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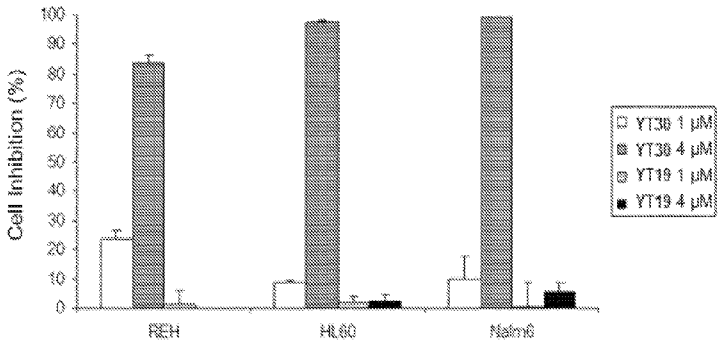
[Continued on next page]

(54) **Title**: TREATMENT OF CANCER AND OTHER CONDITIONS USING A TRANSCRIPTION FACTOR MODULATOR

Fig. 1



(57) **Abstract**: The present disclosure provides novel methods for treating cancer and conditions regulatable by a transcription factor and/or cofactor using specific compounds, as well as compositions, and pharmaceutical formulations. In certain embodiments, the compounds are transcription factor modulators. Hematological cancer includes leukemia, lymphoma, and myeloma. Leukemia is a type of cancer of blood or bone marrow characterized by an abnormal increase of immature leukocytes. The exact cause of leukemia is unknown; however, it generally results from DNA mutations in stem cells.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

TREATMENT OF CANCER AND OTHER CONDITIONS USING A TRANSCRIPTION FACTOR MODULATOR

PRIORITY CLAIM

[0001] This application claims priority to United States Patent Application Serial No. 13/844,396, filed March 15, 2013, and United States Provisional Patent Application Serial No. 61/773,798, filed March 6, 2013, which are incorporated herein by reference in their entirety, as if fully set forth herein.

BACKGROUND

[0002] Hematological cancer includes leukemia, lymphoma, and myeloma. Leukemia is a type of cancer of blood or bone marrow characterized by an abnormal increase of immature leukocytes. The exact cause of leukemia is unknown; however, it generally results from DNA mutations in stem cells.

[0003] Leukemia is the most common malignant tumor in children (Leukemia in Children). Among all cancers, leukemia is most common and the leading cause of death for children and teens under 20 years old (Blood Cancers: Leukemia, Lymphoma, and Myeloma). Although leukemia can be classified into a large variety of groups, one of the most commonly used methods is to classify leukemia into four major subtypes: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) (Types of Leukemia, National Cancer Institute).

[0004] Since it is not possible to remove leukemia via surgery, standard treatment options for leukemia are chemotherapy and radiotherapy. Among the four major subtypes, CML may be treated with the introduction of imatinib (Gleevec) into chemotherapy with some success. Unfortunately, CML only accounts for about 15% of adult leukemia (Faderl et al, 1999). Other leukemia patients still rely on traditional chemotherapeutic drugs (e.g., cisplatin), most of which are cytotoxic in nature.

[0005] Cytotoxic drugs act to disrupt cell proliferation by directly destroying cellular DNA, incorporating into the DNA template and interfering with DNA synthesis, inhibiting microtubule assembly/disassembly, impairing nucleic acid synthesis, or disrupting protein synthesis. Unfortunately, cytotoxic drugs function in a non-specific manner and kill both cancer cells and normal cells, resulting in severe adverse side effects for patients. Further, by interfering with DNA synthesis,

cytotoxic drugs may also induce new DNA mutations that could result in the occurrence of new cancers (Carew et al., 2003; Sturm et al., 2003).

[0006] Given the lack of an effective treatment option and the negative side effects associated with current treatment options there is a need to develop a new generation of target-specific drugs for the treatment of leukemia and other cancers with improved therapeutic benefits and reduced side effects.

SUMMARY

[0007] One aspect of the present disclosure relates to methods of treating cancer by administering one or more compounds disclosed herein or a composition or pharmaceutical formulation thereof.

[0008] Another aspect relates to the use of one or more compounds disclosed herein, or a composition or pharmaceutical formulation thereof, in the manufacture of a medicament for the treatment of a cancer. In certain embodiments, the cancer is breast cancer, central nervous system cancer, colon cancer, prostate cancer, lung cancer, leukemia, renal cancer, ovarian cancer, melanoma, liver cancer, and/or cervical cancer. In certain embodiments, when the cancer is leukemia, the type of leukemia may include, but is not limited to, acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma.

[0009] Another aspect described herein relates to a method of treating a condition regulatable by a transcription factor and/or cofactor comprising administering to the subject a therapeutically effective amount of one or more compounds disclosed herein or a composition or pharmaceutical formulation thereof.

[0010] Another aspect relates to the use of one or more compounds disclosed herein or a composition or pharmaceutical formulation thereof in the manufacture of a medicament for the treatment of a condition regulatable by a transcription factor and/or cofactor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 – Growth inhibition of REH, HL60, and Nalm-6 leukemia cell lines in the presence of different concentrations of YT30 and inactive YT19.

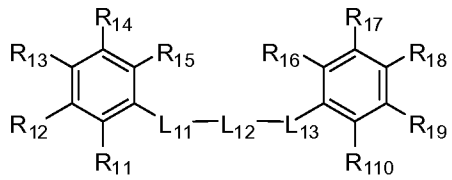
[0012] Figure 2 – Cumulative survival of BALB/c nude mice bearing acute

lymphoblastic leukemia injected with YT30 or solvent control.

DETAILED DESCRIPTION

[0013] ***I. Compounds***

[0014] In certain embodiments, the compounds disclosed herein comprise a structure of Formula I:



Formula I,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

R_{11}-R_{19} and R_{110} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, amino, alkylamino, dialkylamino, arylamino, heteroarylamino, hydroxy, haloalkyl, and halogen, and optionally, two or more substituents of R_{11}-R_{19} and R_{110} combine together to form a ring of up to 12 atoms;

L_{11} and L_{13} are linking groups each independently selected from the group consisting of amino, alkylamino, arylamino, oxa, keto, NHC(=O), NR(C=O), S(=O) and -$S(=O)_2$; and

L_{12} is a linking group selected from the group consisting of a chain of up to 10 carbon atoms, wherein up to three atoms are replaced with one or more hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur atom, and said one or more hetero atoms are optionally further substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, benzo, hydroxy, alkoxy, aryloxy, oxa, keto, amido, sulfonamido, and fluoro. In certain of these embodiments, the compounds are transcription factor modulators.

[0015] In certain embodiments:

R_{11}, R_{15}, R_{16}, and R_{110} are each independently selected from the group consisting of NH_2 and H, at least one of R_{11} and R_{15} is H, and at least one of R_{16} and R_{110} is H;

R_{12} and R_{14} are each independently selected from the group consisting of H, aryl (e.g. phenyl), alkyl (e.g. methyl, ethyl, isopropyl), hydroxyl, and arylcarbonyl (e.g. phenyl carbonyl);

R_{13} is selected from the group consisting of H, alkylamino (e.g. dimethyl amino), arylcarbonyl (e.g. phenyl carbonyl) and aryl (e.g. phenyl);

R_{17} and R_{19} are each independently selected from the group consisting of H, halogen (e.g. Br, F), heteroaryl (e.g. pyridinyl), alkoxy (e.g. $-OCH_3$), and haloalkyl (e.g. CF_3);

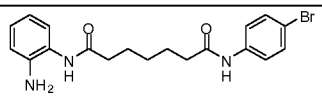
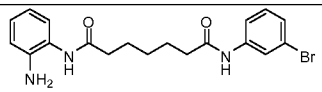
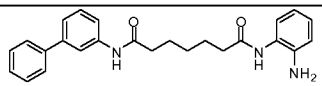
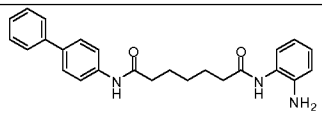
R_{18} is selected from the group consisting of H and halogen (e.g. Br);

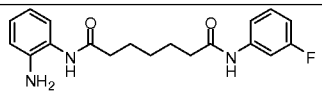
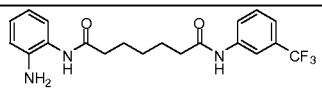
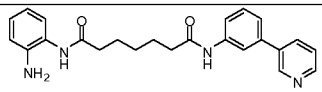
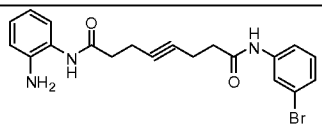
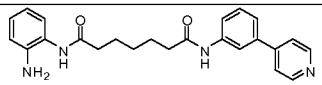
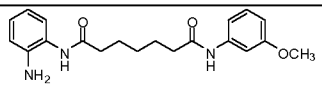
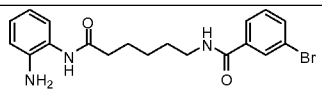
$-L_{11}$-and $-L_{13}$- are independently -NH-C(=O)- or -C(=O)-NH-; and

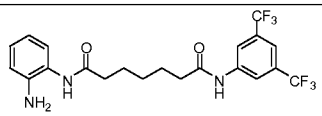
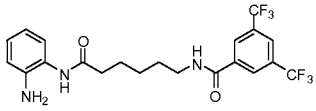
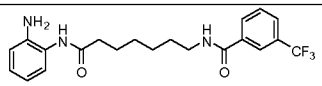
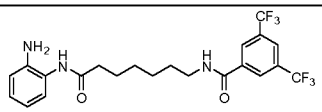
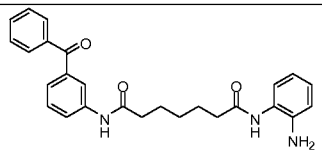
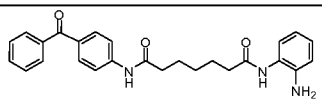
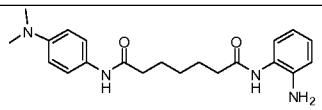
$-L_{11}-L_{12}-L_{13}$- is a symmetric structure of -NH-C(=O)-L_{12}-C(=O)-NH-, or an asymmetric structure of -NHC(=O)-L_{12}-NH-C(=O)-, or -C(=O)-NH-L_{12}-C(=O)-NH-.

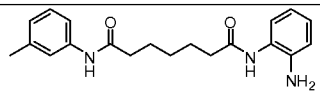
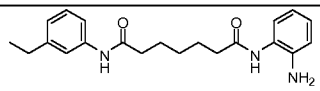
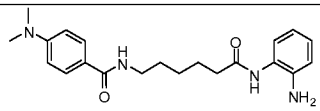
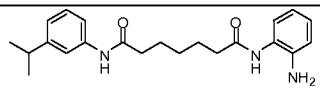
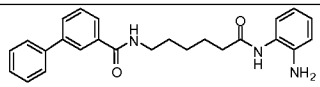
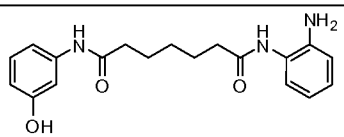
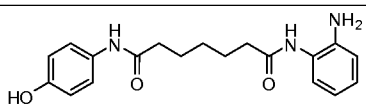
[0016] Embodiments of compounds of Formula I include, without limitation, the compounds listed in Table 1.

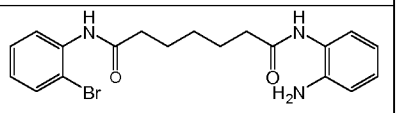
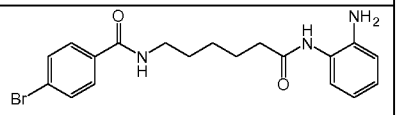
Table 1. Exemplary Compounds of Formula I

Compound Name	Structure
YT29	
YT30	
YT45	
YT46	

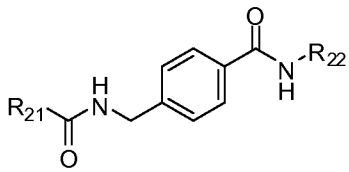
Compound Name	Structure
YT53	
YT54	
YT58	
YT61	
YT62	
YT63	
YT65	

Compound Name	Structure
YT67	
YT68	
YT73	
YT74	
YT76	
YT77	
YT78	

Compound Name	Structure
YT79	
YT80	
YT99	
YT 108	
YT116	
YT134	
YT135	

Compound Name	Structure
YT138	
YT139	

[0017] In certain embodiments, the compounds disclosed herein comprise a structure of Formula II:



Formula II

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

R_{21} and R_{22} are each independently selected from the group consisting of aryl and heteroaryl.

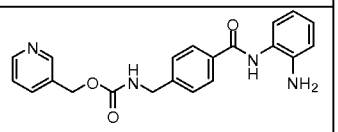
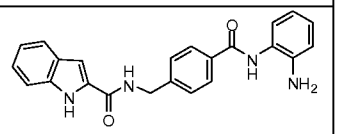
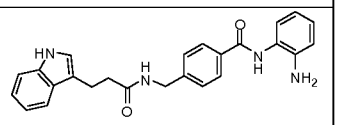
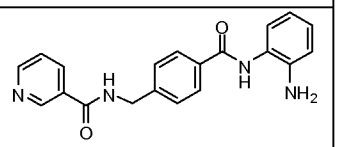
[0018] In certain embodiments:

R_{21} is selected from the group consisting of heteroarylalkoxy (e.g. wherein alkoxy is C_1-C_2 alkoxy, and heteroaryl is pyridinyl or benzopyrrolyl), heteroarylalkyl (e.g. wherein alkyl is C_1-C_2 alkyl, and heteroaryl is pyridinyl or benzopyrrolyl), and heteroaryl (e.g. pyridinyl); and

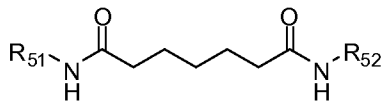
R_{22} is aryl (e.g. aminophenyl). In certain of these embodiments, the compounds are transcription factor modulators.

[0019] Embodiments of compounds of Formula II include, without limitation, the compounds listed in Table 2.

Table 2. Exemplary Compounds of Formula II

Compound Name	Structure
YT91	
YT118	
YT121	
YT123	

[0020] In certain embodiments, the compounds disclosed herein comprise a structure of Formula V:



Formula V

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

R_{51} and R_{52} are each independently selected from the group consisting of alkyl, aryl, and heteroaryl. In certain of these embodiments, the compounds are transcription factor modulators.

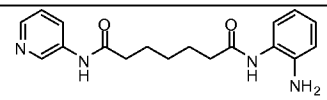
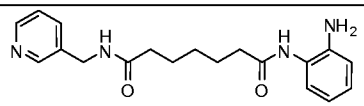
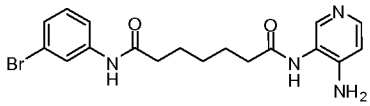
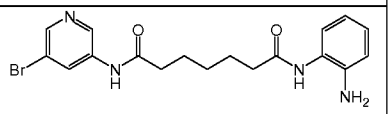
[0021] In certain embodiments:

R_{51} is heteroaryl (e.g. pyridinyl, optionally substituted with e.g. amino (e.g. NH_2) or halogen (e.g. Br)); and

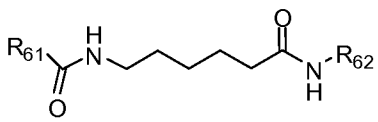
R_{52} is aryl (e.g. phenyl, optionally substituted with e.g. amino (e.g. NH_2) or halogen (e.g. Br)).

[0022] Embodiments of compounds of Formula V include, without limitation, the compound listed in Table 3.

Table 3. Exemplary Compounds of Formula V

Compound Name	Structure
YT51	
YT132	
YT136	
YT137	

[0023] In certain embodiments, the compounds disclosed herein comprise a structure of Formula VI:



Formula VI

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

R_{61} and R_{62} are independently selected from the group consisting of aryl, and heteroaryl. In certain of these embodiments, the compounds are transcription factor modulators.

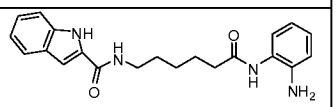
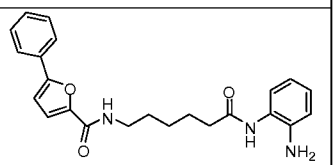
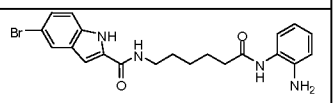
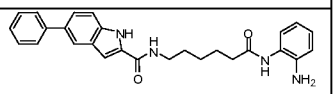
[0024] In certain embodiments:

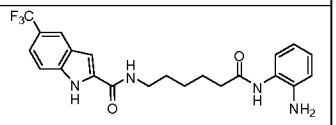
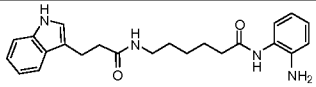
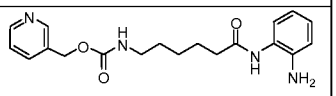
R_{61} is selected from the group consisting of heteroaryl (e.g. benzopyrrolyl, benzopyrrolyl substituted with halogen (e.g. Br), haloalkyl (e.g. CF3), or aryl (e.g. phenyl); and furanyl substituted with aryl (e.g. phenyl)), heteroarylalkyl (e.g. wherein alkyl is C_2-alkyl, and heteroaryl is benzopyrrolyl), and heteroarylalkoxy (e.g. wherein alkoxy is C_1-alkoxy, and heteroaryl is pyridinyl); and

R_{62} is aryl (e.g. aminophenyl).

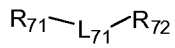
[0025] Embodiments of compounds of Formula VI include, without limitation, the compounds listed in Table 4.

Table 4. Exemplary Compounds of Formula VI

Compound Name	Structure
YT86	
YT88	
YT109	
YT110	

Compound Name	Structure
YT117	
YT127	
YT131	

[0026] In certain embodiments, the compounds disclosed herein comprise a structure of Formula VII:



Formula VII

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

R_{71} and R_{72} are each independently selected from the group consisting of aryl, and heteroaryl; and

L_{71} has a structure of $-L_{72}-L_{73}-L_{74}-$, wherein:

$-L_{72}-$ and $-L_{73}-$ are -C(=O)-N-; and

L_{73} is an alkyl chain of up to 10 carbons, optionally inserted with:

.

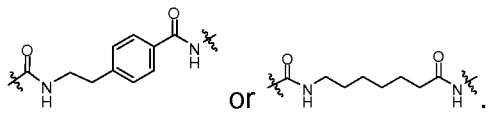
In certain of these embodiments, the compounds are transcription factor modulators.

[0027] In certain embodiments:

R_{71} is heteroaryl (e.g. benzopyrrolyl);

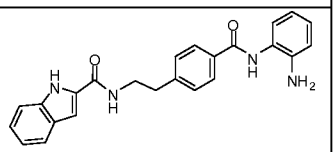
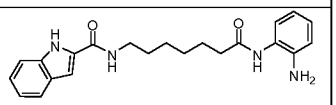
R_{72} is aryl (e.g. aminophenyl); and

L_{71} is:

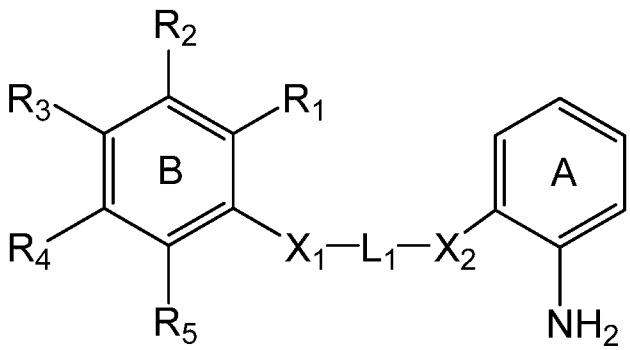


[0028] Embodiments of compounds of Formula VII include, without limitation, the compounds listed in Table 5.

Table 5. Exemplary Compounds of Formula VII

Compound Name	Structure
YT122	
YT128	

[0029] In another embodiment, the compounds disclosed herein comprise a structure of Structure I:



Structure I,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

A and B rings are each independently selected from the group consisting of phenyl, pyridyl and N-alkylated pyridyl rings;

R_1-R_5 are each independently selected from the group consisting of hydrogen, halogen, and haloalkyl, wherein at least one or two of R_1-R_5 are halogen and/or haloalkyl;

X_1 and X_2 are independently selected from –NHC(=O)- or –C(=O)-NH-; and

L_1 is $–(CH_2)_n$-, where n is 4, 5, 6, 7, or 8, where one or more $–CH_2$- moieties are optionally replaced with one or more substituents selected from the group consisting of -O-, -S-, -C(=O)-, -S(=O)-, $-S(=O)_2$-, -NH-C(=O)-, -C(=O)-NH-, -NR- (wherein R is hydrogen, alkyl or aryl), -C=C-, carbon-carbon triple bond, phenylene (e.g. 1, 4-phenylene) and cyclohexylene (e.g. 1, 4-cyclohexylene). In certain of these embodiments, the compounds are transcription factor modulators.

[0030] In certain embodiments, L_1 is $–(CH_2)_n$-, where n is 4, 5, 6, 7, or 8.

[0031] In certain embodiments, $-X_1-L_1-X_2$-is $–NHC(=O)-L_1–C(=O)NH$-.

[0032] In certain embodiments, $-X_1-L_1-X_2$-is $–C(=O)-NH-L_1–C(=O)NH$-.

[0033] In certain embodiments, A ring is a phenyl ring, and B ring is a pyridyl ring or N-alkylated pyridyl ring.

[0034] In certain embodiments, both A and B rings are phenyl rings.

[0035] In certain embodiments, A ring is a pyridyl ring, and B ring is a phenyl ring or N-alkylated pyridyl ring.

[0036] In certain embodiments, both A and B rings are pyridyl rings.

[0037] In certain embodiments, A ring is an N-alkylated pyridyl ring, and B ring is a phenyl ring or pyridyl ring.

[0038] In certain embodiments, both A and B rings are N-alkylated pyridyl rings.

[0039] In certain embodiments, R_4 and/or R_5 are/is haloalkyl (e.g. trifluoromethyl).

[0040] In certain embodiments, R_4 and/or R_5 are/is halogen (e.g. Br).

[0041] In certain embodiments, one of R_4 and R_5 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

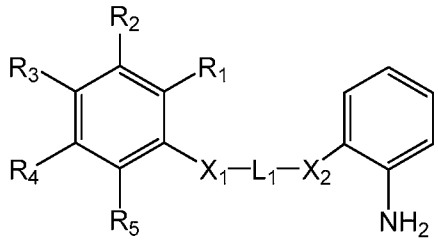
[0042] In certain embodiments, R_3 and/or R_4 are/is haloalkyl (e.g. trifluoromethyl).

[0043] In certain embodiments, R_3 and/or R_4 are/is halogen (e.g. Br).

[0044] In certain embodiments, one of R_3 and R_4 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

[0045] In another embodiment, the compounds disclosed herein comprise a

structure of Structure II:



Structure II,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein R_1-R_5, X_1, X_2, and L_1 are defined the same as above. In certain of these embodiments, the compounds are transcription factor modulators.

[0046] In certain embodiments, R_4 and/or R_5 are/is haloalkyl (e.g. trifluoromethyl).

[0047] In certain embodiments, R_4 and/or R_5 are/is halogen (e.g. Br).

[0048] In certain embodiments, R_3 and/or R_4 are/is haloalkyl (e.g. trifluoromethyl).

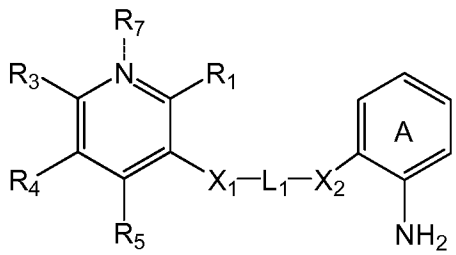
[0049] In certain embodiments, R_3 and/or R_4 are/is halogen (e.g. Br).

[0050] In certain embodiments, L_1 is $–(CH_2)_n-$, where n is 4, 5, 6, 7, or 8.

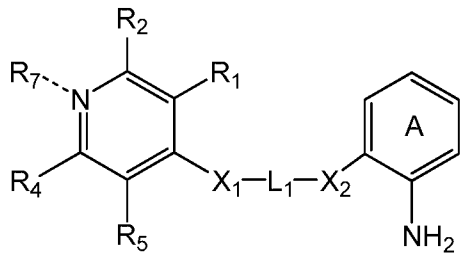
[0051] In certain embodiments, $-X_1-L_1-X_2-$ is $–NHC(=O)-L_1–C(=O)NH-$.

[0052] In certain embodiments, $-X_1-L_1-X_2-$ is $–C(=O)-NH-L_1–C(=O)NH-$.

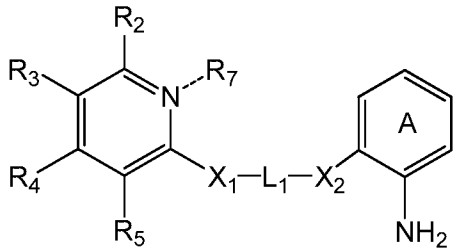
[0053] In another embodiment, the compounds disclosed herein comprise a structure selected from the group consisting of Structures IIIA-IIIC:



Structure IIIA,



Structure IIIB,



Structure IIIC,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

A ring, R_1-R_5, X_1, X_2, and L_1 are defined the same as above; and

R_7 is alkyl group having 1-3 carbon atoms (e.g. methyl). In certain of these embodiments, the compounds are transcription factor modulators.

[0054] In certain embodiments, the N-alkylated pyridine ring of Structures IIIA-IIIC may be positively charged and form a salt with one or more suitable counterions (e.g., without limitations, anions derived from pharmaceutically acceptable acids described herein, e.g. acetate, fluoroacetate or other carboxylate).

[0055] In certain embodiments, R_4 and/or R_5 are/is haloalkyl (e.g. trifluoromethyl).

[0056] In certain embodiments, R_4 and/or R_5 are/is halogen (e.g. Br).

[0057] In certain embodiments, one of R_4 and R_5 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

[0058] In certain embodiments, R_3 and/or R_4 are/is haloalkyl (e.g. trifluoromethyl).

[0059] In certain embodiments, R_3 and/or R_4 are/is halogen (e.g. Br).

[0060] In certain embodiments, one of R_3 and R_4 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

[0061] In certain embodiments, A ring is a phenyl ring.

[0062] In certain embodiments, A ring is a pyridyl ring.

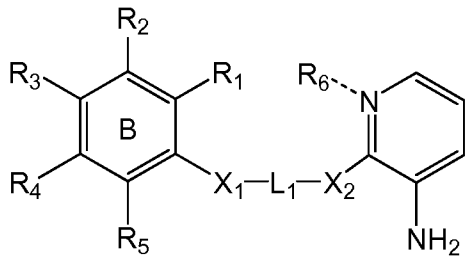
[0063] In certain embodiments, A ring is an N-alkylated pyridyl ring.

[0064] In certain embodiments, L_1 is $–(CH_2)_n-$, where n is 4, 5, 6, 7, or 8.

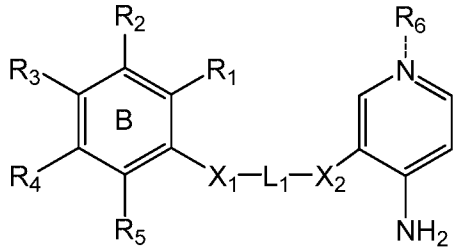
[0065] In certain embodiments, $-X_1-L_1-X_2-$is –NHC(=O)-L_1–C(=O)NH-.

[0066] In certain embodiments, $-X_1-L_1-X_2-$is –C(=O)-NH-L_1–C(=O)NH-.

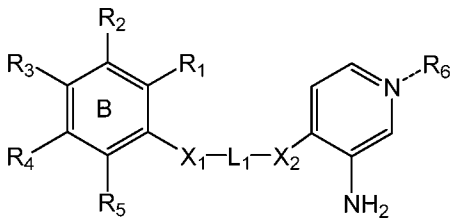
[0067] In another embodiment, the one or more compounds disclosed herein comprise a structure selected from the group consisting of Structures IVA-IVD:



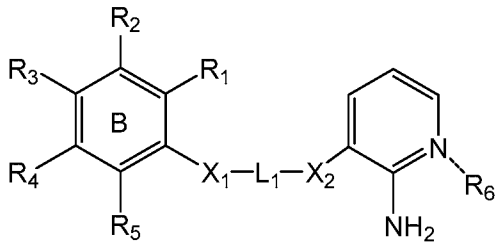
Structure IVA



Structure IVB



Structure IVC



Structure IVD

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

B ring, R_1-R_5, X_1, X_2, and L_1 are defined the same as above; and

R_6 is alkyl group having 1-3 carbon atoms (e.g. methyl). In certain of these embodiments, the compounds are transcription factor modulators.

[0068] In certain embodiments, the N-alkylated pyridine ring of Structures IVA-IVD may be positively charged and form a salt with one or more suitable counterions (e.g., without limitations, anions derived from pharmaceutically acceptable acids described herein, acetate, fluoroacetate or other carboxylate).

[0069] In certain embodiments, R_4 and/or R_5 are/is haloalkyl (e.g. trifluoromethyl).

[0070] In certain embodiments, R_4 and/or R_5 are/is halogen (e.g. Br).

[0071] In certain embodiments, one of R_4 and R_5 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

[0072] In certain embodiments, R_3 and/or R_4 are/is haloalkyl (e.g. trifluoromethyl).

[0073] In certain embodiments, R_3 and/or R_4 are/is halogen (e.g. Br).

[0074] In certain embodiments, one of R_3 and R_4 is haloalkyl (e.g. trifluoromethyl), and the other is halogen (e.g. Br).

[0075] In certain embodiments, B ring is a phenyl ring.

[0076] In certain embodiments, B ring is a pyridyl ring.

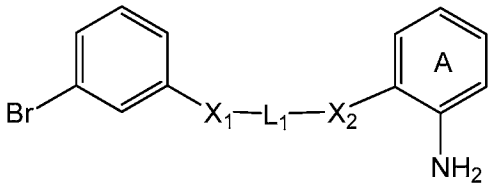
[0077] In certain embodiments, B ring is an N-alkylated pyridyl ring.

[0078] In certain embodiments, L_1 is $-(CH_2)_n-$, where n is 4, 5, 6, 7, or 8.

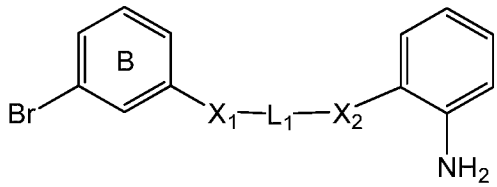
[0079] In certain embodiments, $-X_1-L_1-X_2-$ is $-NHC(=O)-L_1-C(=O)NH-$.

[0080] In certain embodiments, $-X_1-L_1-X_2-$ is $-C(=O)-NH-L_1-C(=O)NH-$.

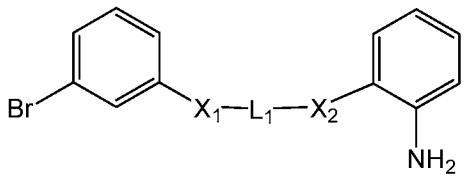
[0081] In another embodiment, the compounds disclosed herein comprise a structure selected from the group consisting of Structures VA-VE:



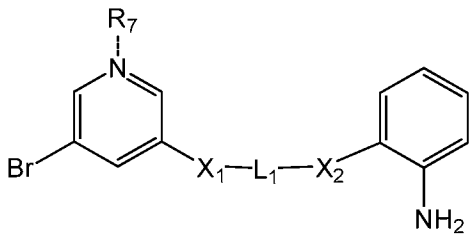
Structure VA



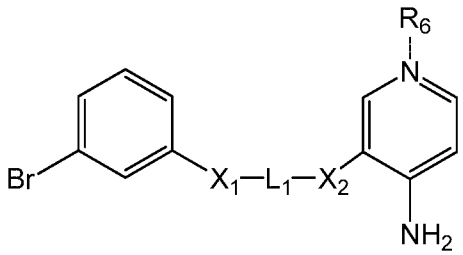
Structure VB



Structure VC



Structure VD



Structure VE,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein A ring, B ring, R_1-R_7, X_1, X_2, and L_1 are defined the same as above. In certain of these embodiments, the compounds are transcription

factor modulators.

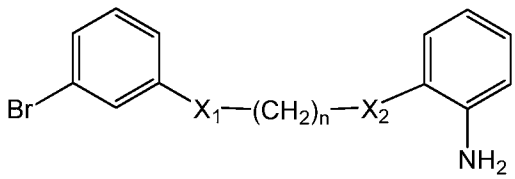
[0082] In certain embodiments, the N-alkylated pyridine ring of Structures VA-VE may be positively charged and form a salt with one or more suitable counterions (e.g., without limitations, anions derived from pharmaceutically acceptable acids described herein, e.g. acetate, fluoroacetate or other carboxylate).

[0083] In certain embodiments, L_1 is $-(CH_2)_n-$, where n is 4, 5, 6, 7, or 8.

[0084] In certain embodiments, $-X_1-L_1-X_2-$ is $-NHC(=O)-L_1-C(=O)NH-$.

[0085] In certain embodiments, $-X_1-L_1-X_2-$ is $-C(=O)-NH-L_1-C(=O)NH-$.

[0086] In another embodiment, the compounds disclosed herein comprise a structure of Structure VI:



Structure VI

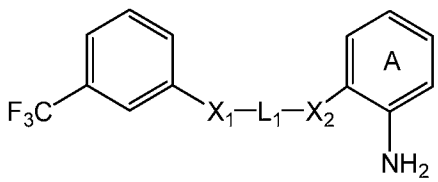
including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein n, X_1, and X_2 are defined the same as above.

[0087] In certain embodiments, n is 4, 5, 6, 7, or 8.

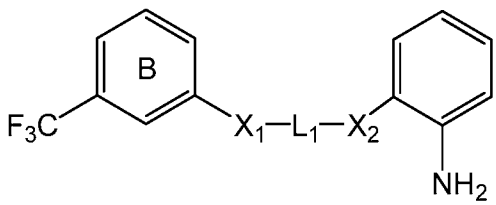
[0088] In certain embodiments, $-X_1-(CH_2)_n-X_2-$ is $-NHC(=O)-(CH_2)_n-C(=O)NH-$.

[0089] In certain embodiments, $-X_1-(CH_2)_n-X_2-$ is $-C(=O)-NH-(CH_2)_n-C(=O)NH-$.

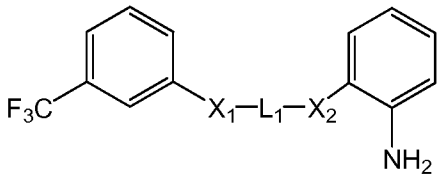
[0090] In another embodiment, the compounds disclosed herein comprise a structure selected from the group consisting of Structures VIIA-VIIE:



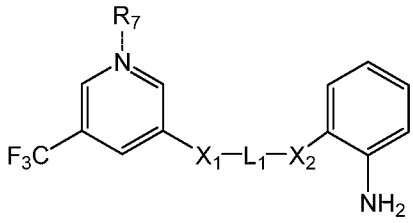
Structure VIIA



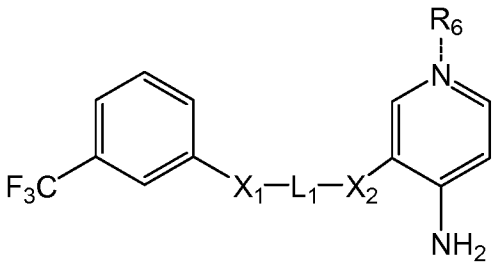
Structure VIIB



Structure VIIC



Structure VIID



Structure VIIE,

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein A ring, B ring, R_1-R_7, X_1, X_2, and L_1 are defined the same as above. In certain of these embodiments, the compounds are transcription factor modulators.

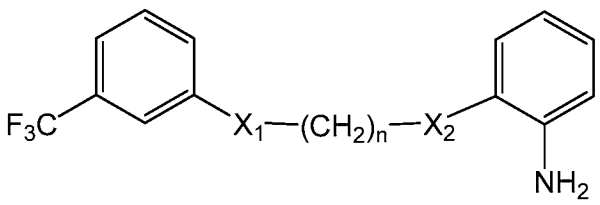
[0091] In certain embodiments, the N-alkylated pyridine ring of Structures VIIA-VIIE may be positively charged and form a salt with one or more suitable counterions (e.g., without limitations, anions derived from pharmaceutically acceptable acids described herein, e.g. acetate, fluoroacetate or other carboxylate).

[0092] In certain embodiments, L_1 is $-(CH_2)_n-$, where n is 4, 5, 6, 7, or 8.

[0093] In certain embodiments, $-X_1-L_1-X_2-$is $-NHC(=O)-L_1-C(=O)NH-$.

[0094] In certain embodiments, $-X_1-L_1-X_2-$is $-C(=O)-NH-L_1-C(=O)NH-$.

[0095] In another embodiment, the compounds disclosed herein comprise a structure of Structure VIII:



Structure VIII

including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein n, X_1, and X_2 are defined the same as above. In certain of these embodiments, the compounds are transcription factor modulators.

[0096] In certain embodiments, n is 4, 5, 6, 7, or 8.

[0097] In certain embodiments, -X_1-$(CH_2)_n$-X_2-is –NHC(=O)-$(CH_2)_n$–C(=O)NH-.

[0098] In certain embodiments, -X_1-$(CH_2)_n$-X_2-is –C(=O)-NH- $(CH_2)_n$–C(=O)NH-.

[0099] As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Optionally, an alkyl group may contain one or more unsaturated bonds (e.g. -C=C-, and carbon-carbon triple bond).

[00100] As used herein, the term "cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes an alkyl linker through which it may be attached, preferably a C_1-C_6 alkyl linker as defined above. Such a ring may be optionally fused to one or more cycloalkyl ring(s), aryl ring(s), and/or heteroaryl ring(s). Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[00101] As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12-membered cycloalkyl ring containing one or more heteroatomic substitutions on the ring selected from S, O or N. Such a ring may be optionally fused to one or more cycloalkyl ring(s), heterocyclic ring(s), aryl ring(s), and/or heteroaryl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, piperazine, and the like.

[00102] As used herein, the term "aryl" refers to an aromatic cyclic hydrocarbon ring (such as phenyl ring) and which optionally includes an alkyl linker through which it may be attached, preferably a C_1-C_6 alkyl linker as defined above. Such a ring may be optionally fused to one or more other aryl ring(s). Examples of "aryl" groups include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, imidazolyl as well as substituted derivatives thereof.

[00103] As used herein, the term "heteroaryl" refers to an aromatic cyclic hydrocarbon ring containing one or more heteroatomic substitutions on the ring

selected from S, O or N, and which optionally includes an alkyl linker through which it may be attached, preferably a C_1-C_6 alkyl linker as defined above. Such a ring may be optionally fused to one or more other aryl ring(s) and/or heteroaryl ring(s). Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzopyrrolyl, benzothiophenyl, indolyl, indazolyl, and substituted derivatives thereof.

[00104] As used herein, the term "halogen" or "halo" refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

[00105] As used herein, the term "alkoxy" refers to an alkyl group wherein one or more hydrogen and/or carbon atoms are substituted with oxygen or hydroxyl group.

[00106] As used herein, the term "aryloxy" refers to an aryl group wherein one or more hydrogen atoms are substituted with oxygen or hydroxyl group.

[00107] As used herein, the term "alkylamino" refers to an alkyl group wherein one or more hydrogen and/or carbon atoms are substituted with nitrogen or amino group.

[00108] As used herein, the term “arylamino” refers to an amino group substituted with at least an aryl or heteroaryl group on nitrogen. In certain embodiments, the nitrogen is further substituted with one or more substituents selected from the group consisting of alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl.

[00109] As used herein, the term "haloalkyl" refers to an alkyl group wherein one or more hydrogen and/or carbon atoms are substituted with halogen atom.

[00110] As used herein, the term "alkylcarbonyl" refers to R’-C(=O)-, wherein R’ is an optionally substituted alkyl group.

[00111] As used herein, the term "arylcarbonyl" refers to R-C(=O)-, wherein R is an optionally substituted aryl group.

[00112] As used herein, the term "substituted" refers to substitution(s) on one or more atoms, wherein each atom may be substituted with one or more substituents described above. Further examples of substitutions include, without limitation, halogen, alkyl, alkoxy, alkylamino, haloalkyl, -CN, and alkylcarbonyl.

[00113] Unless otherwise specified, all substituents intend to include optionally substituted substituents, i.e. further substituted or not. For example, an alkyl group may be an unsubstituted alkyl group, or a substituted alkyl group as defined supra.

[00114] As used herein, a compound or a composition that is "pharmaceutically acceptable" is suitable for use in contact with the tissue or organ of a biological subject without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. If said compound or composition is to be used with other ingredients, said compound or composition is also compatible with said other ingredients.

[00115] As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (e.g., compounds disclosed herein) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, aqueous solution (e.g. buffer), methanol, ethanol and acetic acid. Preferably, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, aqueous solution (e.g. buffer), ethanol and acetic acid. Most preferably, the solvent used is water or aqueous solution (e.g. buffer). Examples for suitable solvates are the mono- or dihydrates or alcoholates of the compound according to the invention.

[00116] As used herein, pharmaceutically acceptable salts of a compound refers to any pharmaceutically acceptable acid and/or base additive salt of the compound (e.g., compounds disclosed herein). Suitable acids include organic and inorganic acids. Suitable bases include organic and inorganic bases. Examples of suitable inorganic acids include, but are not limited to: hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. Examples of suitable organic acids include but are not limited to: acetic acid, trifluoroacetic acid, formic acid, oxalic acid, malonic acid, succinic acid, tartaric acid, maleic acid, fumaric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, lactic acid, citric acid and mandelic acid. Examples of suitable inorganic bases include, but are not limited to: ammonia, hydroxyethylamine and hydrazine. Examples of suitable organic bases include, but are not limited to, methylamine, ethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. The invention

further provides for the hydrates and polymorphs of all of the compounds described herein.

[00117] ***II. Compositions***

[00118] The compounds disclosed herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, compositions comprising the compounds disclosed herein may include mixtures of stereoisomers or mixtures of enantiomers, as well as purified stereoisomers, purified enantiomers, stereoisomerically enriched mixtures, or enantiomerically enriched mixtures. The composition provided herein also include the individual isomers of the compound represented by the structures described above as well as any wholly or partially equilibrated mixtures thereof. The compositions disclosed herein also cover the individual isomers of the compound represented by the structures described above as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the structures described above are included within the scope of the structures and preferably the structures corresponding thereto.

[00119] Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent. The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

[00120] It is also possible to obtain optically active compounds comprising the structure of the transcription factor modulators disclosed herein by the methods described above by using starting materials which are already optically active.

[00121] ***III. Pharmaceutical formulations***

[00122] As used herein, a pharmaceutical formulation comprises a therapeutically effective amount of one or more of the compounds or compositions thereof disclosed herein. In certain embodiments, the pharmaceutical formulation

further comprises a pharmaceutically acceptable carrier.

[00123] As used herein, a “therapeutically effective amount,” "therapeutically effective concentration" or "therapeutically effective dose" is an amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder.

[00124] This amount will vary depending upon a variety of factors, including but not limited to the characteristics of the compounds, compositions, or pharmaceutical formulations thereof (including activity, pharmacokinetics, pharmacodynamics, and bioavailability thereof), the physiological condition of the subject treated (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication) or cells, the nature of the pharmaceutically acceptable carrier or carriers in the formulation, and the route of administration. Further, an effective or therapeutically effective amount may vary depending on whether the compound, composition, or pharmaceutical formulation thereof is administered alone or in combination with other drug(s), other therapy/therapies or other therapeutic method(s) or modality/modalities. One skilled in the clinical and pharmacological arts will be able to determine an effective amount or therapeutically effective amount through routine experimentation, namely by monitoring a cell’s or subject's response to administration of the one or more compounds, compositions, or pharmaceutical formulations thereof and adjusting the dosage accordingly. A typical dosage may range from about 0.1 mg/kg to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage may range from about 0.1 mg/kg to about 100 mg/kg; or about 1 mg/kg to about 100 mg/kg; or about 5 mg/kg up to about 100 mg/kg. For additional guidance, see Remington: The Science and Practice of Pharmacy, 21st Edition, Univ. of Sciences in Philadelphia (USIP), Lippincott Williams & Wilkins, Philadelphia, PA, 2005, which is hereby incorporated by reference as if fully set forth herein for additional guidance for determining a therapeutically effective amount.

[00125] As used herein, the term “about” refers to ±10%, ±5%, or ±1%, of the value following “about.”

[00126] A “pharmaceutically acceptable carrier” is a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting an

active ingredient from one location, body fluid, tissue, organ (interior or exterior), or portion of the body, to another location, body fluid, tissue, organ, or portion of the body. Each carrier is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients, e.g., the transcription factor modulators described herein or other ingredients, of the formulation and suitable for use in contact with the tissue or organ of a biological subject without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

[00127] Pharmaceutically acceptable carriers are well known in the art and include, without limitation, (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) alcohol, such as ethyl alcohol and propane alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[00128] The pharmaceutical formulations disclosed herein may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like.

[00129] The concentration of the one or more compounds disclosed herein in a pharmaceutical formulation can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the biological subject's needs. For example, the concentration of the compounds disclosed herein can be about 0.0001% to about 100%, about 0.001% to about 50%, about 0.01% to about 30%, about 0.1% to about 20%, about 1% to about 10% wt.

[00130] A suitable pharmaceutically acceptable carrier may be selected taking

into account the chosen mode of administration, and the physical and chemical properties of the compounds.

[00131] One skilled in the art will recognize that a pharmaceutical formulation containing the one or more compounds disclosed herein or compositions thereof can be administered to a subject by various routes including, without limitation, orally or parenterally, such as intravenously. The composition may also be administered through subcutaneous injection, subcutaneous embedding, intragastric, topical, and/or vaginal administration. The composition may also be administered by injection or intubation.

[00132] In one embodiment, the pharmaceutical carrier may be a liquid and the pharmaceutical formulation would be in the form of a solution. In another embodiment, the pharmaceutically acceptable carrier is a solid and the pharmaceutical formulation is in the form of a powder, tablet, pill, or capsules. In another embodiment, the pharmaceutical carrier is a gel and the pharmaceutical formulation is in the form of a suppository or cream.

[00133] A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or table-disintegrating agents, it can also be an encapsulating material. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active-ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to about 99% of the one or more transcription factor modulators disclosed herein. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

[00134] Besides containing an effective amount of the one or more compounds described herein or compositions thereof, the pharmaceutical formulations provided herein may also include suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers.

[00135] The pharmaceutical formulation can be administered in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its

anhydrides copolymerized with ethylene oxide) and the like.

[00136] Additional pharmaceutical formulations will be evident to those skilled in the art, including formulations involving binding agent molecules in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, PCT/US93/0082948 which is incorporated herein by reference as if fully set forth herein for the techniques of controlled release of porous polymeric microparticles for the delivery of pharmaceutical formulations. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate, poly (2-hydroxyethyl-methacrylate), ethylene vinyl acetate or poly-D (-)-3-hydroxybutyric acid. Sustained-release compositions also include liposomes, which can be prepared by any of several methods known in the art.

[00137] ***IV. Methods of treatment***

[00138] One aspect of the present disclosure relates to methods of treating a cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of one or more compounds, compositions, or pharmaceutical formulations disclosed herein.

[00139] Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound, composition, or formulation being used, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated, include, without limitation, subject age, weight, gender, diet, time of administration, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Administration of the compound, composition, or pharmaceutical formulation may be effected continuously or intermittently. In any treatment regimen, the compound, composition, or pharmaceutical formulation may be administered to a subject either singly or in a cocktail containing two or more compounds or compositions thereof, other therapeutic agents, compositions, or the like, including, but not limited to, tolerance-inducing agents, potentiators and side-effect relieving agents. All of these agents

are administered in generally-accepted efficacious dose ranges such as those disclosed in the Physician's Desk Reference, 41st Ed., Publisher Edward R. Barnhart, N.J. (1987), which is herein incorporated by reference as if fully set forth herein. In certain embodiments, an appropriate dosage level will generally be about 0.001 to about 50 mg per kg subject body weight per day that can be administered in single or multiple doses. Preferably, the dosage level will be about 0.005 to about 25 mg/kg, per day; more preferably about 0.01 to about 10 mg/kg per day; and even more preferably about 0.05 to about 1 mg/kg per day. In some embodiments, the daily dosage may be between about 10^{-6} g/kg to about 5 g/kg of body weight.

[00140] "Treating" or "treatment" of a condition may refer to preventing the condition, slowing the onset or rate of development of the condition, reducing the risk of developing the condition, preventing or delaying the development of symptoms associated with the condition, reducing or ending symptoms associated with the condition, generating a complete or partial regression of the condition, or some combination thereof. With regard to cancer specifically, "treating" or "treatment" may refer to reducing the size or number of tumors, slowing or preventing tumor growth, reducing or preventing malignancy of a tumor, lowering a tumor grade or preventing an increase in tumor grade.

[00141] In some embodiments, the one or more compounds disclosed herein or compositions or pharmaceutical formulations thereof may be administered in combination with one or more additional therapeutic agents for the treatment of cancer. "In combination" or "in combination with," as used herein, means in the course of treating the same cancer in the same subject using two or more agents, drugs, treatment regimens, treatment modalities or a combination thereof, in any order. This includes simultaneous administration (in the same or separate formulations), as well as administration in a temporally spaced order of up to several days apart. Such combination treatment may also include more than a single administration of any one or more of the agents, drugs, treatment regimens or treatment modalities. Further, the administration of the two or more agents, drugs, treatment regimens, treatment modalities or a combination thereof may be by the same or different routes of administration.

[00142] Examples of therapeutic agents that may be administered in combination with the compounds disclosed herein or compositions or pharmaceutical formulations thereof include, but are not limited to, anti-cancer agents and

radioisotopes. The therapeutic agent may also include a metal, metal alloy, intermetallic or core-shell nanoparticle bound to a chelator that acts as a radiosensitizer to render the targeted cells more sensitive to radiation therapy as compared to healthy cells.

[00143] In one embodiment, the therapeutic agent is an anti-cancer agent. Anti-cancer agents that may be used in accordance with certain embodiments described herein are often cytotoxic or cytostatic in nature and may include, but are not limited to, alkylating agents; antimetabolites; anti-tumor antibiotics; topoisomerase inhibitors; mitotic inhibitors; hormones (e.g., corticosteroids); targeted therapeutics (e.g., selective estrogen receptor modulators (SERMs)); toxins; immune adjuvants, immunomodulators, and other immunotherapeutics (e.g., therapeutic antibodies and fragments thereof, recombinant cytokines and immunostimulatory molecules - synthetic or from whole microbes or microbial components); enzymes (e.g., enzymes to cleave prodrugs to a cytotoxic agent at the site of the tumor); nucleases; antisense oligonucleotides; nucleic acid molecules (e.g., mRNA molecules, cDNA molecules or RNAi molecules such as siRNA or shRNA); chelators; boron compounds; photoactive agents and dyes. Examples of anti-cancer agents that may be used as therapeutic agents in accordance with certain embodiments of the disclosure include, but are not limited to, 13-cis-retinoic acid, 2-chlorodeoxyadenosine, 5-azacitidine, 5-fluorouracil, 6-mercaptopurine, 6-thioguanine, actinomycin-D, adriamycin, aldesleukin, alitretinoin, all-transretinoic acid, alpha interferon, altretamine, amethopterin, amifostine, anagrelide, anastrozole, arabinosylcytosine, arsenic trioxide, amsacrine, aminocamptothecin, aminoglutethimide, asparaginase, azacytidine, bacillus calmette-guerin (BCG), bendamustine, bexarotene, bicalutamide, bortezomib, bleomycin, busulfan, calcium leucovorin, citrovorum factor, capecitabine, canertinib, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, cortisone, cyclophosphamide, cytarabine, darbepoetin alfa, dasatinib, daunomycin, decitabine, denileukin diftitox, dexamethasone, dexasone, dexrazoxane, dactinomycin, daunorubicin, decarbazine, docetaxel, doxorubicin, doxifluridine, eniluracil, epirubicin, epoetin alfa, erlotinib, everolimus, exemestane, estramustine, etoposide, filgrastim, fluoxymesterone, fulvestrant, flavopiridol, floxuridine, fludarabine, fluorouracil, flutamide, gefitinib, gemcitabine, ozogamicin, goserelin, granulocyte - colony stimulating factor, granulocyte macrophage-colony stimulating factor, hexamethylmelamine,

hydrocortisone hydroxyurea, interferon alpha, interleukin – 2, interleukin-11, isotretinoin, ixabepilone, idarubicin, imatinib mesylate, ifosfamide, irinotecan, lapatinib, lenalidomide, letrozole, leucovorin, leuprolide, liposomal Ara-C, lomustine, mechlorethamine, megestrol, melphalan, mercaptopurine, mesna, methotrexate, methylprednisolone, mitomycin C, mitotane, mitoxantrone, nelarabine, nilutamide, octreotide, oprelvekin, oxaliplatin, paclitaxel, pamidronate, pemetrexed, PEG Interferon, pegaspargase, pegfilgrastim, PEG-L-asparaginase, pentostatin, plicamycin, prednisolone, prednisone, procarbazine, raloxifene, romiplostim, ralitrexed, sapacitabine, sargramostim, satraplatin, sorafenib, sunitinib, semustine, streptozocin, tamoxifen, tegafur, tegafur-uracil, temsirolimus, temozolamide, teniposide, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tretinoin, trimitrexate, alrubicin, vincristine, vinblastine, vindestine, vinorelbine, vorinostat, and zoledronic acid.

[00144] Therapeutic antibodies and functional fragments thereof, that may be used as anti-cancer agents in accordance with certain embodiments of the disclosure include, but are not limited to, alemtuzumab, bevacizumab, cetuximab, edrecolomab, gemtuzumab, ibritumomab tiuxetan, panitumumab, rituximab, tositumomab, and trastuzumab and other antibodies associated with specific diseases listed herein.

[00145] Toxins that may be used as anti-cancer agents in accordance with certain embodiments of the disclosure include, but are not limited to, ricin, abrin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtheria toxin, Pseudomonas exotoxin, and Pseudomonas endotoxin.

[00146] Radioisotopes that may be used as therapeutic agents in accordance with certain embodiments of the disclosure include, but are not limited to, ^{32}P, ^{89}Sr, ^{90}Y, ^{99m}Tc, ^{99}Mo, ^{131}I, ^{153}Sm, ^{177}Lu, ^{186}Re, ^{213}Bi, ^{223}Ra and ^{225}Ac.

[00147] The frequency of dosing will depend upon the pharmacokinetic parameters of the therapeutic agents in the pharmaceutical formulation (e.g. the one or more compounds disclosed herein) used. Typically, a pharmaceutical formulation is administered until a dosage is reached that achieves the desired effect. The formulation may therefore be administered as a single dose, or as multiple doses (at the same or different concentrations/dosages) over time, or as a continuous infusion. Further refinement of the appropriate dosage is routinely made. Appropriate

dosages may be ascertained through use of appropriate dose-response data. Long-acting pharmaceutical formulations may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

[00148] In certain embodiments, the one or more compounds disclosed herein or compositions or pharmaceutical formulations thereof may be administered in combination with a therapeutic agent or radiotherapy. In some embodiments, the one or more compounds or compositions or pharmaceutical formulations thereof may be used in combination with imatinib (Gleevec), and in certain cancers being treated. In some of these embodiments the cancer being treated is leukemia. In certain embodiments, the type of leukemia may include, but is not limited to, acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma. In certain of these embodiments, the type of leukemia may be treatable by a compound disclosed herein, including but not limited to YT30.

[00149] In certain embodiments, the cancer is breast cancer, central nervous system cancer, colon cancer, prostate cancer, lung cancer, leukemia, renal cancer, ovarian cancer, melanoma, liver cancer, and/or cervical cancer.

[00150] In certain embodiments, the cancer is leukemia. In certain of these embodiments, the type of leukemia may include, but is not limited to, acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma. In certain embodiments, the ALL is T-cell ALL and/or B-cell ALL. In certain embodiments, the leukemia may be treatable by one or more compounds selected from the group consisting of YT29, YT30, YT45, YT46, YT51, YT53, YT54, YT58, YT61~YT63, YT65, YT67, YT68, YT73, YT74, YT76~YT80, YT86, YT88, YT91, YT99, YT108~YT110, YT116~YT118, YT121~YT123, YT127, YT128, YT131, YT132, and YT134~YT139. In certain embodiments, the leukemia may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula II, Formula V, Formula VI, Formula VII, Structure I,

Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, and Structure VIII. In certain of these embodiments, the leukemia is ALL.

[00151] In certain embodiments, the cancer is breast cancer. In certain of these embodiments, the type of breast cancer may be metastatic adenocarcinoma, infiltrating ductal carcinoma, papillary infiltrating ductal carcinoma, and/or metastatic mammary gland carcinosarcoma. In certain embodiments, the breast cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, YT88, and YT128. In certain embodiments, the breast cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00152] In certain embodiments, the cancer is central nervous system cancer. In certain of these embodiments, the type of central nervous system cancer is glioblastoma, astrocytoma, and/or glial cell neoplasm. In certain embodiments, the central nervous system cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, YT88, and YT128. In certain embodiments, the central nervous system cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00153] In certain embodiments, the cancer is colon cancer. In certain of these embodiments, the colon cancer may be treatable by a compound including, but not limited to, YT30. In certain of these embodiments, the colon cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00154] In certain embodiments, the cancer is cervical cancer. In certain of

these embodiments, the type of cervical cancer may be positive for human papilloma virus (HPV) 16 and/or HPV 18. In certain of these embodiments, the cervical cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, YT88, and YT128. In certain embodiments, the cervical cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00155] In certain embodiments, the cancer is ovarian cancer. In certain of these embodiments, the ovarian cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, YT88, and YT128. In certain embodiments, the ovarian cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00156] In certain embodiments, the cancer is prostate cancer. In certain of these embodiments, the prostate cancer may be treatable by one or more compounds selected from the group consisting of YT30 and YT88. In certain embodiments, the prostate cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00157] In certain embodiments, the cancer is renal cancer. In certain of these embodiments, the renal cancer may be clear cell carcinoma metastasis, renal cell carcinoma, renal spindle cell carcinoma and/or hypernephroma. In certain embodiments, the renal cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, YT88, and YT128. In certain embodiments, the renal cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure

VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00158] In certain embodiments, the cancer is lung cancer. In certain of these embodiments, the lung cancer may be non-small cell lung cancer (NSCLC), large cell carcinoma, squamous cell carcinoma, and /or adenocarcinoma. In certain embodiments, the lung cancer may be treatable by one or more compounds selected from the group consisting of YT30, YT86, and YT128. In certain embodiments, the lung cancer may be treatable by one or more compounds comprising a structure selected from the group consisting of Formula I, Formula VI, Formula VII, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00159] In certain embodiments, the cancer is melanoma. In certain of these embodiments, the type of melanoma may be malignant amelanotic melanoma and/or melanotic melanoma. In certain embodiments, the melanoma may be treatable by a transcription factor modulator including, but not limited to, YT30. In certain embodiments, when the cancer is melanoma, the melanoma may be treatable by one or more transcription factor modulators comprising a structure selected from the group consisting of Formula I, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, and Structure VI.

[00160] In some embodiments, specific compounds disclosed herein may be preferred for the treatment of specific cancer types. Table 6 provides a non-limiting list of specific cancer types that can be treated by specific compounds provided herein. In other embodiments, the cancer types listed in Table 6 may be treatable by one or more compounds other than those listed in the table, and one or more compounds listed in Table 6 may be used to treat types of cancer other than those listed.

Table 6: Cancers Treatable by One or More Compounds Disclosed Herein

Compound		Cancer Treated
Formula I	YT29	leukemia (ALL)
	YT30 Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC,	**Breast cancer** (mammary gland adenocarcinoma); **central nervous system** (glioblastoma, glial cell neoplasm); **colon cancer**; **prostate cancer**; **lung cancer**

	Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI	(non-small cell lung cancer (NSCLC), squamous cell carcinoma, large cell carcinoma); **leukemia** (AML, APL, CML, CML (imatinib resistant), multiple myeloma, T-cell ALL), B-cell ALL(B), B-cell myelomonocytic, lymphoma, myeloma); **renal cancer** (renal cell carcinoma, renal spindle cell carcinoma, clear cell carcinoma); **ovarian cancer**; **melanoma** (malignant amelanotic melanoma); **liver cancer; cervical cancer** (HPV 18 and/or 16 positive)
	YT45	leukemia (ALL)
	YT46	leukemia (ALL)
	YT99	leukemia (ALL)
	YT108	leukemia (ALL)
	YT53	leukemia (ALL)
Formula I	YT54 Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, Structure VIII	leukemia (ALL)
	YT58	leukemia (ALL)
	YT61	leukemia (ALL)
	YT62	leukemia (ALL)
	YT63	leukemia (ALL)
	YT65	leukemia (ALL)
	YT67	leukemia (ALL)
	YT68	leukemia (ALL)
	YT73	leukemia (ALL)
	YT74	leukemia (ALL)
	YT76	leukemia (ALL)
	YT77	leukemia (ALL)
	YT78	leukemia (ALL)

	YT79	leukemia (ALL)
	YT80	leukemia (ALL)
	YT116	leukemia (ALL)
	YT134	leukemia (ALL)
	YT135	leukemia (ALL)
	YT138	leukemia (ALL)
	YT139	leukemia (ALL)

Formula II	YT91	leukemia (ALL)
	YT118	leukemia (ALL)
	YT121	leukemia (ALL)
	YT123	leukemia (ALL)
Formula V	YT51	leukemia (ALL)
	YT132	leukemia (ALL)
	YT136	leukemia (ALL)
	YT137	leukemia (ALL)
Formula VI	YT86	**breast cancer** (adenocarcinoma, mammary gland carcinoma, infiltrating ductal carcinoma, papillary infiltrating ductal carcinoma); **central nervous system** (glioblastoma, glial cell neoplasm); **cervical cancer** (HPV 18 and/or 16 positive) ; **lung cancer** (non-small cell lung cancer (NSCLC)); **leukemia** (AML, APL, CML, T-cell ALL, B-cell ALL, lymphoma); **renal cancer** (renal spindle cell carcinoma, renal cell carcinoma); **ovarian cancer**
Formula VI	YT88	**breast cancer** (adenocarcinoma, mammary gland carcinoma, infiltrating ductal carcinoma, papillary infiltrating ductal carcinoma); **central nervous system** (glioblastoma, astrocytoma, glial cell neoplasm); **cervical cancer** (HPV 18 and/or 16 positive); **prostate cancer**; **leukemia** (AML, APL, CML, T-cell ALL, B-cell ALL, lymphoma); **renal cancer** (renal spindle cell carcinoma, renal cell carcinoma); **ovarian cancer**
	YT109	leukemia (ALL)
	YT110	leukemia (ALL)
	YT117	leukemia (ALL)
	YT127	leukemia (ALL)
	YT131	leukemia (ALL)
Formula VII	YT122	leukemia (ALL)
	YT128	**breast cancer** (adenocarcinoma, mammary

		gland carcinoma, infiltrating ductal carcinoma, papillary infiltrating ductal carcinoma); **central nervous system** (glioblastoma, glial cell neoplasm); **cervical cancer** (HPV 18 and/or 16 positive); **lung cancer** (non-small cell lung cancer (NSCLC); **leukemia** (AML, APL, CML, ALL); **renal cancer** (renal spindle cell carcinoma, renal cell carcinoma); **ovarian cancer**

[00161] Another aspect of the present disclosure relates to the use of one or more compounds disclosed herein or compositions or pharmaceutical formulations thereof in the manufacture of a medicament for the treatment of cancer. For this aspect, the compounds, compositions, and formulations are the same as disclosed above, and the treatment of cancer is the same as described supra.

[00162] Another aspect described herein relates to a method of treating a condition regulatable by a transcription factor and/or cofactor comprising administering to the subject a therapeutically effective amount of one or more compounds disclosed herein or compositions or pharmaceutical formulations thereof. In some embodiments, the condition is a disease related to dysfunction of a transcription factor and/or cofactor. In certain of these embodiments, the compounds provided herein are transcription factor modulators. In certain embodiments, the transcription factor is selected from the group consisting of forkhead box protein P3 (FOXP3) and myocyte enhancer factor 2 (MEF2). In certain embodiments, the transcription factor modulators binds to a highly conserved hydrophobic groove on the MADS-box of MEF2. In certain embodiments, the condition is a cancer as described above, and the suitable compounds, compositions, or pharmaceutical formulations are the same as disclosed herein.

[00163] In certain embodiments where the compounds provided herein are transcription factor modulators, the compounds may selectively bind a transcription factor or cofactor.

[00164] In certain embodiments where the compounds provided herein are transcription factor modulators, the compounds may modulate the function of

transcription factors that are associated with certain diseases. In certain embodiments, the diseases are cancers as described herein.

[00165] In certain embodiments where the compounds provided herein are transcription factor modulators, the compounds may directly bind the transcription factor and modulate its interaction with transcription cofactors such as transcription co-activators and co-repressors. In certain embodiments, the transcription cofactor is selected from the group consisting of calcineurin binding protein 1, histone deacetylases (HDACs), E1A binding protein P300, CREB binding protein, extracellular signal-regulated kinase 5, myoblast differentiation protein, Smad protein, nuclear factor of activated T cell, myocardin, and positive transcription elongation factor b. In some embodiments, the transcription cofactor is a Class IIa HDAC.

[00166] Another aspect of the present disclosure relates to the use of one or more compounds disclosed herein or compositions or pharmaceutical formulations thereof in the manufacture of a medicament for the treatment of a condition regulatable by a transcription factor and/or cofactor. For this aspect, the one or more compounds or compositions or pharmaceutical formulations thereof, the transcription factors and/or cofactors, and the conditions regulatable by the transcription factor and/or cofactor are the same as disclosed above, and the treatment of the condition is the same as described supra.

[00167] The following examples are intended to illustrate various embodiments of the invention. As such, the specific embodiments discussed are not to be construed as limitations on the scope of the invention. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of invention, and it is understood that such equivalent embodiments are to be included herein. Further, all references cited in the disclosure are hereby incorporated by reference in their entireties, as if fully set forth herein.

EXAMPLES

Example 1: Effect of compounds on the growth of a variety of leukemia cell lines.

Methods

[00168] *Treatment of cells.* Various human leukemia cells were grown to the logarithmic growth phase and seeded into 24-well plates. Plated cells were

incubated at 37ºC in a 5% CO_2 humidified incubator for 24 hours and treated with various concentrations of YT30 or other compounds disclosed herein. Treated cells were further incubated for 72 hours and then were examined for cell proliferation. Cell proliferation was determined using the CellTiter-Glo Luminescence Cell Viability assay (Promega Corporation, Madison, WI) according to the manufacturer's protocol. The calculated inhibition rate was determined with the following formula: Inhibition rate (%) = (1–Luminescence of experimental group/Luminescence of control group) X 100. IC_{50} is the calculated concentration of a compound needed to inhibit half of the maximum cell growth (equivalent to cell growth in control group) based on the corresponding dose-response curve under the described experimental conditions.

Results

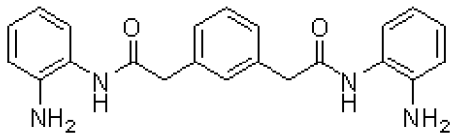
[00169] *YT30 inhibits cell proliferation of numerous leukemia cell lines.* Table 7 provides the YT30 IC_{50} (μM) concentrations for inhibiting various leukemia cell lines. YT30 inhibited the proliferation of all leukemia cell lines tested. The strongest YT30 cell growth inhibition was observed in the Jurkat, HL60, RS4, MOLT-4, and SEM leukemia cells under the described experimental conditions.

Table 7. YT30 inhibits cell growth of various leukemia cell lines

Cell lines	Leukemia sub-type	IC_{50} (μM)
HL60	AML (subtype APL)	1.04
K-562	CML	1.82
K562R	CML (Gleevec resistant)	3.21
U266	Multiple myeloma	8.29
RPMI-8226	Multiple myeloma	2
MOLT-4	ALL (T-cell)	1.13
Jurkat	ALL (T-cell)	0.91
NALM-6	ALL (B-cell)	2.36
RCH-ACV	ALL (B-cell)	0.79
RS4;11	ALL (B-cell)	1.05
SEM	ALL (B-cell)	1.15
MV4-11	B-myelomonocytic (Biphenotypic B-cell leukemia)	4.06
BaF3 BCR-ABL	Mouse cell line with BCR-ABL	3.40

BaF3 BCR-ABL T315I	Mouse cell line with BCR-ABL with T315I point mutation (Gleevec resistant)	1.11
SR	Lymphoma	6.89
CCRF-CEM	ALL (T-cell)	1.53

[00170] Figure 1 shows that treatment of REH, HL60, and Nalm-6 leukemia cells with 4 μM of YT30 was sufficient to significantly inhibit cell growth. In contrast, treatment of the same cells with 4 μM of the inactive YT19 failed to inhibit cell growth. The structure of the inactive YT19 compound is:



[00171] *YT30, YT54, and other compounds inhibited the growth of the Nalm-6 leukemia cell line.* Table 8 displays the survival percentage of Nalm-6 leukemia cells that were treated with YT30, YT54, and numerous other compounds.

Table 8. YT30, YT54 and other compounds inhibit the growth of Nalm-6 leukemia cells

Cell Line: Nalm-6		
Name: YT	**Conc. (μM)**	**% survival**
YT29	5	0.65
YT 30	5	0.52
YT 45	5	0.42
YT 46	5	0.46
YT 51	5	60.48
YT 53	5	1.44
YT 54	5	0.49
YT 58	5	0.52
YT 61	5	45.25
YT 62	5	0.55
YT 63	5	0.59

YT 65	5	0.58
YT 67	5	1
YT 68	5	0.84
YT 73	5	6.5
YT 74	5	0.7
YT 76	5	0.41
YT 77	5	0.42
YT 78	5	44.38
YT 79	5	2.27
YT 80	5	0.47
YT 86	5	0.46
YT 88	5	0.44
YT 91	5	0.53
YT 99	5	0.95
YT 108	5	0.42
YT 109	5	0.44
YT 110	5	0.39
YT 116	5	0.42
YT 117	5	0.42
YT 118	5	0.44
YT 121	5	0.58
YT 122	5	0.44
YT 123	5	0.72
YT 127	5	2.47
YT 128	5	0.43
YT 131	5	53.92
YT 132	5	96.98
YT 134	5	33.70
YT 135	5	52.22
YT 136	5	100.00
YT 137	5	1.03
YT138	5	23.86

YT 139	5	0.55

Example 2: Compound YT30 significantly inhibited disease progression in BALB/c nude mice with acute B cell lymphoblastic leukemia and increased the lifespan of those mice.

Methods

[00172] *Inducing B cell lymphoblastic leukemia in BALB/c nude mice and treatment with YT30.* BALB/c nu/nu nude mice were 4 to 5 weeks old with an average weight of 22.4±1.03 grams. The mice were raised under specific pathogen-free (SPF) conditions and had access to food and water freely. Cyclophosphamide at about 130mg/kg per day was administrated with intraperitoneal (IP) injection for 2 days. Twenty-four hours later, a suspension of $3.5X10^6$ or $5X10^6$ Nalm-6 cells (0.2 mL) were injected through tail vein of each BALB/c nude mouse. Five days later, the mice were randomly divided into a YT30 treated group (n=5) and a solvent control group (n=5).

[00173] Mice in the YT30 treated group were intraperitoneally injected with 200 µL of YT30 (50 mg/kg) once a day, for 5 days a week, and for 3 or 4 weeks. The mice in the solvent control group were intraperitoneally injected with the same volume of solvent (20% DMSO, 80% of 20% w/v (2-hydroxypropyl)-β-cyclodextrin in PBS), and were on the same treatment schedule as the YT30 treated group. The body weights of the mice were recorded prior to the start of the treatment and at least twice a week thereafter. The dosages were adjusted according to the body weight to conform to the 50 mg/kg/day treatment plan. Each mouse of every group was also monitored daily for any other symptoms of side effects including change in behavior, activity or posture, areas of redness and swelling, and food and water withdrawal. The mice were euthanized when moribund or if weight loss was more than 20% during the experiment. Dates of death were recorded.

Results

[00174] YT30 significantly extended the survival time of BALB/c nude mice with acute lymphoblastic leukemia (Table 9 and Figure 2). The mice in the control group developed hind limb paralysis and hunch back with disease progression at approximately 28 days. Mice in the control group also had rapid weight loss, reduced activity, loss of appetite and lack of energy. The general conditions of the YT30 treated group were significantly better than the control group throughout the

course of treatment. The average life span of the 3 week YT30 treated group was 48.8±9.7 days in contrast to 36.6±3.9 days for the control group with mice in both groups having received an inoculation of $5x10^6$ Nalm-6 cells (Table 9). When the mice were inoculated with $3.5x10^6$ Nalm6 cells, the median survival time for the mice was 45 days for the control group and >340 days for the YT30 treated group (Table 9). The median survival time was used instead of average survival time because three out of five mice in the YT30 treated group appeared to be cured. These three mice were euthanized 341 days after treatment was started.

[00175] The results demonstrated that YT30 significantly inhibited leukemia progression in Balb/c nude mice. Moreover, the data shows that YT30 treatment at an early stage of leukemia development further increased life span and decreased disease progression even more. All of the data were analyzed with Microsoft Excel or SPSS14.0 statistical software count data using the x±s. The difference between the groups was statistically significant with $P<0.05$.

Table 9. IP administration of YT30 increased the life span of BABL/c nude mice with leukemia

Animal	Cell type	Drug delivery	Frequency	Period	Initial inoculated cell numbers	Average life span after inoculation for control group (days)	Average life span after inoculation for IP 50 mg/KG group (days)
Balb/c nude mice	Nalm-6	IP	qd for 5 days/week	3 weeks	$5 X 10^6$	36.6 +/- 3.9	48.8+/- 9.7
				4 weeks	$3.5 X 10^6$	*MST45	*MST＞340
*MST= Median survival time							

Example 3: YT30 and other transcription modulators inhibited the growth of many different cancer cells lines

[00176] YT30 was tested for growth inhibition against 67 human cancer cell lines derived from diverse tissues including the National Cancer Institute human cancer cell lines (NCI-60). These cell lines were grown to the logarithmic growth phase and seeded into 96-well plates. Plated cells were incubated at 37ºC in a 5%

CO_2 humidified incubator for about 24 hours. Cells in different wells were treated with various concentrations of YT30, YT86, YT88, or YT128. Treated cells were further incubated for 72 hours and then were examined for cell viability. Cell viabilities were determined by the CellTiter-Glo Luminescence Cell Viability assay kit (Promega Corporation, Madison, WI) according to manufacturer's protocol. Cell growth inhibition rates were determined by the following formula: Inhibition rate (%) = (1–Luminescence of compound treated group/Luminescence of DMSO control group) X 100. IC_{50} is the calculated concentration of a compound needed to inhibit half of the maximum cell growth (equivalent to cell growth in control group) based on the corresponding dose-response curve under the described experimental conditions.

Results

[00177] YT30 growth inhibition was detected in 49 of the 67 human cancer cell lines (Table 10). YT30 inhibited the growth of breast, central nervous system (CNS), colon, prostate, non-small cell lung cancer (NSCLC), leukemia, renal, ovarian, melanoma, liver, and cervical cancer cell lines (Table 10).

Table 10. YT30-induced growth inhibition of various human cancer cell lines

Cancer Type	Cell Lines	IC_{50}(μM)	Cancer Type	Cell Lines	IC_{50}(μM)
Breast	MCF7	6.84	Leukemia	RPMI-8226	2
	MDA-MB231	14.22		SR	6.89
	HS 578T	10.82		RCH-HCV	0.79
	MDA-MB-468	-		SEM	1.15
	BT-549	-	Renal	786-0	-
	T-47D	-		A498	13.86
CNS	U251	7.36		ACHN	12.50
	SF-268	-		CAK1	11.72
	SF-295	10.30		RXF 393	-
	SF-539	10.78		SN12C	9.52
	SNB-19	-		TK-10	16.06
	SNB-75	-		UO-31	10.66
Colon	HCT116	13.01	Ovary	IGROV1	-
	Colo 205	14.37		OVCAR-3	9.17
	HCT-2998	-		OVCAR-4	-
	HCT-15	-		OVCAR-5	11.93
	HT29	-		OVCAR-8	6.74

	KM12	-		SK-OV-3	8.09
	SW-620	11.03		NCI/ADR-RES	-
Prostate	DU-145	4.98		MDA-MB-435	10.42
	PC-3	9.79		LOX IMVI	3.03
NSCLC	A549	3.41		MALME-3M	5.84
	EKVX	4.57	**Melanoma**	M14	6.13
	HOP-62	29.60		SK-MEL-2	4.60
	HOP-92	10.99		SK-MEL-28	5.99
	NCI-H226	12.66		SK-MEL-5	3.87
	NCI-H23	11.00		UACC-257	6.10
	NCI-H322M	-		UACC-62	5.20
	NCI-H460	5.41	**Liver**	HepG2	12.67
	NCI-H522	8.15	**Cervical**	Caski	5
Leukemia	HL60	1.04		HeLa	4.3
	K562	1.82		C33A	-
	CCRF-CEM	1.53		siHa	13.06
	MOLT-4	1.13			

[00178] Additionally, YT86 and YT128 inhibited the growth of breast, central nervous system (CNS), cervical, lung, leukemia, renal, and ovarian cancer cells (Table 11). YT88 inhibited the growth of breast, central nervous system (CNS), cervical, prostate, leukemia, renal, and ovarian cancer cells (Table 11). All of the various cell lines and their characteristics of which compounds inhibit cell growth are listed in Table 12.

Table 11. YT86, YT88, and YT128 growth inhibition of various human cancer cell lines

Tissue Type	Cell Line	YT128	YT86	YT88
Breast	MCF-7	8.52	5.86	3.80
	MDA-MB-231	6.75	5.81	4.28
	NCI/ADR-RES	14.57	-	14.17
	HS 578T	8.39	8.85	5.67
	MDA-MB-435	9.74	8.31	7.59
	MDA-MB-468	11.22	7.04	7.42
	BT-549	9.14	13.48	10.56

	T-47D	12.62	12.5	15.03
CNS	U251	5.00	4.47	4.38
	SF-268	13.42	14.92	14.42
	SF-295	8.61	7.41	6.83
	SF-539	7.61	7.76	6.91
	SNB-19	13.83	14.15	9.61
	SNB-75	-	-	11.18
Cervical	Caski	10.91	11.31	14.18
	HeLa	6.58	6.74	6.02
	C33A	-	-	-
	siHa	9.70	8.78	9.07
Colon	HCT116			
	Colo 205			
	HCT-2998			
	HCT-15			
	HT29			
	KM12			
	SW-620			
Prostate	DU-145	-	-	16.24
	PC-3			
Lung	A549	12.83	10.88	-
	EKVX			
	HOP-62			
	HOP-92			

	NCI-H226			
	NCI-H23			
	NCI-H322M			
	NCI-H460			
	NCI-H522			
Leukemia	HL60	5.86	4.81	6.97
	K562	5.03	5.64	5.74
	CCRF-CEM	4.24	3.17	2.65
	MOLT-4	5.08	3.09	3.00
	RPMI-8226			
	SR	5.96	6.40	5.89
Renal	786-0	9.47	-	13.79
	A498	7.46	9.55	9.54
	ACHN			
	CAKI-1			
	RXF 393			
	SN12C	7.11	8.00	7.25
	TK-10	12.07	17.22	13.43
	UO-31	6.58	7.51	9.53
Ovarian	IGROV1			
	OVCAR-3	6.91	7.20	6.57
	OVCAR-4	13.63	14.26	11.86

	OVCAR-5	6.87	5.99	5.66
	OVCAR-8			
	SK-OV-3			
Melanoma	LOX IMVI			
	MALME-3M			
	M14			
	SK-MEL-2			
	SK-MEL-28			
	SK-MEL-5			
	UACC-257			
	UACC-62			
Liver	HepG2			

Table 12. Characteristics of cell lines exhibiting inhibited cell growth

Modulator and Formula	Cell Line Name	Tissue of origin	Histology	Source	Ploidy	p53 (WT/MT)[1]	MDR[2]	Doubling time
YT30 YT86 YT88 YT128 Formulas I, VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	BR:MCF7	Breast	Adenocarcinoma-mammary gland; breast; metastatic site: pleural effusion;	Pleural effusion	3n-, Hypotriploid (58-68)	WT	14	25.4
	BR:MDA_MB_231	Breast	Adenocarcinoma-mammary gland; breast; epithelial; metastatic site: pleural effusion;	Pleural effusion	2n+, Hyperdiploid (47-57)	MT	29	41.9
	BR:HS 578T	Breast	Carcinosarcoma-mammary gland; breast	Primary	2n+, Hyperdiploid (47-57)	MT	NA	53.8

YT86 YT88 YT128 Formulas VI, VII	BR:BT_549	Breast	Papillary infiltrating ductal carcinoma-mammary gland; breast	Metastasis	3n+/-, Near-triploid 69+/- (58-80)	?	-45	53.9
	BR:T47D	Breast	infiltrating ductal carcinoma	NA	2n+, Hyperdiploid (47-57)	MT	19	45.5
	CNS:SF_268	CNS	Glioblastoma, ud	NA	2n+, Hyperdiploid (47-57)	MT	-38	33.1
	CNS:SNB_19	CNS	Glioblastoma, ud	NA	3n+/-, Near-triploid 69+/- (58-80)	MT	-41	34.6
YT88 Formula VI	CNS:SNB_75	CNS	Astrocytoma	NA	2n+, Hyperdiploid (47-57)	MT	-38	62.8
YT30 YT86 YT88 YT128 Formulas I, VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	CNS:SF_295	CNS	Glioblastoma, ud	NA	5n+/-, Near-pentaploid 115+/- (104-126)	MT	91	29.5
	CNS:SF_539	CNS	Glial cell neoplasm	NA	4n+/-, Near-tetraploid 92+/- (81-103)	WT	-40	35.4
	CNS:U251	CNS	Glioblastoma, ud	NA	2n+, Hyperdiploid (47-57)	MT	-19	23.8
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	CO:COLO205	Colon	Adenocarcinoma	Ascites	3n, Triploid (69)	MT	7	23.8
	CO:HCT_116	Colon	carcinoma-vpd	NA	2n-, Hypodiploid (35-45)	?	26	17.4
	CO:SW_620	Colon	Carcinoma-ud	NA	2n+/-, Near-diploid 46+/- (35-57)	MT	31	20.4
YT30 YT86 YT88 YT128 Formulas I, VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	LE:CCRF_CEM	Leukemia	ALL	NA	2n+/-, Near-diploid 46+/- (35-57)	MT	35	26.7
	LE:HL_60	Leukemia	Pro myelocytic leukemia	PBL	2n+/-, Near-diploid 46+/- (35-57)	MT	-11	28.6
	LE:K_562	Leukemia	CML	Pleural effusion	3n-, Hypotriploid (58-68)	MT	-1	19.6
	LE:MOLT_4	Leukemia	ALL (cells were taken when patient was in relapse)	PB	4n, Tetraploid (92)	WT	10	27.9

	LE:SR	Leukemia	Lymphoma	NA	2n+/-, Near-diploid 46+/- (35-57)	?	4	28.7
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	LE:RPMI_8226	Leukemia	Myeloma	PB	3n-, Hypotriploid (58-68)	WT	-3	33.5
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	ME:LOXIMVI	Melanoma	Malignant amelanotic melanoma	NA	3n+/-, Near-triploid 69+/- (58-80)	WT	12	20.5
	ME:MALME_3M	Melanoma	Malignant melanotic melanoma	Metastasis	4n+/-, Near-tetraploid 92+/- (81-103)	WT	22	46.2
	ME:M14	Melanoma	Melanotic melanoma	NA	3n+/-, Near-triploid 69+/- (58-80)	MT	14	26.3
	ME:SK_MEL_2	Melanoma	Malignant melanotic melanoma	Metastasis	4n-, Hypotetraploid (81-91)	WT	14	45.5
	ME:SK_MEL_28	Melanoma	Malignant melanotic melanoma	NA	4n-, Hypotetraploid (81-91)	MT	11	35.1
	ME:SK_MEL_5	Melanoma	Malignant melanotic melanoma	Metastasis	4n+, Hypertetraploid (93-103)	WT	12	25.2
	ME:UACC_257	Melanoma	Melanotic melanoma	NA	3n+, Hypertriploid (70-80)	WT	26	38.5
	ME:UACC_62	Melanoma	Melanotic melanoma	NA	3n+/-, Near-triploid 69+/- (58-80)	WT	8	31.3
	ME:MDA_MB_435	Melanoma	Ductal carcinoma-mammary gland; breast; duct; metastatic site: pleural effusion;	Pleural effusion	2n+, Hyperdiploid (47-57)	MT	20	25.8

YT30 YT86 YT128 Formulas I, VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	LC:A549	Non-Small Cell Lung	Adenocarcinoma-p/md	NA	3n+/-, Near-triploid 69+/- (58-80)	WT	10	22.9
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	LC:EKVX	Non-Small Cell Lung	Adenocarcinoma-md	NA	3n+/-, Near-triploid 69+/- (58-80)	MT	-9	43.6
	LC:HOP_62	Non-Small Cell Lung	adenocarcinoma-ud	NA	4n+, Hypertetraploid (93-103)	MT	61	39
	LC:HOP_92	Non-Small Cell Lung	Large cell-ud	NA	4n+/-, Near-tetraploid 92+/- (81-103)	MT	-4	79.5
	LC:NCI_H226	Non-Small Cell Lung	Squamous cell carcinoma-vpd	NA	3n, Triploid (69)	MT	7	61
	LC:NCI_H23	Non-Small Cell Lung	Adenocarcinoma-ud	NA	2n+, Hyperdiploid (47-57)	MT	-2	33.4
	LC:NCI_H460	Non-Small Cell Lung	Large Cell Carcinoma-ud	Pleural effusion	2n+/-, Near-diploid 46+/- (35-57)	WT	25	17.8
	LC:NCI_H522	Non-Small Cell Lung	Adenocarcinoma-vpd	NA	2n+/-, Near-diploid 46+/- (35-57)	MT	16	38.2
YT30 YT86 YT88 YT128 Formulas I,VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	OV:OVCAR_3	Ovarian	Adenocarcinoma-md	Ascites	3n+/-, Near-triploid 69+/- (58-80)	MT	-12	34.7
	OV:OVCAR_5	Ovarian	Adenocarcinoma-wd	NA	2n+, Hyperdiploid (47-57)	MT	13	48.8

YT86 YT88 YT128 Formulas VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	OV:OVCAR_4	Ovarian	Adenocarcinoma-md	NA	3n+/-, Near-triploid 69+/- (58-80)	WT	-4	41.4
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	OV:OVCAR_8	Ovarian	Carcinoma-ud	NA	2n+, Hyperdiploid (47-57)	MT	7	26.1
	OV:SK_OV_3	Ovarian	Adenocarcinoma-vpd	Ascites	4n+/-, Near-tetraploid 92+/- (81-103)	?	15	48.7
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	PR:PC_3	Prostate	Adenocarcinoma- prostate; metastatic site: bone;	NA	4n, Tetraploid (92)	MT	11	27.1
YT30 YT88 Formula I,VI Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	PR:DU_145	Prostate	Prostate; metastatic site: brain; carcinoma	Metastasis	3n+/-, Near-triploid 69+/- (58-80)	?	4	32.3
YT88 YT128 Formula VI, VII Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	RE:786_0	Renal	Adenocarcinoma	NA	4n+/-, Near-tetraploid 92+/- (81-103)	MT	-44	22.4
YT30 Formula I Structures I, II, IIIA, IIIB, IIIC,	RE:ACHN	Renal	Renal cell carcinoma-p/md	NA	2n+/-, Near-diploid 46+/- (35-57)	WT	120	27.5

IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	RE:CAKI_1	Renal	Clear cell carcinoma	Metastasis	3n, Triploid (69)	WT	171	39
YT30 YT86 YT88 YT128	RE:A498	Renal	Adenocarcinoma	NA	3n, Triploid (69)	WT	78	66.8
	RE:SN12C	Renal	Renal cell carcinoma-pd	NA	3n, Triploid (69)	MT	-86	29.5
Formulas I,VI, VII	RE:TK_10	Renal	Renal Spindle cell carcinoma	NA	4n, Tetraploid (92)	MT	-4	51.3
Structures I, II, IIIA, IIIB, IIIC, IVA, IVB, IVC, IVD, VA, VB, VC, VD, VE, and VI	RE:UO_31	Renal	Renal cell carcinoma-vpd	NA	2n+/-, Near-diploid 46+/- (35-57)	WT	59	41.7

1. MT= mutant; WT=wild type
2. MDR=Multidrug Resistance (Wu et.al., 1992)

Example 4: Combination therapy of YT30 and imatinib inhibited leukemia

[00179] Growth inhibition experiments were performed as previously described. The combination of YT30 and imatinib displayed a synergistic effect in growth inhibition of a Nalm-6, a leukemia cell line. After 72hrs, combination of YT30 and Imatinib showed an increase in growth inhibition compared to addition of each agent alone (Table 13). For example, 1μM YT30 alone induced growth inhibition by 8.4%, 10μM imatinib induced growth inhibition by 44%, but the combination of 1μM YT30 and 10μM imatinib induced growth inhibition by 97%. The synergistic effects were also observed when the YT30 and imatinib were combined with other concentrations.

Table 13. Inhibition of leukemia growth with the combination of YT30 and imatinib

YT30 concentrations (μM)	Imatinib concentrations (μM)	72hr growth inhibition (%)
0	0	0
0.5	0	2.5
1	0	8.4
0	5	0
0.5	5	9
1	5	28
0	10	44

0.5	10	67
1	10	94

Example 5: YT30 inhibition of subcutaneous leukemia tumor growth in mouse model

[00180] *Tumor transplantation and treatment of NOD/SCID mice*. Female Nonobese Diabetic/Severe Combined Immunodeficiency (NOD/SCID) mice that were 4-6 weeks old were used in the experiment. The mice were fed under specific pathogen free (SPF) conditions. Food and water were available to the mice at will. A suspension of 1×10^7 cells per mouse B-myelomonocytic leukemia MV4-11 cells (0.2 mL) in logarithmic phase were inoculated subcutaneously into the right back of the NOD/SCID nude mice.

[00181] The general conditions of the mice and the growth of the transplanted tumor were monitored. When the transplanted tumor grew to about 100 mm^3 in size, the NOD/SCID mice were divided into four groups with five mice in each group so that each group of mice had a similar average tumor size. The control group received an intraperitoneal (IP) injection of 0.2 mL of solvent (20% DMSO, 80% of 20% w/v (2-hydroxypropyl)-β-cyclodextrin made in PBS). The imatinib group received gavage of 100 mg/kg/day imatinib. The high dosage group received an intraperitoneal injection of 50 mg/kg/day of YT30 (0.2 mL in volume) suspended in solvent (20% DMSO, 80% of 20% w/v (2-hydroxypropyl)-β-cyclodextrin made in PBS), while the low dosage group received IP injection of 25 mg/kg/day YT30 (0.2 mL in volume). Frequency of the administration was once per day and the experiment lasted 27 days after treatment started.

[00182] The body weights of the mice were recorded prior to the start of treatment and twice every week thereafter. Each mouse of every group was monitored daily for any other symptoms of side effects including change in behavior, activity or posture, areas of redness and swelling, and food and water withdrawal. Caliper measurements of the longest perpendicular tumor diameters were performed every 2 days to estimate the tumor volume; the following formula: $4\pi/3 \times (\text{width}/2)^2 \times (\text{length}/2)$ was used to calculate the three-dimensional volume of an ellipse. The tumor inhibition rate was calculated according to tumor volume: Tumor inhibition rate by size (%) = (Tumor volume of the control group–Tumor volume of the treated

group)/Tumor volume of the control group X 100. The mice were euthanized on the next day after the final injection and the subcutaneous tumor nodules were taken out intact and weighed. The tumor inhibition rate was calculated again according to tumor weight: Tumor inhibition rate by weight (%) = (Tumor weight of the control group–Tumor weight of the treated group)/Tumor weight of the control group X 100).

Table 14. YT30 inhibited subcutaneous leukemia tumor growth in a mouse model

Group	Dosage mg/kg	Admini-stration	Average body weight (g, $\bar{X}$ ±s)		Body Weight Change (%)	Tumor Weight (g, $\bar{X}$ ±s)	Tumor Growth Inhibition by Weight (%)	Tumor Size (mm^3)	Tumor Growth Inhibition by Size (%)
			Initial	End Point					
Control			21.74 ±0.90	21.53 ±1.15	-3.6	2.20 ± 0.64		2189.68 ±575.83	
Imatinib	100	p.o. x27 days	22.17 ±1.19	22.06 ±1.74	-1.0	1.29 ± 0.42	41.7	1040.51 ±422.38	52.5
YT30 50 mg/kg	50	I.P. x27 days	21.02 ±0.97	18.86 ±1.38	-6.8	0.91 ± 0.27	58.8	774.63 ±269.10	64.6
YT30 25 mg/kg	25	I.P. x27 days	21.61 ±1.18	21.33 ±1.26	-1.0	1.35 ± 0.47	38.8	1072.31 ±296.29	51.0

Results

YT30 inhibited the growth of subcutaneously transplanted leukemia tumors in NOD/SCID mice. About one week after seeding the NOD/SCID mice with MV4-11 cells, all of the transplanted tumors grew to a size around 100 mm^3. The rate of successful transplantation was 100%. After 27 days of treatment with YT30, tumor growth inhibition by size is 58.8% for the high dosage YT30 treatment group and 38.8% for the low dosage YT30 treatment group (Table 14). The difference in tumor growth inhibitions between the high dosage and the low dosage group demonstrated clear dose-response relationship. The tumor weight was also significantly less than that of the control group, and the difference was statistically significant.

Example 6: YT30 growth inhibition of chronic myelogenous leukemia (CML) tumors in SCID mice transplanted with K562 cells

Methods

[00183] *Tumor transplantation and treatment of SCID mice.* Male Severe Combined Immunodeficiency (SCID) mice that were 4-6 weeks old were used in the experiment. The mice were fed under specific pathogen free (SPF) conditions. Food and water were available to the mice at will. A suspension of 8 X 10^6 chronic myelogenous leukemia K562 cells (0.2 mL) was inoculated subcutaneously into the right back of the SCID mice.

[00184] The general conditions of the mice and the growth of the transplanted tumor were monitored. When the transplanted tumor grew to about 100 mm^3 in size, the SCID mice were divided into four groups with eight mice in each group so that each group of mice had a similar average tumor size. The control group received an intraperitoneal injection (IP) of 0.2 mL solvent (20% DMSO, 80% of 20% w/v (2-hydroxypropyl)-β-cyclodextrin made in PBS). The imatinib group received oral gavage of 100 mg/kg/day imatinib suspended in 0.5% sodium carboxymethyl cellulose. The YT30 treated groups received either intraperitoneal injection of 50 mg/kg/day of YT30 (0.2 mL in volume) suspended in solvent (20% DMSO, 80% of 20% w/v (2-hydroxypropyl)-β-cyclodextrin made in PBS) or oral gavage of 90 mg/kg/day YT30 in solvent (Cremophor RH40:TW80:PEG400 (2:1:1)). Frequency of the administration was once per day and the experiment lasted 16 days after initiation of the treatment.

[00185] The body weights of the mice were recorded prior to the start of treatment and twice every week thereafter. Each mouse of every group was monitored daily for any other symptoms of side effects including change in behavior, activity or posture, areas of redness and swelling, and food and water withdrawal. Caliper measurements of the longest perpendicular tumor diameters were performed every 2 days to estimate the tumor volume; the following formula: $4\pi/3 \times (\text{width}/2)^2 \times (\text{length}/2)$ was used to calculate the three-dimensional volume of an ellipse. The tumor inhibition rate was calculated according to tumor volume: Tumor inhibition rate by size (%) = (Tumor volume of the control group–Tumor volume of the treated group)/Tumor volume of the control group X 100. The SCID mice were euthanized 2 hours after the final injection and the subcutaneous tumor nodules were taken out

intact and weighed. The tumor inhibition rate was calculated again according to tumor weight: Tumor inhibition rate by weight (%) = (Tumor weight of the control group–Tumor weight of the treated group)/Tumor weight of the control group X 100.

Results

[00186] *YT30 inhibited the growth of leukemia tumors subcutaneously transplanted in SCID mice with human chronic myeloid leukemia cells (K562).* At 12 days after inoculation of K562 cells in SCID mice all of the transplanted tumors grew to a size around 100 mm^3. The rate of successful transplantation was 100%. After 16 days of treatment with YT30, tumor growth inhibition by weight was 40.76% for the intraperitoneal YT30 treatment group and 33.17% for the oral YT30 treatment group (Table 15).

Table 15. K562 (CML) tumor growth inhibition by weight and size in SCID mice treated with YT30

Group	Dosage mg/kg	Admini-stration	Average body weight (g, $\bar{x}$ ±s)		Body weight change (%)	Tumor weight (g, $\bar{x}$ ±s)	Tumor growth inhibition by weight (%)	Tumor size (mm^3, $\bar{x}$ ±s)	Tumor growth inhibition by size (%)
			Initial	End point					
Control			18.70 ±0.59	18.02 ±2.33	-3.64	3.65±2.27		3112.78± 1661.65	
Imatinib	100	p.o. × 16 days	18.99 ±1.23	18.37 ±0.54	-3.26	2.63±1.09	27.91	1744.05± 1049.95	43.97
YT30:50 mg/kg	50	i.p.× 16 days	18.34 ±0.73	16.75 ±1.57	-8.67	2.16±1.86	40.76	1741.11± 1218.90	44.07
YT30:90 mg/kg	90	p.o. × 16 days	18.69 ±1.36	17.70 ±2.03	-5.30	2.44±0.92	33.17	1812.71± 581.68	41.77
p.o. = oral i.p. = intraperitoneal									

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REFERENCES

The references, patents and published patent applications listed below, and all references cited in the specification above are hereby incorporated by reference in their entireties, as if fully set forth herein.

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CLAIMS

What is claimed is:

1. A method of treating a cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of one or more compounds or a composition or pharmaceutical formulation thereof, wherein the one or more compounds comprise a structure selected from the group consisting of YT54, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, and Structure VIII, including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein:

A and B rings are each independently selected from the group consisting of phenyl, pyridyl and N-alkylated pyridyl rings;

R_1-R_5 are each independently selected from the group consisting of hydrogen, halogen, alkyl, and haloalkyl, wherein at least one or two of R_1-R_5 are halogen and/or haloalkyl;

R_6 and R_7 are an alkyl group having 1-3 carbon atoms;

X_1 and X_2 are independently selected from –NHC(=O)- or –C(=O)-NH-; and

L_1 is $–(CH_2)_n$-, where n is 4, 5, 6, 7, or 8, where one or more $–CH_2$- moieties are optionally replaced with one or more substituents selected from the group consisting of -O-, -S-, -C(=O)-, -S(=O)-, $-S(=O)_2$-, -NH-C(=O)-, -C(=O)-NH-, -NR-, -C=C-, carbon-carbon triple bond, phenylene, 1, 4-phenylene and cyclohexylene, 1, 4-cyclohexylene, wherein R is hydrogen, alkyl or aryl.

2. The method according to claim 1, wherein L_1 is $–(CH_2)_n$-, where n is 4, 5, 6, 7, or 8.

3. The method according to claim 2, wherein:

R_3 and R_4 are halogen; and

R_1, R_2, and R_5 are hydrogen.

4. The method according to claim 3, wherein the halogen is bromine.

5. The method according to claim 2, wherein the cancer or tumor is selected from the group consisting of breast cancer, central nervous system cancer, colon cancer, prostate cancer, lung cancer, leukemia, renal cancer, ovarian cancer, melanoma, liver cancer, and cervical cancer.

6. The method according to claim 4, wherein the cancer or tumor is selected from the group consisting of breast cancer, central nervous system cancer, colon cancer, prostate cancer, lung cancer, leukemia, renal cancer, ovarian cancer, melanoma, liver cancer, and cervical cancer.

7. The method according to claim 2, wherein the cancer treated is leukemia selected from the group consisting of acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma.

8. The method according to claim 4, wherein the cancer treated is leukemia selected from the group consisting of acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma.

9. The method according to claim 7, wherein the one or more compounds are selected from the group consisting of YT29, YT30, YT53, YT54, YT61, YT65, YT67, YT68, YT73, YT74, and YT139, or pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts or pharmaceutically acceptable stereoisomers thereof.

10. The method according to claim 7, wherein the leukemia is resistant to Imatinib or Gleevec.

11. The method according to claim 7, wherein the leukemia has a p53 mutation in the genome of the leukemia cells.

12. The method according to claim 7, wherein the leukemia has wild type p53 in the genome of the leukemia cells.

13. The method according to claim 7, wherein the leukemia has a Multidrug Resistance value between 1 and 50.

14. The method according to claim 7, wherein the leukemia has a Multidrug Resistance value between -15 and 0.

15. The method according to claim 2, wherein the one or more compounds or a composition or pharmaceutical formulation thereof may be administered orally or by intraperitoneal injection.

16. The method according to claim 2, wherein the one or more compounds or a composition or pharmaceutical formulation thereof may be administered in combination with a pharmaceutically effective amount of imatinib.

17. A method of treating cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of one or more compounds or a composition or pharmaceutical formulation thereof, wherein the one or more compounds comprise a structure selected from the group consisting of YT45, T46, YT51, YT58, YT62~YT63, YT76~YT80, YT86, YT88, YT91, YT99, YT108~YT110, YT116~YT118, YT121~YT123, YT127, YT128, YT131, YT134~YT136, and 137~139 including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof.

18. The method of claim 17, wherein the cancer is leukemia selected from the group consisting of acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia

(CML), CML (imatinib resistant), multiple myeloma, B-cell myelomonocytic leukemia, T-cell myelomonocytic leukemia, biphenotypic B-cell leukemia, and/or lymphoma.

19. The method of claim 18, wherein the one or more compounds or a composition or pharmaceutical formulation thereof may be administered in combination with a pharmaceutically effective amount of Imatinib or one or more compounds of claim 1.

20. The method of claim 18, wherein the one or more compounds or a composition or pharmaceutical formulation thereof may be administered orally or by intraperitoneal injection.

Fig. 1

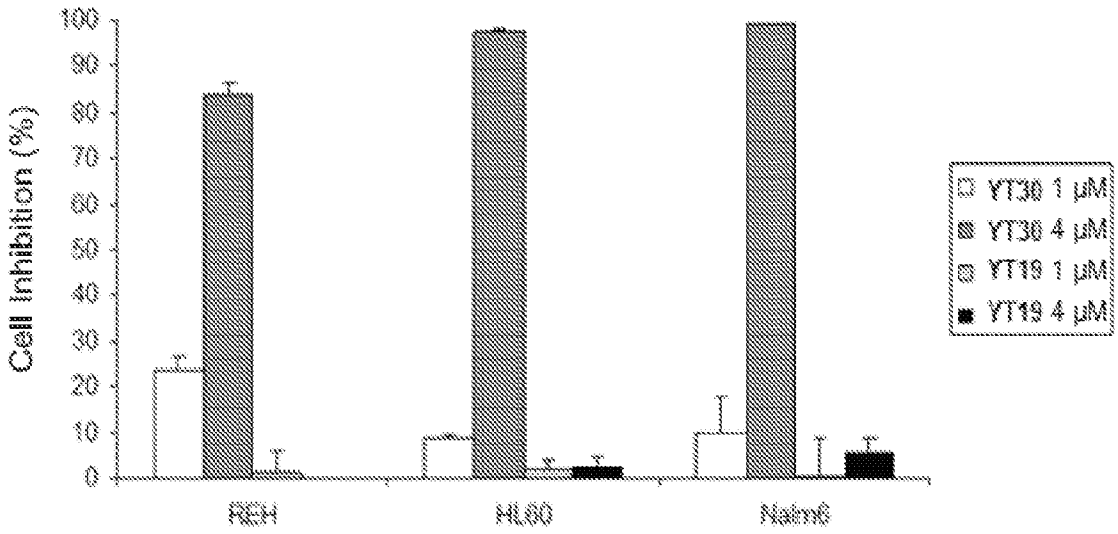
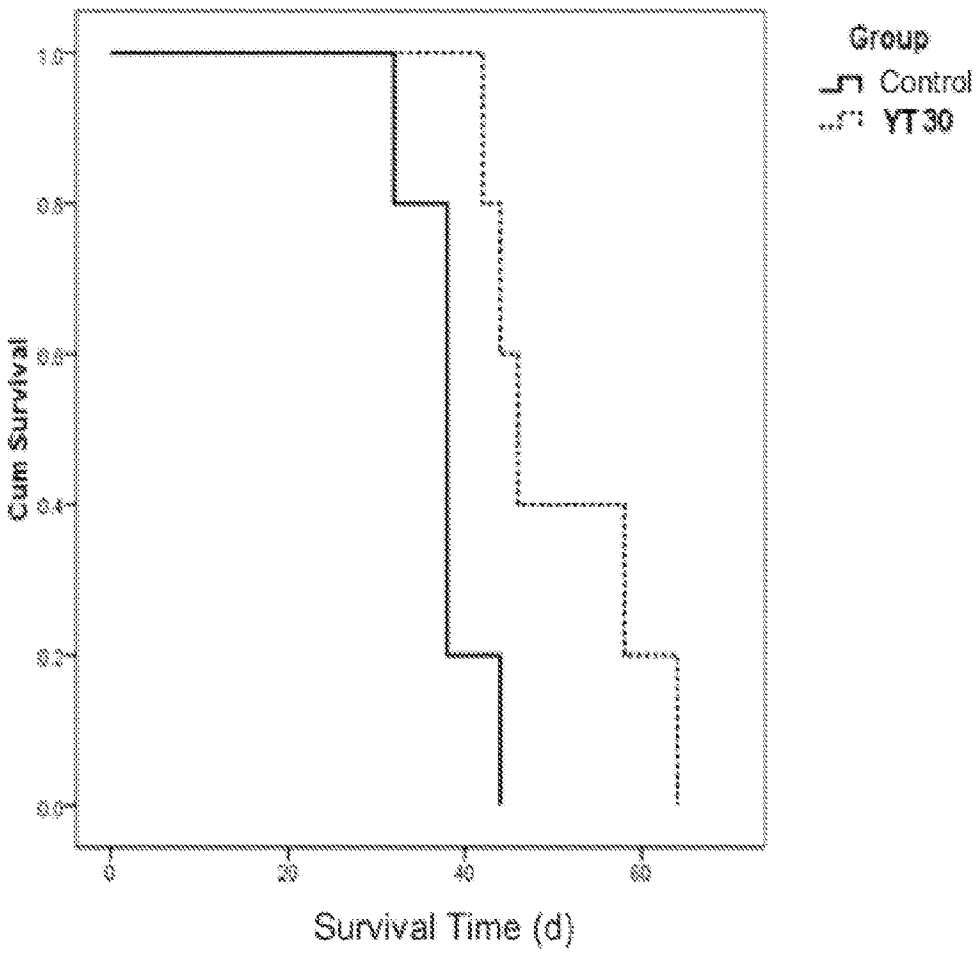

Cell Inhibition (%)
100
90
80
70
60
50
40
30
20
10
0
REH
HL60
Nalm6
YT30 1 μM
YT30 4 μM
YT19 1 μM
YT19 4 μM

Fig. 2


Group
Control
YT30
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
Survival Time (d)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021449

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/167 (2014.01)
USPC - 514/613
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/165, 31/167, 31/185; A61P 35/00 (2014.01)
USPC - 436/501; 514/513, 613, 616

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/00, 31/165, 31/19; C07D 239/42 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	JAYATHILAKA et al. "Inhibition of the function of class IIa HDACs by blocking their interaction with MEF2" Nucleic Acids Research, 2012, Vol. 40, No. 12, Pgs. 5378-5388. [retrieved on 16 July 2014]. Retrieved from the Internet. <URL: http://nar.oxfordjournals.org/content/40/12/5378.full.pdf+html>. entire document	1, 2, 5, 7, 9 — 10-16
Y	US 2011/0319447 A1 (SUN et al) 29 December 2011 (29.12.2011) entire document	10, 15, 16
Y	US 2011/0081331 A1 (HAUPT et al) 07 April 2011 (07.04.2011) entire document	11
Y	US 2008/0131526 A1 (SEBTI et al) 05 June 2008 (05.06.2008) entire document	12
Y	WU et al. "Multidrug-resistant Phenotype of Disease-oriented Panels of Human Tumor Cell Lines Used for Anticancer Drug Screening" Cancer Research, 1992, 52, pg. 3029-3034. [retrieved on 16 July 2014]. Retrieved from the Internet. <URL: http://cancerres.aacrjournals.org/content/52/11/3029.full.pdf>. entire document	13, 14
A	US 2011/0275674 A1 (CHEN et al) 10 November 2011 (10.11.2011) entire document	1, 2, 5, 7, 9-16

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2014	12 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021449

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 5, 7, and 9-16

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/021449

<Continued from Box III: Observations where unity of invention is lacking>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-20 are drawn to a method of treating cancer or a tumor in a subject comprising administering a compound selected from the group consisting of YT54, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, and Structure VIII.

The first invention of Group I+ is restricted to a method of treating cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of YT54 including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, or a pharmaceutical composition thereof. It is believed that claims 1, 2, 5, 7, and 9-16 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional method to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method of treating cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of a compound of Structure I including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, wherein: A and B rings are each phenyl; R1-R5 are each independently selected from the group consisting of hydrogen, halogen, wherein at least one or two of R1-R5 are halogen; X1 and X2 are -NHC(=O)-; and L1 is -(CH2)n-, where n is 4; or a pharmaceutical composition thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element responsible for treating cancer or a tumor, requiring the selection of alternatives for the compound from YT54, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, and Structure VIII.

The Groups I+ share the technical features of a method of treating cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of a compound selected from the group consisting of YT54, Structure I, Structure II, Structure IIIA, Structure IIIB, Structure IIIC, Structure IVA, Structure IVB, Structure IVC, Structure IVD, Structure VA, Structure VB, Structure VC, Structure VD, Structure VE, Structure VI, Structure VIIA, Structure VIIB, Structure VIIC, Structure VIID, Structure VIIE, and Structure VIII or species thereof, including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, or a pharmaceutical composition thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2011/0275674 to Chen et al. teach method of treating cancer or a tumor in a subject comprising administering to the subject a therapeutically effective amount of a compound of Structure I (see applicant's Para [0013]) including pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, pharmaceutically acceptable salts and pharmaceutically acceptable stereoisomers thereof, or a pharmaceutical composition thereof (Para. [0011], invention described in this application can also be extended to modulating the activity of other transcription factors such as the forkhead/winged helix transcription factor FOXP3...small molecules that bind FOXP3 and modulate its interaction with co-repressors and co-activators could have therapeutic application in autoimmune diseases, transplant rejection and cancer therapy; Para. [0032], the present invention targets the interaction between the transcription factor MEF2 and class IIa HDACs. The activity of MEF2 is controlled by class IIa HDACs that bind MEF2 on specific promoters to repress target gene expression...Some small molecule inhibitors of HDACs (HDACi) that are being developed for the treatment of a variety of cancers...; Para. [0079], ... administering to a patient a pharmaceutically effective amount of a blocking agent, in which the blocking agent is capable of blocking the binding of a HDAC to a transcription factor...), wherein A and B rings are independently phenyl; R1-R5 are independently selected from the group consisting of hydrogen and halogen; X1 and X2 are independently selected from -NHC(=O)- or -C(=O)-NH-; and L1 is -(CH2)n-, where n is 5 (Para. [0115], further preferred embodiment, the provided compounds are selected from the following list of compounds (FIG. 2), see structure of compounds 9 and 10).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>