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PATENT HIGHLIGHT

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Inhibitors of Tropomyosin-Receptor Kinases (Trk's): Potential Pain Therapy and More

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Title:	TrkA Kinase Inhibitors, Compositions and Methods Thereof		
Patent Application Number:	WO 2013/176970 A1	**Publication date:**	28 November 2013
Priority Application:	US 61/650,019	**Priority date:**	22 May 2012
Inventors:	Stachel, S. J.; Egbertson, M.; Brnardic, E.; Jones, K.; Sanders, J. M.; Henze, D. A.		
Assignee Company:	Merck Sharp & Dohme Corp., 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907, USA		
Disease Area:	Disorders associated with abnormal activities of Trk's, such as pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, and neurodegenerative diseases.	**Biological Target:**	Inhibition of tropomyosin-related kinases (Trk's)

Summary:

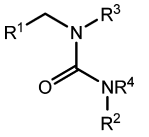
The invention in this patent application relates to urea derivatives represented generally by formula **I** that are Trk inhibitors and may potentially provide treatments for pain, inflammation, cancer, restenosis, atherosclerosis, psoriasis, thrombosis, and other disorders associated with abnormal activities of Trk's.

Tropomyosin-receptor kinases (Trk's) are high affinity binding protein kinase receptors that are made up of three members TrkA, TrkB, and TrkC. They bind to and mediate the signal transduction derived from the Neurotrophins. TrkA is activated by Nerve Growth Factor (NGF), TrkB is activated by Brain-Derived Neurotrophic Factor (BDNF), and Neurotrophin 4−5 (NT-4/5), and TrkC is activated by Neurotrophin 3 (NT-3). Trk's are implicated in several processes and disorders:

- Studies have shown that the interaction of TrkA and NGF is required for the survival of certain peripheral neurons involved in mediating pain signaling in pancreatic cancer and showed also a correlation between increased expression of TrkA and increased level of pain signaling.
- Increased expression of TrkA and NGF was observed in human osteoarthritis chondrocytes.
- Mouse studies showed the expression of TrkA and TrkC receptors in the bone forming area and the localization of NGF in almost all bone forming cells of bone fracture models.
- Studies on neuroblastoma showed an association between overexpression, activation, amplification, and/or mutation of Trks and several cancers.
- Studies have shown that modulation of the neutrophin/Trk pathway has an effect in the etiology of neurodegenerative diseases such as multiple sclerosis, Parkinson's disease and Alzeheimer's disease.

Trk inhibitors such as the compounds disclosed in this patent application may potentially be useful in the treatment of multiple types of acute and chronic pain, including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, and bone fracture. However, the therapeutic implications of Trk inhibitors may extend beyond pain therapy. Trk inhibitors may also be useful in treating osteoporosis, rheumatoid arthritis, and bone metastases. They also show promise in the treatment of inflammatory lung diseases such as asthma, inflammatory bowel diseases, such as ulcerative colitis and Chron's disease, and inflammatory skin diseases, such as atopic dermatitis, eczema, and psoriasis. The Trk inhibitors may also be useful in the treatment of cancer, inflammation, neurodegenerative diseases, and certain infectious diseases.

Important Compound Classes:



Formula (**I**)

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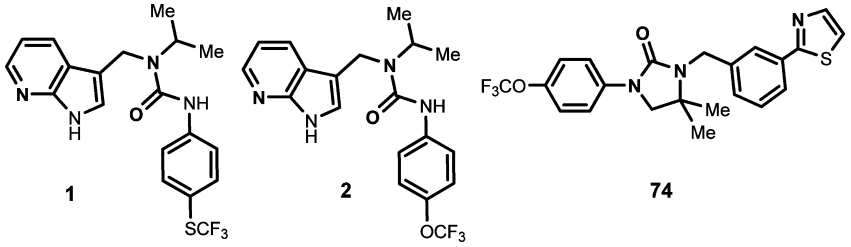
Key Structures: The inventors disclosed the structures of 163 examples of formula **I** including the following three compounds:



Biological Assay: The inventors stated that TrkA kinase activity was measured as the ability of the enzyme to phosphorylate a fluorescently labeled peptide substrate.

Biological Data: IC_{50} values for the compounds of this invention range between 5 nM and 10000 nM. The values for the above three examples are listed in the following table:

Example	TrkA EC_{50} (nM)
1	6.5
2	11.3
74	1005

Note: The inventors mentioned IC_{50} in the text but reported EC_{50} in the table of data.

Claims: Claims 1−18: composition of matter; variations of formulas **I**

Claim 19: composition of matter; 163 examples of formula **I**

Claim 20: pharmaceutical composition

Claim 21: use of a compound as a medicament for the treatment of a disease or disorder mediated by the Trk receptors

Claim 22: method of treating a disease or disorder mediated by the Trk receptors

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Eibl, J. K.; Strasser, B. C.; Ross, G. M. *Neurochem. Int.* **2012**, *61* (8), 1266−1275.

Nantermet, P. G.; Henze, D. A. *Annu. Rep. Med. Chem.* **2011**, *46*, 19−32.

Hefti, F. F.; Rosenthal, A.; Walicke, P. A.; Wyatt, S.; Vergara, G.; Shelton, D. L.; Davies, A. M. *Trends Pharmacol. Sci.* **2006**, *27* (2), 85−91.

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Notes

The authors declare no competing financial interest.