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An unorthodox metal-free synthesis of dihydro-6*H*-quinoline-5-ones in ethanol/water using a non-nucleophilic base and their cytotoxic studies on human cancer cell line†

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A DBU-catalysed metal-free domino reaction strategy has been developed for the facile synthesis of dihydro-6*H*-quinoline-5-ones. This protocol employs a very expedient route to the synthesis of pyridine frameworks using β-chloro-α,β-unsaturated aldehydes, 1,3-diketones, and ammonium acetate in ethanol : water (1 : 1) solvent under eco-friendly conditions. Diverse types of acyclic and cyclic β-chloro-α,β-unsaturated aldehydes were used to obtain a variety of dihydro-6*H*-quinoline-5-ones. The mechanism of the domino reaction was established by isolating the intermediate compound, which was subjected to the next step of the reaction to obtain the target product. The structure of the intermediate was established from spectral and single crystal XRD studies. Most of the synthesized dihydro-6*H*-quinoline-5-one derivatives were found to be cytotoxic to the HeLa cell lines, showing profound cytotoxicity in MTT assays. The DNA fragmentation assay showed no fragmented DNA in the treated sets, which indicated that the compounds did not induce apoptosis of the HeLa cells. In most of the cases, autophagic cell death was evident from fluorescence microscopy studies, though necrosis was also observed in some cases.

Introduction

In the recent eon of research, the discovery of small molecules with the efficiency to work in complex biological processes to prevent diseases has been one of the major challenges facing researchers.[1] This trend has clearly indicated a paradigm shift of the spotlight from natural product chemistry to combinatorial chemistry.[2] Among numerous nitrogen heterocycles, quinoline is a scaffold of crucial importance with respect to biomedical use. Several quinoline derivatives, isolated from natural resources or prepared synthetically, show a wide variety of biological activities.[3] One such type of important quinoline moiety is dihydroquinoline, which exhibits interesting biological and pharmaceutical activities including antitubercular (1), anti-HIV (2), anticancer (3), apical sodium-dependent bile acid transporter (ASBT) inhibition (4), (Fig. 1) *etc.* Compounds, streptonigrin (5), ascidiathiazones and lavendamycin, (Fig. 1) showed antibiotic, anticancer, and antiproliferative activities, respectively.[3]

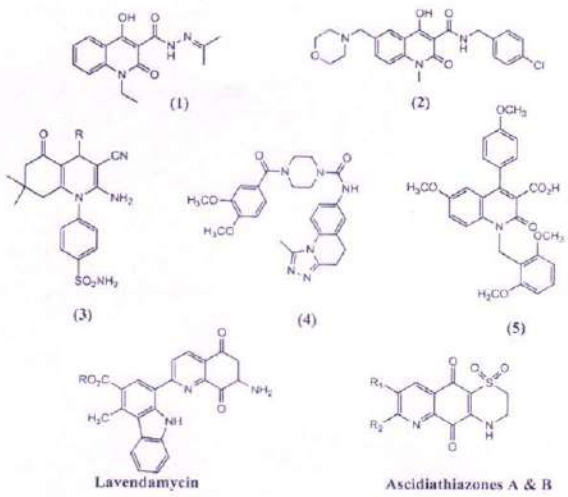

Fig. 1 Some naturally occurring quinoline derivatives.

Numerous skeletal analogues incorporating these crucial moieties have been prepared using synthetic approaches to

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