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Viewpoint

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Substituted Pyridines as Sodium Channel Blockers

Patent Highlight

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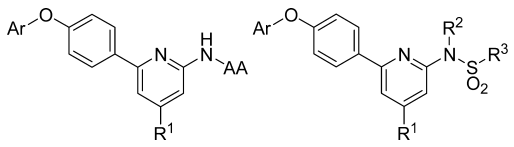
Title:	Substituted Pyridines As Sodium Channel Blockers		
Patent Application:	WO2012/085650	**Publication Date:**	June 28, 2012
Priority Application:	US61/426318	**Priority Date:**	December 22, 2012
Inventors:	Ni, C.; Park, M.; Shao, B.; Tafese, L.; Yao, J.; Youngman, M.; Zhou, X.		
Assignee Company:	Purdue Pharma L.P.		
Disease Area:	Pain	**Biological Target:**	Voltage-Gated Sodium Channel $Na_v1.7$

Summary: Voltage-gated sodium channels are found in both the peripheral and the central nervous system and are the primary mechanism for generation of the rapid upstroke portion of the action potential of excitable cells. Proper function of these channels is critical to normal neuronal function, while aberrant channel function is associated with several medical conditions, including pain. It has been suggested that Nav1.7, a tetrodotoxin-sensitive channel that is preferentially expressed in peripheral sympathetic and sensory neurons, plays a key role in acute, inflammatory, and neuropathic pain. In addition, it has been demonstrated that a number of local anesthetics, such as lidocaine and bupivacaine, exert their biological effects by interfering with sodium ion influx, further suggesting a link between pain sensation and sodium channels. The present disclosure describes a series of substituted aminopyridines useful as NaV1.7 blockers for the treatment of pain.

Important Compound Classes:



Definitions:

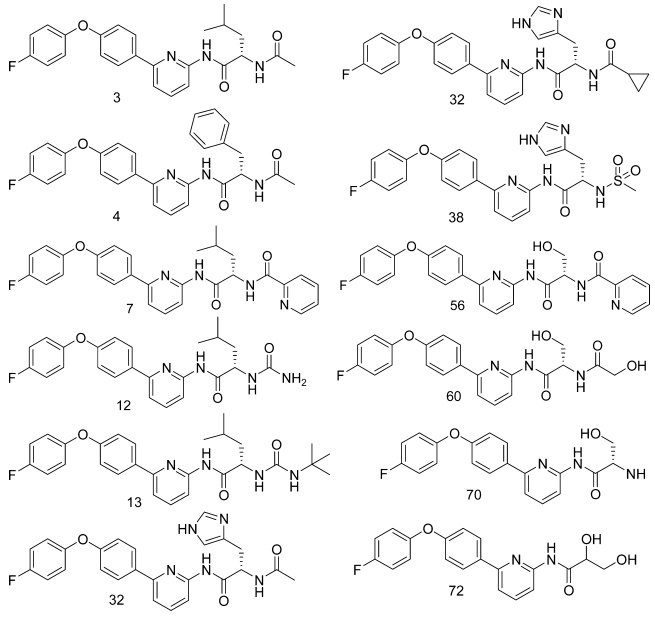
Ar = Substituted aryl ring

AA = Substituted amino acid side chain

R^1 = Hydrogen, halogen, substituted alkyl

R^2 = Hydrogen, substituted alkyl

Key Structures:



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Biological Assay: Nav1.7 FLIPR TETRA sodium dye assay with KCl salt and electrophysiological patch clamp (EP).

Biological Data:

Compound number	FLIPR IC_{50} (μM)	EP K_i	Compound number	FLIPR IC_{50} (μM)	EP K_i
3	0.042	0.194	33	0.11	0.206
4	0.064	0.13	38	0.14	0.019
7	0.067	0.059	56	0.14	0.195
12	0.096	0.257	60	0.46	0.113
13	0.075	0.075	70	0.27	0.046
32	0.086	0.025	72	0.074	0.143

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.

Additional Information: Additional possible indications suggested include neurodegeneration, cardiac arrhythmia, epilepsy, mental retardation, and movement disorder.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.