ACS Medicinal Chemistry Letters

Patent Highlight

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Modulation of TRPV1 Receptor for Treatment of Pain and Other Disorders

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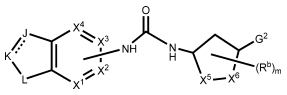
Title:	TRPVl Antagonists		
Patent Application Number:	WO 2012/134943 A1	**Publication Date:**	October 4, 2012
Priority Application:	U.S. 61/467,533	**Priority Date:**	March 25, 2011
Inventors:	Gomtsyan, A.; Daanen, J. F.; Gfesser, G. A.; Kort, M. R.; Lee, C.-H.; McDonald, H. A.; Puttfarcken, P. S.; Voight, E. A.; Kym, P.		
Assignee Company:	Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064, United States		
Disease Area:	Pain, cough, bladder overactivity and urinary incontinence	**Biological Target:**	The Transient Receptor Potential Vaniloid 1 (TRPV1)

Summary:

The invention in this patent application describes urea derivatives represented generally by Formula (I) that may potentially treat disorders modulated by the transient receptor potential vanilloid-1 (TRPV1) receptor such as pain, cough, bladder overactivity, and urinary incontinence.

TRPV1 (also named capsaicin receptor and vanilloid receptor 1) is a nonselective cation channel with high Ca^{2+} permeability; it may be activated by different noxious stimuli including low pH (<6), heat (>43 °C), and chemicals such as capsaicin, resiniferatoxin, and other vanilloids. It is found mainly in the nociceptive neurons, and it is also found on many tissues including the sensory afferents, which innervate the bladder. When TRPV1 is activated, it causes the transmission and modulation of pain (nociception). Exposure to capsaicin activates the TRPV1 receptor and causes a burning sensation. However, upon prolonged exposure, desensitization (or deactivation) of TRPV1 occurs, which results in an analgesic effect; such an effect is mediated by calcium ions flux. Additionally, injection of capsaicin or resiniferatoxin into the bladder has resulted in amelioration of incontinence symptoms. The antinociceptive effect of capsaicin has led to clinical testing of capsaicin analogue antagonists as analgesic agents to block TRPV1 activation for the treatment of pain. The first of these analogues is capsazepine, a TRPV1 antagonist that reduces inflammation-induced hyperalgesia in animal models and blocks activation of TRPV1 in response to capsaicin, acid, or heat. TRPV1 antagonists represent a novel and attractive therapeutic approach for the treatment of pain and may also treat other disorders modulated by the TRPV1 receptor.

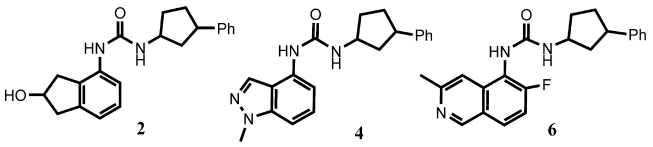
Important Compound Classes:



Formula (I)

Key Structures:

The patent application describes the synthesis of 146 examples of formula (I); all of the compounds were listed by chemical names. The application claims 146 specific compounds (claim 25), and some of these compounds were reclaimed (claims 32, 34, 36, and 38). Nine common compounds in these claims are listed below with their example numbers. The first three structures were generated from their names without stereochemistry for structural representation:



2 4 6

1-[(2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-4-yl]-3-[(1*R*,3*S*)-3-phenylcyclopentyl]urea (**2**)

1-(1-methyl-1*H*-indazol-4-yl)-3-[(1*R*,3*S*)-3-phenylcyclopentyl]urea (**4**)

1-(6-fluoro-3-methylisoquinolin-5-yl)-3-[(1*R*,3*S*)-3-phenylcyclopentyl]urea (**6**)

1-(1*H*-indazol-4-yl)-3-[(1*R*,3*S*)-3-phenylcyclopentyl]urea (**7**)

1-(1*H*-indazol-4-yl)-3-[(1*S*,3*S*)-3-phenylcyclopentyl]urea (**14**)

1-(6-fluoro-3-methylisoquinolin-5-yl)-3-[(1*S*,3*R*)-3-phenylcyclopentyl]urea (**27**)

1-(1*H*-indazol-4-yl)-3-[(1*S*,3*R*)-3-phenylcyclopentyl]urea (**28**)

1-(1*H*-indazol-4-yl)-3-[(1*S*,4*R*)-4-phenylcyclopent-2-en-1-yl]urea (**48**)

1-(1-methyl-2-oxo-1,2-dihydroquinolin-5-yl)-3-((1*R*,3*S*)-3-phenylcyclopentyl)urea (**51**)

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Biological Assays: The following biological assays were described for testing the compounds:

In Vitro Evaluations:

(i) Capsaicin Activation Assay

(ii) Acid Activation Assay

In Vivo Evaluations:

(i) Rat Tail Immersion Protocol

(ii) Rat Acute Capsaicin-Induced Flinching Behavior

(iii) Capsaicin-Induced Secondary Mechanical Hypersensitivity

(iv) Sodium Iodoacetate-Induced Knee Joint Osteoarthritic Pain Model

(v) Chronic Constriction Injury Model of Neuropathic Pain

(vi) Spinal Nerve Ligation Model of Neuropathic Pain

Recent Review Articles:

1. Szallasi, A.; Sheta, M. *Expert Opin. Invest. Drugs* **2012**, *21* (9), 1351−1369.

2. Brandt, M. R.; Beyer, C. E.; Stahl, S. M. *Pharmaceuticals* **2012**, *5*, 114−132.

3. Xia, R.; Dekermendjian, K.; Lullau, E.; Dekker, N. *Adv. Exp. Med. Biol.* 2011, *704* (Transient Receptor Potential Channels), 637−665.

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Notes

The author declares no competing financial interest.