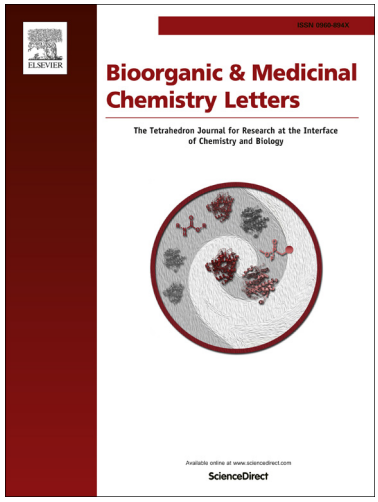

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Synthesis and cytotoxic activity of nitric oxide-releasing isosteviol derivatives

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ABSTRACT

Fifteen novel hybrids containing diterpene skeleton and nitric oxide (NO) donor were prepared from isosteviol. All the compounds were tested on preliminary cytotoxicity, and the results showed that six target compounds (**8c**, **10b**, **14a**, **14c**, **18c**, and **18d**) exhibited anti-proliferation activity on HepG2 cells, with **8c** (IC_{50} = 4.24 μM) and **18d** (IC_{50} = 2.75 μM) superior to the positive control CDDO-Me (2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-acid methyl ester, IC_{50} = 4.99 μM); eleven target compounds (**8a-c**, **9a-c**, **10a-b**, **14a**, **14c**, **18d**) exhibited anti-proliferation activities on B16F10 cells at different levels, among them, seven compounds were more potent than comptothecin (IC_{50} = 2.78 μM) and CDDO-Me (IC_{50} = 5.85 μM), particularly, **10b** (IC_{50} = 0.02 μM) presented the strongest effect, which was slected as a candidate for further study.

Keywords: isosteviol; furoxan; cytotoxicity; structural modification; NO-donor

Isosteviol (ent-16-oxobeyeran-19-oic acid, **1**, **Figure 1**), bearing distinctive tetracyclic skeleton of beyerane can be obtained by acid hydrolysis of stevioside in good yield.[1, 2] Recently, isoteviol and its derivatives have attracted considerable interest because of their wide biological activities including antihyperglycemia,[3] anti-hypertension,[4] anti-inflammation,[5] antitumor,[6-9] antimicrobial activity[10] and so on. In the process of looking for potent antitumor derivatives of isosteviol, some structure activity relationships (SARs) were summarized, for example, exo-methylene cyclopentanone and *a*-methylenelactone are crucial structures to produce antitumor effects. The parent structures of the new compounds in this paper were designed on the basis of the SARs above.

Meanwhile, nitric oxide (NO) played dual roles in the occurrence and development of tumor, *i.e.* high concentration of NO was cytotoxic to tumor cells by leading to apoptosis and blocking spread and migration, whereas relatively low level of NO promoted tumor growth and proliferation.[11] NO donors refer to compounds that can release a certain amount of NO by the action of enzymes and non-enzymes, including organic nitrates, furoxans, metal-NO complexes, nitrosothiols, and NONOates, *etc*. With the development of NO donors, NO-donating drugs gradually emerged and developed rapidly. Among these, the most successful drug is NO-nonsteroidal anti-inflammatory drugs (NO-NSAIDs), which reduced the side effect of NSAIDs on the one hand and increased the anti-cancer effect on the other hand.[12] Our group had discovered several novel NO-releasing derivatives of natural compounds such as NO-oleanolic acid or NO-ursolic acid hybrids with desirable cytotoxic activity. [13-17]

Considering the SARs of isoteviol derivatives, the anti-proliferation activity of NO, and the

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