

TRPV4 Antagonists: Potential Treatment for Congestive Heart Failure, Bladder Dysfunctions, and Pain

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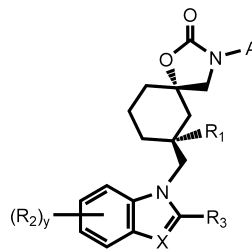
Title:	TRPV4 Antagonists	Publication Date:	December 20, 2012
Patent Application Number:	WO 2012/174342 A1	Priority Date:	June 17, 2011
Priority Application:	US 61/498,104		
Inventors:	Brooks, C.; Cheung, M.; Eidam, H.-S.; Goodman, K. B.; Hammond, M.; Hilfiker, M. A.; Patterson, J. R.; Stoy, P.; Ye, G.		
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Disease Area:	Pain, genetic motor neuron disorders, cardiovascular disease, osteoarthritis, and other disorders modulated by TRPV4	Biological Target:	Transient Receptor Potential Vanilloid-4 (TRPV4)

Summary: The invention in this patent application relates to spirocarbamate analogues represented generally by Formula (I). These compounds possess activity as TRPV4 antagonists and may potentially treat disorders modulated by this receptor such as pain, cardiovascular disease, and osteoarthritis.

Transient receptor potential vanilloid-4 (TRPV4) is a polymodal ion channel that is expressed at high levels in the kidney, liver, lung, heart, and central nervous system; it is activated by a variety of stimuli including warm temperatures and hypotonicity. TRPV4 has been shown to be involved in pulmonary edema induced by heart failure. It has also been implicated in a number of physiological and pathophysiological processes such as pain, genetic motor neuron disorders, cardiovascular disease, and osteoarthritis.

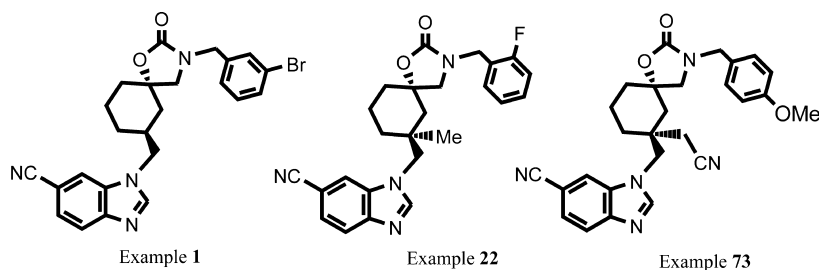
TRPV4 antagonism may potentially provide significant clinical benefits in many of these areas. It is being considered as a clinical target for the treatment of ventilator-induced lung injury, inflammatory and neuropathic pain treatment, bladder dysfunctions, congestive heart failure, motor neuron disorders, or osteoarthritis and other disorders.

Important Compound Classes:



Formula (I)

Key Structures: The patent application describes 77 compounds of Formula (I); the three structures below are representative examples selected randomly:



Biological Assay:

- Ligand-gated assay
- Hypotonicity assay (BHK cells)
- Fluorescent imaging plate reader (FLIPR) assay
- Patch clamp experiments

Biological Data: Data from ligand-gated assay:
All of the examples described in the patent application possessed TRPV4 biological activity with IC_{50} values ranging from 0.001 nM to 1 μ M.

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- Claims:**
- Claims 1–4: Composition of matter, variations of Formula (I)
 - Claim 5: 77 specific compounds of Formula (I) listed by chemical names
 - Claim 6: Pharmaceutical composition
 - Claims 7–10: Methods of treating congestive heart failure, overactive bladder, pain, cardiovascular disease, motor neuron disorders, or osteoarthritis
- Recent Review Articles:**
1. Ferrer-Montiel, A.; Fernandez-Carvajal, A.; Planells-Cases, R.; Fernandez-Ballester, G.; Gonzalez-Ros, J. M.; Messeguer, A.; Gonzalez-Muniz, R. *Expert. Opin. Ther. Pat.* **2012**, *22* (9), 999–1017.
 2. Vincent, F.; Duncton, M. A. J. *Curr. Top. Med. Chem.* (Sharjah, United Arab Emirates) **2011**, *11* (17), 2216–2226.

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Notes

The authors declare no competing financial interest.