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Chaturvedula et al.

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(45) **Date of Patent: Jun. 10, 2008**

(54) **CONSTRAINED COMPOUNDS AS CGRP-RECEPTOR ANTAGONISTS**

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(51) **Int. Cl.**

C07D 487/04	(2006.01)
C07D 401/14	(2006.01)
C07D 519/00	(2006.01)
A61P 25/06	(2006.01)
A61K 31/55	(2006.01)

(52) **U.S. Cl.** **514/212.06**; 540/521

(58) **Field of Classification Search** 540/521; 514/212.06

See application file for complete search history.

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(57) **ABSTRACT**

The invention encompasses constrained bicyclic and tricyclic CGRP-receptor antagonists, methods for identifying them, pharmaceutical compositions comprising them, and methods for their use in therapy for treatment of migraine and other headaches, neurogenic vasodilation, neurogenic inflammation, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.

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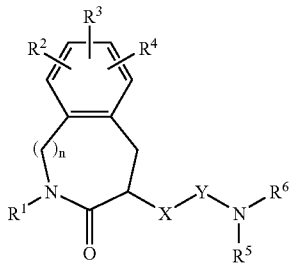

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CONSTRAINED COMPOUNDS AS CGRP-RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application Ser. Nos. 60/624,655 filed Nov. 3, 2004 and 60/678,099 filed May 5, 2005.

BACKGROUND OF THE INVENTION

Calcitonin gene-related peptide (CGRP) is a naturally occurring 37-amino-acid peptide first identified in 1982 (Amara, S. G. et al, *Science* 1982, 298, 240-244). Two forms of the peptide are expressed (αCGRP and βCGRP) which differ by one and three amino acids in rats and humans, respectively. The peptide is widely distributed in both the peripheral (PNS) and central nervous system (CNS), principally localized in sensory afferent and central neurons, and displays a number of biological effects, including vasodilation.

When released from the cell, CGRP binds to specific cell surface G protein-coupled receptors and exerts its biological action predominantly by activation of intracellular adenylate cyclase (Poyner, D. R. et al, *Br J Pharmacol* 1992, 105, 441-7; Van Valen, F. et al, *Neurosci Lett* 1990, 119, 195-8.). Two classes of CGRP receptors, $CGRP_1$ and $CGRP_2$, have been proposed based on the antagonist properties of the peptide fragment CGRP(8-37) and the ability of linear analogues of CGRP to activate $CGRP_2$ receptors (Juaneda, C. et al. *TiPS* 2000, 21, 432-438). However, there is lack of molecular evidence for the $CGRP_2$ receptor (Brain, S. D. et al, *TiPS* 2002, 23, 51-53). The $CGRP_1$ receptor has three components: (i) a 7 transmembrane calcitonin receptor-like receptor (CRLR); (ii) the single transmembrane receptor activity modifying protein type one (RAMP1); and (iii) the intracellular receptor component protein (RCP) (Evans B. N. et al., *J Biol Chem*. 2000, 275, 31438-43). RAMP1 is required for transport of CRLR to the plasma membrane and for ligand binding to the CGRP-receptor (McLatchie, L. M. et al, *Nature* 1998, 393, 333-339). RCP is required for signal transduction (Evans B. N. et al., *J Biol Chem*. 2000, 275, 31438-43). There are known species-specific differences in binding of small molecule antagonists to the CGRP-receptor with typically greater affinity seen for antagonism of the human receptor than for other species (Brain, S. D. et al, *TiPS* 2002, 23, 51-53). The amino acid sequence of RAMP1 determines the species selectivity, in particular, the amino acid residue Trp74 is responsible for the phenotype of the human receptor (Mallee et al. *J Biol Chem* 2002, 277, 14294-8).

Inhibitors at the receptor level to CGRP are postulated to be useful in pathophysiologic conditions where excessive CGRP receptor activation has occurred. Some of these include neurogenic vasodilation, neurogenic inflammation, migraine, cluster headache and other headaches, thermal injury, circulatory shock, menopausal flushing, and asthma. CGRP receptor activation has been implicated in the pathogenesis of migraine headache (Edvinsson L. *CNS Drugs* 2001; 15(10):745-53; Williamson, D. J. *Microsc. Res. Tech*. 2001, 53, 167-178.; Grant, A. D. *Brit. J. Pharmacol*. 2002, 135, 356-362.). Serum levels of CGRP are elevated during migraine (Goadsby P J, et al. *Ann Neurol* 1990; 28: 183-7) and treatment with anti-migraine drugs returns CGRP levels

elevated basal CGRP levels compared to controls (Ashina M, et al., *Pain* 2000, 86(1-2): 133-8.2000). Intravenous CGRP infusion produces lasting headache in migraineurs (Lassen L H, et al. *Cephalalgia* 2002 February; 22(1):54-61). Preclinical studies in dog and rat report that systemic CGRP blockade with the peptide antagonist CGRP(8-37) does not alter resting systemic hemodynamics nor regional blood flow (Shen, Y-T. et al, *J Pharmacol Exp Ther* 2001, 298, 551-8). Thus, CGRP-receptor antagonists may present a novel treatment for migraine that avoids the cardiovascular liabilities of active vasoconstriction associated with non-selective $5\text{-}HT_{1B/1D}$ agonists, 'triptans' (e.g., sumatriptan).

A number of non-peptidic, small molecule CGRP-receptor antagonists have been recently reported. WO 04/091514, WO 04/092166 and WO 04/092168 disclose cyclic compounds containing an amide bond in the ring as CGRP antagonists. WO 97/09046 and equivalents disclose inter alia quinine and quinidine related compounds which are ligands, in particular antagonists, of CGRP-receptor. WO 98/09630 and WO 98/56779 and equivalents disclose inter alia variously substituted, nitrobenzamide compounds as CGRP-receptor antagonists. WO 01/32649, WO 01/49676, and WO 01/32648 and equivalents disclose inter alia a series of 4-oxobutanamides and related cyclopropane derivatives as CGRP-receptor antagonists. WO 00/18764, WO 98/11128 and WO 00/55154 and equivalents disclose inter alia benzimidazolinyl piperidines as antagonists to CGRP-receptor. Unrelated to CGRP, a series of somatostatin antagonists have been disclosed in WO 99/52875 and WO 01/25228 and equivalents. See also U.S. Pat. Nos. 6,344,449, 6,313,097, 6,521,609, 6,552,043, US 20030181462, US20030191068 and WO 03/076432 and related applications. Thus, novel CGRP-receptor antagonists effective for the treatment of neurogenic inflammation, migraine and other disorders would be greatly advantageous.

DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I and II which are CGRP antagonists. The invention also encompasses compositions incorporating these compounds and methods of using these compounds in therapeutic treatment.

One aspect of the invention is a compound of Formula I

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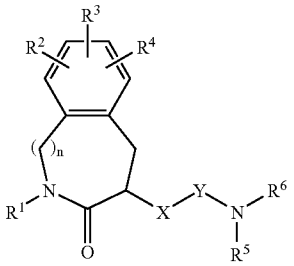


wherein:

R^1 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{5-7}cycloalkenyl,

$C_{1-6}(C_{3-7}$cycloalkyl)alkyl, C_{1-6}haloalkyl, $C_{1-6}(C_{1-6}$alkoxy)alkyl, $C_{1-6}(Ar^1)$alkyl,

$C_{1-6}(NR^7R^8)$alkyl, N—(R^9)-pyrrolidinyl or N—(R^9)-piperidinyl;

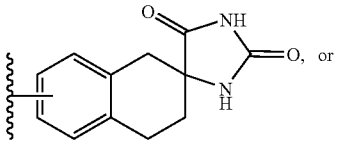
R^3 is hydrogen, hydroxy, halo, C_{1-6}alkyl, or C_{2-6}alkenyl; or R^2 and R^3 taken together are $CHNNR^5$;

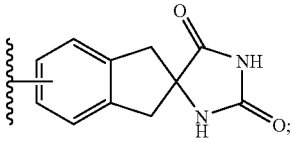
R^4 is hydrogen, halo or C_{1-6}alkyl, or C_{2-6}alkenyl;

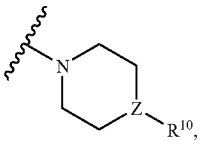
R^5 is hydrogen or C_{1-6}alkyl;

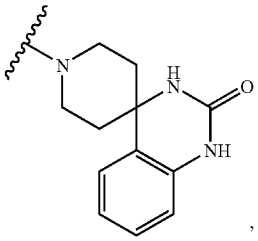
R^6 is hydrogen, C_{1-6}alkyl,

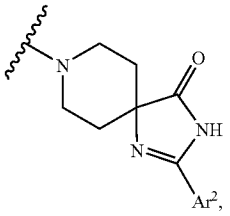
or NR^5R^6 taken together is

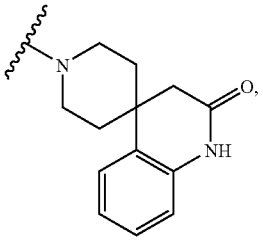


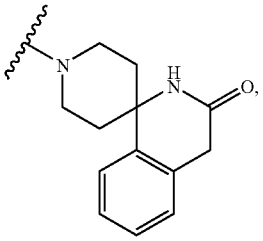


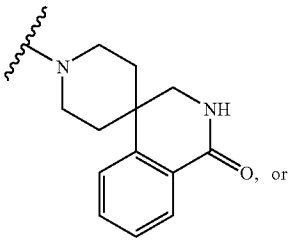


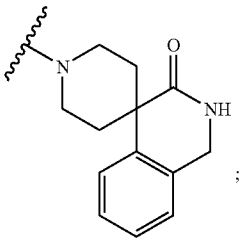












R^7 is hydrogen or C_{1-6}alkyl;

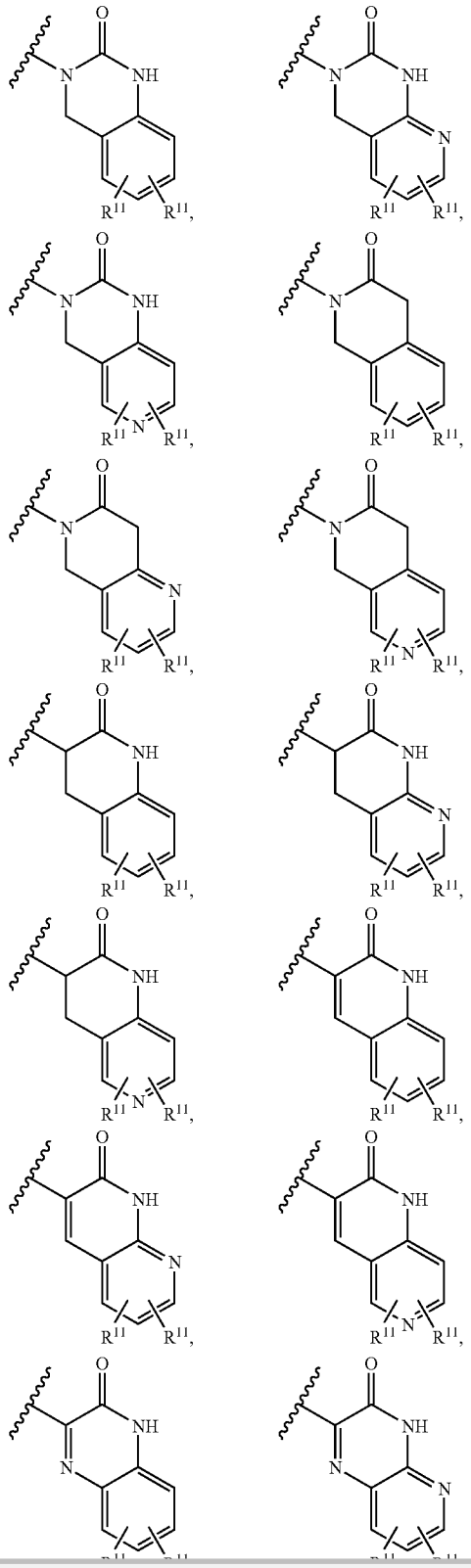
R^8 is hydrogen or C_{1-6}alkyl; or

NR^7R^8 taken together is selected from the group consisting of pyrrolidinyl, piperidinyl, N—(R^9)-piperazinyl, morpholinyl, and thiomorpholinyl;

R^9 is hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, or C_{1-6}alkoxycarbonyl;

R^{10} is phenyl, naphthyl, pyridinyl, pyridinyl N-oxide, quino- from the group consisting of halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy, and phenyl;

or R^{10} is selected from the group consisting of



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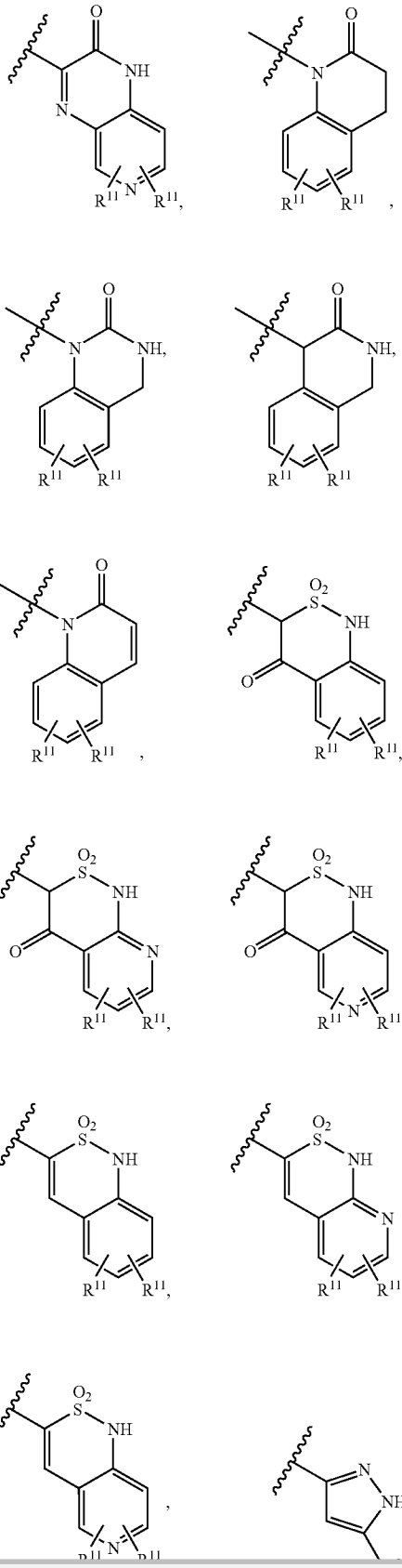

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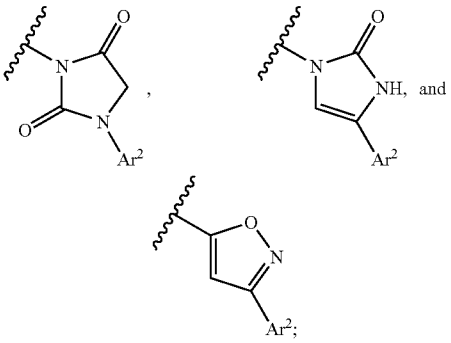


R^{11} is hydrogen, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{1-6}alkoxy;

Ar^1 is phenyl, naphthyl, pyridinyl, or imidazolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6}alkyl, and C_{1-6}haloalkyl;

Ar^2 is phenyl, naphthyl, or pyridinyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6}alkyl, and C_{1-6}haloalkyl;

X-Y is aminocarbonyl, oxycarbonyl, methylenecarbonyl, ethylene, or amino(cyano)iminomethyl;

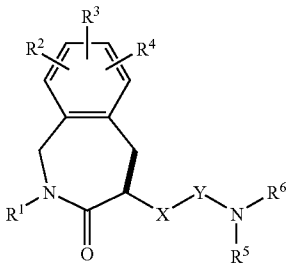
Z is N or CH; and

n is 0 or 1;

or a pharmaceutically acceptable salt or solvate thereof.

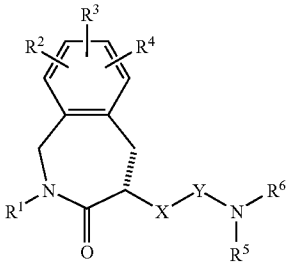
Another aspect of the invention is a compound of Formula Ia.

Ia



Another aspect of the invention is a compound of Formula Ib.

Ib



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