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Comment: di(1,N^6-ethenoadenosine)-5′,5‴-P^1,P^4-tetraphosphate, a fluorescent enzymatically active derivative of Ap_4A

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Rotllán et al. have recently reported in this journal the synthesis of di(1,N^6-ethenoadenosine)-5′,5‴-P^1,P^4-tetraphosphate ($\varepsilon Ap_4\varepsilon A$), a fluorescent derivative of diadenosine tetraphosphate (Ap_4A), by the direct modification of Ap_4A with chloroacetaldehyde. The 7-fold enhancement of fluorescence observed upon enzymic hydrolysis of this compound to 1,N^6-etheno-AMP (εAMP) by crude cellular extracts led the authors to suggest that it may be of use as a sensitive substrate for the assay of the specific Ap_4A hydrolases that are found in all tissues [1]. The clear implication of this paper is that this is a new analogue of Ap_4A and that the potential application to the assay of Ap_4A hydrolases is also novel.

It is unfortunate that the authors appear to be entirely unaware of several previous reports of the synthesis and applications of etheno- derivatives of Ap_4A and other related dinucleoside polyphosphates. The first of these appeared in 1975 when Feldhaus et al. reported the synthesis of asymmetrically-modified 1,N^6-etheno-Ap_5A (εAp_5A) by the diphenyl phosphochloridate-mediated condensation of adenosine 5′-tetraphosphate with εAMP [2]. This compound was used as a sensitive fluorescent probe for the nucleotide binding site of skeletal muscle adenylate kinase. $\varepsilon Ap_4\varepsilon A$ itself was first synthesized from Ap_4A and chloroacetaldehyde in 1984 and shown to be a potentially useful substrate for snake venom phosphodiesterase [3,4]. These authors also synthesized the mono-substituted εAp_4A from εADP and ADP using carbonyldiimidazole. The most comprehensive investigation of these compounds was provided by David Shugar's group who synthesized $\varepsilon Ap_2\varepsilon A$, $\varepsilon Ap_3\varepsilon A$ and $\varepsilon Ap_4\varepsilon A$ directly from the parent nucleotides as above and characterized them extensively with regard to their use as substrates for potato nucleotide pyrophosphatase and snake venom phosphodiesterase [5]. In their paper, Wierzchowski et al. also discussed the potential value of $\varepsilon Ap_3\varepsilon A$ and $\varepsilon Ap_4\varepsilon A$ as substrates for the continuous fluorimetric assay of the specific dinucleoside polyphosphate hydrolases [5]. Finally, Suzuki et al. have described the inhibition of histone H1 ADP-ribosylation catalyzed by bovine thymus poly(ADP-ribose)transferase by both εAp_4A and $\varepsilon Ap_4\varepsilon A$ (synthesized by Shumvantseva) [6].

The properties of $\varepsilon Ap_4\varepsilon A$ described by Rottlán et al. are identical to those described by previous authors; thus their paper makes no further contribution to what is already known about these compounds and their possible uses.

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