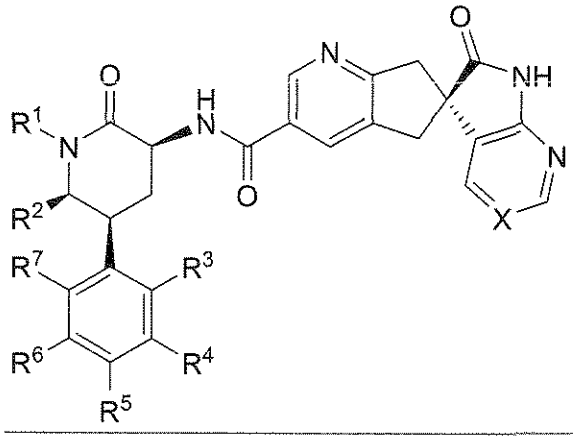
(1992) *Ann. NY Acad. Sci.* **657**, 397-404; Schini *et al.* (1994) *Am. J. Physiol.* **267**, H2483-H2490; Zheng *et al.* (1993) *J. Virol.* **67**, 5786-5791); shock, sepsis (Beer *et al.* (2002) *Crit. Care Med.* **30**, 1794-1798); opiate withdrawal syndrome (Salmon *et al.* (2001) *Nature Neurosci.* **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 ~~OF THE INVENTION~~

The present ~~invention~~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 ~~invention~~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 a first aspect, there is provided a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, 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.

In a second aspect, there is provided a pharmaceutical composition which comprises an inert carrier and the compound as defined above, or a pharmaceutically acceptable salt thereof.

In a third aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for the manufacture of a medicament for the treatment of headache.

In a fourth aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for use in medicine.

In a fifth aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for use in acute treatment of migraine headache or cluster headache.

In a sixth aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof for use in prophylactic treatment of migraine headache or cluster headache.

DETAILED DESCRIPTION OF THE INVENTION

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