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Synthesis of new sorafenib/ruthenium complexes and development of polymeric carrier systems to investigate drug potentials

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Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. The development of novel molecules and targeted therapies has gained attention because of currently available chemotherapeutic methods of limitations such as side effects/toxicity of existing drugs, high metastatic rates, and drug resistance. The improvement of the design of metal-based therapeutic agents which have a very important role in cancer treatment, have been accelerated by the development of platinum complexes. In the treatment of anticancer properties of metal complexes, many studies have been carried out on the development of new compounds with less toxic effect. Ruthenium is thought to have a lower side-effect profile, especially in platinum-resistant cancers and all other cancers, due to the greater accumulation of ruthenium, especially in cancer cells and hypoxic environments as well. Studies of anticancer and antimetastatic properties of ruthenium complexes have been published. Ruthenium complexes have been shown to be effective compounds in many cancers such as melanoma, lymphoma, breast and gastrointestinal cancers. It has been emphasized in many research articles that ruthenium complexes of phenanthroline-like compounds' toxicity are lower and show higher cytotoxic and apoptotic activity as compared with cisplatin. In cancer, activation of tyrosine kinases and intracellular pathway increases proliferation and angiogenesis and prevents apoptosis. Sorafenib is a multikinase inhibitor that has been approved for renal cell carcinoma, hepatocellular carcinoma, thyroid cancer, and the study of Sorafenib continues in other types of cancers. Sorafenib, which inhibits tumor proliferation and angiogenesis, in addition to Raf kinase also inhibits receptor tyrosine kinases such as VEGFR, PDGFRβ, c-KIT, RET. Receptor tyrosine kinases play a role in many cellular events such as proliferation and differentiation, cell survival and metabolism, cell cycle control. The fact studies that obtaining new metal complexes of the known drug active substances and investigation of their activities enable to reach the new drug substance in a shorter time and a lower cost has led to a remarkable increase in the researches in this field. Based on this data, in this study, firstly Sorafenib and ruthenium complexes of Sorafenib bearing hetrocyclic structures prepared as regards to valuable literature data. The structures of the obtained compounds were elucidated by elemental analysis, NMR, UV-Vis, FT-IR and APCI-LC/MS methods. Biological activity studies of the obtained products are performed. In this part of the study, MTT assay, cell cycle assay, apoptosis/cell death assay, *in vitro* tyrosine kinase assay, Western blot assay will be conducted. In addition, copolymers of poly (ethylene glycol) methyl ether-block-poly (D, L-lactate) (PEG-b-PLA) obtained to prepare polymeric micelles with active Sorafenib/metal complexes and drug release profiles examined. Finally, molecular modeling studies conducted by utilizing project outputs

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