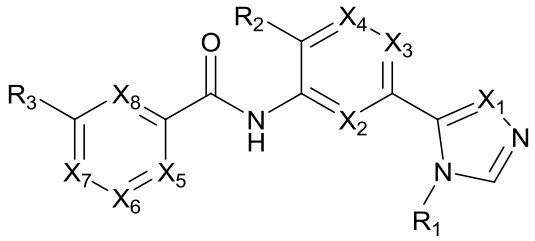
What is claimed is:

1. Use of a therapeutically effective amount of an ASK1 inhibitor in the manufacture of a medicament for treating and/or preventing nonalcoholic steatohepatitis (NASH) in combination with a therapeutically effective amount of a FXR agonist, wherein the ASK1 inhibitor is a compound of formula (I):



(I)

wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to three substituents selected from halo, oxo, alkyl, cycloalkyl, heterocyclyl, aryl, aryloxy, $-NO_2$, R^6, $-C(O)-R^6$, $-OC(O)-R^6-C(O)-O-R^6$, $C(O)-N(R^6)(R^7)$, $-OC(O)-N(R^6)(R^7)$, $-S-R^6$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)(R^7)$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-N(R^6)-S(=O)_2-R^6$, -CN, and $-O-R^6$, and wherein the alkyl, cycloalkyl, heterocyclyl, phenyl, and phenoxy are optionally substituted by from one to three substituents selected from alkyl, cycloalkyl, alkoxy, hydroxyl, and halo; wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_1-C_{15} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, all of which are optionally substituted with from one to three substituents selected from halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, -CN, lower alkoxy, $-CF_3$, aryl, and heteroaryl; or

R^6 and R^7 when taken together with the nitrogen to which they are attached form a heterocycle;

R^2 is hydrogen, halo, cyano, alkoxy, or alkyl optionally substituted by halo;

R^3 is aryl, heteroaryl, or heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to five substituents selected from alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halo, oxo, $-NO_2$, haloalkyl, haloalkoxy, -CN, $-O-R^6$, $-O-C(O)-R^6$, $-O-C(O)-N(R^6)(R^7)$, $-S-R^6$, $-N(R^6)(R^7)$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-R^6$, $-C(O)-N(R^6)(R^7)$, and $-N(R^6)-S(=O)_2-R^7$, wherein the alkyl, alkoxy, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with from one to five substituents selected from halo, oxo, $-NO_2$, alkyl, haloalkyl, haloalkoxy, $-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^6$, $-C(O)-N(R^6)(R^7)$, -CN, $-O-R^6$, cycloalkyl, aryl, heteroaryl and heterocyclyl; with the proviso that the heteroaryl or heterocyclyl moiety includes at least one ring nitrogen atom;

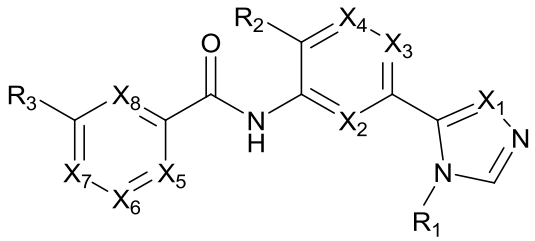
X^1, X^2, X^3, X^4, X^5, X^6, X^7 and X^8 are independently $C(R^4)$ or N, in which each R^4 is independently hydrogen, alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, halo, $-NO_2$, haloalkyl, haloalkoxy, -CN, $-O-R^6$, $-S-R^6$, $-N(R^6)(R^7)$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^6$, $-C(O)-N(R^6)(R^7)$, or $-N(R^6)-S(=O)_2-R^7$, wherein the alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is further optionally substituted with from one to five substituents selected from halo, oxo, $-NO_2$, $-CF_3$, $-O-CF_3$, $-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^7$, $-C(O)-N(R^6)(R^7)$, -CN, $-O-R^6$; or

X^5 and X^6 or X^6 and X^7 are joined to provide optionally substituted fused aryl or optionally substituted fused heteroaryl; and

with the proviso that at least one of X^2, X^3, and X^4 is $C(R^4)$; at least two of X^5, X^6, X^7, and X^8 are $C(R^4)$; and at least one of X^2, X^3, X^4, X^5, X^6, X^7 and X^8 is N;

or a pharmaceutically acceptable salt, or a mixture thereof.

2. Use of a therapeutically effective amount of a FXR agonist in the manufacture of a medicament for treating and/or preventing nonalcoholic steatohepatitis (NASH) in combination with a therapeutically effective amount of an ASK1 inhibitor, wherein the ASK1 inhibitor is a compound of formula (I):



(I)

wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to three substituents selected from halo, oxo, alkyl, cycloalkyl, heterocyclyl, aryl, aryloxy, $-NO_2$, R^6, $-C(O)-R^6$, $-OC(O)-R^6-C(O)-O-R^6$, $C(O)-N(R^6)(R^7)$, $-OC(O)-N(R^6)(R^7)$, $-S-R^6$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)(R^7)$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-N(R^6)-S(=O)_2-R^6$, -CN, and $-O-R^6$, and wherein the alkyl, cycloalkyl, heterocyclyl, phenyl, and phenoxy are optionally substituted by from one to three substituents selected from alkyl, cycloalkyl, alkoxy, hydroxyl, and halo; wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_1-C_{15} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, all of which are optionally substituted with from one to three substituents selected from halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, -CN, lower alkoxy, $-CF_3$, aryl, and heteroaryl; or

R^6 and R^7 when taken together with the nitrogen to which they are attached form a heterocycle;

R^2 is hydrogen, halo, cyano, alkoxy, or alkyl optionally substituted by halo;

R^3 is aryl, heteroaryl, or heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to five substituents selected from alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halo, oxo, $-NO_2$, haloalkyl, haloalkoxy, -CN, $-O-R^6$, $-O-C(O)-R^6$, $-O-C(O)-N(R^6)(R^7)$, $-S-R^6$, $-N(R^6)(R^7)$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-R^6$, $-C(O)-N(R^6)(R^7)$, and $-N(R^6)-S(=O)_2-R^7$, wherein the alkyl, alkoxy, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with from one to five substituents selected from halo, oxo, $-NO_2$, alkyl, haloalkyl, haloalkoxy, $-N(R^6)(R^7)$, $-C(O)-R^6$,

-C(O)-O-R^6, -C(O)-N(R^6)(R^7), -CN, -O-R^6, cycloalkyl, aryl, heteroaryl and heterocyclyl; with the proviso that the heteroaryl or heterocyclyl moiety includes at least one ring nitrogen atom;

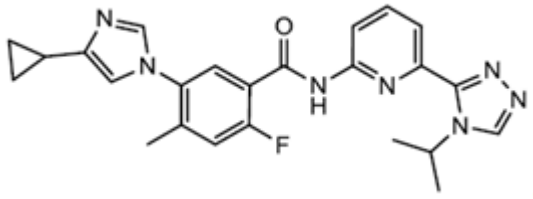
X^1, X^2, X^3, X^4, X^5, X^6, X^7 and X^8 are independently C(R^4) or N, in which each R^4 is independently hydrogen, alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, halo, -NO_2, haloalkyl, haloalkoxy, -CN, -O-R^6, -S-R^6, -N(R^6)(R^7), -S(=O)-R^6, -S(=O)$_2$$R^6$, -S(=O)$_2$-N($R^6$)($R^7$), -S(=O)$_2$-O-$R^6$, -N($R^6$)-C(O)-$R^7$, -N($R^6$)-C(O)-O-$R^7$, -N($R^6$)-C(O)-N($R^6$)($R^7$), -C(O)-$R^6$, -C(O)-O-$R^6$, -C(O)-N($R^6$)($R^7$), or -N($R^6$)-S(=O)$_2$-$R^7$, wherein the alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is further optionally substituted with from one to five substituents selected from halo, oxo, -NO_2, -CF_3, -O-CF_3, -N(R^6)(R^7), -C(O)-R^6, -C(O)-O-R^7, -C(O)-N(R^6)(R^7), -CN, -O-R^6; or

X^5 and X^6 or X^6 and X^7 are joined to provide optionally substituted fused aryl or optionally substituted fused heteroaryl; and

with the proviso that at least one of X^2, X^3, and X^4 is C(R^4); at least two of X^5, X^6, X^7, and X^8 are C(R^4); and at least one of X^2, X^3, X^4, X^5, X^6, X^7 and X^8 is N;

or a pharmaceutically acceptable salt, or a mixture thereof.

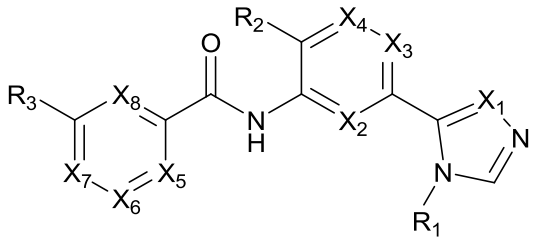
3. The use according to claim 1 or claim 2, wherein the ASK1 inhibitor has the following structure:



4. The use according to any one of claims 1 to 3, wherein the ASK1 inhibitor and the FXR agonist are administered together.

5. The use according to any one of claims 1 to 3, wherein the ASK1 inhibitor and the FXR agonist are administered separately.

6. A pharmaceutical composition comprising a therapeutically effective amount of an ASK1 inhibitor and a therapeutically effective amount of a FXR agonist, wherein the ASK1 inhibitor is a compound of formula (I):



(I)

wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to three substituents selected from halo, oxo, alkyl, cycloalkyl, heterocyclyl, aryl, aryloxy, $-NO_2$, R^6, $-C(O)-R^6$, $-OC(O)-R^6-C(O)-O-R^6$, $C(O)-N(R^6)(R^7)$, $-OC(O)-N(R^6)(R^7)$, $-S-R^6$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)(R^7)$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-N(R^6)-S(=O)_2-R^6$, -CN, and $-O-R^6$, and wherein the alkyl, cycloalkyl, heterocyclyl, phenyl, and phenoxy are optionally substituted by from one to three substituents selected from alkyl, cycloalkyl, alkoxy, hydroxyl, and halo; wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_1-C_{15} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, all of which are optionally substituted with from one to three substituents selected from halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, -CN, lower alkoxy, $-CF_3$, aryl, and heteroaryl; or

R^6 and R^7 when taken together with the nitrogen to which they are attached form a heterocycle;

R^2 is hydrogen, halo, cyano, alkoxy, or alkyl optionally substituted by halo;

R^3 is aryl, heteroaryl, or heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to five substituents selected from alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halo,

oxo, -NO_2, haloalkyl, haloalkoxy, -CN, -O-R^6, -O-C(O)-R^6, -O-C(O)-N(R^6)(R^7), -S-R^6, -N(R^6)(R^7), -S(=O)-R^6, -S(=O)$_2$$R^6$, -S(=O)$_2$-N($R^6$)($R^7$), -S(=O)$_2$-O-$R^6$, -N($R^6$)-C(O)-$R^7$, -N($R^6$)-C(O)-O-$R^7$, -N($R^6$)-C(O)-N($R^6$)($R^7$), -C(O)-$R^6$, -C(O)-$R^6$, -C(O)-N($R^6$)($R^7$), and -N($R^6$)-S(=O)$_2$-$R^7$, wherein the alkyl, alkoxy, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with from one to five substituents selected from halo, oxo, -NO_2, alkyl, haloalkyl, haloalkoxy, -N(R^6)(R^7), -C(O)-R^6, -C(O)-O-R^6, -C(O)-N(R^6)(R^7), -CN, -O-R^6, cycloalkyl, aryl, heteroaryl and heterocyclyl; with the proviso that the heteroaryl or heterocyclyl moiety includes at least one ring nitrogen atom;

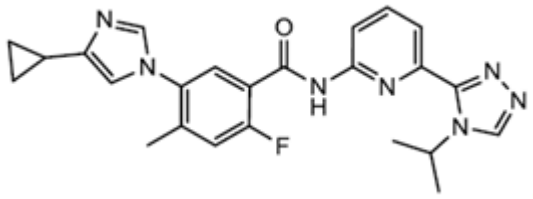
X^1, X^2, X^3, X^4, X^5, X^6, X^7 and X^8 are independently C(R^4) or N, in which each R^4 is independently hydrogen, alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, halo, -NO_2, haloalkyl, haloalkoxy, -CN, -O-R^6, -S-R^6, -N(R^6)(R^7), -S(=O)-R^6, -S(=O)$_2$$R^6$, -S(=O)$_2$-N($R^6$)($R^7$), -S(=O)$_2$-O-$R^6$, -N($R^6$)-C(O)-$R^7$, -N($R^6$)-C(O)-O-$R^7$, -N($R^6$)-C(O)-N($R^6$)($R^7$), -C(O)-$R^6$, -C(O)-O-$R^6$, -C(O)-N($R^6$)($R^7$), or -N($R^6$)-S(=O)$_2$-$R^7$, wherein the alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is further optionally substituted with from one to five substituents selected from halo, oxo, -NO_2, -CF_3, -O-CF_3, -N(R^6)(R^7), -C(O)-R^6, -C(O)-O-R^7, -C(O)-N(R^6)(R^7), -CN, -O-R^6; or

X^5 and X^6 or X^6 and X^7 are joined to provide optionally substituted fused aryl or optionally substituted fused heteroaryl; and

with the proviso that at least one of X^2, X^3, and X^4 is C(R^4); at least two of X^5, X^6, X^7, and X^8 are C(R^4); and at least one of X^2, X^3, X^4, X^5, X^6, X^7 and X^8 is N;

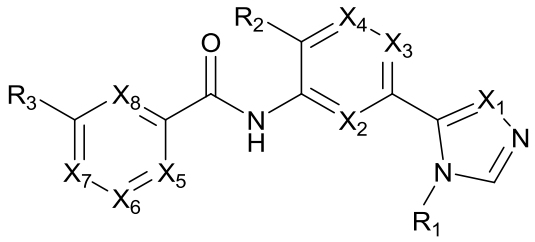
or a pharmaceutically acceptable salt, or a mixture thereof.

7. The pharmaceutical composition according to claim 6, wherein the ASK1 inhibitor has the following structure:



8. The pharmaceutical composition according to claim 6 or claim 7, further comprising a pharmaceutically acceptable carrier.

9. Use of a therapeutically effective amount of an ASK1 inhibitor and a therapeutically effective amount of a FXR agonist in the manufacture of a medicament for treating and/or preventing nonalcoholic steatohepatitis (NASH), wherein the ASK1 inhibitor is a compound of formula (I):



(I)

wherein:

R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to three substituents selected from halo, oxo, alkyl, cycloalkyl, heterocyclyl, aryl, aryloxy, $-NO_2$, R^6, $-C(O)-R^6$, $-OC(O)-R^6-C(O)-O-R^6$, $C(O)-N(R^6)(R^7)$, $-OC(O)-N(R^6)(R^7)$, $-S-R^6$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)(R^7)$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-N(R^6)-S(=O)_2-R^6$, -CN, and $-O-R^6$, and wherein the alkyl, cycloalkyl, heterocyclyl, phenyl, and phenoxy are optionally substituted by from one to three substituents selected from alkyl, cycloalkyl, alkoxy, hydroxyl, and halo; wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, C_1-C_{15} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, all of which are optionally substituted with from one to three substituents selected from halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, -CN, lower alkoxy, $-CF_3$, aryl, and heteroaryl; or

R^6 and R^7 when taken together with the nitrogen to which they are attached form a heterocycle;

R^2 is hydrogen, halo, cyano, alkoxy, or alkyl optionally substituted by halo;

R^3 is aryl, heteroaryl, or heterocyclyl, wherein the aryl, heteroaryl, and heterocyclyl are optionally substituted with from one to five substituents selected from alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halo, oxo, $-NO_2$, haloalkyl, haloalkoxy, -CN, $-O-R^6$, $-O-C(O)-R^6$, $-O-C(O)-N(R^6)(R^7)$, $-S-R^6$, $-N(R^6)(R^7)$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-R^6$, $-C(O)-N(R^6)(R^7)$, and $-N(R^6)-S(=O)_2-R^7$, wherein the alkyl, alkoxy, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with from one to five substituents selected from halo, oxo, $-NO_2$, alkyl, haloalkyl, haloalkoxy, $-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^6$, $-C(O)-N(R^6)(R^7)$, -CN, $-O-R^6$, cycloalkyl, aryl, heteroaryl and heterocyclyl; with the proviso that the heteroaryl or heterocyclyl moiety includes at least one ring nitrogen atom;

X^1, X^2, X^3, X^4, X^5, X^6, X^7 and X^8 are independently $C(R^4)$ or N, in which each R^4 is independently hydrogen, alkyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocyclyl, halo, $-NO_2$, haloalkyl, haloalkoxy, -CN, $-O-R^6$, $-S-R^6$, $-N(R^6)(R^7)$, $-S(=O)-R^6$, $-S(=O)_2R^6$, $-S(=O)_2-N(R^6)(R^7)$, $-S(=O)_2-O-R^6$, $-N(R^6)-C(O)-R^7$, $-N(R^6)-C(O)-O-R^7$, $-N(R^6)-C(O)-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^6$, $-C(O)-N(R^6)(R^7)$, or $-N(R^6)-S(=O)_2-R^7$, wherein the alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl is further optionally substituted with from one to five substituents selected from halo, oxo, $-NO_2$, $-CF_3$, $-O-CF_3$, $-N(R^6)(R^7)$, $-C(O)-R^6$, $-C(O)-O-R^7$, $-C(O)-N(R^6)(R^7)$, -CN, $-O-R^6$; or

X^5 and X^6 or X^6 and X^7 are joined to provide optionally substituted fused aryl or optionally substituted fused heteroaryl; and

with the proviso that at least one of X^2, X^3, and X^4 is $C(R^4)$; at least two of X^5, X^6, X^7, and X^8 are $C(R^4)$; and at least one of X^2, X^3, X^4, X^5, X^6, X^7 and X^8 is N;

or a pharmaceutically acceptable salt, or a mixture thereof.