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Title: Natural products as scaffold for the development of GABA A receptor ligands

Abstract in English:

In the course of this thesis, novel γ-aminobutyric acid type A (GABA(A)) receptor modulators from plant origin belonging to different classes of secondary metabolites – alkaloids, stilbenoids, abietan diterpenes and (neo)lignans – were identified. In order to evaluate the potential medical use of these natural products and their derivatives, GABA(A) receptors of different subunit composition and transient receptor potential vanilloid type 1 (TRPV1) channels were expressed in Xenopus laevis oocytes and their interaction with these natural products or derivatives was studied by means of two-microelectrode voltage-clamp technique.

Derivatisation of piperine [1-[5-(1,3-Benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine] and honokiol [2-(4-hydroxy-3-prop-2-enyl-phenyl)- 4-prop-2-enyl-phenol] led to the development of more potent, more efficacious and more selective GABA(A) receptor ligands. Structural modifications of piperine diminished interaction with TRPV1 channels and thereby prevented the heat and pain inducing effects of this natural product. Piperine derivative 24 [(2E,4E)-5-(1,3-benzodioxol-5-yl))-N,N-diisopropyl-2,4-pentadienamide] inhibited capsaicin-induced activation of TRPV1 receptors (95 % reduction of current amplitude; IC50 = 39.3±3.0 μM), and modulated GABA(A) receptors more efficaciously and more potently than piperine (α1β2γ2S: Emax = 359±4 %; EC50 = 21.5±1.7 μM). Piperine derivative 6 [(2E,4E)-N,N-dibutyl-5-(4-methoxyphenyl)penta-2,4-dienamide] displayed a higher efficacy than piperine (α1β2γ2S: Emax = 1363±57 %; EC50 = 7.5±1.0 μM) as well as β2/3 GABA(A) receptor subunit selectivity, and also did not activate TRPV1 channels. Batatasin III (α1β2γ2S: Emax = 1513±177 %; EC50 = 52.5±17.0 μM), a dihydrostilbene derived from the orchid species Pholidota chinensis, and dehydroabietic acid (α1β2γ2S: Emax = 682±45 %; EC50 = 8.7±1.3 μM) found in Olibanum, were identified as novel GABA(A) receptor modulators. Seven nitrogenated honokiol derivatives (e.g. 5: 3-acetamido-4'-ethoxy-3',5-dipropylbiphenyl-2-ol) were characterized as highly efficacious and potent GABA(A) receptor modulators (e.g. 5, α1β2γ2S: Emax = 1975±218 %; EC50 = 2.1±1.2 μM) with partial agonist activity.

I conclude that these natural products and derivatives represent promising scaffolds for the development of novel GABA(A) receptor modulators for the treatment of anxiety disorders, epilepsy and various other disease states.