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DNA CLEAVAGE POTENTIAL OF 4-(PIPERIDIN-1-YLMETHYL)-2-(THIOPHEN-2-YL) QUINOLINE ANALOGUES

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Abstract:

*DNA cleavage potential of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline **7(a-j)** derivatives, were studied on Calf-thymus DNA by agarose gel electrophoresis method. The compounds **7e** and **7j** have exhibited almost complete cleavage, whereas the other compounds **7a, 7b, 7c, 7d, 7f, 7g and 7i** have shown partial cleavage of DNA at 100 µg concentration. The compounds **7e** and **7j** can be considered as DNA intercalating agents due to its planarity and their potentiality to cleave the DNA completely. This might be through breaking the base pairs of DNA.*

Keywords: *DNA, Calf-thymus DNA, Thiophene, Agarose gel electrophoresis.*

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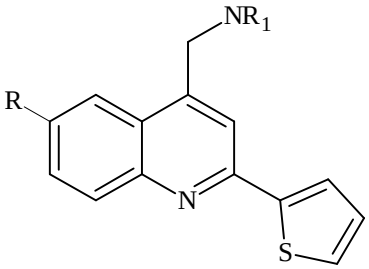
INTRODUCTION:

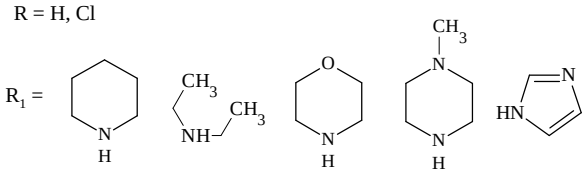
DNA is primary target in many anticancer therapies [1]. Binding of peptides and the small organic molecules to DNA will interfere in both transcription and replication processes. Considering this principle, various disorder/diseases like cancer, cystic fibrosis, etc can be cured [1]. Literature survey reveals that, the clinical efficacy of many drugs correlate with their ability to induce enzyme mediated DNA cleavage [2]. The loci present in the DNA is involved in various regulatory aspects such as gene expression, gene transcription, mutagenesis, carcinogenesis, etc [2]. Hence, designing compounds having the ability to interact and cleave DNA is utmost important not only from the biological point, but also, in terms of therapeutic approach to develop potent drug candidates [3].

The quinoline carboxylic acids and their analogs could imitate ellipticene, exhibit considerable antitumor activity by acting as DNA intercalating agents [4]. The quinolines reveal antitumor activity due to the enlargement of stable complex with DNA [5]. The introduction of a thiophene moiety in the C-2 position of the quinoline ring would possibly enhance the lipophilicity which in turn help for greater penetration of the compounds into the cell and enhance DNA-quinoline binding properties of the prepared compounds and there by augment the anticancer activity [6].

In view of the above facts, and in continuation of our work on the lookout of chemotherapeutic agents [7-10], the DNA cleavage study of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline and its derivatives were considered. The molecules tested are reported earlier from our laboratory [11].



4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl)quinoline 7(a-j)



DNA cleavage studies

The degree of DNA cleavage by the compounds was monitored by agarose gel electrophoresis method [12]. Agarose (0.25 gm) was weighed and dissolved in 25 ml of Tris acetate (TAE) buffer (50 mM, pH 8.0) and gel cassette was placed in the electrophoresis chamber inundated with TAE buffer. To this 20 µl of DNA sample along with bromophenol blue dye in 1:1 ratio with standard DNA marker was loaded. CT-DNA was treated with analogs (40 µM, 2 µl) followed by the dilution of buffer to a total volume of 20 µl. The samples after incubation at 37°C were loaded to the wells.

Electrophoretic mobility was achieved by supplying 50 V of electricity for about 45 min in TAE buffer. The gel along with platform was stained with 100 ml ethidium bromide (10 µg/ml) in sterile distilled water. Ethidium bromide binds to double stranded DNA by intercalation, because of steric hindrance for intercalation in covalently closed circular DNAs; it binds less than linear and open circles [12]. After about 10–15 min the platform and the gel were rinsed with distilled water and the gel was gently placed onto the UV transilluminator. The DNA bands appeared on the gel determined the cleavage by the entitled molecules tested.

RESULT AND DISCUSSION

DNA Cleavage studies

Many anticancer drugs in clinical use (e.g. anthracyclines, mitoxantrone, dactinomycin) interact with DNA through intercalation [13], which can be defined as the process by which compounds

containing planar aromatic or heteroaromatic ring systems are inserted between adjacent base pairs perpendicularly to the axis of the helix and without disturbing the overall stacking pattern due to Watson–Crick hydrogen bonding. Since, many typical intercalating agents contain three or four fused rings that absorb light in the UV–visible region of the electromagnetic spectrum, they are usually known as chromophores. Besides the chromophore, other substituents in the intercalator molecule may highly influence the binding mechanism [14]. DNA being the target for drugs as it regulates many biochemical reactions which occur in the cellular system [14]. The literature studies reveal that the clinical efficacies of many drugs correlate with their ability to induce enzyme-mediated DNA cleavage. Our efforts in the lookout of a possible hit/lead molecule for anticancer therapy, the entitled compounds 7(a-j) were studied for the DNA cleavage by agarose gel electrophoresis method, presented in Figure 1 using calf thymus DNA (CT-DNA) were studied. The cleavage potential of some of the test compounds **7a, 7b, 7c, 7d, 7f, 7g, 7h, 7j** has revealed moderate DNA cleavage activity where as, the compounds **7e** and **7j** have shown complete cleavage of DNA at 100 µg concentration. However, the ability of reactive intermediates involved in the DNA cleavage by the compounds has not been clear. Control experiment does not reveal any significant cleavage of DNA even after prolonged exposure of the substrate, indicating the possibilities to consider **7e** and **7j** as hits.

The compounds **7e** and **7j** reveal complete DNA cleavage at 100 µg concentration, might be due to the presence of 4- imidazole on quinoline ring, which have the nature of rigid and planarity. The intercalation binding force comes from the π–π interactions and hydrophobic interactions between the imidazole ring of the intercalator and the DNA base. However, the compounds **7a, 7b, 7c, 7d, 7f, 7g, 7h, 7j** has revealed moderate DNA cleavage, might be due to the presence of piperidine, diethylamine, morpholine and n-methyl piperzine, which enhance the lipophilicity, thereby decreasing the activity. Hence, the planar aromatic molecules, quinoline, thiophene and imidazoles which were bridged together as pharmacophores can be considered for future development as possible drug candidates.

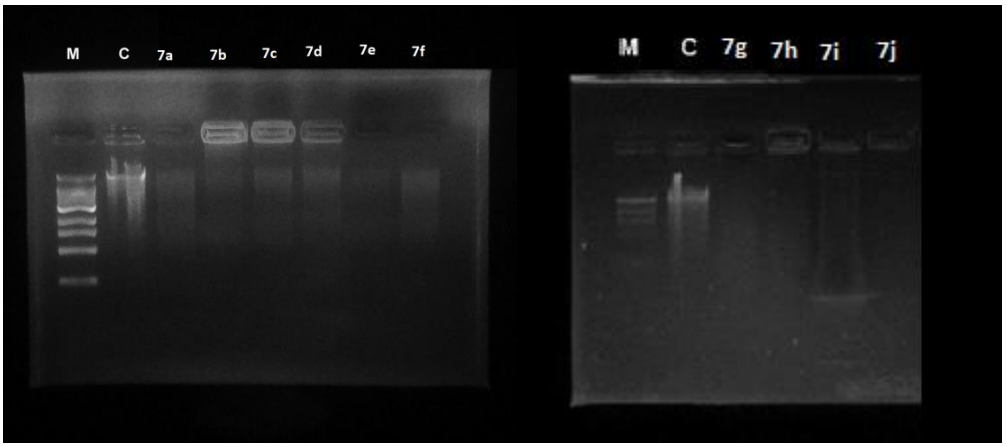


Fig 1. Photograph showing DNA cleavage on agarose gel electrophoresis by the different derivatives of the synthesized compounds 7(a-j).

CONCLUSION:

The DNA cleavage potential of title derivatives on CT-DNA revealed that among the tested compounds, the compounds **7e** and **7j** are found to be promising compared with other derivatives. The **7e** and **7j** can be taken up as possible DNA intercalators because of the planarity in the ring system, as well as it enhance the intercalation of imidazole ring system with the base pairs. The molecules have a fair chance to be developed as possible leads in anticancer drug discovery.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Authors Contribution

Dr. N D Satyanarayan, idea generator and direction of the investigation and overall responsible of the work.

Mr. Harishkumar S, researcher working for Ph.D. involved in the synthesis, characterization.

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