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Research Article

COMPUTATIONAL STUDY OF BUTYL AND NAPHTHYL AMINE DERIVATIVE OF PERYLENE DIIMIDES TARGETTING TELOMERASE ENZYME FOR ANTICANCER ACTIVITY

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ABSTRACT

Objective: Telomeres are protective caps present at the end of the chromosomes and it contains genetic information. From the literature survey, we selected perylene diimides which interact with the telomerase enzyme and possess anticancer activity. Telomestatin a macrocyclic chemical compound that inhibits telomerase activity as well it induces the formation of G-Quadruplex structures in the telomeric region. The main objective of the study was to find the binding affinity of butyl and naphthyl amine derivative of perylene ligands targeting telomerase enzyme for anticancer activity. Telomerase enzyme is responsible for maintaining the length of telomeres and keeping the chromosomes intact longer. Telomeres will become increasingly common with age. Perylene diimides and its derivatives show good biological activity and also *in vitro* studies possess efficient anticancer agent. The butyl and naphthyl amine derivatives are screened by computational techniques to study regarding binding energy and ligand interactions with respect to the targets.

Methods: Butyl and naphthyl amine derivative of perylene diimides is drawn using Accelrys Draw. The structures are retrieved from the previous study. The structures are converted to pdb formats using Discovery Studio Visualizer 4.1. The study was to investigate the binding energy values of butyl and naphthyl amine derivatives of perylene diimides. Auto Dock 4.2 was used to dock the ligand with the targets. The target selected for docking was 3CE5 and 4B18. The results are visualized by Discovery Studio Visualizer 4.1. The results are compared with the standard drug N,N'-bis-(2-(1-piperidino)ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide (PIPER).

Results: From the results, butylamine derivative of perylene diimide possesses good binding energy when compared with standard drug PIPER. This result shows that the butylamine will be effective for anticancer therapy. In future, *in vivo* studies of butylamine derivative of perylene diimide will be carried out.

Keywords: Butylamine, Naphthyl amine, Perylene derivatives, AutoDock 4.2, Docking, Discovery studio visualizer 4.1.

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INTRODUCTION

Perylene moiety is basically used for the dye and the rigid macromolecular structure helps to intercalate the G-quadruplex to inhibition of telomere [1,2]. The perylene pigments are solid and these pigments have received considerable attention in academic as well industrial dye research. At the perylene core, different kinds of substituent can be introduced and the position or the nature of the substituent should be a strong impact on pharmacokinetic and pharmacologic properties [3,4]. In the Bay region, amine groups can be substituted and primary or secondary amine or modified substituent's can be attached at the R2 position. In this study, docking has been done using AutoDock 4.2. The target selected for this study was a telomerase protein (3CE5 and 4B18-PDB ID), and using this as target, we studied and docked the butyl and naphthyl amine derivative of perylene diimide compounds [5].

METHODS

AutoDock 4.2

Molecular docking was performed by the AutoDock 4.2 Tools. It helps to understand the binding properties in a steady-state environment. In this study, we used 3CE5 and 4B18-a telomerase protein.

The calculations of AutoDock are done in several steps: Respective files for the docking analysis have been prepared and saved in coordinate formats. The second step was to calculate the atomic affinities required for the Auto Grid. Finally, the ligands are docked using Auto Dock. The results are analyzed using tools of Auto Dock and the interactions are visualized using Discovery Studio Visualizer 4.1 [6].

Preparation of ligands for docking

Perylene diimide ligands were drawn using Accelrys Draw. The structures are converted from two-dimensional to three dimensional (3D) using discovery studio visualizer 4.1. and saved as.pdb format.

Preparation of protein (3CE5 and 4B18)

The crystallographic structures which are retrieved from RCSB–Protein Data Bank should be in high resolution (www.rcsb.org). The binding selectivity with respect to the protein environment was essential to understand the biological activity of a drug molecule as prototype therapeutic agent. Docking study was performed to understand and correlate their biological efficacy toward the selected binding domain of the protein. We used the AutoDock 4.2 MGL tools version 1.5.6 software packages for the molecular docking experiment and Discovery Studio Visualizer to visualize the results.

The deletion of the both water molecules and the inorganic charges was done to avoid error. Lamarckian genetic algorithm was applied to identify the binding site. Molecular docking analysis was done by the output file of the docking that was generated after the study.

The binding energy, inhibition constant, and the number of hydrogen bonds were considered for the analysis. Butylamine derivative of perylene diimide showed potent binding interactions with the proteins 3CE5 and 4B18 and compared with the standard N,N'-bis-(2-(1-piperidino)ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide (PIPER) [7,8]. The structures of novel butyl and naphthalene perylene diimide derivatives along with the IUPAC are tabulated in Table 1.

The binding energy values are showing equivalent potent values when compared with the standard PIPER. The binding energy values for the compound - butylamine derivatives of Perylene diimide - were −9.67 (3CE5) and −5.33 (4B18) and for the PIPER were −10.46 (3CE5) and −5.59 (4B18) kcal/mol, respectively.

PIPER the standard compound was drawn using Accelrys Draw and converted to 3D structure, saved in.pdb format. The perylene derivatives and PIPER are computed for docking with the two selected targets (3CE5 and 4B18) to compare and to study the ligand interactions and binding energy.

The two compounds of butyl and naphthyl amine derivatives of perylene diimides are docked with the two targets (3CE5 and 4B18) and compared with the PIPER compound. The results are tabulated in Table 2. Among the two perylene compounds, butylamine derivative of perylene diimide possesses good binding energy when compared with the PIPER compound which shows that these compounds possess highest binding affinities and these compounds are tabulated and represented in graph chart in Fig. 1.

The hydrogen bond interactions with the enzyme and the ligand are screened using Discovery Studio 4.1 Visualizer and are tabulated in Tables 3 and 4.

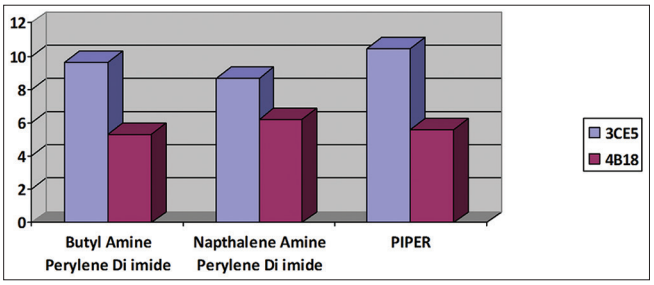
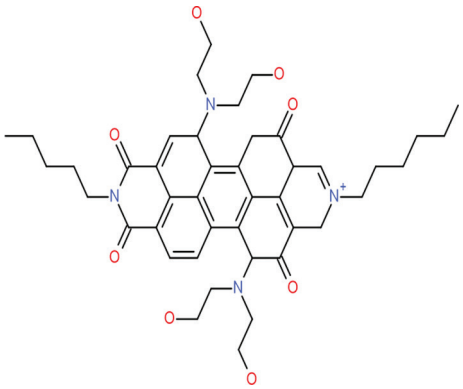
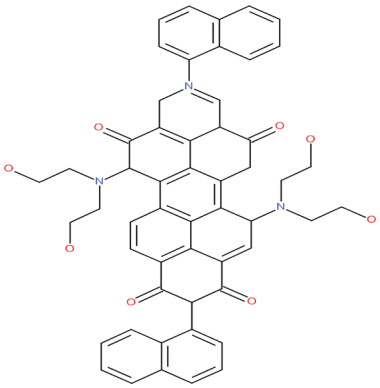
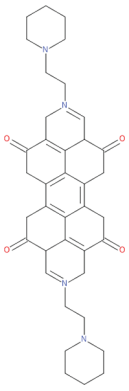


Fig. 1: Results of perylene diimides derivatives with the standard compound N,N'-bis-(2-(1-piperidino)ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide - binding energy (kcal/mol)

Table 1: Structure of novel butyl and naphthyl perylene diimides

SL. No.	Structure	IUPAC name
R_1		5,12-bis (bis (2-hydroxyethyl) amino)-2,9-dihexylanthra[2,1,9-def: 6,5,10-d'e'f'] diisoquinoline-1,3,8,10 (2H,9H)-tetraone
R_2		14,25-Bis[bis (2-hydroxylethyl) amino]-7,18-bis (1-naphthyl)-7.18diazaheptacyclo [14.6.2.22,5.03,12.04,9.013,23.020,24] hexacosa1 (22),4,4 (9),10,13,15,20,23,25-nonaene-6,8,17,19-tetrone
Standard		PIPER

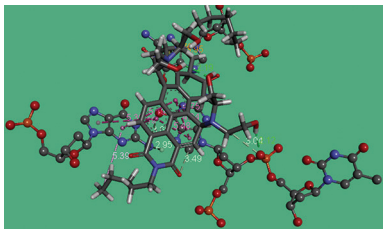
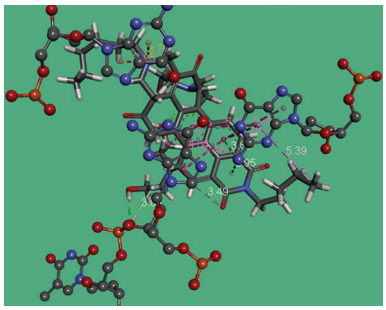
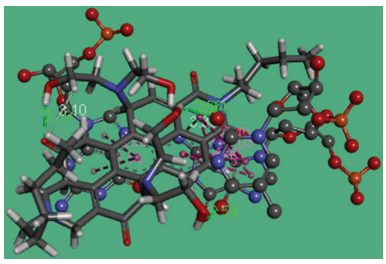
PIPER: N, N'-bis-(2-(1-piperidino) ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide

Table 2: Docking results of butyl and naphthyl amine derivatives of perylene diimides

Compounds	Target PDBs - telomerase inhibitors	
	3CE5	**4B18**
Butylamine perylene diimide		
Binding energies	−9.65	−5.33
Inhibition constant (μM)	83.72 nM	122.99 μM
Hydrogen bond contact	3CE5:A DG3:OP2 3CE5:B DG23:H21	7th: 0:N38 4B18:A: GLN223:OE1
Naphthyl amine perylene diimide		
Binding energies	−8.69	−6.23
Inhibition constant (μM)	424.94 μM	26.99 μM
Hydrogen bond contact	Nil	11th: 0:O18 4B18:B: LYS236:N
PIPER		
Binding energies	−10.46	−5.59
Inhibition constant (μM)	21.69 nM	80.55 μM
Hydrogen bond contact	PIPER: d LIG1:H 3CE5_3A: DG3:OP2	PIPER: 0:O9/PIPER: 0:O6 4B18:A: ARG241:HH21 4B18:A: LYS243:HN

PIPER: N, N'-bis-(2-(1-piperidino) ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide

Table 3: Hydrogen bond interactions with the enzyme and the ligands - 3CE5

S. No.	Compound	3CE5
1.	Butylamine perylene diimide - R1	
2.	Naphthyl Amine- Perylene diimide - R2	
3.	PIPER	

PIPER: N, N'-bis-(2-(1-piperidino) ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide

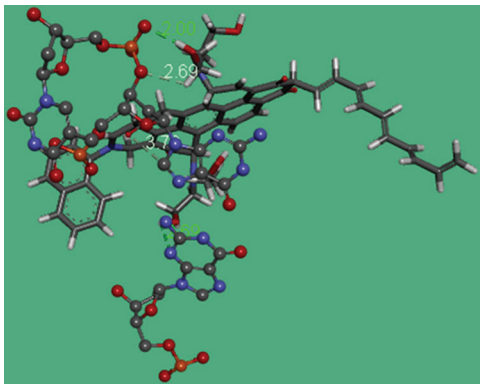
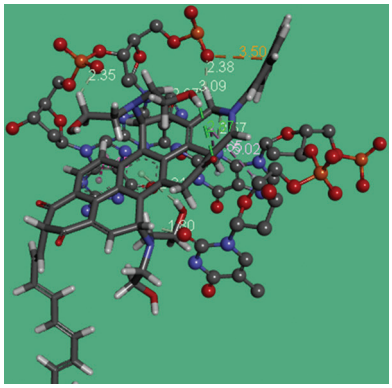
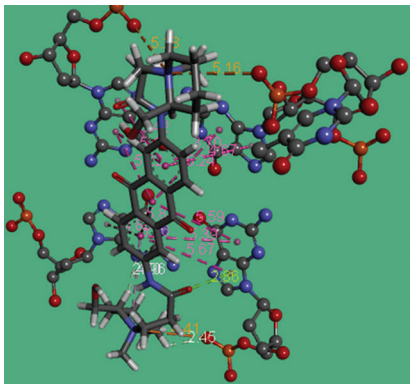
RESULTS

Docking has been done by AutoDock 4.2. After selecting the macromolecule, grid will be generated and saved as.pdbqt format. Once the AutoGrid was generated, docking parameters are carried out using the parameters [9,10]. AutoDock job was done, and the results will be in the format of Complex.pdb files (protein-ligand bound file) and are visualized by Discovery Studio Visualizer 4.1 Visualizer. From the results, butylamine perylene diimide derivative shows good binding energy value when compared with the standard drug PIPER [11].

DISCUSSION

From the docking results, butylamine perylene diimide derivative showed good inhibitory constant value and good binding energy which possesses a good correlation coefficient [12-15]. The interactions with the protein and the ligand show the ligand binds with the protein and

Table 4: Hydrogen bond interactions with the enzyme and the ligands - 4B18

S. No.	Compound	4B18
1.	Butylamine - Perylene diimide - R1	
2.	Naphthyl Amine - Perylene diimide - R2	
3.	PIPER	

PIPER: N, N'-bis-(2-(1-piperidino) ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide

ensure that perylene derivatives are having strong affinity with the targets (3CE5 and 4B18).

CONCLUSION

From the results, the best compound, butylamine perylene diimide derivative will be highly efficient by targeting the telomerase enzyme, and the compound can be used further for *in vivo* studies which will be effective for anticancer therapy [16-18]. The interactions show that the affinity toward the targets was effective when compared with the PIPER ligand. The butylamine perylene diimide derivative can be taken as a Scaffold for further synthetic work and these derivatives have a scope and potential for anticancer activity with respect to the telomerase enzymes.

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AUTHORS' CONTRIBUTIONS

The authors are equally contributed for the research work and preparing the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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