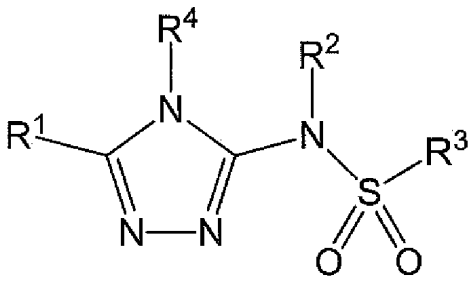
but no pegylation at the N- or C-terminus or another site specific location. The use of internal PEG spacers (short PEG (n=4 or 6), however, was also reported in lower activity peptide analogs with deletions in the middle of the sequence that contained fewer amino acid residues than apelin-13. Murza *et al.* ChemMedChem 7:318-325, 2012. Additionally, PCT/US2013/075773 describes a group of modifications, including substitution of non-canonical amino acids and changes at the N- and C-terminal of the apelin molecule that can affect, *inter alia,* the potency of the molecule. The increased potency can be a result of increased half-life or decreased degradation relative to wild-type apelin.

[010] Despite the advancements that have been made with respect to peptides, a need exists for small molecule agonists of the APJ receptor. However, some progress has been made in this area. For example, WO 2014/044738 discloses various benzimidazole-carboxylic acid amide derivatives as modulators of the APJ Receptor.

[011] A need continues to exist for agonists of the APJ receptor that may be used to treat various cardiovascular and other conditions. The present application discloses such agonists of the APJ receptor s that may be suitable for use as therapeutic agents in treating a variety of conditions. These compounds may find particular benefit in treating cardiovascular conditions. For example, such compounds may be beneficial in treating conditions such as chronic systolic heart failure and chronic diastolic heart failure.

SUMMARY OF THE INVENTION

[012] In one aspect, the invention provides a compound of Formula I or Formula II:



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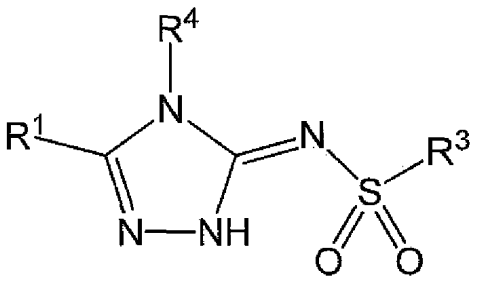


II

or a pharmaceutically acceptable salt thereof, a tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof,

wherein:

R^1 is an unsubstituted pyridyl, pyridonyl, or pyridine N-oxide, or is a pyridyl, pyridonyl, or pyridine N-oxide substituted with 1, 2, 3, or 4 R^{1a} substituents;

R^{1a} in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -C_2-C_6 alkenyl, -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl)-OH, -O-(C_1-C_6 haloalkyl)-O-(C_1-C_6 alkyl), -O-(C_1-C_6 perhaloalkyl)-OH, -O-(C_1-C_6 perhaloalkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, phenyl, -C(=O)-(heterocyclyl), or a heterocyclyl group, wherein the heterocyclyl group of the -C(=O)-(heterocyclyl) or heterocyclyl group is a 3 to 7 membered ring containing 1, 2, or 3 heteroatoms selected from N, O, or S;

R^2 is selected from -H, or C_1-C_4 alkyl or is absent in the compounds of Formula II;

R^3 is selected from an unsubstituted C_1-C_{10} alkyl, a C_1-C_{10} alkyl substituted with 1, 2, or 3 R^{3a} substituents, a group of formula -($CR^{3b}R^{3c}$)-Q, a group of formula –NH-($CR^{3b}R^{3c}$)-Q, a group of formula -($CR^{3b}R^{3c}$)-C(=O)-Q, a

group of formula -($CR^{3d}R^{3e}$)-($CR^{3f}R^{3g}$)-Q, a group of formula -(CR^{3b}=CR^{3c})-Q, or a group of formula -(heterocyclyl)-Q, wherein the heterocyclyl of the -(heterocyclyl)-Q has 5 to 7 ring members of which 1, 2, or 3 are heteroatoms selected from N, O, or S and is unsubstituted or is substituted with 1, 2, or 3 R^{3h} substituents;

R^{3a} in each instance is independently selected from -F, -Cl, -CN, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-NH_2$, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3b} and R^{3c} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), $-NH_2$, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3d} and R^{3e} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), $-NH_2$, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3f} and R^{3g} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), $-NH_2$, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3h} in each instance is independently selected from -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), $-NH_2$, -NH(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, or oxo;

Q is a monocyclic or bicyclic C_6-C_{10} aryl group, a monocyclic or bicyclic heteroaryl group with 5 to 10 ring members containing 1, 2, or 3 heteroatoms selected from N, O, or S, a C_3-C_8 cycloalkyl group, or a 3 to 7 membered heterocyclyl group containing 1, 2, or 3 heteroatoms selected from N, O, or S, wherein the C_6-C_{10} aryl group, the heteroaryl group, the cycloalkyl group, and the

heterocyclyl group are unsubstituted or are substituted with 1, 2, 3, or 4 R^Q substituent;

R^Q in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -C_2-C_6 alkenyl , -C_2-C_6 alkynyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, -S(=O)$_2$-(C_1-C_6 alkyl), phenyl, or a heteroaryl group, and the Q heterocyclyl group may be substituted with 1 oxo substituent;

R^4 is selected from a monocyclic or bicyclic C_6-C_{10} aryl group, a monocyclic or bicyclic heteroaryl group with 5 to 10 ring members containing 1, 2, or 3 heteroatoms independently selected from N, O, or S, or a monocyclic or bicyclic heterocyclyl group with 5 to 10 ring members containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S, wherein the C_6-C_{10} aryl group, the heteroaryl group, or the heterocyclyl group are unsubstituted or are substituted with 1, 2, or 3 R^{4a} substituents;

R^{4a} in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -NH_2, -NH(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), or -C(=O)N(C_1-C_6 alkyl)$_2$, and the heterocyclyl R^4 group may be further substituted with 1 oxo substituent; and

further wherein:

if R^4 is an unsubstituted or substituted phenyl ring and R^3 is a group of formula -(CR^{3b}=CR^{3c})-Q, then at least one of the following is true:

a) R^4 is substituted with at least one -O-(C_1-C_6 alkyl) group;

b) Q is not an oxadiazole;

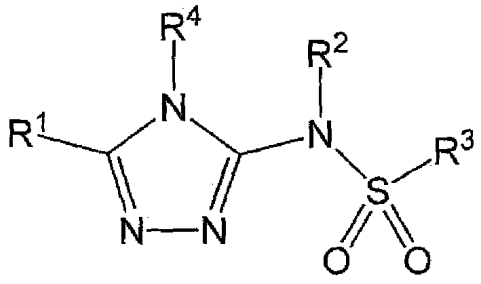
c) R^{3b} is not –H;

d) R^{3c} is not –H;

e) R^1 is not a 2-pyridyl group; or

f) R^4 is substituted with two or more -O-(C_1-C_6 alkyl) groups. In another aspect, the present invention refers to a pharmaceutical composition, comprising the compound of the present invention or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, and at least one pharmaceutically acceptable excipient, carrier, or diluent. In still another aspect, the present invention refers to a kit, the kit comprising: the compound of the present invention or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof.

Also described herein is a compound of Formula I or Formula II:



I

with 5 to 10 ring members containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S, wherein the C_6-C_{10} aryl group, the heteroaryl group, or the heterocyclyl group are unsubstituted or are substituted with 1, 2, or 3 R^{4a} substituents; and

R^{4a} in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -NH_2, -NH(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), or -C(=O)N(C_1-C_6 alkyl)$_2$, and the heterocyclyl R^4 group may be further substituted with 1 oxo substituent.

[013] In some examples of the compound of Formula I or Formula II or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof, at least one of the following is true if R^4 is an unsubstituted or substituted phenyl ring and R^3 is a group of formula -(CR^{3b}=CR^{3c})-Q:

a) R^4 is substituted with at least one -O-(C_1-C_6 alkyl) group;

b) Q is not an oxadiazole;

c) R^{3b} is not –H;

d) R^{3c} is not –H;

e) R^1 is not a 2-pyridyl group; or

f) R^4 is substituted with two or more -O-(C_1-C_6 alkyl) groups.

[014] Numerous other examples of the compound of Formula I or Formula II are set forth herein.

[015] Also provided are pharmaceutical compositions that include at least one pharmaceutically acceptable excipient, carrier or diluent and the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples.

[016] In other examples, the disclosure provides a method of treating a cardiovascular condition. Such methods typically include administering to a subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples. In some such examples, the the cardiovascular condition is heart failure. In some such examples, the

cardiovascular condition is heart failure with reduced ejection fraction whereas in other examples it is heart failure with preserved ejection fraction. Thus, in some examples, the cardiovascular condition is chronic systolic heart failure or chronic diastolic heart failure. In other examples, the cardiovascular condition is acute heart failure whereas in other examples, the cardiovascular condition is hypertension.

[017] In still other examples, the disclosure provides a method of improving cardiac contractility in a subject. Such methods typically include administering to the subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples.

[018] In still other examples, the disclosure provides a method of increasing ejection fraction in a subject suffereing from a cardiovascular condition. Such methods typically include administering to the subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples. In such examples, the ejection fraction is incrased in the subject after administration.

[019] In still other examples, the disclosure provides a method of treating a condition in a subject where it is desired to activate the APJ Receptor. Such methods typically include administering to the subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples. In some such examples, the condition is obesity or diabetes whereas in other such examples, the condition is diabetic nephropathy or chronic kidney disease.

[020] In other examples, the disclosure provides the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a

pharmaceutical composition of any of the examples for use in treating a cardiovascular condition. In some such examples, the the cardiovascular condition is heart failure. In some such

examples, the cardiovascular condition is heart failure with reduced ejection fraction whereas in other examples it is heart failure with preserved ejection fraction. Thus, in some examples, the cardiovascular condition is chronic systolic heart failure or chronic diastolic heart failure. In other examples, the cardiovascular condition is acute heart failure whereas in other examples, the cardiovascular condition is hypertension.

[021] In still other examples, the disclosure provides the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples for improving the cardiac contractility in a subject suffering from a cardiovascular condition.

[022] In still other examples, the disclosure provides the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples for improving the ejection fraction in a subject suffering from a cardiovascular condition.

[023] In still other examples, the disclosure provides the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples or a pharmaceutical composition of any of the examples for treating a condition in a subject where it is desired to activate the APJ Receptor. In some such examples, the condition is obesity or diabetes whereas in other such examples, the condition is diabetic nephropathy.

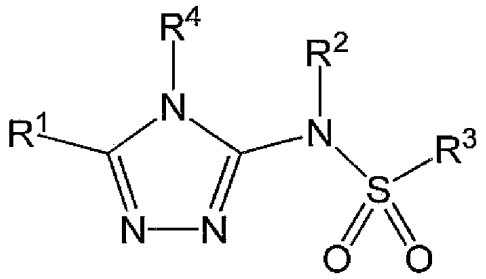
[024] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[025] FIG. 1A is a graph of left ventricular dP/dt_{max} as a function of concentration of Example 371 compared with vehicle in *ex vivo* naive Sprague Dawley rat hearts obtained using the Langendorff apparatus. This shows Example 371 increases load independent cardiac contractility in isolated perfused rat hearts.

WHAT IS CLAIMED IS:

1. A compound of Formula I or Formula II:



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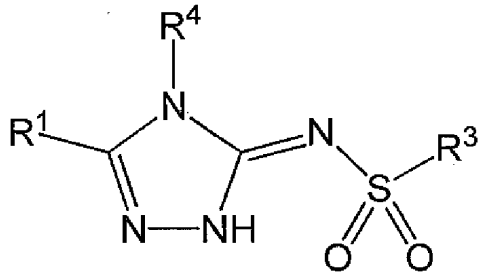


II

or a pharmaceutically acceptable salt thereof, a tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein:

R^1 is an unsubstituted pyridyl, pyridonyl, or pyridine N-oxide, or is a pyridyl, pyridonyl, or pyridine N-oxide substituted with 1, 2, 3, or 4 R^{1a} substituents;

R^{1a} in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -C_2-C_6 alkenyl, -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl)-OH, -O-(C_1-C_6 haloalkyl)-O-(C_1-C_6 alkyl), -O-(C_1-C_6 perhaloalkyl)-OH, -O-(C_1-C_6 perhaloalkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, phenyl, -C(=O)-(heterocyclyl), or a heterocyclyl group, wherein the heterocyclyl group of the -C(=O)-(heterocyclyl) or heterocyclyl group is a 3 to 7 membered ring containing 1, 2, or 3 heteroatoms selected from N, O, or S;

R^2 is selected from -H, or C_1-C_4 alkyl or is absent in the compounds of Formula II;

R^3 is selected from an unsubstituted C_1-C_{10} alkyl, a C_1-C_{10} alkyl substituted with 1, 2, or 3 R^{3a} substituents, a group of formula -($CR^{3b}R^{3c}$)-Q, a group of formula –NH-($CR^{3b}R^{3c}$)-Q,

a group of formula -($CR^{3b}R^{3c}$)-C(=O)-Q, a group of formula -($CR^{3d}R^{3e}$)-($CR^{3f}R^{3g}$)-Q, a group of formula -(CR^{3b}=CR^{3c})-Q, or a group of formula -(heterocyclyl)-Q, wherein the heterocyclyl of the -(heterocyclyl)-Q has 5 to 7 ring members of which 1, 2, or 3 are heteroatoms selected from N, O, or S and is unsubstituted or is substituted with 1, 2, or 3 R^{3h} substituents;

R^{3a} in each instance is independently selected from -F, -Cl, -CN, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NH_2, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3b} and R^{3c} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3d} and R^{3e} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3f} and R^{3g} are independently selected from –H, -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), or –N(C_1-C_6 alkyl)$_2$;

R^{3h} in each instance is independently selected from -F, -Cl, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, or oxo;

Q is a monocyclic or bicyclic C_6-C_{10} aryl group, a monocyclic or bicyclic heteroaryl group with 5 to 10 ring members containing 1, 2, or 3 heteroatoms selected from N, O, or S, a C_3-C_8 cycloalkyl group, or a 3 to 7 membered heterocyclyl group containing 1, 2, or 3 heteroatoms selected from N, O, or S, wherein the C_6-C_{10} aryl group, the heteroaryl group, the cycloalkyl group, and the heterocyclyl group are unsubstituted or are substituted with 1, 2, 3, or 4 R^Q substituent;

R^Q in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -C_2-C_6 alkenyl , -C_2-C_6 alkynyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, -S(=O)$_2$-(C_1-C_6 alkyl), phenyl, or a heteroaryl group, and the Q heterocyclyl group may be substituted with 1 oxo substituent;

R^4 is selected from a monocyclic or bicyclic C_6-C_{10} aryl group, a monocyclic or bicyclic heteroaryl group with 5 to 10 ring members containing 1, 2, or 3 heteroatoms

independently selected from N, O, or S, or a monocyclic or bicyclic heterocyclyl group with 5 to 10 ring members containing 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S, wherein the C_6-C_{10} aryl group, the heteroaryl group, or the heterocyclyl group are unsubstituted or are substituted with 1, 2, or 3 R^{4a} substituents;

R^{4a} in each instance is independently selected from -F, -Cl, -Br, -I, -CN, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_1-C_6 perhaloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -O-(C_1-C_6 perhaloalkyl), -NH_2, -NH(C_1-C_6 alkyl), –N(C_1-C_6 alkyl)$_2$, -C(=O)-(C_1-C_6 alkyl), -C(=O)OH, -C(=O)-O-(C_1-C_6 alkyl), -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), or -C(=O)N(C_1-C_6 alkyl)$_2$, and the heterocyclyl R^4 group may be further substituted with 1 oxo substituent; and

further wherein:

if R^4 is an unsubstituted or substituted phenyl ring and R^3 is a group of formula -(CR^{3b}=CR^{3c})-Q, then at least one of the following is true:

a) R^4 is substituted with at least one -O-(C_1-C_6 alkyl) group;

b) Q is not an oxadiazole;

c) R^{3b} is not –H;

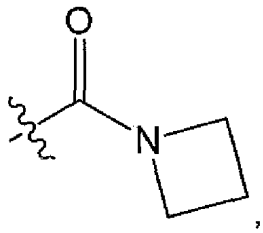
d) R^{3c} is not –H;

e) R^1 is not a 2-pyridyl group; or

f) R^4 is substituted with two or more -O-(C_1-C_6 alkyl) groups.

2. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^1 is an unsubstituted pyridyl or is a pyridyl substituted with 1 or 2 R^{1a} substituents.

3. The compound of claim 2 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^{1a} in each instance is independently selected from –CH_3, -CH_2CH_3, -F, -Cl, -Br, -CN, -CF_3, -CH=CH_2, -C(=O)NH_2, -C(=O)NH(CH_3), -C(=O)N(CH_3)$_2$, -C(=O)NH(CH_2CH_3), -OH, -OCH_3, -$OCHF_2$, -OCH_2CH_3, -OCH_2CF_3, -OCH_2CH_2OH, -$OCH_2C(CH_3)_2OH$, -$OCH_2C(CF_3)_2OH$, -$OCH_2CH_2OCH_3$, -NH_2, -$NHCH_3$, -N(CH_3)$_2$, phenyl, or a group of formula



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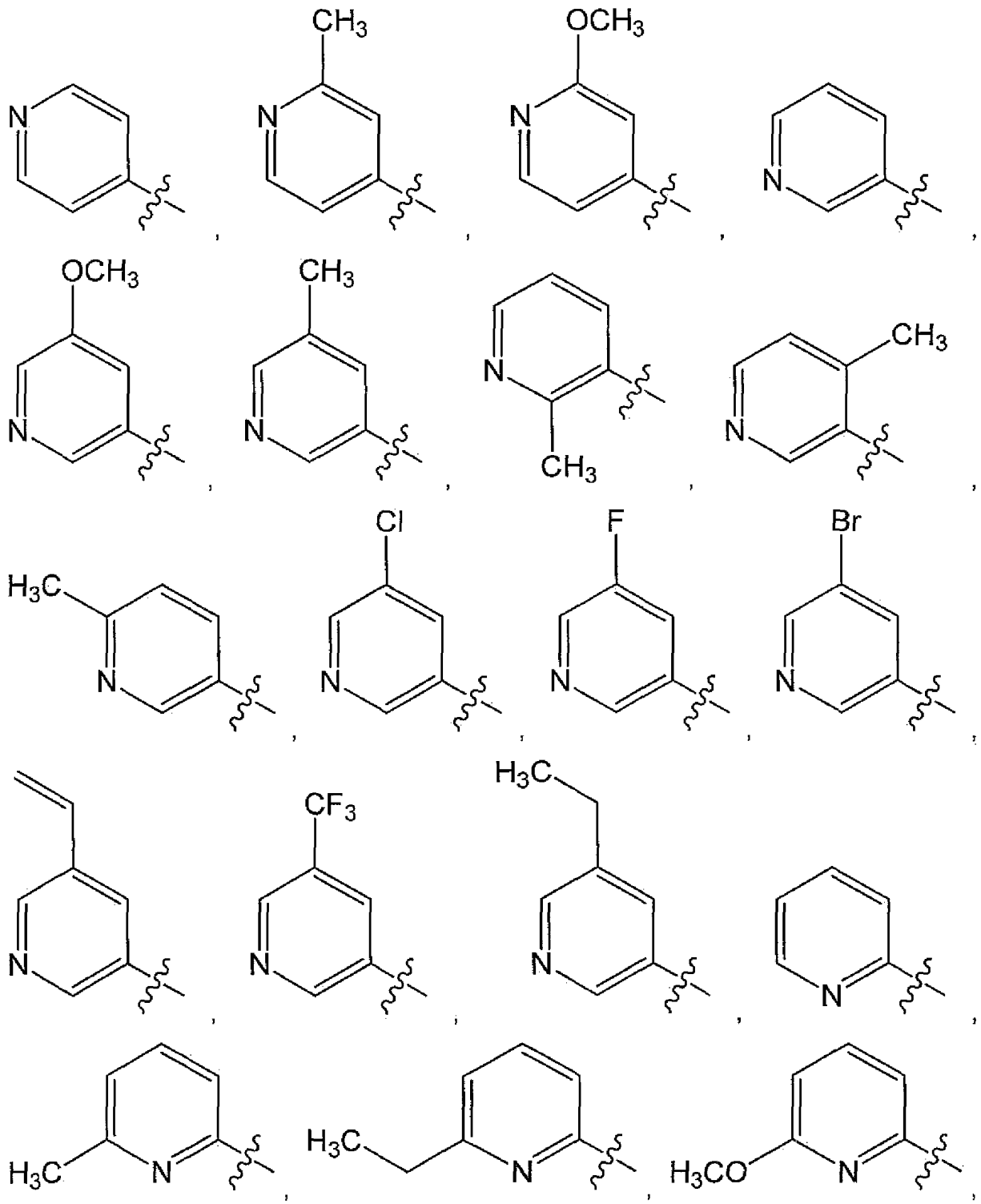
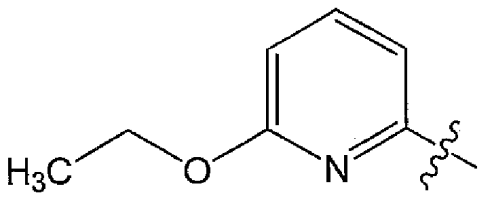
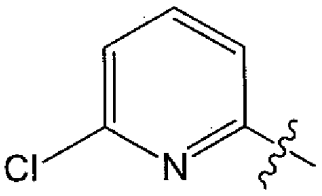
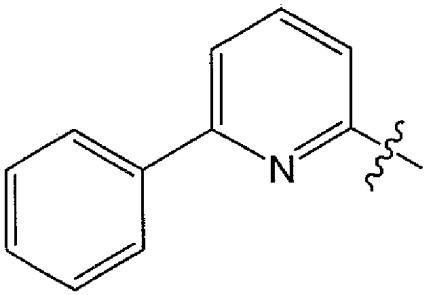
wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

4. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^1 is selected from




H3C
O
N


Cl
N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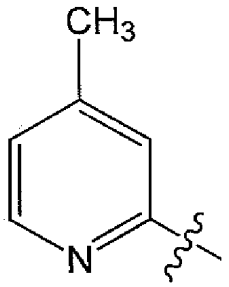
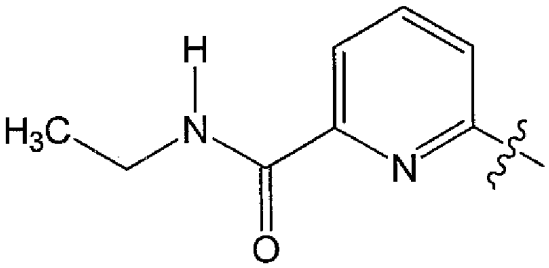
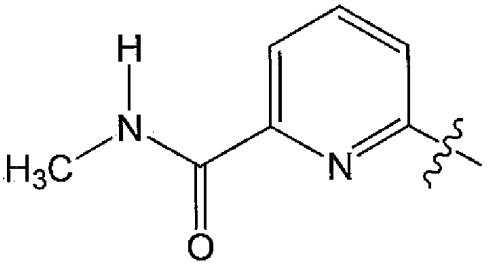
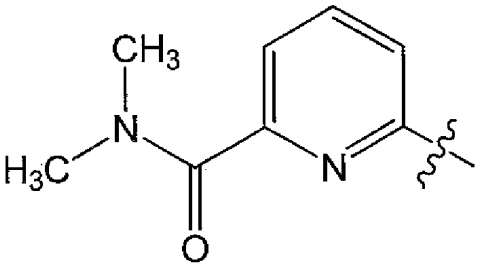

CH3
N


H
H3C
N
N
O


H
N
H3C
N
O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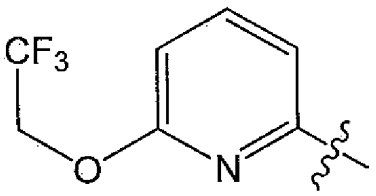
N
H3C
N
O


CF3
O
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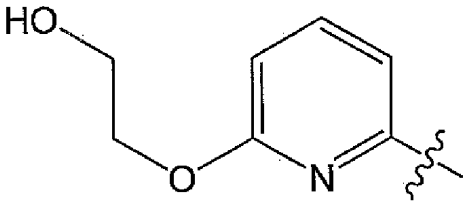
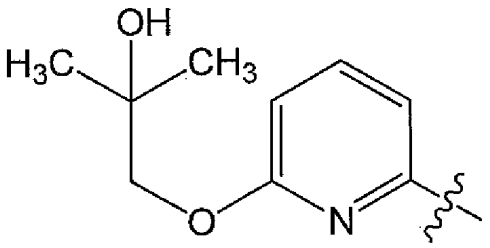

HO
O
N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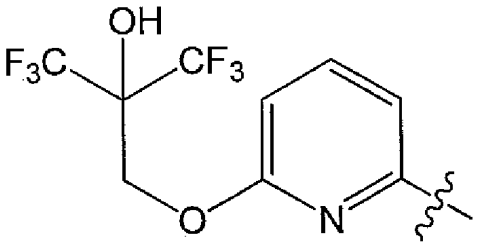
H3C
CH3
O
N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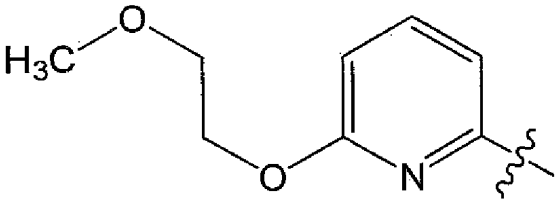
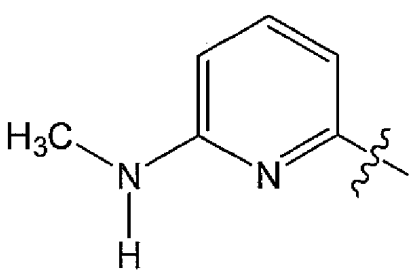
F3C
CF3
O
N


O
H3C
O
N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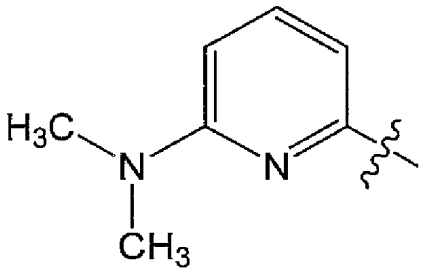
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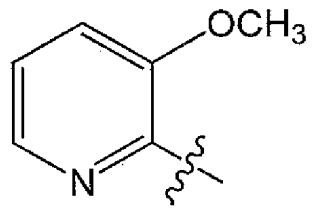
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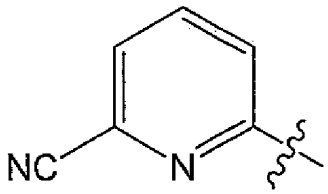
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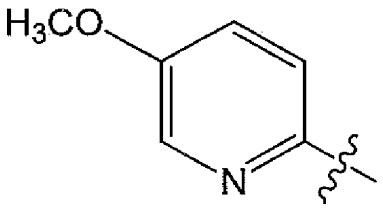
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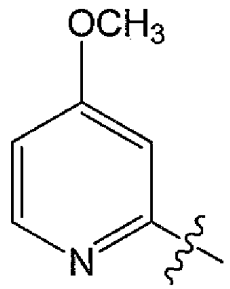
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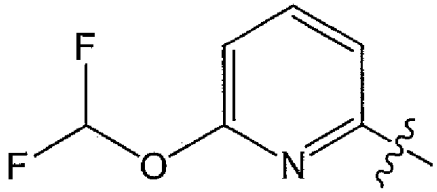
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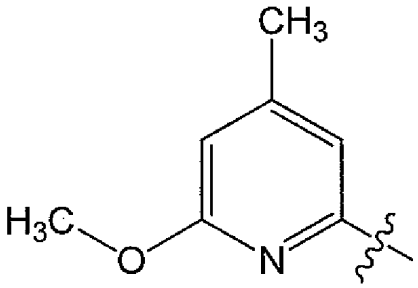
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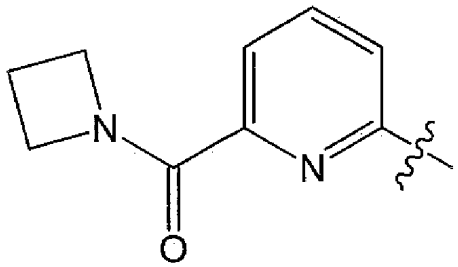
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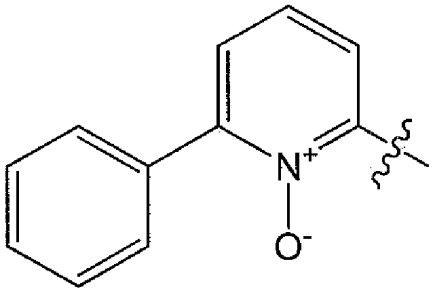
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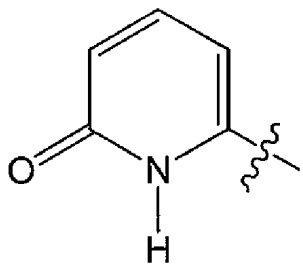
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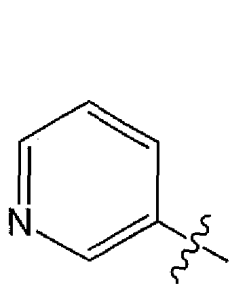
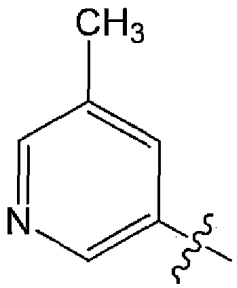
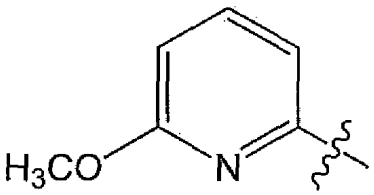
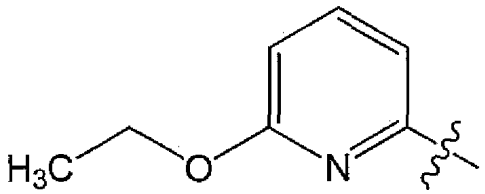
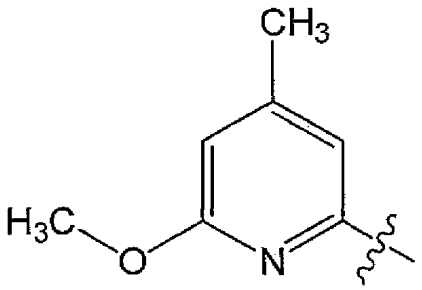
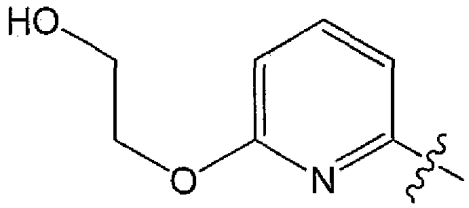
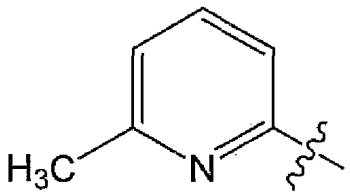
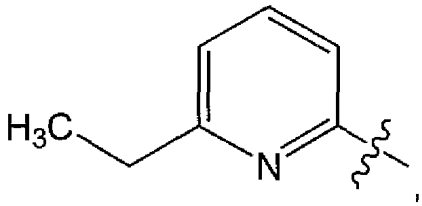
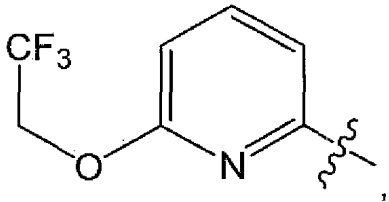
wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

5. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^1 is selected from

wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

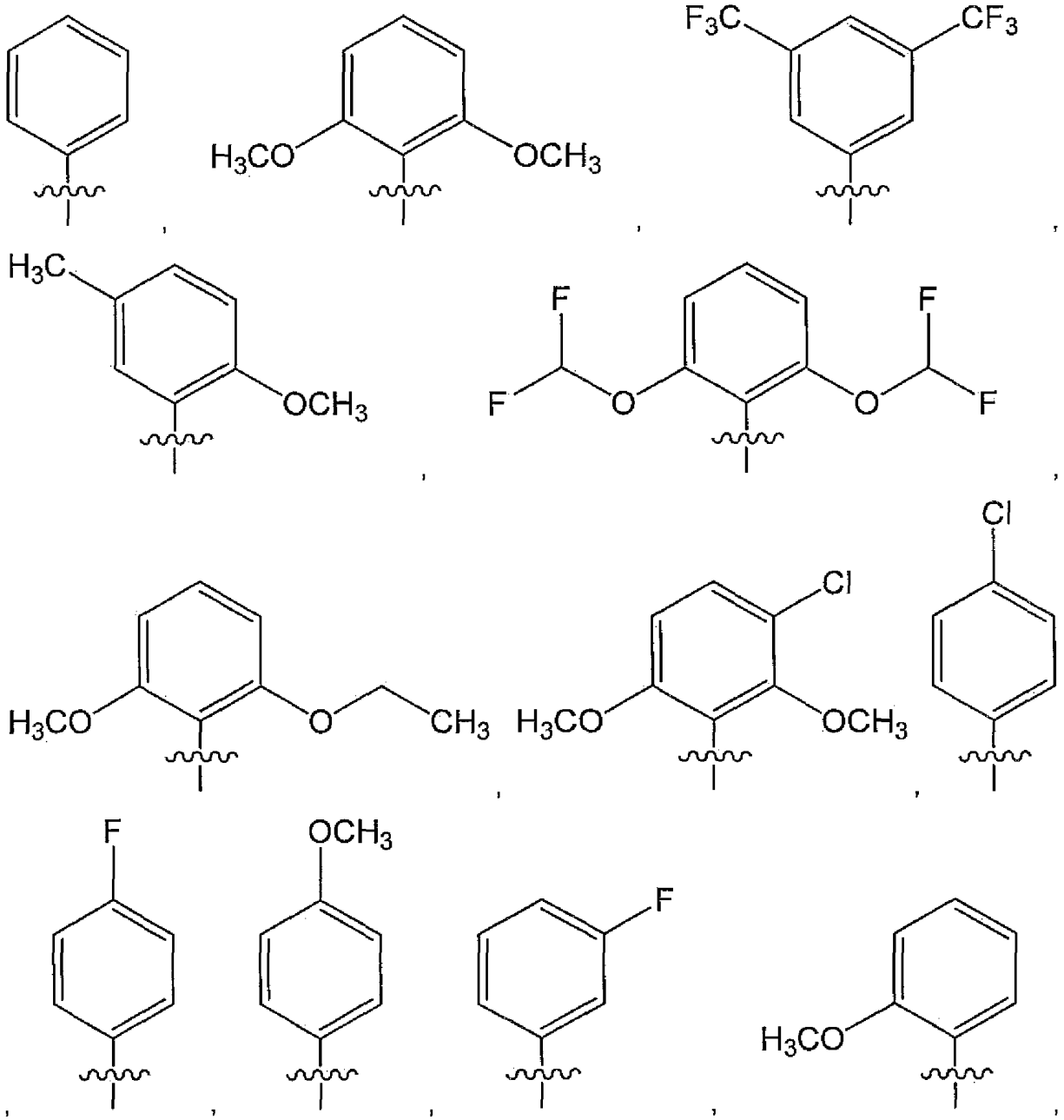
6. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^2 is -H.

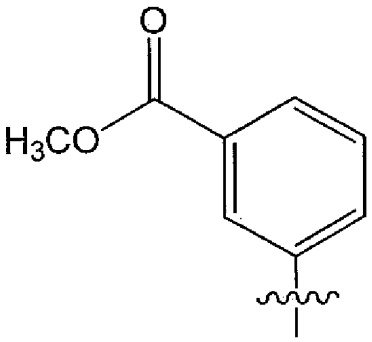
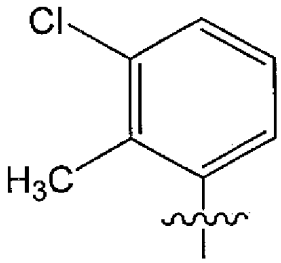
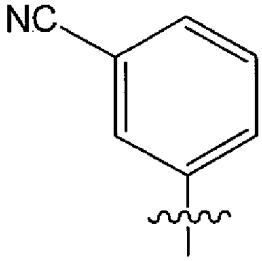
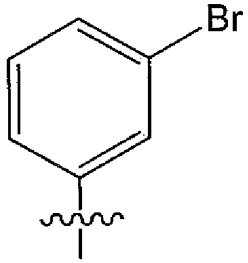
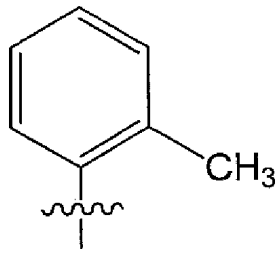
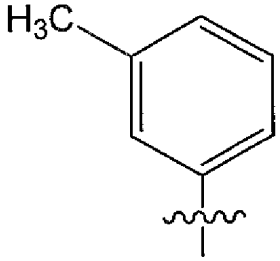
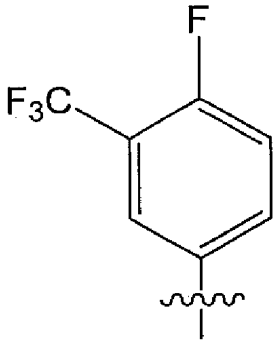
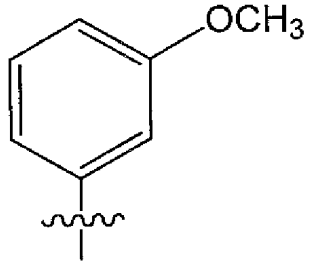
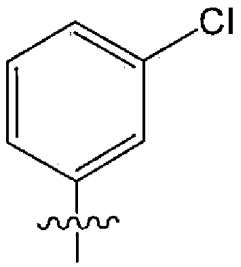
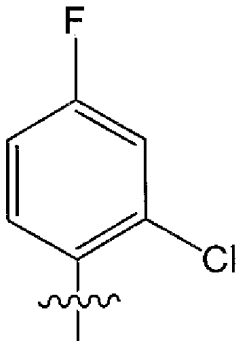
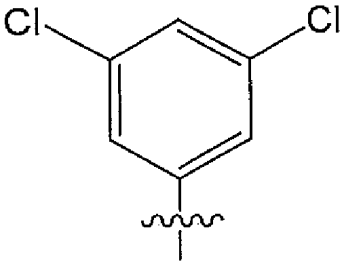
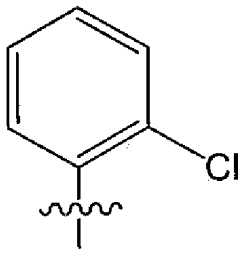
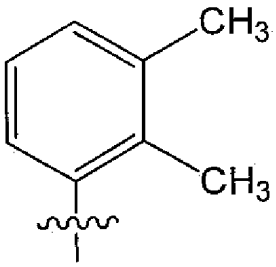
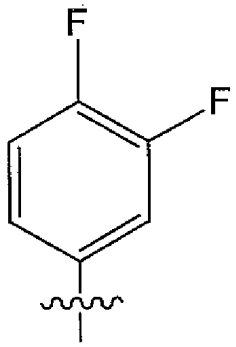
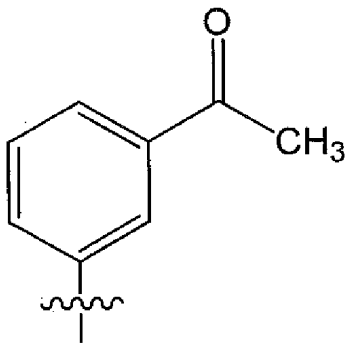
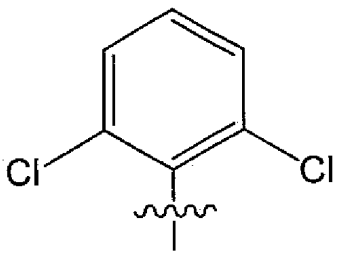
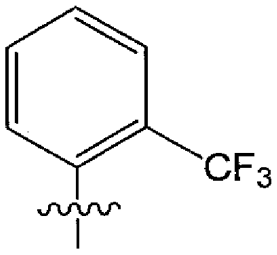
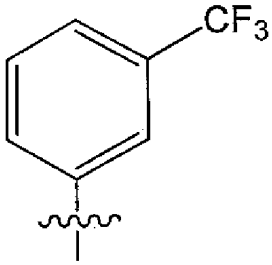
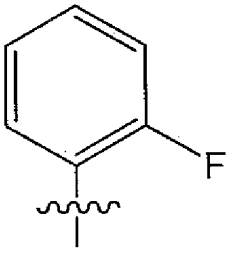
7. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^4 is a phenyl, pyridyl, pyrimidinyl, isoxazolyl, indolyl, naphthyl, or pyridinyl any of which may be unsubstituted or substituted with 1, 2, or 3 R^{4a} substituents.

8. The compound of claim 7 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^{4a} is in each instance independently selected from –

CH_3, -F, -Cl, -Br, -CN, $-CF_3$, $-OCH_3$, $-OCHF_2$, $-OCH_2CH_3$, $-C(=O)OCH_3$, $-C(=O)CH_3$, or $-N(CH_3)_2$.

9. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^4 is selected from



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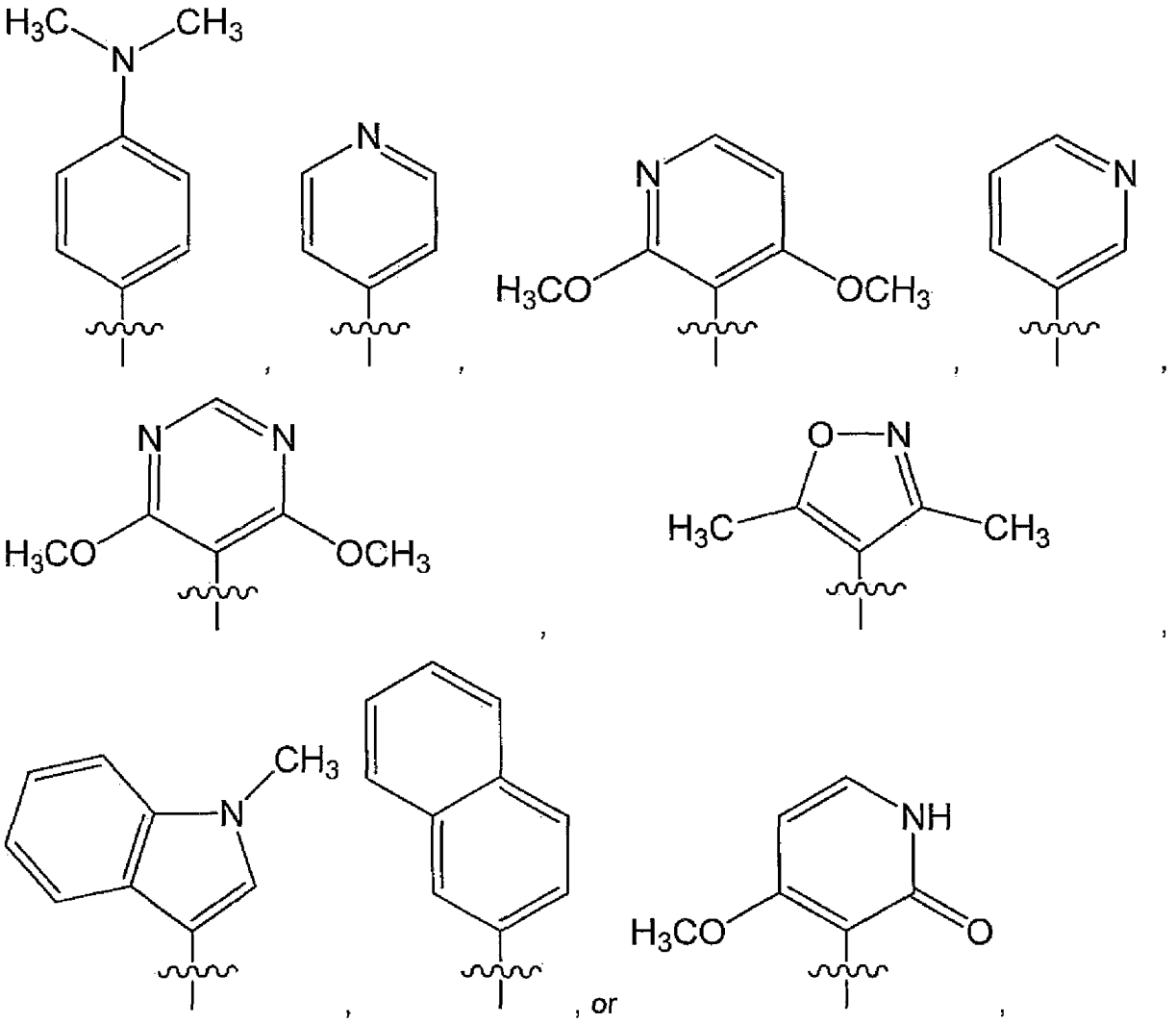


wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

10. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^4 is a phenyl substituted with 1 or 2 R^{4a} substituents.

11. The compound of claim 10 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the 1 or 2 R^{4a} substituents are –O-(C_1-C_2 alkyl) groups.

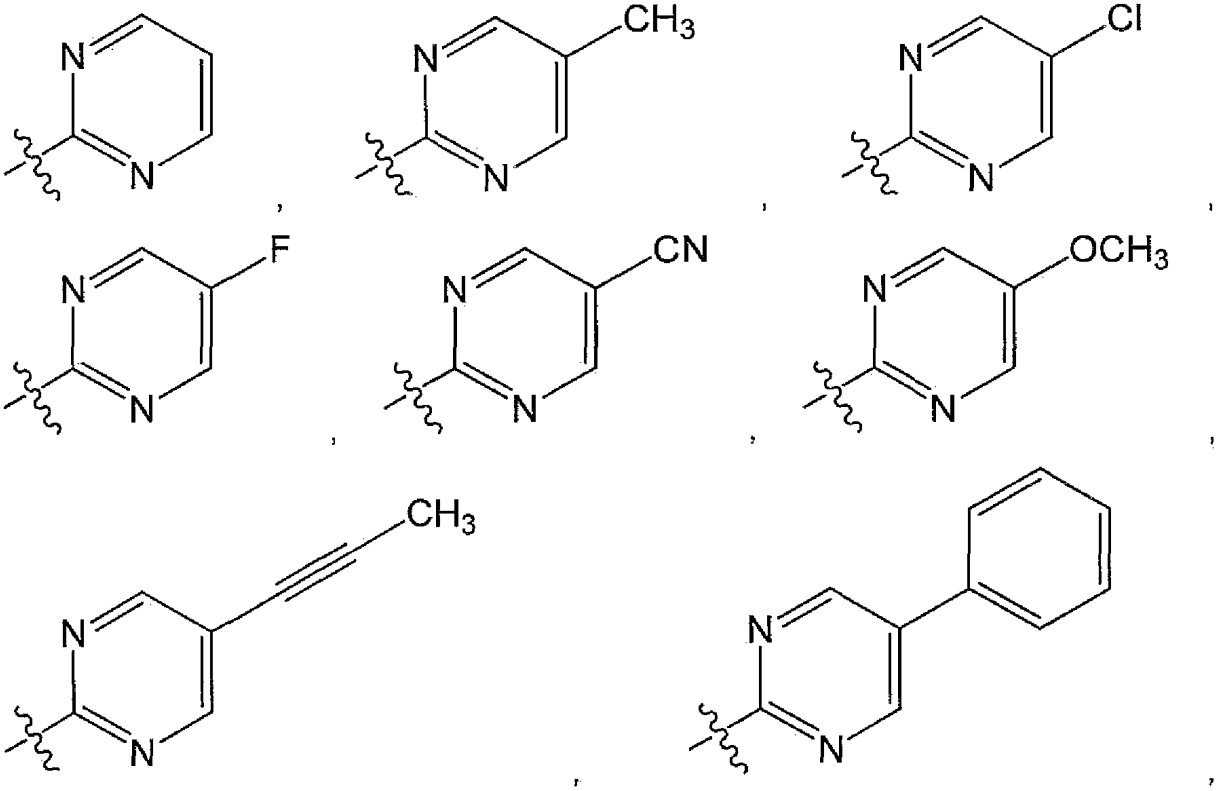
12. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^3 is selected from a group of formula -($CR^{3b}R^{3c}$)-Q, a group of formula –NH-($CR^{3b}R^{3c}$)-Q, a group of formula -($CR^{3b}R^{3c}$)-C(=O)-Q, a group of formula -($CR^{3d}R^{3e}$)-($CR^{3f}R^{3g}$)-Q, a group of

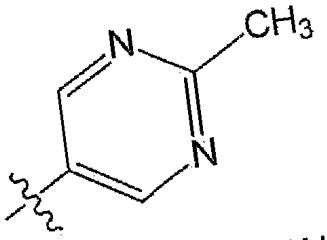
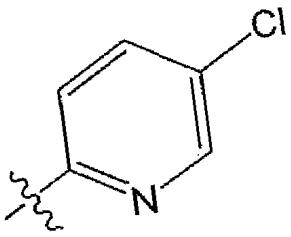
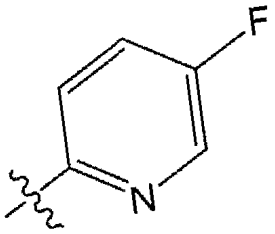
formula -(CR^{3b}=CR^{3c})-Q, or a group of formula -(heterocyclyl)-Q, wherein the heterocyclyl of the -(heterocyclyl)-Q has 5 to 7 ring members of which 1, 2, or 3 are heteroatoms selected from N, O, or S and is unsubstituted or is substituted with 1, 2, or 3 R^{3h} substituents.

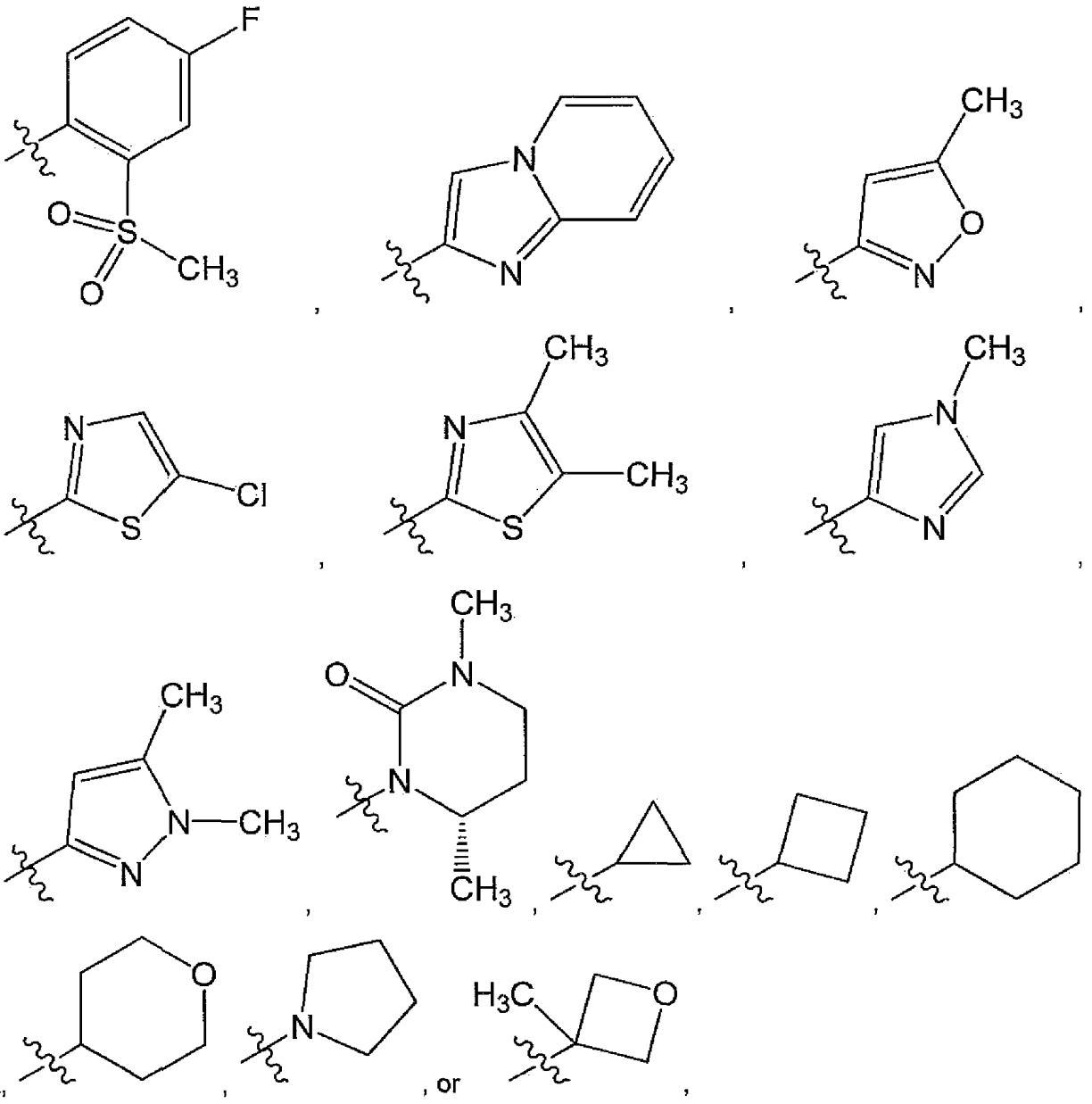
13. The compound of claim 12 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein Q is selected from pyrimidinyl, pyridyl, isoxazolyl, thiazolyl, imidazolyl, phenyl, tetrahydropyrimidinonyl, cyclopropyl, cyclobutyl, cyclohexyl, morpholinyl, pyrrolidinyl, pyrazinyl, imidazo[1,2-a]pyridinyl, pyrazolyl, or oxetanyl any which may be unsubstituted or substituted with 1, 2, or 3, R^Q substituents.

14. The compound of claim 12 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein Q is a monocyclic heteroaryl group with 5 or 6 ring members containing 1 or 2 heteroatoms selected from N, O, or S and Q is unsubstituted or is substituted with 1 or 2 R^Q substituents.

15. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein Q is selected from



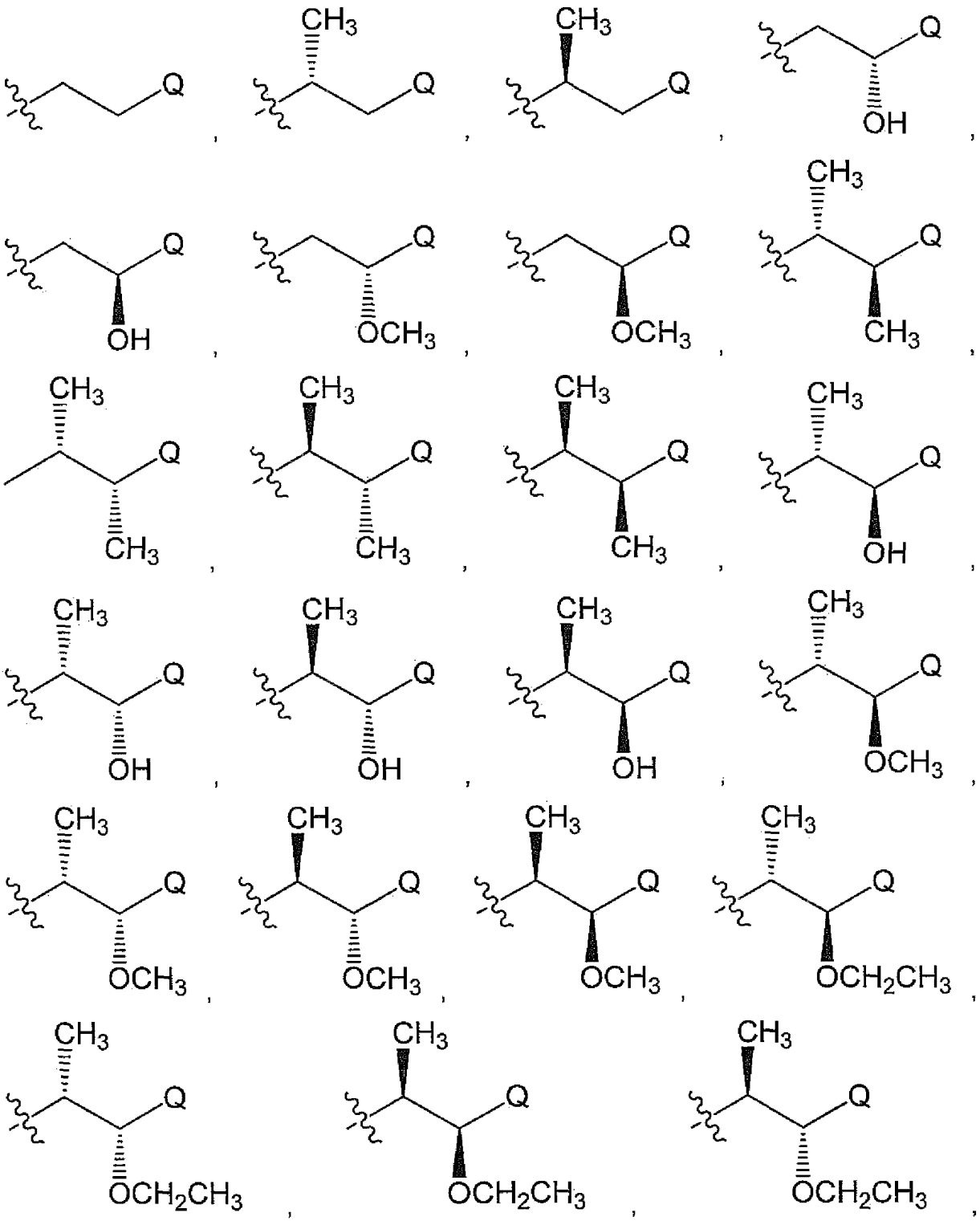


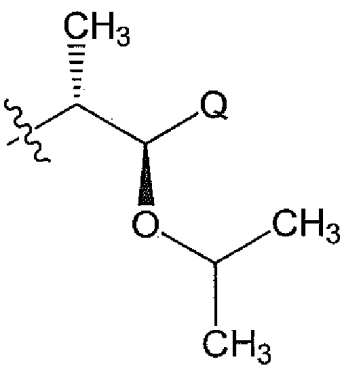
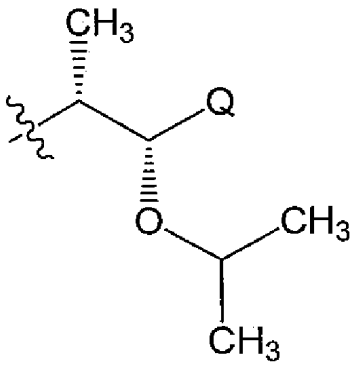
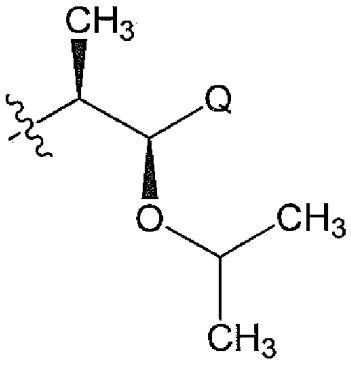
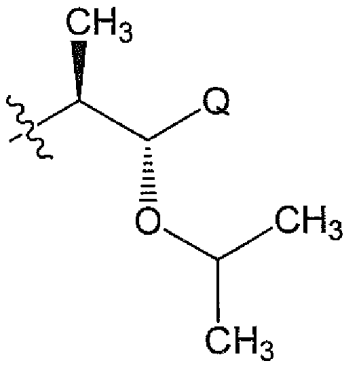
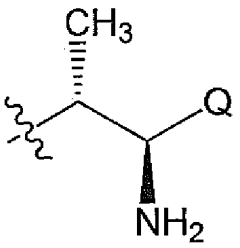
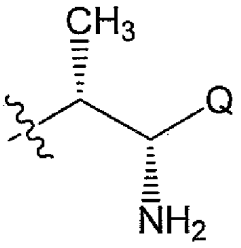
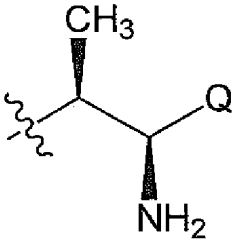
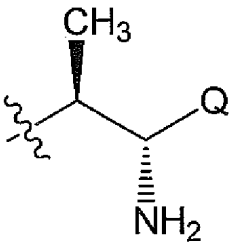
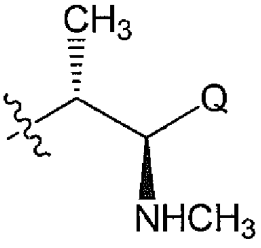
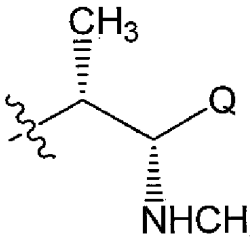
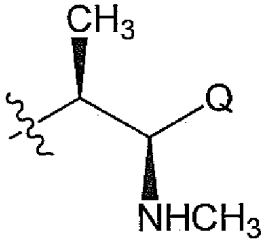
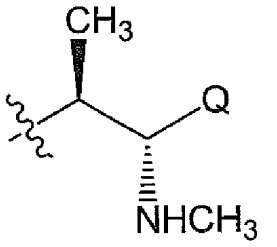
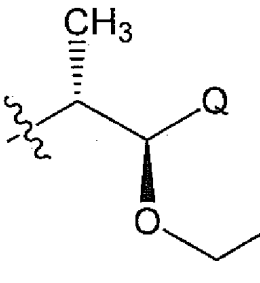
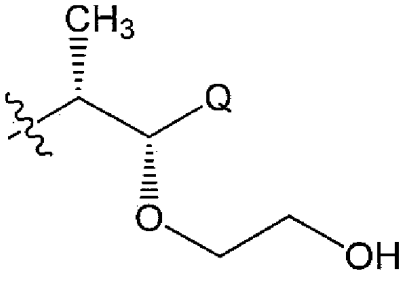
wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

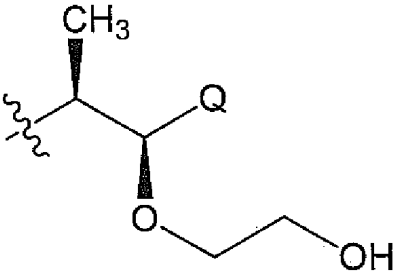
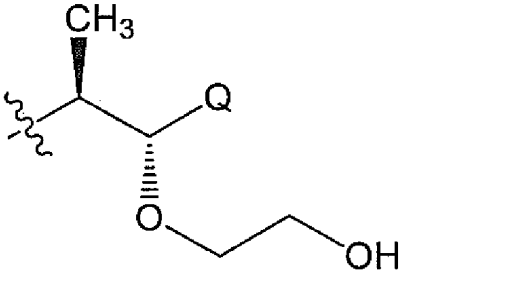
16. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^3 is a group of formula -(heterocyclyl)-Q, wherein the heterocyclyl of the -(heterocyclyl)-Q has 5 to 7 ring members of which 1, 2, or 3 are heteroatoms selected from N, O, or S and is unsubstituted or is substituted with 1, 2, or 3 R^{3h} substituents.

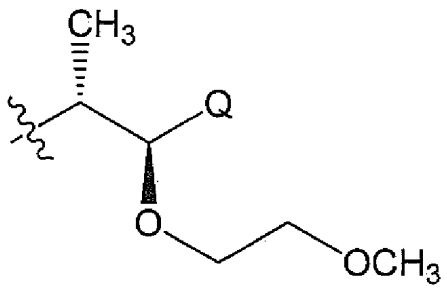
17. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^3 is a group of formula $-(CR^{3d}R^{3e})-(CR^{3f}R^{3g})-Q$.

18. The compound of claim 17 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^3 has the formula

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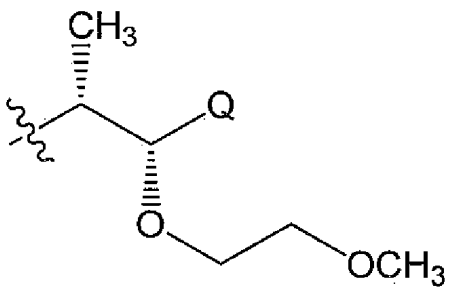
OCH3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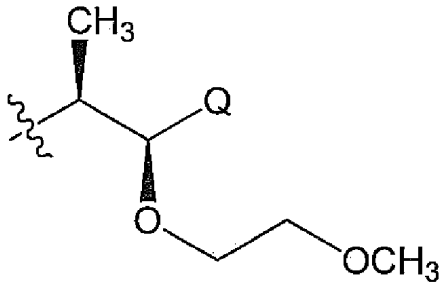
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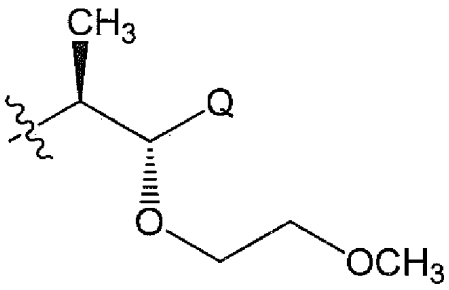
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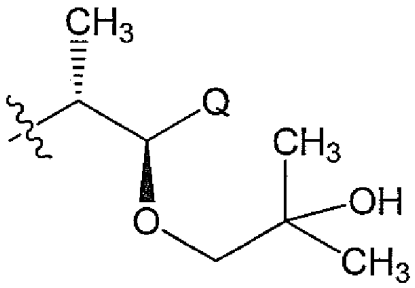
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CH3
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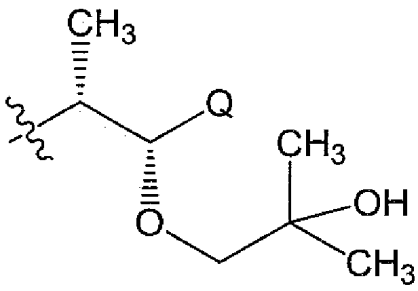
CH3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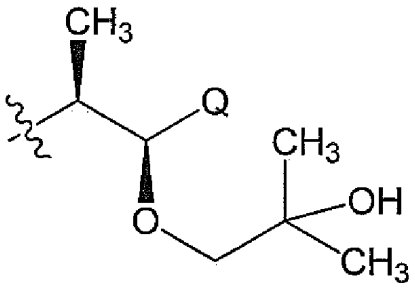
CH3
OH
CH3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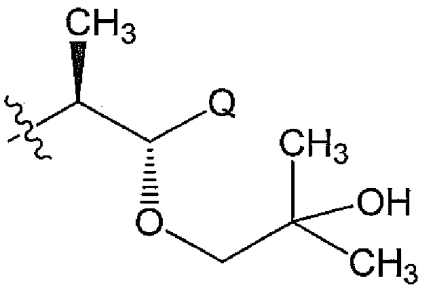
O
CH3
OH
CH3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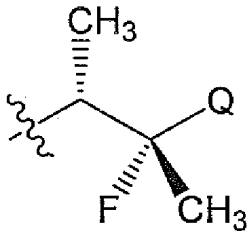
CH3
OH
CH3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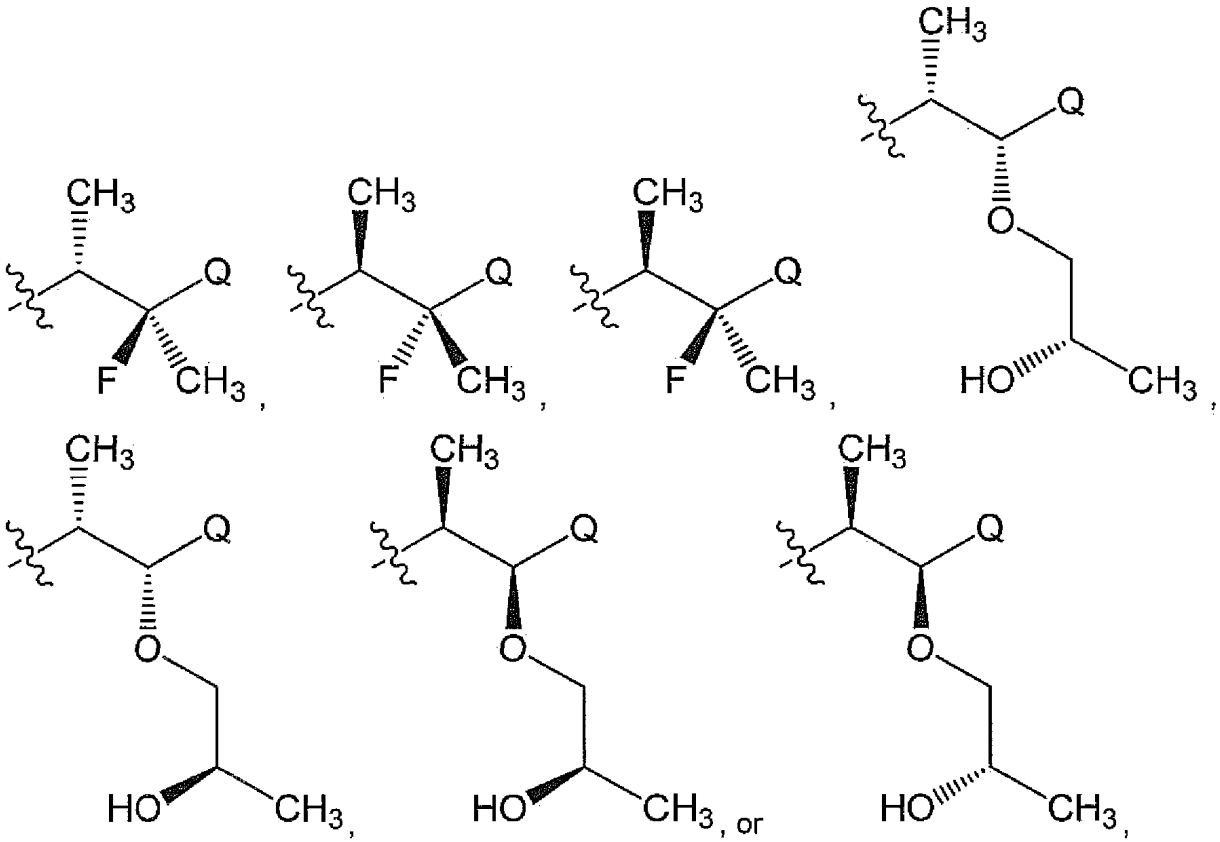
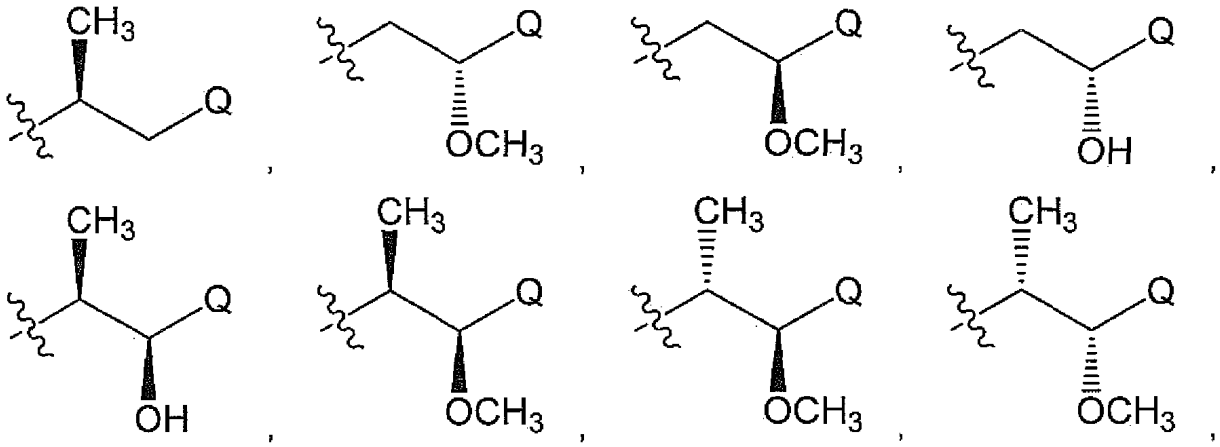
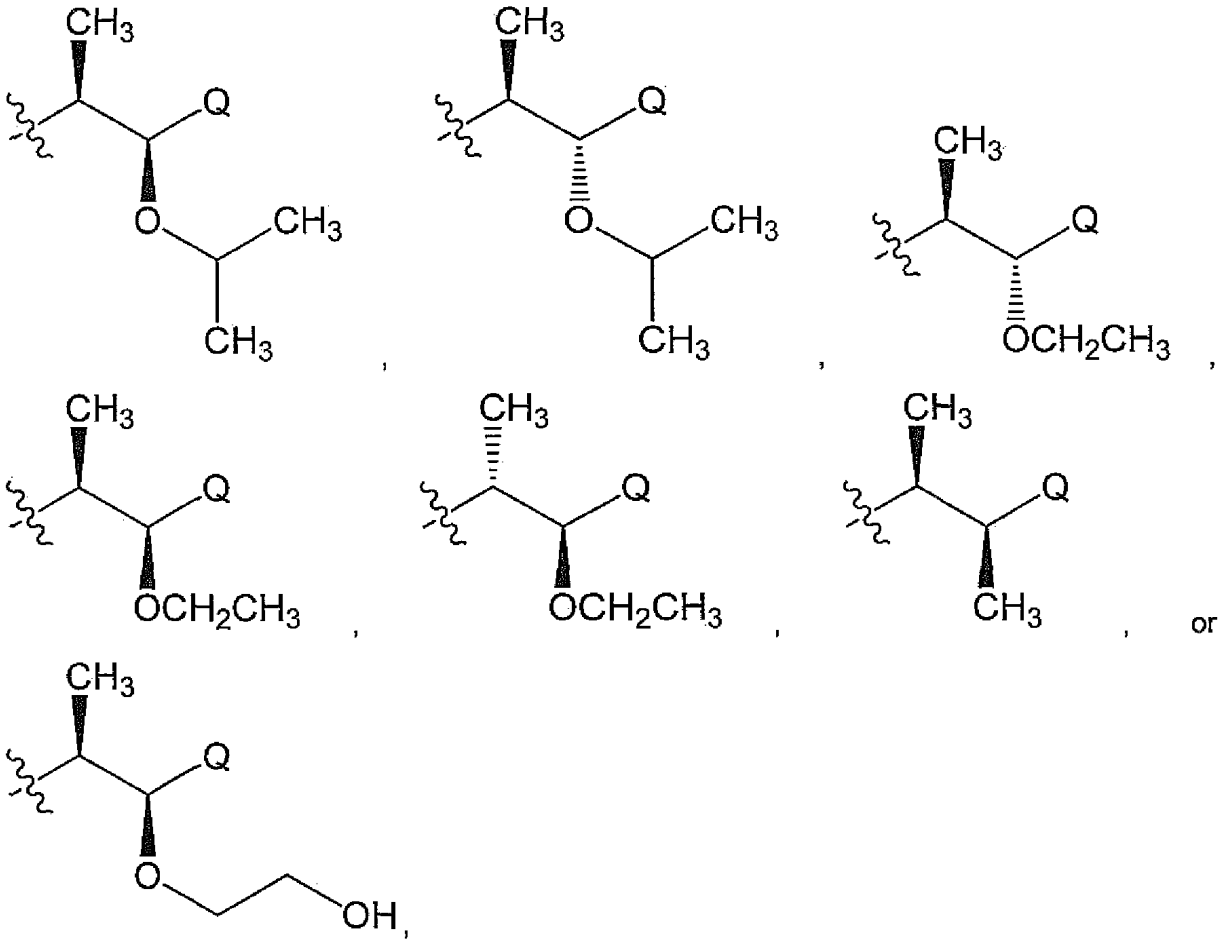


wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

19. The compound of claim 18 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein R^3 has the formula





wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

20. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(6-methoxy-2-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(2S,3R)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-3-(5-methyl-2-pyrimidinyl)-2-butanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-hydroxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1S,2R)-1-(5-chloro-2-pyrimidinyl)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-2-propanesulfonamide;

(1S,2R)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrazinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-hydroxy-1-(5-methyl-2-pyrazinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(2S,3R)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-3-(5-methyl-2-pyrimidinyl)-2-butanesulfonamide;

(1R,2S)-1-(5-chloro-2-pyrimidinyl)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1S,2R)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrazinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(6-methyl-2-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-hydroxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-(5-fluoro-2-pyrimidinyl)-1-methoxy-2-propanesulfonamide;

(2S,3R)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-3-(5-methyl-2-pyrazinyl)-2-butanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-fluoro-2-pyrimidinyl)-2-propanesulfonamide;

(1S,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-(1-methylethoxy)-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-(1-methylethoxy)-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1S,2R)-1-(5-chloro-2-pyrimidinyl)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-2-propanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methoxy-2-pyrazinyl)-2-propanesulfonamide;

(2S,3R)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-3-(5-methyl-2-pyrazinyl)-2-butanesulfonamide;

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-fluoro-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2S)-N-(4-(4,6-dimethoxy-5-pyrimidinyl)-5-(6-methoxy-2-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide;

(1R,2R)-1-(5-chloro-2-pyrimidinyl)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-2-propanesulfonamide; or

(1S,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide.

21. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(6-methoxy-2-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-methoxy-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide.

22. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(2S,3R)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-3-(5-methyl-2-pyrimidinyl)-2-butanesulfonamide.

23. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-ethoxy-1-(5-fluoro-2-pyrimidinyl)-2-propanesulfonamide.

24. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(1S,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-(1-methylethoxy)-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide.

25. The compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, wherein the compound is

(1R,2S)-N-(4-(2,6-dimethoxyphenyl)-5-(5-methyl-3-pyridinyl)-4H-1,2,4-triazol-3-yl)-1-(1-methylethoxy)-1-(5-methyl-2-pyrimidinyl)-2-propanesulfonamide.

26. A pharmaceutical composition, comprising the compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof, and at least one pharmaceutically acceptable excipient, carrier, or diluent.

27. The pharmaceutical composition of claim 26, further comprising at least one additional therapeutic agent selected from an α-blocker, a β-blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), a calcium channel blocker, a diuretic, an inhibitor of the funny current, a myosin activator, or a neutral endopeptidase (NEP) inhibitor.

28. The pharmaceutical composition of claim 26, further comprising at least one additional therapeutic agent selected from an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB).

29. A kit, the kit comprising: the compound of claim 1 or the pharmaceutically acceptable salt thereof, the stereoisomer of any of the foregoing, or the mixture thereof.

30. The kit of claim 29, wherein the kit further comprises at least one additional therapeutic agent selected from an α-blocker, a β-blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), a calcium channel blocker, a diuretic, an inhibitor of the funny current, a myosin activator, or a neutral endopeptidase (NEP) inhibitor.

31. The kit of claim 29, wherein the kit further comprises at least one additional therapeutic agent selected from an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB).