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C_5-curcuminoid-4-aminoquinoline based molecular hybrids: design, synthesis and mechanistic investigation of anticancer activity†

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The privileged scaffolds of curcumin and 4-aminoquinolines are extensively used in the design and synthesis of biodynamic agents having remarkable efficacy against diseases like cancer and malaria. Therefore, we anticipated that covalent hybridization of these two pharmacophores via the triazole linker may lead to molecules with better anticancer activity. The synthesized hybrid compounds were tested for their anti-cancer activity on 60 human cancer cell lines, which represent diverse histologies. Our study has identified a set of these hybrids that showed excellent growth inhibition at nano-molar concentrations. The mechanistic investigations through a series of assays showed apoptotic induction as a cause for their displayed anticancer activity.

1. Introduction

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths in 2008 and expected to cross the figure of around 13 million deaths by 2030. About 70% of the cancer related deaths are mainly due to lung, colon, liver, stomach and breast cancers.[1,2] It is well established that there is no single treatment for cancer and patients often receive a combination of therapies and palliative care, such as surgery, radiation, immunotherapy, chemotherapy or gene therapy, depending on the type and stage of cancer, the health status, age and personal characteristics.[3] Anticancer drugs such as alkylating agents,[4–8] antimetabolites,[9–11] plant alkaloids,[12–15] topoisomerase inhibitors[16,17] and cytotoxic antibiotics[18] have been used extensively in chemotherapy. Among these, natural products show good promise in the development of anticancer molecules[19,20] and curcumin is one such natural product which has been extensively studied over the past few decades.[21] These studies revealed that curcumin shows anticancer activity against prostate cancer,[22] cervical cancer,[23] colorectal carcinoma,[24] leukemia[25] and human breast cancer cells.[26] The clinical use of curcumin has been hampered due to its poor solubility, absorption, bioavailability and rapid metabolism.[27–30] The pharmacokinetic studies reveal that the β-diketone functionality of curcumin is a substrate for liver aldoketo reductases and this may be one of the reasons for its rapid *in vivo* metabolism.[31] To overcome these limitations, several approaches have been explored and replacement of central diketo functionality with mono carbonyl has resulted in many compounds with improved anticancer activity, pharmacokinetic properties and bioavailability (Fig. 1).[32–36]

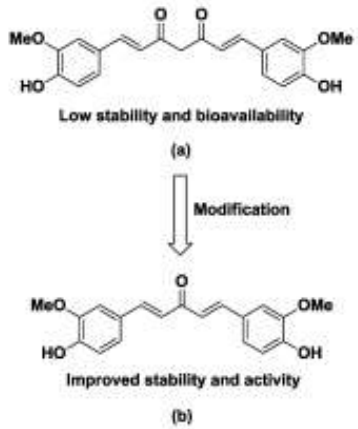

Fig. 1 (a) Curcumin; (b) C5-curcuminoid.

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