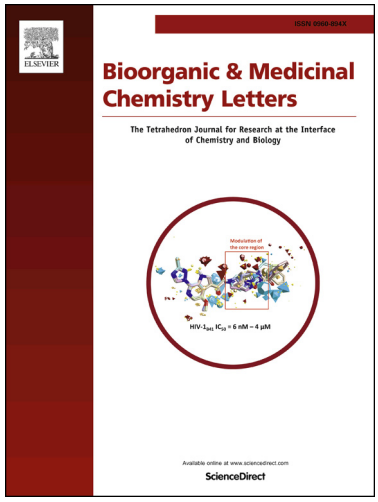

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Investigation of orexin-2 selective receptor antagonists: structural modifications resulting in dual orexin receptor antagonists

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Abstract

In an ongoing effort to explore the use of orexin receptor antagonists for the treatment of insomnia, dual orexin receptor antagonists (DORAs) were structurally modified, resulting in compounds selective for the OX_2R subtype and culminating in the discovery of **23**, a highly potent, OX_2R-selective molecule that exhibited a promising *in vivo* profile. Further structural modification led to an unexpected restoration of OX_1R antagonism. Herein, these changes are discussed and a rationale for selectivity based on computational modeling is proposed.