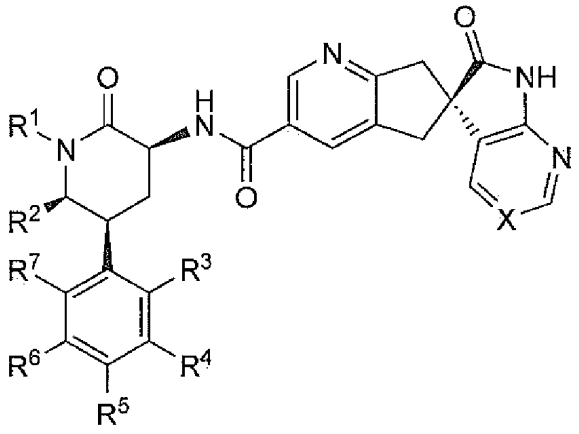
(1992) *Ann. NY Acad. Sci.* **657**, 397-404; Schini *et al.* (1994) *Am. J. Physiol.* **267**, H2483-H2490; Zheng *et al.* (1993) *J. Virol.* **67**, 5786-5791); shock, sepsis (Beer *et al.* (2002) *Crit. Care Med.* **30**, 1794-1798); opiate withdrawal syndrome (Salmon *et al.* (2001) *Nature Neurosci.* **4**, 357-358); morphine tolerance (Menard *et al.* (1996) *J. Neurosci.* **16**, 2342-2351); hot flashes in men and women (Chen *et al.* (1993) *Lancet* **342**, 49; Spetz *et al.* (2001) *J. Urology* **166**, 1720-1723); allergic dermatitis (Wallengren (2000) *Contact Dermatitis* **43**, 137-143); psoriasis; encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases (Rohrenbeck *et al.* (1999) *Neurobiol. Dis.* **6**, 15-34); skin diseases (Geppetti and Holzer, Eds., Neurogenic Inflammation, 1996, CRC Press, Boca Raton, FL), neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus (Herzog *et al.* (2002) *J. Membr. Biol.* **189**, 225); obesity (Walker *et al.* (2010) *Endocrinology* **151**, 4257-4269); inflammatory bowel disease, irritable bowel syndrome, (Hoffman *et al.* (2002) *Scand. J. Gastroenterol.* **37**, 414-422) and cystitis. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

U.S. Patent No. 7,390,798, granted June 24, 2008 and U.S. Patent Publication No.: US 2010/0179166, published July 15, 2010, disclose carboxamide CGRP receptor antagonist. The present invention is directed to a class of highly potent CGRP receptor antagonists as compared to earlier disclosed analogues, pharmaceutical compositions comprising them and their use in therapy.

SUMMARY

The present disclosure is directed to piperidinone carboxamide azaindane derivatives which are highly potent antagonists of CGRP receptors and useful in the treatment or prevention of diseases in which the CGRP is involved, such as migraine. The disclosure is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

In one aspect, there is provided a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof,

for use in the acute or prophylactic treatment of migraine headache or cluster headache in conjunction with one or more agents selected from:

an anti-migraine agent; a 5-$HT_{1B/1D}$ agonist; a 5-HT_{1D} agonist; a 5-HT_{1F} agonist; a cyclooxygenase inhibitor; a non-steroidal anti-inflammatory agent or cytokine-suppressing anti-inflammatory agent; a glucocorticoid; and an analgesic;

wherein:

X is selected from -C(R^8)= or –N=, wherein R^8 is hydrogen, F or CN;

R^1 is selected from the group consisting of: C_{1-4}alkyl, cyclopropylmethyl, cyclobutylmethyl and [1-(trifluoromethyl)cyclopropyl]methyl, each of which is optionally substituted with one or more substituents as allowed by valence independently selected from the group consisting of: F and hydroxy;

R^2 is selected from hydrogen and methyl;

when R^2 is hydrogen then

R^3 is selected from hydrogen, F or Cl;

R^4 is selected from hydrogen, F or Cl;

R^5 is hydrogen;

R^6 is selected from hydrogen or F; and

R^7 is selected from hydrogen, F or Cl;

except that at least two of R^3, R^4, R^6 and R^7 must be F or Cl unless R^3 is F in which case R^4, R^6 and R^7 may all be hydrogen; and if R^4 is Cl then R^7 cannot be Cl;

when R^2 is methyl then

R^3 is selected from hydrogen, methyl, F, Cl, or Br;

R^4 is selected from hydrogen, methyl, F or Cl;

R^5 is selected from hydrogen or F;

R^6 is selected from hydrogen or F; and

R^7 is selected from hydrogen, methyl, F or Cl;
except that if R^5 is F then at least three of R^3, R^4, R^6 and R^7 must be F; and if R^4 is methyl or Cl then R^7 cannot be methyl or Cl.

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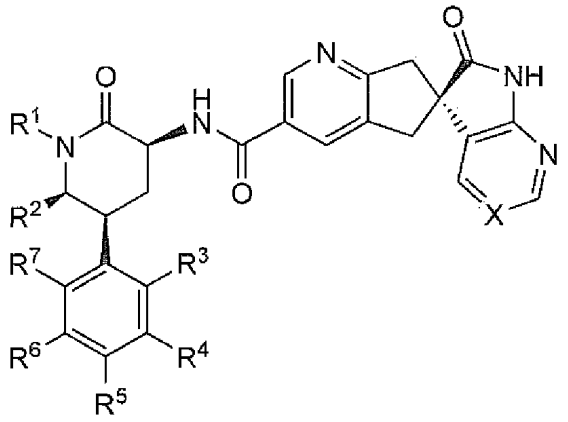
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a genus of compounds of Formula I:

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof,

for use in the acute or prophylactic treatment of migraine headache or cluster headache in conjunction with one or more agents selected from:

an anti-migraine agent; a 5-$HT_{1B/1D}$ agonist; a 5-HT_{1D} agonist; a 5-HT_{1F} agonist; a cyclooxygenase inhibitor; a non-steroidal anti-inflammatory agent or cytokine-suppressing anti-inflammatory agent; a glucocorticoid; and an analgesic;

wherein:

X is selected from -C(R^8)= or –N=, wherein R^8 is hydrogen, F or CN;

R^1 is selected from the group consisting of: C_{1-4}alkyl, cyclopropylmethyl, cyclobutylmethyl and [1-(trifluoromethyl)cyclopropyl]methyl, each of which is optionally substituted with one or more substituents as allowed by valence independently selected from the group consisting of: F and hydroxy;

R^2 is selected from hydrogen and methyl;

when R^2 is hydrogen then

R^3 is selected from hydrogen, F or Cl;

R^4 is selected from hydrogen, F or Cl;

R^5 is hydrogen;

R^6 is selected from hydrogen or F; and

R^7 is selected from hydrogen, F or Cl;

except that at least two of R^3, R^4, R^6 and R^7 must be F or Cl unless R^3 is F in which case R^4, R^6 and R^7 may all be hydrogen; and if R^4 is Cl then R^7 cannot be Cl;

when R^2 is methyl then

R^3 is selected from hydrogen, methyl, F, Cl, or Br;

R^4 is selected from hydrogen, methyl, F or Cl;

R^5 is selected from hydrogen or F;

R^6 is selected from hydrogen or F; and

R^7 is selected from hydrogen, methyl, F or Cl;

except that if R^5 is F then at least three of R^3, R^4, R^6 and R^7 must be F; and if R^4 is methyl or Cl then R^7 cannot be methyl or Cl.

2. A compound of formula I for use as defined in claim 1 wherein the said anti-migraine agent is selected from ergotamine and dihydroergotamine; the said 5-$HT_{1B/1D}$ agonist is selected from sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, and rizatriptan; the said 5-HT_{1D} agonist is PNU-142633; the said 5-HT_{1F} agonist is LY334370; the said cyclooxygenase inhibitor is selected from rofecoib, etoricoxib, celecoxib, valdecoxib and paracoxib; the said non-steroidal anti-inflammatory agent or cytokine-suppressing anti-inflammatory agent is selected from ibuprofen, ketoprofen, fenoprofen, naproxen, indomethacin, sulindac, meloxicam, pirioxicam, tenoicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine, and sulfasalazine; and the said analgesic is selected from aspirin, acetaminophen, phenacetin, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine, and morphine.

3. A compound of formula I for use as defined in claim 1 in conjunction with ergotamine, dihydroergotamine, sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, avitriptan, rizatriptan, rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib.

4. A compound of formula I for use as defined in claim 1 wherein the compound of formula I and said one or more agents are to be administered contemporaneously.

5. A compound of formula I for use as defined in claim 4 wherein the compound of formula I and said one or more agents are to be administered together in a pharmaceutical composition in unit dosage form.

6. A compound of formula I for use as defined in claim 1 wherein the compound of formula I and said one or more agents are to be administered sequentially.

7. A compound of formula I for use as defined in claim 1 wherein the compound of formula I and said one or more agents are to be administered on different overlapping schedules.

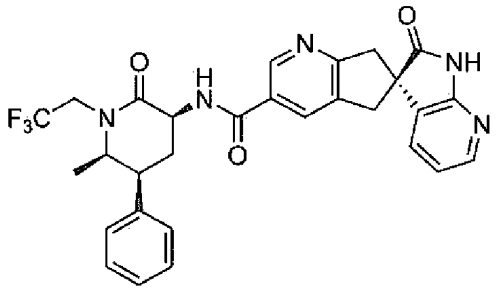
8. A compound of formula I for use as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein X is -CH=.

9. A compound of formula I for use as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-4} alkyl, optionally substituted with 1 to 3 F or hydroxy, or both.

10. A compound of formula I for use as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is 2,2,2-trifluoroethyl.

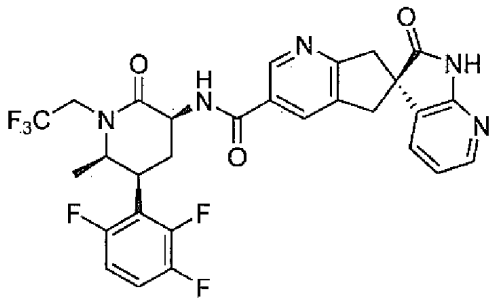
11. A compound of formula I for use as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

12. A compound of formula I for use as defined in claim 1 which is:



or a pharmaceutically acceptable salt thereof.

13. A compound of formula I for use as defined in claim 1 which is:



or a pharmaceutically acceptable salt thereof.