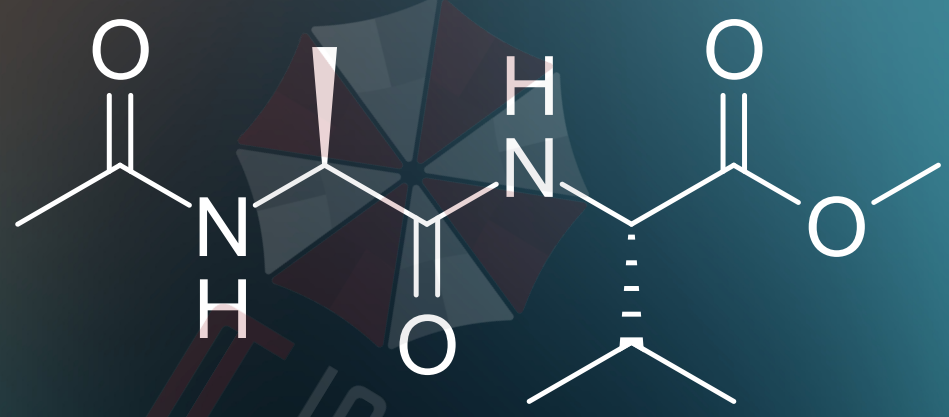

ZZL-7: Rapid Antidepressant Dipeptide Candidate

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History

ZZL-7 is a relatively newly discovered pharmacologically active modified dipeptide with a simple structure. It consists of the amino acids alanine and valine with an N- terminal acetyl cap and a C-terminal methyl ester (NAc-Ala-Val-OMe). It was first mentioned in an article in 2022 in Science magazine in a publication from a Chinese team of scientists. This publication is the only source of scientific data about ZZL-7 to this date. A synthetic approach for the synthesis is also described in this paper.[1]

Mechanism of Action

Authors were investigating the interaction between the serotonin transporter (SERT) and the neuronal nitric oxide synthase (nNOS), which are thought to play a role inthe development of depression. ZZL-7 seems to disrupt this interaction, leading to a decreased transport of the SERT to the cell surface, ultimately resulting in higher synaptic serotonin concentrations.

Preclinical Studies

In wild type mice, ZZL-7 reduced immobility time 2 hours after systematic administration, suggesting a fast antidepressant-like effect. It was also shown that the effect of ZZL-7 effect was directly linked to nNOS.

To investigate whether ZZL-7 could elicit a fast-onset antidepressant effect in depressed mice, ZZL-7 was injected intravenously to mice. ZZL-7 reversed the stress-induced increase in the SERT-nNOS complex in the brain and reversed stress-induced depressions behaviors 2 hours after treatment. The fast- onset antidepressant effect persisted at least for 24 hours. At 30 min after administration of ZZL-7, ZZL-7 was detected in brain tissue, indicating that it crossed the blood-brain barrier readily. It was also demonstrated that ZZL-7 was able to penetrate directly into cells, showing excellent pharmacokinetic properties.

ZZL-7 had no effect on general activity or locomotor activity, memory, or cognition and did not induce aggressive behavior, addiction, or abnormal brain waves. Intragastric administration of ZZL-7 produced antidepressant-like behaviors dose dependently 2 hours after treatment, which shows that oral application effective as well.[1]

Conclusion

ZZL-7 is a promising developmental candidate as antidepressant. It is easy to

synthesize, is orally bioavailable, crosses the blood-brain barrier and has low side effects in mice and a low expected toxicity. However, there is not enough data to support the claims of its efficacy sufficiently, as there is only one paper that is currently reporting on experimental data. More studies are needed.

References

[1] Q. Ye, S.-S. Lin, H. Ulrich, Y. Tang, Decoupling SERT-nNOS Interaction to Generate Fast-Onset Antidepressants, *Neurosci. Bull. 39* (**2023**) 1327-1329. https://doi.org/10.1007/s12264-023-01049-2.

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