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Synthesis of novel antiproliferative hybrid bis-(3-indolyl)methane phosphonate derivatives

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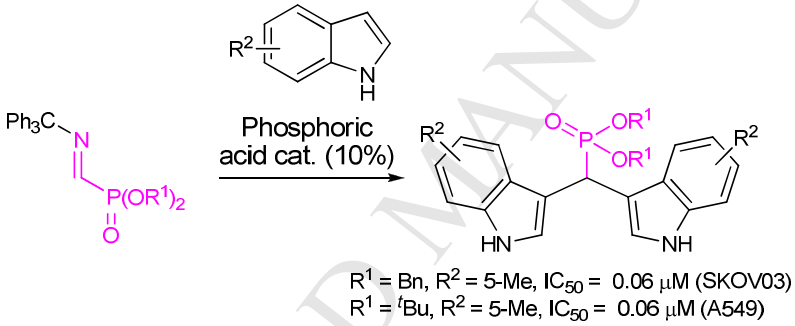
Abstract:

An efficient synthetic methodology for the preparation of phosphorus substituted bis-(3-indolyl)methane through a double nucleophilic addition of indole derivatives to an *in situ* generated α-iminophosphonate is reported. In addition, bis-(3-indolyl)methane substrates showed *in vitro* cytotoxicity, inhibiting the growth of carcinoma human tumor cell lines A549 (carcinomic human alveolar basal epithelial cell) and SKOV03 (human ovarian carcinoma).



1. Introduction:

Due to the notable grown in the life expectancy during the last decades, cancer has become one of the leading causes of death worldwide [1]. The World Health Organization (WHO) reports 8.8 million people died of cancer globally in 2015, being the most common cause of cancer death the cancer of lung with 1,69 million (19,4%) of deaths [2]. Cancer treatment comprises, in most of the cases, a combination of surgery and chemotherapy [3] and here is where Drug Discovery can play a crucial role into this area. There is still a serious need to search for some newer and safer anticancer agents and, therefore, the discovery of new active compounds and the *in vitro* evaluation of their anticancer properties represents an important task in Medicinal Chemistry, in order to improve our toolbox for the treatment of cancer.

Indole framework holds a very high affinity to multiple receptors and enzymes and, accordingly, it is considered a privileged structure in many active medicine compounds for human health and represents a promising scaffold for drug development [4]. In particular, bis-indole family derivatives, are of extraordinary significance in Synthetic and Medicinal Chemistry due to their wide occurrence in nature and their assorted biological activity [5]. Simple bis-(3-indolyl)methane (BIM) **I** and their derivatives (BIMs) **II-VIII** are nitrogen-