[06] Undem and co-workers have reported that P2X3 and P2X2/3 receptors are widely expressed and modulate function of nodose and jugular afferent fibers in mammalian airways (Weigand, Ford and Undem **(2012)** J Physiol. 590(16):4109-20). Additionally, in a guinea pig model of ATP or histamine potentiation of citric acid induced cough, P2X subfamily receptors were implicated although contribution of P2X3 or P2X2/3 receptors was not deduced (Kamei, Takahashi, Yoshikawa, Saitoh **(2005)** Eur J Pharmacol. 528(158-161); Kamei and Takahashi. **(2006)** Eur J Pharmacol. 547:160-164). Finally, it has been shown in human studies that patients with airway disease associated with cough and breathlessness (such as asthma, COPD or pulmonary fibrosis) have excess ATP concentrations in their airway fluids (Esther, Alexis and Picher. **(2011)** Subcell. Biochem. 55:75-93; Lommatzsch et al. **(2010)** Am J Respir Crit Care Med. 181(9):928-34), and that the inhalation by asthmatic patients of nebulized ATP is able to activate airways sensations leading to urge to cough and precipitating cough itself (Pellegrino et al. (1996) J Appl Physiol. 81(2):964-75.; Basoglu et al. (2005) Chest. 128(4):1905-9), although the site of action of this effect of ATP, and receptor(s) involved have not been elucidated.

[07] There is accordingly a need for methods of treating diseases, conditions and disorders mediated by P2X3 and/or P2X2/3 receptors, as well as a need for compounds that act as modulators of P2X receptors, including antagonists of P2X3 and P2X2/3 receptors. Such diseases and disorders are herein shown to include cough, chronic cough and urge to cough, including cough associated with a respiratory disease or disorder. Chronic cough is distressing and functionally disabling, and no novel licensed treatments for cough have appeared in approximately 50 years. The present invention satisfies these needs as well as others.

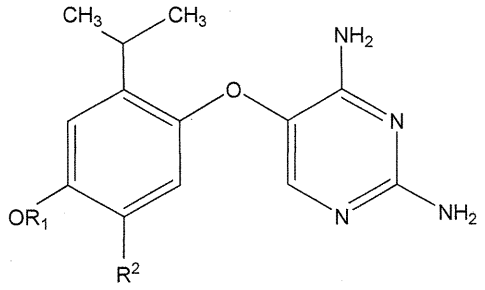
SUMMARY OF THE INVENTION

[08] This ~~invention~~ disclosure pertains to compounds for use in treatment of diseases driven by or mediated by P2X3 or P2X2/3 receptor activation, and more particularly to compounds for use as selective P2X3 and/or P2X3 - P2X2/3 antagonists for treatment of common signs, symptoms and morbidity of diseases mediated by P2X3 and/or P2X2/3 receptors. Such compounds can also be used in the manufacture of a medicament.

[09] The ~~invention~~ disclosure provides compounds for use in treating cough-impacted respiratory diseases using a P2X3 and/or a dual P2X3 - P2X2/3 receptor antagonist. These compounds can also be used in the manufacture of a medicament for treating such disease. More specifically, respiratory diseases can include acute or sub-acute cough, urge to cough, and chronic cough. These respiratory diseases can be largely corrected by antagonism of P2X3-containing receptors (e.g., P2X3 and P2X2/3). Moreover, the compounds exemplified herein (e.g., diaminopyrimidine P2X3/P2X2/3 antagonists) are highly effective at

attenuating the cough-related symptoms of many respiratory diseases including acute and sub-acute cough, urge to cough, and chronic cough.

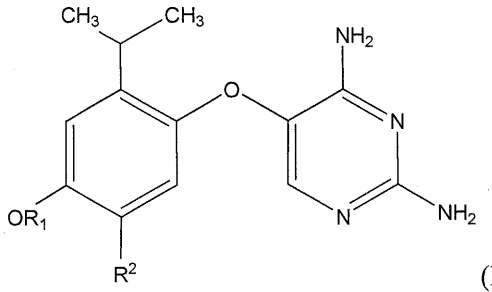
[10] ~~Accordingly, in one aspect, the present invention is directed to~~Disclosed is a method for treating cough or urge to cough associated with a respiratory disease in a subject in need thereof. The method can comprise administering to the subject in need thereof an effective amount of a compound of Formula (I):



[11] (I) or a pharmaceutically acceptable salt thereof.

[12] In one or more embodiments, R^1 is hydrogen or optionally substituted C_1-C_6 alkyl. In one or more embodiments, R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

[13] In one aspect, the present invention provides a compound for use in treating a subject for cough or urge to cough associated with a respiratory disease, wherein the compound is a compound of Formula



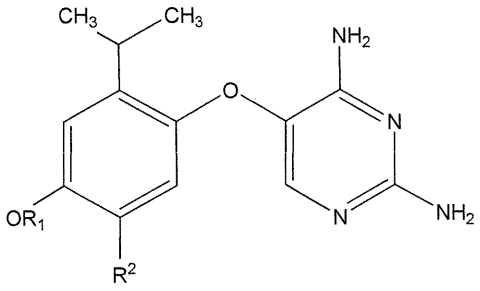
(I): (Formula (I)) or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or optionally substituted C_1-C_6 alkyl, and

[14] wherein , R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

[26] In one or more embodiments, the respiratory symptom, condition or disorder is attenuated by a P2X3 or P2X3-P2X2/3 receptor antagonist. The respiratory disease can be selected from many conditions where cough hypersensitivity prevails, and may include unexplained cough or cough associated with upper respiratory infection, chronic obstructive pulmonary disease (COPD), asthma, or idiopathic pulmonary fibrosis.

[27] In one or more embodiments, the cough is sub-acute or chronic cough, treatment-resistant cough, idiopathic chronic cough, post-viral cough, iatrogenic cough, cough associated with post-nasal drip, cough associated with upper respiratory infection, asthma and/or COPD, cough associated with interstitial disease, cough associated with gastroesophageal reflux disease (GERD) and/or cough associated with smoking or a form of bronchitis. The iatrogenic cough can be induced by an ACE-inhibitor. Additionally, the interstitial disease can be pulmonary fibrosis.

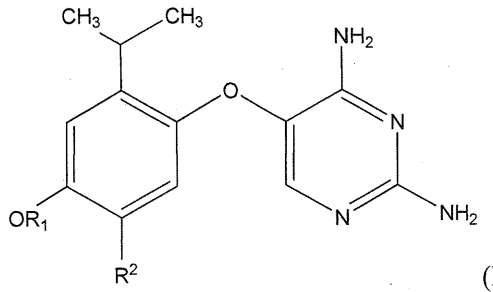
[28] ~~In another aspect, the present invention is directed to~~Also disclosed is a method for treating chronic cough in a patient in need thereof. The method can comprise administering an effective amount of a compound of Formula (I):



[29] (I) or a pharmaceutically acceptable salt thereof. In one or more embodiments, $R^1$is hydrogen or optionally substituted C_1-C_6 alkyl.

[30] In one or more embodiments, R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

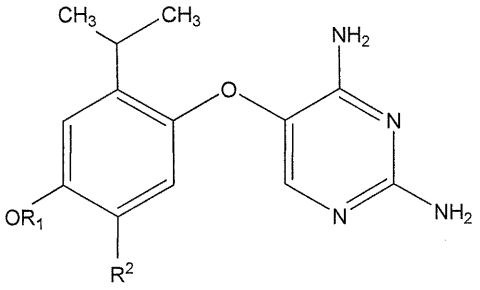
[31] In another aspect, the present invention provides a compound for use in treating chronic cough in a patient in need thereof, wherein the compound is a compound of Formula (I):



(Formula (I)) or a pharmaceutically acceptable salt thereof, wherein $R^1$is hydrogen or optionally substituted C_1-C_6 alkyl, and

In one or more embodiments of any of the above aspects, R^2 is carboxyalkyl. In one or more embodiments of any of the above aspects, R^2 is alkylcarbonyl.

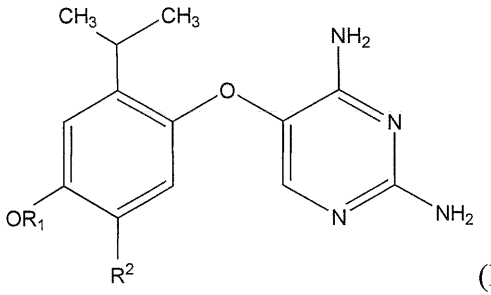
[46] ~~In another aspect, the present invention provides~~Also disclosed is a method of treating neuronal hypersensitivity underlying acute, sub-acute or chronic cough. The method comprises administering an effective amount of a compound of Formula (I):



[47] (I) or a pharmaceutically acceptable salt thereof.

[48] In one or more embodiments, R^1 is hydrogen or optionally substituted C_1-C_6 alkyl. In one or more embodiments, R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

[49] In another aspect, the present invention provides a compound for use in treating neuronal hypersensitivity underlying acute, sub-acute, or chronic cough in a patient in need thereof, wherein the compound is a compound of Formula (I)



[50] (Formula (I)), or a pharmaceutically acceptable salt thereof;

[51] wherein:

[52] R^1 is hydrogen or optionally substituted C_1-C_6 alkyl; and

[53] R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

[54] In another aspect, the present invention provides the use of a compound of Formula (I)

[69] In one or more ~~embodiments~~examples, the ~~invention~~ present disclosure relates to a method for treating the symptoms of cough and urge to cough associated with a respiratory disease by administering a compound of Formula (I). The ~~invention~~ disclosure also relates to compounds for use of a compound of Formula (I) in treating the symptoms of cough and urge to cough associated with a respiratory disease in a subject in need thereof. The invention also relates to the use of a compound of Formula (I) for the manufacture of a medicament for treating the symptoms of cough and urge to cough associated with a respiratory disease in a subject in need thereof. For example, the ~~invention~~ disclosure relates to a method of treatment of the symptoms of chronic cough and/or urge to cough associated with a respiratory disease or disorder mediated by a P2X3 or P2X2/3 receptor antagonist by administering a compound of Formula (I). The invention also relates to compounds of Formula (I) for use for treatment of the symptoms of chronic cough and/or urge to cough associated with a respiratory disease or disorder mediated by a P2X3 or P2X2/3 receptor antagonist. The invention also relates to the use of a compound of Formula (I) in the manufacture of a medicament for treatment of the symptoms of chronic cough and/or urge to cough associated with a respiratory disease or disorder mediated by a P2X3 or P2X2/3 receptor antagonist.

[70] In one or more ~~embodiments~~examples, the ~~invention~~ disclosure relates to methods for reducing daytime chronic cough in idiopathic/treatment-resistant chronic cough. The ~~invention~~ disclosure also relates to a method of treating neuronal hypersensitivity underlying chronic cough. The invention also relates to compounds of Formula (I) for use in reducing daytime chronic cough in idiopathic/treatment-resistant chronic cough, and for treating neuronal hypersensitivity underlying chronic cough. The invention also relates to the use of a compound of Formula (I) in the manufacture of a medicament for reducing daytime chronic cough in idiopathic/treatment-resistant chronic cough, and for treating neuronal hypersensitivity underlying chronic cough.

[71] In one or more ~~embodiments~~examples, the methods of the ~~invention~~ disclosure relate to treating, preventing or ameliorating the respiratory diseases and disorders described herein, or symptoms thereof, described herein in a patient in need thereof by administering a compound selected from Compounds 1-39. For example, the compound is selected from Compounds 6, 7, 13, 17, 21, 28, 35 and 38. For example, the compound is Compound 16. The invention also relates to use of a compound selected from Compounds 1-39 for treating, preventing or ameliorating the respiratory diseases and disorders described herein. The invention also relates to the use of a compound selected from Compounds 1-39 in the manufacture of a medicament for treating, preventing or ameliorating the respiratory diseases and disorders described herein. For example, the compound is selected from Compounds 6, 7, 13, 17, 21, 28, 35 and 38. For example, the compound is Compound 16.

[72] The invention also provides pharmaceutical compositions of the compounds of the present invention and methods of preparing the same.

[73] As set forth in the Detailed Description below, the present invention features a class of P2X3 and P2X2/3 antagonists for treating or alleviating cough and urge to cough, including chronic cough. The present invention has the advantage of addressing the root cause driving cough hypersensitivity in these illnesses instead of merely suppressing central modulation of the symptom perception. For instance, the present ~~invention~~ disclosure offers methods to reduce the activity of afferent nerves that ultimately trigger the persistent and inappropriate urge to cough in a sensitized subject (e.g., a human). The present invention also has the advantage of giving highly selective P2X3 and P2X2/3 antagonists. Further features and advantages are set forth in the Detailed Description below and will be apparent to one of skill in the art.

BRIEF DESCRIPTION OF THE DRAWING

[74] Figure 1 is a graph depicting the effect of Compound 16 on objectively recorded daytime cough frequency (coughs per hour) in treatment-resistant chronic cough patients.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[75] Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

[76] "Agonist" refers to a compound that enhances the activity of another compound or receptor site.

[77] "Alkyl" means the monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. "Lower alkyl" refers to an alkyl group of one to six carbon atoms, i.e. C_1-C_6alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

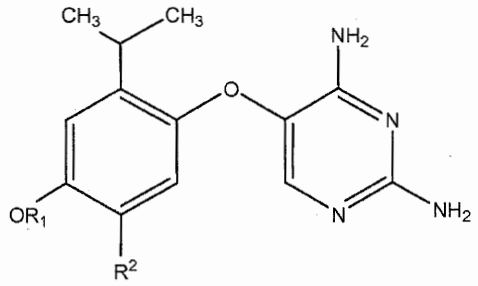
[78] "Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, *e.g.*, ethenyl, propenyl, and the like.

[79] "Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, *e.g.*, ethynyl, propynyl, and the like.

CLAIMS

What is claimed is:

1. A method for treating chronic cough in a patient in need thereof, the method comprising administering an effective amount of a compound of Formula (I):



(I) or a pharmaceutically acceptable salt thereof

wherein:

R^1 is hydrogen or optionally substituted C_1-C_6 alkyl;

R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

2. The method of claim 1, wherein the chronic cough is idiopathic or treatment resistant cough.

3. The method of claim 1 wherein the compound of Formula (I) is administered at about 600 mg twice daily.

4. The method of claim 1, wherein the compound of Formula (I) is administered for about 2 weeks.

5. The method of claim 1, wherein the compound of Formula (I) is administered at about 600 mg twice daily for about two weeks.

6. The method of claim 1, wherein the chronic cough is refractory chronic cough.

7. The method of claim 1, wherein the chronic cough is reduced by about 75%.

8. The method of claim 1, wherein the cough is daytime cough.

9. The method of claim 1, wherein R^1 is hydrogen or methyl.

10. The method of claim 1, wherein R^2 is haloalkyl, aminosulfonyl, alkylsulfonyl alkylcarbonyl or carboxyalkyl.

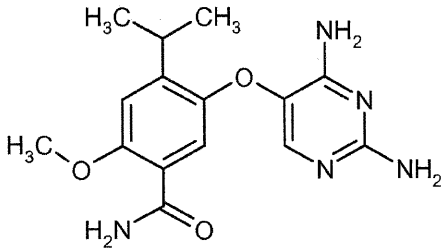
11 The method of claim 1, wherein R^2 is haloalkyl, further wherein alkyl is methyl.

12. The method of claim 1, wherein R^2 is aminosulfonyl.

13. The method of claim 1, wherein R^2 is carboxyalkyl.

14. The method claim 1, wherein R^2 is alkylcarbonyl.

15. The method of any one of claims 1-10, wherein the compound is selected from:



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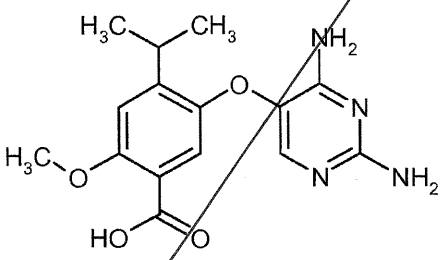

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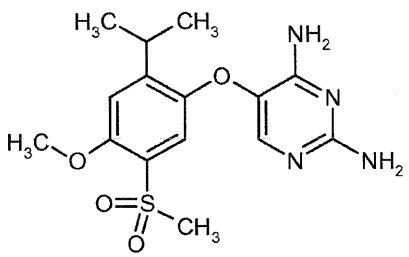

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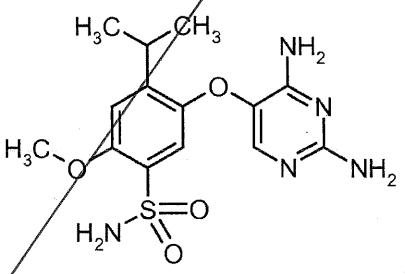

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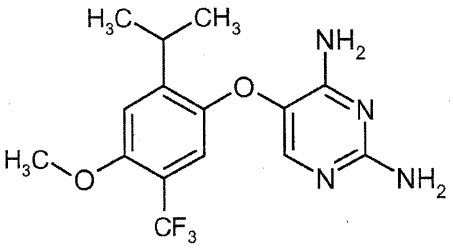

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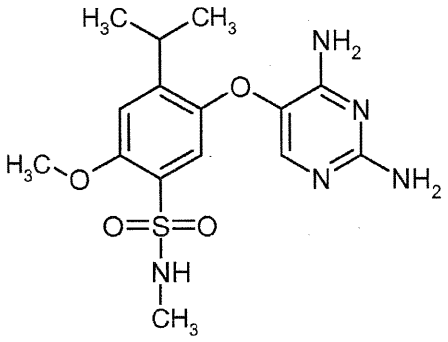

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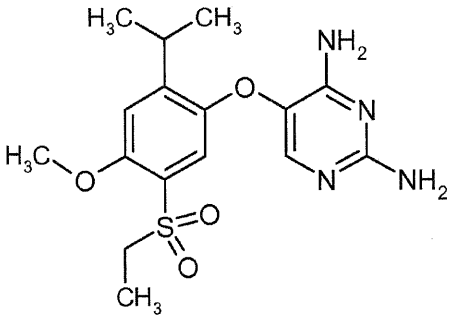

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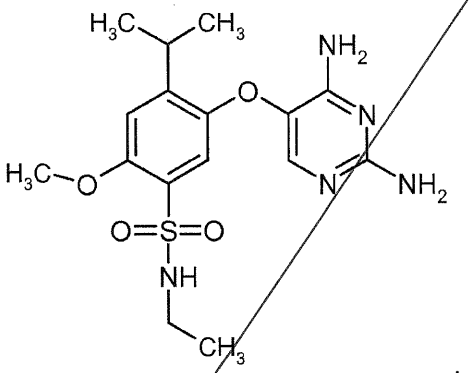

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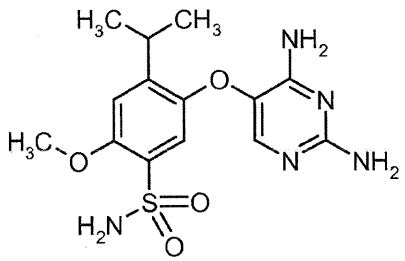
16. The method of any one of claims 1-10, wherein the compound is



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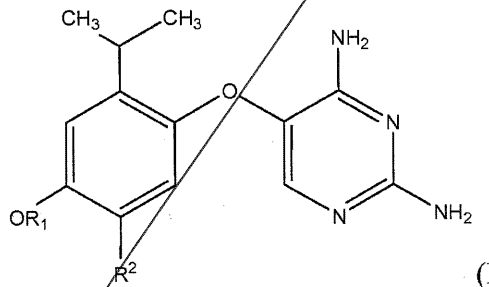
17. A method for treating neuronal hypersensitivity underlying acute, sub-acute or chronic cough, the method comprising administering an effective amount of a compound of Formula (I):

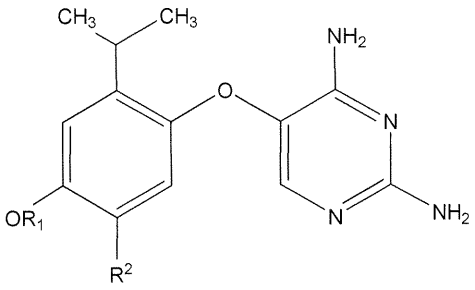


(Formula (I)) or a pharmaceutically acceptable salt thereof

CLAIMS

What is claimed is:

1. Use of a compound of Formula (I):



(I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating chronic cough in a patient in need thereof,

wherein:

R^1 is hydrogen or optionally substituted C_1-C_6 alkyl;

R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

2. The use of claim 1, wherein the chronic cough is idiopathic or treatment resistant cough.

3. The use of claim 1 wherein the compound of Formula (I) is to be administered at about 600 mg twice daily.

4. The use of claim 1, wherein the compound of Formula (I) is to be administered for about 2 weeks.

5. The use of claim 1, wherein the compound of Formula (I) is to be administered at about 600 mg twice daily for about two weeks.

6. The use of claim 1, wherein the chronic cough is refractory chronic cough.

7. The use of claim 1, wherein the chronic cough is reduced by about 75%.

8. The use of claim 1, wherein the cough is daytime cough.

9. The use of claim 1, wherein R^1 is hydrogen or methyl.

10. The use of claim 1, wherein R^2 is haloalkyl, aminosulfonyl, alkylsulfonyl alkylcarbonyl or carboxyalkyl.

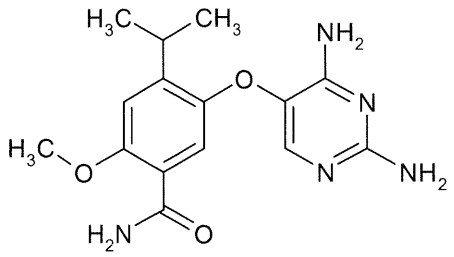
11 The use of claim 1, wherein R^2 is haloalkyl, further wherein alkyl is methyl.

12. The use of claim 1, wherein R^2 is aminosulfonyl.

13. The use of claim 1, wherein R^2 is carboxyalkyl.

14. The use claim 1, wherein R^2 is alkylcarbonyl.

15. The use of any one of claims 1-10, wherein the compound is selected from:



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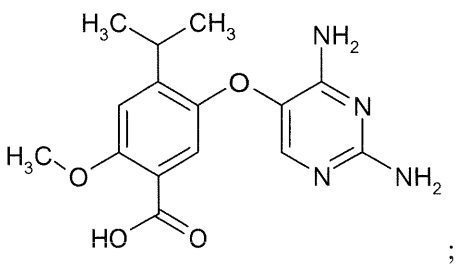

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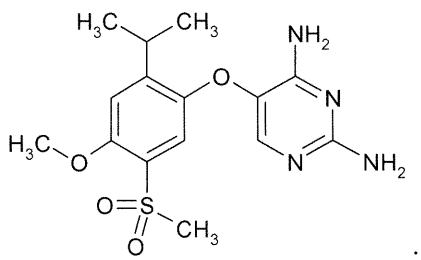

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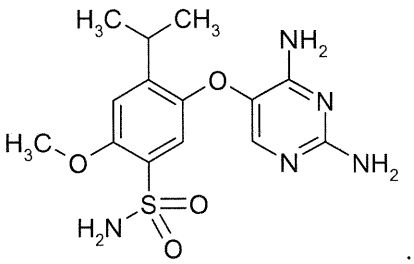

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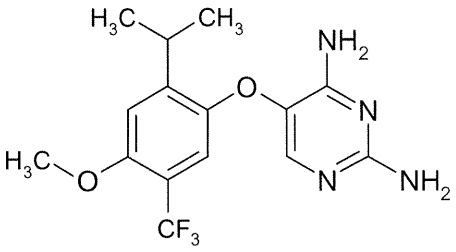
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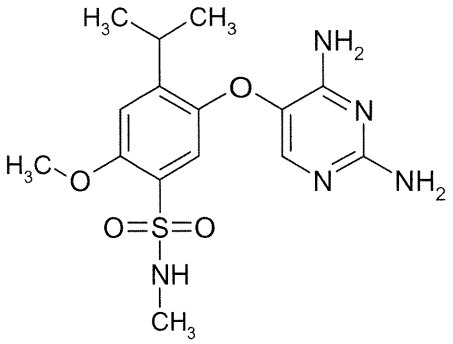
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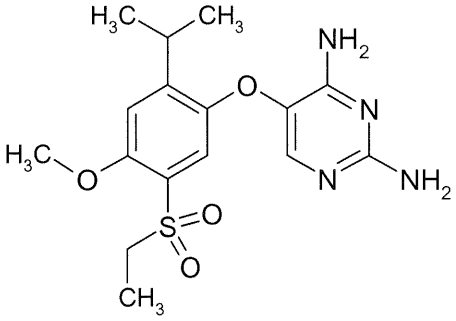
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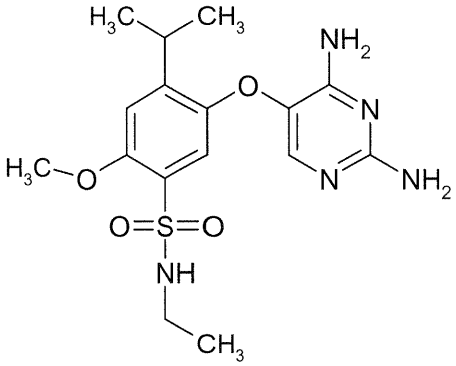
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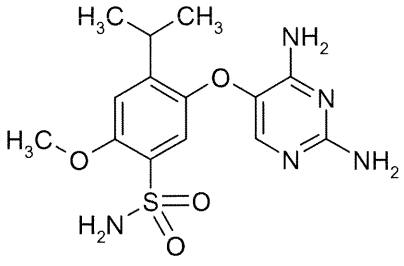
16. The use of any one of claims 1-10, wherein the compound is 
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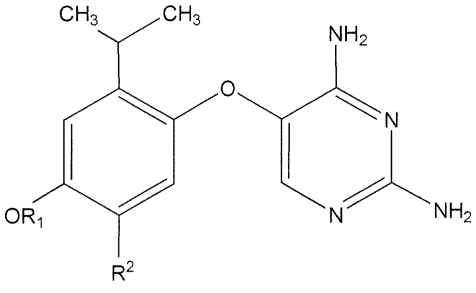
17. Use of a compound of Formula (I):


(Formula (I)) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating neuronal hypersensitivity underlying acute, sub-acute or chronic cough,

wherein:

$R^1$is hydrogen or optionally substituted C_1-C_6 alkyl; and

R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

18. The use of claim 17, wherein the chronic cough is idiopathic or treatment resistant cough.

19. The use of claim 17, wherein the compound of Formula (I) is to be administered at about 600 mg twice daily.

20. The use of claim 17, wherein the compound of Formula (I) is to be administered for about 2 weeks.

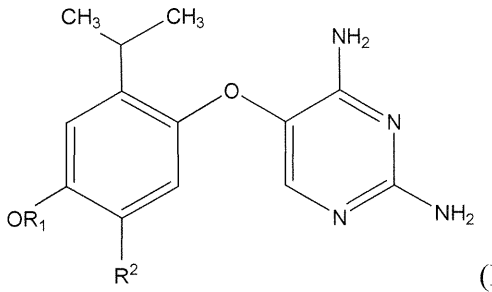
21. The use of claim 17, wherein the compound of Formula (I) is to be administered at about 600 mg twice daily for about two weeks.

22. The use of claim 17, wherein the chronic cough is refractory chronic cough.

23. The use of claim 17, wherein the chronic cough is reduced by about 75%.

24. The use of claim 17, wherein the cough is daytime cough.

25. A compound for use in treating chronic cough in a patient in need thereof, wherein the compound is a compound of Formula (I)



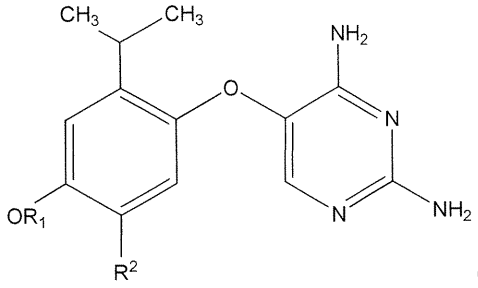
(Formula (I)), or a pharmaceutically acceptable salt thereof;

wherein:

$R^1$is hydrogen or optionally substituted C_1-C_6 alkyl; and

R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

26. A compound for use in treating neuronal hypersensitivity underlying acute, sub-acute, or chronic cough in a patient in need thereof, wherein the compound is a compound of Formula (I)



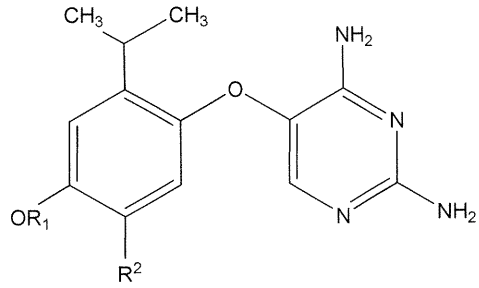
(Formula (I)), or a pharmaceutically acceptable salt thereof;

wherein:

$R^1$is hydrogen or optionally substituted C_1-C_6 alkyl; and

R^2 is: alkyl; alkenyl; alkynyl; amino; aminosulfonyl; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; carboxyalkyl; cyano or alkylcarbonyl.

27. A compound for use in treating cough or urge to cough associated with a respiratory disease in a subject, wherein the compound is a compound of Formula (I):



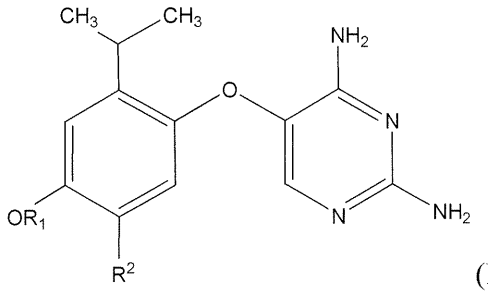
(Formula (I)) or a pharmaceutically acceptable salt thereof,

wherein:

$R^1$is hydrogen or optionally substituted C_1-C_6 alkyl, and

R^2 is alkyl, alkenyl, alkynyl, amino, aminosulfonyl, halo, amido, haloalkyl, alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alkynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano or alkylcarbonyl.

28. Use of a compound of Formula (I)



(Formula (I))

for the manufacture of a medicament for treating chronic cough or urge to cough associated with a respiratory disease in a subject in need thereof, wherein:

$R^1$is hydrogen or optionally substituted C_1-C_6 alkyl; and

R^2 is alkyl, alkenyl, alkynyl, amino, aminosulfonyl, halo, amido, haloalkyl, alkoxy, hydroxy, haloalkoxy, nitro, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxy, alkynylalkoxy, alkylsulfonyl, arylsulfonyl, carboxyalkyl, cyano or alkylcarbonyl.