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Topic of Research: **Structure-guided design of potent and selective microtubule affinity regulating Kinase 4 (MARK4) inhibitors; Approach towards therapeutic management of hepatocellular carcinoma**.

Findings

The work presented in the thesis entitled "**Structure-guided design of potent and selective microtubule affinity regulating Kinase 4 (MARK4) inhibitors; Approach towards therapeutic management of hepatocellular carcinoma**" is mainly focused on the design and development of new anti-cancerous hybrid molecules using computational and rational approaches. Research identifies natural compounds like vanillin as potent anticancerous agents, particularly in controlling various types of cancer. These compounds, including Gingerol, Resveratrol, Quercetin, Fisetin, Apigenin, and Vanillin, may interact with cancer-associated proteins, potentially enhancing anti-hepatocellular treatments. Over forty compounds were synthesized using in silico methods to develop MARK4-specific inhibitors, with compound **5g** showing high inhibitory activity against MARK4 and potential use in MARK4-based anticancer therapies. Research suggests using vanillin-isatin hybrids for MARK4-targeted anticancer therapies, as they showed significant binding, reduced enzyme activity, and inhibited growth and proliferation of HCC cell lines. Preliminary screening data revealed compounds from natural compound libraries showed promising anti-cancerous activity against HepG2 HCC cell lines and inhibition of protein microtubule affinity regulating Kinase 4. Biochemical and biophysical studies confirmed their potency, with cytotoxic evaluations performed on normal human cell lines. Overall, the work is multidisciplinary, applied, engaging, and well-executed. The novel study, which focuses on the development of anticancer drugs and cancer, will undoubtedly advance our understanding of the field. It specifically addresses MARK4 inhibitors as a means of treating hepatocellular carcinoma. The dissertation is structured into five sections. The first chapter covers a succinct overview, a review of the literature on cancer, the development of different FDA-approved natural, synthetic, and semisynthetic drugs, as well as their possible therapeutic targets. MARK4 inhibitors against hepatocellular carcinoma are given particular attention.

It's an intriguing observation that sheds light on how the MARK4 protein regulates and controls cancer. The following chapters are arranged in a sequential manner based on the study's objectives, with the second chapter providing a clear and comprehensive methodology. Every chapter also includes a thorough introduction, well-explained findings, and a conclusion. The thesis concludes with an appropriate and comprehensive bibliography. The thesis has been formatted standard and the majority of the work presented has been published in journals of repute.