学位論文の要旨

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主論文の題名

A novel orexin antagonist from a natural plant was discovered using zebrafish behavioural analysis

主論文の要旨

OBJECTIVE: Phenotypic screening is one of the most practical approaches to the identification of mediators of behaviour, since it is difficult to model brain function in vitro, at a cellular level. We used a zebrafish (*Danio rerio*) behavioural assay to discover novel, natural, neuroactive compounds.

MATERIALS AND METHODS: A zebrafish behavioural assay was performed for seven natural compounds, obtained from plants. The behavioural profiles were compared to those of known psychoactive drugs. We characterised a natural compound exhibiting a behaviour profile similar to that of suvorexant, using *in silico*, *in vitro* and microarray expression analysis.

RESULTS: The behavioural analysis performed in this study classified central nervous system drugs according to their mechanism. Zebrafish treated with a natural compound, 8β-(4'-Hydroxytigloyloxy) costunolide, showed behaviour profiles similar to those of zebrafish treated with suvorexant, a known orexin antagonist. This behavioural assay was validated using in silico and in vitro assays, which revealed that the new compound was a dual orexin receptor antagonist. In addition, transcriptome analysis suggested that 8β-(4'-Hydroxytigloyloxy) costunolide might regulate the NF-κB-related pathway.