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Original article

Synthesis and structure-activity relationships study of α-aminophosphonate derivatives containing a quinoline moiety

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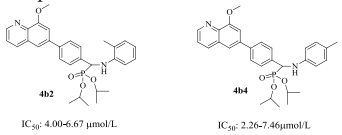

Two series of α-aminophosphonate derivatives containing a quinoline moiety have been designed, synthesized and evaluated for cytotoxic activity against Eca109 and Huh7 cancer cell lines *in vitro*. Among them, compounds **4b2** and **4b4** were found to be more active than Sunitinib against both of two cancer cell lines.

ABSTRACT
Two series of α-aminophosphonate derivatives containing a quinoline moiety have been designed and synthesized by introducing bioactive quinoline scaffold to α-aminophosphonate. The *in vitro* cytotoxic activities of target compounds were first investigated against two human cancer cell lines including Eca109 and Huh7 by MTT assay. Results revealed that most of target compounds exhibited moderate to high antitumor activities against the tested cancer cell lines and some demonstrated more potent inhibitory activities compared with Sunitinib. Among them, compounds **4b2** and **4b4** containing methyl-substituted aniline group were found to be more active than Sunitinib against both of two cancer cell lines, with IC_{50} in the range of 2.26 μmol/L-7.46 μmol/L.

Keywords: Quinoline, α-Aminophosphonate , Synthesis, Antitumor activity, In vitro.

1. Introduction

Cancer has become an important public health concern and a significant cause of death in the human population [1]. Cancer incidence and mortality have been increasing in China, making cancer the leading cause of death since 2010 and a major public health problem in the country [2]. Lung cancer was the leading cause of death in China followed by liver cancer, stomach cancer, esophageal cancer and colorectal cancer [3]. Despite many efforts to fight against cancer, the successful treatment of certain tumor types continues to be a challenge owing to their aggressiveness, the mechanisms of malignant cell metastasis, chemoresistance, and the lack of selectivity of some drugs [4]. Therefore, the development of novel anticancer agents with high efficacy and minimal side effects by synthesizing small and simple molecules is indispensable.

N-heterocyclic compounds are very crucial in drug design [5-7]. Compounds containing quinoline rings are extensively found in several classes of natural and synthetic biologically active compounds [8-10]. Quinoline-bearing structures are well-known due to their broad biological activities [11], such as anticancer [12], antifungal [13], antibacterial [14], antitubercular [15] and antimalarial [16] that have been used in traditional medicine as a remedy. Recently, quinoline-based azolyalkylquinolines bearing different azole groups, such as benzothiazole (SRA-HX-1), tetrazole (SRA-HX-2), and 1,2,4-triazole (SRAHX-3), have been synthesized and reported as potent antitumor agents for breast cancer cells *in vitro* [17]. 8-Hydroxyquinoline derivative (8-hydroxy-2-quinolinecarbaldehyde) has been reported to possess strong antitumor activities against human cancer cell lines and hepatocellular carcinoma Hep3B [18]. Moreover, a novel quinoline derivative **83b1** (8-(4-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquin-oline, has shown to inhibit cancer growth in human esophageal squamous cell carcinoma.[19].The structure of the quinoline derivative is depicted in Fig. 1.

α-Aminophosphonic acids and their corresponding α-amino phosphonates have received much attention in organic and medicinal chemistry because of their pharmacological properties and clinical applications [20-22]. Some of them have been used as potent enzyme inhibitors, antimicrobial, antitumor, antioxidant and antiviral agents [23-28]. It was reported that introduction of