10-2007

16-Aza-ent-beyerane and 16-Aza-ent-trachylobane: Potent Mechanism-Based Inhibitors of Recombinant ent-Kaurene Synthase from Arabidopsis thaliana

Amab Roy
University of Illinois at Urbana-Champaign

Frank G. Roberts
University of Illinois at Urbana-Champaign

P. Ross Wilderman
Iowa State University

Ke Zhou
Iowa State University

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16-Aza-ent-beyerane and 16-Aza-ent-trachylobane: Potent Mechanism-Based Inhibitors of Recombinant ent-Kaurene Synthase from Arabidopsis thaliana

Abstract
The secondary ent-beyeran-16-yl carbocation (7) is a key branch point intermediate in mechanistic schemes to rationalize the cyclic structures of many tetra- and pentacyclic diterpenes, including ent-beyerene, ent-kaurene, ent-trachylobane, and ent-atiserene, presumed precursors to >1000 known diterpenes. To evaluate these mechanistic hypotheses, we synthesized the heterocyclic analogues 16-aza-ent-beyerane (12) and 16-aza-ent-trachylobane (13) by means of Hg(II)- and Pb(IV)-induced cyclizations onto the Δ12 double bonds of tricyclic intermediates bearing carbamoylmethyl and aminomethyl groups at C-8. The 13,16-seco-16-norcarbamate (20a) was obtained from ent-beyeran-16-one oxime (17) by Beckmann fragmentation, hydrolysis, and Curtius rearrangement. The aza analogues inhibited recombinant ent-kaurene synthase from Arabidopsis thaliana (GST-rAtKS) with inhibition constants (IC50) 1 × 10⁻⁷ and 1 × 10⁻⁶ M) similar in magnitude to the pseudo-binding constant of the bicyclic ent-copalyl diphosphate substrate (Km) 3 × 10⁻⁷ M). Large enhancements of binding affinities (IC50) 4 × 10⁻⁹ and 2 × 10⁻⁸ M) were observed in the presence of 1 mM pyrophosphate, which is consistent with a tightly bound ent-beyeranyl⁺/pyrophosphate-ion pair intermediate in the cyclization-rearrangement catalyzed by this diterpene synthase. The weak inhibition (IC50) 1 × 10⁻⁵ M) exhibited by ent-beyeran-16-exo-yl diphosphate (11) and its failure to undergo bridge rearrangement to kaurene appear to rule out the covalent diphosphate as a free intermediate. 16-Aza-ent-beyerane is proposed as an effective mimic for the ent-beyeran-16-yl carbocation with potential applications as an active site probe for the various ent-diterpene cyclases and as a novel, selective inhibitor of gibberellin biosynthesis in plants.

Keywords
alkyl transferases, aryl transferases, Arabidopsis, Aza compounds, Crystallography, Enzyme inhibitors

Disciplines
Biochemistry, Biophysics, and Structural Biology | Natural Products Chemistry and Pharmacognosy

Comments

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Authors
Antibiofouling Polymer-Coated Gold Nanoparticles as a Contrast Agent for in Vivo X-ray Computed Tomography Imaging [J. Am. Chem. Soc. 2007, 129, 7661–7665]. Dongkyu Kim, Sangjin Park, Jae Hyuk Lee, Yong Yeon Jeong,* and Sangyong Jon*

We found that there were two errors in Figure 2. One is in the format of Figure 2 itself, and the other is in the CT value of Ultravist. The format of Figure 2 was not appropriate to compare the efficacy as a CT contrast agent between the PEG-coated gold nanoparticles (GNPs) and Ultravist. In the corrected Figure 2 below, the CT value is denoted as a function of concentration (M in log scale, not mg/mL) of GNPs. On the other hand, the corrected CT value of Ultravist in the corrected Figure 2 revealed that GNPs had about 1.9 times higher X-ray absorption than Ultravist, not 5.7 times as described in the published paper. Despite the above-mentioned errors, however, the concept and the usefulness of GNPs as a CT contrast agent are still valid because those errors might have little influence on the conclusion of the paper. The detailed corrections are described below.

Corrected Figure 2 and the figure caption

The paragraph of page 7663, column 2, lines 17–24 should be rewritten as follows:

Figure 2 shows that 1.27 M of PEG-coated GNPs gave an equivalent X-ray absorption as 2.36 M of Ultravist (corresponding to 300 mg iodine/mL). In other words, at the same concentration, the attenuation coefficient of the PEG-coated GNPs is 1.9 times higher than that of the current iodine-based CT contrast agent.


Page 8035. The wrong DNA sequences were reported in Figure 1. The correct sequences are shown below.

ODN1(X): 5′-CTC TGT GCG CCX GTC TCT-3′
ODN 6: 5′-CTC TGT GCG CC-3′
ODN 7: 5′-CTC TGT GCG CCNQ2-3′

Page 8038. The wrong name of DNA was reported in Table 1. ODN 2(mC) should be corrected to ODN 2( m C).

We thank Prof. Yoshihiro Kudo for bringing this error to our attention.

JA076508K

10.1021/ja076508k
Published on Web 09/25/2007