

q is 1, 2, or 3;

r is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

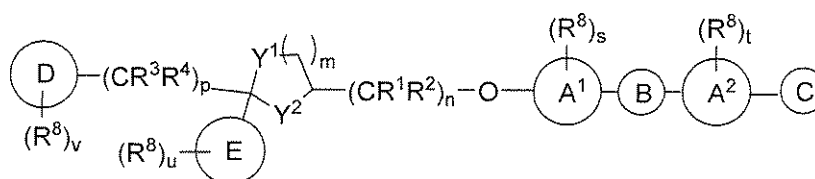
s is 0, 1, 2, 3, or 4;

t is 0, 1, 2, 3, or 4;

u is 0, 1, 2, 3, 4 or 5; and

v is 0, 1, 2, 3, or 4.

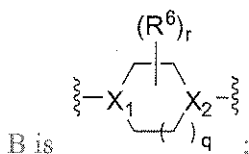
[0004a] In another aspect, there is provided the use of a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (I)

wherein:

A¹ and A² are independently selected from aryl or heteroaryl;



C is optionally substituted 5- or 6-membered heterocyclyl or optionally substituted 5- or 6-membered heteroaryl, wherein the heterocyclyl or the heteroaryl contains 1 to 4 nitrogen atoms;

D is aryl or heteroaryl;

E is aryl, heteroaryl, carbocyclyl, heterocyclyl, or alkyl;

each R¹, R², R³, and R⁴ is independently selected from H, alkyl, haloalkyl, or alkoxy;

X₁ and X₂ are independently selected from N and CR⁵;

R⁵ is H, OH, alkyl, or alkoxy;

each R⁶ is independently alkyl, haloalkyl, halo, alkoxy, -alkylene(NR¹³R¹⁴), or aryl;

each R⁸ is independently selected from alkyl, cycloalkyl, heterocyclyl, halo, hydroxy, nitrile, azido, nitro, alkoxy, haloalkoxy, haloalkyl, hydroxyalkyl, alkoxyalkyl, -alkylene(NR¹³R¹⁴), -alkylene(cycloalkyl), -alkylene(heterocyclyl), aryl, heteroaryl, -SR¹³, -SOR¹³, -SO₂R¹³, -SO₂NR¹³R¹⁴, -NR¹³R¹⁴, -NR¹³SO₂R¹⁴, -NR¹³C(O)R¹⁴, -NR¹³C(O)OR¹⁴, -NR¹³C(O)NR¹³R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, and -C(O)NR¹³R¹⁴; or two adjacent R⁸ form a heterocyclyl ring;

each R¹³ and R¹⁴ is independently selected from H, alkyl, cycloalkyl, heterocyclylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl, aryl,

and heteroaryl; or R^{13} and R^{14} taken together form a heterocycle with the atoms to which they are attached;

Y^1 and Y^2 are independently selected from O, CH_2 , NH, and NR^{13} ;

n is 1, 2, or 3;

m is 1 or 2;

p is 1, 2, 3, or 4;

q is 1, 2, or 3;

r is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

s is 0, 1, 2, 3, or 4;

t is 0, 1, 2, 3, or 4;

u is 0, 1, 2, 3, 4 or 5; and

v is 0, 1, 2, 3, or 4, in the manufacture of a medicament for treating fibrosis, a disorder characterized by fibrosis, or a disease characterized by fibrosis.

[0005] In some embodiments described above or below of a compound of Formula (I), X_1 and X_2 are N

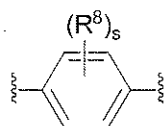
[0006] In some embodiments described above or below of a compound of Formula (I), X_1 is CR^5 and X_2 is N..

[0007] In some embodiments described above or below of a compound of Formula (I), X_1 is N and X_2 is CR^5 .

[0008] In some embodiments described above or below of a compound of Formula (I), q is 1 and r is 0.

[0009] In some embodiments described above or below of a compound of Formula (I), A^1 is aryl.

[0010] In some embodiments described above or below of a compound of Formula (I), A^1 is



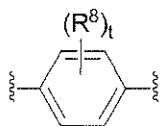
[0011] In some embodiments described above or below of a compound of Formula (I), A^1 is



[0012] In some embodiments described above or below of a compound of Formula (I), A^1 is heteroaryl.

[0013] In some embodiments described above or below of a compound of Formula (I), A^2 is aryl.

[0014] In some embodiments described above or below of a compound of Formula (I), A² is



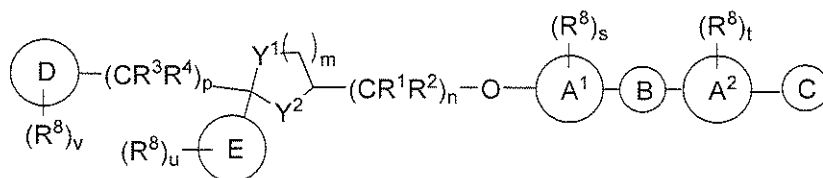
[0015] In some embodiments described above or below of a compound of Formula (I), A² is



[0016] In some embodiments described above or below of a compound of Formula (I), A² is heteroaryl.

CLAIMS

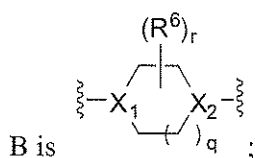
1. ~~A method to treat fibrosis, a disorder characterized by fibrosis, or a disease characterized by fibrosis, the method comprising administering a composition comprising Use of a~~ therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (I)

wherein:

A¹ and A² are independently selected from aryl or heteroaryl;



C is optionally substituted 5- or 6-membered heterocyclyl or optionally substituted 5- or 6-membered heteroaryl, wherein the heterocyclyl or the heteroaryl contains 1 to 4 nitrogen atoms;

D is aryl or heteroaryl;

E is aryl, heteroaryl, carbocyclyl, heterocyclyl, or alkyl;

each R¹, R², R³, and R⁴ is independently selected from H, alkyl, haloalkyl, or alkoxy;

X₁ and X₂ are independently selected from N and CR⁵;

R⁵ is H, OH, alkyl, or alkoxy;

each R⁶ is independently alkyl, haloalkyl, halo, alkoxy, -alkylene(NR¹³R¹⁴), or aryl;

each R⁸ is independently selected from alkyl, cycloalkyl, heterocyclyl, halo, hydroxy, nitrile, azido, nitro, alkoxy, haloalkoxy, haloalkyl, hydroxyalkyl, alkoxyalkyl, -alkylene(NR¹³R¹⁴), -alkylene(cycloalkyl), -alkylene(heterocyclyl), aryl, heteroaryl, -SR¹³, -SOR¹³, -SO₂R¹³, -SO₂NR¹³R¹⁴, -NR¹³R¹⁴, -NR¹³SO₂R¹⁴, -NR¹³C(O)R¹⁴, -NR¹³C(O)OR¹⁴, -NR¹³C(O)NR¹³R¹⁴, -C(O)R¹⁴, -C(O)OR¹⁴, and -C(O)NR¹³R¹⁴; or two adjacent R⁸ form a heterocyclyl ring;

each R¹³ and R¹⁴ is independently selected from H, alkyl, cycloalkyl, heterocyclylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl, aryl,

and heteroaryl; or R¹³ and R¹⁴ taken together form a heterocycle with the atoms to which they are attached;

Y¹ and Y² are independently selected from O, CH₂, NH, and NR¹³;

n is 1, 2, or 3;

m is 1 or 2;

p is 1, 2, 3, or 4;

q is 1, 2, or 3;

r is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

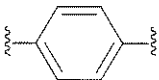
s is 0, 1, 2, 3, or 4;

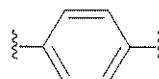
t is 0, 1, 2, 3, or 4;

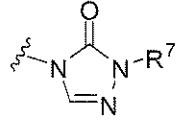
u is 0, 1, 2, 3, 4 or 5; and

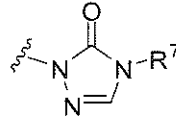
v is 0, 1, 2, 3, or 4, in the manufacture of a medicament for treating fibrosis, a disorder characterized by fibrosis, or a disease characterized by fibrosis.

2. The ~~method-use~~ of claim 1, wherein X₁ and X₂ are N.
3. The ~~method-use~~ of claim 1, wherein X₁ is CR⁵ and X₂ is N.
4. The ~~method-use~~ of claim 1, wherein X₁ is N and X₂ is CR⁵.
5. The ~~method-use~~ of any one of claims 2-4, wherein q is 1 and r is 0.
6. The ~~method-use~~ of any one of claims 1-5, wherein A¹ is aryl.

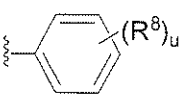
7. The ~~method-use~~ of claim 6 wherein A¹ is .
8. The ~~method-use~~ of any one of claims 1-5, wherein A¹ is heteroaryl.
9. The ~~method-use~~ of any one of claims 1-8, wherein A² is aryl.

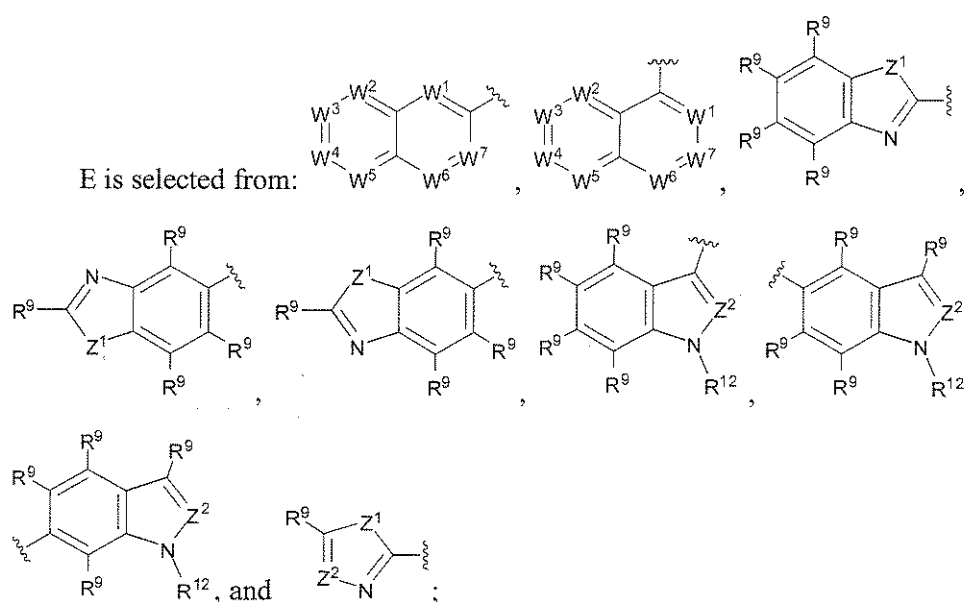
10. The ~~method-use~~ of claim 9, wherein A² is .
11. The ~~method-use~~ of any one of claims 1-8, wherein A² is heteroaryl.
12. The ~~method-use~~ of claim 11, wherein A² is pyridine, pyrazine, pyrimidine, pyridazine, or triazine.

13. The ~~method-use~~ of any one of claims 1-12, wherein C is ; and R⁷ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, -alkylene(NR¹³R¹⁴), cycloalkyl, heterocyclyl, -alkylene(cycloalkyl), or -alkylene(heterocyclyl).

14. The ~~method-use~~ of any one of claims 1-12, wherein C is ; and R⁷ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, -alkylene(NR¹³R¹⁴), cycloalkyl, heterocyclyl, -alkylene(cycloalkyl), or -alkylene(heterocyclyl).

15. The ~~method use~~ of any one of claims 1-14, wherein E is alkyl.
16. The ~~method use~~ of any one of claims 1-14, wherein E is cycloalkyl.
17. The ~~method use~~ of claim 16, wherein E is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
18. The ~~method use~~ of any one of claims 1-14, wherein E is heterocyclyl.
19. The ~~method use~~ of any one of claims 1-14, wherein E is aryl.

20. The ~~method use~~ of claim 19, wherein E is  and u is 0, 1, 2, 3, 4, or 5.
21. The ~~method use~~ of any one of claims 1-14, wherein E is heteroaryl.
22. The ~~method use~~ of claim 21, wherein



$W^1, W^2, W^3, W^4, W^5, W^6,$ and W^7 are independently selected from N and CR^9 ;

Z^1 is NR^{12} , S, or O;

Z^2 is N or CR^9 ;

each R^9 is independently selected from H, halogen, CN, NO_2 , alkyl, $-SR^{10}$, $-OR^{10}$, $-NR^{10}R^{11}$, $NR^{10}C(O)(alkyl)$, $-NR^{10}C(O)(cycloalkyl)$, $-NR^{10}C(O)(heterocycloalkyl)$, $-NR^{10}C(O)(aryl)$, $-NR^{10}C(O)(heteroaryl)$, $-C(O)NR^{10}R^{11}$, $-C(O)NR^{10}(cycloalkyl)$, $-C(O)NR^{10}(heterocycloalkyl)$, $-C(O)NR^{10}(aryl)$, $-C(O)NR^{10}(heteroaryl)$, $-NR^{10}C(O)NR^{10}R^{11}$, $-NR^{10}C(O)NR^{11}(cycloalkyl)$, $-NR^{10}C(O)NR^{11}(heterocycloalkyl)$, $-NR^{10}C(O)NR^{11}(aryl)$, $-NR^{10}C(O)NR^{11}(heteroaryl)$, $-NR^{10}C(O)O(alkyl)$, $-NR^{10}C(O)O(cycloalkyl)$, $-NR^{10}C(O)O(heterocycloalkyl)$, $-NR^{10}C(O)O(aryl)$, $-NR^{10}C(O)O(heteroaryl)$, $-NR^{10}SO_2(alkyl)$, $-NR^{10}SO_2(cycloalkyl)$, $-NR^{10}SO_2(heterocycloalkyl)$, $-NR^{10}SO_2(aryl)$, $-NR^{10}SO_2(heteroaryl)$, $-SO_2NR^{10}R^{11}$,

-SO₂NR¹⁰(cycloalkyl), -SO₂NR¹⁰(heterocycloalkyl), -SO₂NR¹⁰(aryl),

-SO₂NR¹⁰(heteroaryl), haloalkyl, aryl, and heteroaryl;

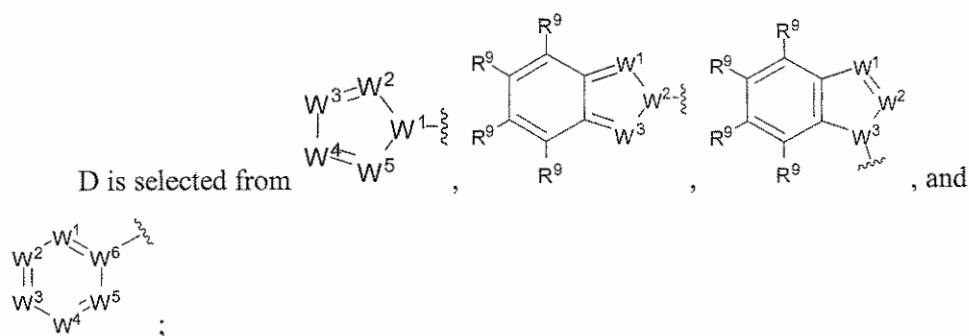
each R¹⁰ and R¹¹ is independently selected from H and alkyl; or R¹⁰ and R¹¹ taken together form a heterocycle with the nitrogen to which they are attached; and

R¹² is H, alkyl or haloalkyl.

23. The ~~method-use~~ of any one of claims 1-22, wherein D is aryl.

24. The ~~method-use~~ of any one of claims 1-22, wherein D is heteroaryl.

25. The ~~method-use~~ of claim 24, wherein



W¹, W², W³, W⁴, and W⁵ are independently selected from N and CR⁹;

W⁶ is N or C; and

each R⁹ is independently selected from H, halogen, CN, NO₂,

alkyl, -SR¹⁰, -OR¹⁰, -NR¹⁰R¹¹,

NR¹⁰C(O)(alkyl), -NR¹⁰C(O)(cycloalkyl), -NR¹⁰C(O)(heterocycloalkyl), -NR¹⁰C(O)(aryl), -NR¹⁰C(O)(heteroaryl), -C(O)NR¹⁰R¹¹, -C(O)NR¹⁰(cycloalkyl), -C(O)NR¹⁰(heterocycloalkyl), -C(O)NR¹⁰(aryl), -C(O)NR¹⁰(heteroaryl), -NR¹⁰C(O)NR¹⁰R¹¹, -NR¹⁰C(O)NR¹¹(cycloalkyl), -NR¹⁰C(O)NR¹¹(heterocycloalkyl), -NR¹⁰C(O)NR¹¹(aryl), -NR¹⁰C(O)NR¹¹(heteroaryl), -NR¹⁰C(O)O(alkyl), -NR¹⁰C(O)O(cycloalkyl), -NR¹⁰C(O)O(heterocycloalkyl), -NR¹⁰C(O)O(aryl), -NR¹⁰C(O)O(heteroaryl), -NR¹⁰SO₂(alkyl), -NR¹⁰SO₂(cycloalkyl), -NR¹⁰SO₂(heterocycloalkyl), -NR¹⁰SO₂(aryl), -NR¹⁰SO₂(heteroaryl), -SO₂NR¹⁰R¹¹, -SO₂NR¹⁰(cycloalkyl), -SO₂NR¹⁰(heterocycloalkyl), -SO₂NR¹⁰(aryl), -SO₂NR¹⁰(heteroaryl), haloalkyl, aryl, and heteroaryl.

26. The ~~method-use~~ of any one of claims 1-25 wherein Y¹ and Y² are O.

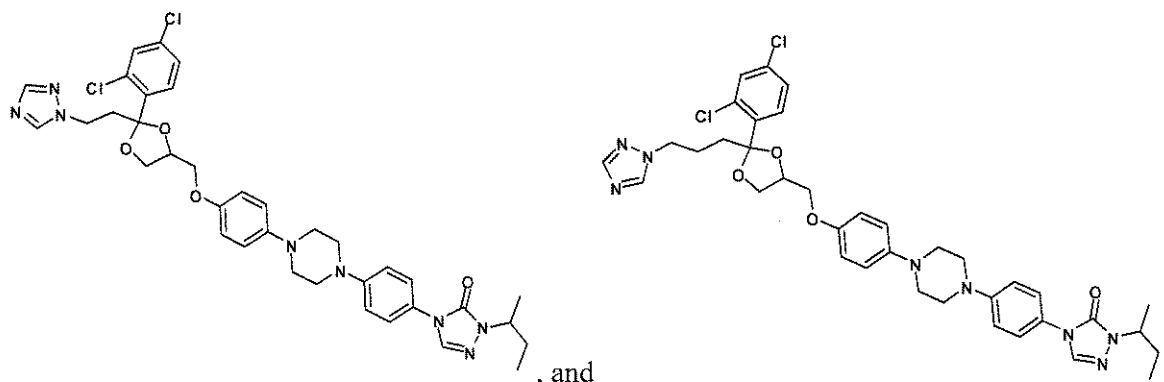
27. The ~~method-use~~ of claim 26 wherein m is 1.

28. The ~~method-use~~ of any one of claims 1-27 wherein p is 1, 2, or 3.

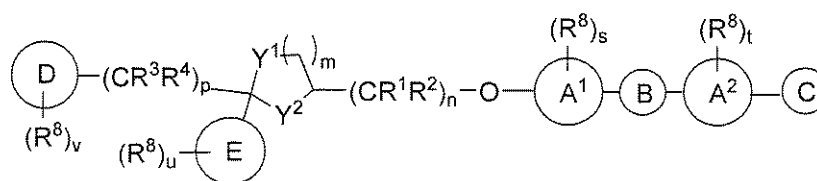
29. The ~~method-use~~ of claim 28 wherein p is 1.

30. The ~~method-use~~ of any one of claims 1-29 wherein R¹, R², R³, and R⁴ are hydrogen.

31. The ~~method-use~~ of claim 1 wherein the compound is selected from:



32. The ~~method use~~ of any one of claims 1-31 wherein the fibrosis is liver fibrosis, idiopathic pulmonary fibrosis, kidney fibrosis, or cardiac fibrosis.
33. The ~~method use~~ of claim 32 wherein the liver fibrosis is associated with the later stages of alcoholic or nonalcoholic liver cirrhosis.
34. The ~~method use~~ of claim 32 wherein the fibrosis is idiopathic pulmonary fibrosis.
35. The ~~method use~~ of any one of claims 1-31 wherein the disease or disorder characterized by fibrosis is a chronic autoimmune disease.
36. The ~~method use~~ of claim 35 wherein the chronic autoimmune disease is rheumatoid arthritis, scleroderma, Crohn's disease or systemic lupus erythematosus.
37. The ~~method use~~ of claim 36 wherein the chronic autoimmune disease is scleroderma.
38. The ~~method use~~ of any one of claims 1-31 wherein the fibrosis is keloid formation resulting from abnormal wound healing.
39. The ~~method use~~ of any one of claims 1-31 wherein the fibrosis occurs after organ transplantation.
40. A compound of Formula (II), a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (II)

wherein:

A¹ and A² are independently selected from aryl or heteroaryl;

