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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/495, 31/445	A1	**(11) International Publication Number:** WO 97/25988 **(43) International Publication Date:** 24 July 1997 (24.07.97)

(21) International Application Number: PCT/US97/00788

(22) International Filing Date: 17 January 1997 (17.01.97)

(30) Priority Data:
60/010,133 17 January 1996 (17.01.96) US

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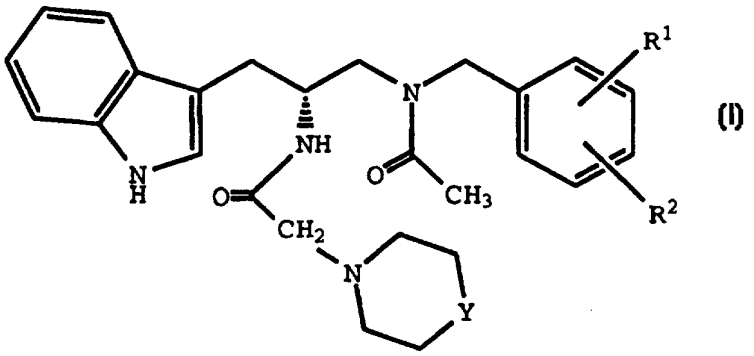
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS OF TREATING OR PREVENTING PAIN OR NOCICEPTION

(57) Abstract

This invention provides methods for the treatment or prevention of pain or nociception in a mammal which comprise administering to a mammal in need thereof an effective amount of a compound of formula (I), where R^1 and R^2 are independently selected from the group consisting of hydrogen, methyl, methoxy, chloro, and trifluoromethyl, with the proviso that no more than one of R^1 and R^2 can be hydrogen; and Y is formula (II), N-R^a, or CH-NR^bR^c, where R^a, R^b, and R^c are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or a pharmaceutically acceptable salt or solvate thereof, in combination with an analgesic whose primary mechanism of action is not as a tachykinin receptor antagonist. This invention also provides pharmaceutical formulations comprising a compound of formula (I) in combination with a traditional analgesic, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.



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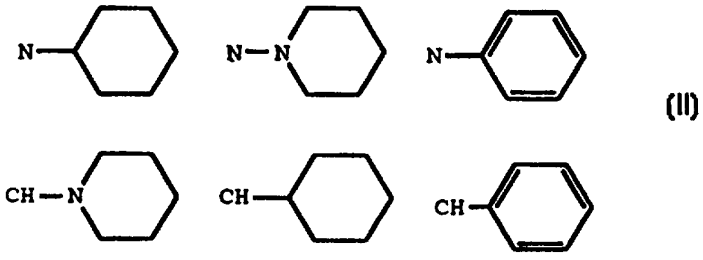

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Title

METHODS OF TREATING OR PREVENTING PAIN OR NOCICEPTION

Background of the Invention

Tachykinins are a family of peptides which share a common amidated carboxy terminal sequence. Substance P was the first peptide of this family to be isolated, although its purification and the determination of its primary sequence did not occur until the early 1970's.

Between 1983 and 1984 several groups reported the isolation of two novel mammalian tachykinins, now termed neurokinin A (also known as substance K, neuromedin L, and neurokinin α), and neurokinin B (also known as neuromedin K and neurokinin β). See, J.E. Maggio, Peptides, 6 (Supplement 3):237-243 (1985) for a review of these discoveries.

Tachykinins are widely distributed in both the central and peripheral nervous systems, are released from nerves, and exert a variety of biological actions, which, in most cases, depend upon activation of specific receptors expressed on the membrane of target cells. Tachykinins are also produced by a number of non-neural tissues.

The mammalian tachykinins substance P, neurokinin A, and neurokinin B act through three major receptor subtypes, denoted as NK-1, NK-2, and NK-3, respectively. These receptors are present in a variety of organs.

Substance P is believed inter alia to be involved in the neurotransmission of pain sensations, including the pain associated with migraine headaches and with arthritis. These peptides have also been implicated in gastrointestinal disorders and diseases of the gastrointestinal tract such as inflammatory bowel disease. Tachykinins have also been implicated as playing a role in numerous other maladies, as discussed infra.

Tachykinins play a major role in mediating the sensation and transmission of pain or nociception, especially migraine headaches. see, e.g., S.L. Shepheard, et al., British Journal of Pharmacology, 108:11-20 (1993); S.M. Moussaoui, et al., European Journal of Pharmacology, 238:421-424 (1993); and W.S. Lee, et al., British Journal of Pharmacology, 112:920-924 (1994).

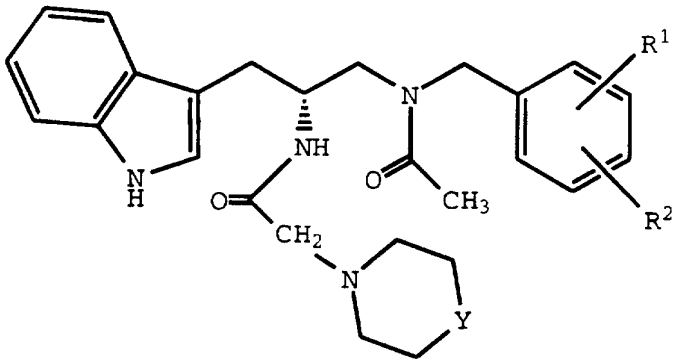
In view of the wide number of clinical maladies associated with an excess of tachykinins, the development of tachykinin receptor antagonists will serve to control these clinical conditions. The earliest tachykinin receptor antagonists were peptide derivatives. These antagonists proved to be of limited pharmaceutical utility because of their metabolic instability.

Recent publications have described novel classes of non-peptidyl tachykinin receptor antagonists which generally have greater oral bioavailability and metabolic stability than the earlier classes of tachykinin receptor antagonists. Examples of such newer non-peptidyl tachykinin receptor antagonists are found in United States Patent 5,328,927, issued July 12, 1994; United States Patent 5,360,820, issued November 1, 1994; United States Patent 5,344,830, issued September 6, 1994; United States Patent 5,331,089, issued July 19, 1994; European Patent Publication 591,040 A1, published April 6, 1994; Patent Cooperation Treaty publication WO 94/01402, published January 20, 1994; Patent Cooperation Treaty publication WO 94/04494, published March 3, 1994; and Patent Cooperation Treaty publication WO 93/011609, published January 21, 1993.

Because of the current dissatisfaction of the currently marketed treatments for pain or nociception within the affected population, there exists a need for a more efficacious and safe treatment.

Summary of the Invention

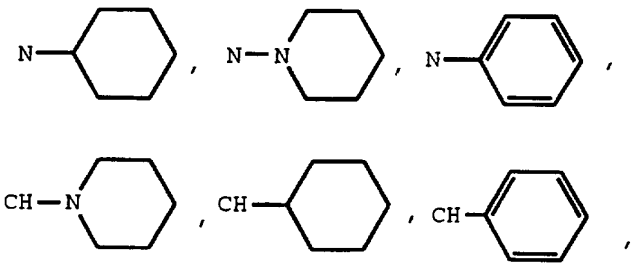
This invention provides methods for the treatment or prevention of pain or nociception in a mammal which comprise administering to a mammal in need thereof an effective amount of a compound of Formula I



I

where R^1 and R^2 are independently selected from the group consisting of hydrogen, methyl, methoxy, chloro, and trifluoromethyl, with the proviso that no more than one of R^1 and R^2 can be hydrogen; and

Y is



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