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PATENT HIGHLIGHT

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Biphenyl-Ethyl-Pyrrolidine Derivatives as Histamine H3 Receptor Modulators for the Treatment of Cognitive Disorders

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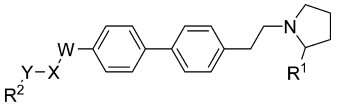
Title:	Biphenyl-Ethyl-Pyrrolidine Derivatives as Histamine H3 Receptor Modulators for the Treatment of Cognitive Disorders		
Patent Application Number:	WO2014110103	**Publication date:**	July 17, 2014
Priority Application:	US 61750475	**Priority date:**	January 9, 2013
Inventors:	Covel, Jonathan A.; Ren, Albert S.; Semple, Graeme; Tran, Thuy-Anh; Wei, Zheng; Xiong, Yifeng		
Assignee Company:	Arena Pharmaceuticals, Inc.		
Disease Area:	Cognitive Disorders	**Biological Target:**	Histamine H3

Summary: Histamine, a biogenic amine neurotransmitter first described by British scientists Henry H. Dale and P. P. Laidlaw in 1910, exerts its influence on biological systems through a series of G-protein coupled receptors (GPCRs) designated H1, H2, H3, and H4. The H3 receptor in particular has been identified as an autoreceptor capable of controlling both the synthesis and release of stored histamine. Activation of this receptor is associated with the release of additional neurotransmitters such as serotonin, acetylcholine, dopamine, and noradrenaline. In addition, the H3 receptor is constitutively active, as signal transduction has been observed in the absence of the natural ligand. These features indicate that a physiological response could be elicited from the H3 receptor systems through the application of agonists, antagonists, and inverse agonists. This has led to an intense interest in the identification of novel ligands capable of modulating the H3 system as a means of therapeutic intervention. Animal studies of H3 antagonists and inverse agonists have indicated that compounds of these types could provide increased wakefulness, reduce the impact of somnolence syndrome, attenuate the symptoms of narcolepsy, and have a positive impact on epilepsy. It has also been suggested that the H3 receptor may play a role in cognitive disorders such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), depression, and schizophrenia. The present discloses a series of compounds capable of modulating H3 receptor activity and may be useful as therapeutic agents for the aforementioned conditions.

Important Compound Classes:



Definitions:

R^1 is C_1-C_4 alkyl;
R^2 is selected from C_1-C_4 alkoxycarbonyl, carboxyl, and tetrazolyl;
W is selected from C_1-C_4 alkylene, C_3-C_7 cycloalkylene, and carbonyl; or
W is absent;
X is selected from −O−, −NHC═O−, and carbonyl; or
X is absent; and
Y is selected from C_1-C_4 alkylene, C_3-C_7 cycloalkylene, and heterocyclylene; or
Y is absent.

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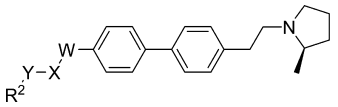
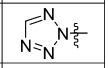
Key Structures:



Entry	W	X	Y	R^2
1	--	--	--	CO_2H
2	CH_2	--	--	CO_2H
3	CH_2CH_2	--	--	CO_2H
4	CH_2	O	CH_2	CO_2Et
5	CH_2	O	CH_2	CO_2H
7	CH_2CH_2	--	--	
8	CH_2CH_2	--	--	
9	CH_2CH_2	--	--	CO_2Me
10	$C(CH_3)_2$	--	--	CO_2H
11	CH_2CH_2	--	--	CO_2Et
12	CH_2CH_2	-NHC=O-	$C(CH_3)_2$	CO_2-tBu
13	CH_2CH_2	-NHC=O-	CH(CH3) (S-isomer)	CO_2-tBu
16		-NHC=O-	$CH_2CH_2CH_2$	CO_2Me
24	CH_2CH_2	-NHC=O-	CH_2	CO_2Me
25		--	--	CO_2Me
27		-NHC=O-	CH_2	CO_2Me
33		-NHC=O-	$CH_2CH_2CH_2$	CO_2H
37	CH_2	--	--	
38	--	-NHC=O-	$C(CH_3)_2$	CO_2Me
43	--	-NHC=O-	CH_2CH_2	CO_2H
45	$CH_2CH_2CH_2$	--	--	CO_2H

Recent Review Articles:

Singh, M.; Jadhav, H. R. Histamine H3 receptor function and ligands: recent developments. *Mini Rev. Med. Chem.* **2013**, *13* (1), 47−57.

Łazewska, D.; Kieć-Kononowicz, K. Recent advances in histamine H3 receptor antagonists/inverse agonists. *Expert Opin. Ther. Pat.* **2010**, *20* (9), 1147−69.

Łażewska, D.; Kieć-Kononowicz, K. New developments around histamine H3 receptor antagonists/inverse agonists: a patent review (2010−present). *Expert Opin. Ther. Pat.* **2014**, *24* (1), 89−111.

Biological Assay:

Human H3 (H3R) HTRF cAMP assay.

Biological Data:

Entry	IC_{50} H3R (nM)	Entry	IC_{50} H3R (nM)	Entry	IC_{50} H3R (nM)
1	3.8	9	1.1	25	3.3
2	8.1	10	3.1	27	1.9
3	2.5	11	1.8	33	2.1
4	0.67	12	0.95	37	0.78
5	5.5	13	2.1	38	1.2
7	0.93	16	15	43	2.5
8	1.2	24	0.99	45	0.97

Claims:

44 Total claims

24 Composition of matter claims

19 Method of use claim

1 Process claim

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Notes

The authors declare no competing financial interest.