including a high resolution computer tomographic scan (HRCT), and open lung or transbronchial biopsies. However, in a significant number of patients, no underlying cause for the pulmonary fibrosis can be found. These conditions of unknown etiology have been termed idiopathic interstitial pneumonias. Histologic examination of tissue obtained at open lung biopsy allows classification of these patients into several categories, including Usual Interstitial Pneumonia (UIP), Desquamative Interstitial Pneumonia (DIP), and Non-Specific Interstitial Pneumonia (NSIP).

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia and is characterized by the UIP pattern on histology. Idiopathic pulmonary fibrosis and other interstitial lung diseases (ILD) are severe conditions of progressive lung scarring with extracellular matrix deposition and lung matrix destruction leading to loss of lung function. IPF pathology is chronic and progressive. IPF is ultimately fatal with a median survival of 3.8 years. Anti-inflammatory, immunosuppressive therapies including corticosteroids have shown limited efficacy in treating IPF. Recommended pharmacologic treatment options for pulmonary fibrosis currently consist of the anti-fibrotic effects of Nintedanib and of Pirfenidone. Nintedanib acts as a multi receptor tyrosine kinase (RTK) inhibitor, blocking VEGF-, FGF- and PDGF-receptor signalling, thereby reducing fibroblast proliferation and differentiation. Pirfenidone interferes with TGF-β signalling thus reducing fibroblast proliferation and differentiation into myofibroblasts.

Both pharmacologic interventions at most achieve a prolongation of progression free survival or reduce the disease burden without a benefit on patient survival. An important unmet need is thus to identify new molecular targets and agents that interfere with key molecular pathways involved in pulmonary fibrosis pathology to prevent progression or reverse fibrosis in patients.

Hepatic steatosis, also sometimes referred to as fatty liver disease, is a condition generally characterized by an abnormal retention of lipids in cells of the liver. Fatty liver disease can have various causes. For example, non-alcoholic fatty liver disease (NAFLD) generally refers to a spectrum of hepatic lipid disorders characterized by hepatic steatosis with no known secondary cause. NAFLD can be subcategorized into (a) nonalcoholic fatty liver (NAFL), defined as the presence of steatosis in the absence of histological evidence of hepatocellular injury, and (b) non-alcoholic steatohepatitis (NASH), hepatic steatosis accompanied by hepatocyte injury and inflammation; NASH may occur with or without fibrosis, but may progress to fibrosis and cirrhosis. There are presently no approved pharmaceuticals for the treatment of NAFLD/NASH.

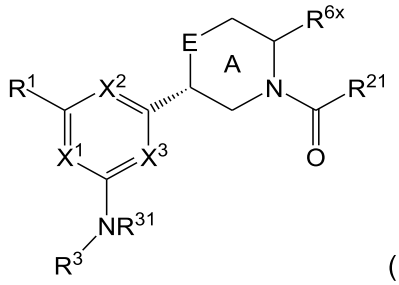
Thus, an objective of the present disclosure is to provide compounds which are able to treat fibrosis or to prevent the development of fibrosis. Furthermore, it is an objective of the present disclosure to provide improved treatment options for patients suffering from fibrotic disease, preferably idiopathic pulmonary fibrosis using the compounds of the disclosure alone or in

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 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-heterocyclyl, and optionally substituted $C_{1–6}$ alkylene-carbocyclyl);

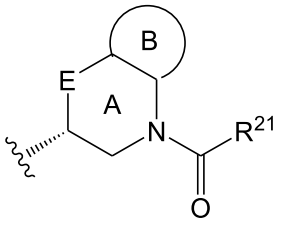
each of X^1, X^2 and X^3 is independently selected from N, CH and CR^x, wherein at least one of said X^1, X^2 and X^3 is N;

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

E is either absent or is selected from $–CH_2–$, $–CHR^x–$, $–CR^x_2–$, –NH–, $–NR^x–$, –O–, $–L^1–L^2–$ and $–L^2–L^1–$, wherein L^1 is selected from $–CH_2–$, $–CHR^x–$, $–CR^x_2–$, –NH–, $–NR^x–$ and –O– and L^2 is selected from $–CH_2–$, $–CHR^x–$ and $–CR^x_2–$;

R^{6x} is halogen, OH, =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with one or more OH, monocyclic aryl optionally substituted with one or more R^{xb}, monocyclic heteroaryl optionally substituted with one or more R^{xb}, monocyclic cycloalkyl optionally substituted with one or more R^{xb}, monocyclic heterocycloalkyl optionally substituted with one or more R^{xb}, monocyclic cycloalkenyl optionally substituted with one or more R^{xb}, monocyclic heterocycloalkenyl optionally substituted with one or more R^{xb}, wherein said R^{xb} is independently selected from halogen, OH, =O, C_{1-4} alkyl, C_{1-2} haloalkyl, C_{1-2} alkyl substituted with one or two OH;

wherein Ring A may further be substituted with one or more groups R^x, wherein any two R^x groups at ring A can be optionally linked and/or any R^x group at ring A can be optionally linked with R^{21}; and/or wherein Ring A may be further substituted with one group R^x so as to form together with R^{6x} a bicyclic moiety having the following partial structure:



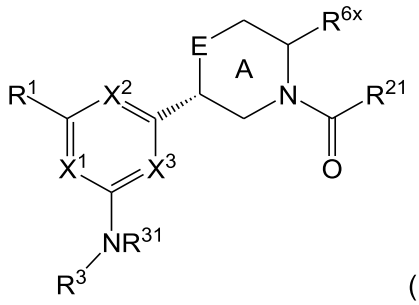
wherein Ring B is an optionally substituted heterocycle or optionally substituted carbocycle;

each R^x is independently selected from halogen, OH, optionally substituted O-C_{1-6} alkyl, optionally substituted NH-C_{1-6} alkyl), optionally substituted N(C_{1-6} alkyl)$_2$, =O, optionally substituted C_{1-6} alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted C_{1-6} alkylene-carbocyclyl), optionally substituted C_{1-6} alkylene-heterocyclyl), optionally substituted O-C_{1-6} alkylene-carbocyclyl, and optionally substituted O-C_{1-6} alkylene-heterocyclyl, and

wherein the optional substituent of the optionally substituted hydrocarbon group, optionally substituted C_{3-6} cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocycle, optionally substituted carbocyclyl, optionally substituted carbocycle and optionally substituted C_{1-6} alkylene is independently selected from C_{1-6} alkyl which is optionally substituted with one or more halogen, halogen, CN, NO_2, oxo, –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*, –N(R*)–$S(O)_2$R*, –OR*, –O–C(O)R*, –O–C(O)–NR*R*, –SR*, –S(O)R*, –$S(O)_2$R*, –$S(O)_2$–NR*R*, –N(R*)–$S(O)_2$–NR*R*, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein each R* is independently selected from H, C_{1-6} alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R* connected to the same nitrogen atom can be optionally linked, and

wherein the optional substituent of the optionally substituted $C_{1–6}$ alkyl and of the optionally substituted $C_{1–6}$ alkylene is independently selected from –halogen, –CN, $–NO_2$, oxo, –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**, $–N(R^{**})–S(O)_2R^{**}$, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, $–S(O)_2R^{**}$, $–S(O)_2–NR^{**}R^{**}$, and $–N(R^{**})–S(O)_2–NR^{**}R^{**}$; wherein R** is independently selected from H, $C_{1–6}$ alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R** connected to the same nitrogen atom can be optionally linked.

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);

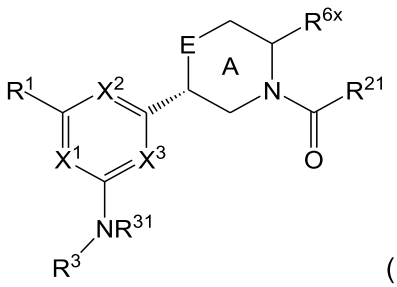
R^3 is selected from –(optionally substituted heterocyclyl), –(optionally substituted carbocyclyl), –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted heterocyclyl) and –(optionally substituted $C_{1–6}$ alkylene)–(optionally substituted carbocyclyl);

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

alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R* connected to the same nitrogen atom can be optionally linked, and wherein the optional substituent of the optionally substituted C_{1-6} alkyl and of the optionally substituted C_{1-6} alkylene is independently selected from –halogen, –CN, $–NO_2$, oxo, –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**, –N(R**)–$S(O)_2$R**, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, –$S(O)_2$R**, –$S(O)_2$–NR**R**, and –N(R**)–$S(O)_2$–NR**R**; wherein R** is independently selected from H, C_{1-6} alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R** connected to the same nitrogen atom can be optionally linked.

In particular, 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-heterocyclyl, and optionally substituted C_{1-6} alkylene-carbocyclyl);

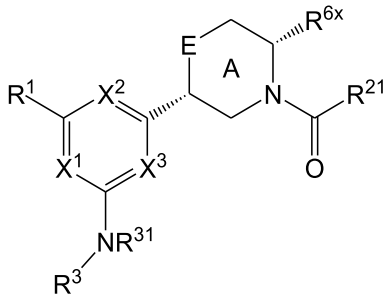
each of X^1, X^2 and X^3 is independently selected from N, CH and CR^x, wherein at least one of said X^1, X^2 and X^3 is N;

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

E is either absent or is selected from $–CH_2–$, $–CHR^x–$, $–CR^x{}_2–$, –NH–, $–NR^x–$, –O–, $–L^1–L^2–$ and $–L^2–L^1–$, wherein L^1 is selected from $–CH_2–$, $–CHR^x–$, $–CR^x{}_2–$, –NH–, $–NR^x–$ and –O– and L^2 is selected from $–CH_2–$, $–CHR^x–$ and $–CR^x{}_2–$;

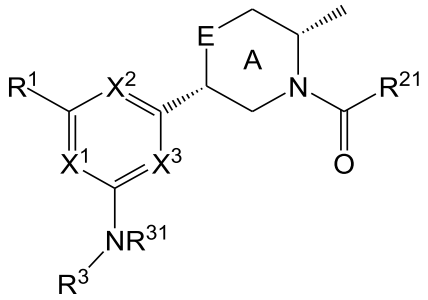
wherein the optional substituent of the optionally substituted $C_{1–6}$ alkyl and of the optionally substituted $C_{1–6}$ alkylene is independently selected from –halogen, –CN, $–NO_2$, oxo, –C(O)R**, –COOR**, –C(O)NR**R**, –NR**R**, –N(R**)–C(O)R**, –N(R**)–C(O)–OR**, –N(R**)–C(O)–NR**R**, $–N(R^{**})–S(O)_2R^{**}$, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, $–S(O)_2R^{**}$, $–S(O)_2–NR^{**}R^{**}$, and $–N(R^{**})–S(O)_2–NR^{**}R^{**}$; wherein R** is independently selected from H, $C_{1–6}$ alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R** connected to the same nitrogen atom can be optionally linked.

In a preferred example of the disclosure, the compound of formula (I) is a compound of formula (V)



(V),

In a more preferred example of the disclosure, the compound of formula (I) is a compound of formula (VI)



(VI)

In another preferred example of the disclosure, X^2 and X^3 are N, and wherein preferably X^1 is CH.

In another preferred example of the disclosure, R^{21} is CH_3 or CH_2CH_3, and wherein preferably R^{21} is CH_3.

In another preferred example of the disclosure, R^{31} is selected from hydrogen and C_{1-2}-alkyl, and wherein preferably R^{31} is hydrogen.

In another preferred example of the disclosure, E is selected from $–CH_2–$, –O–, $–CH_2–O–$ and $–CH_2–CH_2–$, and wherein preferably E is $–CH_2–$.

In another preferred example of the disclosure, the number of groups R^x in Ring A is 0, 1, or 2, and wherein preferably each R^x is independently selected from halogen, OH, $O–C_{1–2}$ alkyl

optionally substituted with one or more R^{xa}, NH–$C_{1–2}$ alkyl optionally substituted with one or more R^{xa}, N($C_{1–2}$ alkyl)$_2$ optionally substituted with one or more R^{xa}, =O, $C_{1–3}$ alkyl optionally substituted with one or more R^{xa}, $C_{1–2}$ haloalkyl, –W–monocyclic carbocyclyl optionally substituted with one or more R^{xa}, –W–monocyclic heterocyclyl optionally substituted with one or more R^{xa}, and wherein –W– is absent, –$C_{1–2}$ alkylene– or –O–$C_{1–2}$ alkylene–, and wherein monocyclic carbocyclyl is selected from phenyl and $C_{3–6}$ cycloalkyl, and wherein monocyclic heterocyclyl is selected from thiophenyl, pyridyl, pyrazinyl and pyrimidinyl, and wherein said R^{xa} is independently selected from Cl, F, and OH.

In another preferred example of the disclosure, R^1 is selected from optionally substituted heterocyclyl and optionally substituted carbocyclyl, and wherein preferably 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, 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/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-.

In another preferred example of the disclosure, 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-.

In another preferred example of the disclosure,

X^2 and X^3 are N, and X^1 is CH;

E is –CH_2–;

R^{21} is CH_3;

R^{6x} is CH_3; and

Ring A does not form a bicyclic moiety.

In another preferred example of the disclosure, 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.

In another preferred example of the disclosure, the fibrotic disease is interstitial lung disease (IDL), optionally the interstitial lung disease is idiopathic interstitial pneumonia (IIP).

In a more preferred example of the disclosure, the idiopathic interstitial pneumonia is selected from the group consisting of chronic fibrosing interstitial pneumonia, smoking-related interstitial pneumonia and acute/subacute interstitial pneumonia.

In another more preferred example of the disclosure, the chronic fibrosing interstitial pneumonia is idiopathic pulmonary fibrosis (IPF).

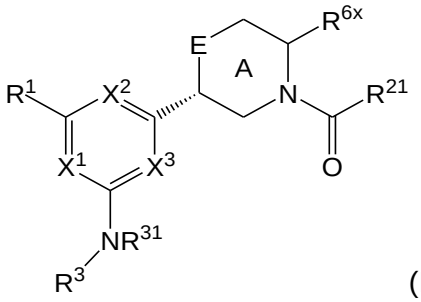
In another preferred example of the disclosure, the fibrotic disease is non-hepatic steatohepatitis (NASH).

Further examples and examples of the present disclosure will be become apparent as this description continues.

DESCRIPTION OF FIGURES

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 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-heterocyclyl, and optionally substituted $C_{1–6}$ alkylene-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;

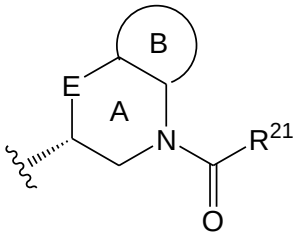
R^{31} is selected from hydrogen, C_{1-6}-alkyl, and C_{1-6}-alkyl substituted with one or more F; wherein R^3 and any R^{31} can be optionally linked; and

E is either absent or is selected from $–CH_2–$, $–CHR^x–$, $–CR^x_2–$, –NH–, $–NR^x–$, –O–, $–L^1–L^2–$ and $–L^2–L^1–$, wherein L^1 is selected from $–CH_2–$, $–CHR^x–$, $–CR^x_2–$, –NH–, $–NR^x–$ and –O– and L^2 is selected from $–CH_2–$, $–CHR^x–$ and $–CR^x_2–$;

R^{6x} is halogen, OH, =O, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ alkyl substituted with one or more OH, monocyclic aryl optionally substituted with one or more R^{xb}, monocyclic heteroaryl optionally substituted with one or more R^{xb}, monocyclic cycloalkyl optionally substituted with one or more R^{xb}, monocyclic heterocycloalkyl optionally substituted with one or more R^{xb}, monocyclic cycloalkenyl optionally substituted with one or more R^{xb}, monocyclic heterocycloalkenyl optionally substituted with one or more R^{xb}, wherein said R^{xb} is independently selected from halogen, OH, =O, $C_{1–4}$ alkyl, $C_{1–2}$ haloalkyl, $C_{1–2}$ alkyl substituted with one or two OH;

wherein Ring A may further be substituted with one or more groups R^x, wherein any two R^x groups at ring A can be optionally linked and/or any R^x group at ring A can be optionally

linked with R^{21}; and/or wherein Ring A may be further substituted with one group R^x so as to form together with R^{6x} a bicyclic moiety having the following partial structure:



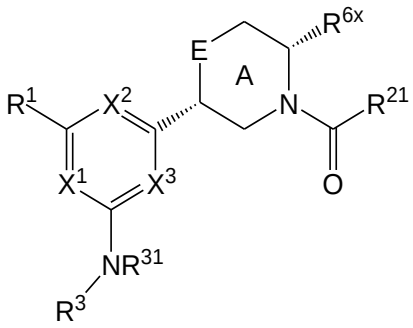
wherein Ring B is an optionally substituted heterocycle or optionally substituted carbocycle;

each R^x is independently selected from halogen, OH, optionally substituted O-$C_{1–6}$ alkyl, optionally substituted NH-$C_{1–6}$ alkyl), optionally substituted N($C_{1–6}$ alkyl)$_2$, =O, optionally substituted $C_{1–6}$ alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted $C_{1–6}$ alkylene-carbocyclyl), optionally substituted $C_{1–6}$ alkylene-heterocyclyl), optionally substituted O-$C_{1–6}$ alkylene-carbocyclyl, and optionally substituted O-$C_{1–6}$ alkylene-heterocyclyl, and

wherein the optional substituent of the optionally substituted hydrocarbon group, optionally substituted $C_{3–6}$ cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocycle, optionally substituted carbocyclyl, optionally substituted carbocycle and optionally substituted $C_{1–6}$ alkylene is independently selected from $C_{1–6}$ alkyl which is optionally substituted with one or more halogen, halogen, CN, NO_2, oxo, –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*, –N(R*)–$S(O)_2$R*, –OR*, –O–C(O)R*, –O–C(O)–NR*R*, –SR*, –S(O)R*, –$S(O)_2$R*, –$S(O)_2$–NR*R*, –N(R*)–$S(O)_2$–NR*R*, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein each R* is independently selected from H, $C_{1–6}$ alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R* connected to the same nitrogen atom can be optionally linked, and

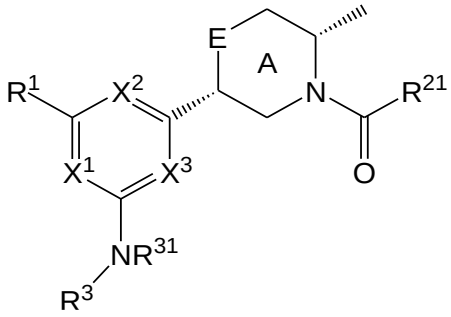
wherein the optional substituent of the optionally substituted $C_{1–6}$ alkyl and of the optionally substituted $C_{1–6}$ alkylene is independently selected from –halogen, –CN, –NO_2, oxo, –C(O)R**, –COOR**, –C(O)NR**R**, –NR**R**, –N(R**)–C(O)R**, –N(R**)–C(O)–OR**, –N(R**)–C(O)–NR**R**, –N(R**)–$S(O)_2$R**, –OR**, –O–C(O)R**, –O–C(O)–NR**R**, –SR**, –S(O)R**, –$S(O)_2$R**, –$S(O)_2$–NR**R**, and –N(R**)–$S(O)_2$–NR**R**; wherein R** is independently selected from H, $C_{1–6}$ alkyl which is optionally substituted with halogen, heterocyclyl which is optionally substituted with halogen or C_{1-6} alkyl, and carbocyclyl which is optionally substituted with halogen or C_{1-6} alkyl; wherein any two R** connected to the same nitrogen atom can be optionally linked.

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 X^2 and X^3 are N, and wherein preferably X^1 is CH.

5. The use according to any one of the preceding claims, wherein R^{21} is CH_3 or CH_2CH_3, and wherein preferably R^{21} is CH_3.

6. The use according to any one of the preceding claims, wherein R^{31} is selected from hydrogen and C_{1-2}-alkyl, and wherein preferably R^{31} is hydrogen.

7. The use according to any one of the preceding claims, wherein E is selected from $–CH_2–$, –O–, $–CH_2–O–$ and $–CH_2–CH_2–$, and wherein preferably E is $–CH_2–$.

8. The use according to any one of the preceding claims, wherein the number of groups R^x in Ring A is 0, 1, or 2, and wherein preferably each R^x is independently selected from halogen, OH, $O–C_{1–2}$ alkyl optionally substituted with one or more R^{xa}, $NH–C_{1–2}$ alkyl optionally substituted with one or more R^{xa}, $N(C_{1–2}$ alkyl$)_2$ optionally substituted with one or more R^{xa}, =O, $C_{1–3}$ alkyl optionally substituted with one or more R^{xa}, $C_{1–2}$ haloalkyl, –W–monocyclic carbocyclyl optionally substituted with one or more R^{xa}, –W–monocyclic

heterocyclyl optionally substituted with one or more R^{xa}, and wherein –W– is absent, $–C_{1–2}$ alkylene– or $–O–C_{1–2}$ alkylene–, and wherein monocyclic carbocyclyl is selected from phenyl and $C_{3–6}$ cycloalkyl, and wherein monocyclic heterocyclyl is selected from thiophenyl, pyridyl, pyrazinyl and pyrimidinyl, and wherein said R^{xa} is independently selected from Cl, F, and OH.

9. The use according to any one of the preceding claims, wherein R^1 is selected from optionally substituted heterocyclyl and optionally substituted carbocyclyl, and wherein preferably 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, 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/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 $-CH_2-NH-CH_2-$.

10. The use according to any one of the preceding claims, wherein 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-.

11. The use according to any one of the preceding claims, wherein
X^2 and X^3 are N, and X^1 is CH;
E is –CH_2–;
R^{21} is CH_3;
R^{6x} is CH_3; and
Ring A does not form a bicyclic moiety.

12. 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.

13. The use according to claim 12, wherein the fibrotic disease is interstitial lung disease (IDL), optionally the interstitial lung disease is idiopathic interstitial pneumonia (IIP).

14. The use according to claim 13, 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.

15. The use according to claim 14, wherein the chronic fibrosing interstitial pneumonia is idiopathic pulmonary fibrosis (IPF).

16. The use according to claim 12, wherein the fibrotic disease is non-hepatic steatohepatitis (NASH).