

CGRP RECEPTOR ANTAGONISTS

The present invention relates to certain novel calcitonin gene-related peptide (CGRP) receptor antagonist compounds, to pharmaceutical compositions comprising the compounds, to methods of using the compounds to prevent or treat certain physiological disorders such as migraine, and to intermediates and processes useful in the synthesis of the compounds.

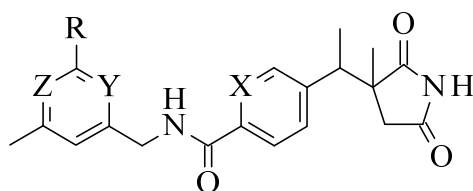
The present invention is in the field of prevention and treatment of migraine and other neurological diseases and disorders thought to be mediated by CGRP (See for example, S. Benemei, *et. al.*, *Current Opinion in Pharmacology*, **9**, 9-14 (2009)).

Migraine is a debilitating disease suffered by millions of people worldwide. Treatment options for migraine include the triptans, such as sumatriptan and zolmitriptan. Unfortunately, currently approved agents available to the patient do not always provide effective treatment, and these agents can be associated with various untoward side effects such as dizziness, paresthesia, and chest discomfort. In addition, triptans possess certain cardiovascular concerns causing them to be contraindicated in patients suffering from substantial underlying cardiovascular disease or uncontrolled hypertension (See T.W. Ho, *et. al.*, *The Lancet*, **372**, 2115-2123 (2008)). Thus, there is a significant unmet need in the prevention and treatment of migraine. CGRP receptor antagonists are desired to provide more effective treatment for or prevention of certain neurological diseases, such as migraine.

United States Patent No. 6,680,387 discloses certain 5-benzyl- or 5-benzylidene-thiazolidine-2,4-diones for the treatment of type-II diabetes mellitus, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

Summary

In one aspect of the present disclosure, there is provided a compound of the formula:



wherein

Y is CH or N;

5 Z is CH or N;

provided that when Y is CH, Z is N and when Y is N, Z is CH;

X is CH or N; and

R is C1-C3 alkyl, C3-C5 cycloalkyl, or CN,

or a pharmaceutically acceptable salt thereof.

10 In another aspect of the present disclosure, there is provided a use of a compound or salt disclosed herein in the manufacture of a medicament for preventing migraine in a patient.

In a further aspect of the present disclosure, there is provided a use of a compound or salt disclosed herein in the manufacture of a medicament for treating migraine in a
15 patient.

In another aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in the treatment of migraine.

20 In another aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in preventing migraine.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound or salt disclosed herein with one or more pharmaceutically acceptable carriers, diluents, or excipients.

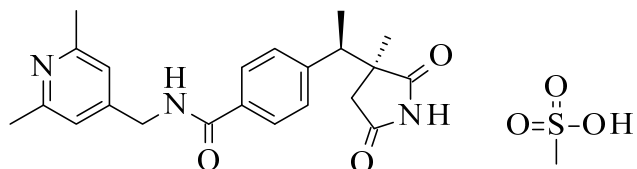
25 In another aspect of the present disclosure, there is provided a process for preparing a pharmaceutical composition, comprising admixing a compound or salt disclosed herein with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Description

The present invention provides certain novel compounds that are antagonists of the CGRP receptor. Furthermore, the present invention provides certain novel compounds that are antagonists of the CGRP receptor which have the potential for an improved side-effect profile in the treatment or prevention of migraine.

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13. The salt according to claim 9 which is:



14. The salt according to claim 13 which is crystalline.

5 15. The salt according to claim 14 which is characterized by a substantial peak in the X-ray diffraction spectrum at diffraction angle 2-theta of at 18.8° in combination with one or more of the peaks selected from the group consisting of 23.2°, 24.7°, and 15.2°; with a tolerance for the diffraction angles of 0.2 degrees.

10 16. Use of a compound or salt of any one of claims 1-15 in the manufacture of a medicament for preventing migraine in a patient.

17. Use of a compound or salt of any one of claims 1-15 in the manufacture of a medicament for treating migraine in a patient.

18. The compound or salt according to any one of claims 1-15 for use in therapy.

15 19. The compound or salt according to any one of claims 1-15 for use in the treatment of migraine.

20. The compound or salt according to any one of claims 1-15 for use in preventing migraine.

20 21. A pharmaceutical composition, comprising a compound or salt according to any one of claims 1-15 with one or more pharmaceutically acceptable carriers, diluents, or excipients.

22. A process for preparing a pharmaceutical composition, comprising admixing a compound or salt according to any one of claims 1-15 with one or more pharmaceutically acceptable carriers, diluents, or excipients.