ANALOGS FOR THE TREATMENT OF DISEASE

CROSS REFERENCE

[0001] This application claims the benefit of International Application No. PCT/CN2021/077706, filed February 24, 2021 and International Application No. PCT/CN2021/142622, filed December 29, 2021, each of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] A biologically active enzyme known as Traf2- and Nck-interacting protein kinase is an enzyme commonly known as the TNIK in humans, and which is encoded by the TNIK gene. TNIK as a serine/threonine kinase is involved in various biological processes. There is a need for new drug candidates that can target TNIK.

SUMMARY

[0003] TNIK is a serine/threonine kinase that is involved in various biological processes including acting as an essential regulatory component of the Wnt signaling pathway. TNIK directly binds TCF4 and b-catenin and phosphorylates TCF4. Additionally, TNIK plays an activator of Wnt target gene expression and modulates the actin cytoskeleton and activates the c-Jun N-terminal kinase pathway, which is responsive to stress. It is also part of a signaling complex composed of NEDD4, RAP2A, and TNIK, which regulates neuronal dendrite extension and arbonization during development. More generally, TNIK may play a role in cytoskeletal rearrangement and regulate cell spreading. TNIK also causes weak Smad1 T322 phosphorylation, involved in TGF-b1 signaling transduction.

[0004] TNIK is considered to be a germinal center kinase (GCK), which can be characterized by an N-terminal kinase domain and a C-terminal GCK domain that serves a regulatory function.

[0005] TNIK activation of Wnt signaling plays important roles in carcinogenesis and embryonic development. Mutations in this gene are associated with an autosomal recessive form of cognitive disability.

[0006] Additionally, TNIK is linked to cancer, including for example, colorectal cancer. As such, TNIK has been identified as an attractive candidate for drugs targeting certain cancers.

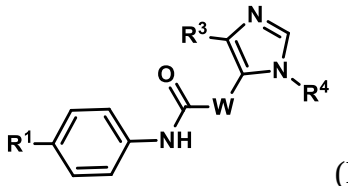
[0007] The current data imply TNIK is a potential target for the generation of small molecule inhibitors to specifically block the Wnt pathway in disease states such as colorectal cancer or the autosomal recessive form of cognitive disability.

[0008] Also, it is known that TGF-β-activated EMT can be identified through the attenuation of Smad and non-Smad signaling pathways, including the Wnt, FF-kB, FAK-Src-paxillin-related focal adhesion, and MAP kinase (ERK and JNK) signaling pathways. As such, therapeutic targets associated with EMT, such as TNIK being target for inhibition, can be used for therapies for treating and/or preventing EMT-based disorders, such as cancer metastasis and fibrosis.

[0009] Accordingly, it would be advantageous to have a TNIK inhibitor that can inhibit the kinase activity of TNIK, as a member of the Ste20 family of MAP kinase kinase kinase (MAP4K).

[0010] The present disclosure addresses the above need and provides additional advantages as well.

[0010a] In an aspect of the present disclosure, there is provided a compound represented by Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

$-N(R^5)_2$, wherein each R^5 is independently selected from hydrogen, and optionally substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, $-O-C_{1-6}$alkyl-O-C(O)($O-C_{1-10}$ alkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

optionally substituted 3 to 8-membered heterocycle; wherein the 3 to 8-membered heterocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, $-S(O_2)NH_2$, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, and optionally substituted C_{1-10} alkyl, wherein the C_{1-10} alkyl is optionally substituted with one or more substituents independently selected at each occurrence from hydroxy, halogen, oxo, $-C_{1-10}$ haloalkyl, $-NH_2$, -CN, and $-NO_2$;

R^3 is selected from optionally substituted C_1-C_6 alkyl, optionally substituted 3- to 10-membered heterocycle and optionally substituted C_{3-10} carbocycle, wherein each of the alkyl, heterocycle and carbocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-6} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;
R^4 is selected from:

hydrogen;

optionally substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -O-C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

optionally substituted C_{3-10} carbocycle, wherein the C_{3-10} carbocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;
W is selected from optionally substituted 5- to 8-membered heteroaryl, wherein the 5- to 8-membered heteroaryl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -S(O_2)NH_2, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

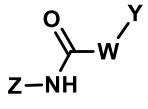
wherein when R^1 is methylpiperazine and W is pyridine, then R^4 is not methyl; and when W is furan and R^4 is cyclopentyl or cyclohexyl, then R^1 is not ethan-1-one.

[0010b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or salt disclosed herein and a pharmaceutically acceptable excipient.

[0010c] In a further aspect of the present disclosure, there is provided a compound or salt disclosed herein or a pharmaceutical composition disclosed herein, for use treating a disease in a subject in need thereof.

[0010d] In another aspect of the present disclosure, there is provided a use of a compound or salt disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a fibrotic disease or condition in a subject in need thereof.

[0011] In some examples, the present disclosure provides a compound represented by Formula (A):



(A);

or a pharmaceutically acceptable salt thereof, wherein:

Z is selected from optionally substituted 3- to 12-membered heterocycle and optionally substituted C_3-C_{12} carbocycle, wherein the substituents on each are independently selected at each occurrence from one or more -$N(R^{10})_2$, halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_1-C_{10} alkyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

wherein the C_1-C_{10} alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, -O-C_{1-6}alkyl-O-C(O)(O-C_{1-10} alkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

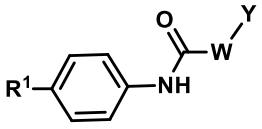
wherein the C_{3-12} carbocycle and 3- to 12-membered heterocycle are each optionally substituted at each occurrence from one or more substituents independently selected from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -$S(O_2)NH_2$, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, and optionally substituted C_{1-10} alkyl, wherein the optional substituents on the C_{1-10} alkyl are independently selected at each occurrence from one or more hydroxy, halogen, oxo, -C_{1-10} haloalkyl, -NH_2, -CN, and -NO_2;

R^{10} is selected from optionally substituted C_1-C_6 alkyl, wherein the optional substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

W is selected from optionally substituted 5- to 8-membered heterocycle and optionally substituted C_3-C_8 carbocycle, wherein the substituents on each are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, wherein the C_{3-12} carbocycle and 3- to 12-membereed heterocycle are each optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, and -O-C_{1-10} alkyl; and

Y is selected from optionally substituted 5- to 8-membered heterocycle and optionally substituted C_3-C_8 carbocycle, wherein the substituents on each are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, wherein the C_{3-12} carbocycle and 3- to 12-membereed heterocycle are each optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, and -O-C_{1-10} alkyl.

[0012] In some examples, the disclosure provides a compound represented by Formula (A*):



(A*);

R^1 is selected from:

-$N(R^5)_2$, wherein R^5 is selected from hydrogen, and optionally substituted C_1-C_6 alkyl, wherein the optional substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

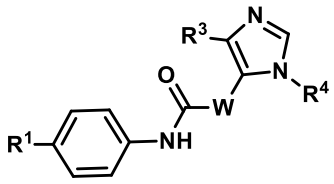
optionally substituted C_1-C_6 alkyl, wherein the substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, -O-C_{1-6}alkyl-O-C(O)(O-C_{1-10} alkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

optionally substituted 3 to 8-membered heterocycle; wherein the optional substituents on the 3 to 8-membered heterocycle are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -$S(O_2)NH_2$, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, and optionally substituted C_{1-10} alkyl, wherein the optional substituents on the C_{1-10} alkyl are independently selected at each occurrence from one or more hydroxy, halogen, oxo, -C_{1-10} haloalkyl, -NH_2, -CN, and -NO_2;

W is selected from optionally substituted 5- to 8-membered heterocycle and optionally substituted C_3-C_8 carbocycle, wherein the substituents on each are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, wherein the C_{3-12} carbocycle and 3- to 12-membereed heterocycle are each optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, and -O-C_{1-10} alkyl; and

Y is selected from optionally substituted 5- to 8-membered heterocycle and optionally substituted C_3-C_8 carbocycle, wherein the substituents on each are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, wherein the C_{3-12} carbocycle and 3- to 12-membereed heterocycle are each optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, and -O-C_{1-10} alkyl.

[0013] In certain examples, the disclosure provides a compound represented by Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

-$N(R^5)_2$, wherein R^5 is selected from hydrogen, and optionally substituted C_1-C_6 alkyl, wherein the optional substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

substituted C_1-C_6 alkyl, wherein the substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, -O-C_{1-6}alkyl-O-C(O)(O-C_{1-10} alkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

optionally substituted 3 to 8-membered heterocycle; wherein the optional substituents on the 3 to 8-membered heterocycle are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -$S(O_2)NH_2$, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle, and optionally

substituted C_{1-10} alkyl, wherein the optional substituents on the C_{1-10} alkyl are independently selected at each occurrence from one or more hydroxy, halogen, oxo, -C_{1-10} haloalkyl, -NH_2, -CN, and -NO_2;

R^3 is selected from optionally substituted C_1-C_6 alkyl, optionally substituted 3- to 10-membered heterocycle and optionally substituted C_{3-10} carbocycle, wherein the optional substituents on each are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-6} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

R^4 is selected from:

hydrogen;

optionally substituted C_1-C_6 alkyl, wherein the optional substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -O-C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle;

optionally substituted C_{3-10} carbocycle, wherein the optional substituents on C_{3-10} carbocycle are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle; and

W is selected from optionally substituted 5- to 8-membered heteroaryl, wherein the substituents on the optionally substituted 5- to 8-membered heteroaryl are independently selected at each occurrence from one or more halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -S(O_2)NH_2, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, 3- to 12-membered heterocycle.

[0014] In some examples, the disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (A), Formula (A*), or Formula (I) and a pharmaceutically acceptable excipient.

[0015] In some examples, the disclosure provides a method of treating or preventing disease comprising administering a compound or salt of Formula (A), Formula (A*), or Formula (I) or a pharmaceutical composition comprising a compound or salt of Formula (A), Formula (A*), or Formula (I) and a pharmaceutically acceptable excipient to a subject in need thereof. In some examples, the disease is a cancer. In some cases, the cancer is selected from colorectal cancer, gastric cancer, breast cancer, lung cancer, pancreatic cancer, prostate cancer, multiple myeloma, chronic myelogenous leukemia, cancer metastasis, fibrosis and psychiatric disorders. In some cases, the pharmaceutical composition can be used as an inhibitor of tumor immunosuppression in combination with chemotherapy or immune checkpoint inhibitor therapy for cancer. In some

cases, the pharmaceutical composition can be used to treat a fibrotic disease or condition including but not limited to chronic kidney fibrosis ("CKD"), liver cirrhosis, pulmonary fibrosis, renal interstitial fibrosis, myocardial infarction, skin fibrosis, systemic sclerosis ("SSc"), and graft-versus-host disease ("GVHD"). In some cases, the pharmaceutical composition can be used to treat kidney fibrosis. In some cases, the pharmaceutical composition can be used to treat skin fibrosis. In some cases, the pharmaceutical composition can be used to treat idiopathic pulmonary fibrosis (IPF). In some cases, the pharmaceutical composition can be used to treat a disease is associated with TNIK kinase.

[0016] In some examples, the disclosure provides a method of inhibiting TNIK kinase comprising administering a compound or salt of Formula (A), Formula (A*), or Formula (I) or a pharmaceutical composition comprising a compound or salt of Formula (A), Formula (A*), or Formula (I) and a pharmaceutically acceptable excipient to a subject in need thereof.

[0017] In some examples, the disclosure provides a method of inhibiting MAP4K4 kinase comprising administering a compound or salt of Formula (A), Formula (A*), or Formula (I) or a pharmaceutical composition comprising a compound or salt of Formula (A), Formula (A*), or Formula (I) and a pharmaceutically acceptable excipient to a subject in need thereof.

[0018] Additional examples and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative examples of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different examples, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0019] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

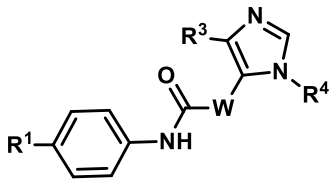
DETAILED DESCRIPTION OF THE INVENTION

[0020] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

$-N(R^5)_2$, wherein each R^5 is independently selected from hydrogen, and optionally substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, -$C_{1\text{-}10}$ haloalkyl, -O-$C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle;

substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, -$C_{1\text{-}10}$ haloalkyl, -O-$C_{1\text{-}10}$ alkyl, -O-$C_{1\text{-}6}$alkyl-O-C(O)(O-$C_{1\text{-}10}$ alkyl), $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle; and

optionally substituted 3 to 8-membered heterocycle; wherein the 3 to 8-membered heterocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, $-S(O_2)NH_2$, -$C_{1\text{-}10}$ haloalkyl, -O-$C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}12}$ carbocycle, 3- to 12-membered heterocycle, and optionally substituted $C_{1\text{-}10}$ alkyl, wherein the $C_{1\text{-}10}$ alkyl is optionally substituted with one or more substituents independently selected at each occurrence from hydroxy, halogen, oxo, -$C_{1\text{-}10}$ haloalkyl, $-NH_2$, -CN, and $-NO_2$;

R^3 is selected from optionally substituted C_1-C_6 alkyl, optionally substituted 3- to 10-membered heterocycle and optionally substituted $C_{3\text{-}10}$ carbocycle, wherein each of the alkyl, heterocycle and carbocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, =S, $C_{1\text{-}6}$ alkyl, -$C_{1\text{-}10}$ haloalkyl, -O-$C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, $C_{2\text{-}10}$ alkynyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle;

R^4 is selected from:

hydrogen;

optionally substituted C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -

NO_2, -NH_2, oxo, =S, -O-C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

optionally substituted C_{3-10} carbocycle, wherein the C_{3-10} carbocycle is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, C_{1-10} alkyl, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

W is selected from optionally substituted 5- to 8-membered heteroaryl, wherein the 5- to 8-membered heteroaryl is optionally substituted with one or more substituents independently selected at each occurrence from halogen, -OH, -CN, -NO_2, -NH_2, oxo, =S, -$S(O_2)NH_2$, -C_{1-10} haloalkyl, -O-C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

wherein when R^1 is methylpiperazine and W is pyridine, then R^4 is not methyl; and when W is furan and R^4 is cyclopentyl or cyclohexyl, then R^1 is not ethan-1-one.

2. The compound or salt of claim 1, wherein R^3 is selected from optionally substituted C_{3-6} carbocycle.

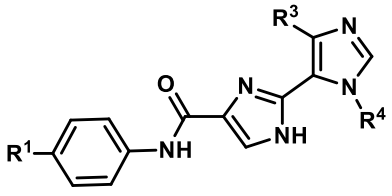
3. The compound or salt of claim 1 or 2, wherein R^3 is optionally substituted phenyl.

4. The compound or salt of claim 3, wherein the optional substituents of the phenyl are selected from halogen and -C_{1-10} haloalkyl.

5. The compound or salt of any one of claims 1 to 4, wherein W is selected from 5- to 6-membered heteroaryl.

6. The compound or salt of any one of claims 1 to 4, wherein the 5- to 6-membered heteroaryl of W are selected from imidazole, furan, and pyridine.

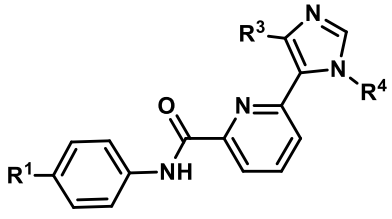
7. The compound or salt of any one of claims 1 to 6, wherein the compound is represented by formula (IIA):



(IIA);

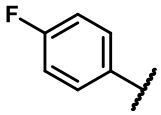
or a pharmaceutically acceptable salt thereof.

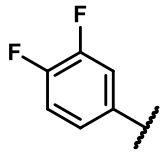
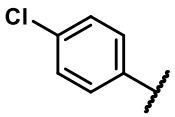
8. The compound or salt of any one of claims 1 to 6, wherein the compound is represented by formula (IIB):



(IIB);

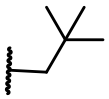
or a pharmaceutically acceptable salt thereof.

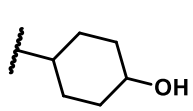
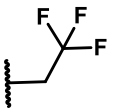
9. The compound or salt of claim 4, wherein R^3 is selected from ,

, and .

10. The compound or salt of any one of claims 1 to 9, wherein R^4 is selected from hydrogen, C_1-C_6 alkyl optionally substituted with one or more substituents selected from halogen, and C_{5-6} carbocycle optionally substituted with one or more substituents selected from hydroxy and amine.

11. The compound or salt of claim 10, wherein R^4 is selected from C_1-C_6 alkyl optionally substituted with one or more substituents selected from fluorine, and C_6 cycloalkyl substituted with hydroxy.

12. The compound or salt of claim 11, wherein R^4 is selected from , ,

, and .

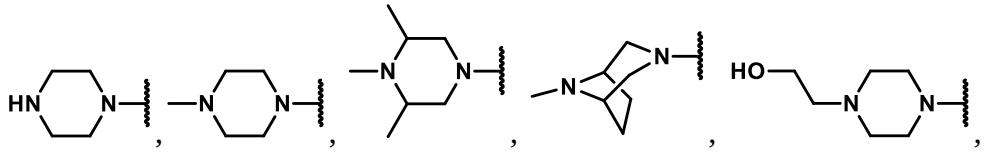
13. The compound or salt of any one of claims 1 to 12, wherein R^1 is selected from:

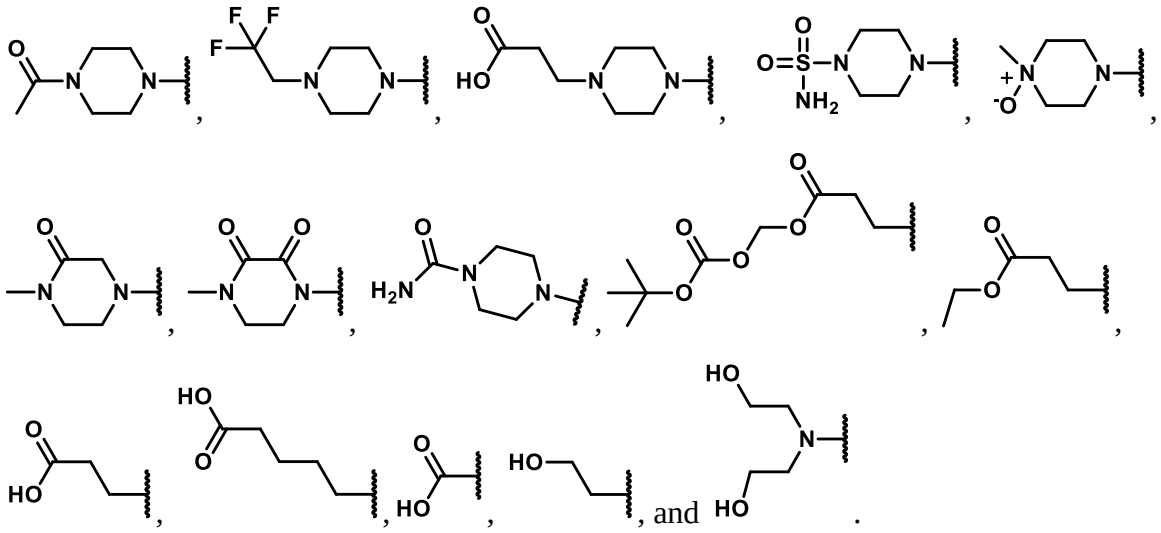
$-N(R^5)_2$, wherein R^5 is selected from optionally substituted C_1-C_6 alkyl, wherein the substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, -CN, $-NO_2$, $-NH_2$, oxo, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl,

substituted C_1-C_6 alkyl, wherein the substituents on C_1-C_6 alkyl are independently selected at each occurrence from one or more halogen, -OH, $-NH_2$, oxo, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, $-O-C_{1-6}$alkyl-O-C(O)($O-C_{1-10}$ alkyl);

optionally substituted 6 to 8-membered heterocycle; wherein the optional substituents on the 6 to 8-membered heterocycle are independently selected at each occurrence from one or more oxo, $-S(O_2)NH_2$, $-NH_2$, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, and optionally substituted C_{1-10} alkyl, wherein the optional substituents on the C_{1-10} alkyl are independently selected at each occurrence from one or more hydroxy, halogen, oxo, $-C_{1-10}$ haloalkyl, $-NH_2$, -CN, and $-NO_2$.

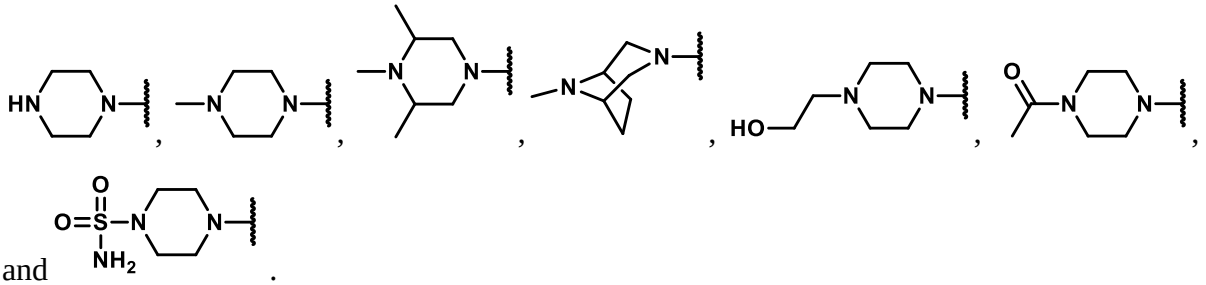
14. The compound or salt of any one of claims 1 to 12, wherein R^1 is selected from



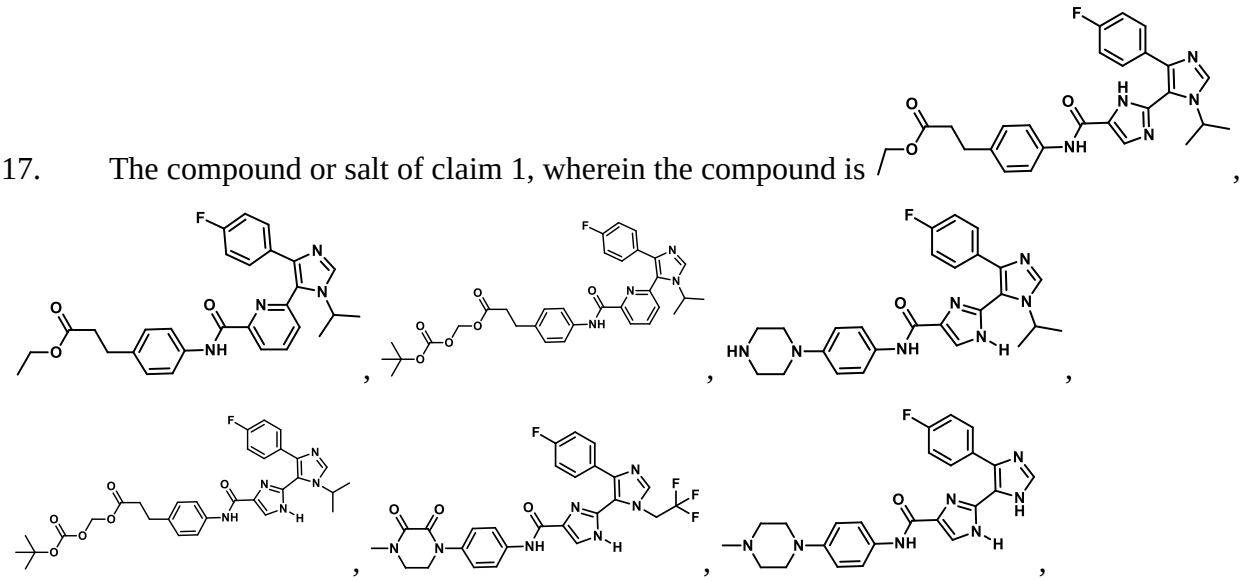


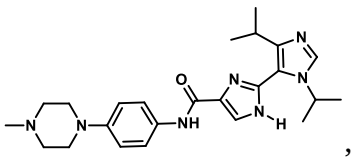
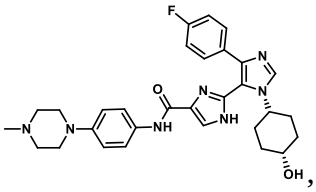
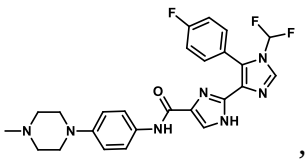
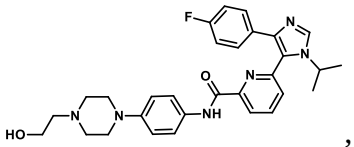
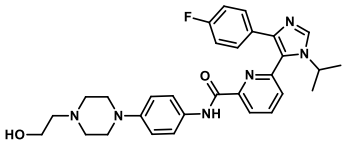
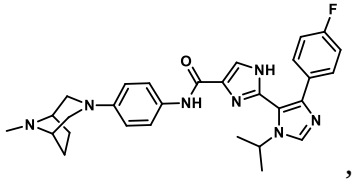
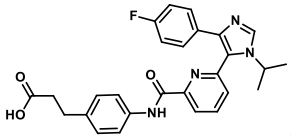
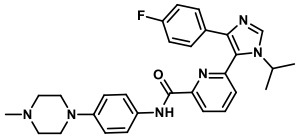
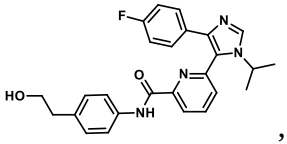
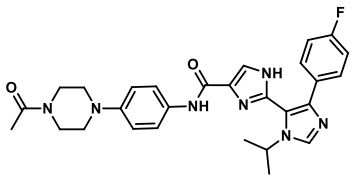
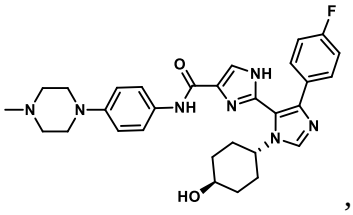
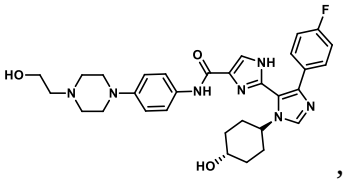
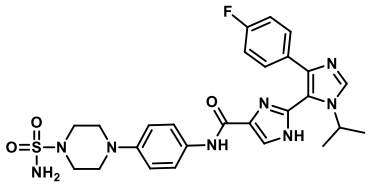
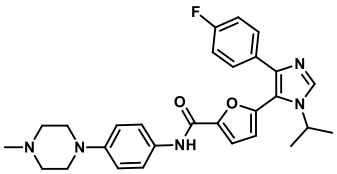
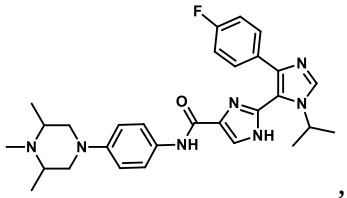
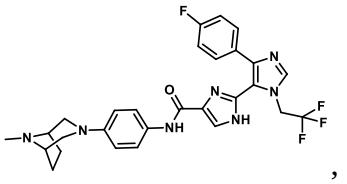
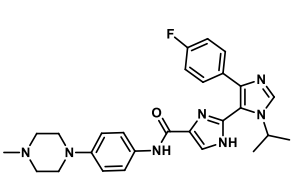
15. The compound or salt of any one of claims 1 to 12, wherein R^1 is selected from optionally substituted 6 to 8-membered saturated heterocycle; wherein the optional substituents are independently selected at each occurrence from one or more $-S(O_2)NH_2$, and optionally substituted C_{1-10} alkyl, wherein the optional substituents on the C_{1-10} alkyl are independently selected at each occurrence from one or more hydroxy, halogen, oxo, $-C_{1-10}$ haloalkyl, and $-NH_2$.

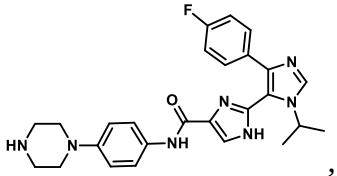
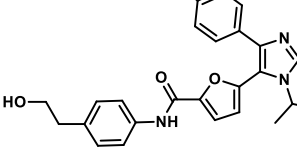
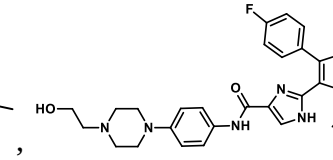
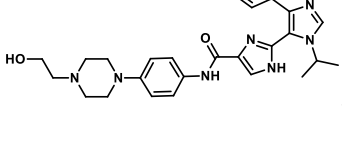
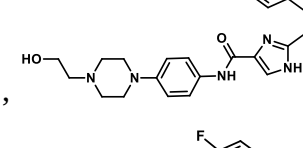
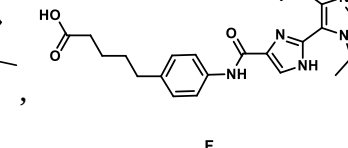
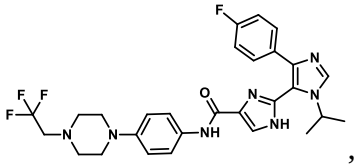
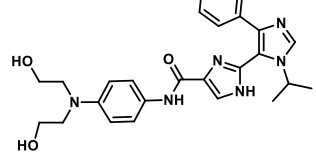
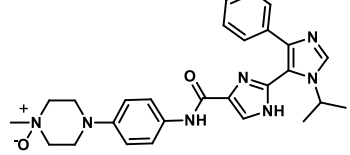
16. The compound or salt of any one of claims 1 to 12, wherein R^1 is selected from



17. The compound or salt of claim 1, wherein the compound is




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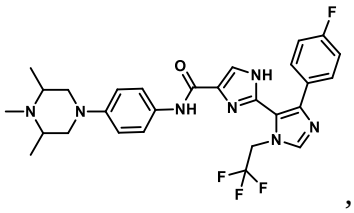
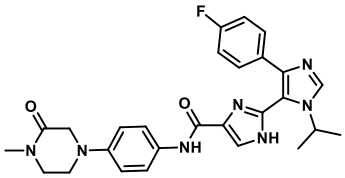
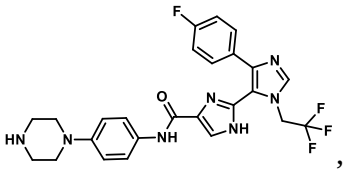
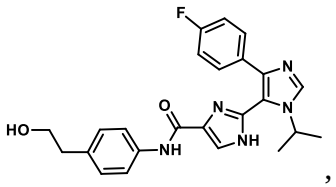
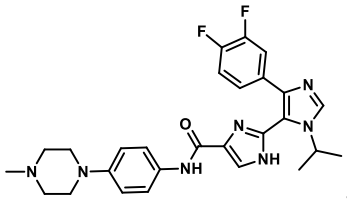
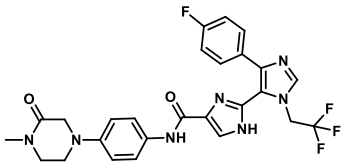
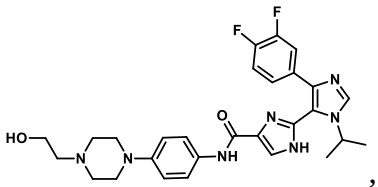
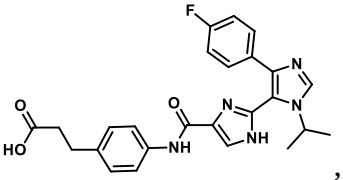
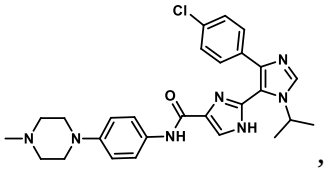
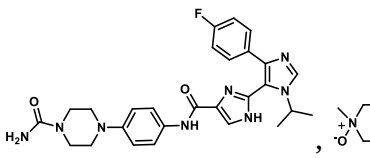
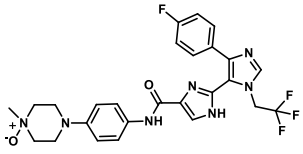
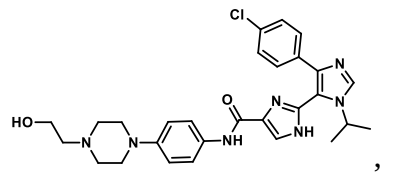
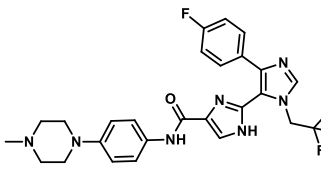
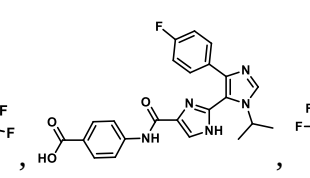
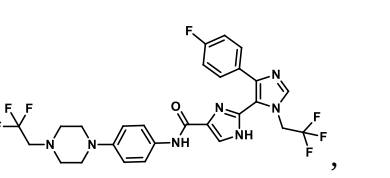
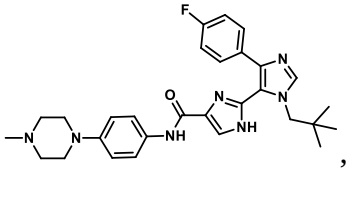
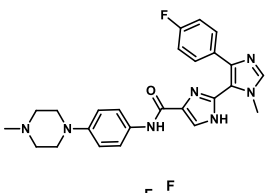
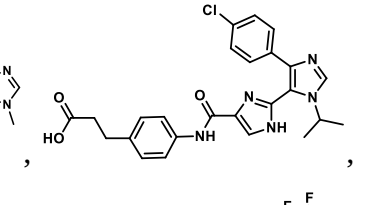
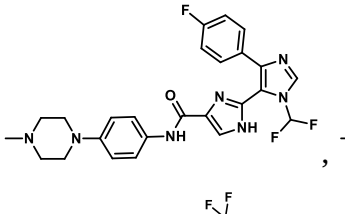
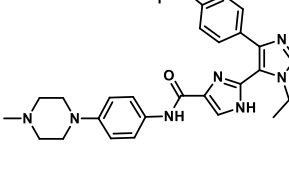
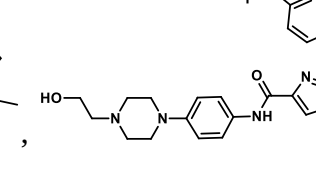
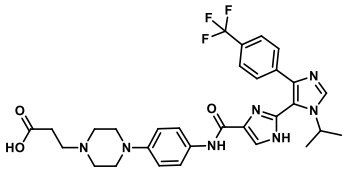
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, or a pharmaceutically acceptable salt of any one thereof.

18. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 17 and a pharmaceutically acceptable excipient.

19. A compound or salt of any one of claims 1 to 17 or a pharmaceutical composition of claim 18, for use treating a disease in a subject in need thereof.

20. Use of a compound or salt of any one of claims 1 to 17, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a fibrotic disease or condition in a subject in need thereof.