USES OF INDOLINONE COMPOUNDS

FIELD

[0001] Methods and compositions for treating acute myeloid leukemia and diffuse large B cell lymphoma using indolinone derivatives are provided.

BACKGROUND

[0002] The EWS-FLI transcription factor present in vast variety of Ewing's sarcoma family of tumors (ESFT) was characterized over ten years ago. Progress in the treatment of Ewing's sarcoma the second most common bone tumor in children and adolescents, has improved survival for patients with localized tumors. However, patients with metastases still fare badly and the therapy carries short and long-term toxicities. The Ewing sarcoma family of tumors (ESFT) is characterized by a chromosomal translocation that generates EWS-FLI1, on oncogenic fusion transcription factor whose continued expression is believed to be critical for ESFT cell survival (Balamuth, NJ, Womer, RB., Lancet Oncology 11, 184-192 (2010)). ETS transcription factors, such as FLI1 and SPIB, are recurrently deregulated in human lymphomas (Bonetti et al, Blood 2013; Lenz et al, PNAS 2008). The small molecule YK-4-279 inhibits binding of EWS1-FLI1 fusion protein to RHA resulting in growth arrest and apoptosis in Ewing sarcoma cells (Erkizan et al, Nat Med 2009) and it was previously showed that YK-4-279 has in vitro anti-lymphoma activity (Chung et al, AACR 2015).

[0003] *In vitro* and *in vivo* studies have demonstrated that the inhibition of the binding of the oncoprotein, EWS-FLI1, to RNA Helicase A (RHA) leads to a decrease in proliferation of ESFT cell lines and a decrease of tumor volume. EWS-FLI1 lacks enzymatic activity, however, the protein-protein interaction between RNA helicase A (RHA) and EWS-FLI1-modulates oncogenesis, and is therefore required for the maintenance of the tumor growth (Hyariye N Erkizan et al. Nature Medicine 15(7) 750-756 (2009)). The paradigm of disrupting key protein interactions may have utility in treatment of diseases including sarcomas with similar translocations, and leukemias with MLL translocations ((Helman LJ, Meltzer P. Mechanisms of sarcoma development. Nat Rev Cancer 2003;3(9):685-94); and Pui CH, et al., N Engl J Med 2004;350(15):1535-48). Moreover, disordered proteins may be

excellent therapeutic targets based on their intrinsic biochemical properties (Cheng Y, LeGall T, Oldfield CJ, *et al.*, Trends Biotechnol 2006;24(10):435-42).

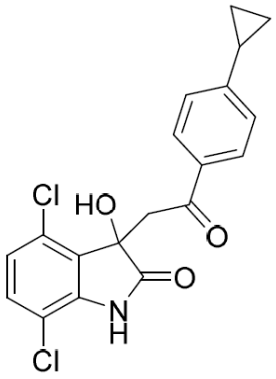
SUMMARY

[0004] Despite years of *in vitro* and xenograft studies with antisense and siRNA directed towards EWS-FLI1, none of these is heretofore practical as a human therapy based on inadequate delivery and stability. Accordingly, there is a need for improved therapies to treat disorders such as ESFTs.

[0005] FLI-1 is a member of the ETS family transcription factors which are normally active in the developing embryo, but not after birth. There are 29 members of this family of transcription factors, four of which, FLI-1, ETV1, ETV4 and ERG, have been associated with a wide range of cancers.

[0006] Therapeutic compounds targeting the inhibition of the binding of oncogenic fusion proteins of FLI1, ETV1, ETV4 or ERG or the transcription factors themselves will have utility in treatment of cancers including the Ewing's sarcoma family of tumors, pancreatic cancer, prostate cancer, glioblastoma, non-small cell lung cancer, and several other cancers. The preferred examples fulfill these needs, and provide other advantages as well.

[0006a] In one aspect of the present disclosure, there is provided a use of a compound having the structure :

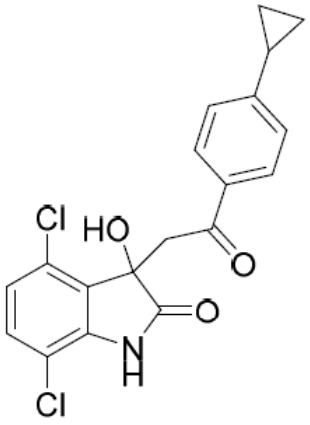


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

[0006b] In another aspect of the present disclosure, there is provided a use of a compound having the structure:

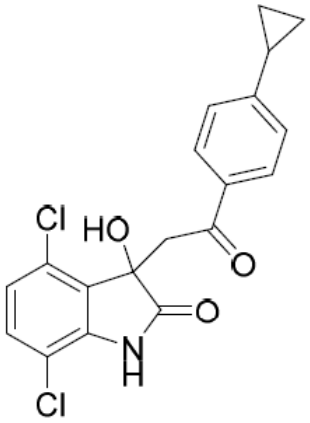


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

[0006c] In a further aspect of the present disclosure, there is provided a use of a combination comprising a compound having the structure:

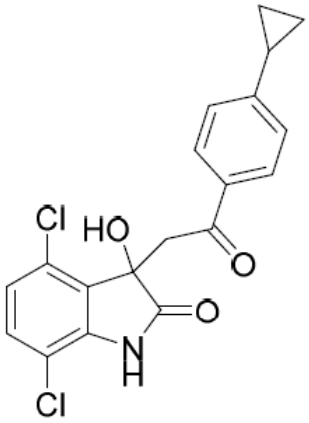


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

[0006d] In another aspect of the present disclosure, there is provided a use of a combination comprising a compound having the structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

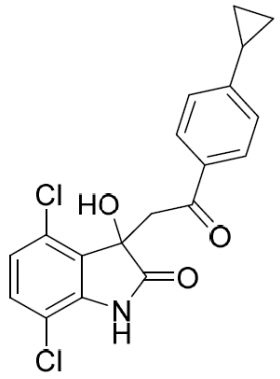
the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

[0006e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising:

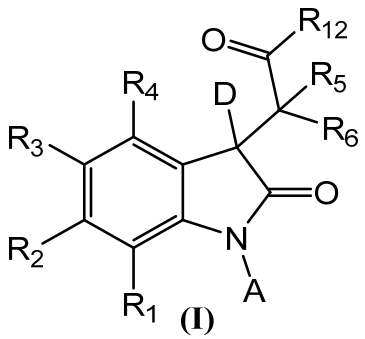
the extra-terminal protein inhibitor OTX015; and

a compound having a structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof.

[0007] Some examples disclosed herein relate to a compound of Formula (I) including forms such as stereoisomers, free forms, pharmaceutically acceptable salts or esters thereof, solvates, or combinations of such forms, wherein A, D, R_1, R_2, R_3, R_4, R_5, R_6, and R_{12} are as defined herein.



(I)

[0008] Some examples disclosed herein relate to methods for treating cancer in a mammal, comprising administering to the mammal an effective amount of one or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one

or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof,. Other examples described herein relate to using one or more compounds of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of cancer.

[0009] Still other examples described herein relate to a compound of Formula (I) including forms such as stereoisomers, free forms, or a pharmaceutically acceptable salt thereof, for treatment of cancer wherein the cancer is selected from the group consisting of Ewing's sarcoma, glioblastoma, acute myeloid leukemia, breast cancer, head & neck cancer, melanoma, non-small cell lung cancer, ovarian cancer, prostate cancer, and uterine cancer. These and other examples are described in greater detail below.

DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 is a diagram illustrating that TK216 (also referred to herein as TK-216, which is 4,7-Dichloro-3-(2-(4-cyclopropylphenyl)-2-oxoethyl)-3-hydroxyindolin-2-one) is active in oncogenesis and inhibits aptosis.

[0011] FIG. 2 shows TK216 treatment inhibited EWS-FLI1 protein interactions, leading to a decrease in transcription and proliferation.

[0012] FIG. 3 shows TK216 reduced transcriptional activity in COS7 cells co-transfected with EWS-FLI1 and NROB1 reporter-luciferase plasmids which contain EWS-FLI1 DNA-binding sites.

[0013] FIG. 4 shows treatment with TK216 resulted in a dose-dependent inhibition of proliferation in Ewing Sarcoma A4573 cell line.

[0014] FIG. 5 shows TK216 displayed anti-proliferative activity in AML cell lines.

[0015] FIG. 6 shows TK216 displayed anti-proliferative activity in DLBCL cell lines.

[0016] FIG. 7 and FIG. 8 show TK216 induced apoptosis in DLBCL cell lines, with the amount of cleaved-Caspase 3 normalized to b-actin and presented as fold over control.

[0017] FIG. 9 shows TK216 displayed synergy when combined with BCL-2 (ABT199) inhibitors, wherein CalcuSyn software was used to determine the Combination Index (CI) using the Chou/Talalay equation.

[0018] FIG. 10 show TK216 displayed synergy when combined with BTK (ACP196) inhibitors, wherein CalcuSyn software was used to determine the Combination Index (CI) using the Chou/Talalay equation.

[0019] FIG. 11 shows TK216 displayed anti-tumor activity in a TMD8 xenograft model.

[0020] FIG. 12 shows treatment with TK216 results in tumor growth inhibition of the TMD-8 xenograft model when compared to vehicle control following 13 days of treatment.

[0021] FIG. 13 is a dose-effect curve for TK216 in combination with venetoclax in the TMD8 cell line, wherein the top curve (×) was for the combination therapy, the middle curve (⊙) was for TK216, and the bottom curve (+) was for venetoclax.

[0022] FIG. 14 is a dose-effect curve for TK216 in combination with venetoclax in the U2932 cell line, wherein the top curve (×) was for the combination therapy, the middle curve (⊙) was for TK216, and the bottom curve (+) was for venetoclax.

[0023] FIG. 15 is a dose-effect curve for TK216 in combination with venetoclax in the HLB1 cell line, wherein the top curve (×) was for the combination therapy, the middle curve (⊙) was for TK216, and the bottom curve (+) was for venetoclax.

[0024] FIG. 16 shows the results of dose-effect testing conducted in DLBLC cell lines (TMD8, HBL1, U2932), indicating a synergistic effect across doses.

[0025] FIG. 17 shows the distribution of IC50 values for TK-216 in lymphoma cell lines by individual histologies. Y-axis: IC50 values. In each box-plot, the line in the middle of the box represents the median and the box extends from the 25th to the 75th percentile (interquartile range, IQ); the whiskers extend to the upper and lower adjacent values (i.e., ±1.5 IQ).

[0026] FIGS. 18A and 18B show apoptosis and cell cycle distribution of TK-216 in DLBCL cell lines. FIG. 18A) Induction of apoptosis in DLBCL cell lines exposed to TK-216 (500nM) for 24, 48 or 72 hrs. In the figures are shown four representative (two ABC and two GCB) results. FIG. 18B) Cell cycle distribution in DLBCL cell lines treated with 500nM

of TK-216 for 24, 48 or 72 hrs. In the figure, two representative (one ABC and one GCB) results are shown. DMSO treatment was used as a control.

[0027] FIG. 19 shows the effects of TK-216 in a xenograft model of ABC-DLBCL. NOD-Scid mice subcutaneously inoculated with TMD8 cells (15×10^6) were split in two groups respectively treated with TK-216 (100 mg/kg, BID, po, n= 9) and control vehicle (n=10). In each box-plot, the line in the middle of the box represents the median and the box extends from the 25th to the 75th percentile (interquartile range, IQ); the whiskers extend to the upper and lower adjacent values (i.e., ±1.5 IQ).

[0028] FIG. 20 shows TK216 combinations in DLBCL cell lines: box-plots of the CI values obtained in individual cell lines. Y-axis: CI values. In each box-plot, the line in the middle of the box represents the median and the box extends from the 25th to the 75th percentile (interquartile range, IQ); the whiskers extend to the upper and lower adjacent values (i.e., ±1.5 IQ); outside values have been omitted from the figure. CIs for TK-216/rituximab in TMD8, TK-216/rituximab in Karpas422, TK-216/rituximab in OCI-LY-10 are not plotted due to CI values > 3. Combinations tested included bendamustine, bortezomib, ibrutinib, idelalisib, lenalidomide, OTX015 (birabresib, CAS No. 202590-98-5), PQR309 (bimiralisib, CAS No. 1225037-39-7 (free base)), selinexor, venetoclax, and vincristine. Synergism was observed for TK216 in combination with bortezomib (TMD8), idelalisib (OCI-LY-10, KARPAS422), lenalidomide (OCI-LY-10, TMD8), OTX015 (KARPAS422), venetoclax (OCI-LY-10, KARPAS422, TMD8), and vincristine (SU-DHL-4). An additive effect was observed for TK216 in combination with bendamustine (KARPAS422), ibrutinib (OCI-LY-10, TMD8), lidelalisib (TMD8), OTX015 (OCI-LY-10, TMD8), PQR309 (KARPAS422, SU-DHL-4, TMD8), selinexor (KARPAS422, TMD8), and vincristine (OCI-LY-10, KARPAS422). No benefit effects was observed for TK216 in combination with bendamustine (OCI-LY-10, SU-DHL-4, TMD8), bortezomib (OCI-LY-10), idelalisib (SU-DHL-4), OTX015 (SU-DHL-4), PQR309 (OCI-LY-10), selinexor (OCI-LY-10, SU-DHL-4), venetoclax (SU-DHL-4), and vincristine (TMD8).

DETAILED DESCRIPTION

[0029] The following description and examples illustrate a preferred embodiment of the present invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope.

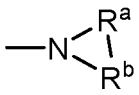
Accordingly, the description of a preferred embodiment should not be deemed to limit the scope of the present invention

[0030] Chromosomal translocations generating oncogenic transcription factors are the hallmark of a variety of tumors, including many sarcomas. Ewing sarcoma family of tumors (ESFTs) are characterized by the t(11;22)(q24;q12) translocation that generates the Ewing sarcoma breakpoint region 1 and Friend leukemia virus integration 1 (EWS-FLI1) fusion transcription factor responsible for the highly malignant phenotype of this tumor. Continued expression of EWS-FLI1 is believed to be critical for ESFT cell survival. EWS-FLI1 is an attractive treatment target for Ewing sarcoma because of its malignant cell specificity. Furthermore, experimental evidence indicates that EWS/FLI expression is essential for Ewing sarcoma tumor cells. In vitro targeting of EWS-FLI1 with antisense oligodeoxynucleotides and RNA interference (RNAi) inhibits Ewing sarcoma cell viability, growth, and oncogenic transformation, supporting EWS-FLI1 attenuation as a potential treatment modality. The therapeutic agents of the preferred embodiments have broad applicability to a larger group of tumors, and are useful as therapeutics for treatment for other oncogenic transcription factor related malignancies such as chemotherapy-resistant sarcomas and leukemias and difficult to treat tumors such as Ewing's sarcoma.

Definitions

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0032] As used herein, any "R" group(s) such as, without limitation, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



In addition, if two "R" groups are described as being "taken together" with the atom(s) to which they are attached to form a ring as an alternative, the R groups may not be limited to the variables or substituents defined previously.

[0033] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one to six carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl, pentyl (straight and branched) and hexyl (straight and branched). Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl (straight and branched) and hexyl (straight and branched). The alkyl group may be substituted or unsubstituted.

[0034] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0035] As used herein, "aryl" refers to a carbocyclic (all carbon) mono-cyclic or multi-cyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups

include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0036] As used herein, "heteroaryl" refers to a mono-cyclic or multi-cyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1 to 5 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0037] As used herein, heterocycloalkyl refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered mono-cyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heterocycloalky may be quaternized. Heterocycloalkyl groups may be unsubstituted or substituted. Examples of such heterocycloalkyl groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane,

tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone, and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0038] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0039] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof.

[0040] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

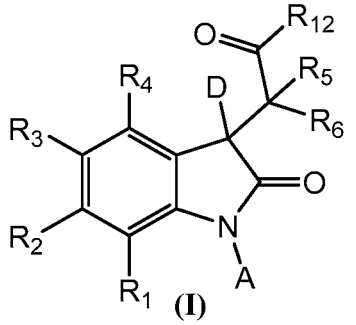
[0041] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0042] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

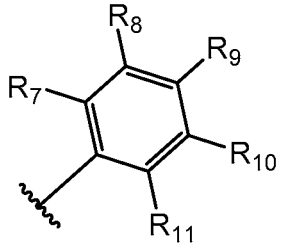
[0043] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Methods of Treatment

[0044] In a first aspect, a method for inducing aptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with an effective amount of a combination of venetoclax and a compound having a structure of Formula (I):



(I)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and $-CF_3$; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and $-O(C_{1-6}$ alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6} alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of C_{3-8} cycloalkyl and  ; wherein R_7, R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, $-O(C_{1-6}$ alkyl), -O(aryl), -O(heteroaryl), $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), $-NHSO_2(C_{1-6}$ alkyl), $-NHSO_2$(aryl), $-NHCONH(C_{1-6}$ alkyl), $-NHCON(C_{1-6}$ alkyl)$_2$, $-N(C_{1-6}$ alkyl)$CONH_2$, $-N(C_{1-6}$ alkyl)$CONH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$CON(C_{1-6}$ alkyl)$_2$, $-SO_2(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl.

[0045] In an embodiment of the first aspect, R_9 is selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(aryl), -O(heteroaryl), -

CO_2H, $-CO_2(C_{1-6}$ alkyl), $-NHSO_2(C_{1-6}$ alkyl), $-NHSO_2$(aryl), $-NHCONH(C_{1-6}$ alkyl), $-NHCON(C_{1-6}$ alkyl)$_2$, $-N(C_{1-6}$ alkyl)$CONH_2$, $-N(C_{1-6}$ alkyl)$CONH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$CON(C_{1-6}$ alkyl)$_2$, $-SO_2(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl.

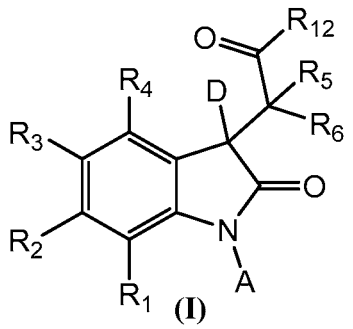
[0046] In an embodiment of the first aspect, the cell is mammalian.

[0047] In an embodiment of the first aspect, the cell is human.

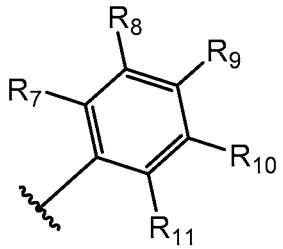
[0048] In an embodiment of the first aspect, the cell is *in vitro*.

[0049] In an embodiment of the first aspect, the cell is *in vivo*.

[0050] In a second aspect, a method of treating acute myeloid leukemia or diffuse large B cell lymphoma is provided, comprising administering to a patient in need thereof an anti-proliferative amount of a combination of venetoclax and a compound having a structure of Formula (I):



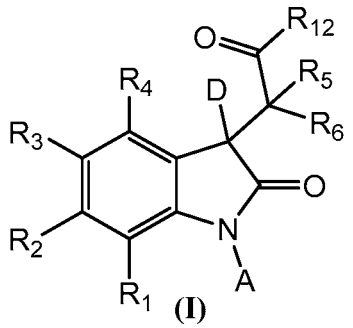
(I)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and $-CF_3$; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and $-O(C_{1-6}$ alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6} alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of C_{3-8} cycloalkyl and  ; wherein R_7, R_8, R_9, R_{10} and R_{11} are

independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(C_{1-6} alkyl), -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl.

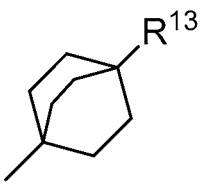
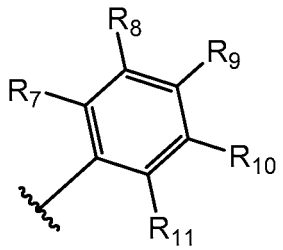
[0051] In an embodiment of the second aspect, R_9 is selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl.

[0052] In a third aspect, use is provided of a combination of venetoclax and a compound having a structure of Formula (I):



(I)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, for the treatment of acute myeloid leukemia or diffuse large B cell lymphoma, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and -CF_3; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and -O(C_{1-6} alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6} alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8}

heterocycloalkyl, , and ; wherein R_7, R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(C_{1-6} alkyl), -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

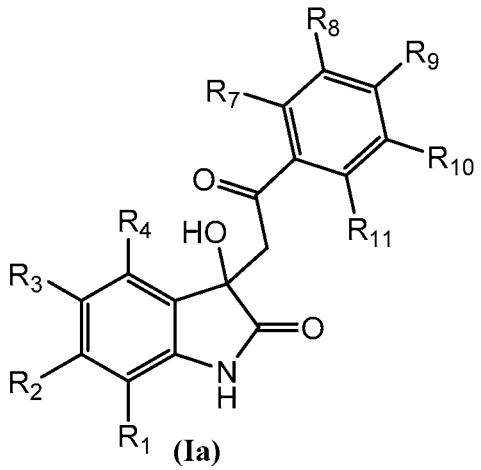
[0053] In an embodiment of the third aspect, R_9 is selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl.

[0054] In an embodiment of the first aspect, R_{12} is unsubstituted, or substituted by a halogen, e.g., Cl or F.

[0055] In an embodiment of the first aspect, the second aspect, or the third aspect, R_9 is selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, and morpholinolyl.

[0056] In an embodiment of the first aspect, the second aspect, or the third aspect, R_9 is selected from the group consisting of isopropyl and cyclopropyl.

[0057] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure of Formula (Ia):

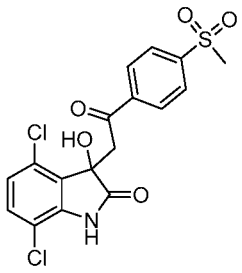


(Ia)

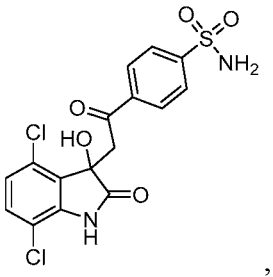
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H and Cl; wherein R_7, R_8, R_{10} and R_{11} are independently selected from the group consisting of H and halogen; and wherein R_9 is independently selected from the group consisting C_{3-8} cycloalkyl and C_{3-8} heterocycloalkyl.

[0058] In an embodiment of the first aspect, the second aspect, or the third aspect, R_1 and R_4 are Cl and R_2 and R_3 are H.

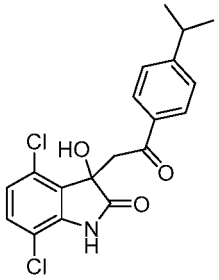
[0059] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure selected from the group consisting of:



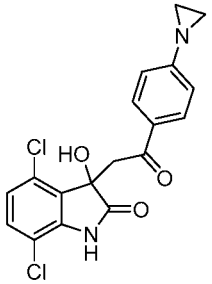
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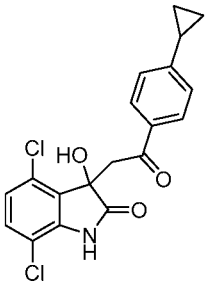
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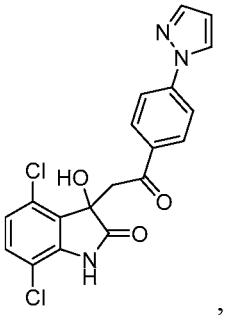
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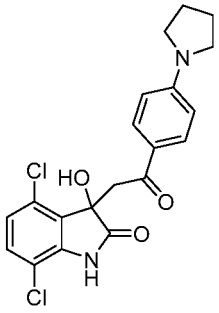
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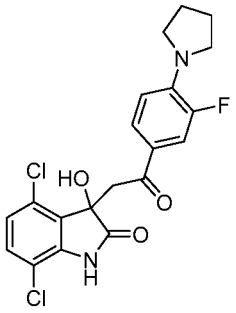
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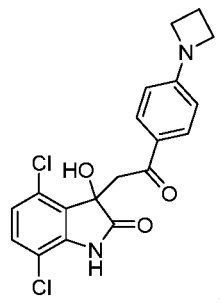
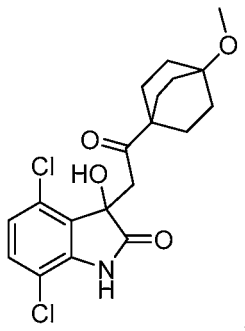
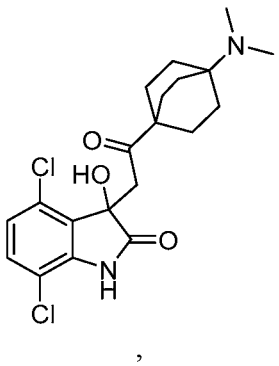
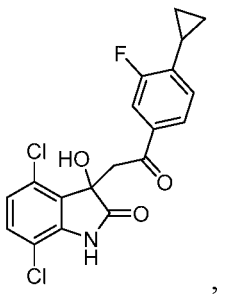
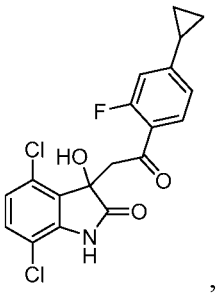
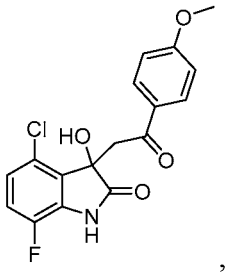
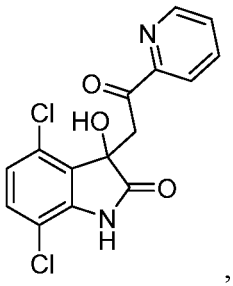
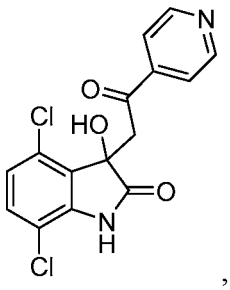
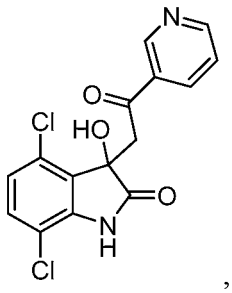
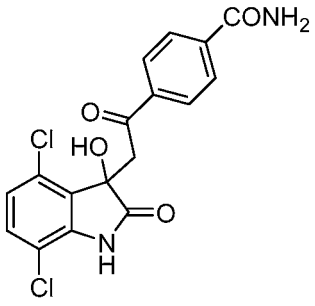
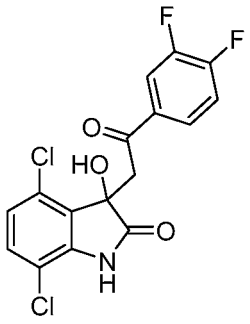
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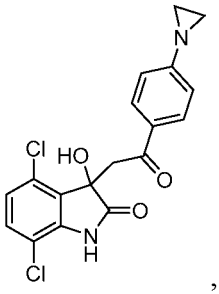
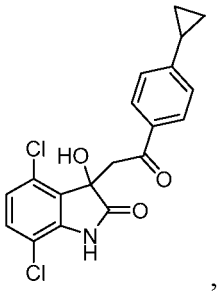
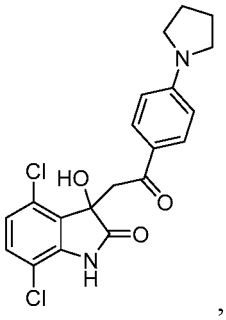


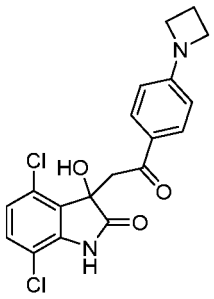
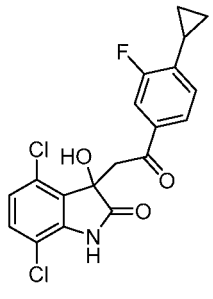
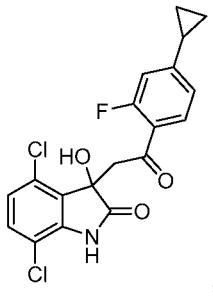
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or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

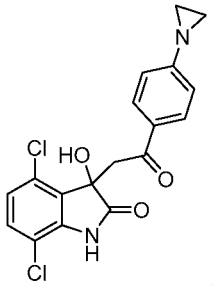
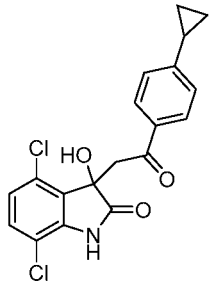
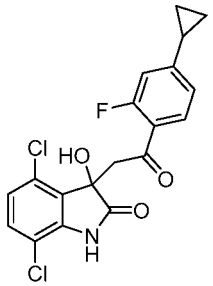
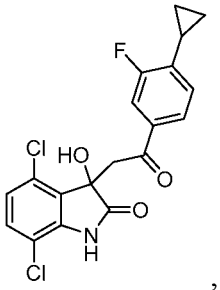
[0060] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound is selected from the group consisting of:


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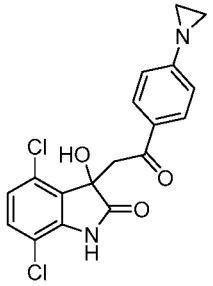
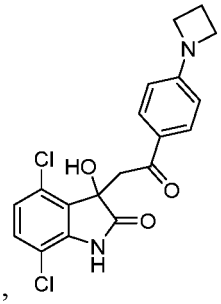
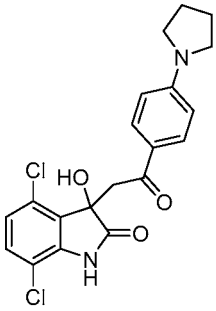
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0061] The method of any one of Claims 1-6, wherein the compound has a structure selected from the group consisting of:

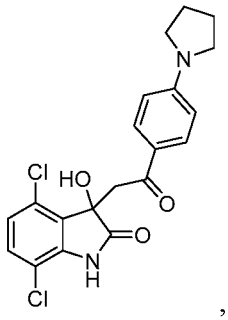
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0062] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure selected from the group consisting of:

or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

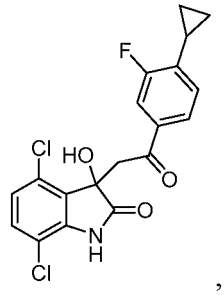
[0063] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure:



,

or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

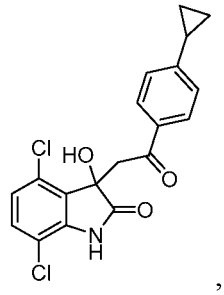
[0064] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure:



,

or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

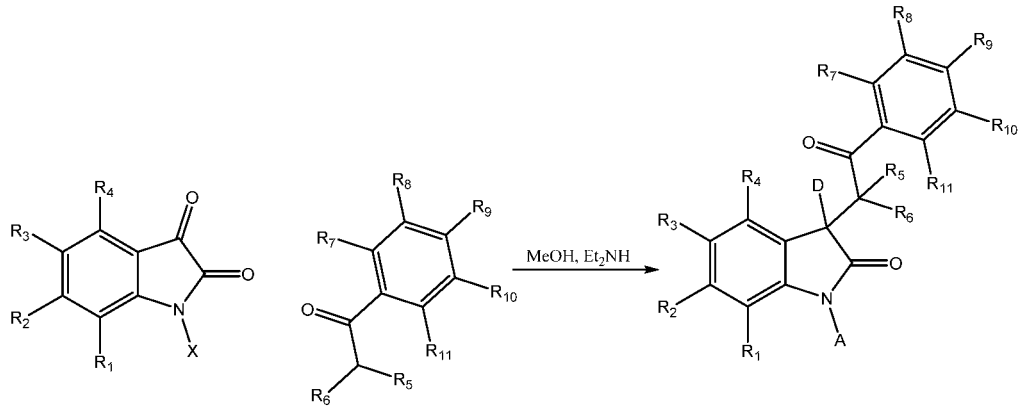
[0065] In an embodiment of the first aspect, the second aspect, or the third aspect, the compound has a structure:



,

or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

Synthetic Methods



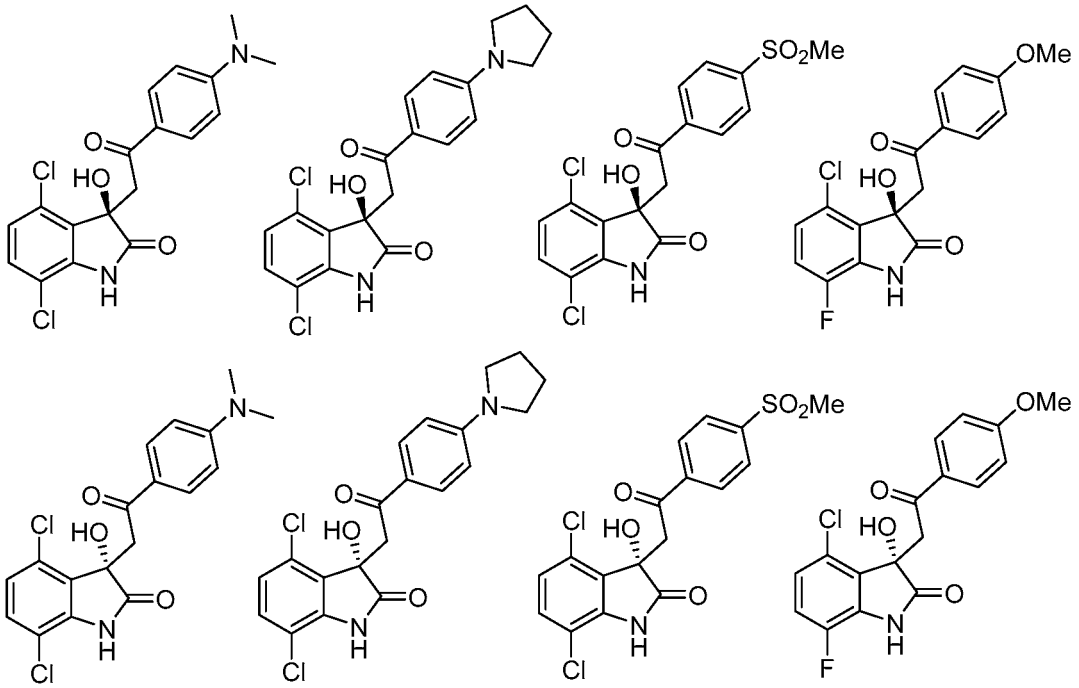
(II) (III) (I)

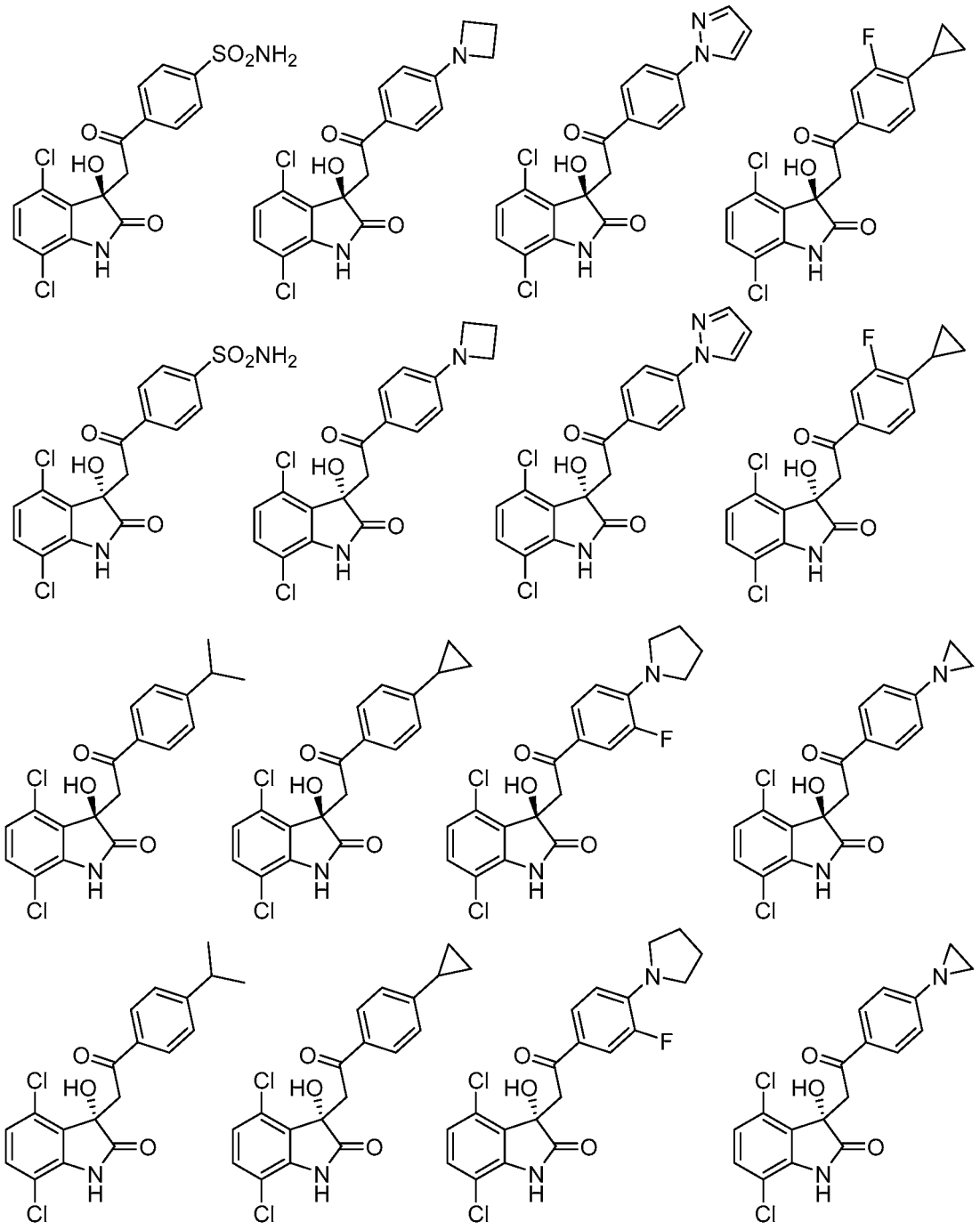
[0066] Compounds of Formula (I) described herein may be prepared in various ways. General synthetic routes to compounds of Formula (I) are shown and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

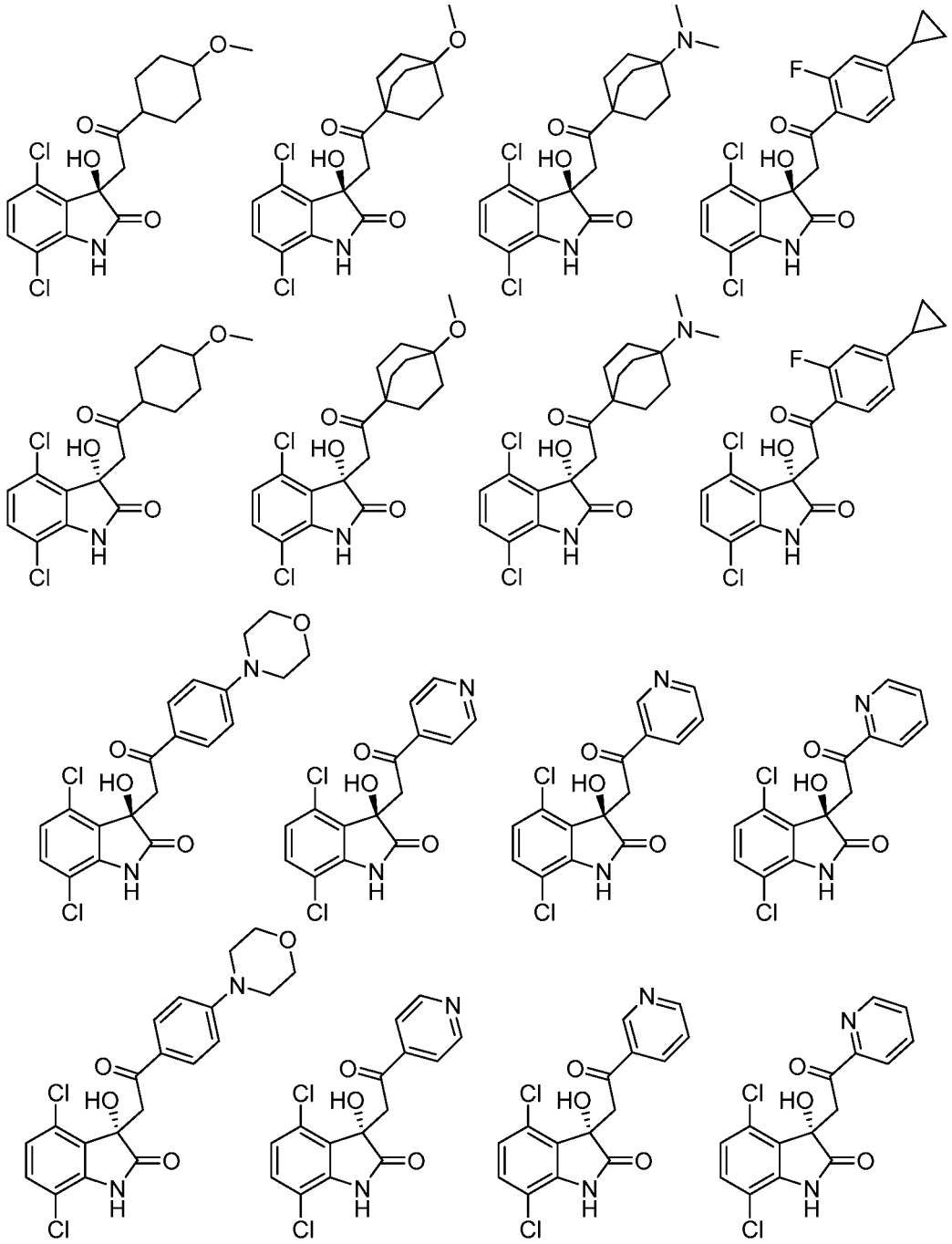
[0067] Depending upon the substituents present, the small molecule inhibitors can be in a form of a pharmaceutically acceptable salt. The terms "pharmaceutically acceptable salt" as used herein are broad terms, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to salts prepared from pharmaceutically acceptable, non-toxic acids or bases. Suitable pharmaceutically acceptable salts include metallic salts, *e.g.*, salts of aluminum, zinc, alkali metal salts such as lithium, sodium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts; organic salts, *e.g.*, salts of lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), procaine, and tris; salts of free acids and bases; inorganic salts, *e.g.*, sulfate, hydrochloride, and hydrobromide; and other salts which are currently in widespread pharmaceutical use and are listed in sources well known to those of skill in the art, such as, for example, The Merck Index. Any suitable constituent can be

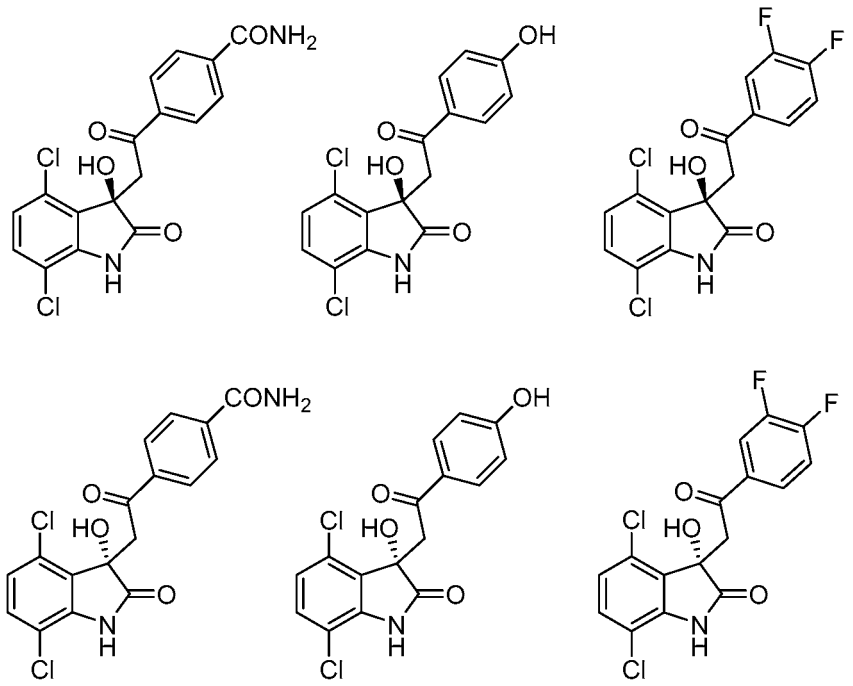
selected to make a salt of the therapeutic agents discussed herein, provided that it is non-toxic and does not substantially interfere with the desired activity.

[0068] The compounds of preferred embodiments can include isomers, racemates, optical isomers, enantiomers, diastereomers, tautomers, and cis/trans conformers. All such isomeric forms are included within preferred embodiments, including mixtures thereof. As discussed above, the compounds of preferred embodiments may have chiral centers, for example, they may contain asymmetric carbon atoms and may thus exist in the form of enantiomers or diastereoisomers and mixtures thereof, e.g., racemates. Asymmetric carbon atom(s) can be present in the (R)- or (S)-configuration, or can be present as mixtures of the (R)- and (S)- forms. The following are isomeric forms of the compounds of Formula (I):









[0069] The compounds can be in amorphous form, or in crystalline forms. The crystalline forms of the compounds of preferred embodiments can exist as polymorphs, which are included in preferred embodiments. In addition, some of the compounds of preferred embodiments may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of the preferred embodiments.

Certain pharmaceutical compositions

[0070] It is generally preferred to administer the inhibitors of preferred embodiments in an intravenous or subcutaneous unit dosage form; however, other routes of administration are also contemplated. Contemplated routes of administration include but are not limited to oral, parenteral, intravenous, and subcutaneous. The inhibitors of preferred embodiments can be formulated into liquid preparations for, *e.g.*, oral administration. Suitable forms include suspensions, syrups, elixirs, and the like. Particularly preferred unit dosage forms for oral administration include tablets and capsules. Unit dosage forms configured for administration once a day are particularly preferred; however, in certain embodiments it can be desirable to configure the unit dosage form for administration twice a day, or more.

[0071] The pharmaceutical compositions of preferred embodiments are preferably isotonic with the blood or other body fluid of the recipient. The isotonicity of the

compositions can be attained using sodium tartrate, propylene glycol or other inorganic or organic solutes. Sodium chloride is particularly preferred. Buffering agents can be employed, such as acetic acid and salts, citric acid and salts, boric acid and salts, and phosphoric acid and salts. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like.

[0072] Viscosity of the pharmaceutical compositions can be maintained at the selected level using a pharmaceutically acceptable thickening agent. Methylcellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the thickening agent selected. An amount is preferably used that will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

[0073] A pharmaceutically acceptable preservative can be employed to increase the shelf life of the pharmaceutical compositions. Benzyl alcohol can be suitable, although a variety of preservatives including, for example, parabens, thimerosal, chlorobutanol, or benzalkonium chloride can also be employed. A suitable concentration of the preservative is typically from about 0.02% to about 2% based on the total weight of the composition, although larger or smaller amounts can be desirable depending upon the agent selected. Reducing agents, as described above, can be advantageously used to maintain good shelf life of the formulation.

[0074] The inhibitors of preferred embodiments can be in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, or the like, and can contain auxiliary substances such as wetting or emulsifying agents, pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, colors, and the like, depending upon the route of administration and the preparation desired. See, *e.g.*, "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (June 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively). Such preparations

can include complexing agents, metal ions, polymeric compounds such as polyacetic acid, polyglycolic acid, hydrogels, dextran, and the like, liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts or spheroblasts. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. The presence of such additional components can influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance, and are thus chosen according to the intended application, such that the characteristics of the carrier are tailored to the selected route of administration.

[0075] For oral administration, the pharmaceutical compositions can be provided as a tablet, aqueous or oil suspension, dispersible powder or granule, emulsion, hard or soft capsule, syrup or elixir. Compositions intended for oral use can be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and can include one or more of the following agents: sweeteners, flavoring agents, coloring agents and preservatives. Aqueous suspensions can contain the active ingredient in admixture with excipients suitable for the manufacture of aqueous suspensions.

[0076] Formulations for oral use can also be provided as hard gelatin capsules, wherein the active ingredient(s) are mixed with an inert solid diluent, such as calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules. In soft capsules, the inhibitors can be dissolved or suspended in suitable liquids, such as water or an oil medium, such as peanut oil, olive oil, fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers and microspheres formulated for oral administration can also be used. Capsules can include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredient in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers.

[0077] Tablets can be uncoated or coated by known methods to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period of time. For example, a time delay material such as glyceryl monostearate can be used. When administered in solid form, such as tablet form, the solid form typically comprises from about 0.001 wt. % or less to about 50 wt. % or more of active ingredient(s), preferably from about 0.005, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09,

0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1 wt. % to about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 45 wt. %.

[0078] Tablets can contain the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients including inert materials. For example, a tablet can be prepared by compression or molding, optionally, with one or more additional ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding, in a suitable machine, a mixture of the powdered inhibitor moistened with an inert liquid diluent.

[0079] Preferably, each tablet or capsule contains from about 1 mg or less to about 1,000 mg or more of an inhibitor of the preferred embodiments, more preferably from about 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 mg to about 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, or 900 mg. Most preferably, tablets or capsules are provided in a range of dosages to permit divided dosages to be administered. A dosage appropriate to the patient and the number of doses to be administered daily can thus be conveniently selected. In certain embodiments it can be preferred to incorporate two or more of the therapeutic agents to be administered into a single tablet or other dosage form (*e.g.*, in a combination therapy); however, in other embodiments it can be preferred to provide the therapeutic agents in separate dosage forms.

[0080] Suitable inert materials include diluents, such as carbohydrates, mannitol, lactose, anhydrous lactose, cellulose, sucrose, modified dextrans, starch, and the like, or inorganic salts such as calcium triphosphate, calcium phosphate, sodium phosphate, calcium carbonate, sodium carbonate, magnesium carbonate, and sodium chloride. Disintegrants or granulating agents can be included in the formulation, for example, starches such as corn starch, alginic acid, sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite, insoluble cationic exchange resins, powdered gums such as agar, karaya or tragacanth, or alginic acid or salts thereof.

[0081] Binders can be used to form a hard tablet. Binders include materials from natural products such as acacia, tragacanth, starch and gelatin, methyl cellulose, ethyl

cellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, and the like.

[0082] Lubricants, such as stearic acid or magnesium or calcium salts thereof, polytetrafluoroethylene, liquid paraffin, vegetable oils and waxes, sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol, starch, talc, pyrogenic silica, hydrated silicoaluminate, and the like, can be included in tablet formulations.

[0083] Surfactants can also be employed, for example, anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, cationic such as benzalkonium chloride or benzethonium chloride, or nonionic detergents such as polyoxyethylene hydrogenated castor oil, glycerol monostearate, polysorbates, sucrose fatty acid ester, methyl cellulose, or carboxymethyl cellulose.

[0084] Controlled release formulations can be employed wherein the amifostine or analog(s) thereof is incorporated into an inert matrix that permits release by either diffusion or leaching mechanisms. Slowly degenerating matrices can also be incorporated into the formulation. Other delivery systems can include timed release, delayed release, or sustained release delivery systems.

[0085] Coatings can be used, for example, nonenteric materials such as methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols, or enteric materials such as phthalic acid esters. Dyestuffs or pigments can be added for identification or to characterize different combinations of inhibitor doses

[0086] When administered orally in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils can be added to the active ingredient(s). Physiological saline solution, dextrose, or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol are also suitable liquid carriers. The pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, such as olive or arachis oil, a mineral oil such as liquid paraffin, or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or

partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsions can also contain sweetening and flavoring agents.

[0087] Pulmonary delivery can also be employed. The compound is delivered to the lungs while inhaling and traverses across the lung epithelial lining to the blood stream. A wide range of mechanical devices designed for pulmonary delivery of therapeutic products can be employed, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. These devices employ formulations suitable for the dispensing of compound. Typically, each formulation is specific to the type of device employed and can involve the use of an appropriate propellant material, in addition to diluents, adjuvants, and/or carriers useful in therapy.

[0088] The compound and/or other optional active ingredients are advantageously prepared for pulmonary delivery in particulate form with an average particle size of from 0.1 μm or less to 10 μm or more, more preferably from about 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9 μm to about 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, or 9.5 μm. Pharmaceutically acceptable carriers for pulmonary delivery of inhibitor include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations can include DPPC, DOPE, DSPC, and DOPC. Natural or synthetic surfactants can be used, including polyethylene glycol and dextrans, such as cyclodextran. Bile salts and other related enhancers, as well as cellulose and cellulose derivatives, and amino acids can also be used. Liposomes, microcapsules, microspheres, inclusion complexes, and other types of carriers can also be employed.

[0089] Pharmaceutical formulations suitable for use with a nebulizer, either jet or ultrasonic, typically comprise the inhibitor dissolved or suspended in water at a concentration of about 0.01 or less to 100 mg or more of inhibitor per mL of solution, preferably from about 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg to about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90 mg per mL of solution. The formulation can also include a buffer and a simple sugar (*e.g.*, for protein stabilization and regulation of osmotic pressure). The nebulizer formulation can also contain a surfactant, to reduce or prevent surface induced aggregation of the inhibitor caused by atomization of the solution in forming the aerosol.

[0090] Formulations for use with a metered-dose inhaler device generally comprise a finely divided powder containing the active ingredients suspended in a propellant with the aid of a surfactant. The propellant can include conventional propellants, such as chlorofluorocarbons, hydrochlorofluorocarbons, hydrofluorocarbons, and hydrocarbons. Preferred propellants include trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, 1,1,1,2-tetrafluoroethane, and combinations thereof. Suitable surfactants include sorbitan trioleate, soya lecithin, and oleic acid.

[0091] Formulations for dispensing from a powder inhaler device typically comprise a finely divided dry powder containing inhibitor, optionally including a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in an amount that facilitates dispersal of the powder from the device, typically from about 1 wt. % or less to 99 wt. % or more of the formulation, preferably from about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 wt. % to about 55, 60, 65, 70, 75, 80, 85, or 90 wt. % of the formulation.

[0092] When a compound of the preferred embodiments is administered by intravenous, parenteral, or other injection, it is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution or oleaginous suspension. Suspensions can be formulated according to methods well known in the art using suitable dispersing or wetting agents and suspending agents. The preparation of acceptable aqueous solutions with suitable pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for injection preferably contains an isotonic vehicle such as 1,3-butanediol, water, isotonic sodium chloride solution, Ringer's solution, dextrose solution, dextrose and sodium chloride solution, lactated Ringer's solution, or other vehicles as are known in the art. In addition, sterile fixed oils can be employed conventionally as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the formation of injectable preparations. The pharmaceutical compositions can also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

[0093] The duration of the injection can be adjusted depending upon various factors, and can comprise a single injection administered over the course of a few seconds or

less, to 0.5, 0.1, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours or more of continuous intravenous administration.

[0094] The compounds of the preferred embodiments can additionally employ adjunct components conventionally found in pharmaceutical compositions in their art-established fashion and at their art-established levels. Thus, for example, the compositions can contain additional compatible pharmaceutically active materials for combination therapy (such as supplementary antimicrobials, antipruritics, astringents, local anesthetics, anti-inflammatory agents, reducing agents, chemotherapeutics and the like), or can contain materials useful in physically formulating various dosage forms of the preferred embodiments, such as excipients, dyes, thickening agents, stabilizers, preservatives or antioxidants. Anti-cancer agents that can be used in combination with the compounds of preferred embodiments include, but are not limited to, vinca alkaloids such as vinblastine and vincristine; anthracyclines such as doxorubicin, daunorubicin, epirubicin; anthracenes such as bisantrene and mitoxantrone; epipodophyllo-toxins such as etoposide and teniposide; and other anticancer drugs such as actinomyocin D, mithomycin C, mitramycin, methotrexate, docetaxel, etoposide (VP-16), paclitaxel, docetaxel, and adriamycin); and immunosuppressants (e.g., cyclosporine A, tacrolimus). In some embodiments, the compounds, compositions and methods provided herein may be in combination with histone deacetylase inhibitors (HDAC), aurora kinase inhibitors, demethylating agents (such as 5-AZA cytidine), immunotherapy with natural killer cells, IGF-IR antibodies, Ewing antigen antibodies, immunosuppressive drugs, and hydroxyurea. Examples of histone deacetylase inhibitors include vorinostat, romidepsin, panobinostat, valproic acid, belinostat, mocetinostat, givinostat, and trichostatin A. Examples of aurora kinase inhibitors include ZM447439, hesperadin, and VX-680. Examples of demethylating agents include 5-azacytidine, 5-azadeoxycytidine, and procaine. Examples of immunosuppressive drugs include 6-mercaptopurine, and azathioprine.

Certain Kits

[0095] The compounds of the preferred embodiments can be provided to an administering physician or other health care professional in the form of a kit. The kit is a package which houses a container which contains the compounds in a suitable pharmaceutical composition, and instructions for administering the pharmaceutical

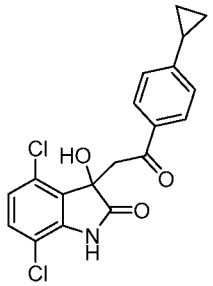
composition to a subject. The kit can optionally also contain one or more additional therapeutic agents, *e.g.*, chemotherapeutics currently employed for treating the sarcomas described herein. For example, a kit containing one or more compositions comprising compounds of the preferred embodiments in combination with one or more additional chemotherapeutic agents can be provided, or separate pharmaceutical compositions containing an inhibitor of the preferred embodiments and additional therapeutic agents can be provided. The kit can also contain separate doses of a compound of the preferred embodiments for serial or sequential administration. The kit can optionally contain one or more diagnostic tools and instructions for use. The kit can contain suitable delivery devices, *e.g.*, syringes, and the like, along with instructions for administering the inhibitor(s) and any other therapeutic agent. The kit can optionally contain instructions for storage, reconstitution (if applicable), and administration of any or all therapeutic agents included. The kits can include a plurality of containers reflecting the number of administrations to be given to a subject.

Examples

[0096] The ETS family of transcription factors is critical for development, differentiation, proliferation, and plays an important role in apoptosis and tissue remodeling. Transcriptional consequences of ETS protein deregulation by overexpression, gene fusion, and modulation by RAS/MAPK and PI3K signaling are linked to alterations in normal cell functions, and lead to increased proliferation, sustained angiogenesis, invasion, and metastasis. Overexpressed ETS proteins and ETS family fusion proteins have been reported in acute myeloid leukemia (AML) and diffuse large B cell lymphoma (DLBCL). In DLBCL, the 11q24.3 region has been identified as a recurrent lesion and a contributor to the pathogenesis of disease, leading to the deregulation of ETS family members, ETS1 and FLI1. Additionally, in AML, the overexpression and translocations of ERG, an ETS family member, has been shown to be associated with poor prognosis in complex or normal karyotypes.

[0097] TK216 is a first in class, small molecule that directly binds EWS-FLI1 inhibiting the biological activity of ETS-family transcription factor oncoproteins and is currently under clinical investigation in patients with Ewing sarcoma. The EWS1-FLI1 is a fusion protein that has been shown to be the driver of Ewing Sarcoma (ES). In preclinical

potency models, TK216 blocked the binding between EWS-FLI1 and RNA helicase A, showed a significant transcriptional decrease in COS7 cells transfected with a EWS-FLI1 responsive promoter (EC_{50} < 100 nM), and inhibited the proliferation of A4573 cells (EWS-FLI1 expressing Ewing sarcoma cell line) at nanomolar concentrations (EC_{50} < 200 nM).



TK216
4,7-Dichloro-3-(2-(4-cyclopropylphenyl)-2-oxoethyl)-3-hydroxyindolin-2-one

[0098] TK216 also had anti-proliferative effects, causes cell cycle arrest, and induces apoptosis in a panel of AML and DLBCL cell lines with deregulated ETS family members. Upregulation of FLI1 and/or ERG ETS family members was observed in the myeloid cell lines evaluated (HL-60, Kasumi-1, ML-2, MOLM-13, MOLM-16, and THP-1). Treatment with TK216 showed a decrease in cellular viability and induced dose-dependent apoptosis of cells at 48 hours. Similarly, in a panel of DLBCL cell lines (TMD-8, HBL-1, U2932, DOHH2, WSU-DLCL2, OCI-Ly18, and OCI-Ly19), TK216 treatment resulted in a decrease in cellular proliferation and an increase in apoptosis. *In vivo* efficacy studies in xenograft models of DLBCL indicated anti-tumor activity consistent with *in vitro* findings, confirming the utility and efficacy of TK216 in the treatment of AML and DLBCL by targeting the aberrant expression and translocations in the ETS-family of transcription factors, which contribute to the pathogenesis of the disease.

[0099] The mechanism of action of TK216 is illustrated in FIG. 1. As illustrated in FIG. 1, TK216 is active in oncogenesis (anchorage-independent growth; tumors in mice), altered gene expression (↑ E2G2 (chromatin regulator; ↑ VEGF-A (angiogenesis)), and alternative splicing (cyclin D1b (activates cell cycle); ARID1A-ex18L (chromatin regulator). TK216 inhibited aptosis (programmed cell death; inhibits tumor growth), altered gene expression (↓ E2G2; ↓ VEGF-A), and variant isoforms (cyclin D1a (slows cell cycle); ARID1A-ex185 (non-oncogenic)).

[0100] TK216 treatment inhibited EWS-FLI1 protein interactions, leading to a decrease in transcription and proliferation. FLI1 was immunoprecipitated following treatment with TK216 or DMSO control in A4573 (see FIG. 2).

[0101] TK216 reduced transcriptional activity in COS7 cells co-transfected with EWS-FLI1 and NROB1 reporter-luciferase plasmids which contain EWS-FLI1 DNA-binding sites, as shown in FIG. 3.

[0102] Treatment with TK216 resulted in a dose-dependent inhibition of proliferation in Ewing Sarcoma A4573 cell line, as shown in FIG. 4.

[0103] TK216 displayed anti-proliferative activity in AML cell lines. The IC_{50} of TK216 for each cell line was determined in a 72 hr CellTiter-Glo assay, as shown in FIG. 5 and TABLE 1.

TABLE 1.

TK216 IC_{50} in AML Cell Lines

Cell line	**TK216-2**	**Cisplatin**
	$IC_{50}(\mu M)$	$IC_{50}(\mu M)$
HL-60	0.363	1.931
Kasumi-1	0.393	4.560
ML-2	0.291	1.395
MOLM-13	0.228	0.798
MOLM-16	0.129	2.190
THP-1	0.152	1.359

[0104] TK216 displayed anti-proliferative activity in DLBCL cell lines. The IC_{50} of TK216 for each cell line was determined in a 72 hr CellTiter-Glo assay, as shown in FIG. 6 and TABLE 2.

TABLE 2.

TK216 IC_{50} in DLBCL Cell Lines

Cell line	TK216
	IC_{50}(μM)
TMD-8	0.152
HBL-1	0.304
DOHH2	0.160
U2932	0.127
WSU-DLCL2	0.897
OCI-Ly18	0.095
OCI-Ly19	0.106

[0105] TK216 induced apoptosis in DLBCL cell lines. Cells were treated with various concentrations of TK216 for 18h and apoptosis was assessed by detection of cleaved-Caspase 3. The amount of cleaved-Caspase 3 was normalized to b-actin and presented as fold over control, as shown in FIG. 7 and FIG. 8.

[0106] TK216 displayed synergy when combined with BCL-2 (ABT199) and BTK (ACP196) inhibitors. The median-effect analysis was used to determine synergism, antagonism, or additivity of TK216 when combined with ABT199 (BCL-2i) and ACP196 (BTKi). CalcuSyn software was used to determine the Combination Index (CI) using the Chou/Talalay equation, as shown in FIG. 9 and FIG. 10.

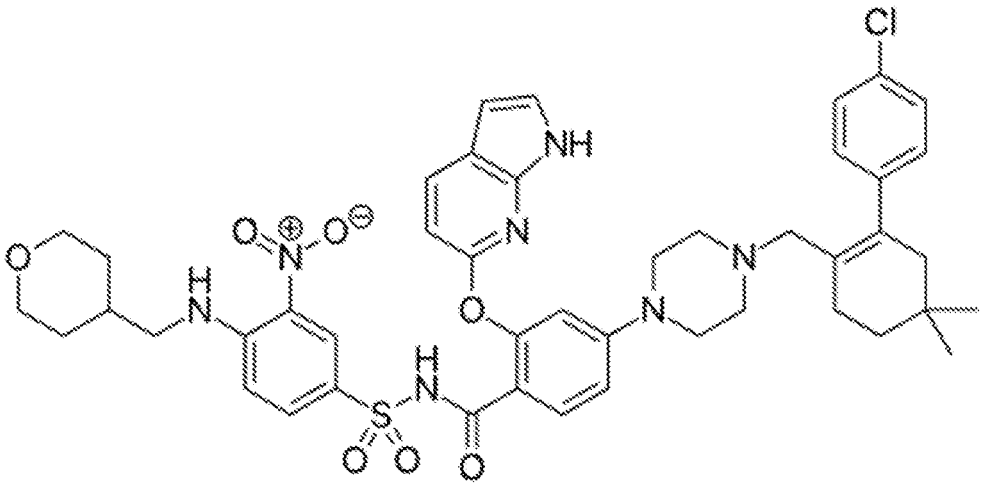
[0107] TK216 displayed anti-tumor activity in a DLBCL xenograft model. The anti-tumor activity of TK216 was assessed in nude mice harboring TMD-8 tumors, a DLBCL-ABC xenograft model. TK216 was administered orally as a solution at 100 mg/kg BID for 13 days. Results are shown in FIG. 11.

[0108] Treatment with TK216 resulted in tumor growth inhibition. TK216 resulted in 77% tumor growth inhibition of the TMD-8 xenograft model when compared to vehicle control following 13 days of treatment, as shown in FIG. 12.

[0109] As the above data demonstrated, TK216 is a first in class, small molecule that directly binds EWS-FLI1 inhibiting the biological activity of ETS-family transcription

factor. In AML and DLBCL cell lines with deregulated ETS-family members, treatment with TK216 resulted in potent inhibition of proliferation and the induction of apoptosis. Combination of TK216 with BCL-2 and BTK inhibitors in DLBCL cell lines lead to synergistic activity and allowed for a more effective inhibition of cell proliferation. Daily, oral administration of TK216 potently inhibited tumor growth in xenograft models of DLBCL with deregulated expression of ETS-family members, and is well-tolerated. The inhibition of the EWS-FLI1 oncogene offers a promising approach for the treatment of Ewing Sarcoma, e.g., relapsed/refractory Ewing Sarcoma.

[0110] Venetoclax (4-(4-{[2-(4-Chlorophenyl)-4,4-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino] phenyl}sulfonyl)-2-1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) is used for the treatment of chronic lymphocytic leukemia, e.g., in patients who have relapsed or have been refractory to previous treatment and who have the 17p deletion genetic mutation.



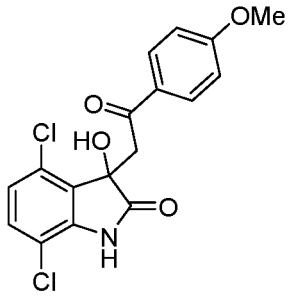
Venetoclax

[0111] TK216 was tested in combination with venetoclax and has been demonstrated to exhibit synergism in dose-effect in DLBCL cell lines. In each of FIGS. 13-15, the top curve (×) was for the combination therapy, the middle curve (⊙) was for TK216, and the bottom curve (+) was for venetoclax. FIG. 13 is a dose-effect curve for TK216 in combination with venetoclax in the TMD8 cell line. FIG. 14 is a dose-effect curve for TK216 in combination with venetoclax in the U2932 cell line. FIG. 15 is a dose-effect curve for TK216 in combination with venetoclax in the HLB1 cell line.

[0112] Dose-effect testing was conducted in DLBLC cell lines (TMD8, HBL1, U2932) indicating a synergistic effect across doses, as shown in FIG. 16.

[0113] ETS transcription factors, such as FLI1 and SPIB, are recurrently deregulated in human lymphomas. The small molecule YK-4-279 (also referred to as YK-279 or YK279, is 4,7-dichloro-3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one) inhibits binding of EWS1-FLI1 fusion protein to RHA with growth arrest and apoptosis in Ewing sarcoma cells, and exhibits *in vitro* anti-lymphoma activity.

YK-4-279



4,7-dichloro-3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one

[0114] TK-216 is a YK-4-279 clinical derivative that is in phase 1 for patients with relapsed or refractory Ewing sarcoma. Preclinical testing has been conducted for TK-216 in lymphoma models.

[0115] 56 lymphoma cell lines [27 diffuse large B cell lymphoma (DLBCL); 10 mantle cell lymphoma; 6 marginal zone lymphoma; 5 anaplastic large T-cell lymphoma; 8 others] were exposed to TK-216 increasing doses for 72h using a Tecan D300e Digital Dispenser and 384 well plates. Cell proliferation was measured with MTT. In vivo study was done in NOD-SCID mice; treatments were started with approximately sc 60mm3 tumor volumes. The study demonstrated TK-216 was very active, with a median IC50 of 449 nM (95% C.I.: 367-506), as shown in FIG. 1. Sensitivity was not affected by the lymphoma cell of origin (B vs T; activated B cell type DLBCL versus germinal center type DLBCL) or MYC and TP53 status. There was a non-statistically significant trend for lower sensitivity in cell lines bearing BCL2 chromosomal translocation (P=0.07, DLBCL only; P=0.06, all cell lines). The anti-tumor activity was mainly cytotoxic, as confirmed performing cell cycle analysis and Annexin V staining in 6 DLBCL cell lines (TMD8, U2932, HBL1, OCI-LY-18,

WSU-DLCL2, DOHH2; TK-216 or DMSO for 24, 48, 72h), in which a time-dependent apoptosis was preceded by a G2/M arrest, as shown in FIG. 2.

[0116] Antitumor activity was then tested using DLBCL TMD8 cells xenografts, as shown in FIG. 3. Compared with a control group (n=10), mice treated with TK-216 (100 mg/Kg, BID; n=9) clearly presented a reduction in tumor growth, already evident at day 3 and becoming much stronger with time (D3, D5, D8, D11: $P<0.01$; D13, P not available since control group had to be stopped due to tumor volume) and a four-times reduction in tumor volume at D11 ($P<0.01$). TK-216 was also tested in combination with other targeted agents in DLBCL cell lines, as shown in FIG. 4. A benefit was observed with the combination of TK-216 with the immunomodulator lenalidomide (synergism in 2/2 activated B cell type DLBCL), with the bromodomain and extra-terminal protein (BET) inhibitor OTX015 (MK-8628) (synergism in 2/4 cells and additive effect in 1/4 cells), with the anti-CD20 monoclonal antibody rituximab (synergism in 2/3 cells) and with the BCL2 inhibitor venetoclax (synergism in 3/4 cells). The latter synergism could be linked to the previously mentioned negative trend between TK-216 IC50 values and the presence of BCL2 translocation.

[0117] The test results demonstrated that TK-216 presented strong preclinical anti-lymphoma activity, both as a single agent and in combination with other therapeutic agents.

[0118] The two main DLBCL subtypes are the germinal center B cell (GCB) and the ABC types, characterized by individual biologic and clinical features. Since up to 40% DLBCL patients are still not cured with the standard treatments, there is the need for novel therapies. YK-4-279 is a small molecule that inhibits binding of the EWS1-FLI1 fusion protein to RHA, resulting in growth arrest and apoptosis in Ewing sarcoma cells. Its derivative, TK-216, is the first in class inhibitor of the ETS-family of transcription factors in phase I (NCT02657005 for relapsed or refractory Ewing sarcoma). Both compounds have shown promising preclinical anti-lymphoma activity. Data has been obtained on their mechanism of action in DLBCL.

[0119] Cell lines were exposed to YK-4-279 or TK-216, alone or in combination with other compounds, for 72h using a Tecan D300e Digital Dispenser and 96 well plates. Cell proliferation was measured with MTT. Synergy was determined with the Chou-Talalay

combination index. Gene expression profiling (GEP) was performed with the Illumina HumanHT 12 Expression BeadChips. In vivo studies were done in NOD-SCID mice and treatments started with 60mm3 tumor volumes sc.

[0120] TK-216 showed strong in vitro and in vivo anti-lymphoma activity. Anti-tumor activity has been demonstrated for YK-4-279 in the same ABC DLBCL model (TMD8 xenograft) as for TK-216. Compared with a control group (n=10), mice treated with YK-4-279 (100 mg/Kg, BID; n=9) clearly presented a reduction in tumor growth at D8 and D11 ($P<0.01$) and D13 (P not available since the control group had to be stopped due to tumor volume). In accordance with combination data showing a specific synergism of TK-216 when combined with the immunomodulatory drug (IMID) lenalidomide in ABC DLBCL, when YK-4-279 was combined with the BTK-inhibitor ibrutinib, the PI3K-delta inhibitor idelalisib, the BET inhibitor OTX-015 and lenalidomide in four DLBCL cell lines (2 ABC, 2 GCB), the biggest benefit was achieved with the combination of YK-4-279 plus lenalidomide with synergism in both ABC DLBCL. Since lenalidomide is active in mantle cell lymphoma (MCL), the synergism of the combination of TK-216 and lenalidomide was confirmed also in two MCL cell lines.

[0121] With the aim to understand the mechanism of action of YK-4-279 and TK-216, the baseline RNA expression levels of the different ETS factors were correlated with sensitivity to the drugs. SPIB was the gene presenting the most significant negative correlation with both YK-4-279 and TK-216, especially among the ABC DLBCL cell lines ($P<0.05$). SPIB is a known oncogene for ABC DLBCL (Lenz et al, PNAS 2008) and is involved in the response to lenalidomide in ABC DLBCL (Yang et al, Cancer Cell 2012). YK-4-279 inhibits the binding of EWS1-FLI1 to the helicases RHA and DDX5 (Selvanathan et al, PNAS 2012). Thus, it was assessed whether YK-4-279 and TK-216 can have a similar effect on SPIB and whether they induce cellular effects similar to lenalidomide. Protein modelling demonstrated that the 3D structure of FLI1 and SPIB are highly overlapping. Co-IP experiments showed the binding of SPIB to RHA and DDX5 in two ABC DLBCL cell lines. The binding to RHA and, to a lesser extent, to DDX5 was decreased upon exposing the cells to TK216 or YK-4-279 (500 nM, 4-10h). Similarly to lenalidomide (Yang et al, Cancer Cell 2012), TK-216 decreased IRF4 and upregulated IRF7 protein in cells. GEP of two ABC DLBCL cell lines exposed to the active (S)- enantiomer or to the inactive (R)-enantiomer

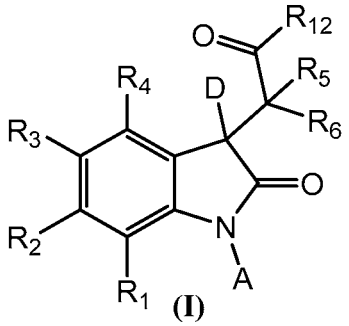
(500 nM, 4-8h) showed that (S)-YK-4-279 caused an important upregulation of multiple snoRNAs - an effect compatible with an interference of the compound on helicases and RNA editing. In ABC DLBCL, the ETS inhibitor YK-4-279 and its clinical derivative TK-216 interfere with SPIB and helicases involved in RNA editing. Moreover, both compounds act similarly to lenalidomide inhibiting IRF4 and upregulating IRF7 and synergize with the IMID in both ABC DLBCL and MCL.

Exemplary Methods and Compositions

[0122] Method 1: A method for inducing aptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma, comprising contacting the cell with an effective amount of a combination of:

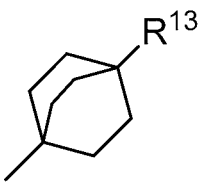
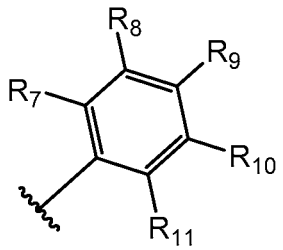
at least one therapeutic agent selected from the group consisting of an immunomodulator, a bromodomain, an extra-terminal protein inhibitor, an anti-CD20 monoclonal antibody, and a BCL2 inhibitor; and

a compound having a structure of Formula (I):



(I)

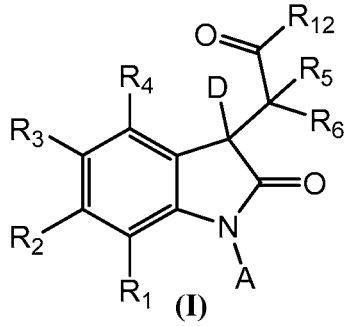
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and $-CF_3$; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and $-O(C_{1-6}$ alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6} alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8}

heterocycloalkyl, , and ; wherein R_7, R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(C_{1-6} alkyl), -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

[0123] Method 2: A method of treating acute myeloid leukemia or diffuse large B cell lymphoma, comprising administering to a patient in need thereof an anti-proliferative amount of a combination of:

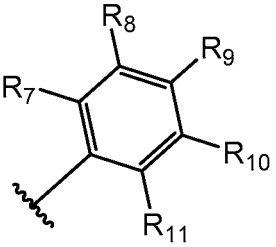
at least one therapeutic agent selected from the group consisting of an immunomodulator, a bromodomain, an extra-terminal protein inhibitor, an anti-CD20 monoclonal antibody, and a BCL2 inhibitor; and

a compound having a structure of Formula (I):



(I)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and -CF_3; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and -O(C_{1-6} alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6} alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted

cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} heterocycloalkyl, , and ; wherein R_7, R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(C_{1-6} alkyl), -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

[0124] Method 3: The method of any one of Methods 1 through 2, wherein R_9 is selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

[0125] Method 4: The method of any one of Methods 1 through 3, wherein the cell is mammalian.

[0126] Method 5: The method of any one of Methods 1 through 4, wherein the cell is human.

[0127] Method 6: The method of any one of Methods 1 through 5, wherein the cell is *in vitro*.

[0128] Method 7: The method of any one of Methods 1 through 6, wherein the cell is *in vivo*.

[0129] Method 8: The method of any one of Methods 1 through 7, wherein the therapeutic agent is an immunomodulator.

[0130] Method 9: The method of any one of Methods 1 through 7, wherein the immunomodulator is lenalidomide.

[0131] Method 10: The method of any one of Methods 1 through 7, wherein the therapeutic agent is a bromodomain and extra-terminal protein inhibitor.

[0132] Method 11: The method of any one of Methods 1 through 7, wherein the bromodomain and extra-terminal protein inhibitor is OTX015.

[0133] Method 12: The method of any one of Methods 1 through 7, wherein the therapeutic agent is an anti-CD20 monoclonal antibody

[0134] Method 13: The method of any one of Methods 1 through 7, wherein the anti-CD20 monoclonal antibody is rituximab.

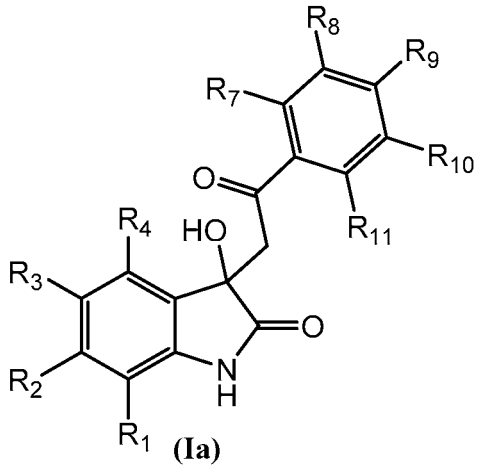
[0135] Method 14: The method of any one of Methods 1 through 7, wherein the therapeutic agent is a BCL2 inhibitor.

[0136] Method 15: The method of any one of Methods 1 through 7, wherein the BCL2 inhibitor is venetoclax.

[0137] Method 16: The method of any one of Methods 1 through 15, wherein R_9 is selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, and morpholinolyl.

[0138] Method 17: The method of any one of Methods 1 through 15, wherein R_9 is selected from the group consisting of isopropyl and cyclopropyl.

[0139] Method 18: The method of any one of Methods 1 through 15, wherein the compound has a structure of Formula (Ia):

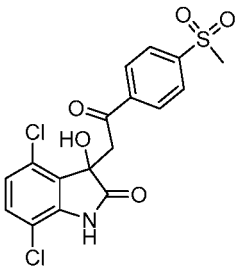
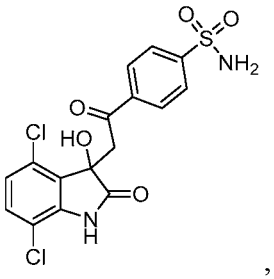
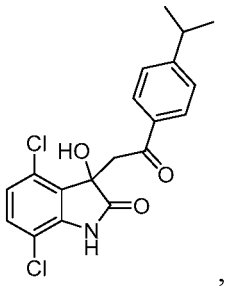
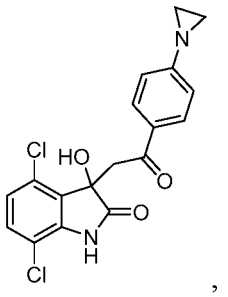
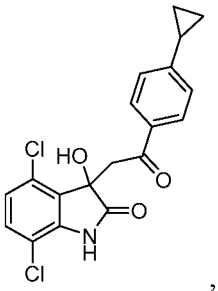
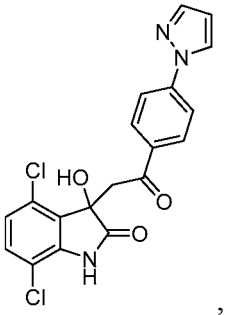
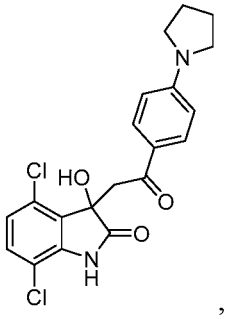
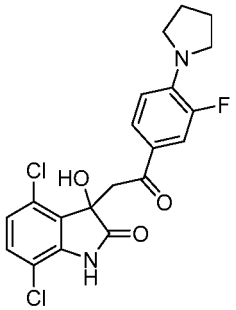
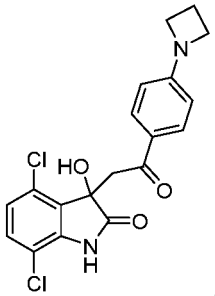
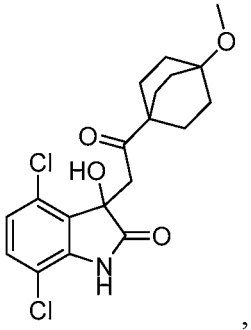
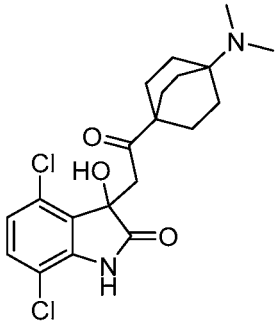
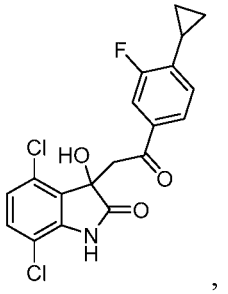


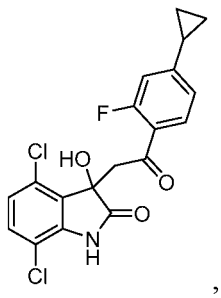
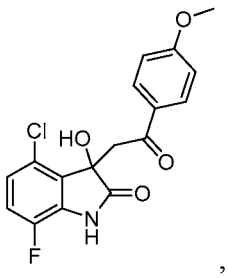
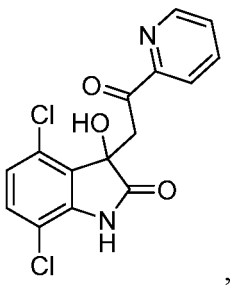
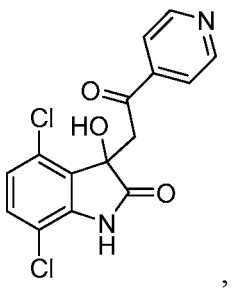
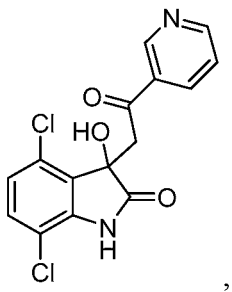
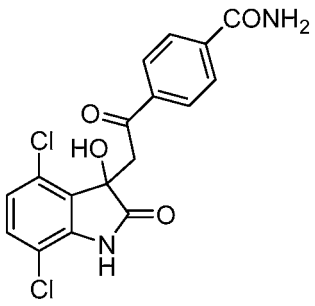
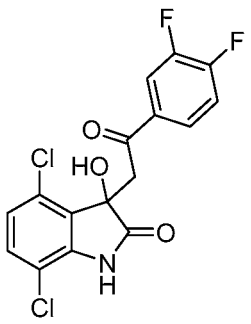
(Ia)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H and Cl; wherein R_7, R_8, R_{10} and R_{11} are independently selected from the group consisting of H and halogen; and wherein R_9 is independently selected from the group consisting C_{3-8} cycloalkyl and C_{3-8} heterocycloalkyl.

[0140] Method 19: The method of any one of Methods 1 through 15, wherein R_1 and R_4 are Cl and R_2 and R_3 are H.

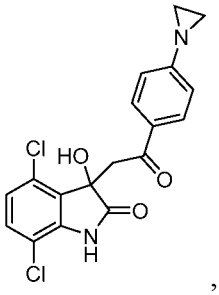
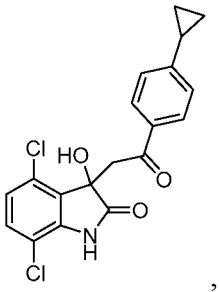
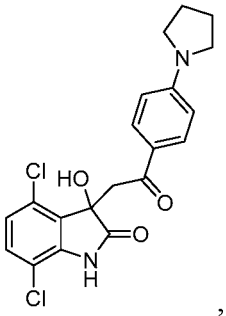
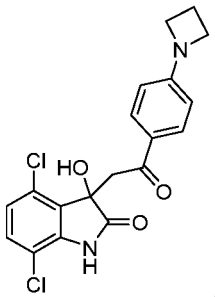
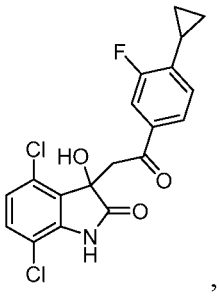
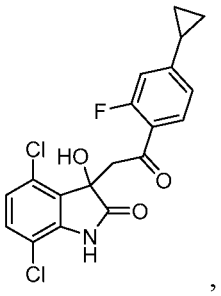
[0141] Method 20: The method of any one of Methods 1 through 15, wherein the compound has a structure selected from the group consisting of:


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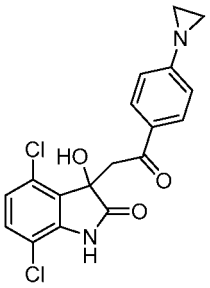
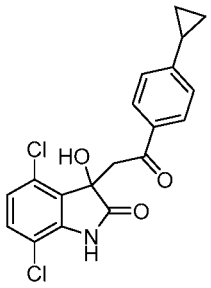
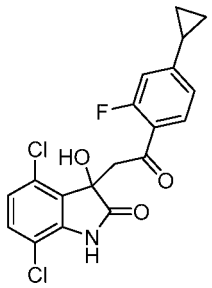
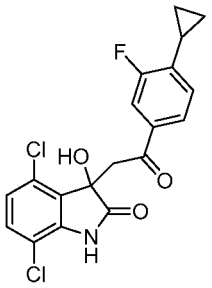
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0142] Method 21: The method of any one of Methods 1 through 15, wherein the compound has a structure selected from the group consisting of:


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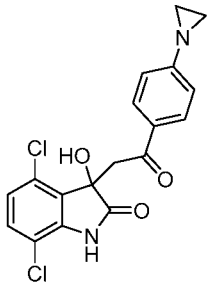
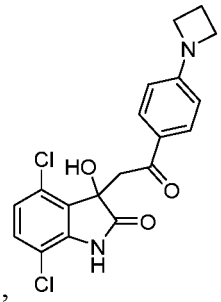
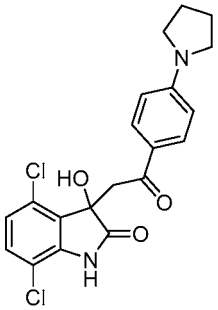
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0143] Method 22: The method of any one of Methods 1 through 15, wherein the compound has a structure selected from the group consisting of:

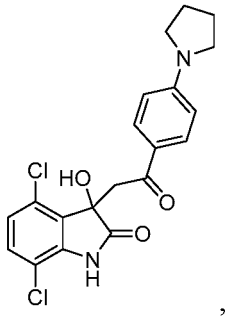
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0144] Method 23: The method of any one of Methods 1 through 15, wherein the compound has a structure selected from the group consisting of:

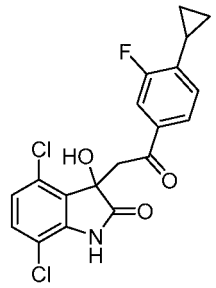
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0145] Method 24: The method of any one of Methods 1 through 15, wherein the compound has a structure:



or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

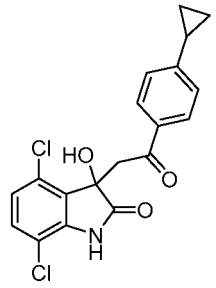
[0146] Method 25: The method of any one of Methods 1 through 15, wherein the compound has a structure:



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or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0147] Method 26: The method of any one of Methods 1 through 15, wherein the compound has a structure:



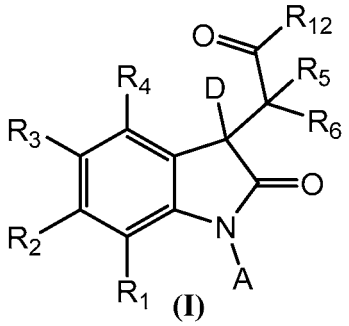
,

or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0148] Composition 27: A pharmaceutical composition, comprising:

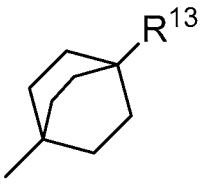
at least one therapeutic agent selected from the group consisting of an immunomodulator, a bromodomain, an extra-terminal protein inhibitor, an anti-CD20 monoclonal antibody, and a BCL2 inhibitor; and

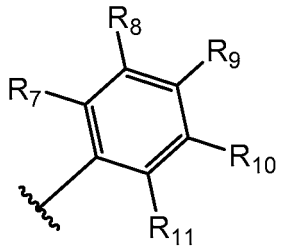
a compound having a structure of Formula (I):



(I)

or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Cl, -CN and $-CF_3$; wherein A is selected from the group consisting of H and C_{1-6} alkyl; wherein D is selected from the group consisting of -OH and $-O(C_{1-6}$ alkyl); wherein R_5 and R_6 are independently selected from the group consisting of H, F, and C_{1-6}

alkyl, or wherein R_5 and R_6 taken together form a substituted or unsubstituted cycloalkyl ring; wherein R_{12} is independently selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} heterocycloalkyl, 

, and 

; wherein R_7, R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(C_{1-6} alkyl), -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

[0149] Composition 28: The composition of Composition 1, wherein R_9 is selected from the group consisting of H, halogen, CN, CF_3, C_{1-6} alkyl, aryl, heteroaryl, -O(aryl), -O(heteroaryl), -CO_2H, -CO_2(C_{1-6} alkyl), -$NHSO_2$(C_{1-6} alkyl), -$NHSO_2$(aryl), -NHCONH(C_{1-6} alkyl), -NHCON(C_{1-6} alkyl)$_2$, -N(C_{1-6} alkyl)$CONH_2$, -N(C_{1-6} alkyl)CONH(C_{1-6} alkyl), -N(C_{1-6} alkyl)CON(C_{1-6} alkyl)$_2$, -SO_2(C_{1-6} alkyl), -SO_2NH_2, -SO_2NH(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$; and wherein R^{13} selected from the group consisting of -O(C_{1-6} alkyl) and –N(C_{1-6} alkyl)$_2$.

[0150] Composition 29: The composition of any one of Compositions 27 through 28, wherein the therapeutic agent is an immunomodulator.

[0151] Composition 30: The composition of any one of Compositions 27 through 28, wherein the immunomodulator is lenalidomide.

[0152] Composition 31: The composition of any one of Compositions 27 through 28, wherein the therapeutic agent is a bromodomain and extra-terminal protein inhibitor.

[0153] Composition 32: The composition of any one of Compositions 27 through 28, wherein the bromodomain and extra-terminal protein inhibitor is OTX015.

[0154] Composition 33: The composition of any one of Compositions 27 through 28, wherein the therapeutic agent is an anti-CD20 monoclonal antibody

[0155] Composition 34: The composition of any one of Compositions 27 through 28, wherein the anti-CD20 monoclonal antibody is rituximab.

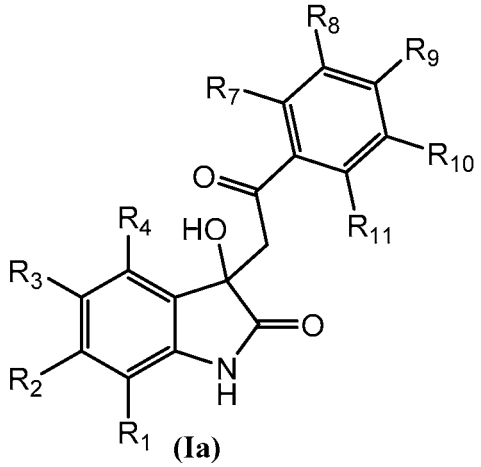
[0156] Composition 35: The composition of any one of Compositions 27 through 28, wherein the therapeutic agent is a BCL2 inhibitor.

[0157] Composition 36: The composition of any one of Compositions 27 through 28, wherein the BCL2 inhibitor is venetoclax.

[0158] Composition 37: The composition of any one of Compositions 27 through 37, wherein R_9 is selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, and morpholinolyl.

[0159] Composition 38: The composition of any one of Compositions 27 through 37, wherein R_9 is selected from the group consisting of isopropyl and cyclopropyl.

[0160] Composition 39: The composition of any one of Compositions 27 through 37, wherein the compound has a structure of Formula (Ia):

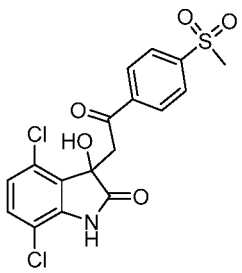
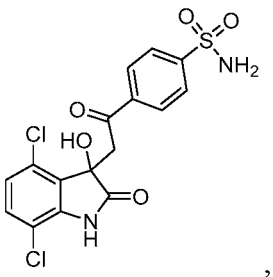
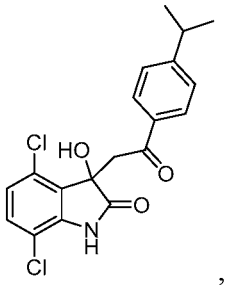
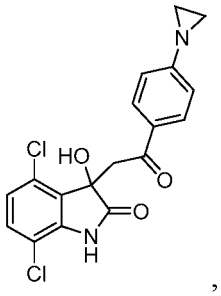
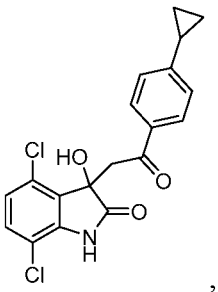
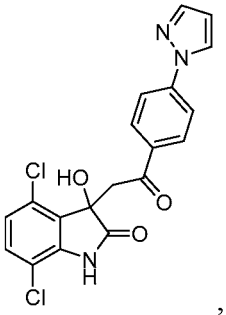
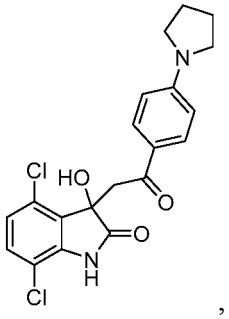
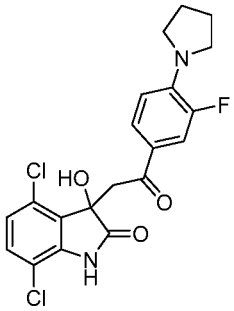
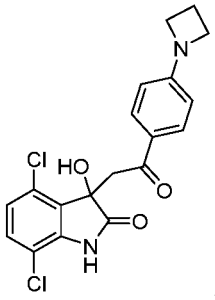
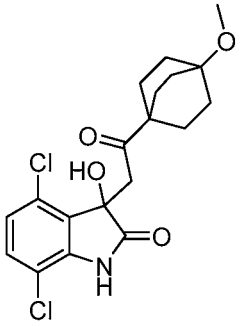
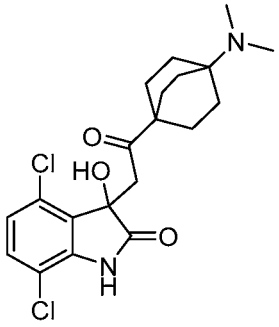
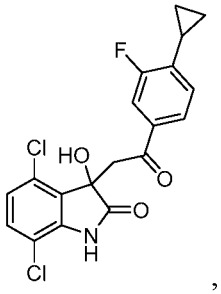
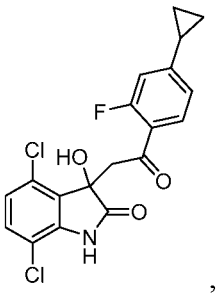
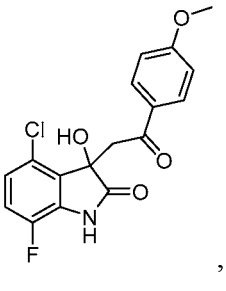
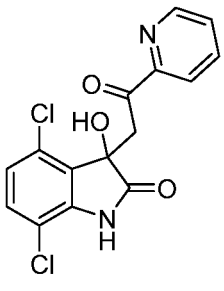
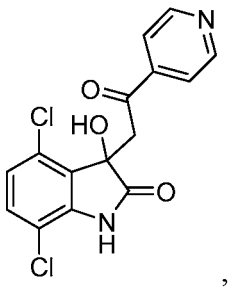


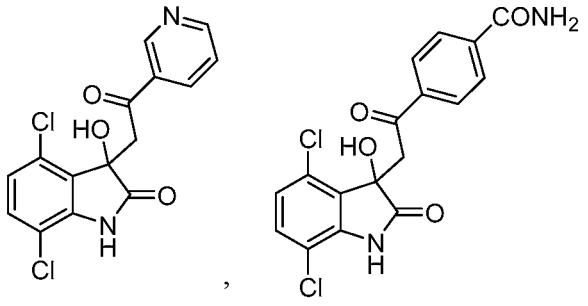
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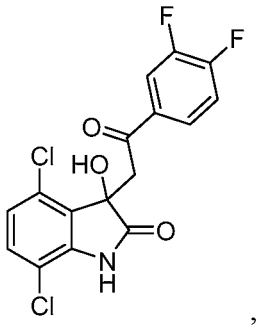
or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H and Cl; wherein R_7, R_8, R_{10} and R_{11} are independently selected from the group consisting of H and halogen; and wherein R_9 is independently selected from the group consisting C_{3-8} cycloalkyl and C_{3-8} heterocycloalkyl.

[0161] Composition 40: The composition of any one of Compositions 27 through 37, wherein R_1 and R_4 are Cl and R_2 and R_3 are H.

[0162] Composition 41: The composition of any one of Compositions 27 through 37, wherein the compound has a structure selected from the group consisting of:

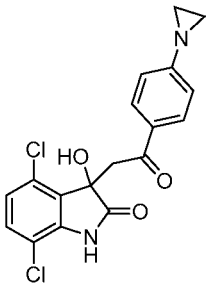
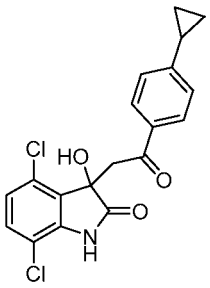
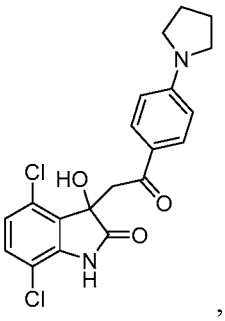
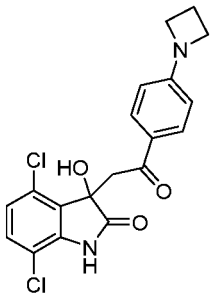
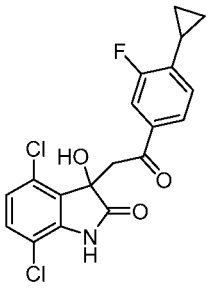
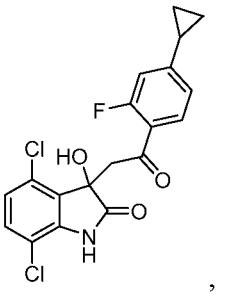

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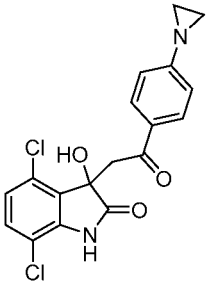
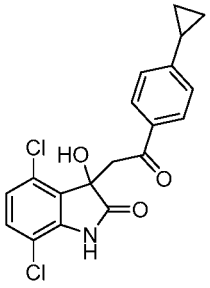
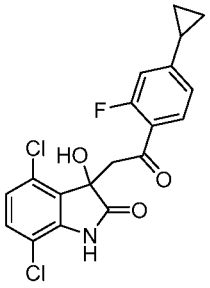
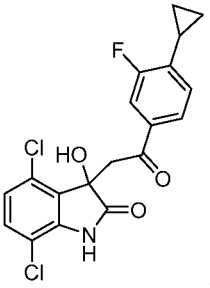
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0163] Composition 42: The composition of any one of Compositions 27 through 37, wherein the compound has a structure selected from the group consisting of:

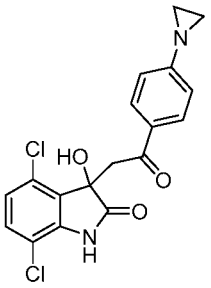
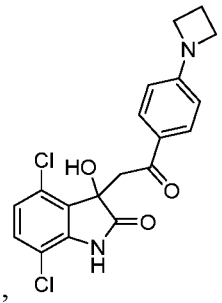
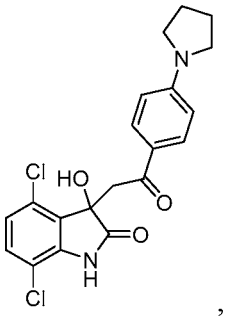
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0164] Composition 43: The composition of any one of Compositions 27 through 37, wherein the compound has a structure selected from the group consisting of:

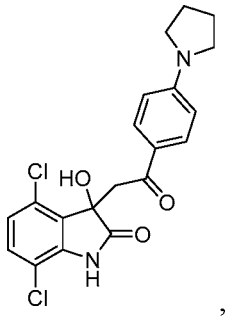
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0165] Composition 44: The composition of any one of Compositions 27 through 37, wherein the compound has a structure selected from the group consisting of:

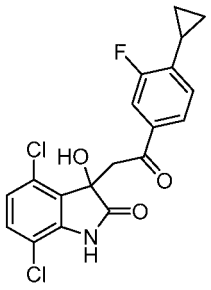
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0166] Composition 45: The composition of any one of Compositions 27 through 37, wherein the compound has a structure:



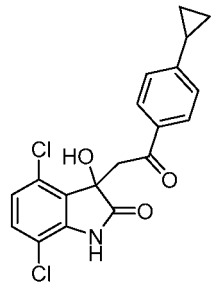
or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0167] Composition 46: The composition of any one of Compositions 27 through 37, wherein the compound has a structure:



or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0168] Composition 47, wherein the compound has a structure:



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or a stereoisomer, a pharmaceutically acceptable salt, ester, or solvate thereof.

[0169] While the disclosure has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive. The disclosure is not limited to the disclosed embodiments. Variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed disclosure, from a study of the drawings, the disclosure and the appended claims.

[0170] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0171] Unless otherwise defined, all terms (including technical and scientific terms) are to be given their ordinary and customary meaning to a person of ordinary skill in the art, and are not to be limited to a special or customized meaning unless expressly so defined herein. It should be noted that the use of particular terminology when describing certain features or aspects of the disclosure should not be taken to imply that the terminology is being re-defined herein to be restricted to include any specific characteristics of the features or aspects of the disclosure with which that terminology is associated.

[0172] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0173] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or

'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; adjectives such as 'known', 'normal', 'standard', and terms of similar meaning should not be construed as limiting the item described to a given time period or to an item available as of a given time, but instead should be read to encompass known, normal, or standard technologies that may be available or known now or at any time in the future; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the invention. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[0174] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0175] It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations.

However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (*e.g.*, "a" and/or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation *is* explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean *at least* the recited number (*e.g.*, the bare recitation of "two recitations," without other modifiers, typically means *at least* two recitations, or *two or more* recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.*, "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (*e.g.*, "a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

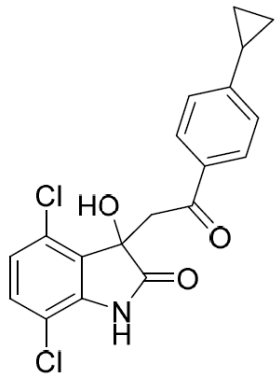
[0176] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term 'about.' Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present

application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0177] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention to the specific embodiments and examples described herein, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

CLAIMS

1. Use of a compound having the structure :

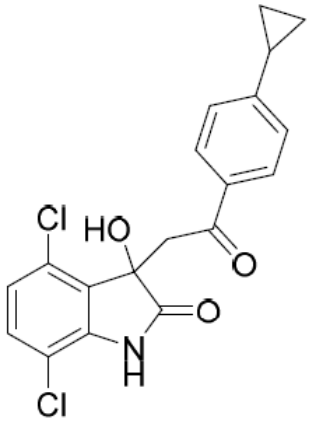


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

2. The use of claim 1, wherein the cell is mammalian.
3. The use of any one of Claims 1-2, wherein the cell is human.
4. Use of a compound having the structure:

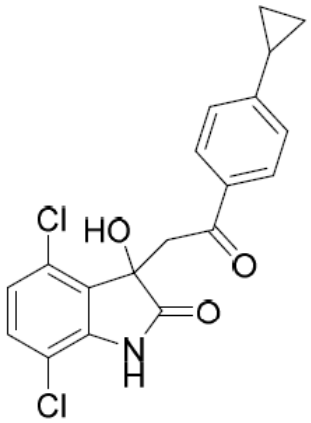


or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof,

in combination with the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

5. Use of a combination comprising a compound having the structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

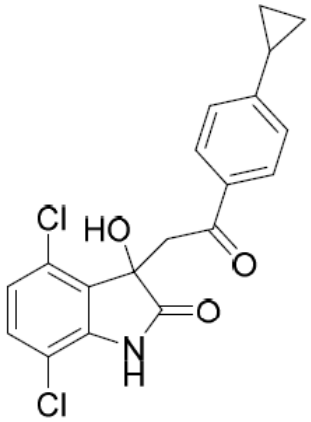
the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for inducing apoptosis in a cell comprising a myeloblast produced in acute myeloid leukemia or a lymphocyte produced in diffuse large B cell lymphoma.

6. The use of claim 5, wherein the cell is mammalian.

7. The use of anyone of claims 5-6, wherein the cell is human.

8. Use of a combination comprising a compound having the structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof, and

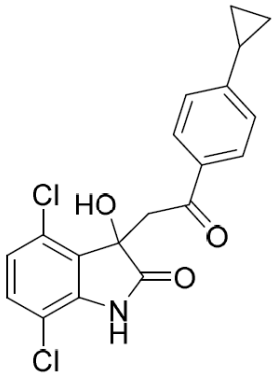
the extra-terminal protein inhibitor OTX015,

in the manufacture of a medicament for treating myeloid leukemia or diffuse large B cell lymphoma.

9. A pharmaceutical composition, comprising:

the extra-terminal protein inhibitor OTX015; and

a compound having a structure:



or a stereoisomer, a pharmaceutically acceptable salt, or solvate thereof.