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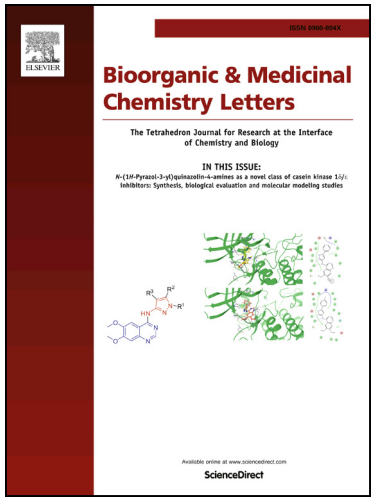

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Synthesis of novel vitamin K derivatives with alkylated phenyl groups introduced at the ω-terminal side chain and evaluation of their neural differentiation activities

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ABSTRACT

Vitamin K is an essential cofactor of γ-glutamylcarboxylase as related to blood coagulation and bone formation. Menaquinone-4, one of the vitamin K homologues, is biosynthesized in the body and has various biological activities such as being a ligand for steroid and xenobiotic receptors, protection of neuronal cells from oxidative stress, and so on. From this background, we focused on the role of menaquinone in the differentiation activity of progenitor cells into neuronal cells and we synthesized novel vitamin K derivatives with modification of the ω-terminal side chain. We report here new vitamin K analogues, which introduced an alkylated phenyl group at the ω-terminal side chain. These compounds exhibited potent differentiation activity as compared to control.

Vitamin K is an essential cofactor of γ-glutamyl carboxylase of Gla proteins related to blood coagulation and bone formation.[1] There are two different kinds of natural vitamin K homologues: vitamin K_1 (also called phylloquinone (PK)), which has a phytyl group for a side chain, and vitamin K_2 (also called menaquinone-n (MK-n)), which has an isoprene unit (Fig. 1).[2, 3]

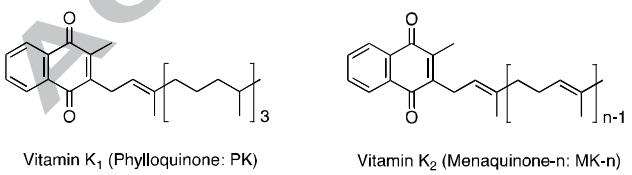

Figure 1. Natural vitamin K homologues

We have reported that MK-4 is biosynthesized in the body by conversion from other dietary vitamin K homologues such as PK or MK-7, and is accumulated in various tissues, especially in brain.[4,5] Therefore, we anticipated that MK-4 would play an important role in the body. In fact, it has been clarified that MK-4 showed various biological activities except the γ-glutamyl carboxylation reaction, such as SXR-mediated transcriptional activity, protective effects from oxidative stress, and so on.[6-8] We especially focused on the differentiation activity from neural progenitor cells (NPCs) to neuronal cells, and synthesized some vitamin K analogues for the purpose of increasing the biological activities. In the previous study, we found that the biological activities of vitamin K analogues were increased by introduction of a phenyl group at the ω-terminal position,[9] and we have already succeeded in obtaining some analogues more potent than MK-4.[10,11] The most potent analogue **1** among our analogues contained a *m*-methylphenyl group at the ω-terminal side chain of MK-3 (Fig. 2).[10]

Based on these previous observations, we predicted that an alkyl group, including the methyl group, would play an important role for differentiation activities, and the potency might parallel the number or position of alkyl groups, which were bound to the terminal phenyl group. Therefore, we synthesized new vitamin K analogues, introduced a phenyl group modified with 2 or 3 methyl groups or a *tert*-butyl group at the ω-terminal position of