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Research Article

APPLICATION OF *IN SILICO* STUDIES TARGETING TELOMERIC G-QUADRUPLEX COMPLEX BY PERYLENE DIIMIDES FOR ANTICANCER THERAPY

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ABSTRACT

Objective: Telomerase enzyme which is expressed in detectable levels and its mechanism was that it increases the length when it binds to telomeres. This eventually leads to extension of lifespan of cells and also makes an attractive target for cancer therapy. Perylene diimides bind to telomerase with duplex genomic DNA, and these G-quadruplex ligands are of responsible for binding affinity with respective proteins. Based on the IC_{50} values of perylene diimides, QSAR has been studied out and the results are elaborated in preliminary research works. From the results of QSAR, the selected perylene ligands are selected for docking choosing telomerase as a target/protein. From the results of *in silico* studies, new compounds are designed and synthesized accordingly. Now, the objective of the study was to dock the final synthesized compounds with the telomerase protein to study regarding the pKi value using G-quadruplex ligand database (G4LDB). The docked results are visualized using Discovery Studio Visualizer 4.1. The results are compared with the standard N,N'-bis-(2-(1-piperidino)ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide (PIPER) drug and these compounds will be effective for anticancer therapy.

Methods: The study was to investigate the docking results of synthesized perylene compounds with the results from G4LDB and visualized by Discovery Studio 4.1 Visualizer. The telomerase proteins selected for the study were extracted from Protein Data Bank, and the proteins selected for the study are 3SC8 and 3CE5. Among the compounds (R1, R2, R3, and R4) screened in G-Quadruplex Ligand Database, compound R3 shows better binding affinity with good pKi value as well the interactions with the protein and ligand show better affinity with the targets and these are compared with the standard drug PIPER drug.

Results: Compound R3 possesses the best binding affinity with the target 3CE5 and 3SC8 which shows that the compound will be effective for anticancer therapy.

Keywords: AutoDock, G-Quadruplex ligand database, Docking, Perylene derivatives.

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INTRODUCTION

G-Quadruplex stabilization promotes apoptosis

G-Quartets are square planar arrangements of four guanine bases [1-5] and these are stable stacks in macromolecule sequences [6-8]. These structures are G-quadruplexes which contain purine tetrads [9]. G-quadruplexes area unit four-stranded guanine-wealthy DNA structures present at the telomeric ends [10]. G-Quadruplex stabilization leads to inhibition of the telomerase activity, which induces the apoptosis [11,12]. The compounds such as PDI, NDI, and hexazole are the possible intercalators acting on the G-quartet structure and stabilize it. For eg: Cationic porphyrin, Quindoline, Berberine and trisubstitutes iso-alloxazines have been incontestable to interfere with the oncogenic transcription invitro [13-15].

The compounds are docked using G-quadruplex ligand database (G4LDB). The G4LDB online docking proceeds as the compounds are converted from two dimensional to three dimensional. This module incorporated 28 docking models of G-quadruplexes. Once ligand has been designed, job for docking has been submitted [16-18].

METHODS

G4LDB

The four synthesized perylene compounds are docked using G-Quadruplex Ligand Database. The perylene compounds are tabulated in Table 1.

In step one, perylene compounds are drawn and the structures are converted to simplified molecular-input line-entry system (SMILES) format using online SMILES translator. In step two, the target (3CE5 and 3SC8) was chosen and the compounds in SMILE format were given for computation. The process will take 15–20 min for completion of the docking job. The results are finally downloaded and the complex. Protein data bank (PDB) structures are visualized using Discovery Studio Visualizer 4.1.

N,N'-bis-(2-(1-piperidino)ethyl)-3,4,9,10-perylene tetracarboxylic acid diimide (PIPER), the standard compound, was downloaded from the same module and computed for docking with the two selected targets (3CE5 and 3SC8) to get to know about the best binding affinity toward the perylene and its ligands [19-21]. The targets selected for the study are as follows: 3CE5 and 3SC8.

The four compounds are docked with the two targets (3CE5 and 3SC8) and compared with the PIPER compound. The results are tabulated in Table 2. Among the four perylene compounds, compound R3 showed good pKi value when compared with the PIPER compound which shows that these compounds possess highest binding affinities and these compounds are represented in Fig. 1.

The hydrogen bond interactions with the enzyme and the ligand are tabulated in Tables 3 and 4.

RESULTS

Docking has been done by G-Quadruplex Ligand Database. This is an online database which was having inbuilt tools and performed by Open Babel 2.3.0 to predict the binding affinity with the targets [22]. The targets (3CE5 and 3SC8) for the docking are selected based on the

Table 1: Structure of novel perylene diimides target molecules

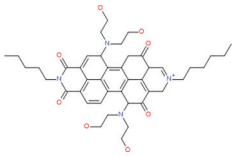
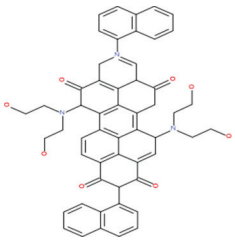
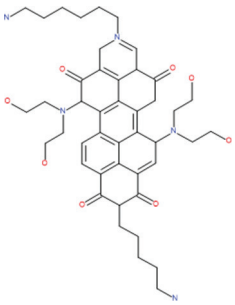
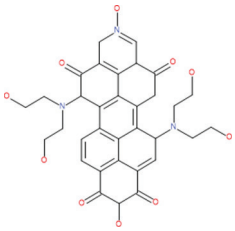
S. No.	Structure	IUPAC name	Molecular weight
R1		5,12-bis (bis (2-hydroxyethyl) amino)-2,9-dihexylanthra[2,1,9-def: 6,5,10-d'e'f'] diisoquinoline-1,3,8,10 (2H,9H)-tetraone	755.40
R2		14,25-Bis[bis (2-hydroxylethyl) amino]-7,18-bis (1-naphthyl)-7.18diazaheptacyclo [14.6.2.22,5.03,12.04,9.013,23.020,24]hexacosa1 (22),4,4 (9), 10,13,15,20,23,25-nonaene-6,8,17,19-tetrone	853.35
R3		7,18-Bis (5-aminopentyloxy)-14,25-bis[bis (2-hydroxyethyl) amino]-7. 18-diazaheptacyclo[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	785.44
R4		1,7-Bis (n-diethanolamino)-*N*, *N*-dihydroxylamine-3,4,9,10- perylenetetracarboxylic diimides	633.23

Table 2: Results of pKi value for the four synthesized perylene compounds

S. No	Compound	Target PDBs	
		3CE5	3SC8
1	R1	4.58	4.59
2	R2	2.71	2.3
3	R3	5.22	5.55
4	R4	4.45	4
5	PIPER	8.84	8.02

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

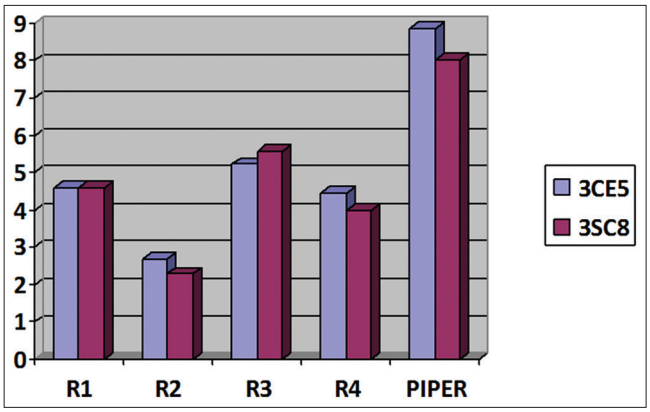


Fig. 1: Results of pKi value for the four synthesized perylene compounds

literature survey, and the four synthesized perylene compounds are docked. From the results, compound R3 is selected and the results of these compounds are visualized using Discovery Studio 4.1 Visualizer.

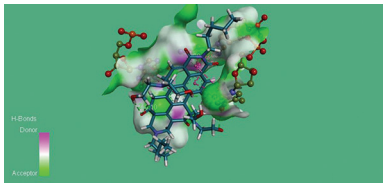
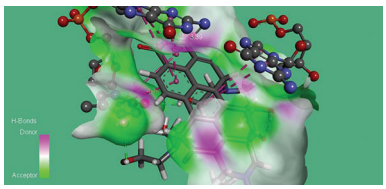
DISCUSSION

From the docking results of G-Quadruplex Ligand Database, compound R3 showed good inhibitory constant pKi value which shows the correlation coefficient and proves that the perylene derivatives will be efficient with the targets (3CE5 and 3SC8).

CONCLUSION

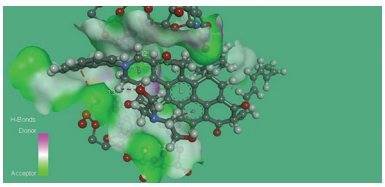
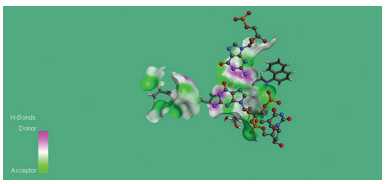
Based on the research work, we selected a set of perylene compounds by analyzing the IC_{50} values from literature survey. QSAR study has been done, and from the results, new compounds are designed from the QSAR equation, and hence, new compounds are designed and biological activity values are predicted. The designed compounds are screened using computational studies using selective targets from PDB, and a scaffold was selected for synthesis. We synthesized four perylene compounds and docked using G-Quadruplex Ligand Database to find the inhibitory value and hydrogen bond interactions with the ligand. The results are tabulated, and among the four perylene compounds, compound R3 showing more potent, the selected best compound R3 targeting the telomerase enzyme, may be used for *in vivo* studies which will be effective for anticancer therapy.

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

S. No	Compound	3CE5
1	R3	
2	PIPER	

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

Table 4: Hydrogen bond interactions with the enzyme and the ligands - 3CS8

S. No	Compound	3SC8
1	R3	
2	PIPER	

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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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