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

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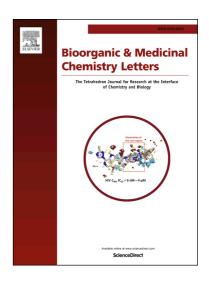
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ACCEPTED MANUSCRIPT

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

Jason W. Skudlarek^{a,*}, Christina N. DiMarco^a, Kerim Babaoglu^b, Anthony J. Roecker^a, Joseph G. Bruno^c, Mark A. Pausch^c, Julie A. O'Brien^c, Tamara D. Cabalu^d, Joanne Stevens^e, Joseph Brunner^f, Pamela L. Tannenbaum^e, W. Peter Wuelfing^g, Susan L. Garson^f, Steven V. Fox^e, Alan T. Savitz^e, Charles M. Harrell^f, Anthony L. Gotter^f, Christopher J. Winrow^f, John J. Renger^f, Scott D. Kuduk[#], and Paul J. Coleman^a

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.

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