ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Heteroaryl Sodium Channel Inhibitors

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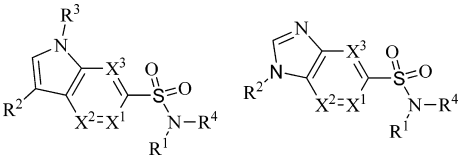
Title:	Heteroaryl Sodium Channel Inhibitors		
Patent Application Number:	WO2013025883A1	**Publication date:**	February, 21st, 2013
Priority Application:	US 61/524,691	**Priority date:**	August 17th, 2011
Inventors:	Dineen, T.; Marx, I. E.; Hguyen, H. N.; Weiss, M.		
Assignee Company:	Amgen, Inc.		
Disease Area:	Chronic Pain	**Biological Target:**	Nav1.7

Summary: Although there are some treatments currently available, chronic pain remains a major unmet medical need. It is well established that the sensation of pain requires electrical signaling through neuronal pathways that involve voltage gated sodium channels. Lidocaine, for example, is a nonselective blocker of voltage gated sodium channels that is effectively employed as an anesthetic. To date, nine voltage gated sodium channels, Nav1.1 through Nav1.9, have been identified, and they are distributed across a range of cell types including skeletal muscle, cardiac tissue, and neurons. The Nav1.7 channel, a tetrodotoxin-sensitive channel, has been specifically implicated in pain disorders. Primary Erythromelaglia and Paroxysmal Extreme Pain Disorder, for example, are the result of mutations that increase Nav1.7 activity. However, the genetic condition Congenital Indifference to Pain is the result of mutations that produce nonfunctional Nav1.7 channels. These findings suggest that Nav1.7 plays a key role in the perception of pain and that compounds capable of attenuating Nav1.7 channel activity would be therapeutically beneficial to patients suffering from chronic pain.

Important Compound Classes:



Definitions:

Each X^1, X^2, or X^3 is independently CR^a or N;

Each R^a is independently hydrogen, halogen, C_{1-6}alkyl, OC_{1-6}alkyl, or CN;

Each R^b is independently hydrogen or C_{1-6}alkyl;

R^1 is a five- or six-membered heteroaryl or heteocycloalkyl group having from one to four heteroatoms independently selected from O, N, or S, or a five- or six-membered aryl or clcyoalkyl group, where the heteroaryl, heterocycloalkyl, aryl, or cycloalkyl group is unsubstituted or substituted with from one to four substituents selected from halogen, C_{1-6}alkyl, OC_{1-6}alkyl, or NR^bR^b;

R^2 is a five- to ten-membered cycloalkyl, aryl, or heteroaryl group, the heteroaryl group having from one to four heteroatoms independently selected from O, N, or S, and where the aryl or heteroaryl group is unsubstituted or substituted with from one to four substituents independently selected from $-CF_3$, $-CHF_2$, CF_2H, OC_{1-6}alkyl, OCF_3, C_{1-6} alkyl, halogen, $-CCR^b$, CN, $-NR^bR^b$, $-S(=O)_2C_{1-6}$alkyl, or Y;

Y is a five- or six-membered heteroaryl or heterocycloalkyl group having from one to four heteroatoms independently selected from O, N, or S, or an aryl or cycloalkyl group, which the heteroaryl, heterocycloalkyl, aryl, or cycloalkyl group is unsubstituted or substituted with $-CF_3$, $-CHF_2$, CF_2H, OC_{1-6}alkyl, OCF_3, C_{1-6}alkyl, halogen, $-CCR^b$, CN, $-NR^bR^b$, $-S(=O)_2C_{1-6}$alkyl, or Z;

Z is a three- to six-membered heterocycloalkyl group having from one to four heteroatoms independently selected from O, N, or S;

R^3 is hydrogen, C_{1-6}alkyl, $C(=O)C_{1-6}$alkyl, $C(=O)OC_{1-6}$alkyl, or $S(=O)_2C_{1-6}$alkyl; and

R^4 is hydrogen or C_{1-6}alkyl.

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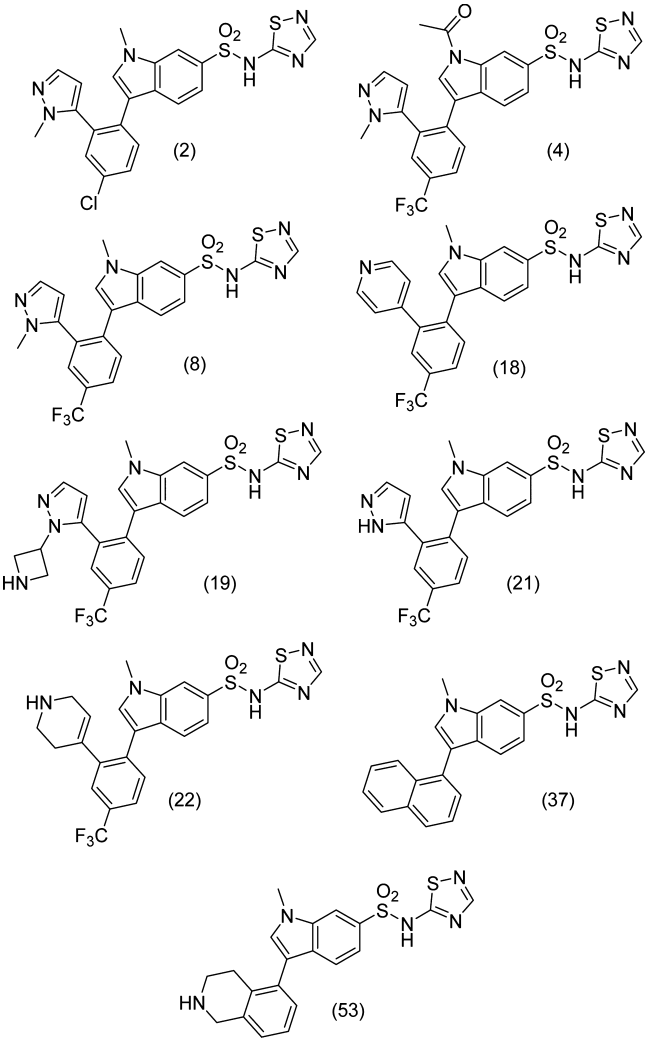
Key Structures:



Recent Review Articles:

1. Dib-Hajj, S. D.; Yang, Y.; Black, J. A.; Waxman, S. G. The NaV1.7 Sodium Channel: from Molecule to Man. *Nat. Rev. Neurosci.* **2013**, *14* (1), 49−62.

2. Dib-Hajj, S. D.; Cummins, T. R.; Black, J. A.; Waxman, S. G. From Genes to Pain: Nav1.7 and Human Pain Disorders. *Trends Neurosci.* **2007**, *30* (11), 555−563.

Biological Assay:

Nav1.7 Ionworks Quattro automated patch clamp, stably transfected HEK293 cells.

Nav1.5 Ionworks Quattro automated patch clamp, stably transfected HEK293 cells.

Biological Data:

Entry	Nav1.7 (μM)	Nav1.5 (μM)	Entry	Nav1.7 (μM)	Nav1.5 (μM)	Entry	Nav1.7 (μM)	Nav1.5 (μM)
2	0.253	>10	18	0.05	>10	22	0.0425	>10
4	0.0505	>10	19	0.263	>10	37	0.306	>10
8	0.147	>10	21	0.0375	>10	53	0.292	>10

Claims:

21 Total claims.

18 Composition of matter claims.

3 Method of use claims.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.