ACS Medicinal Chemistry Letters

Viewpoint

pubs.acs.org/acsmedchemlett

Cyclopropyl-*spiro*-piperidines Useful as Sodium Channel Blockers

Patent Highlight

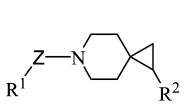
Benjamin Blass*

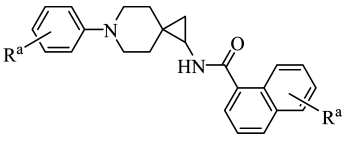
Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140

Title:	Cyclopropyl-*spiro*-piperidines Useful as Sodium Channel Blockers		
Patent Application:	WO2012/047703A2	**Publication Date:**	April 12, 2012
Priority Application:	US61/389463	**Priority Date:**	October 4, 2010
Inventors:	Ho, G. D.; Tulshian, D.; Heap, C. R.		
Assignee:	Schering Corporation		
Disease Area:	Chronic and Neuropathic Pain	**Biological Target:**	Voltage-Gated Sodium Channel $Na_v1.7$

Summary: Voltage-gated ion channels are critical to the generation and propagation of electrical signals and action potentials in neuronal and muscle tissue. The voltage-gated sodium channels in particular mediate the rapid depolarization of cells, creating the rising phase of an action potential, which in turn activates voltage-gated calcium and potassium channels. To date, nine voltage-gated sodium channel subtypes have been identified, and blockers of these channels have been developed as antiarrhythmic agents, anticonvulsants, antiepileptics, and local anesthetics. Voltage-gated sodium channels have also been targeted for the treatment of neuropathic pain, as it has been established that these channels play a critical role in the nerve cells associated with this condition. Specifically, it has been hypothesized that neuropathic pain is a result of increased sodium channel activity in injured nerves and that selective blockade of sodium channels such as Nav1.7 would provide therapeutic relief. The present application describes a series of cyclopropyl-*spiro*-piperidines useful as sodium channel blockers for the treatment of chronic and neuropathic pain.

Important Compound Classes:





Definitions:

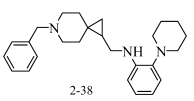
Z = a bond, C_1–C_6 alkyl, C(O), CO_2, CONH, or SO_2

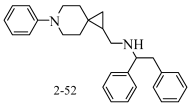
R^1 = H, optionally substituted C_6–C_{10} aryl, optionally substituted C_5–C_{10} heteroaryl

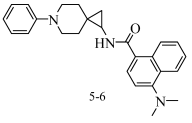
R^2 = H, $(CH_2)_nNR^3R^4$, $(CH_2)_nC_5$–C_{10} heterocyclyl, or $NR^3CO_2R^4$

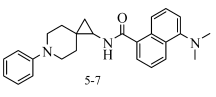
R^a = H, halogen, C_1–C_{10} alkyl, $(CH_2)_nC_3$–C_{10} cycloalkyl, C_6–C_{10} aryl, C_5–C_{10} heteroaryl, C_5–C_{10} heterocyclyl, OR^5, $N(R^5)_2$, $CONHR^5$, CO_2R^5, CN, CF_3, or NO_2

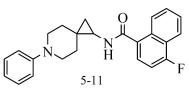
Key Structures:

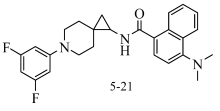

2-38


2-52


5-6


5-7


5-11


5-21

Biological Assay: $Na_v1.7$ FLIPR and electrophysiological patch clamp using HEK293 or CHO-K1 cells.

Biological Data:

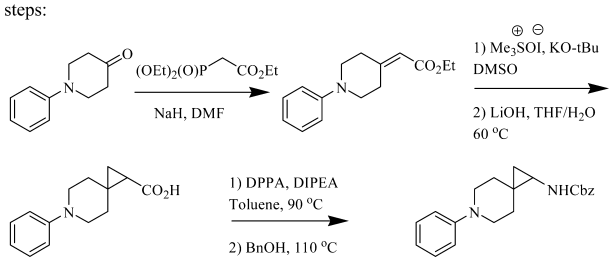
Compound Number	$Na_v1.7$ FLIPR IC_{50} (nM)	Compound Number	$Na_v1.7$ FLIPR IC_{50} (nM)
2-38	291	5-7	237
2-52	177	5-11	188
5-6	98.3	5-21	151

Published: July 30, 2012

dx.doi.org/10.1021/ml300195b | *ACS Med. Chem. Lett.* 2012, 3, 697–698

Synthesis:

Key steps:



Recent Review Articles:

Nantermet, P. G.; Henze, D. A. Recent advances toward pain therapeutics. *Annu. Rep. Med. Chem.* **2011**, *46*, 19−32.

Dib-Hajj, S. D.; Cummins, T. R.; Black, J. A.; Waxman, S. G. Sodium channels in normal and pathological pain. *Annu. Rev. Neurosci.* **2010**, *33*, 325−347.

Priest, B. T. Future potential and status of selective sodium channel blockers for the treatment of pain. *Curr. Opin. Drug Discovery Dev.* **2009**, *12* (5), 682−692.

AUTHOR INFORMATION

Corresponding Author

*Tel: 215-707-1085. E-mail: benjamin.blass@temple.edu.

Notes

The authors declare no competing financial interest.