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Synthesis and Anticancer Activity Evaluation of Azepinobisindoles; The Isomeric Iheyamine A-derivatives

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ABSTRACT

Azepinobisindole derivatives, the isomeric Iheyamine skeleton, were prepared and their anticancer activity evaluation were investigated against two human cancer cell lines, *Hepatocellular carcinoma* (HepG2) and human cervical cancer line (HeLa) as well as the normal cell line (Vero cell line) using MTT assay. The anticancer activity results indicated that 2-methoxy-5-methyl-5H-azepino[2,3-b:4,5-b]diindole was the most active derivative against tested cell lines. Additionally, molecular docking study in silico the possible inhibitory effect of cyclin-dependent kinase 2 (CDK2) by the azepinoindole revealed that all synthesized compounds fit well in the binding cavity of CDK2.

Keywords: Azepinobisindole, Isomeric Iheyamine, Anticancer activity, CDK2, Molecular docking.

INTRODUCTION

Bisindole alkaloids constitute an important class of secondary metabolites with characteristic cytotoxicity and pharmacological activities.[1-5] Azepinobisindole alkaloids are a class of bisindole alkaloids containing a structural moiety of azepine (seven-membered ring) core, which demonstrated diverse biological activities especially anticancer effect. In the past years, number types of indole-fused azepines have been found with potential success in drug discovery. For example, Hyrtimomine A was reported to show anticancer activity against human epidermoid carcinoma KB cells and murine leukemia L1210 cells and showed antimicrobial activity against *Candida albicans* and *Cryptococcus neoformans* by Tanaka *et al.,*[6] Another example was Trigonoliimines C, which was reported with a modest anti-HIV-1 activity[7] and the anticancer activity against human cervical cancer HeLa cells and human histiocytic lymphoma U-937 cells was also reported by Han *et al.,*[8] As illustrated in Fig. 1, Iheyamine A (1), the azepinobisindole isolated from a colonial marine ascidian *Polycitorella* sp. by Sasaki *et al.,* was