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

HEMALATHA CN, VIJEY AANANDHI M*
Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels University, Chennai, Tamil Nadu, India.
Email: hodpchemistry@velsuniv.ac.in

Received: 09 May 2017, Revised and Accepted: 25 May 2017

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.

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 porphyryns, disubstituted anthraquinones, trisubstituted acridine, dibeno 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].

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 (IC₅₀ 1.35 µM) [13]. In the acridine chromophore amine substituent at 9th position shows significant inhibitor activity for the Compound 6 (BRAQ19) (IC₅₀ 0.095 µM) and Compound 7 (IC₅₀ 0.060 µM) [14]. The pentacyclic quinoa iridium salt RHPS4 (Compound 8) (IC₅₀ 0.25 µM) shows good pharmaceutical properties and efficiently transported into tumor cells [15]. Other acridine compounds such as polyyclic acridines (Compound 9) (IC₅₀ 0.37 µM) [16], quaternized quinoa [4, 3, 2-kd] acridinium salts (Compound 10) (IC₅₀ 0.38 µM) [17], and 3, 6- trisubstituted acridine derivatives (Compound 11) (IC₅₀ 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-perylenetetracarboxylicidilmide) with very low IC₅₀ 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 IC₅₀ 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 IC₅₀ 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 19 [DAPER4C 1, 6], and Compound 20 [DAPER 4C 1, 7]) and evaluated for telomerase activity and shows IC₅₀ 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 IC₅₀ 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, bisquinaline 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).

ACKNOWLEDGMENT

The authors are thankful to Vels University (VISTAS) and its management for providing research facilities and encouragement. The author is obliged to DBT - Government of India (BT/Biotech/03/10047/2013-14) for providing financial assistance to carry out the research work. The authors are also thankful to the VLife Science Technologies (Amit Bedi) Pvt. Ltd, Pune, India, for providing the software for the QSAR study.

Table 1: List of G-Quadruplex stabilizing ligands
REFERENCES

1. Chu B, Yuan G, Zhou J, Ou Y, Zhu P. A new telomerase inhibitor and apoptosis-inducing agent in leukemia: Perylene derivative as G-quadruplex ligand Tel03. Drug Dev Res 2008;69:235-41.

2. Miyoshi D, Nakao A, Toda T, Sugimoto N. Effect of divalent cations on the anti-parallel G-Quartet structure of d-(G4T4G4). FEBS Lett 2001;25:3341-6.

3. Keniry MA. Quadruplex structures in nucleic acids. Biopolymers 2000-2001;56:123-46.

4. Mergny JL, Helene C. G-quadruplex DNA: A target for drug design. Nat Med 1998;4:1366.

5. Rossetti L, Franceschin M, Bianco A, Ortaggi G, Savino M. Perylene dimides with different side chains are selective in inducing different G-quadruplex DNA structures and in inhibiting telomerase. Bioorg Med Chem Lett 2002;12(18):2527-33.

6. Harley CB. Telomerase and cancer therapeutics. Nat Rev Cancer 2008;8:167-79.

7. Xu Y. Chemistry in human telomere biology: Structure, function and targeting of telomere DNA/RNA. Chem Soc Rev 2011;40(5):2719-40.

8. Puri N, Girard J. Novel therapeutics targeting telomerase and telomeres. J Cancer 2013;5:10.

9. Sun D, Thompson B, Cathers BE, Salazar M, Kerwin SM, Trent JO, et al. Inhibition of human telomerase by a G-quadruplex-interactive compound. J Med Chem 1997;40:2113-6.

10. Sissi GZ, Lucatello L, Pivetta C, Cadamuro SA, Fox KR, Neidle S, et al. Aminocyclanthraquinone conjugates as telomerase inhibitors: Synthesis, biophysical and biological evaluation. J Med Chem 2008;51:5566-74.

11. Shevchenkikhin AE, Glazunov VA, Dezhkenkova LG, Lushkov VN, Sinkievich YB, Kovalenko LV, et al. Synthesis and cytotoxic properties of 1,11-biss[(aminoethyl)aminio]anthra[2,3,6]thiophene-5,10-diones, novel analogs of antitumor antihyacin-9,14diones. Bioorg Med Chem 2009;17:1861-9.

12. Harrison RJ, Gowen SM, Kelland LR, Neidle S. Human telomerase inhibition by substituted acridine derivatives. Bioorg Med Chem Lett 1999;9:2463-8.

13. Read MA, Wood AA, Harrison RJ, Gowen SM, Kelland LR, Dosanjh HS, et al. Molecular modeling studies on G-quadruplex complexes of telomerase inhibitors: Structure-activity relationships. J Med Chem 1999;42:4538-46.

14. Read M, Harrison RJ, Romagnoli B, Tanious FA, Gowen SH, Reszka AP, et al. Structure-based design of selective and potent G-quadruplex-mediated telomerase inhibitors. Proc Natl Acad Sci U S A 2001;98(9):4844-9.

15. Heald RA, Modi C, Cowson JC, Hutchinson I, Laughton CA, Gowen SM, et al. Antitumor polycyclic acridines. 8.1 synthesis and telomerase-inhibitory activity of methylated pentacyclic acridinium salts. J Med Chem 2002;45:590-7.

16. Heald RA, Stevens MF. Antitumor polycyclic acridines. Palladium(0) mediated syntheses of quinone[4,3,2-k]acridines bearing peripheral substituents as potential telomere maintenance inhibitors. Org Biomol Chem 2003;1:3377-89.

17. Cheng MK, Modi C, Cookson JC, Hutchinson I, Heald RA, McCracken AJ, et al. Antitumor polycyclic acridines 20. Search for DNA G-quadruplex binding selectivity in a series of 8,13-dimethylquinone[4,3,2-k]acridinium salts: Telomere-targeted agents. J Med Chem 2008;51(4):963-75.

18. Harrison RJ, Cuesta J, Chessari G, Read MA, Basra SK, Reszka AP, et al. Trisubstituted acridine derivatives as potent and selective telomerase inhibitors.
inhibitors. J Med Chem 2003;46:4463-76.

19. Fedoroff OY, Salazar M, Han H, Chemeris VV, Kerwin SM, Hurley LH. NMR-based model of a telomerase-inhibiting compound bound to G-quadruplex DNA. Biochemistry 1998;37:12367-74.

20. Kerwin SM, Chen G, Kern JT, Thomas PW. Perylene diimide G-quadruplex DNA binding selectivity is mediated by ligand aggregation. Bioorg Med Chem Lett 2002;12:447-50.

21. Rossetti L, Franceschin M, Schirripa S, Bianco A, Ortaggi G, Savino M. Selective interactions of perylene derivatives having different side chains with inter- and intramolecular G-quadruplex DNA structures. A correlation with telomerase inhibition. Bioorg Med Chem Lett 2005;15:413-20.

22. Franceschin M, Pascucci E, Alvino A, D’Ambrosio D, Bianco A, Ortaggi G, et al. New highly hydrosoluble and not self-aggregated perylene derivatives with three and four polar side-chains as G-quadruplex telomere targeting agents and telomerase inhibitors. Bioorg Med Chem Lett 2007;17:2515-22.

23. Franceschin M, Lombardo CM, Pascucci E, D’Ambrosio D, Micheli E, Bianco A, et al. The number and distances of positive charges of polyamine side chains in a series of perylene diimides significantly influence their ability to induce G-quadruplex structures and inhibit human telomerase. Bioorg Med Chem 2008;16:2292-304.

24. Wheelhouse RT, Sun D, Han H, Han FX, Hurley LH. Cationic porphyrins as telomerase inhibitors: The interaction of tetra-(N-methyl-4-pyridyl) porphine with quadruplex DNA. J Am Chem Soc 1998;120:3261-2.

25. Shi DF, Wheelhouse RT, Sun D, Hurley LH. Quadruplex-active agents as telomerase inhibitors: Synthesis of porphyrins and structure-activity relationship for the inhibition of telomerase. J Med Chem 2001;44:4509-23.

26. Sasaki S, Ehara T, Sakata I, Fujino Y, Harada N, Kimura J, et al. Development of novel telomerase inhibitors based on a bisindole unit. Bioorg Med Chem Lett 2001;11(4):583-5.

27. Ma Y, Ou TM, Tan JH, Hou JQ, Huang SL, Gu LQ, et al. Synthesis and evaluation of 9-O-substituted berberine derivatives containingaza-aromatic terminal group as highly selective telomeric G-quadruplex stabilizing ligands. Bioorg Med Chem Lett 2009;19:3414-7.

28. Franceschin M, Rossetti L, D’Ambrosio A, Schirripa S, Bianco A, Ortaggi G, et al. Natural and synthetic G-quadruplex interactive berberine derivatives. Bioorg Med Chem Lett 2006;16(6):1707-11.

29. Shin-Ya K, Wierzbka K, Matsuo KI, Ohtani T, Yamada Y, Furihata K, et al. Telomestatin, a novel telomerase inhibitor from Streptomyces annulus. J Am Chem Soc 2001;123:1262-3.

30. Kim MY, Vankayalapati H, Shin-Ya K, Wierzbka K, Hurley LH. Telomestatin, a potent telomerase inhibitor that interacts quite specifically with the human telomeric intramolecular G-quadruplex. J Am Chem Soc 2002;124(10):2098-9.

31. Barbieri CM, Srinivasan AR, Rzucek SG, Rice JE, Lavoie EJ, Pilch DS. Defining the mode, energetics and specificity with which a macrocyclic hexaoxazole binds to human telomeric G-quadruplex DNA. Nucleic Acids Res 2007;35:3272-86.

32. Tera M, Sohtome Y, Ishizuka H, Doi T, Takagi M, Shin-Ya K, et al. Design and synthesis of telomestatin derivatives and their inhibitory activity of telomerase. Heterocycles 2006;69:505-14.

33. Riou JF, Guittat L, Mailliet P, Laoui A, Renou E, Petitgenet O, et al. Cell senescence and telomere shortening induced by a new series of G-quadruplex DNA ligands. Proc Natl Acad Sci U S A 2002;99(5):2672-7.

34. Balijepalli1 MK, Buru AS, Sakirulla R, Pichika MR. Cinnamomum genus: A review on its biological activities. Int J Pharm Pharm Sci 2017;9(2):1-11.

35. Nerdy, Putra ED, Haro G, Harahap U, Hutagaol R, Karsono. In silico screening of hesperetin and naringenin ester derivatives as anticancer against p-glycoprotein. Int J Pharm Pharm Sci 2015;7(2):485-8.