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Review Article

G-QUADRUPLEX LIGANDS AS STABILIZER TARGETING TELOMERASE ENZYME AS ANTI CANCER AGENTS

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ABSTRACT

The human telomere stabilization with G-Quadruplex DNA tends to induce apoptosis. The molecular target of telomere cascade with a rigid molecular may show efficacious to treat cancer. The study of intercalation to human telomeric DNA with proposed ligand can be evaluated by the help of biophysical studies and biological studies. G-Quadruplex is one of the key epigenetic episodes of eukaryotes and prokaryotes, generally found in the telomeric end region, immunoglobulin switch recombination and the lagging strand of the DNA. These chemotherapeutic advances are not enough to maintain a life expectancy of cancer affected patients. A number of G-Quadruplex ligands such as acridine, perylene, and anthraquinones have been synthesized reported and evaluated them for the inhibitor activity. Therefore, translational research can pave the novel prospect to treat cancer in a fundamental way. In that connection, basic research showed G-Quadruplex phenomenon of DNA, which is having a great impact in this chemotherapy.

Keywords: Perylene derivatives, G-Quadruplex, Telomerase, Anticancer.

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INTRODUCTION

Guanine-rich nucleic acid sequences are capable of forming four-stranded structures termed G-Quadruplexes. It exists in Telomeres, Gene Promoters' and other important regions of eukaryote genome [1]. These structures have been studied using nuclear magnetic resonance, X-ray diffraction and spectroscopic techniques [2,3] and materialized as a significant biological target for telomerase inhibitors. Telomerase is a ribonucleoprotein enzyme binds to the telomeres which increase their length, and extends the lifespan of cells. A development of potential telomerase inhibitors carried out by the researchers using small molecules which are able to interact with telomeric DNAs and to induce uncommon DNA secondary structures, sequestered to telomerase [4]. A number of compounds have been studied such as porphyrins, disubstituted anthraquinones, trisubstituted acridine, dibenzo phenanthroline derivatives, and perylene derivatives [5]. Other telomerase inhibitors such as telomestatin, RHPS4, BRACO-19 stabilizes to form the G-Quadruplex (GGTTAG) structure, hence decreasing the efficiency of telomerase [6,7]. Several therapeutics targeting telomerase, such as Imetelstat (GRN163L) and Tertomotide (GV1001), are currently in Phase I, II, and III clinical trials to treat a wide range of cancers from solid tumors to non-small cell lung cancer, leukemia, lymphoma, and myeloma [8].

ANTHRAQUINONE DERIVATIVES

A non-nucleoside small molecule (Compound 1) was the first reported compound published by Sun *et al.* [9] and which inhibits (inhibitory concentration 50% [IC_{50}] 23 μM) the telomerase enzyme by interaction with G-Quadruplex. Based on the study more number of isomeric forms of anthraquinones derivatives are screened synthesized and examined them for telomerase inhibitory activity. From the study, primary or tertiary amino groups, the position of the side chains is important for telomerase inhibition. Small library compounds of disubstituted anthraquinone amino acid derivatives, e.g., Compounds 2 and 3 show optimal telomerase inhibition (IC_{50} 0.8-1.5 μM) with the residues Lys or Arg as side chains [10]. Guanidine derivative (Compound 4) also showed potent (IC_{50} 1 μM) inhibitor activity for telomerase enzyme [11].

ACRIDINE DERIVATIVES

3,6 disubstituted acridine derivatives have been proposed by Harrison *et al.* [12] and this study states as the planar aromatic chromophore ring which stabilize, binds to G-Quadruplex and inhibits telomerase. The protonated heterocyclic nitrogen atom (Compound 5) at physiological pH interacts G-quadruplex by increasing electron deficiency (IC_{50} 1.35 μM) [13]. In the acridine chromophore aniline substituent at 9th position shows significant inhibitor activity for the Compound 6 (BRACO19) (IC_{50} 0.095 μM) and Compound 7 (IC_{50} 0.060 μM) [14]. The pentacyclic quinoa iridium salt RHPS4 (Compound 8) (IC_{50} 0.25 μM) shows good pharmaceutical properties and efficiently transported into tumor cells [15]. Other acridine compounds such as polycyclic acridines (Compound 9) (IC_{50} 0.37 μM) [16], quaternized quinoa [4, 3, 2-kl] acridinium salts (Compound 10) (IC_{50} 0.38 μM) [17], and 3, 6, 9- trisubstituted acridine derivatives (Compound 11) (IC_{50} 0.018 μM) have been reported [18] and showed best telomerase inhibitor activity.

PERYLENE DERIVATIVES

Fedoroff *et al.* [19] reported the first potent telomerase inhibitor and iterated G-Quadruplex-binding studies by the Compound 12 (PIPER-N,N'-bis [2-(1-piperidino)-ethyl]-3, 4, 9, 10-perylenetetracarboxylicdiimide) with very low IC_{50} range. A series of PIPER derivatives (e.g., Compound 13 [DAPER] and 14 [PIPER3]) has been synthesized which was found to inhibit telomerase with the IC_{50} values in the range of 10-20 μM [20]. The electrostatic interaction between the ligands plays a major role in telomerase inhibition. Rossetti *et al.* [21] reported a set of PIPER derivatives (e.g., Compound 15 [PIPER6] and Compound 16 [PIPER7]) which was showing to be more efficient than PIPER with the IC_{50} values between 5 and 10 μM. These compounds with different side chains lead to inhibitor activity. Franceschin *et al.* [22,23] reported the distance of positive charges in the side chains and synthesized set of perylene derivatives (e.g., Compound 17 [DAPER 3C], Compound 18 [DAPER3C-Br], Compound 19 [DAPER4C 1, 6], and Compound 20 [DAPER 4C 1, 7]) and evaluated for telomerase activity and shows IC_{50} value at about 5 μM. Further, he synthesized polyamide perylene diimides derivatives (e.g., Compound 21 [POL-3] and Compound 22 [POL-5]), which shows inhibition value between IC_{50} 7 and 10 μM.

PORPHYRINE DERIVATIVES

Wheelhouse *et al*. [24] reported cationic porphyrins, and among them, they found one of the Compound 23 (TMPyP4- [5, 10-15, 20-tetra-(-N-Methyl-4-pyridyl)] porphine) as it stabilizes and stacked with G-Quadruplex DNA and inhibits telomerase enzyme with an IC_{50} value of 6.5±1.4 μM. Analogs of TMPyP4 (e.g., Compound 24 - IC_{50} 5 μM) have been reported and found as the positively charged substituent's on meso positions, and the size of substitution are important, and the face of porphyrins should be available for stacking [25].

BISINDOLE DERIVATIVES

A series of bisindole derivatives has been synthesized by Sasaki *et al*. [26] found as the phosphodiester group and a long alkyl chain would be the most important factors for the telomerase inhibition. Among the compounds, Compounds 25 and 26 were observed potent inhibitors with an IC_{50} value of 3.4 μM and 2.5 μM, respectively. The hydrophobic group in indole derivative was also considered as an important factor for the inhibition.

BERBERINE DERIVATIVES

9 and 13 substituted berberine derivatives have been reported by Ma *et al*. [27] and Franceschin *et al*. [28], and among the compounds, Compounds 27 and 28 were observed to be the potent telomerase inhibitor by stabilizing G-quadruplex DNA with an IC_{50} value of 14 μM.

MACROCYCLIC COMPOUNDS

Telomestatin - Compound 29 was the most potent *in vitro* telomerase inhibitor, and it consists of one thiazoline and seven oxazole rings which will interact with G-Quadruplex with an IC_{50} value of 5 nM [29,30]. Barbieri *et al*. and Tera *et al*. [31,32] synthesized synthetic macrocyclic telomerase derivatives (e.g., Compound 30 {Macrocyclic Hexazole [HXDV]} and Compound 31 [bistrioxazole acetate]) and found that the compound shows strong selectivity toward Quadruplex over duplex or triplex DNA with an IC_{50} value of 2 μM.

TRIAZINE DERIVATIVES

Riou *et al*. [33] reported series of triazine compounds and among the derivatives, bisquinoline substituted triazine Compound 32 (IC_{50} 0.041 μM) observed potent telomerase inhibitor at nanomolar concentration.

CONCLUSION

In this review, we summarized the existing studies on the biological activities of telomerase inhibitors [34]. Numerous compounds have been identified and screened for telomerase inhibitor activity to develop and improve efficacious drugs with less toxicity. *In silico* drug design can play a significant role in all stages of drug development from the preclinical discovery stage to late stage clinical development [35]. Among the targets, telomerase was the enzyme which shows high concentration in carcinogen cells when compared to normal cells. From the various literature, we found out as the compounds acridines, perylene, anthraquinones, macrocyclic compounds, and porphyrins having a unique feature which interrupts the biochemical role present in the telomerase enzyme which stabilizes the G-Quadruplex DNA and arresting the growth of cancerous cells without affecting the normal cells, thus inducing apoptosis. These telomerase inhibitors may have a major role with the current anticancer agents in treating cancerous cells (Table 1).

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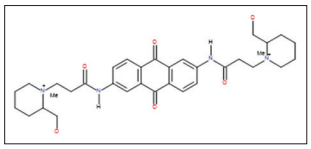
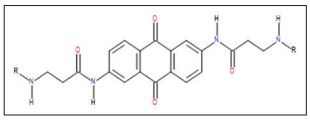
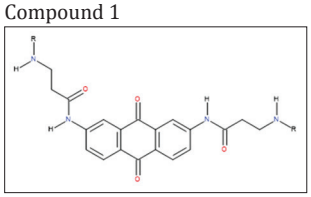
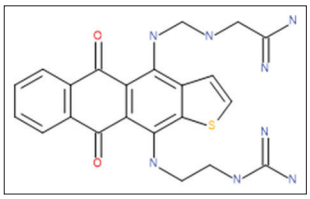
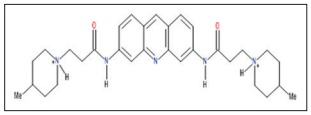
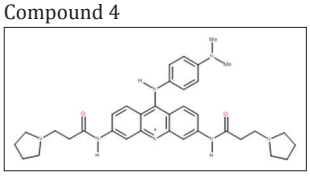
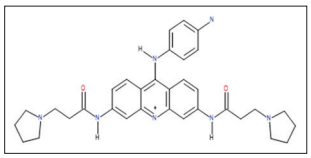
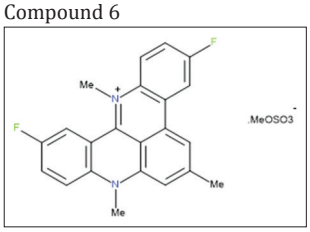
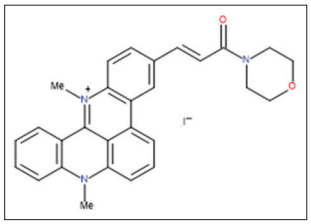
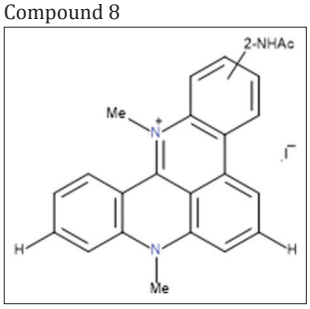
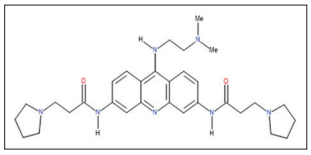
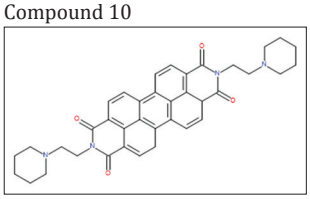
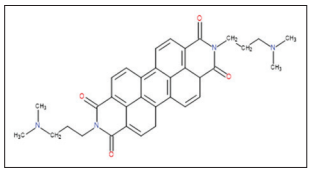
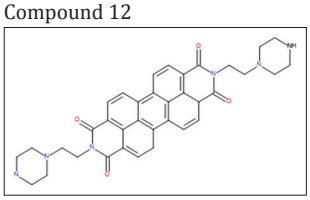
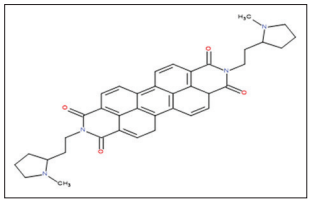
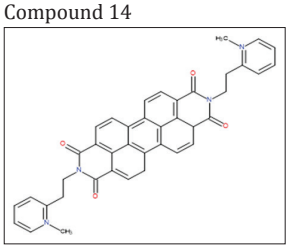
Table 1: List of G-Quadruplex stabilizing ligands

 Compound 1	 Compound 2
 Compound 3	 Compound 4
 Compound 5	 Compound 6
 Compound 7	 Compound 8
 Compound 9	 Compound 10
 Compound 11	 Compound 12
 Compound 13	 Compound 14
 Compound 15	 Compound 16

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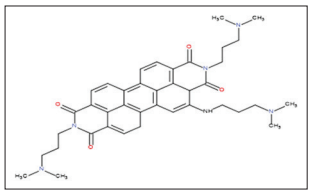

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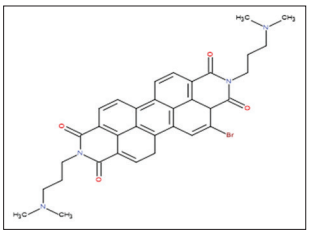

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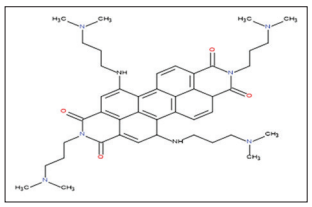

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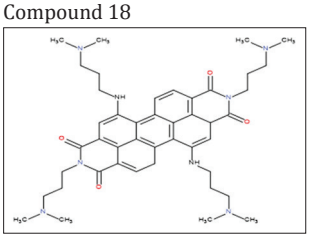

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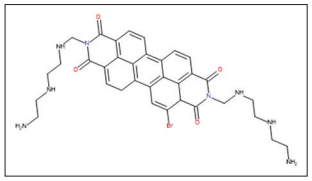

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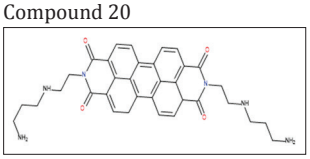

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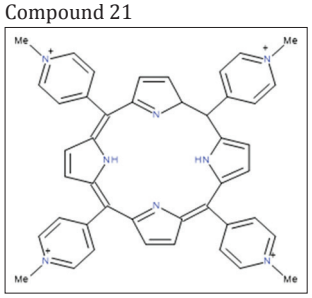

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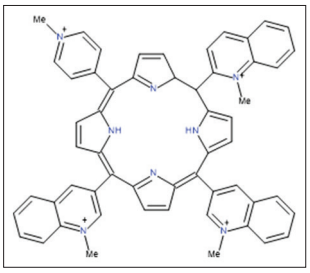

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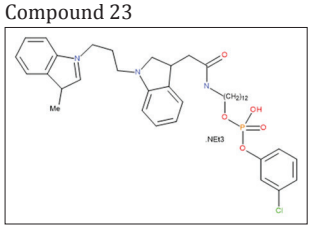

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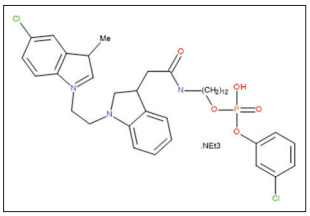

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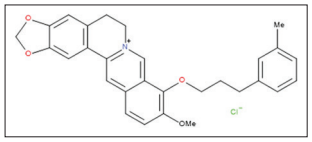

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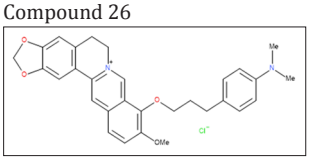

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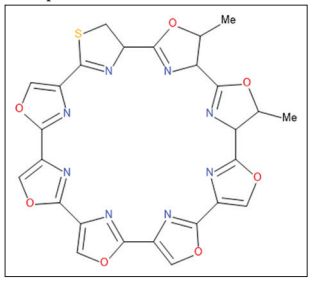

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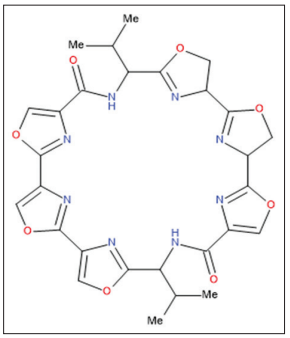

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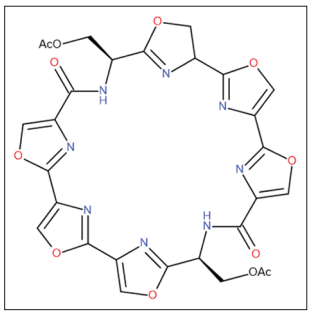

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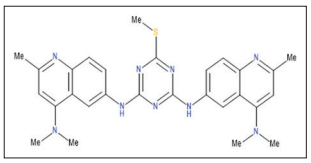

Compound 32

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