R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

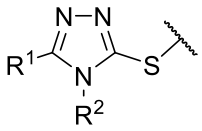
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

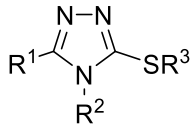
m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

[22b] In another aspect, provided herein is use of a compound in the manufacture of a medicament for the treatment of a neurodegenerative disease, a metabolic disease or a cardiovascular disease, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

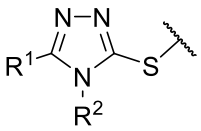
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

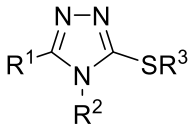
m is a whole number selected from 1-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

[22c] In another aspect, provided herein is use of a compound in the manufacture of a medicament for the treatment of cancer or fibrosis, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkenyl, alkynyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

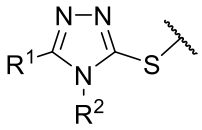
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

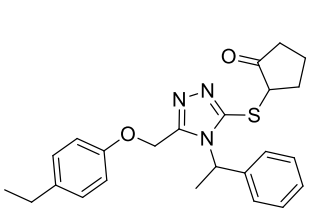
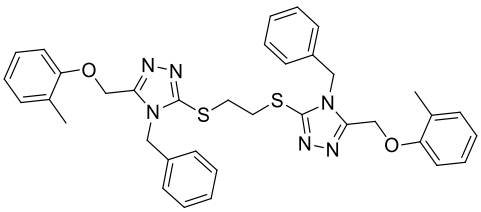
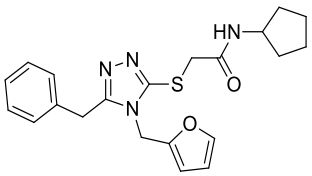
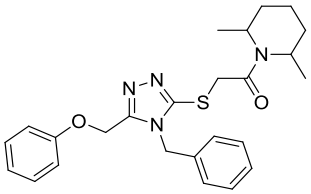
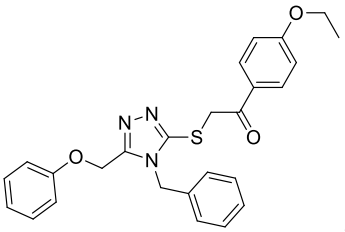
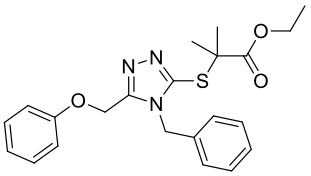
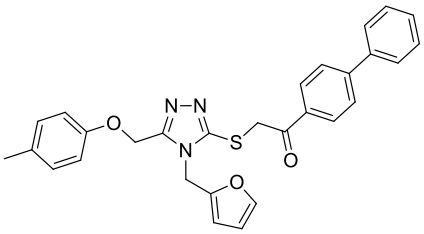
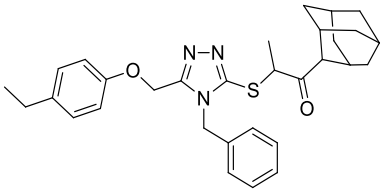
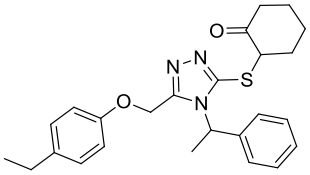
m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

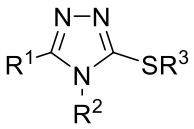
p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

[22d] In another aspect, provided herein is use of a compound in the manufacture of a medicament for the treatment of a bone disease, a neurodegenerative disease, a metabolic disease, a cardiovascular disease, cancer or fibrosis, wherein the compound is selected from the group consisting of:


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,

,

, and

or a pharmaceutically acceptable salt thereof.

[23] Provided herein is a method of inhibiting β-cat or disrupting the interaction between β-cat and TCF4, the method comprising: contacting β-cat with a compound of Formula **1**:



1

[24] or a pharmaceutically acceptable salt thereof, wherein

[25] R^1 is $–(CR^4_2)_mXR^5$;

[26] R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

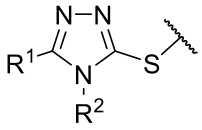
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

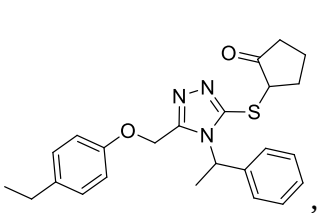
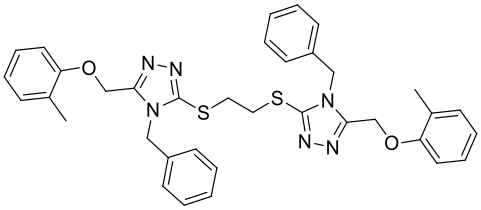
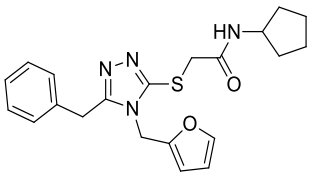
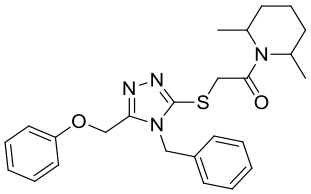
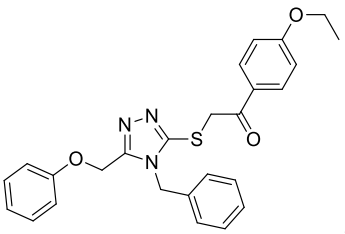
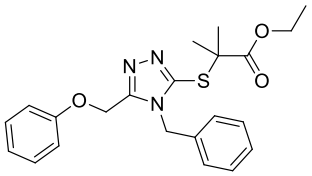
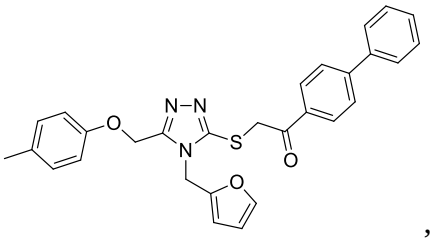
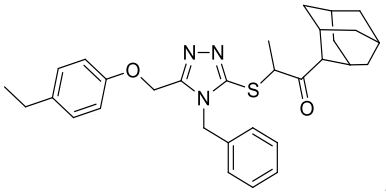
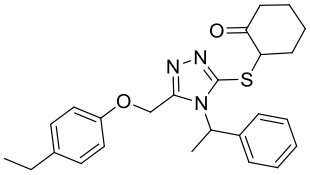
m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

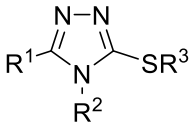
X is -O-, -S-, or is absent.

[35b] In another aspect, provided herein is an *in vitro* method of inhibiting β-cat or disrupting the interaction between β-cat and TCF4, the *in vitro* method comprising: contacting β-cat with a compound selected from the group consisting of:


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, and


or a pharmaceutically acceptable salt thereof.

[36] Provided herein is a method of treating a disease or health condition that is ameliorated by inhibiting β-cat or disrupting the interaction between β-cat and TCF4 in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula **1**:



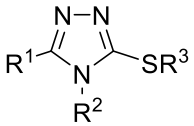
1

[72] m is a whole number selected from 0-4;

[73] n is a whole number selected from 0-4; and

[74] X is -O-, -S-, or is absent.

[74a] In another aspect, provided herein is a compound for use in therapy, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkynyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

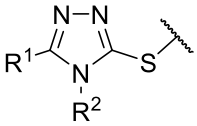
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

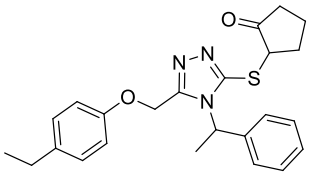
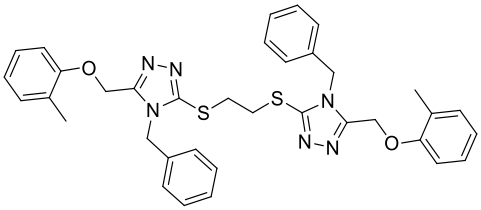
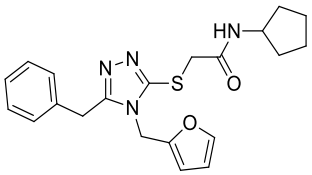
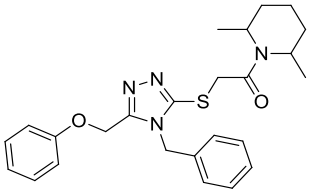
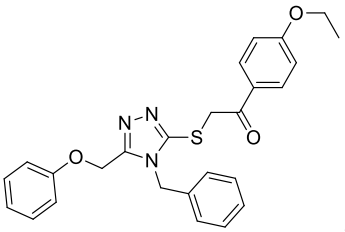
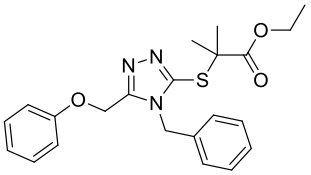
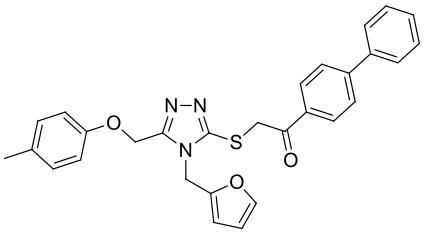
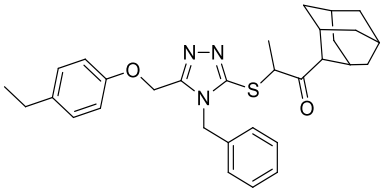
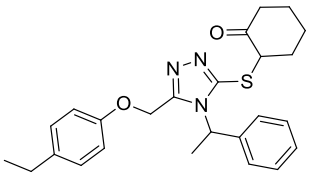
m is a whole number selected from 1-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

[74b] In another aspect, provided herein is a compound for use in therapy, wherein the compound is selected from the group consisting of:


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,

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, and


or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF DRAWINGS

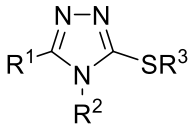
[75] The above and other objects and features of the present disclosure will become apparent from the following description of the disclosure, when taken in conjunction with the accompanying drawings.

[76] **Figure 1** depicts the modelling and docking platform used in the generation of β-catenin structures for ligand discovery. 3 crystal structures were used as the starting models (N = 3). The training library of small molecules contains 3 known inhibitors of β-catenin (M = 3). Within one iteration, every target structure would be further optimized in the presence of each of the 3 known ligands docked.

[77] **Figure 2** depicts an *in silico* investigation of predicted compounds for Wnt signaling inhibition. (**a**) TOPFlash reporter activity of predicted compounds in HEK293T STF cells. The cells were treated with the compounds at 10 μM and simultaneously stimulated with 500 ng/mL of Wnt3A for 24 hr prior to measuring luciferase activity. TOPFlash reporter activities of compound-treated cells were normalized to cell viability and presented as fold change over DMSO treated cells. Error bars represent standard deviation of 4 replicates. (**b**) Secondary dose response inhibition of TOPFlash reporter activity by iCRT3 and hit compounds. The STF cells were treated with the different concentrations of compounds and simultaneously stimulated with 500 ng/mL of Wnt3A for 24 hr prior to measuring luciferase activity. Luciferase activities of cells treated with compounds at the various concentrations were first normalized to cell

What is claimed:

1. Use of a compound in the manufacture of a medicament for the treatment of a bone disease, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

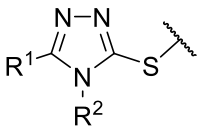
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the

atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

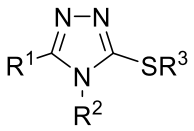
m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

2. Use of a compound in the manufacture of a medicament for the treatment of a neurodegenerative disease, a metabolic disease or a cardiovascular disease, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

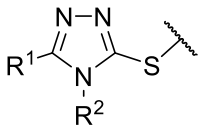
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

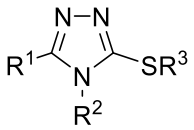
m is a whole number selected from 1-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

X is -O-, -S-, or is absent.

3. Use of a compound in the manufacture of a medicament for the treatment of cancer or fibrosis, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is -(CR^4_2)$_m$XR^5;

R^2 is alkyl, alkenyl, alkynyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, heteroaralkyl, heteroaryl or -(CR^9_2)$_p$$R^{10}$;

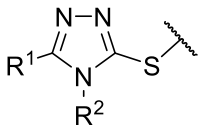
R^3 is -(CR^6_2)$_n$$R^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

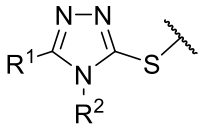
X is -O-, -S-, or is absent.

4. The use of any one of claims 1 to 3, wherein m is 1 or 2; and X is -O- or is absent.

5. The use of any one of claims 1 to 4, wherein R^5 is optionally substituted aryl.

6. The use of any one of claims 1, 2, 4 and 5, wherein R^2 is cycloalkyl, aralkyl, or heteroaralkyl.

7. The use of any one of claims 1 to 6, wherein n is 1 or 2; R^6 for each occurrence is independently hydrogen or alkyl; R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **2**:

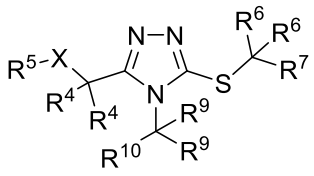


2

R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

8. The use of any one of claims 1 to 7, wherein R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

9. The use of any one of claims 1 to 8, wherein the compound has Formula **3**:



3

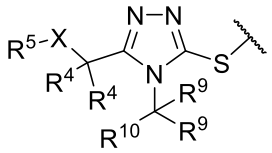
or a pharmaceutically acceptable salt thereof, wherein

R^4 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **4**:



4

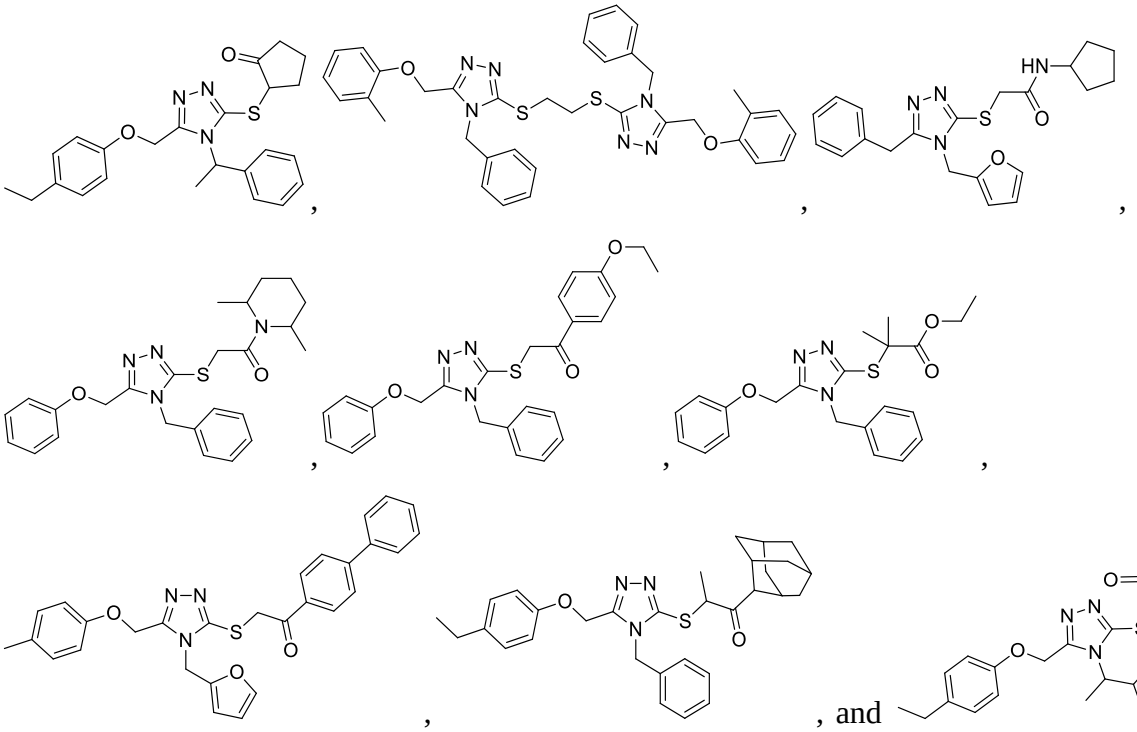
R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl;

R^9 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl; and

X is -O- or absent.

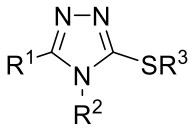
10. Use of a compound in the manufacture of a medicament for the treatment of a bone disease, a neurodegenerative disease, a metabolic disease, a cardiovascular disease, cancer or fibrosis, wherein the compound is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

11. The use of any one of claims 3 to 10, wherein the cancer is selected from the group consisting of colorectal cancer, hepatocellular cancer, melanoma, liver cancer, breast cancer, prostate cancer, and leukemia.

12. An *in vitro* method of inhibiting β-cat or disrupting the interaction between β-cat and TCF4, the *in vitro* method comprising: contacting β-cat with a compound of Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

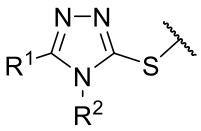
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

m is a whole number selected from 0-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

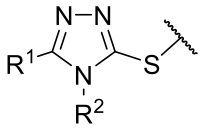
X is -O-, -S-, or is absent.

13. The *in vitro* method of claim 12, wherein m is 1 or 2; and X is -O- or is absent.

14. The *in vitro* method of claim 12 or 13, wherein R^5 is optionally substituted aryl.

15. The *in vitro* method of claim any one of claims 12 to 14, wherein R^2 is cycloalkyl, aralkyl or heteroaralkyl.

16. The *in vitro* method of any one of claims 12 to 15, wherein n is 1; R^6 for each occurrence is independently hydrogen or alkyl; R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:

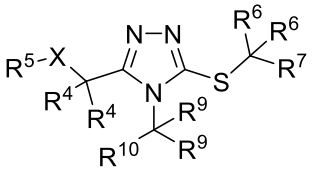


2

R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

17. The *in vitro* method of any one of claims 12 to 16, wherein R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

18. The *in vitro* method of any one of claims 12 to 17, wherein the compound has Formula **3**:



3

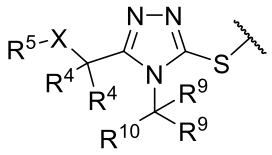
or a pharmaceutically acceptable salt thereof, wherein

R^4 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **4**:



4

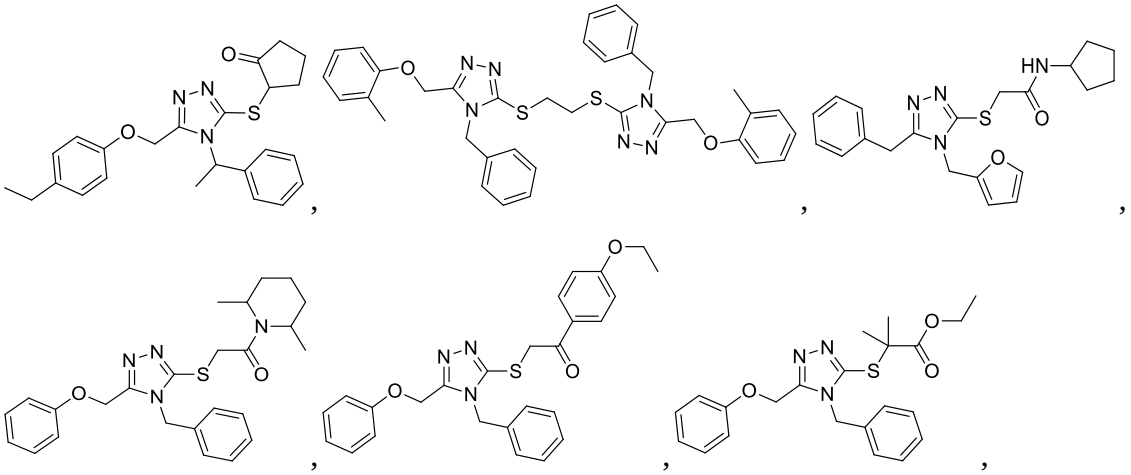
R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl;

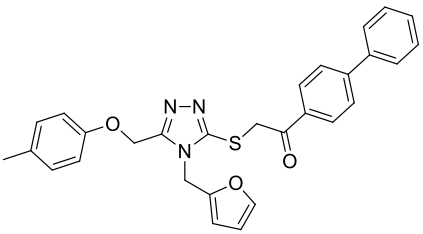
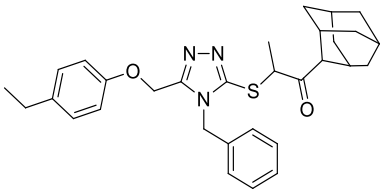
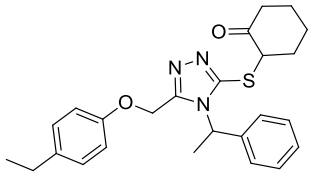
R^9 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl; and

X is -O- or absent.

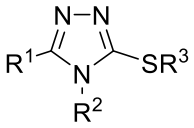
19. An *in vitro* method of inhibiting β-cat or disrupting the interaction between β-cat and TCF4, the *in vitro* method comprising: contacting β-cat with a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

20. A compound for use in therapy, wherein the compound has Formula **1**:



1

or a pharmaceutically acceptable salt thereof, wherein

R^1 is $-(CR^4_2)_mXR^5$;

R^2 is alkyl, alkynyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, heteroaralkyl, heteroaryl or $-(CR^9_2)_pR^{10}$;

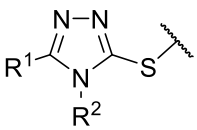
R^3 is $-(CR^6_2)_nR^7$;

R^4 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^4 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of R^6 taken together with the carbon or carbons to which they are attached form a 3-7 membered cycloalkyl;

R^7 is $-(C=O)R^8$, $-(C=O)OR^8$, or $-(C=O)N(R^8)_2$; or R^7 is a moiety having Formula **2**:



2

R^8 for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-7 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 4-7 membered optionally substituted cycloalkyl or a 4-7 membered optionally substituted heterocycloalkyl;

R^9 for each occurrence is independently hydrogen or alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl;

m is a whole number selected from 1-4;

n is a whole number selected from 0-4;

p is a whole number selected from 0-4; and

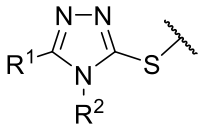
X is -O-, -S-, or is absent.

21. The compound for use of claim 20, wherein m is 1 or 2; and X is -O- or is absent.

22. The compound for use of claim 20 or 21, wherein R^5 is optionally substituted aryl.

23. The compound for use of any one of claims 20 to 22, wherein R^2 is aralkyl or heteroaralkyl.

24. The compound for use of any one of claims 20 to 23, wherein n is 1; R^6 for each occurrence is independently hydrogen or alkyl; R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **2**:



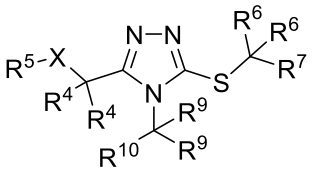
2

R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two R^8 taken together with the nitrogen to which they are attached form a 3-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

25. The compound for use of any one of claims 20 to 24, wherein R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are

attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

26. The compound for use of any one of claims 20 to 25, wherein the compound has Formula **3**:



3

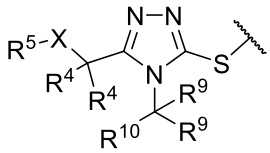
or a pharmaceutically acceptable salt thereof, wherein

R^4 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^5 is optionally substituted aryl or heteroaryl;

R^6 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^7 is -(C=O)R^8, -(C=O)OR^8, or -(C=O)N(R^8)$_2$; or R^7 is a moiety having Formula **4**:



4

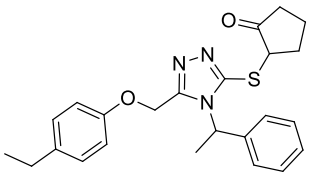
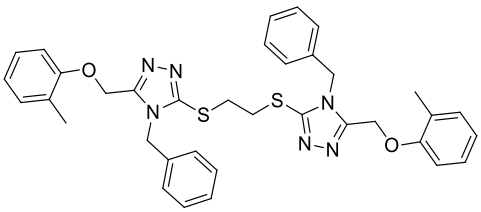
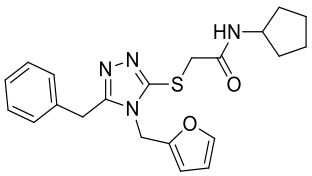
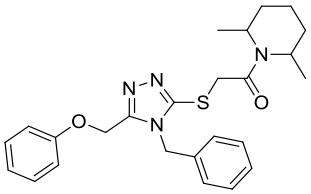
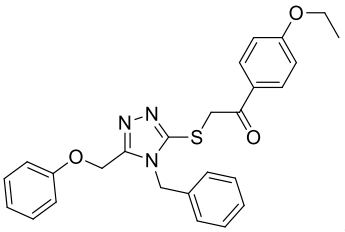
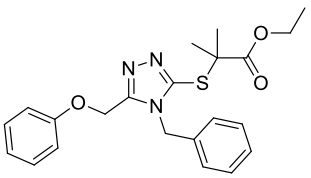
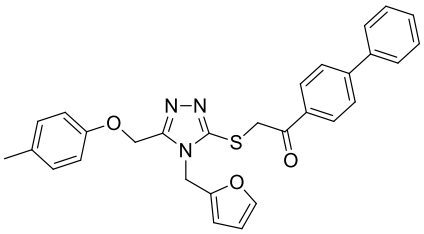
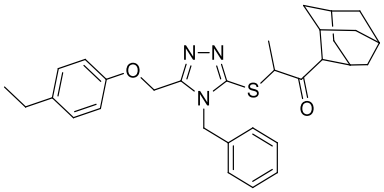
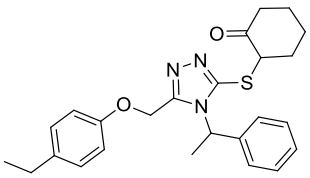
R^8 for each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, and optionally substituted aryl; or two instances of R^8 taken together with the nitrogen to which they are attached form a 5-6 membered heterocycloalkyl; or R^6 and R^8 taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl;

R^9 for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

R^{10} is cycloalkyl, aryl or heteroaryl; and

X is -O- or absent.

27. A compound for use in therapy, wherein the compound is selected from the group consisting of:


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or a pharmaceutically acceptable salt thereof.