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Natural product inspired diastereoselective synthesis of sugar-derived pyrano[3,2-*c*]quinolones and their *in-silico* studies☆

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ABSTRACT

Herein, we report the development of a diastereoselective and efficient route to construct sugar-derived pyrano[3,2-*c*]quinolones utilizing 1-*C*-formyl glycal and 4-hydroxy quinolone annulation. This methodology will open a route to synthesize nature inspired pyrano[3,2-*c*]quinolones. This is the first report for the stereoselective synthesis of sugar-derived pyrano[3,2-*c*]quinolones, where 100% stereoselectivity was observed. A total of sixteen compounds have been synthesized in excellent yields with 100% stereoselectivity. The molecular docking of the synthesized novel natural product analogues demonstrated their binding modes within the active site of type II topoisomerase. The results of the *in-silico* studies displayed more negative binding energies for the all the synthesized compounds in comparison to the natural product huajiosimuline **A**, indicating their affinity for the active pocket. Ten out of the sixteen novel synthesized compounds were found to have comparative or relatively more negative binding energy in comparison to the standard anti-cancer drug, doxorubicin. Additionally, the scalability and viability of this protocol was illustrated by the gram scale synthesis.

1. Introduction

Natural products and its analogues are of paramount significance in medicinal chemistry. Synthesis of nature-inspired molecules is a vital domain of research in drug discovery to explore for new lead compounds [1,2]. However, the synthesis of natural products and its derivatives, specifically the stereoselectivity, is often a strenuous endeavour owing to their structural complexity, stereochemical diversity and intricate design. In continuation to our research on development of newer and efficient methodologies for the synthesis of drug-like small molecules and natural product analogues [3–7], we next targeted the synthesis of sugar derived pyrano[3,2-*c*]quinolone analogues on the nucleus pyrano[3,2-*c*]quinolone, which is an intrinsic component of the naturally occurring pyranoquinoline alkaloids, a member of the Rutaceae family, consisting of pyranoquinolinone as their principal structure [8]. Pyranoquinolone and fused pyrano[3,2-*c*]quinolone motifs are significant constituents of the pharmacological drugs, naturally occurring bioactive molecules as well as synthetic compounds [9–13]. Pyrano[3,2-*c*]quinolones are largely known for their anti-cancer activities [10,14–17], along with their potential to function as anti-malarial [18], anti-bacterial [19], and other agents [20]. Furthermore, pyrano[3,2-*c*]quinolone is an inherent structural constituent of numerous medicinally significant alkaloids (Fig. 1) [21–25].

Furthermore, presence of carbohydrate moiety in natural product-like scaffolds yields conjugate molecules with superior pharmacological properties [26–28] Recently, utilization of carbohydrates as chiral synthons in synthetic processes has tremendously escalated [29–31]. Unsaturated sugars have a significant position among the many carbohydrate derivatives as starting materials for the synthesis of various organic molecules [32,33]. Sugar-derived stereoselective pyrano[3,2-*c*]quinolone derivatives were designed based on *in-silico* studies and were synthesized chemically to obtain the conjugate motifs with astonishing pharmacological characteristics.

On extensive literature search, we found that there is only one report for the synthesis of sugar-based pyrano[3,2-*c*]quinolone derivatives [34]. Wherein, authors have reported the synthesis of glucose and

☆ We dedicate this article to the fond memory of our beloved Late Prof. Ashok K. Prasad.

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