE 9, TYR 14, VAL 17, ALA 31, ASP 75, GLN 120, LEU 123
Analog8a	-11.89	ILE 9, VAL 17, LYS 19, ALA 31, VAL 56, PHE 69, HIS 71, VAL 72, ASP 73, GLN 74, ASP 75, LYS 82, GLN 120, ASN 121, LEU 123, ALA 133	PHE 69, HIS 71, VAL 72, ASP 73, GLN 74, ASP 75
Analog10c	-12.11	ILE 9, GLY 10, TYR 14, VAL 17, ALA 31, VAL 56, PHE 69, GLU 70, HIS 71, VAL 72, LYS 118, GLN 120, ASN 121, LEU 123, ALA 133, ASP 134	ILE 9, GLU 70, GLN 120
Analog12a	-11.52	ILE 9, GLY 10, GLU 11, TYR 14, VAL 17, ALA 31, VAL 56, GLU 70, HIS 71, VAL 72, LYS 118, GLN 120, ASN 121, LEU 123, ALA 133, ASP 134	ILE 9, GLU 11, TYR 14, ALA 31, GLU 70,HIS 71, VAL 72, GLN 120, LEU 123
Analog18b	–11.44	ILE 9, VAL 17, LYS 33, LEU 44, PHE 69, HIS 71, VAL 72, ASP 73, GLN 74, ASP 75, THR 78, ASN 121, LEU 123, ALA 133, ASP 134 and PHE 135	ILE 9, HIS 71, VAL 72, ASP 73, ASP 75, LEU 123, ALA 133, ASP 134 and PHE 135.
Analog19c	–11.17	ILE 9, VAL 17, ALA 31, VAL 56, GLU 70, VAL 72, ASP 75, THR 78, GLN 120, ASN 121, LEU 123, ALA 133, ASP 134	ILE 9, VAL 17, ASP 75, GLN 120, LEU 123
Analog20a	–14.91	ILE 9, GLY 10, GLU 11, TYR 14, VAL 17, HIS 71, VAL 72, ASP 73, GLN 74, ASP 75, LYS 118, ASN 121, LEU 123	TYR 14, HIS 71, VAL 72, GLN 74, ASP 75, GLN 120, LEU 123.
Analog34b	–12.41	Residues ILE 9, GLY 10, TYR 14, VAL 17, LYS 33, VAL 56, PHE 69, ASP 73, GLN 74, ASP 75, THR 78, LYS 82, GLN 120, LEU 123, ALA 133, ASP 134	ILE 9, TYR 14, LYS 33, VAL 56,ASP 75, GLN 120, ALA 133
Analog36b	–11.92	ILE 9, GLY 10, GLU 11, VAL 17, ALA 31, VAL 56, PHE 69, GLU 70, HIS 71, VAL 72, LYS 118, GLN 120, ASN 121, LEU 123, ALA 133, ASP 134	TYR 14, VAL 56,PHE 69,GLU 70, LYS 118, GLN 120, ALA 133, ASP 134
Analog50c	–11.93	ILE 9, GLY 10, GLU 11, TYR 14, VAL 17, VAL 56, PHE 69, GLU 70, GLN 120, ASN 121, LEU 123, ALA 133	ILE 9, GLY 10, GLU 11,TYR 14, PHE 69,GLU 70, GLN 120, LEU 123

TABLE 4: CACO-PERMEABILITY AND EFFLUX PARAMETERS OF DESIGNED COMPOUNDS

Compound	caco74ab	caco74ab-Confidence	caco74ba	caco74ba- Conf.	Efflux	efflux-Conf.
Reference	4.14E-06	Low	4.14E-06	Medium	0	High
Analog 7d	5.76E-07	Low	1.00E-05	High	1	High
Analog 8a	9.08E-07	Medium	8.29E-06	High	1	High
Analog 10c	5.30E-07	Low	2.53E-06	Medium	1	Medium
Analog 12a	2.82E-06	Medium	8.45E-06	High	1	High
Analog 18b	5.92E-06	Low	7.38E-06	High	1	High
Analog 19c	6.10E-06	Low	8.46E-06	High	1	High
Analog 20a	2.01E-06	Medium	8.07E-06	High	1	High
Analog 34b	1.83E-06	Medium	3.73E-06	High	1	High
Analog 36b	1.13E-06	Low	1.41E-05	High	1	High
Analog 50c	1.78E-06	High	7.83E-06	High	1	High

TABLE 5: BBB, FDP, VDSS PARAMETERS OF DESIGNED COMPOUNDS

Compound ID	BBB & BBB-Confidence	Fdp(%) & fdp-Confidence	Protein binding (%) & probind-Confidence	Vdss (L) & vdss-Confidence
Reference	0, High	High, Low	1, High	1000, High
Analog7d	0, Medium	High, Low	1, Medium	100, High
Analog8a	0, High	High, Low	1, High	100, High
Analog10c	0, High	High, Medium	1, High	100, High
Analog12a	0, Medium	High, Low	1, High	100, High
Analog18b	0, High	High, Medium	1, High	1000, High
Analog19c	0, High	High, Low	1, High	1000, High
Analog20a	0, Medium	Medium, Medium	1, High	100, High
Analog34b	0, Medium	High, Low	1, High	100, High
Analog36b	0, Medium	High, Medium	0, High	100, High
Analog50c	0, High	High, Medium	0, High	10, High

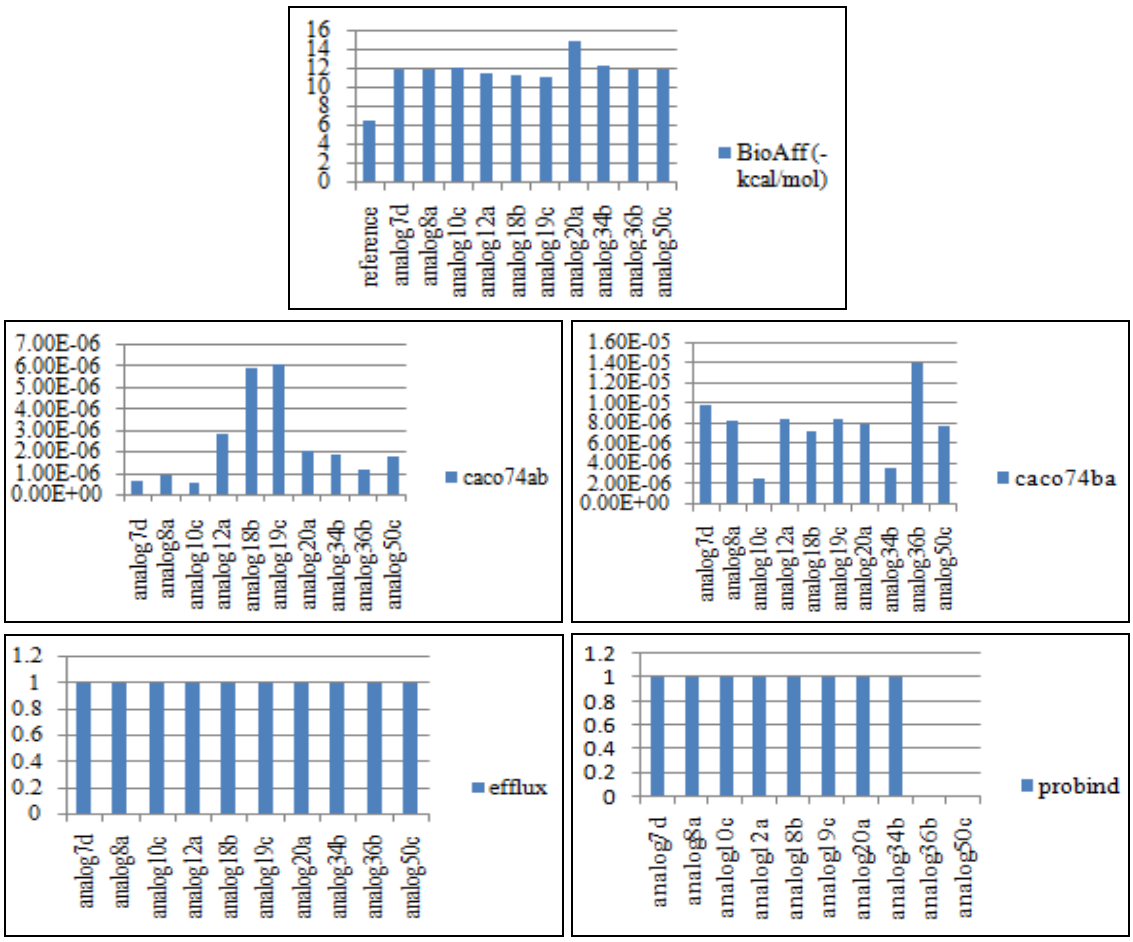

FIG. 3: GRAPHICAL ILLUSTRATION OF VARIOUS PARAMETERS OF LEAD COMPOUNDS

CONCLUSION: Some novel derivatives of N-[5-[(4-ethylpiperazin-1-yl) methyl] pyridin-2-yl]-5-fluoro – 4 - (7 – fluoro – 2 – methyl – 3 – propan - 2-ylbenzimidazol-5-yl) pyrimidin-2-amine and some purine derivatives were designed by contemplating SAR of reference drug and HitsGen data produced by Inventus v 1.1. Subsequently, molecular docking was performed to predict CDK inhibitory activity of designed analogues. The binding interaction patterns of the projected ligand molecules with target *i.e.*, CDK6 were analyzed. The ensuing data from in-silico study explained that all the leads had significantly higher affinity against the target than abemaciclib.

Among these analogues, the compounds having high bio-affinity values were 7d, 8a, 10c, 12a, 18b, 19c, 20a, 34b, 36b and 50c. Three analogues 20a, 34b, and 10c were proved to be most significant leads of this series with highest binding affinities *i.e.* -14.91, -12.41 and -12.11 kcal/mol. Different substitutions on the pyrimidine ring of the abemaciclib were found to have varied electrostatic and hydrophobic interactions with target molecule. In analogue 20a with highest binding energy, the pyrimidine ring was substituted with di-methyl thiazole-4-amine ring at 6-position, which causes a considerable difference in the ligand orientation in the cavity and increases bio-affinity value. The second most potent lead was 34b, in which the pyrimidine ring was replaced by purine ring and it suggest that purine analogues can also be developed as better as CDK inhibitors.

The docking studies revealed that all compounds occupied the same binding pocket in the active site and after analyzing the binding pattern of compounds, we observed that most of them exhibited close binding interaction with hydrophobic residues ILE 9, TYR 14, GLU 70, VAL 72, ASP 75, GLN 120, LEU 123 and electrostatic residues ILE 9, GLY 10, TYR 14, VAL 17, ALA 31, VAL 56, PHE 69, HIS 71, VAL 72, ASP 75, GLN 120, ASN 121, LEU 123, ALA 133 and ASP 134. To study the structure-based pharmacokinetic profile, we have found most top lead properties similar to the reference. The results above indicate that we can speed up the development of targeted therapy for cancer by using molecular mechanics and *in-silico* drug design methods.

Further, the analogues 20a, 34b and 10c have been found as the most significant in the present study and may produce superior outcomes than currently approved drugs in the laboratory. Consequently, these compounds could be considered as leads for prospects to produce more effective anticancer agents.

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REFERENCES:

1. Lamke TL and Williams DA: Foye's principles of medicinal chemistry. Lippincott Williams & Wilkins. 6th Edition 2008; 1147.
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Pineros M and Znaor A Bray F: Cancer statistics for the year 2020: An overview. International Journal of Cancer. 2021; DOI:10.1002/ijc.33588
3. Smith CE and Prasad V: Targeted Cancer Therapies. American Family Physician 2021; 103(3): 155-63.
4. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies
5. Koduru S, Sowmyalakshmi S, Kumar R, Gomathinayagam R. Rohr J and Damodaran C: Identification of a potent herbal molecule for the treatment of breast cancer. BMC Cancer 2009; 9(1): 41; DOI: 10.1186/1471-2407-9-41
6. Sawyers C: Targeted cancer therapy. Nature. 2004 Nov 18.432(7015):294-7; DOI:10.1038/nature03095
7. Targeted therapy as precision medicine, revised jan2021,
8. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/what-is.html
9. https://www.cancer.org/acs/groups/cid/documents/webcontent/003024-pdf.pdf
10. Chatterjee A, Mishra VK, Saha S and Swarnakar S: An Insight into Targeted Therapy for Ovarian Cancer, In Handbook of Oxidative Stress in Cancer: Therapeutic Aspects 2022; 1-22.
11. Lukasik P, Zaluski M and Gutowska I: Cyclin-Dependent Kinases (CDK) and Their Role in Diseases Development–Review. International Journal of Molecular Sciences 2021; 22(6): 2935; DOI:10.3390/ijms22062935
12. Malumbres M and Barbacid M: Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer 2009; 9(3): 153-66; DOI:10.1038/nrc2602
13. Anshabo AT, Milne R, Wang S and Albrecht H: CDK9: A comprehensive review of its biology and its role as a

potential target for anti-cancer agents. Frontiers in Oncology 2021; 11: 1573; DOI:10.3389/fonc.2021.678559
14. Atalay VE and Savas B: Development of potential inhibitors of cell division protein kinase 2 by ligand based drug design. Main Group Chemistry 2021; 1-0. DOI: 10.3233/MGC-210013
15. Otto T and Sicinski P: Cell cycle proteins as promising targets in cancer therapy. Therapy 2017; 156: 157. DOI:10.1038/nrc.2016.138
16. Julve M, Clark JJ and Lythgoe MP: Advances in cyclin-dependent kinase inhibitors for the treatment of melanoma. Expert Opinion on Pharmacotherapy 2021; 22(3): 351-61. DOI:10.1080/14656566.2020.1828348
17. Manohar SM and Joshi KS: Promising Anticancer Activity of Multitarget Cyclin Dependent Kinase Inhibitors against Human Colorectal Carcinoma Cells. Current Molecular Pharmacology 2022; DOI:10.2174/1874467215666220124125809
18. Zhang M, Zhang L, Hei R, Li X, Cai H, Wu X, Zheng Q and Cai C: CDK inhibitors in cancer therapy, an overview of recent development. American Journal of Cancer Research 2021; 11(5): 1913.
19. Kohlmeyer JL: RABL6A Signaling as an Oncogenic Driver and Therapeutic Target in Malignant Peripheral Nerve Sheath Tumors (MPNST).2021. (Doctoral dissertation, The University of Iowa).
20. Garrido-Castro AC and Goel S: CDK4/6 Inhibition in Breast Cancer: Mechanisms of Response and Treatment Failure. Current Breast Cancer Reports 2017; 9(1): 26-33; DOI:10.1007/s12609-017-0232-0
21. Shao H, Foley DW, Huang S, Abbas AY, Lam F and Gershkovich P: Structure-based design of highly selective 2, 4, 5-trisubstituted pyrimidine CDK9 inhibitors as anti-cancer agents. European Journal of Medicinal Chemistry. 2021; 214: 113244. DOI:10.1016/j.ejmech.2021.113244
22. Liu Y, Fu L and Wu J: Transcriptional cyclin-dependent kinases: Potential drug targets in cancer therapy. European Journal of Medicinal Chemistry 2021; 114056; DOI:10.1016/j.ejmech.2021.114056
23. Kelland LR: Flavopiridol, the first cyclin-dependent kinase inhibitor to enter the clinic: current status. Expert Opinion on Investigational Drugs 2000; 9(12): 2903-11; DOI:10.1517/13543784.9.12.2903
24. Andrahennadi S and Sami A: Current landscape of targeted therapy in hormone receptor-positive and HER2-negative breast cancer. Current Oncology 2021; 28(3): 1803-22; DOI:10.3390/curroncol28030168
25. Palbociclib accelerated approval, 2017, https://www.fda.gov/drugs/resources-information-approved-drugs/palbociclib-ibrance#:~:text=FDA%20granted%20palbociclib%20regular%20approval,disease%20progression%20following%20endocrine%20therapy.
26. https://www.drugs.com/history/verzenio.html
27. Ribociclib Approved for HR+/HER2- Metastatic Breast Cancer; http://journals.lww.com/oncology-times/Fulltext/2017/04250/Ribociclib_Approved_for_HR__HER2__Metastatic.27.aspx
28. Marrone TJ, Briggs JM and McCammon JA: Structure-based drug design: computational advances. Annual Review of Pharmacology and Toxicology 1997; 37(1): 71-90. DOI:10.1146/annurev.pharmtox.37.1.71
29. Shaker B, Ahmad S, Lee J, Jung C and Na D: *In-silico* methods and tools for drug discovery. Computers in Biology and Medicine 2021; 137: 104851; DOI:10.1016/j.compbiomed.2021.104851
30. Lee NV, Hu W and Xu M: Spectrum and Degree of CDK Drug Interactions Predicts Clinical Performance Mol Cancer Ther 2016; 15: 2273-2281; DOI:10.1158/1535-7163.MCT-16-0300.
31. Vander Wel SN, Harvey PJ, McNamara DJ and Repine JT: Pyrido [2, 3-d] pyrimidin-7-ones as specific inhibitors of cyclin-dependent kinase 4. Journal of Medicinal Chemistry 2005; 48(7): 2371-87; DOI:10.1021/jm049355+
32. Gupta A, Gandhimathi P and Sharma B: DOCK: An all Atom Energy Based Monte Carlo Docking Protocol for Protein-Ligand Complexes. Protein & Peptide Letters 2007; 14(7): 632-646; DOI:10.2174/092986607781483831
33. Grass GM and Sinko PJ: Physiologically-based pharmacokinetic simulation modelling. Advanced Drug Delivery Reviews 2002; 54(3): 433-51; DOI:10.2165/00137696-200301020-00005

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