SELECTIVE P2X3 MODULATORS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/560,077, filed on September 18, 2017, and is a continiation of U.S. Utility Application No. 15/936,316, filed on March 26, 2018, each of which is herein incorporated by reference in its entirety.

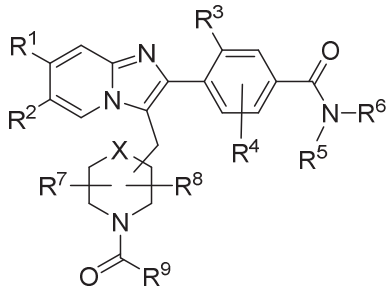
BACKGROUND

[0002] Chronic cough is a cough that lasts for more than eight weeks and is associated with significant adverse social, psychosocial and physical effects on quality of life. It is estimated that, in the United States alone, more than 27 million patients suffer from chronic cough. While an underlying etiology such as gastro-oesophageal reflux, asthma, or allergic rhinitis may contribute to cough in some of these patients, an underlying condition cannot be identified in 10%-40% of chronic cough patients (unexplained chronic cough). A portion of patients with an underlying condition as well as the large majority of unexplained chronic cough patients are not well controlled by current therapies.

BRIEF SUMMARY OF THE DISCLOSURE

[0003] This disclosure provides, for example, methods of avoiding loss of taste response while treating a chronic cough patient with a selective P2X3 modulator. The disclosure also provides for the use of selective P2X3 modulators as medicaments and/or in the manufacture of medicaments for avoiding loss of taste response while treating a chronic cough patient in warm-blooded animals such as humans.

[0003a] In one aspect, provided herein is a use of a selective P2X3 antagonist in the manufacture of a medicament for avoiding loss of taste response while treating chronic cough, wherein the selective P2X3 antagonist is at least 10-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism, and wherein the selective P2X3 antagonist is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



Formula (I);

wherein:

R^1 is selected from the group consisting of cyano, halogen, methyl, and ethyl;

R^2 is selected from the group consisting of hydrogen, halogen, methyl, and ethyl;

R^3 is selected from the group consisting of halogen, methyl, and ethyl;

R^4 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, and methoxy;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, and hydroxy-C_1-C_6-alkyl; or

R^5 and R^6, together with the nitrogen to which they are both attached, form a 5- or 6-member heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, and C_1-C_4-alkyl;

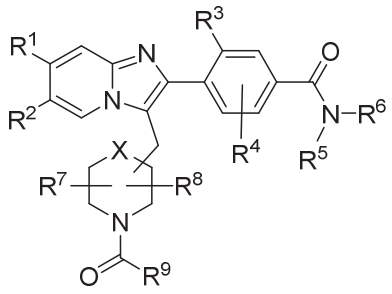
R^7 and R^8 are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

R^9 is selected from the group consisting of C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkyl-C_3-C_6-cycloalkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl; and X is selected from a bond, CH_2, and O.

[0004] In some embodiments is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 10-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 20-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 50-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of

taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 100-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 500-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 1000-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 2000-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism. In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 2700-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism.

[0005] In some examples is a method of avoiding loss of taste response while treating a chronic cough patient, the method comprising administering to the patient a therapeutically effective amount of a selective P2X3 antagonist, wherein the selective P2X3 antagonist is at least 10-fold selective, at least 20-fold selective, at least 50-fold selective, at least 100-fold selective, at least 500-fold selective, at least 1000-fold selective, at least 2000-fold selective, or at least 2700-fold selective, for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism, wherein the selective P2X3 antagonist is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



Formula (I);

wherein:

R^1 is selected from the group consisting of cyano, halogen, methyl, and ethyl;

R^2 is selected from the group consisting of hydrogen, halogen, methyl, and ethyl;

R^3 is selected from the group consisting of halogen, methyl, and ethyl;

R^4 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, and methoxy;

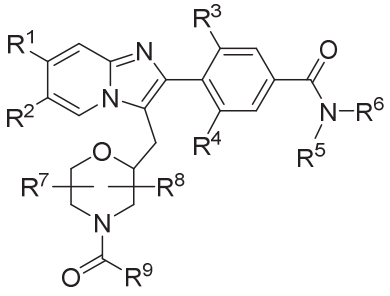
R^5 and R^6 are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, and hydroxy-C_1-C_6-alkyl; or

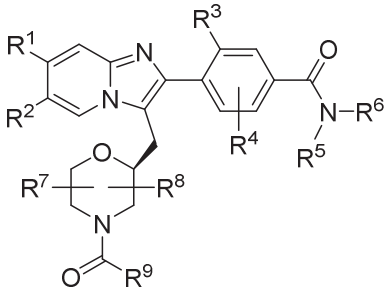
R^5 and R^6, together with the nitrogen to which they are both attached, form a 5- or 6-member heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, and C_1-C_4-alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

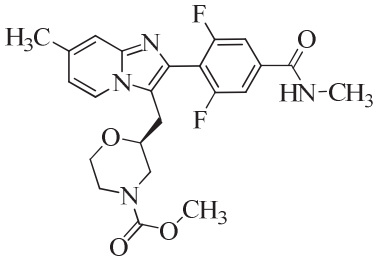
R^9 is selected from the group consisting of C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkyl-C_3-C_6-cycloalkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl; and

X is selected from a bond, CH_2, and O.

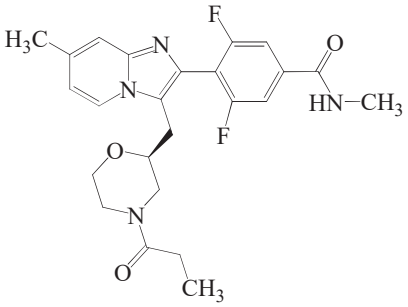
[0006] In some examples, R^1 is methyl. In some examples, R^2 is hydrogen. In some examples, R^3 is fluoro. In some examples, X is O. In some examples, the compound of Formula (I) corresponds in structure to  and R^4 is selected from the group consisting of halogen, methyl, and ethyl. In some examples, R^5 is hydrogen. In some examples, R^6 is C_1-C_6-alkyl. In some examples, R^6 is methyl. In some examples, R^7 is hydrogen. In some examples, R^8 is hydrogen. In some examples, R^9 is C_1-C_6-alkoxy. In some examples, R^9 is methoxy. In some examples, X is O. In some examples, the compound of Formula (I)



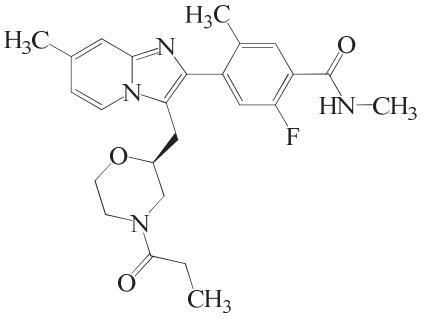
corresponds in structure to . In some examples, the compound of Formula (I) corresponds in structure to:



Compound 1,



Compound 2,



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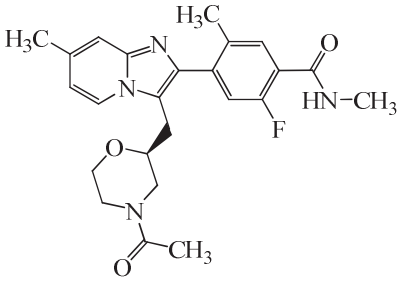

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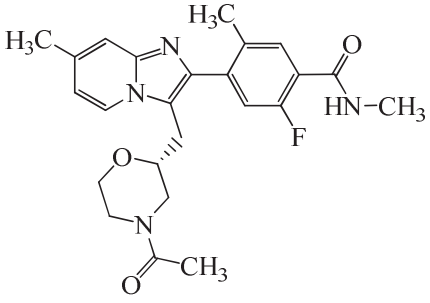

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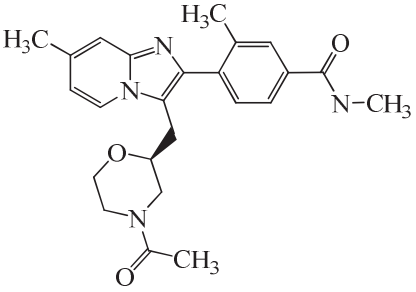

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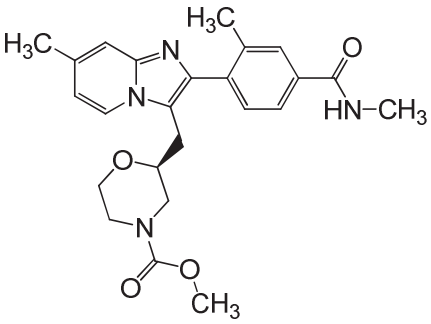

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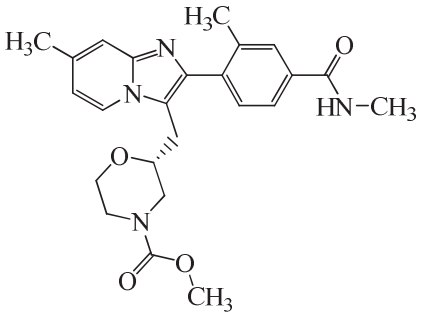

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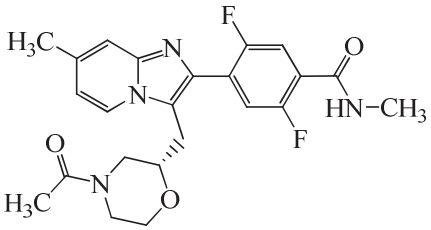

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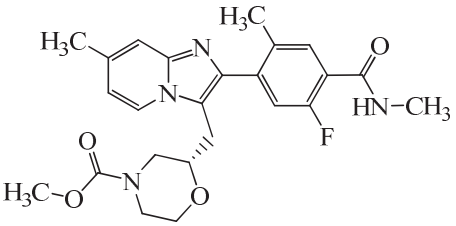

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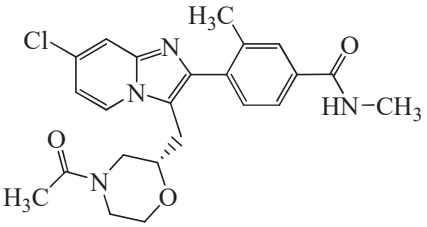

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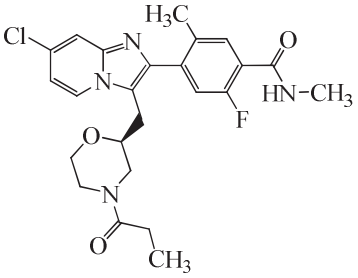

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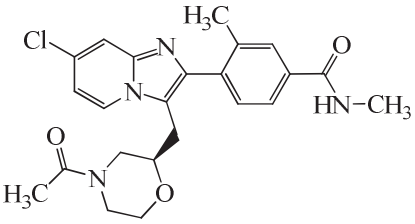

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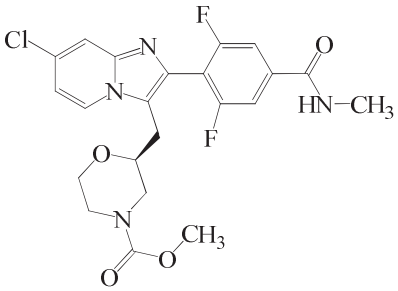

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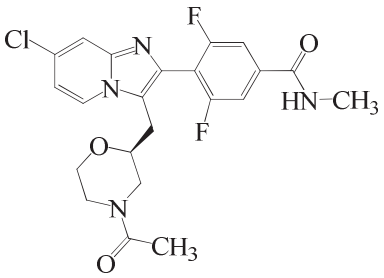

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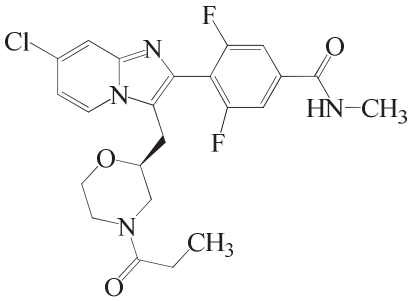

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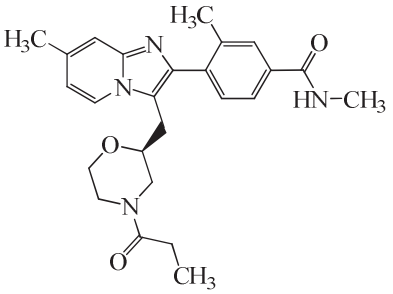

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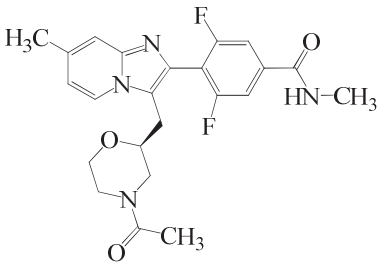

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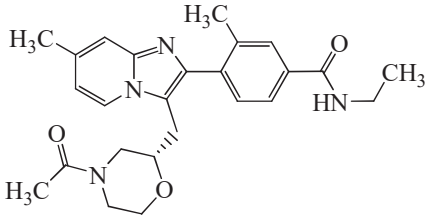

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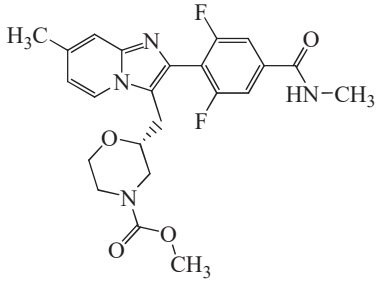

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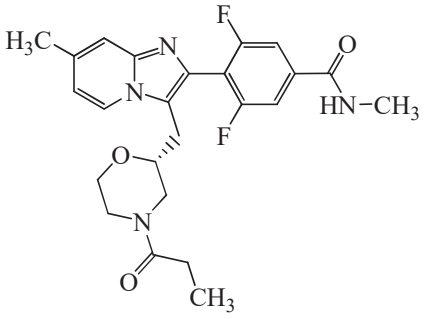

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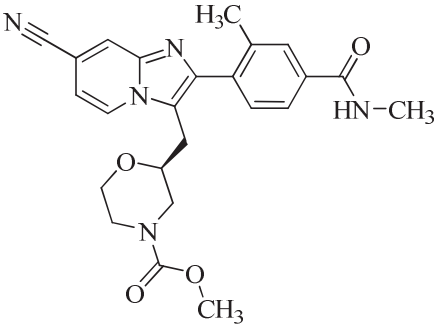

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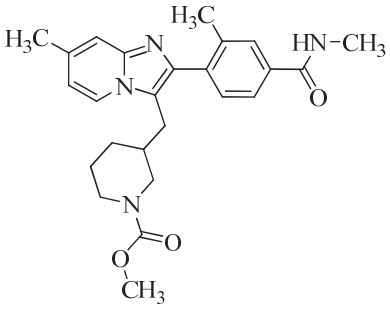

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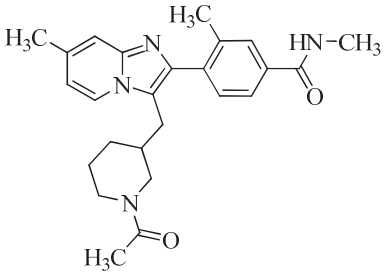

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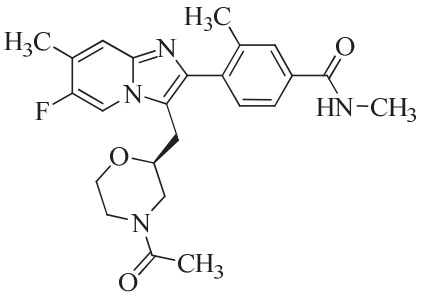

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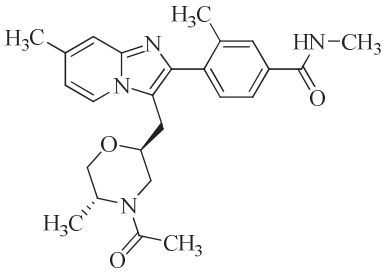
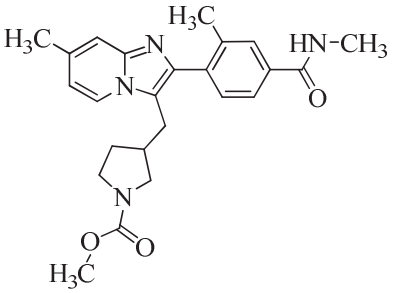


Compound 26,



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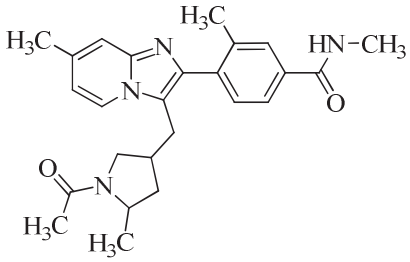

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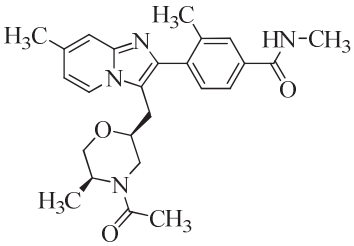

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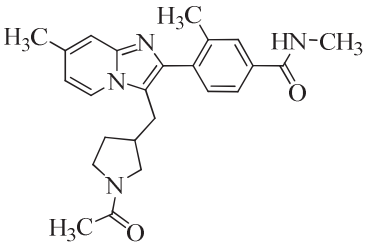

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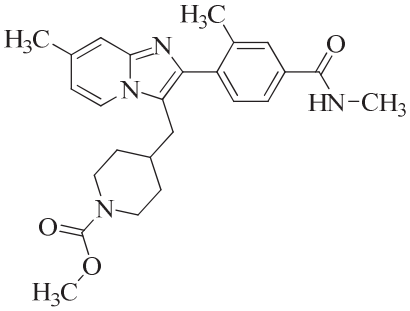

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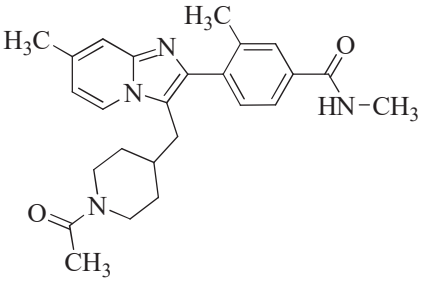
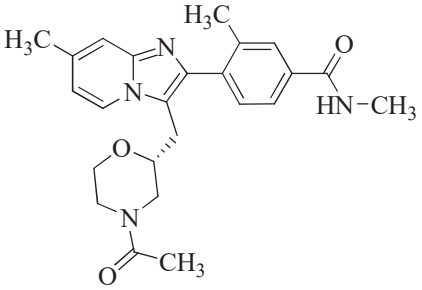
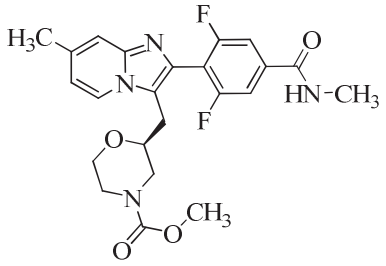


Compound 32, and



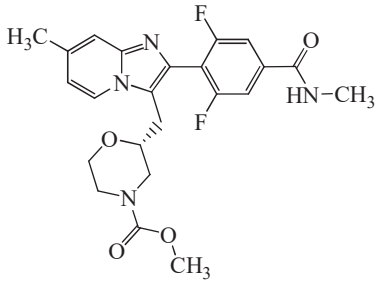
Compound 33.

[0007] In some examples, the compound of Formula (I) corresponds in structure to



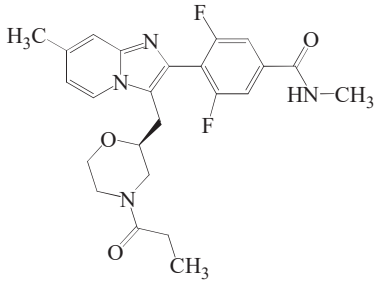
Compound 1.

[0008] In some examples, the compound of Formula (I) corresponds in structure to



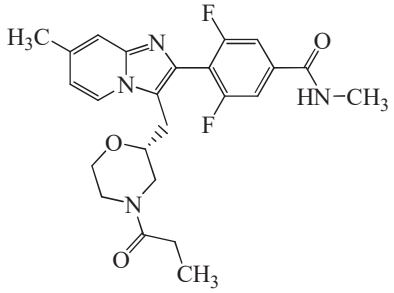
Compound 20.

[0009] In some examples, the compound of Formula (I) corresponds in structure to



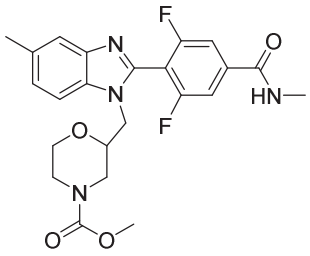
Compound 2.

[0010] In some examples, the compound of Formula (I) corresponds in structure to



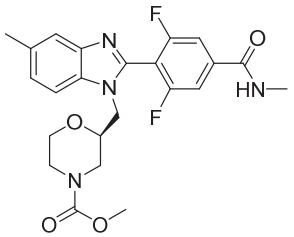
Compound 21.

[0011] In some examples, the compound of Formula (I) corresponds in structure to



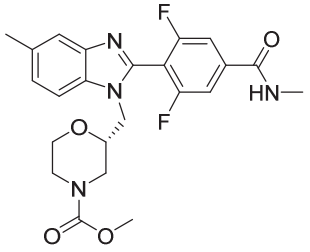
Compound 34.

[0012] In some examples, the compound of Formula (I) corresponds in structure to



Compound 35.

[0013] In some examples, the compound of Formula (I) corresponds in structure to



Compound 36.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Fig. 1 depicts the role of P2X3 receptors in chronic cough.

[0015] Fig. 2 depicts the roles of P2X3 and P2X2/3 receptors in chronic cough and taste function.

[0016] Fig. 3 shows the potency and selectivity of Compound 1 and Gefapixant (also know as AF-219) for human P2X3 and P2X2/3 receptors.

[0017] Fig. 4 shows the anti-tussive effect of Compound 1 and AF-219 at three doses in a guinea pig cough model.

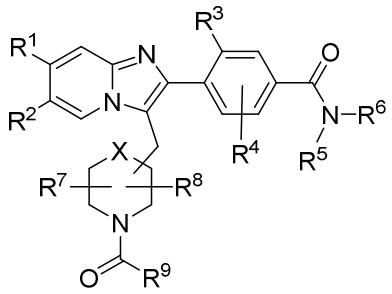
[0018] Fig. 5 shows the the duration of the anti-tussive effect of Compound 1 and AF-219 in a time course study of a guinea pig cough model.

[0019] Fig. 6 shows the effect on taste function of Compound 1 and AF-219 in a two bottle rat taste study.

CLAIMS

We Claim:

1. Use of a selective P2X3 antagonist in the manufacture of a medicament for avoiding loss of taste response while treating chronic cough, wherein the selective P2X3 antagonist is at least 10-fold selective for P2X3 homomeric receptor antagonism versus P2X2/3 heteromeric receptor antagonism, and wherein the selective P2X3 antagonist is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



Formula (I);

wherein:

R^1 is selected from the group consisting of cyano, halogen, methyl, and ethyl;

R^2 is selected from the group consisting of hydrogen, halogen, methyl, and ethyl;

R^3 is selected from the group consisting of halogen, methyl, and ethyl;

R^4 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, and methoxy;

R^5 and R^6 are independently selected from the group consisting of hydrogen, C_1-C_6-alkyl, and hydroxy-C_1-C_6-alkyl; or

R^5 and R^6, together with the nitrogen to which they are both attached, form a 5- or 6-member heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, and C_1-C_4-alkyl;

R^7 and R^8 are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

R^9 is selected from the group consisting of C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkyl-C_3-C_6-cycloalkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl;

and X is selected from a bond, CH_2, and O.

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

3. The use of claim 1 or claim 2, wherein R^2 is hydrogen.

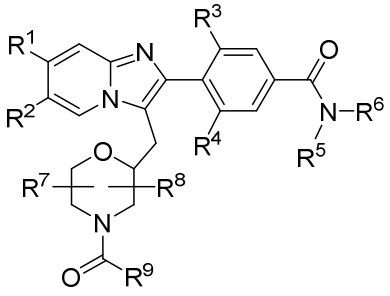
4. The use of any one of claims 1-3, wherein R^3 is fluoro.

5. The use of any one of claims 1-4, wherein R^4 is fluoro.

6. The use of any one of claims 1-5, wherein X is O.

7. The use of any one of claims 1-6, wherein:

the compound corresponds in structure to:



; and

R^4 is selected from the group consisting of halogen, methyl, and ethyl.

8. The use of any one of claims 1-7, wherein R^5 is hydrogen.

9. The use of any one of claims 1-8, wherein R^6 is C_1-C_6-alkyl.

10. The use of any one of claims 1-9, wherein R^6 is methyl.

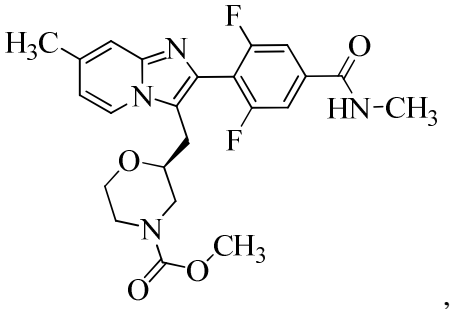
11. The use of any one of claims 1-10, wherein R^7 is hydrogen.

12. The use of any one of claims 1-11, wherein R^8 is hydrogen.

13. The use of any one of claims 1-12, wherein R^9 is C_1-C_6-alkoxy.

14. The use of any one of claims 1-13, wherein R^9 is methoxy.

15. The use of claim 1, wherein the compound corresponds in structure to:



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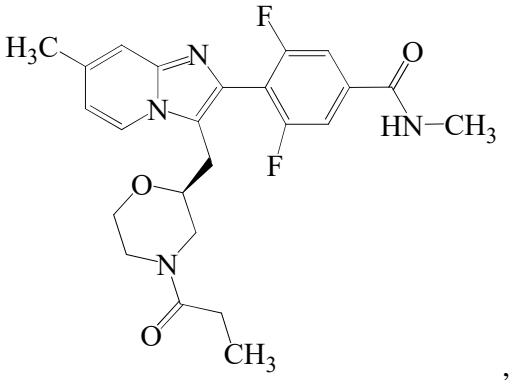

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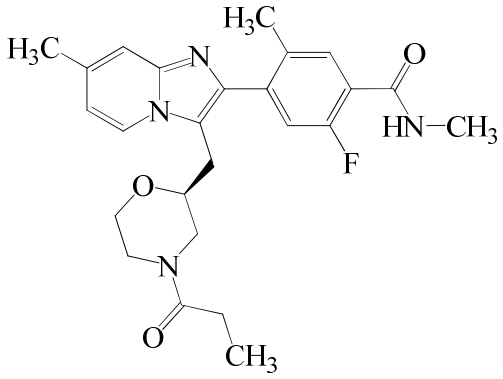

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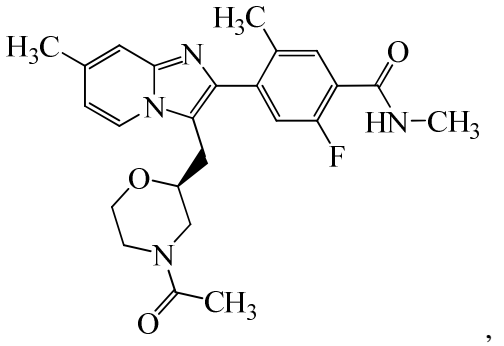

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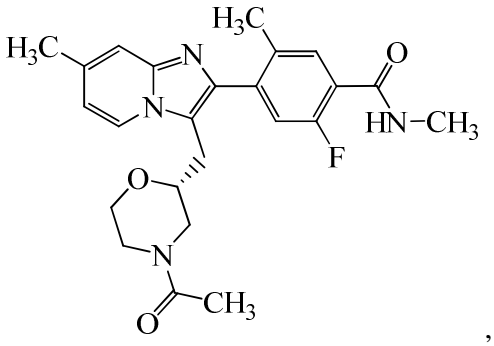
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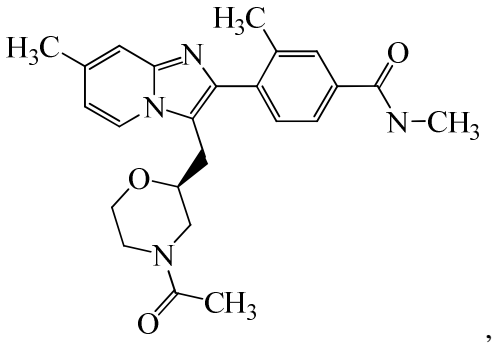
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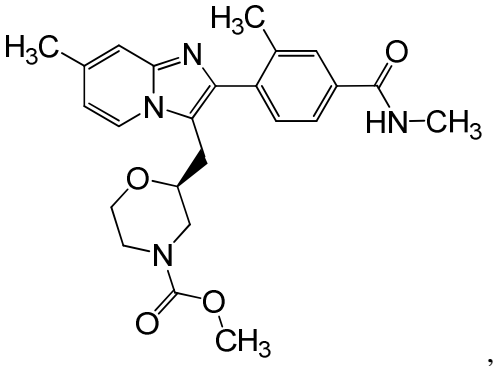
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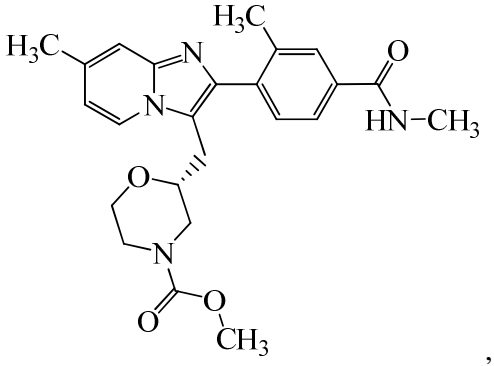
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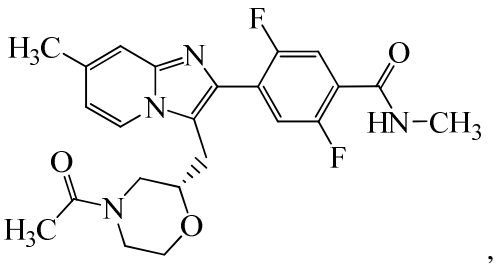
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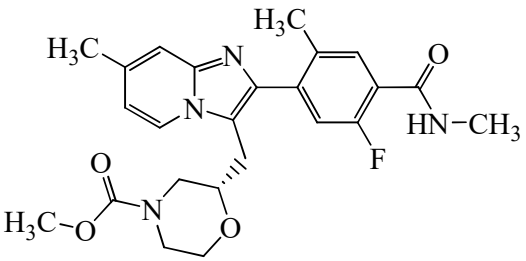
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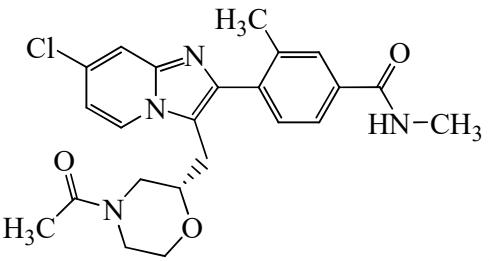
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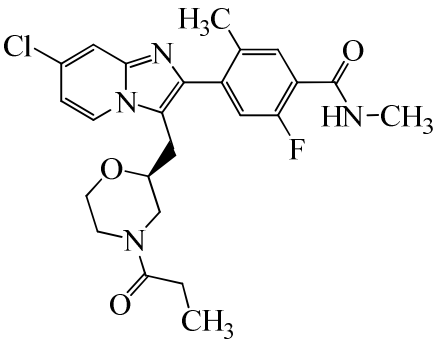
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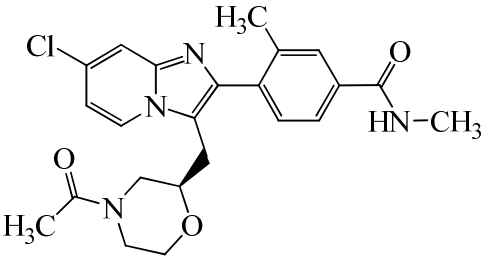
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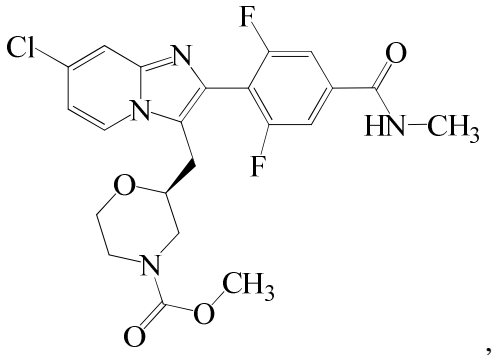
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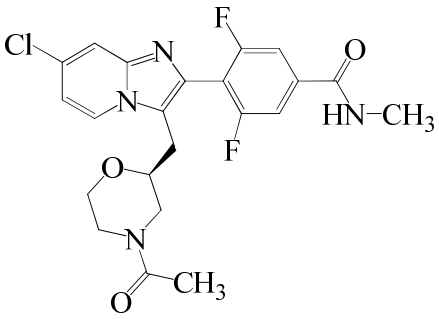
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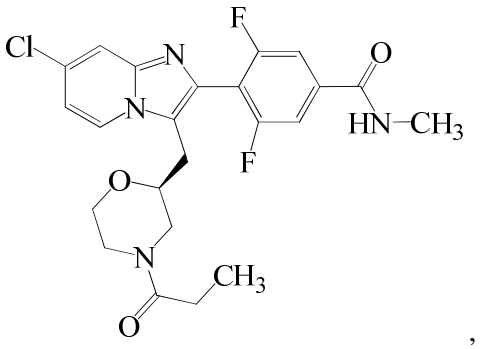
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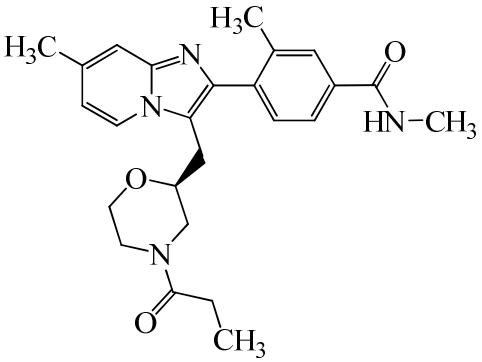
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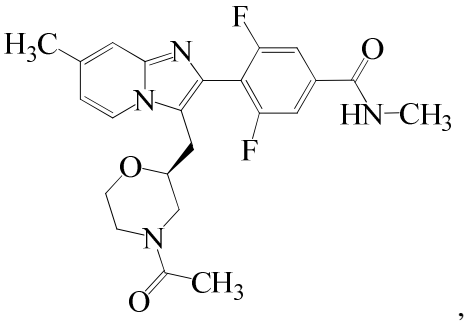
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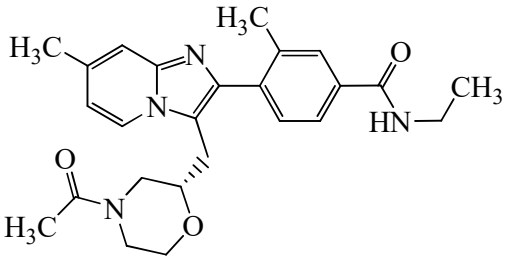
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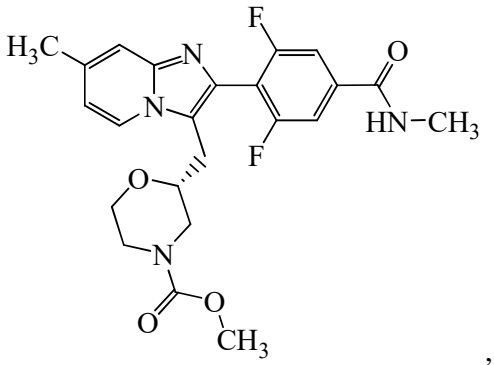
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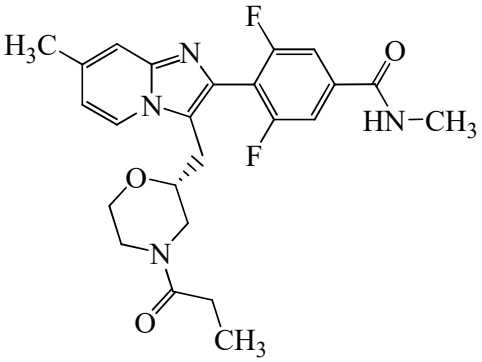
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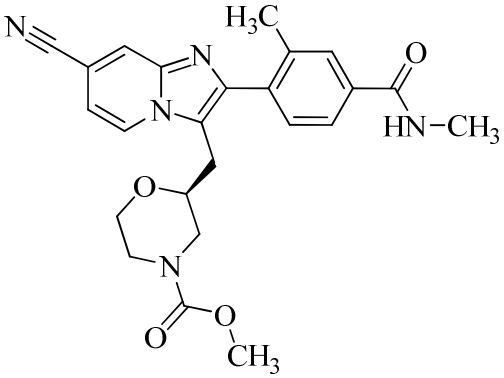
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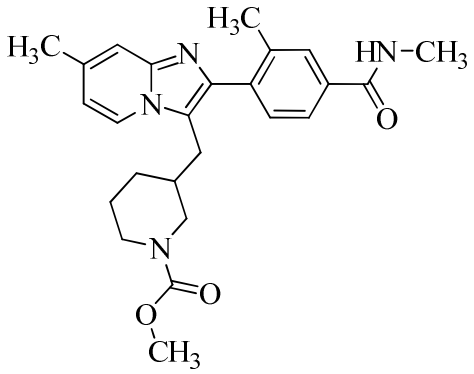
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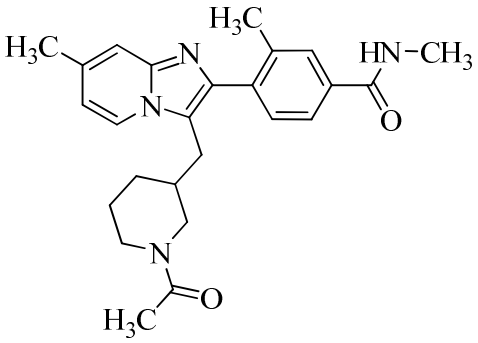
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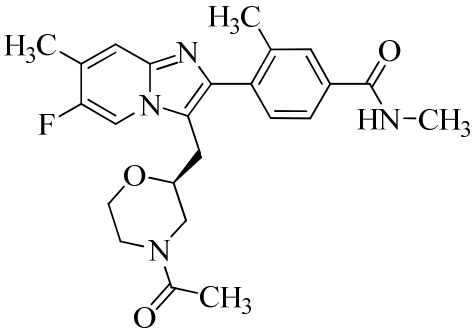
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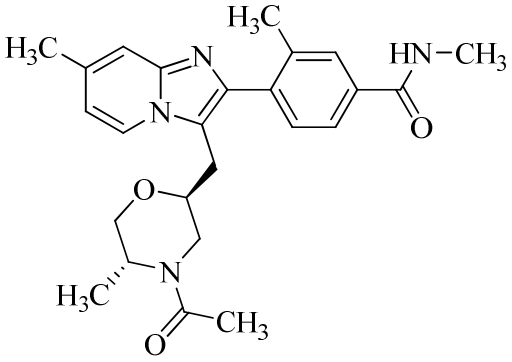
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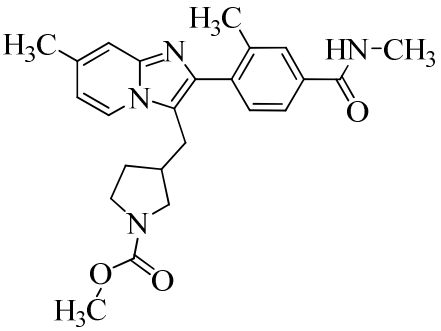
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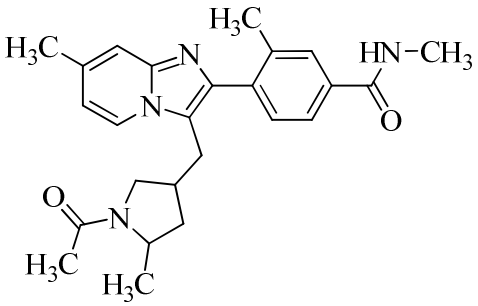
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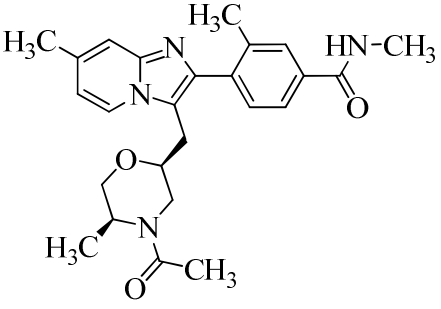
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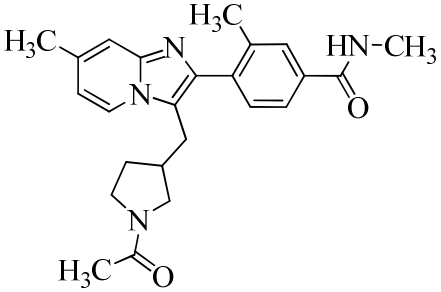
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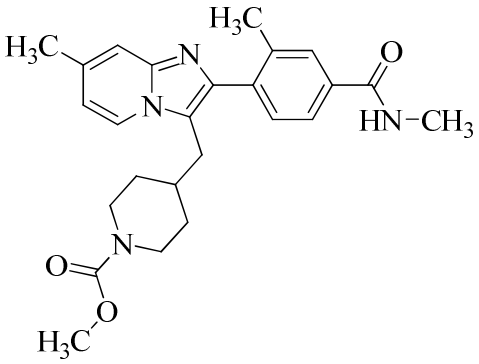

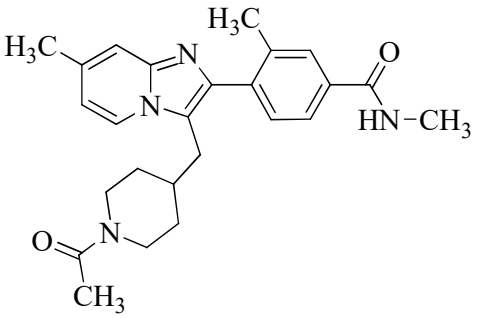

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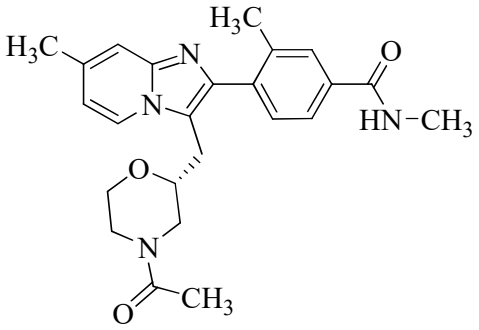

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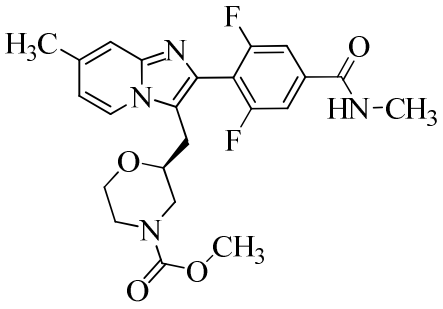
16. The use of claim 1, wherein the compound corresponds in structure to:



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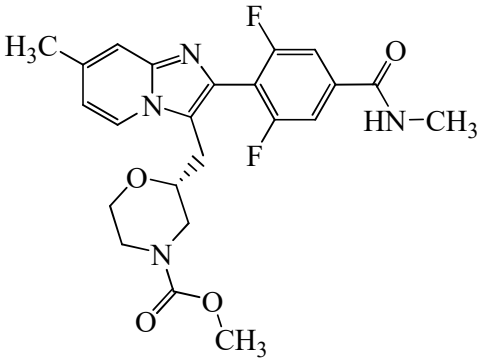
17. The use of claim 1, wherein the compound corresponds in structure to:



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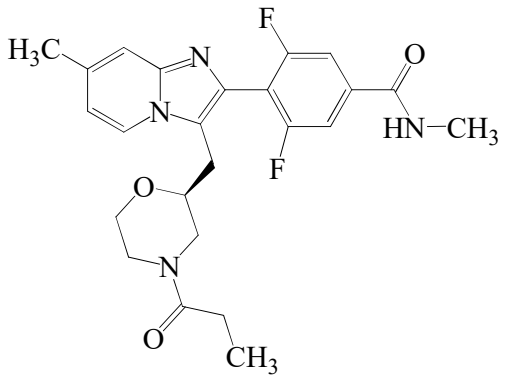
18. The use of claim 1, wherein the compound corresponds in structure to:



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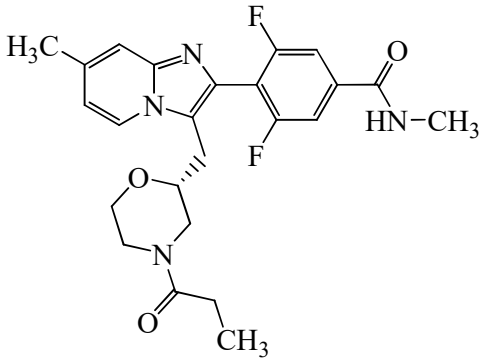
19. The use of claim 1, wherein the compound corresponds in structure to:



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