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PATENT HIGHLIGHT

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# Nav1.7 Inhibitors: Potential Effective Therapy for the Treatment of Chronic Pain

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| **Title:** | Tricyclic Sulfonamide Derivatives | | |
| **Patent Application Number:** | WO 2015/102929 A1 | **Publication date:** | 9 July 2015 |
| **Priority Application:** | PCT/CN20 13/090854 | **Priority date:** | 30 December 2013 |
| **Inventors:** | Chen, S.; He, H.; Lagu, B.; Qin, H.; Wu, C.; Xiao, Y. | | |
| **Assignee Company:** | Novartis AG [CHICH]; Lichtstrasse 35, CH-4056 Basel (CH); (for all designated States except US) | | |
| **Disease Area:** | Chronic pain such as neuropathic, nociceptive and inflammatory pain | **Biological Target:** | The voltage-gated sodium channel 1.7 (Nav1.7) |

**Summary:**

The invention in this patent application relates to tricyclic sulfonamide derivatives represented generally by formula (I). These compounds are sodium channel blockers, in particular they are selective inhibitors of the voltage-gated sodium channel 1.7 (Nav1.7) and may potentially provide useful treatment for chronic pain, including dental pain, pain associated with osteoarthritis, erythromelalgia, diabetic neuropathy, peroxymal extreme pain disorder (PEPD), and ocular pain.

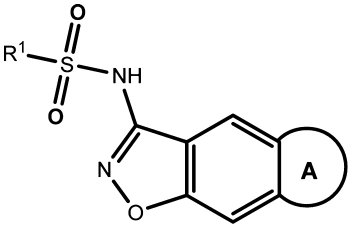
The voltage-gated sodium channel subtypes (Nav) family contains nine known members named Nav1.1 to Nav1.9. The voltage-gated sodium channel 1.7 (Nav1.7) is encoded by the gene SCN9A; studies have identified Nav1.7 in humans as a major contributor to pain signaling and generation. Studies also have shown that the loss of Nav1.7 function in some human subjects is associated with insensitivity to pain. For example, the nonsense mutations in SCN9A were linked to congenital indifference to pain (CIP). Patients with CIP are insensitive to pain; however, they are still able to distinguish between other sensations, such as thermal (hot/cold) and tactile (sharp/dull) stimuli. In contrast, the gain of function mutations in Nav1.7 were associated with severe pathological conditions such as primary erythermalgia, which is linked to mutations T2573A and T2543C in Nav1.7, and PEPD, which is linked to mutations M1627K, T14641, and 11461T located in the inactivation gate area of Nav1.7.

These findings have shown the great potential of the inhibitors of Nav1.7 as analgesics and a therapy for the treatment of chronic pain. However, in order for these inhibitors to be beneficial, they must be highly selective toward Nav1.7 without blocking the essential activities of the other Nav channel subtype family members. Other members of the sodium channel subtype family are involved in different crucial physiological processes such as heart activity (Nav1.5), muscle contraction (Nav1.4), and CNS neurotransmission (Nav1.1, 1.2, and 1.6). Thus, selective inhibitors of Nav1.7 may potentially provide the desired treatment for pain with fewer side effects.

Some Nav1.7 blockers are known in the art such as the tarantula venom peptide Pro-TX-11, which is a potent Nav1.7 inhibitor. Also, several series of compounds including benzazepinone, amino-thiazoles, amino-pyridines, and isoxazoles were reported as Nav1.7 inhibitors.

New selective inhibitors of Nav1.7 channel such as the compounds described in this patent application are still needed and may potentially lead to the development of comprehensive and effective therapies for the prevention and/or treatment of chronic pain and other disorders associated with the functions of Nav1.7.

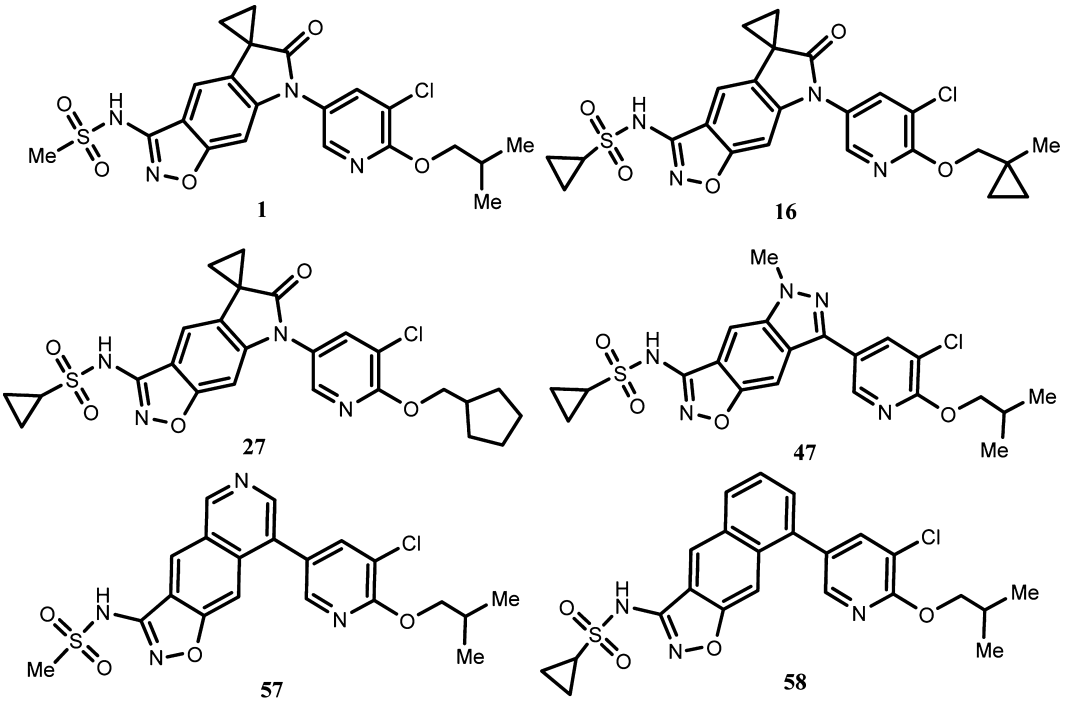
**Important Compound Classes:**




Formula (I)

**Received:** August 3, 2015
**Published:** August 14, 2015

**Key Structures:** The inventors reported the structures and synthesis procedures for 63 compounds of formula (I) including the following representative examples:




**Biological Assay:**

- hNav1.7 Channel In Vitro Patch-Clamp Assay

**Biological Data:** The $IC_{50}$ values obtained from the hNav1.7 Channel in vitro patch-clamp assay were reported for the 63 examples of formula (I). The following table contains the $IC_{50}$ values for the above represented examples.

| Compound | $IC_{50}$ (μM) |
|---|---|
| **1** | 0.15 |
| **16** | 0.06 |
| **27** | 0.09 |
| **47** | 0.40 |
| **57** | 2.36 |
| **58** | 0.01 |

**Recent Review Articles:**

1. de Lera R, M.; Kraus, R. L. *J. Med. Chem.* **2015**, DOI: 10.1021/jm501981g.
2. Sun, S.; Cohen, C. J.; Dehnhardt, C. M. *Pharm. Pat. Anal.* **2014**, *3* (5), 509−521.
3. King, G. F.; Vetter, I. *ACS Chem. Neurosci.* **2014**, *5*, 749−751.
4. Dib-Hajj, S. D.; Yang, Y.; Black, J. A.; Waxman, S. G. *Nat. Rev. Neurosci.* **2013**, *14* (1), 49−62.

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### Notes

The authors declare no competing financial interest.