N^{γ}-Alkyl Derivatives of L-Glutamine As Inhibitors of Glutamine-Utilizing Enzymes

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A general, facile method to synthesize the N^{γ}-alkyl and N^{γ},N^{γ}-dialkyl derivatives of L-glutamine **1a–d** from L-glutamic acid as a starting substrate is presented. The obtained compounds are shown to inhibit three different glutamine-utilizing enzymes, namely: glutaminase, γ-glutamyl transpeptidase, and glucosamine-6-phosphate synthase, with inhibitory constants within the millimolar range.

Key words: L-Glutamine Derivatives, Synthesis, *N*-Alkylamide Formation

Introduction

Structural analogues of L-glutamine exhibit inhibitory properties towards enzymes utilizing this amino acid as a substrate, including glutaminase (EC 3.5.1.2), γ-glutamyl transpeptidase (EC 2.3.2.2) and several amidotransferases catalyzing the transfer of an amino group from the γ-amide function of L-glutamine to different acceptor molecules (Massiere and Badet-Denisot, 1998). One of these enzymes is glucosamine-6-phosphate synthase (GlcN-6-P synthase, EC 2.6.1.16) which catalyzes the first committed step in a pathway leading to the formation of UDP-*N*-acetylglucosamine, providing *N*-acetyl-D-glucosamine for the formation of bacterial peptidoglycan and fungal chitin. For that reason, inhibitors of the enzyme are potential antimicrobial agents. Inhibitory properties of some glutamine analogues with respect to GlcN-6-P synthase and other amidotransferases have been reviewed (Pinkus, 1977). In the present paper we describe the synthesis and enzyme inhibitory properties of four N^{γ}-alkyl analogues of L-glutamine, namely N^{γ}-ethyl- (**1a**), N^{γ}-methyl- (**1b**), N^{γ},N^{γ}-diethyl- (**1c**) and N^{γ},N^{γ}-dimethyl-L-glutamine (**1d**).

According to literature data (Tsushida and Takeo, 1984, 1985a; Chu *et al.*, 1997) both N^{γ}-ethyl-L-glutamine (**1a**) (better known as theanine) and N^{γ}-methyl-L-glutamine (**1b**) have been found in green tea leaves. The research on rats with induced hypertension revealed that this two compounds cause significant reduction in blood pressure (Yokogoshi and Kobayashi, 1998; Yokogoshi *et al.*, 1995). Recent studies have shown that theanine and N^{γ}-methyl-L-glutamine zinc(II) complexes exhibit insulinomimetic activity relative to isolated *in vitro* rodent adipocytes treated with epinephrine and also induce the release of free fatty acids (FFA) from fat cells (Matsumoto *et al.*, 2005). Any particular biological properties of N^{γ},N^{γ}-dialkyl derivatives of L-glutamine have not been reported so far.

Results and Discussion

Syntheses of N^{γ}-alkyl derivatives of L-glutamine have been reported by several authors (Tanaka, 1962; Hashizume, 1951; Lichtenstein, 1942; Sakato *et al.*, 1950; Craig *et al.*, 1988; Furuyama *et al.*, 1964; Gu *et al.*, 2004; Tsushida and Takeo, 1985b). Theanine (N^{γ}-ethyl-L-glutamine) has been most often obtained by aminolysis of *N*-carbobenzyloxy-L-glutamic acid (Hashizume, 1951; Sakato *et al.*, 1950) or L-glutamic acid γ-methyl ester (Kawagishi and Sugiyama, 1992; Tanaka, 1962; Lichtenstein, 1942; Furuyama *et al.*, 1964; Barzily *et al.*, 1956). Alternatively, *N*-phthaloyl-DL-glutamic anhydride was treated with a suitable amine to give N^{α}-phthaloyl-N^{γ}-di- or -monoethyl-DL-glutamine, and subsequent removal of the pththaloyl residue with hydrazine led to the ultimate product,

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