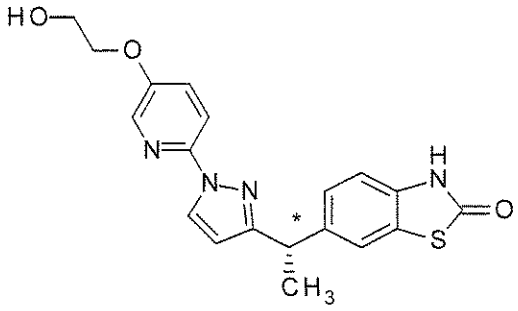
Transmembrane AMPA Receptor Regulatory Proteins (TARPs) are a fairly recently discovered family of proteins that have been found to associate with and modulate the activity of AMPA receptors. Several TARPs are fairly regiospecific in the brain, leading to physiological differentiation of the AMPA receptor activity. As for example, TARP γ2 (stargazin) dependent AMPA receptors are primarily localized in the cerebellum and cerebral cortex and TARP γ8 dependent AMPA receptors are localized primarily in the hippocampus, which region is particularly relevant to seizure origination and/or propagation. It has been theorized that targeting individual TARPs may enable selective modulation of specific brain circuits without globally affecting synaptic transmission. (Gill, Martin B. and Bredt, David S., Neuropsychopharmacology 36(1): 362-363 (2011).)

Levetiracetam ((*S*)-2-(2-oxopyrrolidin-1-yl)butanamide), gabapentin (2-[1-(aminomethyl)cyclohexyl]acetic acid), topiramate (2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate), and carbamazepine (5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide) are current leading therapeutic drugs for epileptic seizures. None of the currently approved drugs appear to act entirely through modulation of AMPA receptors.

Talampanel ((8*R*)-7-Acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo[4,5-h] [2,3]benzodiazepine), selurampanel (BGG492) (N-[7-isopropyl-6-(2-methyl-2H-pyrazol-3-yl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]methanesulfonamide), and parampanel (5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'H)-one) are general (non-TARP dependent/non-selective) AMPA receptor antagonists being tested as anti-epileptics.

Summary

In a first aspect, there is provided a compound of the formula



or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided a pharmaceutical composition comprising 6-((S)-1-{1-[5-(2-hydroxy-ethoxy)-pyridin-2-yl]-1*H*-pyrazol-3-yl}-ethyl)-3*H*-1,3-benzothiazol-2-one, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

In a fourth aspect, there is provided use of a compound or salt as disclosed above for the manufacture of a medicament for the treatment of seizures in a mammal with epilepsy.

In a fifth aspect, there is provided a compound or salt as disclosed above for use in therapy.

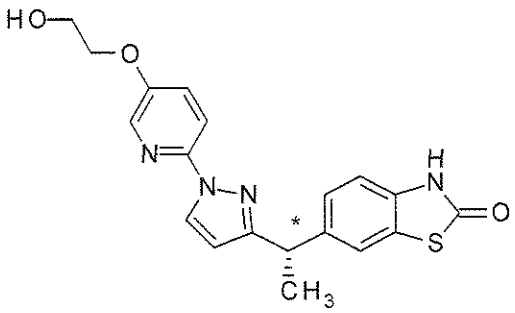
Detailed Disclosure

It is here suggested that a selective, non-competative TARP γ8 dependent AMPA receptor antagonist could be an effective anti-seizure/anti-epiletic therapeutic without the side effects (e.g. sedation, ataxis, and/or dizziness) of general (non-TARP dependent/non-selective) AMPA antagonists or TARP γ2 dependent AMPA antagonists, which are more associated with AMPA receptor antagonism in the cerebellum.

The present invention provides a compound which displays potent and selective TARP γ8-dependent AMPA receptor antagonist activity in vitro, as well as efficacy in animal models of seizure and pain. Thus, the present invention provides a compound which is believed to be useful for the treatment of seizures in patients with epilepsy, as for example simple and/or complex partial onset seizures, and/or primary and/or

We Claim:

1. A compound of the formula

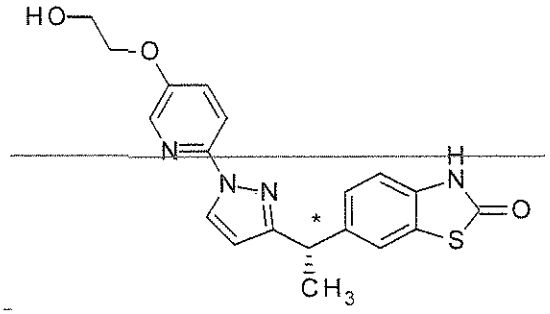


or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 which is 6-((S)-1-{1-[5-(2-hydroxy-ethoxy)-pyridin-2-yl]-1*H*-pyrazol-3-yl}-ethyl)-3*H*-1,3-benzothiazol-2-one.

3. A pharmaceutical composition comprising 6-((S)-1-{1-[5-(2-hydroxy-ethoxy)-pyridin-2-yl]-1*H*-pyrazol-3-yl}-ethyl)-3*H*-1,3-benzothiazol-2-one, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

~~4. A method of treating seizures in a mammal with epilepsy comprising administering to a mammal in need of such treatment an effective amount of a compound of the formula~~



~~or a pharmaceutically acceptable salt thereof.~~

~~5. The method of Claim 4 wherein the mammal is a human.~~

~~6. The method of Claim 4 wherein the seizures are simple or complex partial onset seizures.~~

~~7. The method of Claim 6 wherein the mammal is a human.~~

~~8. The method of Claim 4 wherein the seizures are primary or secondary generalized seizures.~~

~~9. The method of Claim 8 wherein the mammal is a human.~~

4. Use of a compound or salt according to either Claim 1 or 2 in the manufacture of a medicament for the treatment of seizures in a mammal with epilepsy.

5. The use according to Claim 4 wherein the seizures are simple or complex partial onset seizures.

6. The use according to Claim 4 wherein the seizures are primary or secondary generalized seizures.

7. The use according to any one of Claims 4, 5, or 6, wherein the mammal is a human.

8. The use of a compound or salt according to either Claim 1 or 2 in the manufacture of a medicament for the treatment of pain.

9~~10~~. A compound or salt according to either Claim 1 or 2 for use in therapy.

~~11. A compound or salt according to either Claim 1 or 2 for use in the treatment of seizures in a mammal with epilepsy.~~

~~12. The compound for use according to Claim 11 wherein the seizures are simple or complex partial onset seizures.~~

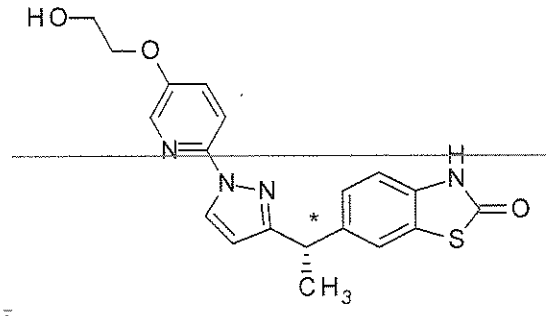
~~13. The compound for use according to Claim 11 wherein the seizures are primary or secondary generalized seizures.~~

~~14. The compound or salt for use according to any one of Claims 11, 12, or 13, wherein the mammal is a human.~~

~~15. The compound or salt for use according to any one of Claims 11, 12, 13, or 14, wherein the use is in simultaneous, separate, or sequential combination with another anti-epileptic drug.~~

~~16. The compound or salt for use according to Claim 15, wherein the other anti-epileptic is levetiracetam, gabapentin, topiramate, or carbamazepine.~~

17. A method of treating pain in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of the formula



or a pharmaceutically acceptable salt thereof.

18. The method of Claim 17 where the mammal is a human.

19. A compound or salt according to either Claim 1 or 2 for use in the treatment of pain in a mammal.

20. The compound or salt for use according to any one of Claim 19, wherein the mammal is a human.