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Modulation of GABAA-receptors by honokiol and derivatives: subtype selectivity and structure-activity relationship.

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Abstract

A series of 31 analogues of the neolignan honokiol (a major constituent of Magnolia officinalis) was synthesized, and their effects on GABA(A) receptors expressed in Xenopus oocytes were investigated. Honokiol enhanced chloride currents (I(GABA)) through GABA(A) receptors of seven different subunit compositions with EC(50) values ranging from 23.4 μM (α(5)β(2)) to 59.6 μM (α(1)β(3)). Honokiol was most efficient on α(3)β(2) (maximal I(GABA) enhancement 2386%) > α(2)β(2) (1130%) > α(1)β(2) (1034%) > α(1)β(1) (260%)). On α(1)β(2)-receptors, N-substituted compounds were most active with 3-acetylamino-4'-O-methylhonokiol (31), enhancing I(GABA) by 2601% (EC(50) (α(1)β(2)) = 3.8 μM). Pharmacophore modeling gave a model with an overall classification accuracy of 91% showing three hydrophobic regions, one acceptor and one donor region. Unlike honokiol, 31 was most efficient on α(2)β(2)- (5204%) > α(3)β(2)- (3671%) > α(1)β(2)-receptors (2601%), suggesting a role of the acetamido group in subunit-dependent receptor modulation.

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