Mcrobial transformation of isosteviol oxime and the inhibitory effects on NF-kappaB and AP-1 activation in LPS-stimulated macrophages.

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Abstract

Microbial transformation of isosteviol oxime (ent-16-E-hydroxyiminobeyeran-19-oic acid) (2) with Aspergillus niger BCRC 32720 and Absidia pseudocylindrospora ATCC 24169 yielded several compounds. In addition to bioconverting the d-ring to lactone and lactam moieties, 4alpha-carboxy-13alpha-hydroxy-13,16-seco-ent-19-norbeyeran-16-oic acid 13,16-lactone (7) and 4alpha-carboxy-13alpha-amino-13,16-seco-ent-19-norbeyeran-16-oic acid 13,16-lactam (10), one known compound, ent-1beta,7alpha-dihydroxy-16-oxo-beyeran-19-oic acid (6), and five new compounds, ent-7alpha-hydroxy-16-E-hydroxyiminobeyeran-19-oic acid (3), ent-1beta,7alpha-dihydroxy-16-E-hydroxyiminobeyeran-19-oic acid (4), ent-1beta-hydroxy-16-E-hydroxyiminobeyeran-19-oic acid (5), ent-8beta-cyanomethyl-13-methyl-12-podocarpen-19-oic acid (8), and ent-8beta-cyanomethyl-13-methyl-13-podocarpen-19-oic acid (9), were isolated from the microbial transformation of 2. Elucidation of the structures of these isolated compounds was primarily based on 1D and 2D NMR, and HRESIMS data, and 3-5 were further confirmed by X-ray crystallographic analyses. Additionally, the inhibitory effects of all of these compounds were evaluated on NF-kappaB and AP-1 activation in LPS-stimulated RAW 264.7 macrophages. Among the compounds tested, 5 and 10 significantly inhibited NF-kappaB activation, with 5 showing equal potency to dexamethasone; 3 and 6-9 significantly inhibited AP-1 activation, particularly 8, which showed more inhibitory activity than dexamethasone.