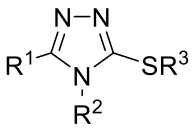
[07] There thus exists a need for improved methods for inhibiting the β-cat-TCF4 interaction and attendant attenuation of downstream Wnt signalling that address or overcome at least some of the aforementioned challenges.

[08] There also exists the need for therapeutic agents that are able to treat a disease or health condition that is ameliorated by inhibiting β-cat or disrupting the interaction between β-cat and TCF4.

**SUMMARY**

[09] Using existing protein x-ray crystal structures and biological activities of known β-cat-TCF4 interaction inhibitors, here a computational model is described that better predicts potential small molecule inhibitors of this protein-protein interaction surface. To demonstrate the predictability of the computational model system, *in silico* screening of a library of small molecules was carried out and identified 27 compounds as potential binders to β-cat. Experimental validation of the hit compounds identified 3 potent inhibitors of Wnt reporter activity of which compound GB1874 was found to elicit robust Wnt tumor inhibitory phenotypes both *in vitro* and *in vivo* phenotypic assays. Based on these results and further *in silico* and biological screening, a family of compounds that strongly inhibit Wnt reporter activity were identified.

[10] ~~In one aspect, provided~~Provided herein is use of a compound in the manufacture of a medicament for the treatment of a disease or health condition that is ameliorated by inhibiting β-catenin (β-cat) or disrupting the interaction between β-cat and T-cell factor 4 (TCF4), wherein the compound has Formula **1**:




**1**

[11] or a pharmaceutically acceptable salt thereof, wherein

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

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

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

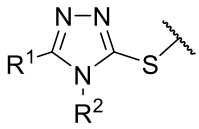
[15] $R^4$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl,

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;

[16] $R^5$ is hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

[17] $R^6$ 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;

[18] $R^7$ 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**

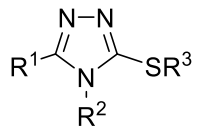
[19] $R^8$ for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which they are attached form a 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;

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

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

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

[22a] In one aspect, provided herein is 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

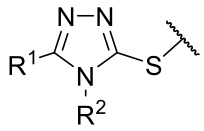
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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**

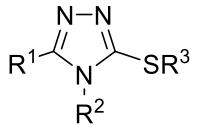
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 0-4;

n 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

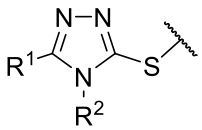
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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**

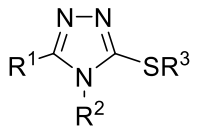
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 1-4;

n 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

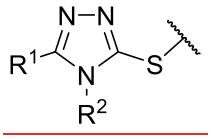
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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)O$R^8$, or -(C=O)N($R^8$)$_2$; or $R^7$ is a moiety having Formula **2**:



**2**

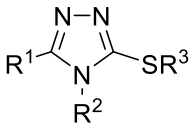
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 0-4;

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

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

[23] ~~In another aspect, provided~~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 –($CR^4_2$)$_m$X$R^5$;

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

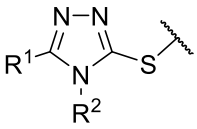
[27] $R^3$ is $–(CR^6_2)_nR^7$;

[28] $R^4$ 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;

[29] $R^5$ is hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

[30] $R^6$ 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;

[31] $R^7$ 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**

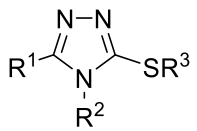
[32] $R^8$ for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which they are attached form a 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;

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

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

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

[35a] 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 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

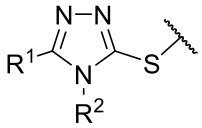
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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**

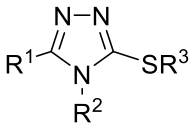
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 0-4;

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

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

[36] ~~In another aspect, provided~~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**

[37] or a pharmaceutically acceptable salt thereof, wherein

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

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

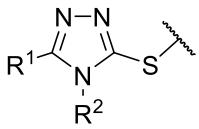
[40] $R^3$ is $-(CR^6_2)_nR^7$;

[41] $R^4$ 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;

[42] $R^5$ is hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

[43] $R^6$ 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;

[44] $R^7$ 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**

[45] $R^8$ for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, 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;

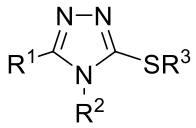
[46] m is a whole number selected from 0-4;

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

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

[49] ~~In another aspect, provided~~Provided herein is a compound for use in treating a disease or health condition that is ameliorated by inhibiting β-cat or disrupting the interaction between β-cat and TCF4, wherein the compound has Formula **1**:

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



**1**

[63] or a pharmaceutically acceptable salt thereof, wherein

[64] $R^1$ is $–(CR^4_2)_mXR^5$;

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

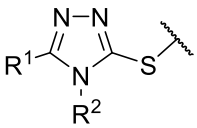
[66] $R^3$ is $–(CR^6_2)_nR^7$;

[67] $R^4$ 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;

[68] $R^5$ is hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl;

[69] $R^6$ 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;

[70] $R^7$ 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**

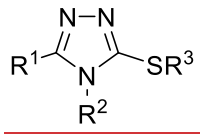
[71] $R^8$ for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which they are attached form a 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;

[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, cycloalkylalkyl heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

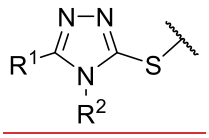
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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 hydrogen, 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 optionally substituted 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;

m is a whole number selected from 1-4;

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

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

**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.

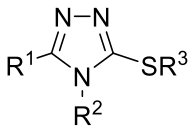
[77] **Figure 2** depicts an *in silico* investigation of predicted compounds for Wnt signaling inhibition. (**a**) TOPFlash reporter activity of predicted compounds in HEK293T STF cells. The cells were treated with the compounds at 10 μM and simultaneously stimulated with 500 ng/mL of Wnt3A for 24 hr 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

viability at the same concentration and presented as fold change over DMSO treated cells. $IC_{50}$ values were calculated using a four-parameter nonlinear regression. Error bars represent standard deviation of 3 replicates. (**c)** Chemical structures of iCRT3 and the top 3 hit compounds. (**d**) The predicted binding modes of iCRT3 (i), and 3 novel hits found in this study: GB8679 (ii), GB6853 (iii), and GB1874 (iv) in the optimized, most enriching β-catenin structure (partial transparent surface). The docked ligands were highlighted (solid stick), and the critical β-catenin binding site residues (partial transparent stick). The TCF4 peptide fragment (solid line) from β-catenin/TCF4 crystal complex structure (PDBID 1JPW) is also shown here to indicate the PPI interface.

[78] **Figure 3** depicts the effect of hit compounds on HCT116 cells via the Wnt signaling pathway. (a) Co-immunoprecipitation of β-catenin and its endogenous binding partners.

What is claimed:

1. ~~The use~~Use of a compound in the manufacture of a medicament for the treatment of a ~~disease or health condition that is ameliorated by inhibiting β-catenin (β-cat) or disrupting the interaction between β-cat and T-cell factor 4 (TCF4)~~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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

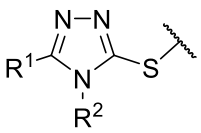
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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 ~~hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl,~~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**

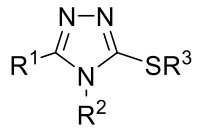
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 0-4;

n 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

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

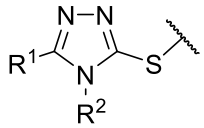
$R^4$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two instances of $R^4$ taken together with the carbon or carbons to which 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**

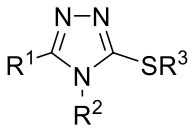
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, optionally substituted aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which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

m is a whole number selected from 1-4;

n 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 $-(CR^4_2)_mXR^5$;

$R^2$ is alkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

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

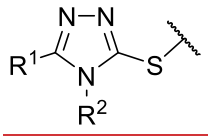
$R^4$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl,

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 hydrogen, 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 optionally substituted 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;

m is a whole number selected from 0-4;

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

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

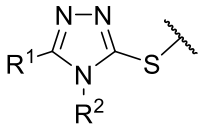
~~2.~~4. The use of ~~claim 1~~any one of claims 1 to 3, wherein m is 1 or 2; and X is -O- or is absent.

~~3.~~5. The use of ~~claim 2~~any one of claims 1 to 4, wherein $R^5$ is ~~cycloalkyl or~~optionally substituted aryl.

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

~~5.~~7. The use of ~~claim 1~~any one of claims 1, 2, 4 and 5, wherein $R^2$ is $-(CR^9{}_2)_pR^{10}$, wherein p is a whole number selected from 0-4; $R^9$ for each occurrence is independently hydrogen or alkyl; and $R^{10}$ is cycloalkyl, aryl or heteroaryl.

~~6.~~8. The use of ~~claim 1~~any one of claims 1 to 7, 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)O$R^8$, or -(C=O)N($R^8$)$_2$; or $R^7$ is a moiety having Formula **2**:

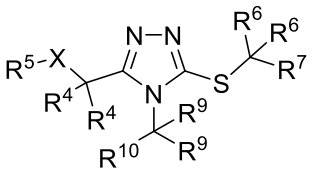


**2**

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

~~7.~~9. The use of ~~claim 6~~any one of claims 1 to 8, wherein $R^8$ for each occurrence is independently selected from the group consisting of hydrogen, 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 optionally substituted heterocycloalkyl; or $R^6$ and $R^8$ taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

~~8.~~10. The use of ~~claim 1~~any one of claims 1 to 9, wherein the compound has Formula **3**:



**3**

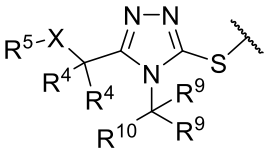
or a pharmaceutically acceptable salt thereof, wherein

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



**4**

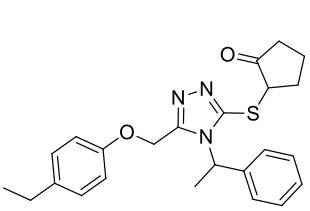
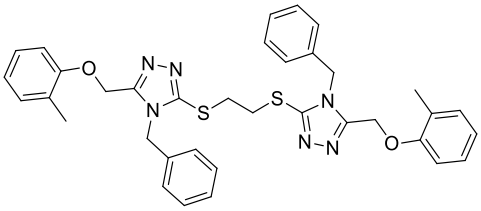
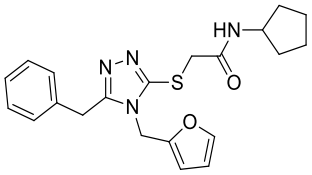
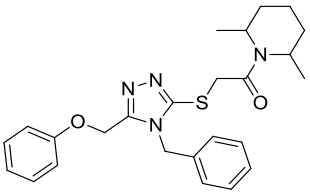
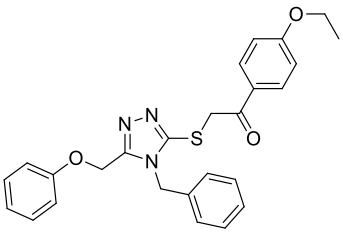
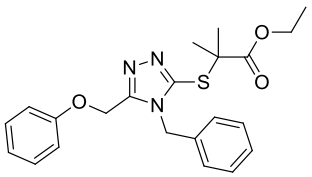
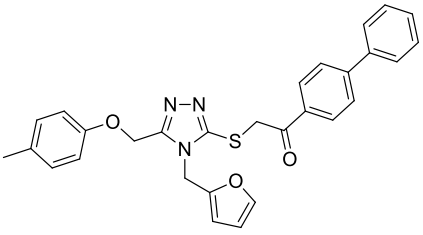
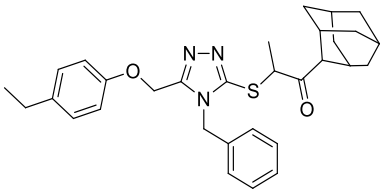
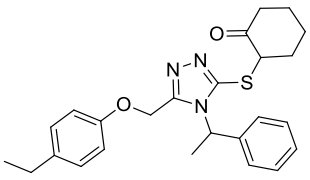
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and optionally substituted aryl; or two instances of $R^8$ taken together with the nitrogen to which they are attached form a 5-6 membered optionally substituted heterocycloalkyl; or $R^6$ and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

~~9.~~11. The use of ~~claim 1~~any one of claims 1 to 10, wherein the compound is selected from the group consisting of:

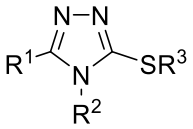

,

,

,

,

,

,

,

, and


or a pharmaceutically acceptable salt thereof.

~~10. The use of claim 1, wherein the disease or health condition is selected from the group consisting of cancer, neurodegenerative, a metabolic disease, a cardiovascular disease, fibrosis, and a bone disease.~~

~~11.~~12. The use of ~~claim 1~~any one of claims 3 to 11, wherein the ~~disease or health condition is a~~ cancer is selected from the group consisting of colorectal cancer, hepatocellular cancer, melanoma, liver cancer, breast cancer, prostate cancer, and leukemia.

~~12.~~13. 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, cycloalkylalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

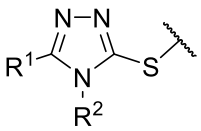
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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 ~~hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl,~~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 hydrogen, 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 optionally substituted 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;

m is a whole number selected from 0-4;

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

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

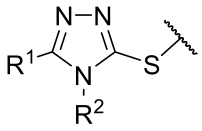
~~13.~~14. The *in vitro* method of claim ~~12~~13, wherein m is 1 or 2; and X is -O- or is absent.

~~14.~~15. The *in vitro* method of claim ~~13~~13 or 14, wherein $R^5$ is ~~cycloalkyl or~~optionally substituted aryl.

~~15.~~16. The *in vitro* method of claim ~~12~~any one of claims 13 to 15, wherein $R^2$ is cycloalkyl, aralkyl or heteroaralkyl.

~~16.~~17. The *in vitro* method of claim ~~12~~any one of claims 13 to 16, wherein $R^2$ is $-(CR^9_2)_pR^{10}$, wherein p is a whole number selected from 0-4; $R^9$ for each occurrence is independently hydrogen or alkyl; and $R^{10}$ is cycloalkyl, aryl or heteroaryl.

~~17.~~18. The *in vitro* method of ~~claim 12~~any one of claims 13 to 17, 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**:

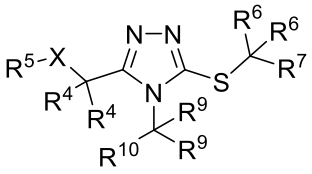



**2**

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

~~18.~~19. The *in vitro* method of ~~17~~any one of claims 13 to 18, wherein $R^8$ for each occurrence is independently selected from the group consisting of hydrogen, 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 optionally substituted heterocycloalkyl; or $R^6$ and $R^8$ taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

~~19.~~20. The *in vitro* method of ~~claim 12~~any one of claims 13 to 19, wherein the compound has Formula **3**:



**3**

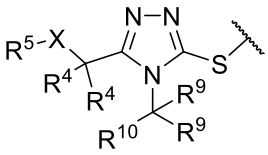
or a pharmaceutically acceptable salt thereof, wherein

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



**4**

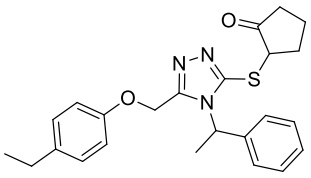
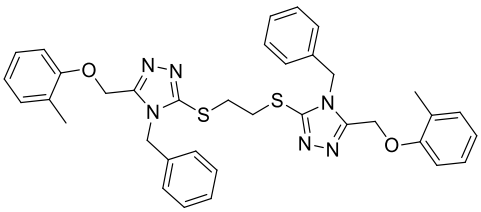
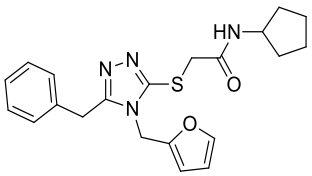
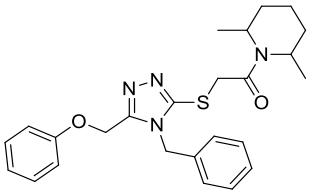
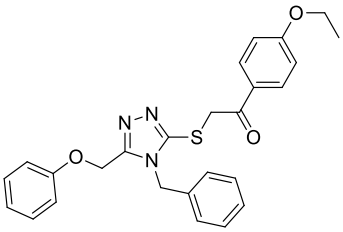
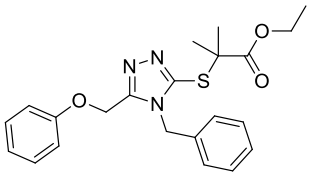
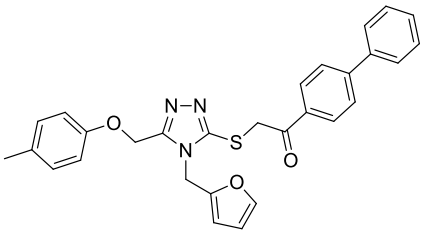
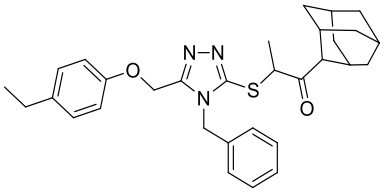
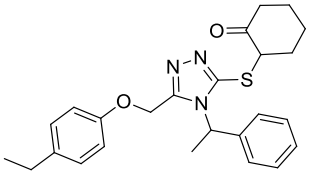
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and optionally substituted aryl; or two instances of $R^8$ taken together with the nitrogen to which they are attached form a 5-6 membered optionally substituted heterocycloalkyl; or $R^6$ and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

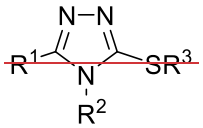
X is -O- or absent.

~~20.~~21. The *in vitro* method of ~~claim 12~~any one of claims 13 to 20, wherein the compound is selected from the group consisting of:


,

,

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,

,

,

,

, and


or a pharmaceutically acceptable salt thereof.

~~21. 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**~~

~~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, or heteroaryl;~~

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

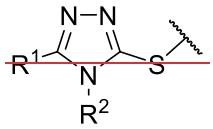
~~$R^4$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl,~~

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 hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, 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**

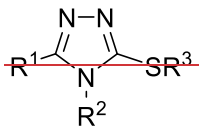
$R^8$ for each occurrence is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, and heteroaralkyl; or two $R^8$ taken together with the nitrogen to which they are attached form a 3-7 membered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

m is a whole number selected from 0-4;

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

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

22. A compound for use in treating a disease or health condition that is ameliorated by inhibiting β-cat or disrupting the interaction between β-cat and TCF4, 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, or heteroaryl;

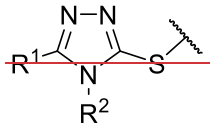
$R^3$ is $(CR^6{}_2)_nR^7$;

$R^4$ 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 hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, 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, 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 cycloalkyl or 4-7 heterocycloalkyl;

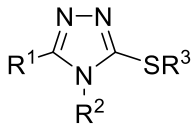
m is a whole number selected from 0-4;

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

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

23. The compound for use according to claim 22, wherein the disease or health condition is selected from the group consisting of cancer, neurodegenerative, a metabolic disease, a cardiovascular disease, fibrosis, and a bone disease.

~~24.~~22. 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, ~~alkenyl,~~ alkynyl, ~~cycloalkyl,~~ cycloalkenyl, cycloalkylalkyl heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, heteroaralkyl, or heteroaryl;

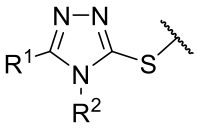
$R^3$ is $-(CR^6_2)_nR^7$;

$R^4$ 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 ~~hydrogen, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl,~~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 hydrogen, 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 optionally substituted 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;

m is a whole number selected from ~~0~~1-4;

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

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

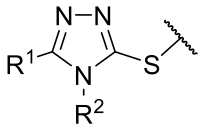
23. The compound for use of claim 22, wherein m is 1 or 2; and X is -O- or is absent.

24. The compound for use of claim 22 or 23, wherein $R^5$ is optionally substituted aryl.

25. The compound for use of any one of claims 22 to 24, wherein $R^2$ is aralkyl or heteroaralkyl.

26. The compound for use of any one of claims 22 to 25, wherein $R^2$ is $-(CR^9_2)_pR^{10}$, wherein p is a whole number selected from 0-4; $R^9$ for each occurrence is independently hydrogen or alkyl; and $R^{10}$ is cycloalkyl, aryl or heteroaryl.

27. The compound for use of any one of claims 22 to 26, 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**:

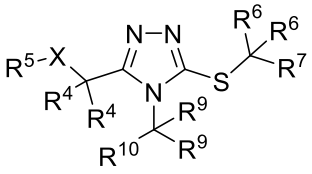



**2**

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

28. The compound for use of any one of claims 22 to 27, wherein $R^8$ for each occurrence is independently selected from the group consisting of hydrogen, 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 optionally substituted heterocycloalkyl; or $R^6$ and $R^8$ taken together with the atoms to which they are attached form a 5-6 membered cycloalkyl.

29. The compound for use of any one of claims 22 to 28, wherein the compound has Formula **3**:



**3**

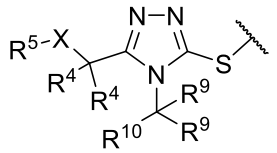
or a pharmaceutically acceptable salt thereof, wherein

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



**4**

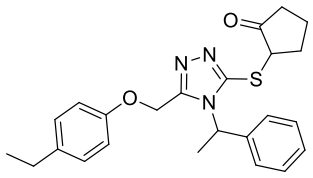
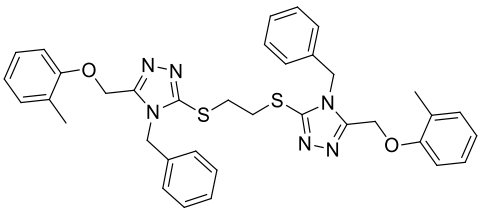
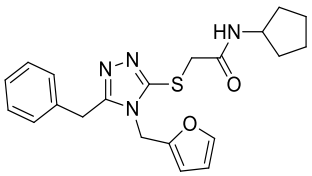
$R^8$ for each occurrence is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and optionally substituted aryl; or two instances of $R^8$ taken together with the nitrogen to which they are attached form a 5-6 membered optionally substituted heterocycloalkyl; or $R^6$ and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

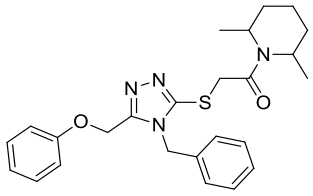
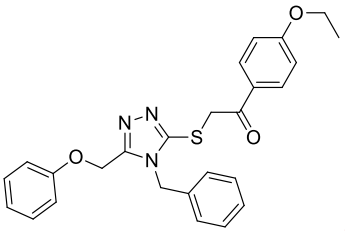
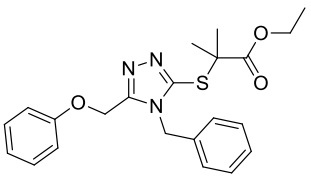
$R^9$ for each occurrence is independently selected from the group consisting of hydrogen and alkyl;

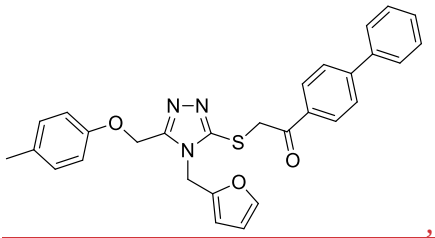
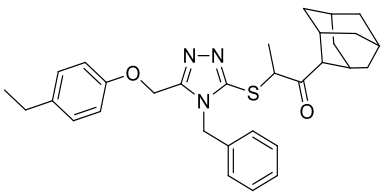
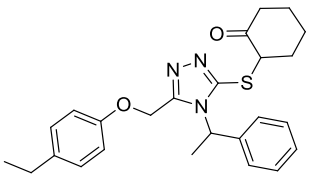
$R^{10}$ is cycloalkyl, aryl or heteroaryl; and

X is -O- or absent.

30. The compound for use of any one of claims 22 to 29, wherein the compound is selected from the group consisting of:

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, , ,

, , and 

or a pharmaceutically acceptable salt thereof.