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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

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

Reuben J. Peters
Iowa State University, rjpeters@iastate.edu

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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 $\Delta 12$ 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) $1 \times 10\text{-}7$ and $1 \times 10\text{-}6$ M) similar in magnitude to the pseudo-binding constant of the bicyclic ent-copalyl diphosphate substrate (Km) $3 \times 10\text{-}7$ M). Large enhancements of binding affinities (IC50) $4 \times 10\text{-}9$ and $2 \times 10\text{-}8$ 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) $1 \times 10\text{-}5$ 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.

Authors

Amab Roy, Frank G. Roberts, P. Ross Wilderman, Ke Zhou, Reuben J. Peters, and Robert M. Coates

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ADDITIONS AND CORRECTIONS

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 I/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.
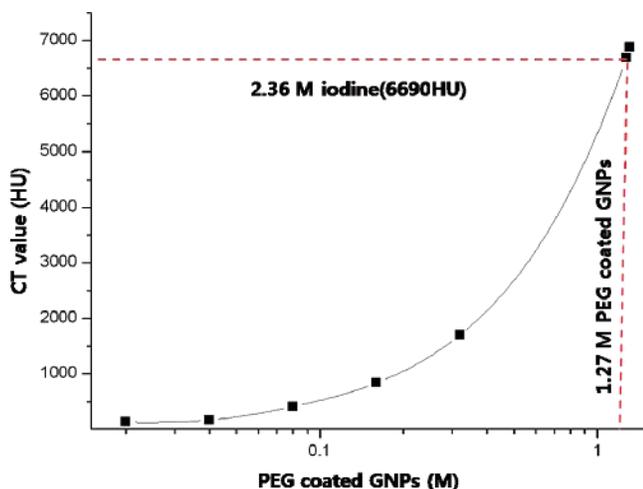

Figure 2. HU measurements of the PEG-coated GNPs in vitro. The measurements show that 1.27 M of PEG-coated GNPs gives an equivalent X-ray absorption as 2.36 M (300 mg iodine/mL) of the conventional iodine contrast agent, Ultravist.

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One-Electron Photooxidation and Site-Selective Strand Cleavage at 5-Methylcytosine in DNA by Sensitization with 2-Methyl-1,4-naphthoquinone-Tethered Oligonucleotides [*J. Am. Chem. Soc.* **2007**, *129*, 8034–8040]. Kazuhito Tanabe,* Hisatsugu Yamada, and Sei-ichi Nishimoto*

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 CC**NQ$_2$**-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.

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