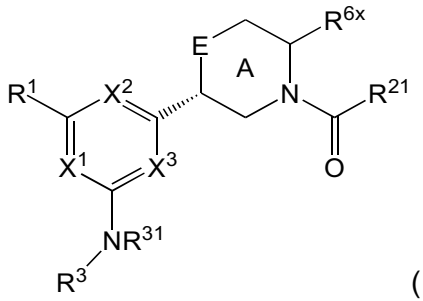
combination therapy.

BRIEF SUMMARY OF THE DISCLOSURE

The present disclosure provides methods of treating fibrotic disease preferrably idiopathic pulmonary fibrosis (IPF) or non-alcoholic steatohepatitis (NASH); methods of increasing survival time in an individual with fibrotic disease; and methods of reducing risk of death in an individual with fibrotic disease. The methods generally involve administering a therapeutically effective amount of compounds of the formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, to an individual with fibrotic disease.

In one aspect, there is provided a use of a compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, for the manufacture of a medicament for treating fibrotic disease



(I)

wherein

R^1 is selected from phenyl, a 5- or 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, S and N, wherein one or two carbon ring atoms of said monocyclic or said bicyclic heteroaryl are optionally oxidized, and wherein said phenyl, said 5- or 6-membered monocyclic heteroaryl and said 8-10 membered bicyclic heteroaryl is independently optionally substituted with one or more substituents selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, –O–C_{1-6} alkyl, –O–C_{1-6} haloalkyl, OH, –(C_{1-2}alkylene)–O–(C_{1-4}alkylene)–OR*, –O–(C_{1-4}alkylene)–OR*, –(C_{1-2}alkylene)–O–(C_{1-4}alkylene)–N(R°°)$_2$, –O–(C_{1-4}alkylene)–N(R°°)$_2$, CN, =O, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R*)–C(O)R*, –N(R*)–C(O)–OR*, –N(R*)–C(O)–NR*R*, –O–C(O)R*, –O–C(O)–NR*R*, and 3-6 membered monocyclic carbocyclyl and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, S and N, each monocyclic carbocyclyl and heterocyclyl independently optionally substituted with one or more substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, –O–C_{1-4} alkyl, –O–C_{1-4} haloalkyl, –OH, =O, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, C_{1-4}

alkyl, $C_{1–4}$ haloalkyl, and wherein each R°° is independently selected from H, $C_{1–4}$ alkyl, or together with the nitrogen atom to which they are attached form a six-membered monocyclic heterocyclyl, and/or wherein each monocyclic heterocyclyl is independently optionally substituted with one bivalent substituent selected from C_{1-3} alkylene, C_{1-3} alkylene substituted with 1 to 4 F, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH$;

R^{21} is selected from $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl and $C_{3–4}$ cycloalkyl;

R^3 is selected from phenyl, a 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, B, S and N, wherein one or two carbon ring atoms of said monocyclic or said bicyclic heteroaryl are optionally oxidized, and wherein said phenyl, said 6-membered monocyclic heteroaryl and said 8-10 membered bicyclic heteroaryl is independently optionally substituted with one or more substituents selected from halogen, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $–O–C_{1–6}$ alkyl, $–O–C_{1–6}$ haloalkyl, –OH, –CN, =O, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R**)–C(O)R*, –N(R**)–C(O)–OR*, –N(R**)–C(O)–NR*R*, –O–C(O)R*, –O–C(O)–NR*R*, and 3-6 membered monocyclic carbocyclyl and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, B, S and N, each monocyclic carbocyclyl and heterocyclyl independently optionally substituted with one or more substituents independently selected from halogen, cyclopropyl, $–C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, $–O–C_{1–4}$ alkyl, $–O-C_{1–4}$ haloalkyl, –OH, =O, $–C_{1-3}$alkylene–OR*, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, cyclopropyl, cyclobutyl, oxetanyl, $–C_{1-2}$alkylene–OH, $–C_{1-2}$alkylene–$O-C_{1–2}$alkyl, phenyl, and wherein each R** is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and/or wherein each monocyclic heterocyclyl is independently optionally substituted with one bivalent substituent selected from C_{1-3} alkylene such as $-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-$, C_{1-3} alkylene substituted with 1 to 4 F, $-CH_2-O-CH_2-$ and $-CH_2-NH-CH_2$;

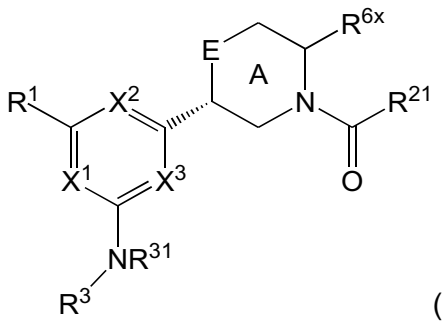
X^1 is CH;

X^2 and X^3 are N;

R^{31} is hydrogen; and

E is$–CH_2–$;

R^{6x} is selected from $C_{1–3}$ alkyl and $C_{1–2}$ haloalkyl, Thus, in an example, the present disclosure provides a compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, for use in a method of treating fibrotic disease



(I)

wherein

R^1 is selected from halogen and –(optionally substituted hydrocarbon group which contains from 1 to 20 carbon atoms and optionally 1 to 15 heteroatoms selected from O, N and S);

R^{21} is selected from hydrogen, –(optionally substituted $C_{1–6}$ alkyl) which may contain one to three oxygen atoms between carbon atoms, and –(optionally substituted $C_{3–6}$ cycloalkyl);

R^3 is selected from –(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted heterocyclyl) and –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted carbocyclyl);

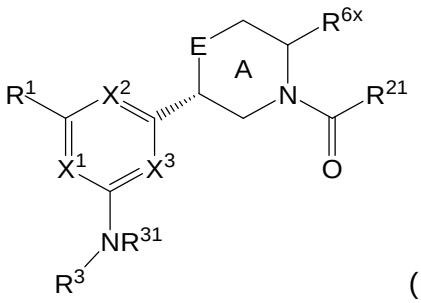
each of X^1, X^2 and X^3 is independently selected from N, CH and CR^x, wherein at least one of said X^1, X^2 and X^3 is N, wherein further preferably at least one of said X^2 and X^3 is N; and

wherein again further preferably X^2 and X^3 are both N, and wherein still further preferably X^2 and X^3 are both N, and X^1 is CH;

R^{31} is selected from –hydrogen, $–C_{1-6}$-alkyl, and –(C_{1-6}-alkyl substituted with one or more F); wherein R^3 and any R^{31} can be optionally linked; and

CLAIMS

1. Use of a compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, solvate, cocrystal, tautomer, racemate, enantiomer, or diastereomer or mixture thereof, for the manufacture of a medicament for treating fibrotic disease



(I)

wherein

R^1 is selected from phenyl, a 5- or 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, S and N, wherein one or two carbon ring atoms of said monocyclic or said bicyclic heteroaryl are optionally oxidized, and wherein said phenyl, said 5- or 6-membered monocyclic heteroaryl and said 8-10 membered bicyclic heteroaryl is independently optionally substituted with one or more substituents selected from halogen, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, –O–$C_{1–6}$ alkyl, –O–$C_{1–6}$ haloalkyl, OH, –($C_{1–2}$alkylene)–O–($C_{1–4}$alkylene)–OR*, –O–($C_{1–4}$alkylene)–OR*, –($C_{1–2}$alkylene)–O–($C_{1–4}$alkylene)–N(R°°)$_2$, –O–($C_{1–4}$alkylene)–N(R°°)$_2$, CN, =O, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R*)–C(O)R*, –N(R*)–C(O)–OR*, –N(R*)–C(O)–NR*R*, –O–C(O)R*, –O–C(O)–NR*R*, and 3-6 membered monocyclic carbocyclyl and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, S and N, each monocyclic carbocyclyl and heterocyclyl independently optionally substituted with one or more substituents independently selected from halogen, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, –O–$C_{1–4}$ alkyl, –O–$C_{1–4}$ haloalkyl, –OH, =O, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and wherein each R°° is independently selected from H, $C_{1–4}$ alkyl, or together with the nitrogen atom to which they are attached form a six-membered monocyclic heterocyclyl, and/or wherein each monocyclic heterocyclyl is independently optionally substituted with one bivalent substituent selected from C_{1-3} alkylene, C_{1-3} alkylene substituted with 1 to 4 F, -CH_2-O-CH_2- and -CH_2-NH-CH_2;

R^{21} is selected from $C_{1–2}$ alkyl, $C_{1–2}$ haloalkyl and $C_{3–4}$ cycloalkyl;

R^3 is selected from phenyl, a 6-membered monocyclic heteroaryl and a 8-10 membered bicyclic heteroaryl, each independently comprising one or more ring heteroatoms independently selected from O, B, S and N, wherein one or two carbon ring atoms of said monocyclic or said bicyclic heteroaryl are optionally oxidized, and wherein said

phenyl, said 6-membered monocyclic heteroaryl and said 8-10 membered bicyclic heteroaryl is independently optionally substituted with one or more substituents selected from halogen, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, –O–$C_{1–6}$ alkyl, –O–$C_{1–6}$ haloalkyl, –OH, –CN, =O, –C(O)R*, –COOR*, –C(O)NR*R*, –NR*R*, –N(R**)–C(O)R*, –N(R**)–C(O)–OR*, –N(R**)–C(O)–NR*R*, –O–C(O)R*, –O–C(O)–NR*R*, and 3-6 membered monocyclic carbocyclyl and 3-6 membered monocyclic heterocyclyl comprising 1 to 4 heteroatoms selected from O, B, S and N, each monocyclic carbocyclyl and heterocyclyl independently optionally substituted with one or more substituents independently selected from halogen, cyclopropyl, –$C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, –O–$C_{1–4}$ alkyl, –O-$C_{1–4}$ haloalkyl, –OH, =O, –C_{1-3}alkylene–OR*, –C(O)R* and –C(O)NR*R*; wherein each R* is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, cyclopropyl, cyclobutyl, oxetanyl, –C_{1-2}alkylene–OH, –C_{1-2}alkylene–O-$C_{1–2}$alkyl, phenyl, and wherein each R** is independently selected from H, $C_{1–4}$ alkyl, $C_{1–4}$ haloalkyl, and/or wherein each monocyclic heterocyclyl is independently optionally substituted with one bivalent substituent selected from C_{1-3} alkylene such as -CH_2-CH_2- and -CH_2-CH_2-CH_2-, C_{1-3} alkylene substituted with 1 to 4 F, -CH_2-O-CH_2- and -CH_2-NH-CH_2;

X^1 is CH;

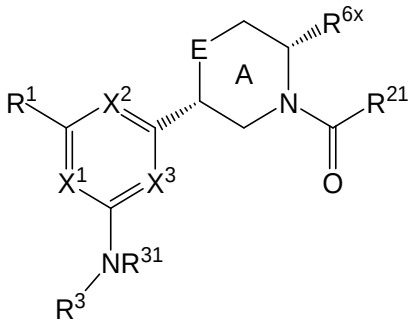
X^2 and X^3 are N;

R^{31} is hydrogen; and

E is–CH_2–; and

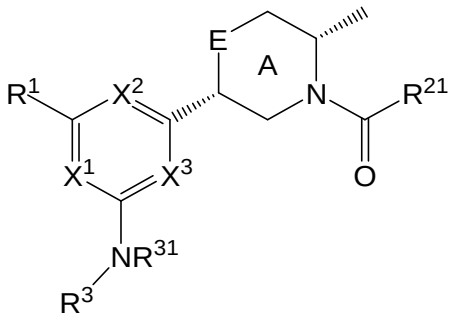
R^{6x} is selected from $C_{1–3}$ alkyl and $C_{1–2}$ haloalkyl.

2. The use according to claim 1, wherein the compound of formula (I) is a compound of formula (V)



(V),

3. The use according to claim 1 or claim 2, wherein the compound of formula (I) is a compound of formula (VI)



(VI)

4. The use according to any one of the preceding claims, wherein R^{21} is CH_3.

5. The use according to any one of the preceding claims, wherein
R^{21} is CH_3; and
R^{6x} is CH_3.

6. The use according to any preceding claim, wherein the fibrotic disease is selected from the group consisting of pulmonary fibrosis, idiopathic pulmonary fibrosis, radiation-induced pneumonitis, radiation fibrosis, acute respiratory distress syndrome, chronic obstructive pulmonary disease, interstitial lung disease, myocardial infarction, cardiac fibrosis and hypertrophy, ischemic stroke, ischemic kidney disease, renal fibrosis, rheumatoid arthritis, liver fibrosis, NASH (non-alcoholic steatohepatitis), chronic hepatitis, cirrhosis, inflammatory bowel disease, Crohn's disease, scleroderma, keloid, post-operative fibrosis, chemotherapy induced fibrosis (e.g., chemotherapy induced pulmonary fibrosis or ovarian cortical fibrosis), nephrogenic systemic fibrosis, retroperitoneal fibrosis, myelofibrosis, mediastinal fibrosis, cystic fibrosis, asbestosis, asthma, pulmonary hypertension, systemic fibrosis, skin fibrosis, hypertension induced renal and cardiac fibrosis.

7. The use according to claim 6, wherein the fibrotic disease is interstitial lung disease (IDL), optionally the interstitial lung disease is idiopathic interstitial pneumonia (IIP).

8. The use according to claim 7, wherein the idiopathic interstitial pneumonia is selected from the group consisting of chronic fibrosing interstitial pneumonia, smoking-related interstitial pneumonia and acute/subacute interstitial pneumonia.

9. The use according to claim 8, wherein the chronic fibrosing interstitial pneumonia is idiopathic pulmonary fibrosis (IPF).

10. The use according to claim 6, wherein the fibrotic disease is non-alcoholic steatohepatitis (NASH).