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SYNTHESIS AND BIOLOGICAL EVALUATION OF THEANINE AND 4-SUBSTITUTED DERIVATIVES ON GLUTAMATERGIC SYNAPSES

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Introduction:

L-Theanine, (L- γ -glutamylethylamide) is a non-protein amino acid that occurs naturally in the tea plant (*Camellia sinensis*)¹. It presents a similar chemical structure with glutamate and glutamine (fig 1), which are the most important neurotransmitters related to memory. The theanine acts directly on the central nervous system and shows neuroprotective effects^{2,3}. Besides the graceful favorable physiological functions, a cooperative effect of theanine with several antitumor agents has also been reported⁴. Theanine is able to cross the blood-brain barrier via leucine-perfering transport system.

Firstly our work has been focused on production of L or D-Theanine and its derivatives L or D-5-N propylglutamine by an easy and efficient protocol assisted by microwaves irradiation.

In the other hand we are engaged in synthesis of new 4-substituted Theanine derivatives by using (S)-pyroglutamate as starting compound. The key step of this new strategy is a regio and stereospecific alkylation on C4 induced by (S) configuration of C2, the high steric hindrance of protecting groups and the nature of alkylating reagent (Scheme 1 and 2). The (2S, 4R) configuration of C-benzylated Theanine has been confirmed by X Ray analysis of crystallized **2a** intermediate compound (fig. 2) and NMR spectroscopy of each derivatives (**2a**, **2b** and **2c**).

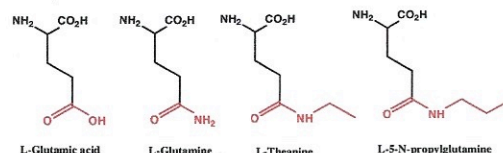


Fig.1

Scheme.1: Synthesis of optically pure (2S, 4S)-benzyl derivatives of Theanine from (S) pyroglutamic acid.

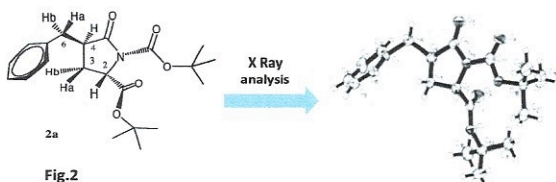
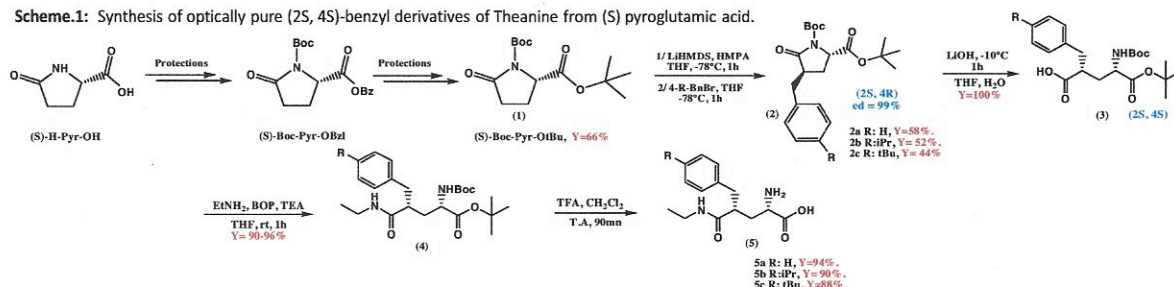
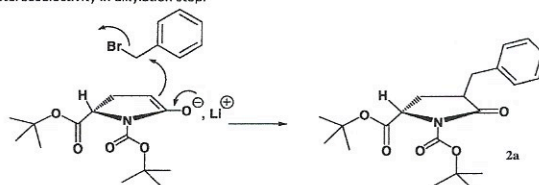
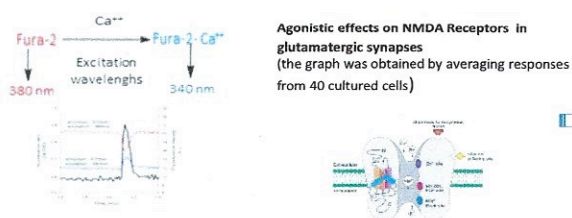


Fig.2

Scheme.2: Stereospecificity in alkylation step.



Preliminary biological results : fura-2 experiments and spectrofluorimetry



Conclusion:

A concise, asymmetric synthesis of enantiomerically pure 4-alkylated theanine derivatives as new analogue of L-Theanine was reported herein, the key step is a regio- and stereoselective C-benylation.

The synthetic C-4-alkylated L-Theanine will be tested for their neuroprotective effect on NMDA receptors in glutamatergic synapses on hippocampal neuron culture by intracellular calcium measurement (fura 2 experiments).

As preliminary results, the optically pure L and D γ -N-propylglu and D-Theanine revealed a more potent agonistic effect than L-Theanine. They also displayed positive modulator effects on NMDA-mediated responses.

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