ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Pyrrolopyridine or Pyrazolopyridine Derivatives

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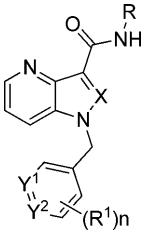
Title:	Pyrrolopyridine or Pyrazolopyridine Derivatives		
Patent/Patent Application Number:	WO2015028483A1	**Publication date:**	March 5, 2015
Priority Application:	EP13182351.0	**Priority date:**	August 30, 2013
Inventors:	Ballard, T. M.; Flohr, A.; Groebke Zbinden, K.; Pinard, E.		
Assignee Company:	Hoffmann-La Roche, Inc.		
Disease Area:	Central Nervous System	**Biological Target:**	Muscarinic Ml receptor

Summary: The muscarinic receptors (mAChRs) are a family of G-protein coupled receptors (GPCRs) that are activated by acetylcholine (ACh), an important neurotransmitter. To date, five distinct individual mAChRs, M1−M5, have been identified. The M1 receptor is primarily located in the brain, with highest expression levels found in the striatum, thalamus, hippocampus, and cortex. It has been demonstrated that modulation of M1 receptor activity can have an impact on disorders of the central nervous system including schizophrenia and Alzheimer's disease. Specifically, Xanomeline improved cognitive scores and reduced psychotic-like behavior in Alzheimer's disease. In addition, M1 receptor activity plays an important role in memory and learning, as well as the regulation of dopamine and NMDA receptor activity. The M1 receptor has been the subject of intense study directed toward the identification of novel therapies for diseases and disorders of the central nervous system. The present disclosure describes a series of novel pyrrolopyridine and pyrazolopyridine that are positive allosteric modulators (PAM) of the M1 receptor. These compounds may be useful for the treatment of diseases mediated by the M1 receptor such as Alzheimer's disease, cognitive impairment, schizophrenia, pain, and sleep disorders.

Important Compound Classes:



Definitions:

R^1 is halogen, lower alkyl, lower alkoxy, cyano, phenyl, $C(O)NHCH_3$, $C(O)NH_2$, lower alkyl substituted by halogen, or is a five-membered heteroaryl group, optionally substituted by lower alkyl;

Y^1 is N or CH;

Y^2 is CH;

and if Y^1 is CH, Y^1 and Y^2 may form together with the C atoms to which they are attached a ring, containing $-CH{=}N-N(CH_3)-$, $-CH{=}N-N(H)-$;

X is CH or N;

R is $(CH_2)_m$-cyc1oalkyl, optionally substituted by hydroxy, lower alkoxy, or lower alkyl, or is tetrahydropyran, optionally substituted by hydroxy, or is lower alkoxy, substituted by hydroxy, or is lower alkyl substituted by one or two hydroxy, or is $(CH_2)_m$-pyridinyl, optionally substituted by hydroxy, lower alkyl, or lower alkyl substituted by hydroxy, or is L-phenyl, optionally substituted by hydroxy, lower alkyl, or lower alkyl substituted by hydroxy, and

L is a bond, $-CH(CH_2OH)-$ or $-CH_2CH(OH)-$;

n is 0, 1, or 2;

m is 0 or 1;

or to a pharmaceutically acceptable acid addition salt, to a racemic mixture, or to its corresponding enantiomer and/or optical isomers thereof.

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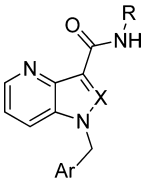
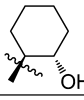
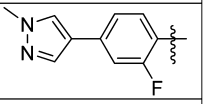
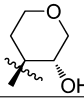
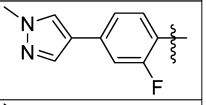
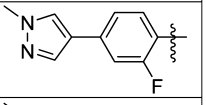
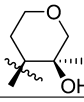
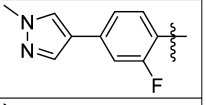
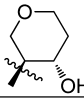
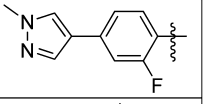
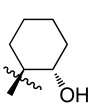
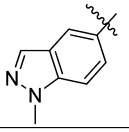
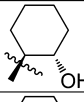
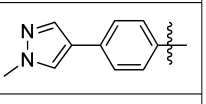
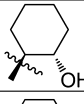
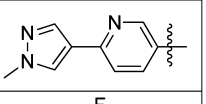
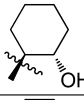
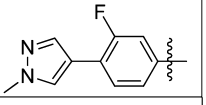
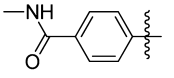
Key Structures:



Entry	R	X	AR
2		CH_2	
4		CH_2	
6		N	
40		CH_2	
41		CH_2	
52		CH_2	
55		CH_2	
56		CH_2	
59		CH_2	
61		CH_2	

Recent Review Articles:

1. Foster, D. J.; Choi, D. L.; Conn, P. J.; Rook, J. M. Activation of M1 and M4 muscarinic receptors as potential treatments for Alzheimer's disease and schizophrenia. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 183−191.

1. Davie, B. J.; Christopoulos, A.; Scammells, P. J. Development of M1 mAChR allosteric and bitopic ligands: prospective therapeutics for the treatment of cognitive deficits. *ACS Chem. Neurosci.* **2013**, *4* (7), 1026−1048.

1. Kuduk, S. D.; Beshore, D. C. Novel M1 allosteric ligands: a patent review. *Expert Opin. Ther. Pat.* **2012**, *22* (12), 1385−1398.

Biological Assay:

Muscarinic Ml receptor positive allosteric modulator assay.

Compounds were assessed for their ability to modulate muscarinic M1 receptor activity in CHO cells genetically engineered to express either the rat or human muscarinic M1 receptor. The assays were executed on a Fluorometric Imaging Plate Reader System (FLIPR, Molecular Devices) by measuring the effect of varying concentrations of the test compounds on basal and acetylcholine-stimulated Ca^{2+} levels.

Biological Data:

Entry	EC_{50} hPAM (nM)	EC_{50} rPAM (nM)	Entry	EC_{50} hPAM (nM)	EC_{50} rPAM (nM)
2	9.8	34.6	52	71.5	162.5
4	28.5	58.6	55	11.1	13.8
6	25.3	71.5	56	34.8	71.1
40	47.9	63.2	59	15.5	18.0
41	30.3	51	61	9.1	18

Claims:

25 Total claims

18 Composition of matter claims

1 Process claim

6 Method of use claims

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Notes

The authors declare no competing financial interest.