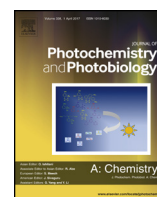




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## Transformation of 6-tetrahydrobiopterin in aqueous solutions under UV-irradiation



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### ABSTRACT

Melanogenesis disturbance leads to several pathologies, including vitiligo disease. Ultraviolet (UV) narrowband phototherapy (308 or 311 nm) is used in treating vitiligo; however, the mechanism of phototherapy is not yet understood. Vitiligo is accompanied by three-fivefold increased *de-novo* synthesis of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (H<sub>4</sub>Bip), its excess and its further oxidation can be considered as significant factors in the pathogenesis of vitiligo. (H<sub>4</sub>Bip), as the phenylalanine 4-hydroxylase coenzyme, catalyzes the oxidation of phenylalanine to tyrosine (a melanin precursor). In this context, photo-transformation of H<sub>4</sub>Bip in aqueous buffer solutions has been studied. HPLC–MS/MS has demonstrated that pterin products of H<sub>4</sub>Bip autoxidation (7,8-dihydropterin (H<sub>2</sub>Ptr), dihydroanthopterin and pterin) predominate over biopterin products (7,8-dihydrobiopterin (H<sub>2</sub>Bip) and biopterin). We have shown that UV irradiation accelerates the autoxidation while the products of oxidative degradation of H<sub>4</sub>Bip act as photosensitizers. The distinctive feature of photooxidation of H<sub>4</sub>Bip from autoxidation is the formation of dihydropterin (H<sub>2</sub>Ptr)<sub>2</sub> and dihydrobiopterin (H<sub>2</sub>Bip)<sub>2</sub> dimers. By means of HPLC–MS/MS it was found that formation of dihydropterin dimers is the predominant process. The signal of molecular ion of the dimer (H<sub>2</sub>Ptr)<sub>2</sub> (*m/z* = 331) was almost a thousand times higher than the signal of (H<sub>2</sub>Bip)<sub>2</sub> (*m/z* = 479). The key point of the dimerization is photoexcitation (at 310–320 nm) of the intermolecular complex (qH<sub>2</sub>Ptr–H<sub>2</sub>Ptr) generated in dark. As a result of the photoreaction azacyclobutane dimers have been formed. In the case of alternation of dark and light intervals H<sub>4</sub>Bip converted into dimers with 96 % yield. The data obtained are discussed in the context of UV-B narrowband vitiligo phototherapy.

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### 1. Introduction

(6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (H<sub>4</sub>Bip) is a coenzyme for the series of enzymes: NO synthases, alkylglycerol monooxygenases and aromatic amino acid hydroxylases. H<sub>4</sub>Bip is the coenzyme of phenylalanine hydroxylase (EC 1.14.16.1) catalyzing the oxidation of phenylalanine to tyrosine by molecular oxygen in the process of melanogenesis [1]. Melanogenesis disturbance leads to a characteristic feature of certain dermatological

pathologies, including vitiligo disease, which results in the emergence of depigmented skin patches. The patients with vitiligo appeared to have three-fivefold increased *de-novo* synthesis of H<sub>4</sub>Bip; its excess and its further oxidation can be considered as important factors in the pathogenesis of vitiligo [2–6]. Pterin and its reduced forms absorb light in the ultraviolet spectral region. Recently, tetrahydrocyanopterin has been described as a chromophore within a photoreceptor of several cyanobacteria [7,8]. The role that pterins perform as photoreceptors and as photosensitizers of metabolic reactions is not well understood. It is obvious, however, that these issues are vitally important for photobiology [9] and photomedicine. Apart from our recent work [10], the photochemistry of H<sub>4</sub>Bip coenzyme has never been studied. We have demonstrated that biopterin, which has been formed in H<sub>4</sub>Bip solution as a result of the dark oxidation, acts as the

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