ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Piperazion[1,2-A]indol-1-ones and [1,4]Diazepino[1,2-A]indol-1-ones

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Title:	Piperazion[1,2-A]indol-1-ones and [1,4]diazepino[1,2-A]indol-1-one		
Patent/Patent Application Number:	WO2014/023674	**Publication date:**	February 13th, 2014
Priority Application:	EP 12179381.4	**Priority date:**	August 6th, 2012
Inventors:	Ceccarelli, S. M.; Jagasia, R.; Roetne, R.; Wichmann, J.		
Assignee Company:	Hoffman-La Roche Inc.		
Disease Area:	CNS, neurodegenerative disease, and psychiatric disorders	**Biological Target:**	Neural stem cells

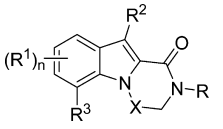
Summary:

Neurogenesis, the conversion of stem cells into functioning neurons, occurs primarily in two areas of the adult brain. Neurogenesis in the subventricular zone of the lateral ventricles produces neurons that migrated through the rostral migratory stream to the olfactory bulb where they become interneurons. In the subgranular zone of the dentate gyrus of the hippocampus, however, neurogenesis produces new dentate granule cells. Under normal physiological conditions, neurogenesis in other regions of the adult CNS is very limited, but it is believed that neurogenesis could be induced after stroke or traumatic brain injury.

It has been suggested that hippocampal adult neurogenesis is an important contributor to cognitive and emotional states, but the precise mechanism of this effect remains a mystery. Specifically, recent research has demonstrated a correlation between physical exercise, exposure to an enriched environment and typical antidepressants, and an increase in adult hippocampal neurogenesis. Chronic stress, depression, sleep deprivation, and aging, however, have been similarly correlated with decreased adult neurogenesis and negative cognitive/emotional states.

Promoting neurogenesis in the adult brain may be a viable pathway for the treatment of neurodegenerative disease and neuropsychiatric diseases such as schizophrenia, obsessive-compulsive personality disorder, major depression, bipolar disorders, anxiety disorders, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, and a number of additional conditions and diseases. The present disclosure describes a series of compounds capable of inducing neurogenesis that may be useful for treating or preventing the aforementioned disease.

Important Compound Classes:



Definitions:

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkoxy substituted by halogen, or cyano;

R^2 is hydrogen, lower alkyl, or lower alkyl substituted by halogen;

R^3 is phenyl, benzo[1,3]dioxolyl, 2,3-dihydro-benzofuran-5-yl, or a 5- and 6-membered heteroaryl, wherein phenyl and the 5- and 6-membered heteroaryl groups may be substituted by one or more substituents, selected from cyano, nitro, amino, and lower di-alkylamino, lower alkyl sulfonyl, lower alkoxy, lower alkoxy substituted by halogen, halogen, lower alkyl, lower alkyl substituted by halogen, or lower alkyl substituted by hydroxyl;

X is $-CH(\text{lower alkyl})-$, $-CH_2-$, $-CH_2CH_2-$, or $-CH(\text{lower alkyl})CH_2-$;

R is hydrogen or lower alkyl;

n is 1 or 2.

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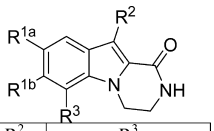
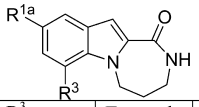
Key Structures:



Example	R^{1a}	R^{1b}	R^2	R^3
12	F	H	H	Phenyl
18	F	H	H	4-F-Phenyl
19	F	H	H	4-CH_3O-Phenyl
21	F	H	H	4-Pyridyl
23	F	H	H	4-Cl-Phenyl
25	F	H	H	4-CF_3-Phenyl
39	F	F	H	4-CH_3O-Phenyl
67	Cl	H	CH_3	4-CH_3O-Phenyl
75	F	H	CH_3	4-CH_3O-Phenyl
79	CN	H	CH_3	4-CH_3O-Phenyl
167	CN	H	CH_3	2,4-di-Cl-Phenyl



Example	R^{1a}	R^3	Example	R^{1a}	R^3
15	F	Phenyl	17	F	4-F-Phenyl
16	F	4-CH_3O-Phenyl	20	F	4-Pyridyl

Recent Review Articles:

1. Kohman, R. A.; Rhodes, J. S. Neurogenesis, inflammation and behavior. *Brain, Behav., Immun.* **2013**, *27*, 22−32.
2. Kazanis I. Neurogenesis in the adult mammalian brain: how much do we need, how much do we have? *Curr. Top. Behav. Neurosci.*; **2013**, *15*, 3−29.
3. Tofighi, R.; Tamm, C.; Moors, M.; Ibrahim, W.; Norhamidah, W.; Ceccatelli, S. Neural stem cells. *Neuromethods*; **2011**, *56*, 63−85.
4. Wu, Q.; Wang, X. Neuronal stem cells in the central nervous system and in human diseases. *Protein Cell* **2012**, *3* (4), 262−270.

Biological Assay: Neural stem cell proliferation assay.

Biological Data:

Example	EC_{50} (nM)	Example	EC_{50} (nM)
12	37	23	19
15	84	25	23
16	9	39	5
17	50	67	8
20	37	75	5
18	26	79	4
19	7	167	2
21	36		

Claims: 22 Total claims
17 Composition of matter claims
5 Method of use claims

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Notes
The authors declare no competing financial interest.