# Substituted Prolines / Piperidines as Orexin Receptor Antagonists

## STATEMENT OF GOVERNMENT SUPPORT

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## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. provisional application serial number 61/596,062, filed February 7, 2012, the disclosure of which is incorporated herein by reference in its entirety.

## BACKGROUND

Orexins are a family of homologous peptides including species orexin A, or OR-A, and orexin B, or OR-B. Orexin A is a 33 amino acid peptide and orexin B is a 28 amino acid peptide (Sakurai T. et al., Cell (1998), 92, 573-585). Orexins are produced in neurons of the lateral hypothalamus and bind to at least two distinct G-protein-coupled receptors, termed $OX_1$ and $OX_2$ receptors. The receptor $OX_1$ is selective for OR-A, while the receptor $OX_2$ can bind both OR-A and OR-B. Orexins are found to stimulate food consumption, regulate states of sleep and wakefulness, and may be involved in neural mechanisms of drug abuse and addiction.

## SUMMARY

The present ~~invention~~disclosure is directed to compounds that can modulate the bioactivity of an orexin receptor such as $OX_1$ or $OX_2$, or both; to pharmaceutical compositions and combinations comprising a compound of the ~~invention~~present disclosure; to methods of treatment of malconditions in patients wherein modulation of an orexin receptor is medically indicated; and to methods of preparation of compounds of the ~~invention~~present disclosure.

In various ~~embodiments~~examples, the ~~invention~~present disclosure provides receptor-modulatory non-peptidic small molecules that can activate or inhibit one or more classes of orexin receptors in the human nervous system. In

~~various embodiments~~one aspect, the ~~invention~~present disclosure provides a compound of formula (I),

$(CH_2)_{0-p}S(O)_2N(R)_2$, $(CH_2)_{0-p}SO_3R$, $(CH_2)_{0-p}C(O)R$, $(CH_2)_{0-p}C(O)C(O)R$, $(CH_2)_{0-p}C(O)CH_2C(O)R$, $(CH_2)_{0-p}C(S)R$, $(CH_2)_{0-p}C(O)OR$, $(CH_2)_{0-p}OC(O)R$, $(CH_2)_{0-p}C(O)N(R)_2$, $(CH_2)_{0-p}OC(O)N(R)_2$, $(CH_2)_{0-p}C(S)N(R)_2$, $(CH_2)_{0-p}NH$-$C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)R$, $(CH_2)_{0-p}N(R)N(R)C(O)OR$, $(CH_2)_{0-p}N(R)N(R)CON(R)_2$, $(CH_2)_{0-p}N(R)SO_2R$, $(CH_2)_{0-p}N(R)SO_2N(R)_2$, $(CH_2)_{0-p}N(R)C(O)OR$, $(CH_2)_{0-p}N(R)C(O)R$, $(CH_2)_{0-p}N(R)C(S)R$, $(CH_2)_{0-p}N(R)C(O)N(R)_2$, $(CH_2)_{0-p}N(R)C(S)N(R)_2$, $(CH_2)_{0-p}N(COR)COR$, $(CH_2)_{0-p}N(OR)R$, $(CH_2)_{0-p}C(=NH)N(R)_2$, $(CH_2)_{0-p}C(O)N(OR)R$, or $(CH_2)_{0-p}C(=NOR)R$; and,

R is independently at each occurrence hydrogen, $(C_1-C_{12})$-alkyl, $(C_2-C_{12})$-alkenyl, $(C_2-C_{12})$-alkynyl, $(C_3-C_{10})$-cycloalkyl, $(C_3-C_{10})$-cycloalkenyl, [$(C_3-C_{10})$cycloalkyl or $(C_3-C_{10})$-cycloalkenyl]-[$(C_1-C_{12})$-alkyl or $(C_2-C_{12})$-alkenyl or $(C_2-C_{12})$-alkynyl], $(C_6-C_{10})$-aryl, $(C_6-C_{10})$-aryl-[$(C_1-C_{12})$-alkyl or $(C_2-C_{12})$-alkenyl or $(C_2-C_{12})$-alkynyl], mono- or bicyclic 3-10 membered heterocyclyl, mono- or bicyclic 3-10 membered heterocyclyl-[$(C_1-C_{12})$-alkyl or $(C_2-C_{12})$-alkenyl or $(C_2-C_{12})$-alkynyl], mono- or bicyclic 5-10 membered heteroaryl, or mono- or bicyclic 5-10 membered heteroaryl-[$(C_1-C_{12})$-alkyl or $(C_2-C_{12})$-alkenyl or $(C_2-C_{12})$-alkynyl];

m is 0, 1, 2, 3, 4, 5, or 6; n is 1, 2, or 3; p = 0, 1, or 2; r = 0, 1, 2, or 3;

or any salt or hydrate thereof.

In various ~~embodiments~~examples, the ~~invention~~present disclosure provides pharmaceutical compositions comprising a compound of the ~~invention~~present disclosure and a pharmaceutically acceptable excipient.

In another aspect, there is provided an invitro method of modulating an orexin receptor comprising contacting the receptor with an effective amount or concentration of a compound of any one of claims 1-14.

In various ~~embodiments~~examples, the ~~invention~~present disclosure provides a method of modulating an orexin receptor, such as $OX_1$ or $OX_2$, or both, comprising contacting the receptor with an effective amount or concentration of a compound of the invention.

In one aspect, there is provided use of a compound of any one of claims 1-14 in the manufacture of a medicament for treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating.

In a further aspect, there is provided use of a compound, as defined herein, in the manufactor of a medicament for treating a malcondition in a patient.

In yet another aspect, there is provided the use as defined herein wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, or renal disease.

In various ~~embodiments~~examples, the ~~invention~~present disclosure provides a method of treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating, comprising administering to the patient a compound of the invention in a dose, at a frequency, and for a duration to provide a beneficial effect to the patient. The orexin receptor can be $OX_1$, or can be $OX_2$. In various ~~embodiments~~examples, the malcondition can comprise an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep

16. An invitro method of modulating an orexin receptor comprising contacting the receptor with an effective amount or concentration of a compound of any one of claims 1-14.

17. The method of claim 16 wherein modulating an orexin receptor is antagonism of the orexin receptor.

~~18. The method of claim 16 wherein contacting is *in vivo* in a tissue or system of a patient.~~

~~19.~~18. ~~A method of treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating, comprising administering to the patient~~Use of a compound of any one of claims 1-14 in the manufacture of a medicament for treating a malcondition in a patient wherein modulation of an orexin receptor is medically indicating ~~in a dose, at a frequency, and for a duration to provide a beneficial effect to the patient~~.

~~20.~~19. The ~~method~~use of claim ~~19~~18 wherein modulating an orexin receptor is antagonism of the orexin receptor.

~~21.~~20. The ~~method~~use of claim ~~19~~18 wherein the compound is a selective modulator of an orexin receptor $OX_1$.

~~22.~~21. The ~~method~~use of claim ~~19~~18 wherein the compound is a selective modulator of an orexin receptor $OX_2$.

~~23.~~22. The ~~method~~use of claim ~~19~~18 wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, or renal disease.

~~24.~~23. The ~~method~~use of claim ~~23~~22 wherein the drug addiction comprises addiction to cocaine, opiates, or nicotine.

~~25.~~24. The ~~method~~use of claim ~~23~~22 wherein modulating an orexin receptor is antagonism of the orexin receptor.

~~26.~~25. Use of a compound of any of claims 1-14 in the manufactor of a medicament for ~~treatment of~~ treating a malcondition in a patient.

~~27.~~26. The use of claim ~~26~~25 wherein the malcondition comprises an eating disorder, obesity, alcoholism or an alcohol-related disorder, drug abuse or addiction, a sleep disorder, a cognitive dysfunction in a psychiatric or neurologic disorder, depression, anxiety, panic disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's chorea, head ache, migraine, pain, gastrointestinal diseases, epilepsy, inflammations, immune-related diseases, endocrine-related diseases, cancer, hypertension, behavior disorder, mood disorder, manic depression, dementia, sex disorder, psychosexual disorder, or renal disease.

~~28.~~27. The use of claim ~~27~~26 wherein the drug addiction comprises addiction to cocaine, opiates, or nicotine.