Comparative Insilicoanalysis of Drug Likeness Score, Bioavailability, Molecular Docking Score and Toxicity Prediction of Anti-Malarial Drug and Its Derivatives

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Abstract

Malaria is depraving the socio-economic condition of mankind and, therefore constant needs for the discovery of novel drugs are required. The generation of a high rate efficacy of malarial antagonists are being created by chemical library. High yielding information have been gathered from databases which has aimed towards facilitating novel molecules to be explored by substituting functional groups on the basis of electron accepting and withdrawal groups, as well as set of algorithms being used for defining the electron density and other descriptors of the molecular structure. The new derivate of A1T drug which has been modified by replacing H- group with $-NH_3^+$ group which is electron withdrawal group with inductive effects and atoms with no lone pair electrons but has a partial positive charge fulfilling Lipinski's rule and showing good drug likeness score with log P below 5 therefore easily permeable across cell membrane, TPSA below 160 Å, *n* violations =1 which confirms that the new derivate easily binds to receptor, only exception is molecular mass >500. Moreover, it has also showed good bioactivity score with moderately activeness as the value is less than 0 and when docked with achiral potent inhibitors of plasmepsin showing intermolecular hydrophobic interactions giving moldock score -161.9 kcal/moland least environmental toxicity with -0.08 from which has improvised potency, selectivity and pharmacokinetic properties comparatively better than the pro drug A1T.

KEYWORDS: electron density, logP, blood-brain permeability, pharmacokinetic properties.

Introduction

The word "malaria" comes from the Italian "mal'aria" for "bad airs." It was not until the 1880s and 1890s that Alphonse Laveran, Ronald Ross, Battista Grassi, and others were able to identify the malaria parasite and link the transmission of malaria to mosquitoes. Although the understanding of the mosquito cycle led to a number of new approaches invector control in the early 20th century, malaria prophylaxis and therapy continued to draw on earlier remedies. Indeed, what is remarkable about malarial fevers is that two herbal treatments, cinchona bark and qinghao, were used to treat malaria effectively for hundreds of years prior to the under-standing of the mosquito cycle.

Today both quinine (derived from the cinchona bark) and artemisinin (from qinghao) remain of prime importance in the control of malaria. The practice of Western

medicine changed dramatically during the 19th and 20th centuries, as herbal remedies were gradually replaced by pure chemical compounds and, later, synthetic drugs. So, the treatment of malaria undergoes important scientific developments. Malaria was among the first diseases to be treated by pure chemical compound-quinine isolated from the cinchona bark in 1820. It was, sub-sequently, the first disease to be treated by a synthetic compound-methylene blue. In addition, malaria parasites were among the first pathogenic microbes to out-smart medical intervention and become drug resistant. Malaria was one of the best-studied diseases in Western medicine until the middle of the 20th century.

Until that time, malaria was still endemic in North America and Europe. It also had great importance because it represented an obstacle to the expansion of European nations into the tropical world. It also played an important role in the major wars of both the 19th and 20th centuries. The situation has changed, and, until recently, interest in malaria in Western nations has waned even though the disease at a global scale has not. The aim of this work is to provide an overview of antimalarial drug resistance with a particular emphasis on the pharmacokinetic features of the drug and its analogues in the reduction of the burden of malaria.

The main target to reduce the heinous effects of the fatal disease on behalf of predicting the toxicity, solubility of the drugs and its analogues, which have given rise to measure the burden of drug resistance and predicting the impact of strategies . It has been aimed to demonstrate how a bioeconomic model might be developed and deployed to address these issues and to clarify policy options. Emanation of new molecules can be treated with novel biochemical targets which has been resulted from molecular modeling and further validated by the path of molecular dynamics, so as to improve the drug efficacy and eradicating effects of malaria parasite. Though, streamline generation of chemically diverse and effective drugs being used still, there has been a quick resistance in the target sites. Artemisinin along with its derivatives have been used for treating the patients, but their declined affects have been shown in the area where malaria is endemic, for e.g. Thai-Cambodian border. Therefore, amalgamating the studies of Genomics along with the implementation of structure based drug designing hold a breakthrough towards eliminating the infectious disease.

Fatal effects of parasite can be reduced by employing in silico methods where new novel molecules can be designed and generated by chemical library and virtually screening of the molecules to the targets may give an assumption of the best docking result corresponding toits lowest energy value.

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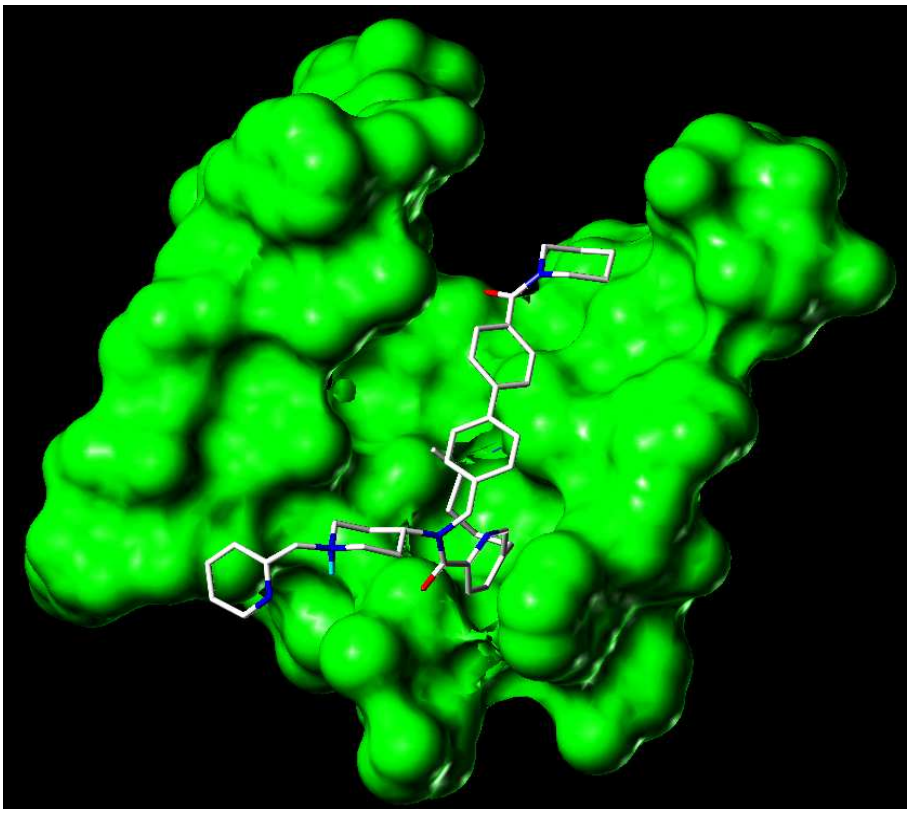


Figure 1: Molecular docking of A1T against Plasmepsinsreceptor binding on its active site.

Methodology

2.1. Compound library selection

Two potential drugs (A1T and A2T) with their pharmacokinetics and pharmacodynamics profile were chosen as the leads of their respective classes with their antagonistic affect to the receptors found suitable to create a library of antagonists targeting achiral, potent inhibitors of Plasmepsinsreceptor. Chemical and structure modification in the leads has been carried out by substituting with electron withdrawal and electron accepting functional groups, which are further, filtered utilising Lipinski's Rule and validating the drug likeness score.

2.2. Molecular modelling of achiral, potent inhibitors of Plasmepsins receptors.

After retrieving sequence of achiral, potent inhibitors of Plasmepsins receptorfrom uniprot**(P35348)**, **BLASThas resulted in 36% identityand core conserved similarity 71 % with similar template ofchain A beta2 adreno receptor (PDB ID 2IGX A) and (PDB ID 2IGY A) havingsequence length of 365 in Homo sapiens from Protein DatabaseBank (PDB).**Protein modelling has been performed using Swiss Model server.Structural validation of the modeled 3D Plasmepsinsreceptor was assessed using most popular structurevalidation tool Procheckand Ramchandranplot.

2.3. Antagonists binding site identification and molecular docking parameters

Molecular docking program Molegro Virtual Docker (MVD)based on PLP score and PLANTS Score provided a flexible plat form for docking of the compound library of 15 designedcandidates. GRID resolution was set to 0.30 Å . Antagonists wereevaluated on the basis of the internal ES (Internal electrostaticInteraction), internal hydrogen bond interactions andsp2esp2 torsions. Thecentre of binding site was set on theCoordinates values X ¼ 41.71, Y ¼ -3.04, and Z ¼ -14.36.

Lipinski's Rule

Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997.

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME")

Results

Physiochemical properties

The physicochemical properties as melting point, molecular formula of the compounds, attached functional group (R), SMILES of the compounds (1a-1p) are summarized in Table 1, moreover, compound code has been given to every single compound, according to which chemical structure of each and every compounds have been described in figure 1.

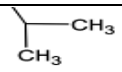
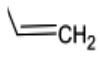
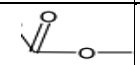
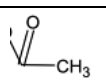
Drug likeness calculation on the basis of Lipinski rule of five and bioactivity score

The drug likeness score was calculated by considering milogP (partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds, volume. The drug likeness score and the calculated value of various parameters of the isolated compounds (1-17) are in Table 2.

The bioactivity scores of the isolated compounds (1a-1p) are compared with standard drug on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor in Table 3. Calculated drug likeness of each compound and compared with specific activity of each compound and results were compared with standard drug. In case of activeness of organic compound, probability of bioactivity has to be (> 0), for moderate activeness it has to be (-5.0-0.0) and inactive after (< -5.0).

Figure 1: showing a1t drug (i.e. 1a in table1) through molinspiration, predicting properties like miLogP, TPSA, n atoms, MW and etc..

Table 1: Compound code, side chain, Molecular formula and m.p. of drugs and its analogues.

Compound code	R	m.p.	Molecular formula	SMILE
1a	-CH_3	117.4	$C_{42}H_{50}N_4O_2$	CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1b		138	$C_{47}H_{52}N_4O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c7ccc(CCCCc6ccccc6)cc7
1c		119	$C_{42}H_{47}F_3N_4O_2$	FC(F)(F)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1d		112	$C_{43}H_{52}N_4O_2$	CCCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1e		111.7	$C_{43}H_{50}N_4O_2$	C=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1f		95.9	$C_{43}H_{50}N_4O_2$	C=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1g		121	$C_{41}H_{47}ClN_4O_2$	ClCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1h		144	$C_{42}H_{47}N_5O_2$	N#CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1i		201	$C_{42}H_{48}N_4O_3$	O=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1j		130.9	$C_{43}H_{50}N_4O_4$	O=C(OC)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1k		118.4	$C_{43}H_{50}N_4O_3$	CC(=O)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1l		178	$C_{41}H_{47}FN_4O_2$	FCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1m		159.8	$C_{41}H_{49}N_5O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCCN)cc6

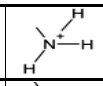
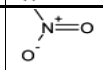
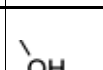
1n		159.8	$C_{41}H_{50}N_5O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCC[NH3+])cc6
1o		142.8	$C_{41}H_{47}N_5O_4$	O=N(=O)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1p		126	$C_{41}H_{47}N_4O_3$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCCO)cc6

Table 2: Drug likeness score for compound

Compound code	mi log P	TPSA	nAtoms	M.W.	nOH	nOHNH	nViolation	nrot b	Volume
1a	6.99	56.74	48	642	6	0	2	12	634
1b	7.64	56.74	53	704.9	6	0	2	13	689
1c	7.01	56.74	51	696.8	6	0	2	13	648.9
1d	7.5	56.74	49	656.9	6	0	2	13	650.9
1e	7.47	56.74	50	670.9	6	0	2	13	667.5
1f	6.97	56.74	49	654.8	6	0	3	13	645.3
1g	6.194	56.74	48	663	6	0	2	12	631
1h	5.28	80.54	49	656.8	7	0	2	12	634
1i	5.9	73.8	49	656.8	7	0	2	13	636.5
1j	5.6	83.05	51	686	8	0	2	14	662
1k	5.63	73.8	50	670.8	7	0	2	13	653
1l	5.8	56	48	646.8	6	0	2	12	622.5
1m	4.3	82.7	48	643.8	7	2	1	12	628
1n	2.2	84.3	48	644.8	7	3	1	12	629.69
1o	5.37	102.5	50	673.8	9	0	2	13	640.9
1p	4.95	76.97	48	644	7	1	1	12	625.6

Table 3: Bioactivity Score of the compound

Comp. code	GPCR Ligand	Nuclear Reactor Ligand	Protease Inhibitor	Enzyme Inhibitor
1a	-0.22	-0.85	-0.07	-0.61
1b	-0.88	-1.72	-0.55	-1.36
1c	-0.56	-1.28	- 0.28	-1.00
1d	-0.33	-1.00	-0.14	-0.74
1e	-0.45	-1.15	-0.19	-0.88
1f	-0.34	-0.97	-0.15	-0.73
1g	-0.30	-0.91	-0.13	-0.64
1h	-0.39	-1.09	-0.15	-0.77
1i	-0.30	-0.98	-0.05	-0.67
1j	-0.59	-1.33	-0.32	-1.03
1k	-0.50	-1.15	-0.26	-0.27
1l	-0.08	-0.70	0.06	-0.57
1m	-0.17	-0.87	-0.02	-0.56
1n	**-0.17**	**-0.82**	**-0.04**	**-0.58**
1o	-0.53	-1.21	-0.28	-0.86
1p	-0.21	-0.82	-0.04	-0.58

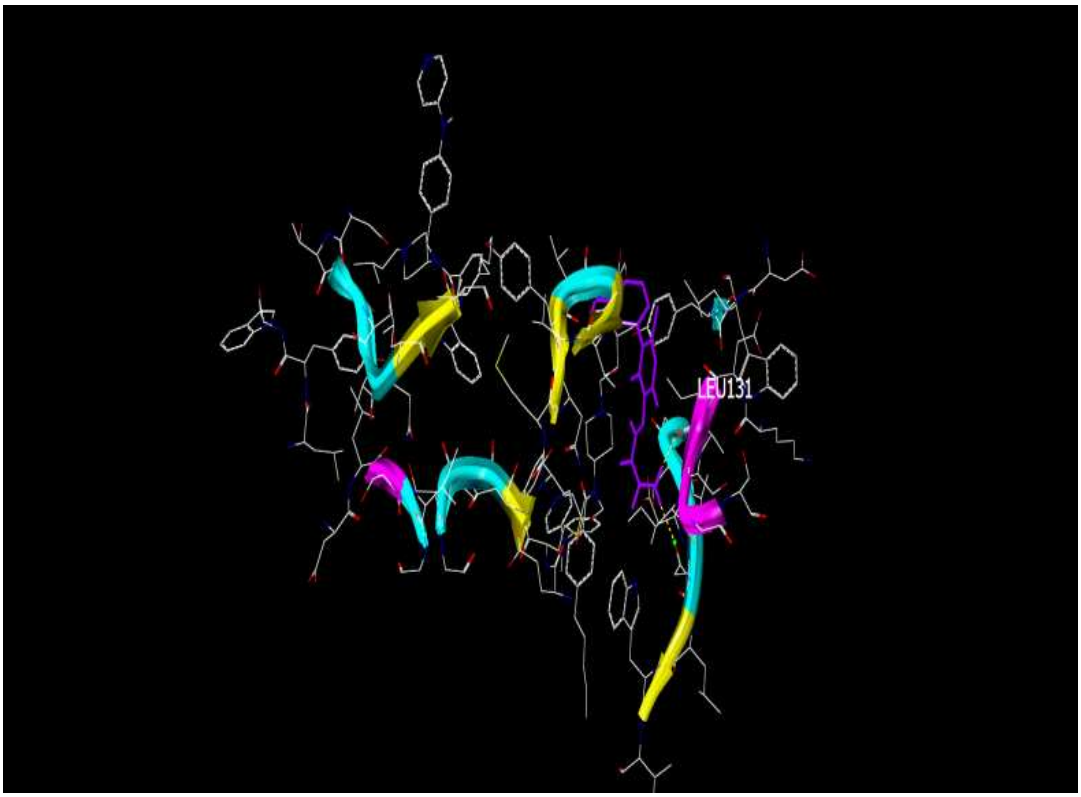


Figure 2.1: Docking interaction of A1T drug targeting against Plasmepsins receptor binding at LEU 131.

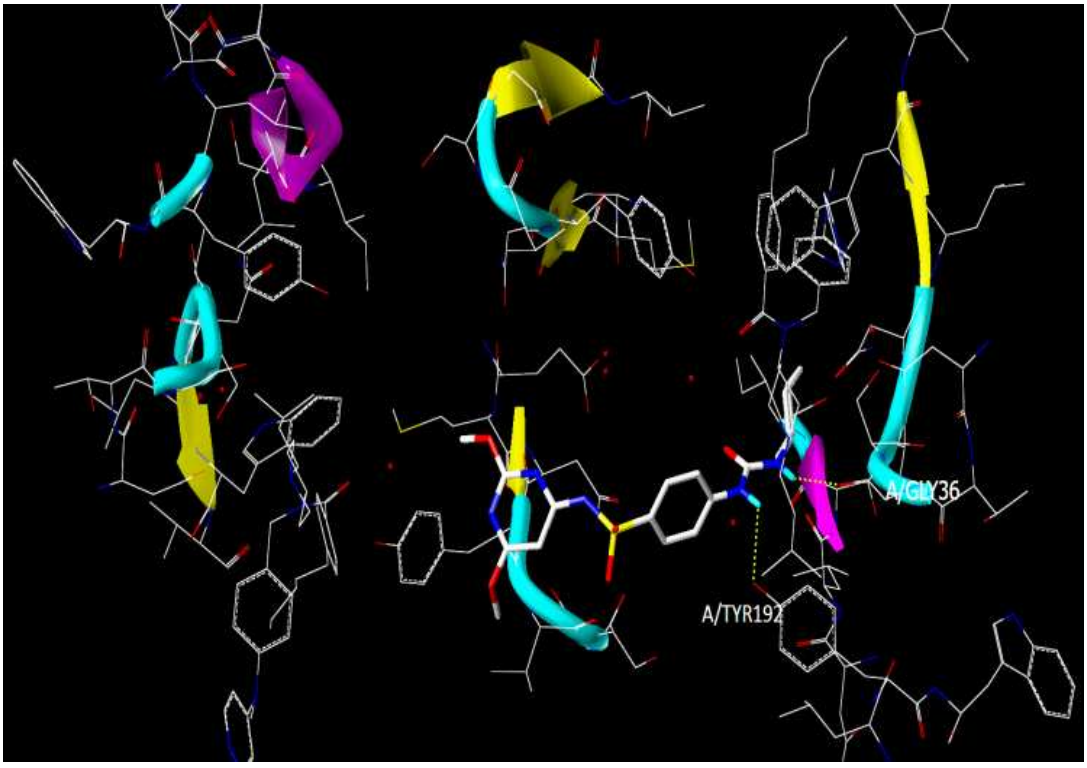


Figure 2.2: Docking interaction of 1n targeting against Plasmepsins receptor binding at TYR 192.

Table 4: Comparative analysis of docking score, H-bond interactions, rerank score between five derivates and its prodrug

Target	Drug_code	Moldock score grid	H-bond interaction	Re-rank score	torsion
2IGX	A1T	**-167.8**	-	-137.72	12
	1m	-127.31	-3.7		12
	1o	-147.37	0	-113.83	12
	p	-138.6	-5.26	-91.4	12
	1n	**-168.9**	-2.33	-77.51	12
2IGY	A2T	**-143**	-	-106.08	12
	1m	-130.8	0	-93.11	12
	1o	-143.22	-1.6	1.7	12
	1p	-138.06	-2.41	-67.06	12
	1n	**-157**	-1.73	-88.31	12

DISCUSSION

These properties are calculated and discussed on the basis ofLipinski's rule and its component. The compound code 1n containing $-NH_3^+$ group fulfil Lipinski's rule and shows good drug likeness score (Table 2.) .Milog P of this compound was found below 5 that means this shows good permeability across cell membrane. TPSA below 160 Å2, *n* violations =1or <0 that means compound easily binds to receptor, onlyexception is molecular mass >500, *n* rotb< 5, No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. hydrogen bond acceptor≤ 10 (The sum of Os and Ns). Compound1a-1p was taken for further calculation of bioactivity score from Table 3 where compounds 1a-1p showed good bioactivity score with moderatelyactiveness as the values are less than 0. Compound code (1n) showed good drug likeness score and bioactivity score, than other compounds and also showed least environmental toxicity i.e. -0.08.

CONCLUSION

With the increase in drug-resistant strains of the malaria parasite, its affects cause scourge to mankind. Though, information regarding availability of the genome sequence provides a wide range of novel targets for drug design along with a collaborative knowledge of Parasite Biology, Genomics and Combinatorial Chemistry have played into existence. The application of functional genomic tools with modern approaches such as structure-based drug design and combinatorial chemistry havelead to develop effectively new molecules against drug-resistantmalarial strains and therefore generating analogue with code (1n) which has showed better results rather than the drug which has been available in the market

ACKNOWLEDGEMENT

The authors wish to thanks BIFC, D.G.P.G. College, Civil Lines, Kanpur funded by DBT for providing necessary soft wares and financial assistance to Abheek Chaudhuri for completing the work .

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