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Title of Thesis: DNA Binding and Anticancer Studies of Some Nitrogen and Sulphur Heterocyclic Compounds.

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ABSTRACT

The present research work deals with the synthesis, DNA binding, anticancer and docking studies of some novel heterocyclic compounds. The thesis comprises of five chapters.

Chapter 1 deals with the general introduction of cancer, the importance of heterocyclic compounds in the development of anticancer drugs.

Chapter 2 describes the detailed information of the materials used in the research work. Besides, details of the experimental methodologies have been given in this chapter.

Chapter 3 discusses the facile syntheses, characterization, DNA binding ADMET and docking studies of thiazolidine-2,4-diones (**2A-3R**). The compounds were obtained in good yields (60-85%) and were characterized by spectroscopic techniques. All the compounds had good solubilities in PBS at physiological pH. The synthesized compounds interacted with DNA through minor grooves and the appearances of hypochromism were the indication of binding of these compounds with DNA through non-covalent mode. The values of DNA binding constants (7.07×10^2 - 2.50×10^8 M^{-1}) indicated good binding ability of the compounds. The high cytotoxicities with IC_{50} in the range of 12-50 μM of these TZD derivatives against HepG2 cells indicated good anticancer activities. Compounds **2A, 3A, 3B, 3F, 3G, 3H, 3K** and **3Q** were found as the most active compounds against HepG2 cell line and **3C** and **3E** were found the most potent against A431 and FaDu cancer cell lines. Furthermore, the most active compounds of the series displaying good theoretical drug likeness and ADMET properties and BBB penetration which are certainly enlightening and helpful in future anticancer drug discovery efforts. The compounds (**3A-3R**) interacted with DNA through intercalation and minor grooves. The docking affinities of **3A-3R** varied from 5.4 to 6.6 kcal/mol, formed one to four hydrogen bonds with the nucleobases of DNA.

Chapter 4 describes the syntheses, characterization, DNA binding, anticancer activities, drug likeness, ADMET and docking studies of oxopyrrolidine derivatives (**1-12**). The oxopyrrolidine derivatives were obtained in good yields. The derivatives showed good

anticancer activities against MCF-7 cancer cell line (19-108% cell viability at 1.0 nM). Moreover, the compounds showed good anticancer activities against BV-2, FaDu, MDA-MB-231, K562, COLO-205, PC-3, A431 and WRL-68 cancer cell lines. Overall, from the anticancer assays, compounds **4, 6, 7, 9** and **10** can be considered as potent compounds and warrant their studies on other cancer cell lines. The values of DNA binding constants indicated a strong binding ability of synthesized compounds with DNA. DNA-compound adducts were mainly stabilized by hydrogen bonding, van der Waals and electrostatic attractions. The compounds interacted with DNA through minor grooves. The occurrence of hypochromism was an indication of binding of the compounds with DNA through both intercalation and electrostatic attractions. The pharmacological properties of the synthesized compounds indicated that all the compounds are in good agreement with the parameters set for orally bioavailable and non-toxic drugs, and thus we envisage the safe future of the reported compounds as drug leads. The DNA docked poses of **1-12** compounds were found to bind in a co-crystalized ligand like manner. The binding affinities of **1-12** followed the order **9>8>10>12>1>4 ≈ 5 ≈ 11>2 ≈ 6>3>7**. During interaction with DNA, **1-12** oriented themselves in such a way that their substituted phenyl and oxopyrrolidine rings were inside DNA minor grooves while thiadiazole rings containing amine groups were outside the grooves.

Chapter 5 describes the syntheses, characterization, DNA binding and antiproliferative activities of rhodanines (**RD1-7**). All the synthesized compounds were purified and successfully characterized with 66-84% yield. The values of DNA binding constants (K_b), K_{sv} and cell line studies were signals towards their good anticancer activities. These results were due to good DNA interacting ability of the reported compounds. The results showed that all the compounds (**RD1-7**) interacted with DNA through non-covalent mode of binding. The values of DNA binding constants K_b ranged from 1.0×10^5 to 7.4×10^{-2} M^{-1} and K_{sv} are also well agreed to each other. The occurrence of slight bathochromism and moderate hypochromism was an indication of binding of these compounds with DNA through mixed mode (partial intercalation and groove attraction). The antiproliferative activity and DNA binding affinity of the compounds **RD1, RD2, RD5** and **RD7** were promising and significant. The docking poses of **RD1-7** were found to muddle with DNA in a co-crystallized manner. Almost all the thiazolidine core based compounds were favoured to interrelate with DNA *via* minor groves. It may be because of small size and maximum possible interactions *via* H-bondings and hydrophobically.